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PROFILAXIS ANTIBIÓTICA EN LA CIRUGÍA DE IMPLANTES ORALES

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Profilaxis antibiótica en la cirugía de implantes orales

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2. Contenidos

LISTA DE ABREVIATURAS

AEMPS: Agencia Española de Medicamentos y Productos Sanitarios

AMX: Amoxicilina

ARI: Aumento de riesgo absoluto

ARR: Reducción Absoluta del Riesgo

BID: Dos veces al día

BL: Nivel óseo

CLX: Clorhexidina

CONSORT: Consolidated Standards of Reporting Trials (Normas consolidadas de notificación de ensayos)

CSIC: Consejo Superior de Investigaciones Científicas

DDD: Dosis diaria definida

ECA: Ensayo clínico aleatorizado

EVA: Escala visual analógica

FNOMCeO: Federación Nacional de Órdenes de Médicos y Odontólogos

GC: Grupo de control

GRADE: Grading of Recommendations, Assessment, Development and Evaluations (Graduación de Recomendaciones, Valoración, Desarrollo y Evaluaciones)

Gráficos Q-Q: Gráficos de cuantiles-cuantiles

IAO: Academia Italiana de Osteointegración

IBM: International Business Machines Corporation

IME: Índice Médico Español

IC: Intervalo de confianza

KNMT: Real Asociación Dental Holandesa

MA: Edad media

mg: miligramo

MH: Mantel- Haenszel

N: Newton's

n: Tamaño de la muestra

NNH: Número necesario para dañar

NNT: Número necesario para tratar

NS: No estimable

NVOI: Asociación Holandesa de Implantología Oral

OR: Odds Ratio

PICOS: Paciente, intervención, comparación, resultado y tipo de estudio

POA: Amoxicilina oral postoperatoria

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses (Elementos de información preferidos para revisiones sistemáticas y meta-análisis)

PROA: Programa Español de Vigilancia Antimicrobiana en Atención Primaria

QD: Una vez al día

QID: 4 veces al día

RevMan: Review Manager: Gestor de revisiones

RR: Riesgo Relativo

SD: desviación estándar

SDOAP: Dosis única de amoxicilina oral en el preoperatorio

SICOI: Sociedad de Cirugía Oral y Odontología de Implantes

SIO: Sociedad Italiana de Osteointegración

SPSS: Paquete estadístico para las ciencias sociales

STROBE: Strengthening the Reporting of Observational studies in Epidemiology (Refuerzo del informe de estudios observacionales en epidemiología)

TESEO: Base de datos de las tesis doctorales en España

TG: Grupo de prueba

TID: 3 veces al día

TL: Nivel tisular

UE: Unión Europea

3. Síntesis

3.1. Resumen

INTRODUCCIÓN

Tras la pérdida de uno o varios dientes, la colocación de un implante oral para restaurar dicha ausencia es cada vez más frecuente. En España se utilizan aproximadamente entre 1,2 y 1,4 millones de implantes al año, siendo uno de los países con una frecuencia más alta de realización de dicho tratamiento. Los antibióticos profilácticos se presriben para prevenir los fracasos del implante e infecciones postoperatorias. Sin embargo, este tratamiento sigue siendo controvertido y existe incertidumbre en torno a su indicación y la pauta posológica de administración más adecuada.

OBJETIVOS

El objetivo de esta tesis doctoral es aportar información sobre la indicación de la profilaxis antibiótica en cirugía de implantes orales en pacientes sanos y condiciones ordinarias. Asimismo, analizar las pautas de prescripción realizada por los profesionales clínicos y la existencia de consensos en diferentes países para realizar esta profilaxis.

METODOS

Se analizó la literatura científica mediante tres meta-análisis destinados a determinar el nivel de evidencia y esclarecer los consensos existentes en la literatura. Se realizó un ensayo clínico para estudiar la eficacia y efectividad de la clindamicina oral y se evaluó mediante una encuesta transversal la prescripción de antibióticos profilácticos por parte de los clínicos en tres países diferentes: España, Italia y Países Bajos.

RESULTADOS

Una única dosis preoperatoria de 1, 2 o 3 gramos de amoxicilina una hora antes de la cirugía podría ser eficaz en la prevención de fracasos del implante oral. En los casos de alergia a la amoxicilina, se suele recomendar clindamicina, que en el ensayo clínico desarrollado no ha demostrado ser eficaz ni efectivo en la prevención ni del fracaso ni de la infección. Las dosis y pautas posológicas de antibióticos profilácticos utilizadas en la práctica clínica identificadas por las encuestas son muy diferentes de los consensos alcanzados, pudiéndose observar un probable sobretratamiento de los pacientes.

CONCLUSIONES

La prescripción rutinaria de antibióticos preventivos en implantología debe juzgarse de forma individual para cada paciente. En pacientes sanos no alérgicos a amoxicilina se podría emplear una dosis única preoperatoria de 1, 2 o 3 gramos. En pacientes alérgicos a los beta-lactámicos, la administración de 600 mg de clindamicina oral, no muestra eficacia ni efectividad en la prevención de fracasos e infecciones y podría ser un factor de riesgo para la pérdida del implante. Además, la mayoría los profesionales no siguen los consejos de la literatura sobre cirugía de implantes orales en pacientes sanos y condiciones ordinarias, utilizando regímenes muy variados y dosis de antibióticos muy superiores a las recomendadas en las publicaciones científicas.

3.2. Introducción

3.2.1. Implantes orales

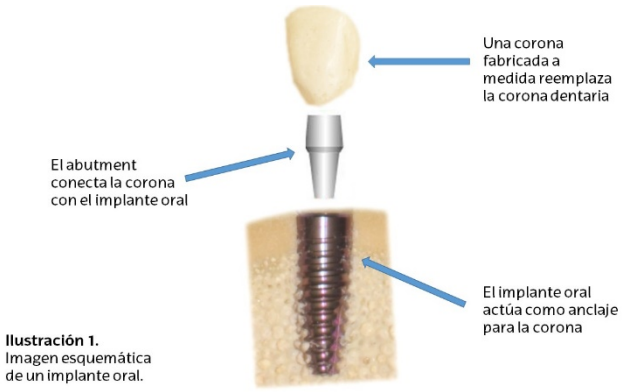


Ilustración 1.
Imagen esquemática de un implante oral.

Tras la pérdida de un diente se produce una falta tanto de su parte visible denominada corona, como de su raíz que está oculta por la encía y el hueso alveolar. La pérdida de un diente es un fenómeno muy común y suele ser consecuencia de caries, enfermedad periodontal, un problema endodóntico (pulpar) o un traumatismo. En el 2010, aproximadamente el 2.3% de la población mundial, representando 158 millones de personas de todo el planeta, sufría una pérdida severa de dientes [1]. Según una nota de prensa del Consejo General de Dentistas de España fechada el 28 de octubre de 2021, 25 millones de habitantes han perdido al menos un diente en nuestro país.

Los implantes orales o bien denominados implantes dentales, son productos sanitarios que sirven como reemplazo artificial de la raíz dental. Un implante oral se coloca en el hueso maxilar, mandibular o zigomático de tal modo que se fusiona con el hueso natural del paciente. Este fenómeno se denomina oseointegración. De este modo el implante oral se convierte en una fuerte y robusta base o pilar para el posterior reemplazo del diente [2].

Los implantes orales pueden servir para reemplazar un diente individual mediante una corona simple, varios dientes a la vez mediante un puente o todos los dientes de una arcada mediante una prótesis o una sobredentadura. Los implantes orales también

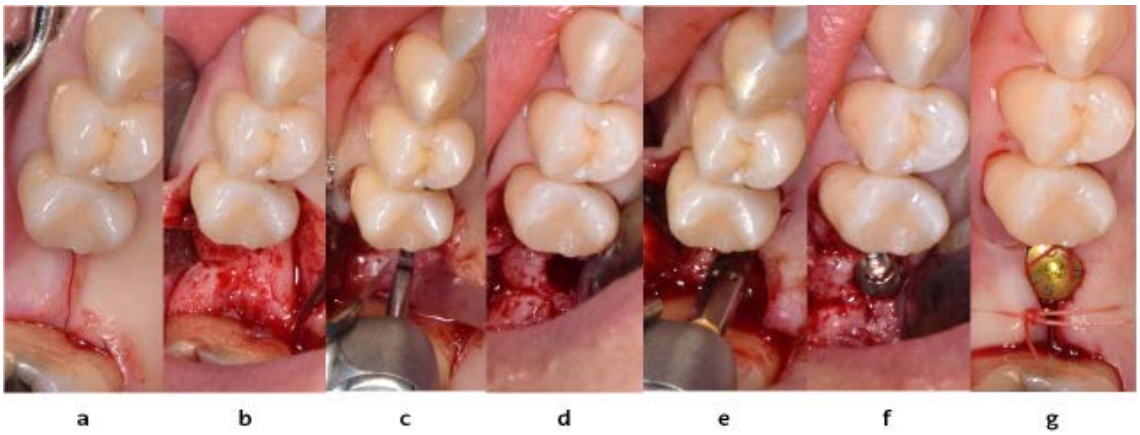


Ilustración 2.
Procedimiento quirúrgico realizado para la inserción de un implante oral en la arcada superior derecha: incisión crestal de la encía e intrasulcular de los dientes adyacentes (a), elevación de un colgajo muco-perióstico (b), fresado del hueso alveolar de acuerdo al protocolo del fabricante (c), ostectomía completada (d), inserción del implante de acuerdo con el torque y la velocidad indicada por el fabricante (e), implante de nivel óseo posicionado en el hueso alveolar (f), inserción del pilar de cicatrización y cierre del colgajo por medio de una sutura reabsorbible de cuatro ceros (g).

pueden servir como anclaje y transmisión de fuerzas en los tratamientos de ortodoncia [3].

La mayoría de implantes dentales exigen, comúnmente, 5 pasos básicos para su colocación: la incisión en el tejido blando y elevación de un colgajo mucoperióstico, preparación del lecho implantario mediante el fresado del hueso alveolar, colocación del implante y adaptación del tejido blando mediante la colocación sobre el implante de un pilar de cicatrización también llamado “healing abutment”.

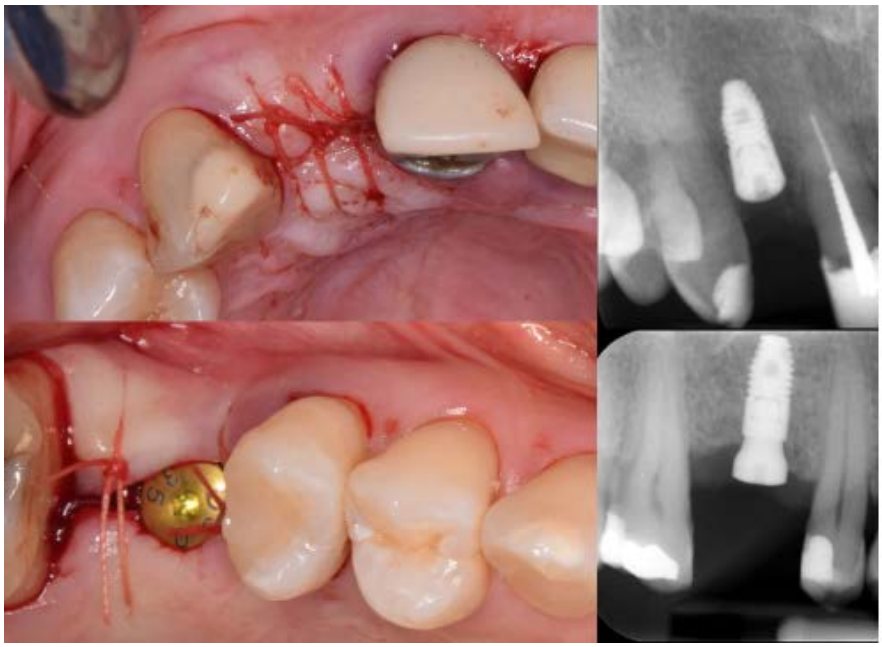
Alternativamente, se puede proceder a la colocación de un tornillo de cicatrización o “cover screw” y finalmente el cierre del colgajo [4].

Existen también diferentes secuencias de colocación de un implante tras la extracción dental. Se puede realizar un implante inmediatamente después de la exodoncia, colocarlo de dos semanas a dos meses tras la extracción o retrasarlo tres o más meses tras la extracción [5].

Cuando el volumen óseo residual es insuficiente, es común realizar procedimientos de aumento óseo antes o junto con la colocación de implantes orales término también conocido como regeneración ósea guiada [6].

Existen además varias opciones a la hora de restaurar la corona del diente perdido mediante una prótesis o “cargar” el implante. Se puede realizar una carga inmediata tras el procedimiento quirúrgico, una carga temprana dos semanas después de la intervención quirúrgica o una carga tardía hasta tres meses más tarde de la cirugía de implantes orales [7].

La supervivencia de los implantes dentales esta descrita en varios estudios longitudinales y varía entre el 90-95% [8]. A pesar del alto porcentaje de supervivencia, los fracasos del implante y otras complicaciones postoperatorias pueden ocurrir [9].



a **Ilustración 3.** Implante de nivel óseo posicionado en el maxilar superior y sumergido debajo de la encía tras la colocación de un tornillo de cicatrización (cover screw) y una sutura reabsorbible de cuatro ceros (a).

b Implante de nivel óseo posicionado en el maxilar superior y conectado con la cavidad oral por medio de un pilar de cicatrización (b). A la derecha de las fotografías clínicas, las respectivas radiografías.

Estos fracasos y complicaciones son muy poco tolerados tanto por los pacientes como por los profesionales.

Tras la inserción de un implante dental, las infecciones periimplantarias son unas de las más frecuentes complicaciones. Se denominan mucositis si existen signos de inflamación en ausencia de pérdida ósea alrededor del implante, o periimplantitis si existe pérdida ósea junto a los signos típicos de inflamación de los tejidos blandos. La prevalencia de mucositis y periimplantitis varía entre un 1% y un 63.4% dependiendo de los estudios [10]. Cuando la periimplantitis es establecida, su tratamiento es complejo, el hueso periimplantario se reabsorbe pudiendo provocar la pérdida del implante. Una de las causas relacionadas con las infecciones periimplantarias ha sido la inoculación de bacterias durante el procedimiento quirúrgico [9].

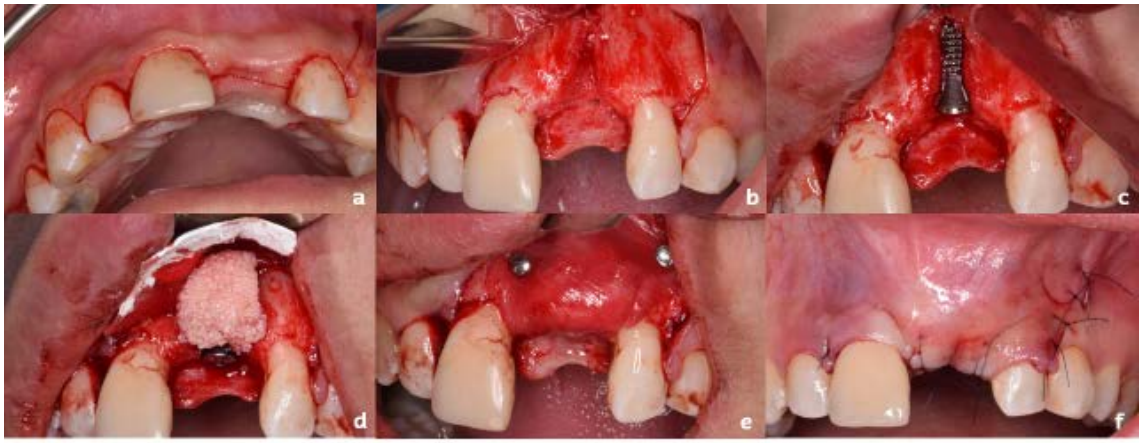


Ilustración 4.
Procedimiento quirúrgico realizado para la inserción de un implante oral en la arcada superior izquierda por medio de un procedimiento de aumento óseo concomitante: incisión crestal de la encía e intrasulcular de los dientes adyacentes e incisión de descarga (a), elevación de un colgajo mucoperióstico y exposición del defecto óseo (b), fresado del hueso alveolar de acuerdo al protocolo del fabricante e inserción del implante (c), recubrimiento del defecto y el implante con un xenoinjerto óseo (d), recubrimiento del substituto óseo por medio de una membrana de colágeno reabsorbible y fijación con pins (e), cierre del colgajo mucoperióstico (g).

3.2.2. Profilaxis en implantología oral

El término “profilaxis” proviene del griego antiguo; de *pro* (griego moderno: προ, romanización: *pro*) cuyo significado es “antes de” y de *phulaxis* (griego moderno: φύλαξις, romanización: *phýas*), cuyo significado es literalmente “guardián”. Según la Real Academia de la Lengua Española “profilaxis” significa preservación de la enfermedad. También podría definirse como el conjunto de medidas que se toman para proteger o preservar a alguien de las enfermedades.

En este proyecto, los antibióticos profilácticos se definieron como aquellos antibióticos prescritos en el período perioperatorio junto con la cirugía de implantes orales para prevenir las infecciones postoperatorias y los fracasos de los implantes orales [11,12].

Debido a las posibles complicaciones relacionadas con la cirugía de implantes orales, se han estudiado varios tratamientos periquirúrgicos antimicrobianos a base de antisépticos y antibióticos para la profilaxis de las infecciones postimplantarias y los fracasos del implante oral.

La clorhexidina puede ser una opción de relevancia y bajo riesgo, ya que altera el biofilm bacteriano (colonia de bacterias adheridas entre sí y a las superficies del implante, tejido dental o encía) y reduce la inflamación de los tejidos periimplantarios [13,14].

El uso de antibióticos profilácticos en la cirugía de implantes orales se remonta a los años iniciales de la implantología oral. En las primeras publicaciones, se administraba sistemáticamente penicilina 1 hora preoperatoria y los 10 siguientes días postoperatorios tras la cirugía de implantes orales para favorecer la oseointegración [15]. Poco tiempo después esta práctica ha sido rebatida por otras publicaciones [16].

En la actualidad, parece no existir un consenso establecido sobre el uso e indicaciones de la profilaxis antibiótica en la colocación de implantes orales en pacientes sanos y en condiciones ordinarias [17]. Una revisión sistemática llevada a cabo por la Cochrane concluyó que podría ser sensato sugerir el uso rutinario de una dosis única de 2 g de amoxicilina profiláctica justo antes de la colocación de un implante oral. Sin embargo, no se pudo clarificar si el uso complementario de antibióticos postoperatorios era beneficioso, ni qué antibiótico sería el más efectivo [9].

Del mismo modo, la evidencia científica relativa al uso profiláctico de antibióticos para reducir el riesgo de infección en los procedimientos de regeneración ósea guiada previos o junto a la colocación de implantes orales son muy limitadas [6]. Sin embargo, es más probable que los profesionales prescriban antibióticos con el uso de injertos óseos y a medida que aumenta la complejidad del procedimiento para disminuir las posibilidades de desarrollar una infección [18].

La selección del antibiótico, la dosis y la pauta posológica varían según los estudios. El grupo de los beta-lactámicos han sido los antibióticos más utilizados para profilaxis en odontología. Dentro de este grupo, la amoxicilina es frecuentemente la primera elección debido a su eficacia contra *streptococcos* y anaerobios orales. Si el paciente tiene una historia de reacciones anafilácticas al grupo de las penicilinas, la amoxicilina es comúnmente sustituida por la clindamicina [19]. Esto también parece ocurrir con las cirugías de implantes orales [20,21].

El uso profiláctico de antibióticos en odontología sí parece estar bien documentado para prevenir complicaciones en pacientes que están en riesgo de desarrollar endocarditis infecciosa o pacientes inmunocomprometidos [22]. Según otros autores, la colocación de implantes dentales tras la realización de un colgajo mucoperióstico no desentraña un riesgo significativo de bacteriemia, con lo que su uso profiláctico, aún en pacientes de riesgo sería cuestionable [23].

Existen diversos ensayos clínicos que utilizan amoxicilina con diferentes pautas posológicas en pacientes sanos y condiciones ordinarias (1 hora preoperatoria, dos días en el postoperatorio o una semana tras la colocación del implante) y dosis (1, 2 o 3 gramos) para la profilaxis de complicaciones postoperatorias tales como la infección, la inflamación y el fracaso del implante dental [24-30].

Sin embargo, siendo la clindamicina una de los antibióticos comúnmente prescritos en pacientes alérgicos a la amoxicilina [31,32], no se dispone de ensayos clínicos que evalúen su efecto en la prevención de fracasos o infecciones postoperatorias tras la cirugía de implantes orales en pacientes sanos y en los que no se realizara una regeneración o aumento óseo. Por este motivo, se requirieron nuevas investigaciones clínicas con antibióticos diferentes a la amoxicilina para aumentar la poca evidencia existente sobre antibióticos alternativos en pacientes alérgicos a las penicilinas [12]. A pesar de que varios estudios pretéritos concluyeran que tanto la penicilina como la clindamicina eran efectivas en la reducción de infecciones en los lechos óseos en los que se ha realizado regeneración ósea para la colocación de implantes orales [33, 34], nuevas investigaciones retrospectivas señalan que la alergia a las penicilinas y el uso alternativo de la clindamicina podrían estar asociadas con el aumento de fracasos de implantes orales y de la propia regeneració ósea [35-38].

Se han publicado en el pasado distintas revisiones sistemáticas y meta-análisis que estudiaban el efecto profiláctico de la amoxicilina en la cirugía de implantes orales [9, 11, 39-41]. No obstante, sigue sin existir suficiente evidencia y no está claro si el uso de antibióticos es beneficioso ni cuál ni cómo sería el tratamiento antibiótico más efectivo para prevenir las infecciones o pérdidas del implante oral tras la intervención [27, 29, 30]. Ante la ausencia de protocolos, la prescripción profiláctica de antibióticos tras la colocación de un implante dental se ha convertido una práctica muy frecuente.

Por otro lado, el empleo de antibióticos prescritos por dentistas ha aumentado en los últimos años [42] y los costes estimados, sólo en EE.UU., para los antibióticos usados para profilaxis en tratamientos dentales exceden los 145 mil millones de dólares anuales [43].

Del mismo modo, la terapia con implantes dentales tampoco deja de aumentar. Sólo en EE.UU. aproximadamente 500.000 implantes dentales son colocados cada año [44]. Además, el mercado mundial de implantes dentales está creciendo constantemente y se espera que crezca a unos 13 mil millones de dólares para el año 2023 [45].

La evolución en el número de implantes dentales empleados en España ha sufrido una enorme progresión. En el año 2004 se colocaron 400.000 implantes en el 2008 fueron 813.000 y en el 2016 la cifra alcanzó los 1.076.000, según el proyecto "*Implant Flash Analysis*", realizado por la empresa KeyStone®. España es probablemente el país con la ratio más elevada de implantes por habitante en Europa, y quizá también en el mundo. Con aproximadamente un millón de pacientes sometidos a tratamientos de

implantología oral cada año, se encuentra en tercer lugar en volumen de personas tratadas con esta terapéutica, sólo por detrás de Alemania e Italia. Considerando 2012 como año base, el número de implantes vendidos, y probablemente colocados, ha aumentado un 35% [46]. Según una nota de prensa del Consejo General de Dentistas de España fechada el 28 de octubre de 2021, se colocan entre 1,2 y 1,4 millones de implantes al año en nuestro país.

Dado el gran número de implantes dentales que se colocan en todo el mundo, la cantidad de antibióticos utilizados para prevenir complicaciones puede suponer un dato de relevancia a nivel epidemiológico y de salud pública. Además, el Consejo General de Dentistas de España informaba en una nota de prensa fechada el 29 de octubre de 2021 que cerca del 10% de las prescripciones de antibióticos en España provienen de los dentistas, "por lo que la profesión debe tomar medidas urgentes, ya que su utilización indebida está incrementando la resistencia a infecciones y, por tanto, supone una amenaza para la salud".

3.2.3. Reacciones adversas a la antibioterapia

El uso irracional de los antibióticos puede dar lugar a un aumento injustificado de los costos y las reacciones adversas como alergias, toxicidad, trastornos gastrointestinales y resistencias bacterianas [47, 48]. Esta última condición se ha convertido recientemente en una importante amenaza en todo el mundo. Los estudios epidemiológicos han demostrado una relación directa entre el consumo de antibióticos y la aparición y diseminación de cepas de bacterias resistentes [49].

La preocupación por la aparición, cada vez más frecuente, de nuevas cepas bacterianas resistentes a todo tipo de antibióticos y las superinfecciones sigue en ascenso. Las enfermedades farmacorresistentes ya causan al menos 700.000 muertes al año en todo el mundo, y en el escenario más alarmante, la cifra podría aumentar a 10 millones de muertes al año para 2050 si no se toman medidas [50].

El daño económico causado por la resistencia no controlada a los antimicrobianos podría ser comparable al de la crisis financiera mundial de 2008-2009 debido al aumento espectacular de los gastos en atención sanitaria, al impacto en la producción de alimentos y piensos, el comercio y los medios de vida. Para 2030, la resistencia a los antimicrobianos podría llevar a 24 millones de personas a la pobreza extrema [50].

Muchos profesionales y pacientes no ven en las resistencias antibióticas una razón para abstenerse del uso de antibióticos. Además, los datos aportados por el Eurobarómetro especial en abril de 2016 sobre la resistencia antimicrobiana indican que ni la sociedad europea ni la española poseen un conocimiento adecuado sobre la finalidad ni el mecanismo de acción de los antibióticos [51].

Una de las iniciativas desarrolladas en España durante el año 2015 propuesta por el Ministerio de Sanidad, Servicios Sociales e Igualdad en su plan estratégico y de acción

para reducir el riesgo de selección y diseminación de la resistencia a los antibióticos fue la de limitar el uso profiláctico de antibióticos a casos con necesidades clínicas definidas en Salud Humana. Para ello se propuso diseñar y difundir herramientas para la promoción del uso prudente de antibióticos. Durante el 2016 se fijaba el objetivo de desarrollar la documentación referente a la limitación del uso profiláctico de antibióticos [52].

3.2.4. Marco teórico

Para la profilaxis antibiótica en la cirugía de implantes orales cada profesional puede estar empleando el fármaco y la posología que considere más adecuada, pero se desconoce cuál es realmente la frecuencia con la que se prescriben antibióticos profilácticos en la colocación de implantes en España y si ésta es similar a la de otros países de nuestro entorno. También se desconoce qué antibióticos y posología están siendo prescritos con mayor frecuencia, además de la evidencia que respalda esas prescripciones antibióticas para prevenir la infección y el fracaso de los implantes orales. Como publicaron Deeb y sus colaboradores en un estudio realizado en profesionales de EE.UU., la falta de consenso puede provocar que los profesionales no utilicen la profilaxis antibiótica acorde con las recomendaciones basadas en la evidencia publicada en la literatura científica [17].

Este proyecto pretende averiguar si el uso profiláctico de antibióticos en la cirugía de implantes orales es eficaz en la prevención de infecciones postoperatorias y el fracaso del implante oral. Para ello, se realizó primero una revisión sistemática y meta-análisis de la literatura científica. Posteriormente, se realizó una encuesta destinada a los profesionales de la salud oral de nuestro país y de otros países de nuestro entorno para evaluar cuáles son sus hábitos de profilaxis antibiótica en implantología oral, valorar el nivel de consenso clínico y determinar si siguen las últimas recomendaciones publicadas en la literatura científica. Consecutivamente, se realizó una revisión sistemática y meta-análisis de todas las encuestas transversales que habían tenido el mismo objetivo con el fin de comparar diferentes poblaciones y sus prescripciones. Debido a que con frecuencia los pacientes alérgicos a los antibióticos beta lactámicos eran tratados preventivamente con clindamicina, se realizó una revisión sistemática y meta-análisis para comprobar la eficacia de la clindamicina en la cirugía oral. Por último y tras demostrar la ausencia de evidencia al respecto, se diseñó y se llevó a cabo, un ensayo clínico aleatorizado, doble ciego y controlado con placebo para aportar nueva evidencia científica sobre el efecto de la clindamicina en la profilaxis antibiótica en la cirugía de implantes orales realizada a pacientes sanos y sin necesidad de regeneración ósea, en un lecho implantario sin infección previa.

3.2.5. Justificación de la unidad temática

La unidad temática de todos estos estudios se basa en tres líneas de investigación fundamentales del programa de doctorado en salud pública de la Universidad del País Vasco: la epidemiología clínica, la investigación en servicios de salud y la farmacoepidemiología. El uso de antibióticos profilácticos en implantología oral puede suponer un gran problema a nivel epidemiológico debido a la aparente falta de consenso clínico en su prescripción y al creciente número de cirugías de implantología oral que se realizan. La aparición de resistencias bacterianas es una complicación cada vez más frecuente debido principalmente al uso irracional de antibióticos y supone unas graves consecuencias de gran relevancia a nivel farmacoepidemiológico. Las investigaciones en los servicios de salud oral que se realizaron en este sentido son fundamentales para detectar, prevenir y evitar riesgos y costes injustificados para el sistema sanitario, la economía y la sociedad.

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3.2. Objetivos e Hipótesis

3.2.1. Objetivos generales

El principal objetivo de este proyecto es aportar información al clínico sobre cual debe ser su actitud sobre la prescripción preventiva de antibióticos a un paciente al que se lo van a colocar implantes tanto si el paciente es alérgico a los antibióticos beta-lactámicos como si no lo es.

También queremos conocer si la prescripción preventiva de antibióticos en la cirugía de implantes es igual en diversos países y si se siguen las recomendaciones aportadas por la literatura.

Nuestro objetivo es dar respuesta a las siguientes cuestiones:

1: A este paciente al que le voy a colocar un implante ¿le debo pautar antibiótico para evitar la infección y/o el fracaso de estos implantes? De ser así, ¿cuál debe ser nuestro tratamiento preventivo? Realizamos una revisión sistemática y meta-análisis para conocer la evidencia disponible.

2: ¿Y si este paciente es alérgico a los antibióticos beta-lactámicos? Comprobamos que la eficacia de los tratamientos preventivos que se proponen en pacientes alérgicos a dicho grupo de antibióticos no están basados en ensayos clínicos que avalen su eficacia. En nuestro medio uno de los más empleado es la clindamicina, por ello realizamos una revisión sistemática sobre la eficacia de la clindamicina preventiva en cirugía oral y al comprobar que no hay ninguna información sobre su empleo en implantología, diseñamos y realizamos un ensayo clínico aleatorizado y ciego con placebo.

3: Nos preguntamos si los profesionales de la implantología prescriben antibióticos preventivos siguiendo las pautas publicadas en la literatura. Realizamos tres encuestas, una en España, otra en Países Bajos y una tercera en Italia, para que junto con otras encuestas publicadas en otros países poder concluir cuales son las actitudes sobre la prescripción preventiva de antibióticos en implantología en la actualidad.

3.2.2. Objetivos e hipótesis específicas

Antibióticos preventivos en cirugía de implantes orales. Revisión sistemática y meta-análisis

Objetivos Analizar la evidencia científica disponible sobre la eficacia de la profilaxis antibiótica sistémica para prevenir la infección y/o el fracaso en la colocación de implantes dentales. Para posteriormente evaluar si algún régimen antibiótico previene los fracasos de los implantes dentales y/o las infecciones postoperatorias.

Hipótesis nula La prescripción de antibióticos peri-operatorios en la colocación de implantes orales no es eficaz ni efectiva en la profilaxis de la infección postoperatoria y/o del fracaso del implante. No existen diferencias estadísticamente significativas en las incidencias de fracaso del implante y/o infección postoperatoria entre los pacientes tratados con profilaxis antibiótica peri-implantaría y los que no reciben ningún tipo de profilaxis antibiótica.

Rodríguez Sánchez F, Rodríguez Andrés C, Arteagoitia I. Which antibiotic regimen prevents implant failure or infection after dental implant surgery? A systematic review and meta-analysis. J Craniomaxillofac Surg. 2018 Apr;46(4):722-736. doi: 10.1016/j.jcms.2018.02.004. Epub 2018 Feb 26. PMID: 29550218.

Clindamicina preventiva en cirugía oral. Revisión sistemática y meta-análisis

Objetivos *E*valuar el efecto de la clindamicina (con cualquier tipo de vía de administración, régimen o dosis) para prevenir las complicaciones infecciosas en pacientes sometidos a cualquier tipo de cirugía oral, incluida la colocación de implantes dentales.

Hipótesis nula La clindamicina, con cualquier tipo de vía de administración, régimen o dosis, no es efectiva para prevenir complicaciones infecciosas en pacientes sometidos a cualquier tipo de cirugía oral, tampoco lo es en la cirugía de colocación de implantes.

Arteagoitia I, Rodríguez Sánchez F, Figueras A, Arroyo-Lamas N. Is clindamycin effective in preventing infectious complications after oral surgery? Systematic review and meta-analysis of randomized controlled trials. Clinical Oral Investigations.

Bajo revisión

Clindamicina preventiva en la cirugía de implantes orales. Ensayo clínico aleatorizado y controlado

Objetivos Analizar la eficacia frente a placebo de una pauta antibiótica profiláctica sistémica (una dosis única de 600 mg de clindamicina administrada una hora antes de la cirugía por vía oral) en la disminución de la incidencia de infección y/o pérdida del implante tras la cirugía de implantes orales en pacientes sanos cuando se colocan implantes en lechos sin infección previa ni se requiere regeneración ósea.

Hipótesis nula No existen diferencias en la incidencia acumulada de fracaso del implante y/o infección en la inserción de implantes orales cuando se emplea una pauta antibiótica sistémica de clindamicina, (600 mg una hora antes de la cirugía) frente a la misma pauta de placebo.

Santamaría G, Rodríguez Sánchez F, Rodriguez C, Barbier L Arteagoitia I, Effect of Preoperative Clindamycin Preventing Implant Failures and Postoperative Infections after Oral Implant Surgery: a Randomized Placebo-controlled Clinical Trial. Clinical oral implants research.

Enviado a la revista

Hábitos de prescripción antibiótica en cirugía de implantes orales. Encuestas transversales en España, Países Bajos e Italia y meta-análisis de encuestas transversales

Objetivos Identificar los patrones de prescripción antibiótica sistémica utilizados en las cirugías de implantes orales en pacientes sanos por profesionales en España, Países Bajos e Italia. Evaluar la dosis y los tipos de antibióticos prescritos y contrastar la dosis media de antibióticos prescritos con el régimen recomendado basado en pruebas en pacientes sanos y en condiciones sencillas: una única dosis preoperatoria de amoxicilina de 2 g. Un objetivo adicional de este estudio fue evaluar las diferencias en la dosis y el tipo de antibiótico entre los países y los regímenes de prescripción.

Hipótesis nula se postularon de la siguiente manera: (1) la dosis media de antibióticos profilácticos prescritos por cirugía de implantes orales es igual a una dosis única de 2.000 mg y (2) no hay variaciones en la dosis media de antibióticos prescritos entre los diferentes países y regímenes de prescripción.

Arteagoitia I, Rodríguez-Andrés C, Rodríguez-Sánchez F. Antibiotic prophylaxis habits in dental implant surgery among dentists in Spain. A cross-sectional survey. Med Oral Patol Oral Cir Bucal. 2018 Sep 1;23(5):e608-e618. doi: 10.4317/medoral.22626. PMID: 30148475; PMCID: PMC6167099.

Rodríguez Sánchez F, Arteagoitia I, Rodríguez Andrés C, Bruers J. Antibiotic prophylaxis prescribing habits in oral implant surgery in the Netherlands: a cross-sectional survey. BMC Oral Health. 2019 Dec 12;19(1):281. doi: 10.1186/s12903-019-0981-4. PMID: 31830979; PMCID: PMC6909651

Rodríguez Sánchez F, Arteagoitia I, Rodríguez Andrés C, Caiazzo A. Antibiotic prophylaxis habits in oral implant surgery among dentists in Italy: a cross-sectional survey. BMC Oral Health. 2019 Dec 2;19(1):265. doi: 10.1186/s12903-019-0943-x. PMID: 31791306; PMCID: PMC6889412.

Rodríguez Sánchez F, Arteagoitia I, Teughels W, Rodríguez Andrés C, Quirynen M. Antibiotic dosage prescribed in oral implant surgery: A meta-analysis of cross-sectional surveys. PLoS One. 2020 Aug 18;15(8):e0236981. doi: 10.1371/journal.pone.0236981. PMID: 32810135; PMCID: PMC7446810.

3.3. Herramientas metodológicas y Resultados

3.3.1. Antibióticos preventivos en cirugía de implantes orales. Revisión sistemática y meta-análisis

RESUMEN

Objetivos: Evaluar qué régimen antibiótico previene los fracasos de los implantes dentales o las infecciones postoperatorias tras la colocación de los mismos.

Métodos: Revisión sistemática y meta-análisis. Fuentes de datos: Se realizaron búsquedas en Pubmed, Cochrane, Science Direct y EMBASE a través de OVID hasta agosto de 2017. Solo se incluyeron ensayos clínicos controlados aleatorios (ECA) que utilizaron antibióticos. Las medidas de resultado se establecieron en los fracasos de los implantes dentales o en la incidencia de infección postoperatoria después de la cirugía de implantes dentales. Tres revisores realizaron de forma independiente la evaluación del riesgo de sesgo y la extracción de datos. Se realizaron meta-análisis estratificados de los datos binarios mediante modelos de efectos fijos con STATA® 14. Se estimó la razón de riesgo (RR) y el intervalo de confianza (IC) del 95%.

Resultados: Se incluyeron nueve artículos correspondientes a 15 ECA. Todos los ECAs probaron sólo amoxicilina oral. Análisis del fracaso del implante: RR global=0,53 (*p*=0,005, IC del 95%: 0,34-0,82) y NNT global=55 (IC del 95%, 33-167). La amoxicilina oral en dosis única preoperatoria (SDOAP) es beneficiosa (RR=0,50, IC: 0,29-0,86. *p*=0,012), en comparación con la amoxicilina oral postoperatoria (POA): RR= 0,60, CI: 0,28-1,30. *p*=.197). Análisis de la infección postoperatoria: RR global=0,76 (*p*=0,250, IC 95%: 0,47-1,22). Ni la SDOAP (RR=0,82, IC=0,46-1,45, *p*=0,488) ni la POA (RR=0,64, IC=0,27-1,51, *p*=0,309) son beneficiosas. I2=0,0%, pruebas de chi-cuadrado *p*≈1.

Conclusiones: Sólo la SDOAP es efectiva y eficaz para prevenir los fracasos de los implantes, pero no fue significativa para las infecciones postoperatorias tras las cirugías de implantes dentales.

MÉTODOS

Protocolo y registro

Para abordar el propósito de la investigación, los autores diseñaron e implementaron una revisión sistemática y un meta-análisis. La investigación se llevó a cabo y se informa de acuerdo con las recomendaciones de la declaración de los Elementos de Información Preferidos para Revisiones Sistemáticas y Meta-Análisis (PRISMA) [1].

Los detalles del protocolo de esta revisión sistemática se registraron en PROSPERO (CRD42017054364) y pueden consultarse en: https://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42017054364.

Criterios de elegibilidad

La muestra objetivo estaba compuesta por todos los artículos publicados que presentaban una evaluación de la eficacia de los antibióticos para prevenir la infección postoperatoria o el fracaso de los implantes dentales tras su colocación.

Para su inclusión en el estudio, las publicaciones debían ser ECAs (con o sin placebo) que incluyeran pacientes de cualquier edad o sexo que se sometieran a una cirugía de implante dental. Los estudios debían haber analizado la eficacia de cualquier antibiótico en cualquier dosis o régimen de tratamiento (preoperatorio, postoperatorio o ambos) para prevenir la infección postoperatoria o el fracaso de los implantes dentales tras su colocación.

Se excluyeron las publicaciones si eran series de casos, estudios retrospectivos o no eran ensayos clínicos aleatorios. También se excluyeron los artículos que no evaluaban la incidencia postoperatoria de la infección del sitio del implante o el fracaso del implante dental, o si lo hacían, pero el implante se colocaba en lechos con infección perirradicular o con patología apical. Los autores no utilizaron criterios restrictivos para definir la infección postoperatoria o el fracaso de los implantes dentales. No hubo restricciones por idioma o año de publicación.

Fuentes de información

Se realizaron búsquedas en las siguientes bases de datos electrónicas hasta agosto de 2017: Medline/PubMed, Scopus, Science-Direct, Web of Science, Evidence-Based Dentistry, ClinicalTrials.gov, el Registro de Ensayos Clínicos de la UE y el Registro Cochrane Central de Ensayos Controlados, así como en la base de datos de tesis doctorales del Consejo General de Universidades de España (TESEO), en las bases de datos bibliográficas del Consejo Superior de Investigaciones Científicas (CSIC) y en el Índice Médico Español (IME).

Búsqueda

Los términos buscados fueron descriptores de cada uno de los componentes de Paciente, Intervención, Comparación y Resultado (PICO): cirugía de implantes dentales, colocación de implantes dentales, antibióticos, amoxicilina, fracaso del implante, pérdida del implante e infección postoperatoria. Se aplicaron los siguientes filtros: humanos, ensayos clínicos, meta-análisis y ensayos controlados aleatorios. La búsqueda electrónica en la base de datos Medline/PubMed se realizó utilizando MeSH y algoritmos de búsqueda conectados con operadores booleanos como palabras clave para los títulos y resúmenes: ((randomized controlled trials OR controlled clinical trial OR randomized controlled trials OR random allocation OR double-blind method OR single-blind method OR clinical trial OR clinical trials OR ("clinical trial") OR ((singl* OR doubl* OR trebl* OR tripl*) AND (mask* OR blind*)) OR ("latin square") OR placebos OR placebo* OR random* OR research design OR comparative study OR evaluation studies OR follow-up studies OR prospective studies OR cross-over studies OR control* OR prospective* OR volunteer*) NOT animal) AND (amoxicillin) AND (dental implant failure OR dental implant loss OR postoperative infection) AND (dental implant placement OR dental implant surgery)).

Para las bases de datos en español, se utilizaron los siguientes términos: (antibióticos O amoxicilina) AND (fracaso implante O pérdida implante) AND (implante dental).

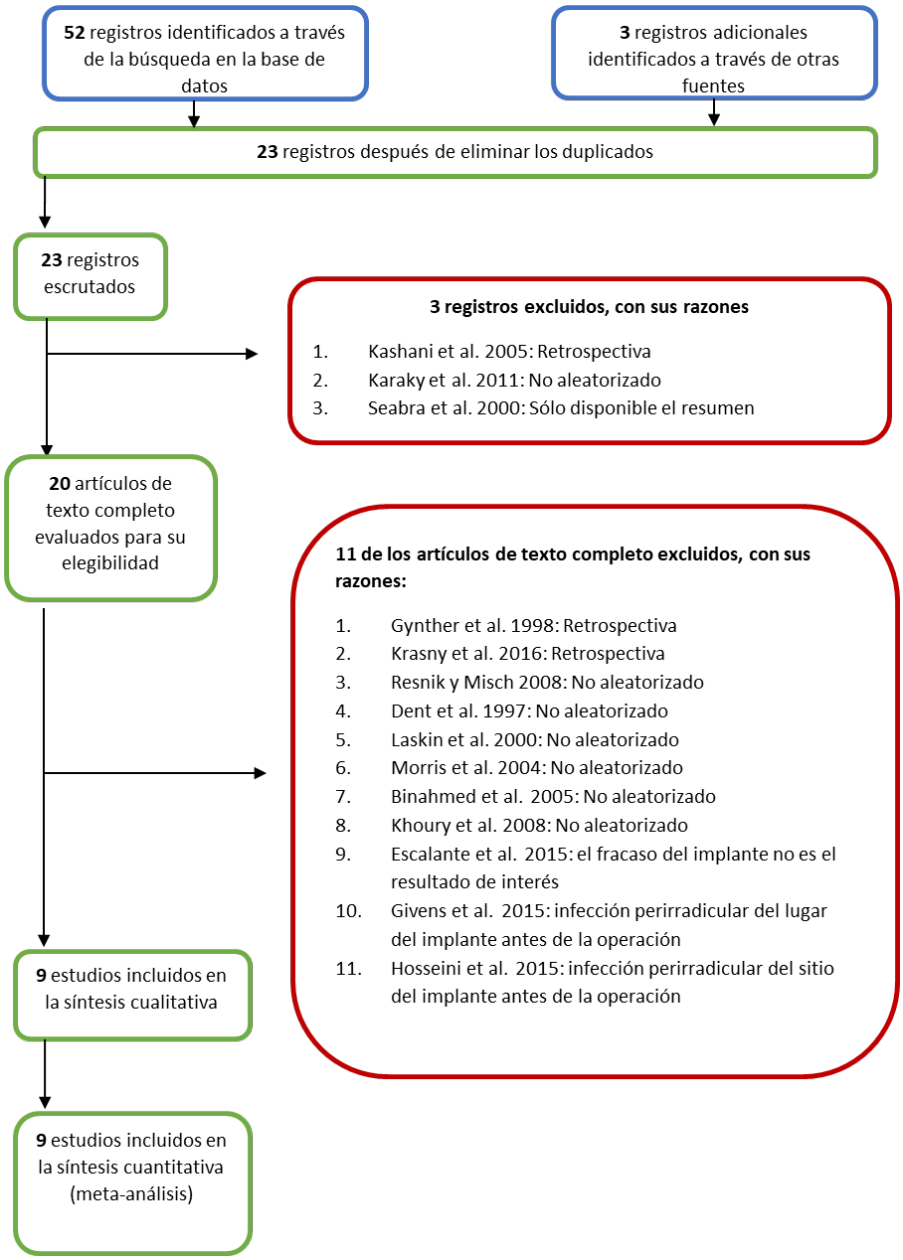
Los autores revisaron las referencias de todos los trabajos recuperados, y cuando identificaron trabajos potencialmente no publicados, contactaron con los autores correspondientes para solicitar una copia del informe del estudio.

Selección de estudios

Tres investigadores realizaron de forma independiente la búsqueda en las bases de datos aplicando los criterios mencionados.

Se excluyeron tres registros después de eliminar los duplicados, ya que sus títulos especificaban que eran retrospectivos y no aleatorios [2, 3]. El tercero era un resumen de un congreso sin información suficiente para evaluar la aleatorización y el riesgo de sesgo [4]. A partir de ahí, se evaluó la elegibilidad de 20 artículos a texto completo y se excluyeron 11. Dos de ellos se excluyeron porque eran estudios retrospectivos, 6 porque no se realizó ningún método de aleatorización, uno por ser un artículo de resumen, otro porque el fracaso del implante no era el resultado de interés, y 2 artículos porque utilizaban implantes colocados en lechos con infección perirradicular y patología apical [4-15] (Figura 1).

Figura 1. Diagrama de Flujo



Proceso de recogida de datos

Todos los estudios seleccionados fueron examinados de forma independiente por dos investigadores que extrajeron los datos de cada artículo. Cuando los datos explícitos de algunas variables no se indicaban en el texto, se calcularon utilizando los datos de las tablas cuando fue posible. En caso de incertidumbre, se contactó con los autores para obtener la información necesaria. Se consultó a un tercer investigador en caso de desacuerdo.

Infección postoperatoria:

Los autores de los estudios incluidos en este meta-análisis aplicaron diferentes criterios diagnósticos para la definición de infección postoperatoria. Los términos más utilizados para definir este resultado fueron la presencia de supuración, fístula y absceso o exudación de pus con dolor, sensibilidad, edema, hinchazón, eritema y calor en el lugar del implante o fiebre.

Los términos supuración y exudación de pus se consideraron como infección postoperatoria durante el proceso de recogida de datos. Cuatro estudios informaron del término supuración [16-19]. El ECA realizado por Tan et al. (2014) informó del porcentaje de pacientes con supuración en las semanas 1, 2, 4 y 8 después de la intervención quirúrgica [19]. Sin embargo, no se explicitó si los datos de cada semana se informaron de forma independiente. Por lo tanto, era imposible distinguir si un paciente que tenía signos de infección en una semana era la misma persona con los mismos signos en otra semana en el mismo grupo de tratamiento. Se contactó con los autores y se resolvió la duda, ya que se comprobó que el porcentaje de pacientes con supuración en cada semana se comunicaba de forma independiente. El estudio realizado por Arduino et al. (2015) [20] utilizó el término exudación de pus.

Fracaso del implante:

El resultado del fracaso del implante se definió esencialmente como un implante móvil que tuvo que ser retirado mecánicamente debido a la falta de osteointegración. El estudio realizado por Arduino et al. (2015) no informó del número total de implantes analizados en cada grupo (prueba y control) tras las pérdidas de seguimiento y las exclusiones [20]. Además, el ECA realizado por Caiazzo et al. (2011) no informó del número total de pacientes que tuvieron fracasos de implantes en cada grupo [21]. Por este motivo, se contactó con los autores de ambos ECAs, que facilitaron con éxito estos datos (Tabla 1).

El artículo publicado por Nolan et al. (2014) [18] no informaba del número total de implantes insertados en cada grupo, y también se contactó con el autor correspondiente, pero en este caso, lamentablemente, los datos brutos no estaban disponibles. Por esta razón, este estudio fue excluido del análisis realizado por el número de fracasos de los implantes. No obstante, los autores utilizaron los datos disponibles en este estudio para los análisis por el número de pacientes que tuvieron un fracaso del implante y el número de pacientes que sufrieron una infección postoperatoria.

Los artículos realizados por Caiazzo et al. (2011) y Tan et al. (2014) incluyeron 3 grupos de tratamiento con amoxicilina y un grupo de control. En este meta-análisis, cada grupo de tratamiento se incluyó como un ECA independiente utilizando el mismo grupo de control proporcionado por los investigadores [21,19].

En 2 artículos, los pacientes del grupo de control también fueron tratados con amoxicilina con un régimen de dosis diferente al del grupo de tratamiento [20, 22]. Estos grupos de control podrían considerarse como grupos de tratamiento en diferentes ECA, para lo cual sería necesario un nuevo grupo de control.

Para ello, los autores construyeron un nuevo grupo de control para cada análisis. Los nuevos grupos de control se basaron en el cálculo del número medio de sujetos que presentaban las variables de resultado (pacientes que tuvieron un fracaso del implante, número total de fracasos del implante y pacientes que tuvieron una infección postoperatoria) en los grupos de control de los otros ECA incluidos en cada análisis [16-19, 21, 23, 24]. Del mismo modo, también se calculó el número medio de sujetos que no presentaban las variables de resultado (implantes con éxito, pacientes que no tuvieron fracasos de implantes y pacientes que no tuvieron infecciones postoperatorias) en los grupos de control de los otros ECA [16-19, 21, 23, 24].

Estos grupos de control recién construidos estaban compuestos por 4 pacientes que tuvieron un fracaso de implante y 94 pacientes que no tuvieron ningún fracaso de implante para el primer análisis (fracaso de implante por pacientes), 4 fracasos de implante y 130 implantes exitosos para el segundo análisis (fracaso de implante por implantes), y 2 pacientes que tuvieron una infección postoperatoria y 76 pacientes sin infecciones postoperatorias para el último análisis.

Los autores imputaron los datos de estos grupos de control recién construidos para los 2 estudios mencionados [20, 22].

Elementos de datos y análisis

La variable predictora fue el uso o no de antibióticos en cada ECA. Los datos registrados incluían lo siguiente: tipo de antibiótico, vía de administración y régimen de tratamiento (antes o después de la colocación del implante). En todos los estudios, el único tipo de antibiótico utilizado fue la amoxicilina oral.

Los autores realizaron un meta-análisis estratificado con 3 variables de resultado diferentes: 1.-Número de pacientes que tuvieron un fracaso del implante; 2.-Número de fracasos del implante; y 3.-Número de pacientes que sufrieron una infección postoperatoria. Se llevó a cabo un análisis estratificado para contrastar el efecto de los antibióticos orales exclusivamente preoperatorios frente a los antibióticos postoperatorios (utilizados tanto exclusivamente en el postoperatorio como como uso adjunto en un régimen perioperatorio).

Los autores no utilizaron criterios restrictivos para definir la infección postoperatoria y el fracaso del implante.

Los autores también registraron la presencia o ausencia de efectos adversos.

Las variables restantes describían las características de la muestra de cada artículo (tamaño de la muestra, sexo, edad media de las pacientes, número de fumadoras y uso de anticonceptivos) y las características del diseño del estudio en cada artículo (tipo de estudio, número de grupos de tratamiento, proceso de aleatorización, asignación secreta, cegamiento, pérdidas de seguimiento, materiales de prueba, materiales de control, materiales de co-tratamiento, tipo de implante y tipo de cirugía). Los datos recogidos se enumeran en la Tabla 1.

Riesgo de sesgo en los estudios individuales

Se utilizó la herramienta de la Colaboración Cochrane con el fin de evaluar el riesgo de sesgo individual de cada ECA incluido a nivel de estudio. El gráfico de riesgo de sesgo (Figura 2) y el resumen de riesgo de sesgo (Figura 3) se generaron utilizando Review Manager 5.3 (The Cochrane Collaboration 2014). Se recogieron datos cuantitativos y cualitativos sobre las pérdidas de seguimiento, el proceso de aleatorización, el cegamiento y otros factores que podrían ser fuentes potenciales de sesgo (Tabla 1).

Medida de resumen

La eficacia del tratamiento se evaluó mediante el riesgo relativo (RR) (Figura 4). La eficacia del tratamiento con antibióticos se evaluó mediante el número necesario para tratar (NNT). Se estimaron los NNT globales ajustados al peso de cada estudio para todos los análisis.

Síntesis de los resultados

Todos los análisis se realizaron con STATA® 14 (StataCorp LP, College Station, TX) [25]. Los autores evaluaron la heterogeneidad entre los distintos estudios mediante el estadístico I2, y gráficamente con los gráficos de l'Abbé (Figura 5). El RR global, resultante de la combinación de diferentes estudios, se calculó con un modelo de efectos fijos con ponderaciones calculadas mediante el método de Mantel-Haenszel [26].

Riesgo de sesgo en los estudios

El sesgo de publicación se evaluó gráficamente mediante gráficos de embudo (Figura 6).

La calidad de la evidencia se evaluó con el sistema de Grading of Recommendations Assessment, Development and Evaluation (GRADE), considerando cada variable de resultado de forma independiente (Tabla 2 y 3). El sistema GRADE se desarrolló para calificar la calidad de la evidencia y la fuerza de las recomendaciones [27-28].

RESULTADOS

Selección de estudios

En total, se incluyeron en este meta-análisis 9 artículos publicados desde 2008. La figura 1 presenta un diagrama de flujo del proceso de selección de estudios con una lista de los estudios excluidos y los motivos de su exclusión.

Los análisis finales, por el número de pacientes que tuvieron un fracaso del implante y por el número de infecciones postoperatorias, se realizaron en 15 ECA correspondientes a 9 artículos [16-19, 20, 21, 23, 24].

Además, 14 ECA correspondientes a 8 artículos se incluyeron finalmente en el meta-análisis por el número de fracasos de los implantes [16-19, 21, 23, 24].

Características de los estudios

En los estudios revisados, sólo se evaluó un tipo de antibiótico: la amoxicilina. Se utiliza en varias dosis y regímenes terapéuticos. Los regímenes preoperatorios fueron los siguientes: dosis única de 1 gramo [22, 24], 2 gramos [16, 17, 19, 20, 21, 23] o 3 gramos 1 hora antes de la cirugía [18]. Los regímenes postoperatorios fueron los siguientes: 2 gramos inmediatamente después de la cirugía [19], 1 gramo dos/tres veces al día durante una semana [21] o durante dos días después de la colocación del implante [20], y 500 mg tres veces al día durante dos [24] o tres días después de la cirugía [19, 22]. Varios estudios combinaron antibióticos preoperatorios y postoperatorios [19, 21, 22, 24]. La tabla 1 presenta las principales características de los 9 ECAs incluidos en el meta-análisis.

Tabla 1. Caracteristicas de los estudios

Estudio, año y país	Tipo de estudio	Método de aleatorización	Ciego	Material de prueba (qué y qué dosis)	Material de control	Materiales de co-tratamiento	Pacientes del grupo de prueba	Pacientes del grupo de control	Criterios de diagnóstico	Medida cuantitativa de resultados y LTF	Período de seguimiento	Reacciones adversas
Abu-Ta'a et al. 2008 Bélgica	ECA de grupos paralelos	Muestreo aleatorio	Doble ciego	AMX 1 g por os, 1 h antes de la operación y 500 mg 4 veces al día, 2 días después de la operación	Sin antibióticos	Enjuague postoperatorio con CLX al 0,12% durante 1 minuto. durante 7-10 días	n=40 hombre= 23 mujer= 17 MA= 60 Rango= 27-82 n implantes= 128	n=40 hombre= 20 mujer= 20 MA= 57 Rango= 26-88 n implantes= 119	**Infección postoperatoria:** Drenaje purulento (pus) o fístula en la región operada, con dolor o sensibilidad, hinchazón localizada, enrojecimiento y calor o fiebre **Fracaso del implante:** Signos de infección y/o radiolucencias periimplantarias radiográficas y/o juzgar un fracaso tras realizar una cirugía de colgajo exploratoria	**Grupo de prueba:** Pacientes con infección: 1/40 Tasa de supervivencia (implantes): 128/128 (100%) Pacientes que tuvieron fallos en los implantes: 0/40 **Grupo de control:** Pacientes con infección: 4/40 Tasa de supervivencia (implantes): 114/119 (96%)	5 meses después de la colocación del implante	Sin efectos secundarios del antibiótico fueron reportados

										Pacientes que tuvieron fallos en los implantes: 3/40 **LTF:** 0		
Esposito et al. 2008 Italia	ECA de grupos paralelos	Doce listas de aleatorización restringida generadas por ordenador	Doble ciego	2 g de AMX por vía oral (2 comprimidos de 1 g) 1 hora antes de la colocación del implante	2 comprimidos idénticos de placebo 1 hora antes de la colocación del implante	Enjuague postoperatorio con CLX al 0,2% durante 1 min. dos veces al día durante al menos 1 semana En el grupo de control, 1 paciente fue tratado con antibióticos debido a una gripe 2 días después de la colocación del implante	n= 158 Mujeres= 78 (49,4%) MA (rango)= 47,8 (18-78) No fumadores=99 (62,7%) Duración (rango)= 27 m (3-130) Número total de implantes= 341 Tomó antibióticos postoperatorios= 2	n= 158 Mujeres: 96 (60,8%) MA (rango)= 47,9 (19-76) No fumadores= 108 (68,4%) Duración (rango)= 26,5 m (4-125) Número total de implantes=: 355 Tomó antibióticos postoperatorios= 1	**Infección postoperatoria:** Supuración, fístula, absceso. **Fracasos de los implantes:** Movilidad del implante y/o cualquier infección que obligue a retirarlo	**Grupo de prueba:** Fallos en los implantes: 2/341 Pacientes con infección: 3/158 Pacientes con fallos en los implantes: 2/158 LTF: 0, Pacientes excluidos: 7 **Grupo de control:** Fallos en los implantes: 9/355 Pacientes con infección: 2/158 Pacientes con fallos en los implantes: 8/158	4 meses después de la colocación del implante	Se produjo 1 acontecimiento adverso en el grupo de placebo (picor durante 1 día) y 1 en el grupo de AMX (diarrea y somnolencia).

										LTF: 0, Pacientes excluidos: 7		
Anitua et al. 2009 España	ECA de grupos paralelos	Tabla de números aleatorios	Doble ciego	2 g de AMX oral 1 hora antes de la cirugía del implante	2 comprimidos de placebo administrados por vía oral 1 hora antes de la cirugía del implante	Enjuague con CLX al 0,2% durante 1 minuto antes de la operación. Inmediatamente después de la cirugía y los 3 días siguientes dexametasona intravenosa o intramuscular. Acetaminofén como medicación de rescate (máximo 1 g/8 horas). También se permitió el uso de Metamizol (575 mg, 1 o dos comprimidos /8 horas)	n= 52 Mujeres= 37 (71%) Hombres= 15 (29%) MA= 49 (±12) Fumadores= 10 (19%) No fumadores= 42 (81%) Duración (valor medio ±SD)= 41,03 m (±29) Maxilares= 26 (51%) Mandibular= 25 (49%) Zona anterior= 11 (22%) Zona posterior= 39 (78%) Tipo de carga inmediata= 1 (2%)	n= 53 Mujeres= 33 (62%) Hombres= 20 (38%) MA= 47 (±12) Fumadores= 8 (15%) No fumadores= 45 (85%) Duración (valor medio ±SD)= 41,71 m (±27) Maxilares= 21 (40%) Mandibular= 32 (60%) Zona anterior= 12 (23%) Posterior= 40 (77%) Tipo de carga inmediata= 1 (2%)	**Infección postoperatoria:** Inflamación, dolor, fiebre por calor y secreción. **Supervivencia de los** implantes**: Se** comprobó la estabilidad de los implantes con Osstell (Ostell, Göteborg, Suecia).	**Grupo de prueba:** Infecciones postoperatorias: 6/52 Fallos en los implantes: 2/52 LTF: 0 **Grupo de control:** Infecciones postoperatorias: 6/53 Fallos en los implantes: 2/53 LTF: 1	3 meses después de la colocación del implante	NR

Esposito et al. 2010 Italia	ECA de grupos paralelos	Lista de aleatorización restringida generada por ordenador	Triple ciego	2 g de AMX por vía oral (dos comprimidos de 1 g) 1 hora antes de la colocación del implante	2 comprimidos idénticos de placebo una hora antes de la colocación del implante	Enjuague bucal de CLX al 0,2% durante 1 minuto antes de la colocación del implante y enjuague bucal de CLX al 0,2% durante 1 minuto dos veces al día durante al menos 1 semana en el postoperatorio	n= 252 Mujeres= 138 (54,8%) MA (rango)= 49,1 (18-85) No fumadores= 171 (67,9%) Fumar hasta 10 cigarrillos/día = 55 (21,8%) Fumar más de 10 cigarrillos/día = 26 (10,3%) Duración (rango)= 32 m (4-190) n implantes= 489 Tipo de carga inmediata= 60 Tomó antibióticos postoperatorios 2 (0,8%)	n= 254 Mujeres 132 (52,0%) MA (rango) 47,6 (18-86) No fumadores 166 (65,4%) Fumar hasta 10 cigarrillos/día 60 (23,6%) Fumar más de 10 cigarrillos/día 28 (11%) Duración (rango) 31 m (5-180) Número total de implantes 483 Tipo de carga inmediata= 76 Tomaron antibióticos postoperatorios 6 (2,4%)	**Infección postoperatoria:** Supuración, fístula, absceso. **Fracasos de los implantes:** Movilidad del implante medido y/o cualquier infección que dicte la retirada del implante	**Grupo de prueba:** Fallos en los implantes: 7/489 Pacientes que tuvieron fallos en los implantes: 5/252 Pacientes que tuvieron infecciones postoperatorias: 4/252 LTF: 0, Pacientes excluidos: 2 **Grupo de control:** Fracasos de los implantes: 13/483 Pacientes que tuvieron fallos en los implantes: 12/254 Pacientes que tuvieron infecciones postoperatorias: 8/254 LTF: 0, Excluido: 1	4 meses después de la colocación del implante	No se observaron efectos adversos de los antibióticos en ningún grupo

Caiazzo et al. 2011 Italia	ECA de grupos paralelos	Listas de aleatorización generadas por ordenador	NR	**Grupo 1:** Dosis única de antibiótico profiláctico consistente en AMX 2 g 1 hora antes de la cirugía **Grupo 2:** Tratamiento antibiótico preoperatorio y postoperatorio consistente en AMX 2 g 1 hora antes de la cirugía y 1 g dos veces al día durante 7 días después de la cirugía **Grupo 3:** Cobertura antibiótica postoperatoria consistente en AMX 1 g dos veces al día iniciada después de la cirugía y continuada durante 1 semana después de la misma	**Grupo 4:** Sin tratamiento antibiótico	Enjuague con solución de gluconato de CLX al 0,2% durante 1 minuto antes de cada procedimiento y dos veces al día durante los 15 días siguientes a la cirugía	**Grupo 1:** n= 25 Mujeres: 12 Hombres: 13 MA=52 n implantes= 35 **Grupo 2:** n= 25 Mujeres: 13 Hombres: 12 MA=45 n implantes= 36 **Grupo 3:** n= 25 Mujeres: 18 Hombres: 7 MA=42 n implantes= 48	**Grupo 4:** n= 25 Mujeres: 15 Hombres: 10 MA=43 n implantes= 29	**Infección postoperatoria:** Edema interno y externo, eritema interno y externo, dolor, calor y exudados. **Fracaso del implante**: Retirada mecánica del implante por falta de osteointegración	**Grupo 1:** Infecciones: 0/35 Fallos en los implantes: 0/35 Pacientes que tuvieron fallos en los implantes: 0/25 **Grupo 2:** Infecciones: 0/36 Fracasos de los implantes: 0/36 Pacientes que tuvieron fallos en los implantes: 0/25 **Grupo 3:** Infecciones: 0/48 Fracasos de los implantes: 0/48 Pacientes que tuvieron fallos en los implantes: 0/25 **Grupo 4:** Infecciones: 0/29	3 meses después de la colocación del implante	No se observaron efectos adversos de los antibióticos en ningún grupo

										Fallos en los implantes: 2/29 Pacientes que tuvieron fallos en los implantes: 2/25 LTF= NR		
K. E. El-Kholey 2014 Arabia Saudí	ECA de grupos paralelos	Lista de números aleatorios generada por ordenador	NR	**Grupo1:** dosis única de 1 g de AMX oral 1 h antes de la operación, y ningún antibiótico postoperatorio **Grupo 2:** 1 g de AMX oral 1 h antes de la operación seguido de AMX oral postoperatorio, 500 mg cada 8 h durante 3 días	*	Enjuague bucal con CLX al 0,12% durante 1 minuto antes de la intervención y durante 5 días en el postoperatorio. Paracetamol 500 mg cuatro veces al día según sea necesario.	**Grupo 1:** n=40 Mujeres=4 Hombres=16 MA (±SD)= 32,2 ±7,7 Número de implantes maxilares= 23 Número de implantes mandibulares= 24 Total de implantes= 47 **Grupo 2:** n=40 Mujeres:26 Hombres:14 MA (±SD)= 30 ±6,8 Implantes maxilares= 20 Implantes mandibulares= 23	*	**Infección postoperatoria:** Hinchazón, dolor, eritema, sensibilidad o formación de pus en el lugar de la cirugía **Éxito de la osteointegración:** Buena estabilidad del implante a 25 N cm con ausencia de cualquier signo clínico o radiográfico de infección	**Grupo1:** Infecciones en las heridas: 0/47 Fracasos de los implantes: 0/47 Pacientes que tuvieron fallos en los implantes: 0/40 LTF= 0 **Grupo 2:** Infecciones en las heridas: 0/43 Fallos en los implantes: 0/43 Pacientes que tuvieron fallos en los implantes: 0/40 LTF= 0	3 meses después de la colocación del implante	NR

							n implantes= 43					
Nolan et al. 2014 Irlanda	ECA de grupos paralelos	NR	Doble ciego	3 g de AMX por vía oral, 1 hora antes de la cirugía.	Cápsulas de placebo (con azúcar) por vía oral, 1 hora antes de la cirugía	Enjuague bucal de CLX al 0,2% durante al menos 60 segundos antes de la cirugía y 4-5 veces al día durante la primera semana postoperatoria	n= 27 Mujer= 16 Hombre= 11 <40 años= 16 40-60 años=7 >60 años= 4 No fumadores= 20 Fumadores= 7	n= 28 Mujer= 20 Hombre= 8 <40 años= 15 40-60 años=10 >60 años= 3 No fumadores= 22 Fumadores= 6	Oseointegración registrada por 2 examinadores independientes: Éxito = Inmóvil Fracaso = Móvil	**Grupo de prueba:** Pacientes que tuvieron un fracaso del implante= 0/27 Pacientes con infección= 0/27 **Grupo de control:** Número de pacientes que han tenido un fracaso del implante= 5/28 Número de pacientes con infección= 2/28 LTF= 16, Exclusiones después de la aleatorización= 12	4 meses después de la colocación del implante	NR Sólo la EVA y los hematomas, pero no hay datos cuantitativos.

Tan et al. 2014	ECA de grupos paralelos	Cuadros de aleatorización. Aleatorización en bloques de ocho, por lo que en cada bloque de ocho inscripciones, había dos sujetos asignados aleatoriamente a uno de los cuatro grupos de intervención	Un solo ciego	**Grupo 1:** 2 g de amoxicilina en el preoperatorio, 1 h antes de la colocación del implante convencional. **Grupo 2:** 2 g de AMX inmediatamente después de la operación. **Grupo 3:** 2 g de amoxicilina preoperatoriamente, 1 h antes de la colocación del implante y 500 mg tres veces al día (cada 8 horas) los días 2 y 3	**Grupo 4:** 2 g de un placebo preoperatorio, 1 h antes de la colocación del implante sin ningún antibiótico	Enjuague previo al 0,2 % de CLX durante 1 minuto	**Grupo 1 (PC)** n = 81 Mujeres= 49,4%. Hombres = 50,6%. MA= 48,8 No fumador 81,5% Fumador 18,5% **Grupo 2 (T1)** n = 82 Mujeres= 42,7%. Hombre= 57,3% MA= 47,8 No fumador 80,5% Fumador 19,5% **Grupo 3 (T2)** n = 86 Mujer= 45,3% Hombres = 54,7%. MA= 46,9 No fumador 80.2% Fumador 19.8%	**Grupo 4 (NC)** n = 80 Mujeres= 44,7%. Hombres = 55,3%. MA= 45,1 No fumador 80,0% Fumador 20 % Anchura del hueso alveolar B-L (media, mm): 7,91 Anchura del hueso alveolar M-D (media, mm) 11,33	**Infección postoperatoria:** Supuración **Fracaso del implante:** Implante inestable que se perdió	**Grupo 1:** Fracasos de los implantes: 0/81 Pacientes con fallos en los implantes: 0/81 Pacientes con infecciones postoperatorias: 2/81 **Grupo 2:** Fracasos de los implantes: 0/82 Pacientes con fallos en los implantes: 0/82 Pacientes con infecciones postoperatorias: 0/82 **Grupo 3:** Fracasos de los implantes: 0/86 Pacientes con fallos en los	2 meses después de la colocación del implante	No hay diferencias estadísticamente significativas entre los 4 grupos de tratamiento en cuanto a la hemorragia, la hinchazón, el dolor y los hematomas. Otros eventos adversos NR.

										implantes: 0/86 Pacientes con infecciones postoperatorias: 2/86 **Grupo 4:** Fracasos de los implantes: 1/80 Pacientes con fallos en los implantes: 1/80 Pacientes con infecciones postoperatorias: 0/80 LTF: NR para cualquier grupo		
Arduino et al. 2015 Italia	ECA de grupos paralelos	Dos listas de aleatorización generadas por ordenador	Doble ciego	**Grupo1:** 2 g de AMX por vía oral (2 comprimidos de 1 g) 1 hora antes de la cirugía **Grupo 2:** 2 g de AMX por vía oral (2 comprimidos de 1 g) 1 hora antes de la	*	Aclarar con CLX al 0,2% 1 min inmediatamente antes de la cirugía	**Grupo 1:** n= 180 MA (SD)= 49,3 (13,9) Mujer= 101 Hombre= 79 Fumadores= 57 (31,7%) Implantes mandibulares= 202	*	**Fracaso del implante:** Movilidad del implante o retirada del mismo por dolor o infección **Infección postoperatoria:**	**Grupo 1:** Fracasos de los implantes: 5/244 Pacientes con fallos en los implantes: 5/166 (3%) Pacientes con infecciones	10 meses después de la colocación del implante	**Grupo1:** No hay eventos adversos **Grupo 2:** 3 eventos adversos: 2 hombres con hinchazón abdominal, 1 mujer con erupción

				cirugía y 1 g la tarde del día de la cirugía y 1 g dos veces al día durante 2 días después de la cirugía			Implantes maxilares= 76 Número de implantes= 278 **Grupo 2:** n= 180 MA (SD)= 51,6 (14,4) Mujer= 88 Hombre= 92 Fumadores= 37 (20,6%) Implantes mandibulares= 173 Implantes maxilares= 116 Número de implantes= 289		Supuración, fístula, absceso	postoperatorias: 2/166 LTF: 9 Pérdida de todos los datos=5 Pacientes excluidos del análisis= 14 **Grupo 2:** Fracasos de los implantes: 8/285 Pacientes con fallos en los implantes: 5/177 (2.8%) Pacientes con infecciones postoperatorias: 2/177 LTF: 1 Pérdida de todos los datos= 2 Pacientes excluidos = 3		cutánea y edema laríngeo con una reacción grave que requirió la interrupción del tratamiento y el ingreso temporal en el hospital. No hay diferencias estadísticamente significativas entre ambos grupos

*AMX: Amoxicilina; CLX: Clorhexidina; N: Newton's, n: población; RCT: Ensayo Controlado Aleatorio; n: tamaño de la muestra; MA: edad media; SD: derivación estándar; NR: No informado; LTF: Perdido durante el seguimiento.*Indica estudios cuyos datos han sido imputados del grupo control calculado.*

Riesgo de sesgo en los estudios

El gráfico de riesgo de sesgo (Figura 2) ilustra la proporción de estudios con cada uno de los juicios (riesgo bajo, riesgo alto, riesgo poco claro). El resumen del riesgo de sesgo (Figura 3) presenta todos los juicios en una tabulación cruzada de estudio por entrada.

Figura 2. Grafico del riesgo de sesgo

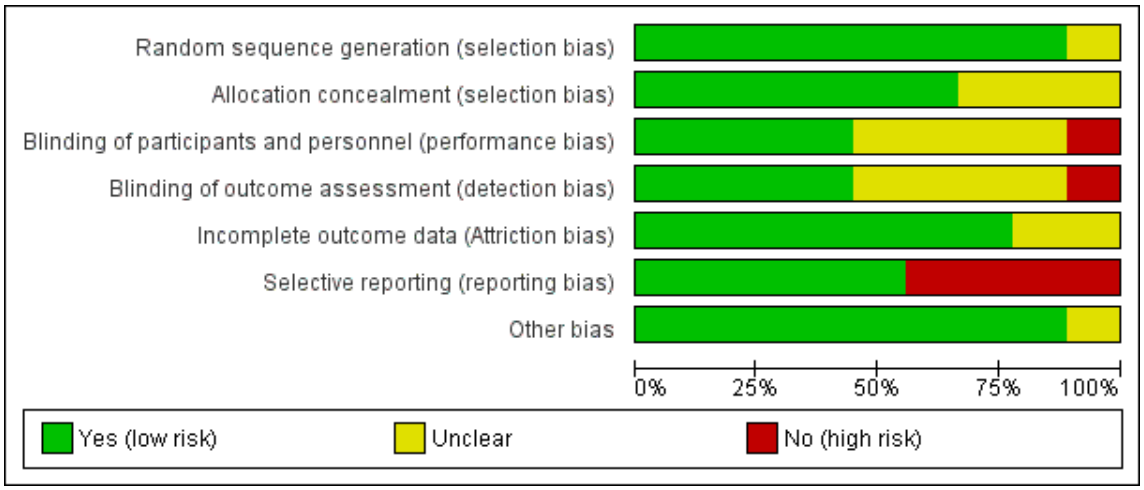
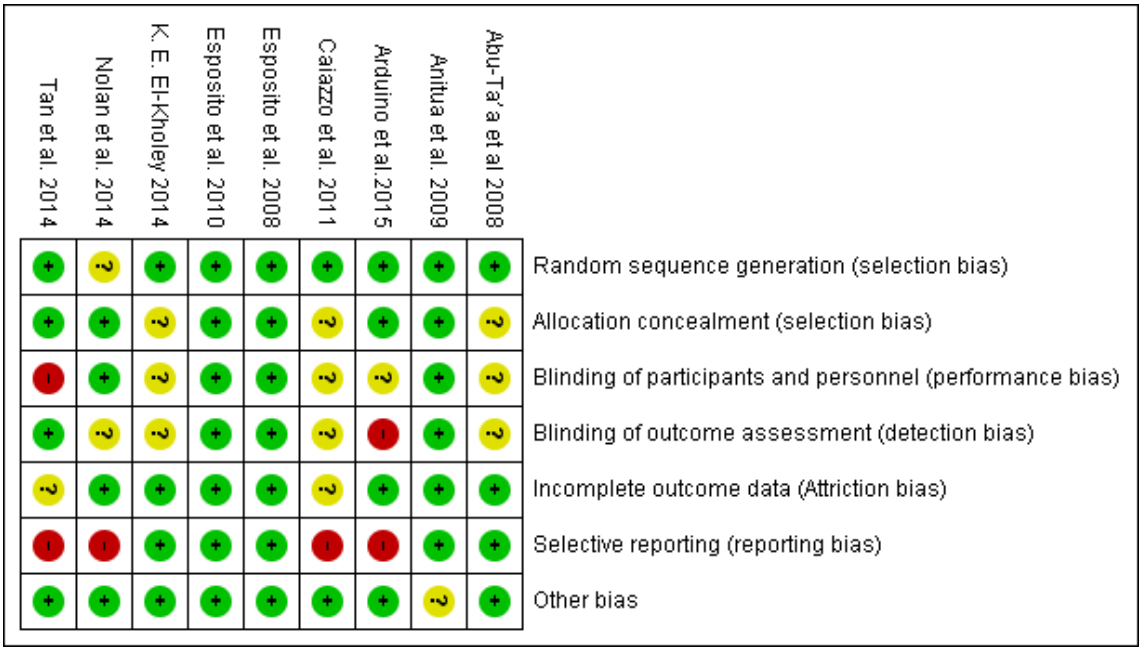


Figura 3. Sumario del riesgo de sesgo



El ECA realizado por Anitua et al. (2009) podría presentar un posible riesgo de sesgo de información, ya que el Instituto de Biotecnología (BTI®, Vitoria, España) proporcionó la financiación y controló el análisis y los resultados del ensayo.

Tabla 2. Tabla de Evidencia

Evaluación de la calidad							Resumen de los resultados				
Nº Participantes (estudios)	Riesgo de sesgo	Inconsistencia	Indirecta	Imprecisión	Sesgo de publicación	Calidad general de las pruebas	Tasas de eventos del estudio (%)		Efecto relativo (IC 95%)	Efectos absolutos previstos	
							Grupo de control (sin AMX)	Grupo de tratamiento (con AMX)		Riesgo sin antibióticos	Diferencia de riesgo con los antibióticos
Fracaso del implante por parte de los pacientes (seguimiento: mediana de 4 meses)											
2982 (15 ECA)	no es importante	no es importante	no es importante	importante [a]	ninguno	⊕⊕⊕◯ MODERADO	56/1469 (3.8%)	31/1513 (2.0%)	RR global 0,53 (0,34 a 0,82)	38 por cada 1.000	18 menos por cada 1.000 (25 menos a 7 menos)
Fracaso de los implantes dentales (seguimiento: mediana de 4 meses)											
3870 (14 ECA)	no es importante	no es importante	no es importante	importante [b]	ninguno	⊕⊕⊕◯ MODERADO	54/1873 (2.9%)	33/1997 (1.7%)	RR global 0,54 (0,35 a 0,85)	29 por cada 1.000	13 menos por cada 1.000 (19 menos a 4 menos)
Infección postoperatoria (seguimiento: mediana de 4 meses)											
2500 (15 ECA)	no es importante	no es importante	no es importante	muy grave [c,d,e]	ninguno	⊕⊕◯◯ LOW	36/1172 (3.1%)	29/1328 (2.2%)	RR global 0,76 (0,47 a 1,22)	31 por cada 1.000	7 menos por cada 1.000 (16 menos a 7 más)

CI: intervalo de confianza; RR: razón de riesgo; RCT: ensayo clínico controlado aleatoriamente; AMX: Amoxicilin Explicaciones:

a. Menos de 300-400 eventos (pacientes que tuvieron un fallo en el implante) b. Menos de 300-400 eventos (fracasos de implantes) c. Los CI del 95% incluyen el efecto nulo, pero también incluyen el beneficio. d. El CI 95% inferior (0,47) < 0,75 e. Menos de 300-400 eventos (pacientes que sufrieron una infección postoperatoria)

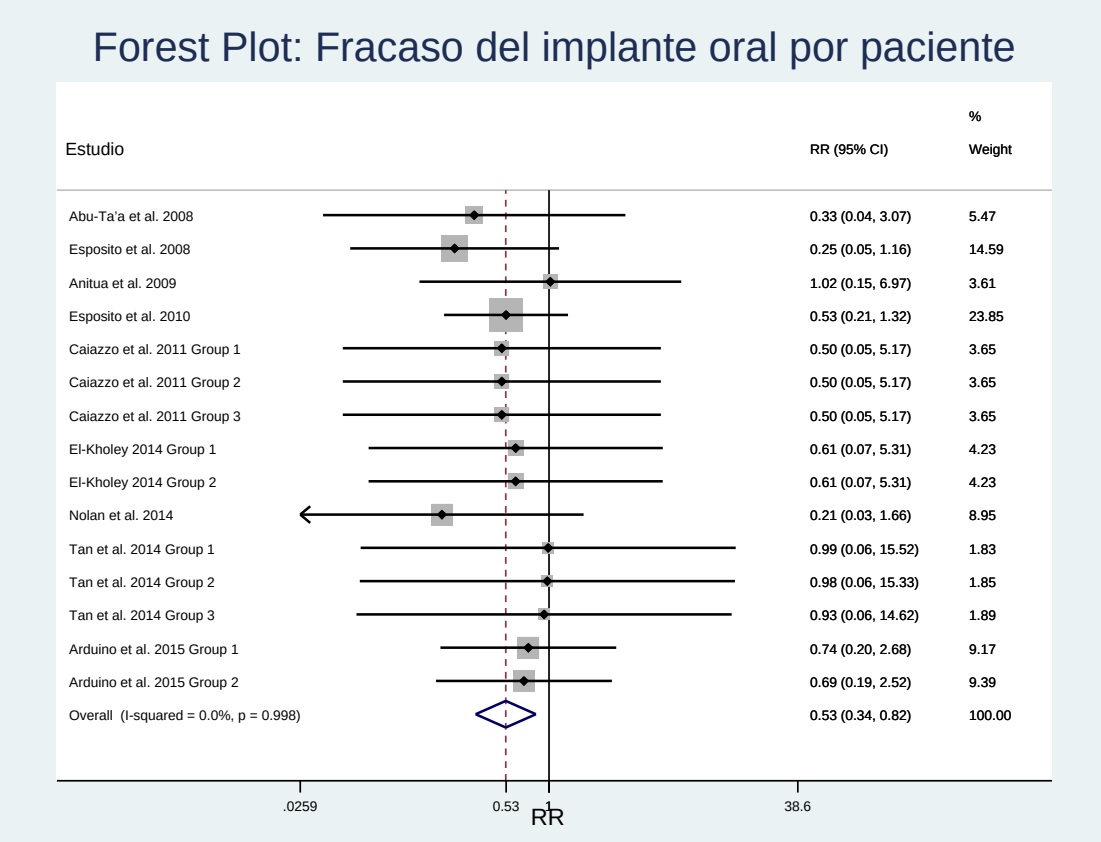
Tabla 3: Grados de calidad de la evidencia

Grado	Definición
Alto	Estamos muy seguros de que el efecto real se acerca al de la estimación del efecto.
Moderado	Tenemos una confianza moderada en la estimación del efecto: Es probable que el efecto real se acerque a la estimación del efecto, pero existe la posibilidad de que sea sustancialmente diferente
Bajo	Nuestra confianza en la estimación del efecto es limitada: El efecto real puede ser sustancialmente diferente de la estimación del efecto.
Muy bajo	Tenemos muy poca confianza en la estimación del efecto: Es probable que el verdadero efecto sea sustancialmente diferente de la estimación del efecto

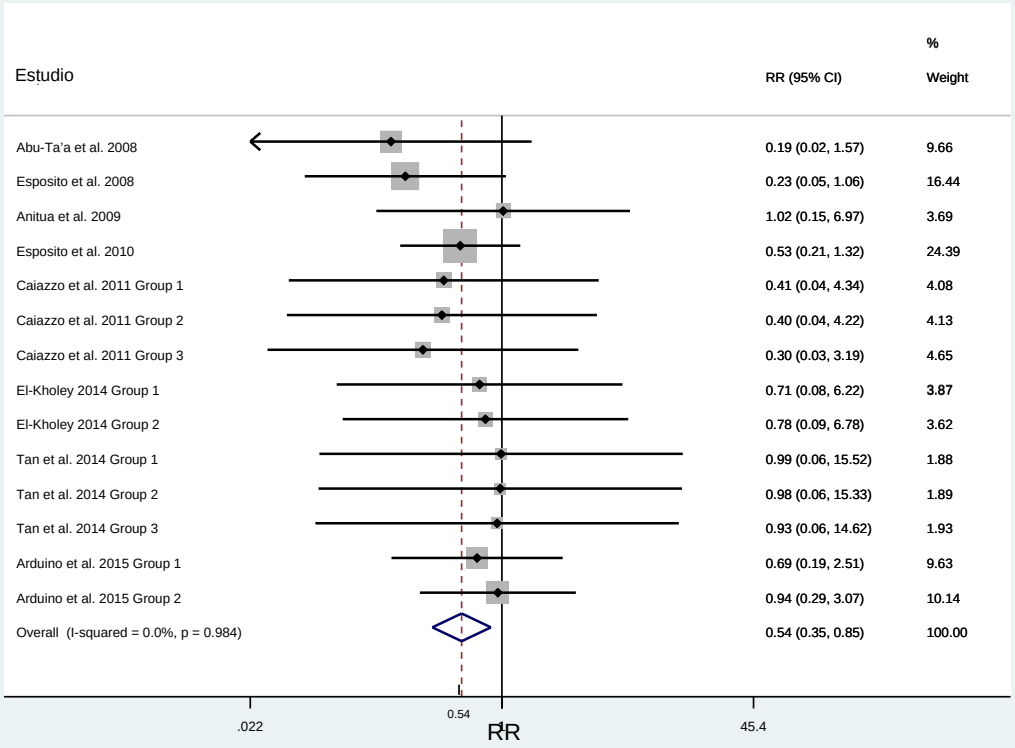
Resultados de los estudios individuales

Los diagramas de bosque presentados en la Figura 4 son representaciones gráficas de las estimaciones del RR y de los intervalos de confianza (IC) del 95% obtenidos con las muestras de cada uno de los estudios. El área de cuadrados grises alrededor del RR es proporcional al peso del estudio en el análisis. Los IC, indicados por una línea horizontal continua que cruza la línea vertical en un RR igual a 1, corresponden a los estudios con resultados no significativos. El gráfico también indica el RR global basado en todos los estudios con un rombo y una línea de puntos.

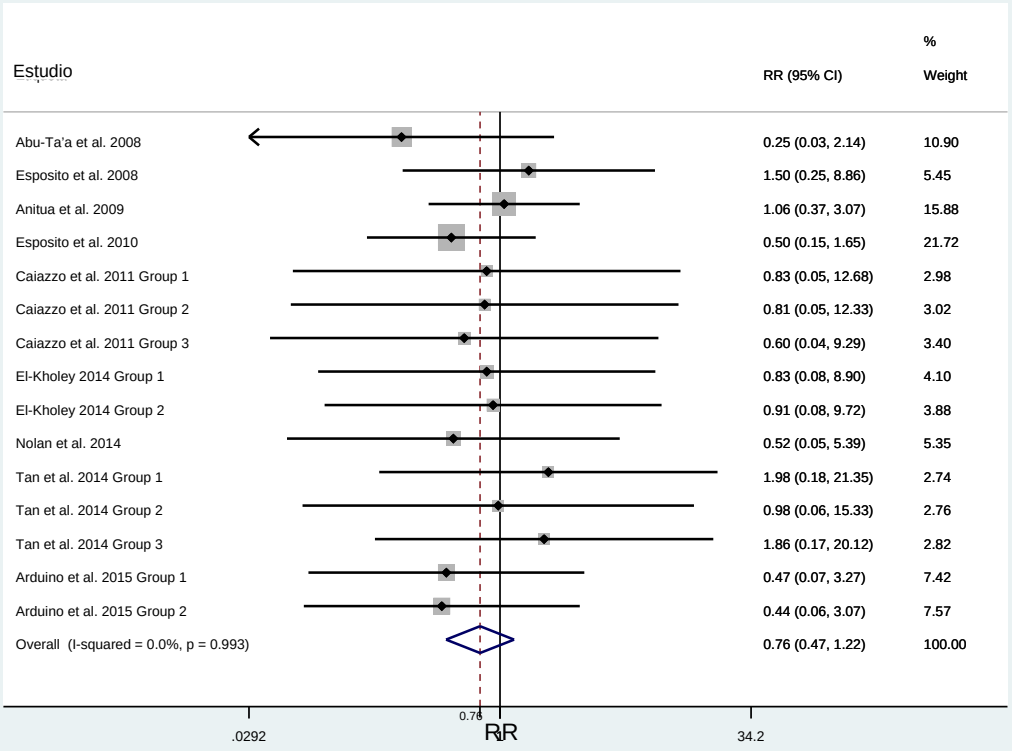
Figura 4. Diagramas de Forest



Forest plot: Fracaso del implante oral por implante



Forest plot: Infecciones postoperatorias



Síntesis de los resultados

Análisis del fracaso de los implantes por paciente:

Se observó que una dosis única de amoxicilina oral en el preoperatorio (SDOAP) antes de la cirugía de implantes evitaba significativamente (*p*=0,012) que los pacientes desarrollaran fracasos de los implantes dentales (RR = 0,50; IC: 0,29-0,86), mientras que el uso postoperatorio de amoxicilina oral (exclusivamente en el postoperatorio y como complemento de la amoxicilina preoperatoria) no logró significativamente (*p*=0,197) un efecto profiláctico (RR = 0,60; IC: 0,28-1,30).

El RR global del análisis realizado por el número de pacientes que tuvieron un fracaso del implante fue de 0,53 (IC del 95%, de 0,34 a 0,82), que es significativamente diferente de 1 (*p*=0,005).

El NNT global estimado para el análisis realizado por el número de pacientes que tuvieron un fracaso del implante fue de 55. Teniendo en cuenta el IC del 95%, sería necesario tratar a entre 33 y 167 pacientes con amoxicilina para evitar que un solo paciente sufriera un fracaso del implante. El NNT para la SDOAP fue de 67 (IC del 95%, de 26 a 125), y el NNT para el uso postoperatorio de amoxicilina oral fue de 53 (IC del 95%, de 30 a 200).

Análisis del fracaso del implante por implante:

La SDOAP antes de la cirugía de implantes resultó ser significativamente (*p*=0,024) eficaz para prevenir los fracasos de los implantes dentales (RR = 0,52; IC: 0,30-0,92). Sin embargo, el uso postoperatorio de amoxicilina oral (exclusivamente en el postoperatorio y como complemento de la amoxicilina preoperatoria) no resultó significativo (*p*=0,137) para prevenir los fracasos de los implantes dentales (RR = 0,58; IC: 0,28-1,19).

El RR global del análisis realizado por el número de fracasos de los implantes fue de 0,54 (IC del 95%, de 0,35 a 0,85), que también es significativamente diferente de 1 (*p*=0,007).

El NNT global del análisis por el número de fracasos de los implantes se estimó en 77. Si se tiene en cuenta también su IC del 95%, sería necesario tratar entre 43 y 250 implantes dentales con amoxicilina para evitar el fracaso de 1 implante. El NNT para el SDOAP fue de 77 (IC del 95%, de 32 a 250), y el NNT para el uso postoperatorio de amoxicilina oral fue también de 77 (IC del 95%, de 42 a 500).

Análisis de la infección postoperatoria:

Ni la amoxicilina oral postoperatoria (RR= 0,64, IC: 0,27-1,51) ni el SDOAP (RR=0,82, IC: 0,46-1,45) resultaron prevenir significativamente (*p*=0,309 y *p*=0,488, respectivamente) las infecciones postoperatorias tras la cirugía de implantes dentales.

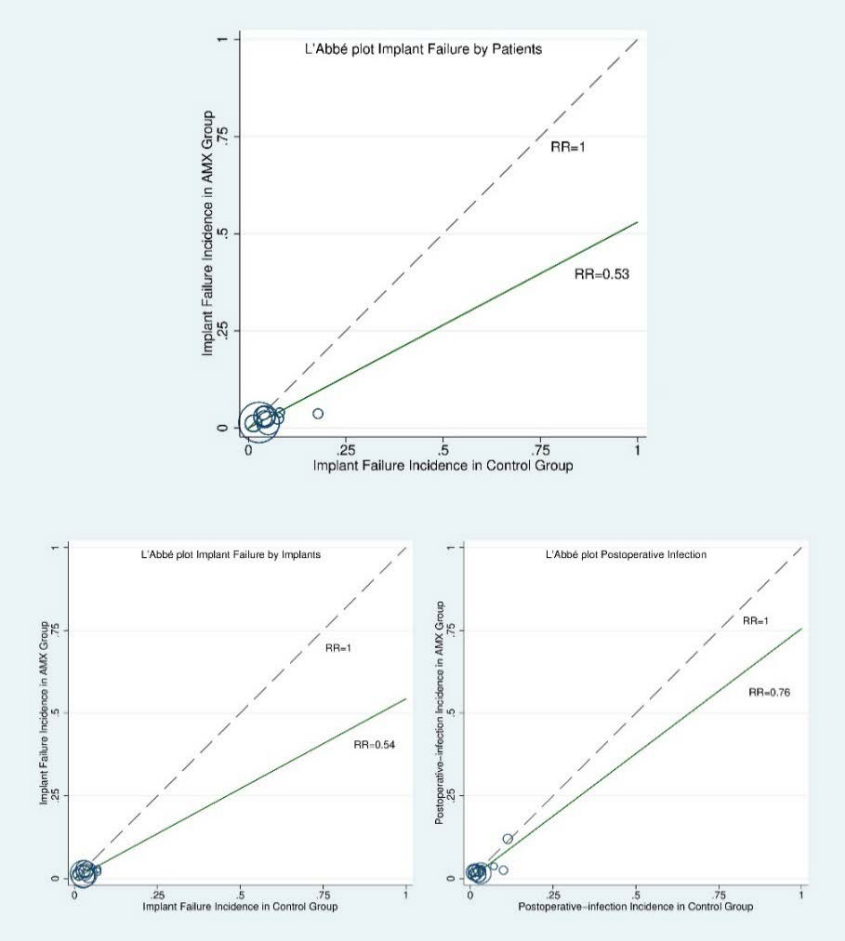
El RR global del análisis realizado por el número de infecciones postoperatorias fue de 0,76 (IC del 95%, de 0,47 a 1,22), que no es significativamente diferente de 1 (*p*=0,250).

El NNT global calculado para el análisis realizado por el número de pacientes que presentaron infección postoperatoria fue de 143. El IC del 95% revela que sería necesario tratar a entre 50 y 200 pacientes con amoxicilina para prevenir sólo 1 caso de infección postoperatoria. El NNT para la SDOAP fue de 100 (IC del 95%, de 32 a 100), y el NNT para el uso postoperatorio de amoxicilina oral fue de 143 (IC del 95%, de 50 a 200).

Análisis de heterogeneidad:

La heterogeneidad, indicada por el estadístico I^2, fue de 0,0 para los 3 análisis, ya que los valores de *p* fueron próximos a 1. Este hecho proporciona evidencia suficiente para aceptar la hipótesis nula de ausencia de heterogeneidad entre los resultados de los estudios incluidos en este meta-análisis. En los gráficos de l'Abbé (Figura 5), cada círculo corresponde a cada estudio incluido en los análisis, siendo el área del círculo proporcional al peso del estudio. En los gráficos, los autores no observaron ningún patrón relevante de heterogeneidad, estando todos los círculos agrupados en la misma región, independientemente de su tamaño y riesgo basal.

Figura 5. Diagramas l'Abbé combinados



Reacciones adversas:

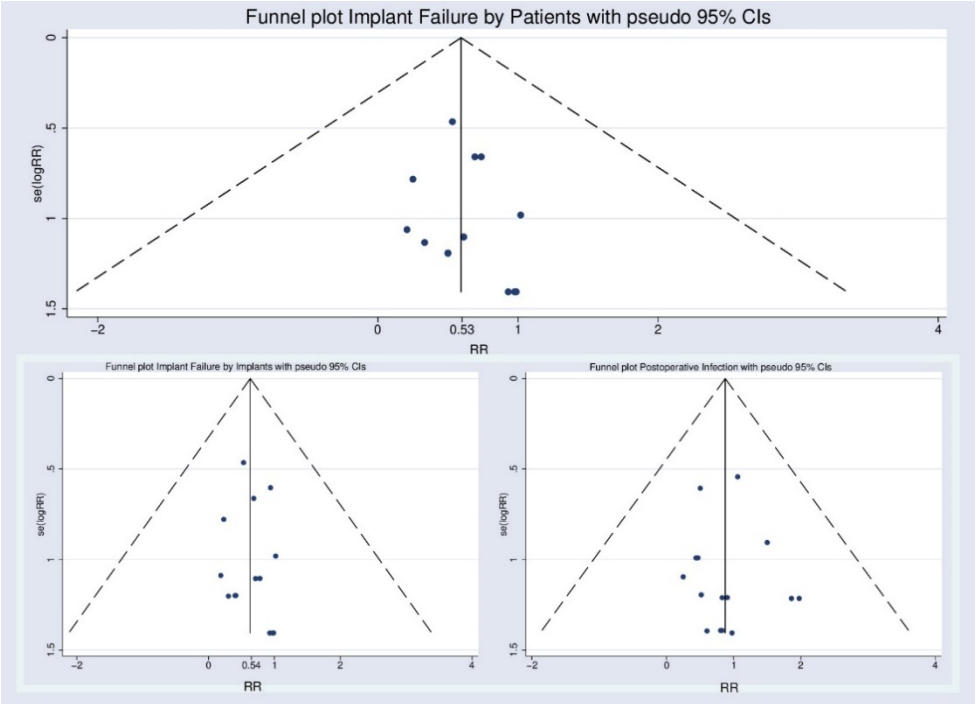
El estudio realizado por Esposito et al. (2008) informó de 1 evento adverso que se produjo en el grupo de placebo (picor durante 1 día) y 1 en el grupo de antibióticos (diarrea y somnolencia), pero la diferencia no fue significativa (*p*=1). La investigación realizada por Arduino et al. (2015) no informó de ningún acontecimiento adverso en el grupo 1. Sin embargo, en el grupo 2, dos hombres (de 53 y 73 años) informaron de hinchazón abdominal con distensión y ardor de estómago y 1 paciente femenina (de 78 años) informó de erupción cutánea y edema laríngeo. Esta paciente, que no informó en la anamnesis de ninguna posible alergia a ningún tipo de antibiótico, experimentó una reacción profundamente grave que requirió la interrupción del tratamiento y el ingreso temporal en el hospital. Los autores no encontraron diferencias significativas entre los dos grupos.

En los 3 artículos incluidos [16, 21, 24] no se informó de reacciones adversas a la amoxicilina, y en 4 de los artículos incluidos [18, 19, 23, 22] no hay información sobre reacciones adversas a la amoxicilina.

Riesgo de sesgo en los estudios

Los funnel plots (Figura 6) sugieren una ausencia de sesgo de publicación considerando la dispersión simétrica de los puntos en referencia a un RR igual a 0,53, 0,54 y 0,74, respectivamente.

Figura 6. Diagramas Funnel combinados



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3.3.2. Clindamicina preventiva en cirugía oral. Revisión sistemática y meta-análisis

RESUMEN

Objetivos: Los pacientes alérgicos a la amoxicilina son frecuentemente tratados en nuestro medio con clindamicina. En los casos en los que se prescribe amoxicilina preventiva en procedimientos de cirugía oral, como es el caso de la cirugía de implantes, es habitual el empleo de clindamicina preventiva. Nuestro objetivo es determinar el efecto de la clindamicina en la prevención de la infección tras la cirugía oral.

Métodos: Esta revisión sistemática y meta-análisis siguió la declaración PRISMA, el marco PICO y sólo incluyó ensayos clínicos controlados aleatorios. En todos los estudios se administró clindamicina para prevenir infecciones en pacientes sometidos a cirugía oral. Dos investigadores independientes realizaron la búsqueda, la extracción de datos y la evaluación del riesgo de sesgo. Los estudios incluidos se clasificaron según el tipo de cirugía oral. Además, se recogieron los datos de los pacientes, los procedimientos y las variables de resultado. Se calcularon los cocientes de riesgo (CR) y los intervalos de confianza (IC) del 95% mediante el modelo de Mantel-Haenszel y el número necesario a tratar (NNT). Por último, se estimaron las posibles fuentes de heterogeneidad.

Resultados: Siete ensayos de 540 artículos, cumplieron los criterios de inclusión y se incluyeron en la síntesis cualitativa. Se analizaron cuantitativamente cuatro artículos que evaluaban el efecto de la clindamicina oral en la cirugía de terceros molares. El RR global fue de 0,66 (IC 95%=0,38-1,16), siendo no estadísticamente significativo (p=0,15). No hubo heterogeneidad entre los estudios I2=0, p=0,44. El NNT fue de 29 (IC 95%=12--57).

Conclusiones: La efectividad de la clindamicina no pudo ser evaluada excepto en la extracción de terceros molares. La clindamicina oral es ineficaz para prevenir la infección en la cirugía de terceros molares. No existen estudios sobre la eficacia de la clindamicina en la colocación rutinaria de implantes para prevenir las complicaciones infecciosas y/o el fracaso de los implantes.

MÉTODOS

Este estudio se realizó de acuerdo con los Elementos de Información Preferidos para Revisiones Sistemáticas y Meta-Análisis (PRISMA). Antes de realizar la revisión, se establecieron sus métodos. El número de registro del protocolo fue CRD42021226241. Accesible en: https://www.crd.york.ac.uk/prospero/#recordDetails

Se contrastó la hipótesis nula (H_0) con un nivel de significación de p=0,05, de que el uso preventivo de la clindamicina no es eficaz para reducir la infección en la cirugía oral.

Criterios de elegibilidad

Sólo se incluyeron ensayos clínicos aleatorios (ECA) controlados con placebo o sin ningún tratamiento, independientemente de si eran doblemente ciegos o no. Al menos los pacientes de uno de los grupos debían haber recibido clindamicina preventiva (con cualquier tipo de vía de administración, régimen o dosis) para prevenir complicaciones infecciosas después de cualquier tipo de procedimiento de cirugía oral. Los artículos se clasificaron según el tipo de cirugía oral en el que se probó la eficacia de la clindamicina.

Se excluyeron todos los estudios que no cumplían los criterios de inclusión; destacan especialmente los ensayos en los que el grupo de control recibió un tratamiento antibiótico.

Fuentes de información

Para realizar la búsqueda se utilizaron las siguientes bases de datos electrónicas Pubmed/Medline, Registro Central Cochrane de Ensayos Controlados (CENTRAL), Web of Science, Embase Ovid y Scopus. También se realizó una búsqueda manual. Se realizaron búsquedas en todas las bases de datos hasta enero de 2021.

Búsqueda

La estrategia de búsqueda se basó en el marco PICO. Población (P): Los pacientes fueron evaluados para su inclusión en el análisis independientemente de su edad, sexo, patologías previas o hábitos, como el tabaquismo. Se incluyeron todos los estudios que evaluaban cualquier tipo de procedimiento quirúrgico oral. Intervención (I): Profilaxis antibiótica con clindamicina administrada por vía oral, intravenosa o tópica y prescrita antes, durante y/o después de la cirugía oral. Comparación (C): Placebo o ningún tratamiento administrado perioperatoriamente. Resultado (O): Las variables de resultado incluyeron todos los signos de infección postoperatoria (dolor, fiebre, hinchazón, trismo e infección de la herida o del sitio quirúrgico), alveolitis seca, otras complicaciones relacionadas y acontecimientos adversos. Dos investigadores independientes realizaron la selección del estudio hasta enero de 2021.

La búsqueda electrónica en la base de datos PubMed/Medline se realizó utilizando el tesauro MeSH y algoritmos de búsqueda conectados con operadores booleanos como palabras clave para los títulos y resúmenes. Estas son algunas de las diferentes estrategias de búsqueda utilizadas:

("clindamycin"[MeSH Terms] OR "clindamycin"[All Fields] OR "clindamycine"[All Fields]) AND ("surgery, oral"[MeSH Terms] OR ("surgery"[All Fields] AND "oral"[All Fields]) OR "oral surgery"[All Fields] OR ("oral"[All Fields] AND "surgery"[All Fields]) OR "oral surgery"[All Fields] OR "oral surgical procedures"[MeSH Terms] OR ("oral"[All Fields] AND "surgical"[All Fields] AND "procedures"[All Fields]) OR "oral surgical procedures"[All Fields] OR ("oral"[All Fields] AND "surgery"[All Fields]).

("clindamycin"[MeSH Terms] OR "clindamycin"[All Fields] OR "clindamycine"[All Fields]) AND ("dental implants"[MeSH Terms] OR ("dental"[All Fields] AND "implants"[All Fields]) OR "dental implants"[All Fields]).

("clindamycin"[MeSH Terms] OR "clindamycin"[All Fields] OR "clindamycine"[All Fields]) AND ("tooth extraction"[MeSH Terms] OR ("tooth"[All Fields] AND "extraction"[All Fields]) OR "tooth extraction"[All Fields] OR ("dental"[All Fields] AND "extraction"[All Fields]) OR "dental extraction"[All Fields]).

("clindamycin"[MeSH Terms] OR "clindamycin"[All Fields] OR "clindamycine"[All Fields]) AND (("mouth"[MeSH Terms] OR "mouth"[All Fields] OR "oral"[All Fields]) AND ("biopsie"[All Fields] OR "biopsy"[MeSH Terms] OR "biopsy"[All Fields] OR "biopsied"[All Fields] OR "biopsies"[All Fields] OR "biopsy s"[All Fields] OR "biopsying"[All Fields] OR "biopsys"[All Fields] OR "pathology"[MeSH Subheading] OR "pathology"[All Fields])).

No se utilizaron restricciones en cuanto al idioma o la fecha de publicación. Los filtros activados fueron: humanos y ensayos clínicos.

Selección de estudios

La estrategia de búsqueda produjo los resultados que se muestran en la figura 1. Las bases de datos que no aparecen en esta figura no aportaron ninguna publicación relevante. Dos investigadores independientes realizaron la selección de los estudios (IA y AF), se solicitó un tercer investigador en caso de conflicto (FR). Los artículos incluidos y excluidos con los motivos de exclusión se registraron en la Tabla 1.

Proceso de recogida de datos

Se diseñó un protocolo de recogida de datos, en el que cada estudio seleccionado fue revisado de forma independiente por dos investigadores (IA y NAL), y las diferencias se resolvieron consultando a un tercer analista (FR). Cuando no había datos explícitos en el texto principal, los cálculos se realizaron utilizando los resultados en tablas o figuras, cuando era posible. En caso de falta o duda sobre datos de interés en el artículo, se contactó con los autores.

Datos

La tabla 2 incluía todos los datos registrados en cada estudio. Los estudios se clasificaron según el tipo de cirugía oral realizada. Además, cuando se probó más de un antibiótico en el mismo estudio, sólo se recogió la información relativa a los pacientes que fueron tratados con clindamicina y los que pertenecían a los grupos de control.

Riesgo de sesgo en los estudios individuales

Se utilizó la herramienta de la Colaboración Cochrane para evaluar el riesgo de sesgo individual de cada ECA incluido en el análisis cuantitativo (Figura 2). El sesgo de cada estudio se analizó utilizando el enfoque recomendado para evaluar el riesgo de sesgo en los estudios incluidos en las revisiones Cochrane.

Medidas de resumen

La eficacia del tratamiento se evaluó considerando el riesgo relativo (RR). Las diferencias en las incidencias entre los grupos de tratamiento y control o el riesgo atribuible se utilizaron para evaluar la importancia clínica del tratamiento con clindamicina. Además, se calculó el número necesario para tratar (NNT).

Síntesis de los resultados

El análisis se llevó a cabo mediante el software STATA® IC 13 y Review Manager (RevMan) 5.2 versión (Copenhague: The Cochrane Collaboration, 2012). Se evaluó la heterogeneidad de los diferentes estudios mediante el estadístico I2. El riesgo relativo global, resultante de la combinación de los resultados de los diferentes estudios, se calculó con el modelo inverso de Mantel-Haenszel (MH) ponderado por la varianza. Se utilizó una corrección empírica para los estudios con tamaños del efecto nulos en uno de sus brazos, y se excluyeron del análisis los estudios con un tamaño del efecto nulo en ambos brazos.

RESULTADOS

Selección de estudios

Se identificaron 540 registros tanto en las bases de datos como en la búsqueda manual (Figura 1). Tras eliminar los duplicados, se seleccionaron 38 artículos para la evaluación del texto completo. Tras la evaluación del texto completo, se incluyeron siete en la síntesis cualitativa. En primer lugar, se excluyeron todos los artículos que no analizaban la infección clínicamente. Nueve artículos [1-9] estudiaron la bacteriemia, tres artículos [10-12] estudiaron la influencia de la clindamicina en el microbioma oral. Bulut et al. (2001) [13] estudiaron los niveles de la fase aguda de las proteínas. No se pudo encontrar un artículo [14] y se excluyó. Posteriormente, los artículos se clasificaron según el tipo de cirugía oral en la que se probó la eficacia de la clindamicina. La tabla 1 muestra los estudios que se incluyeron y los que se excluyeron con sus motivos.

Figura 1: Diagrama de flujo PRISMA

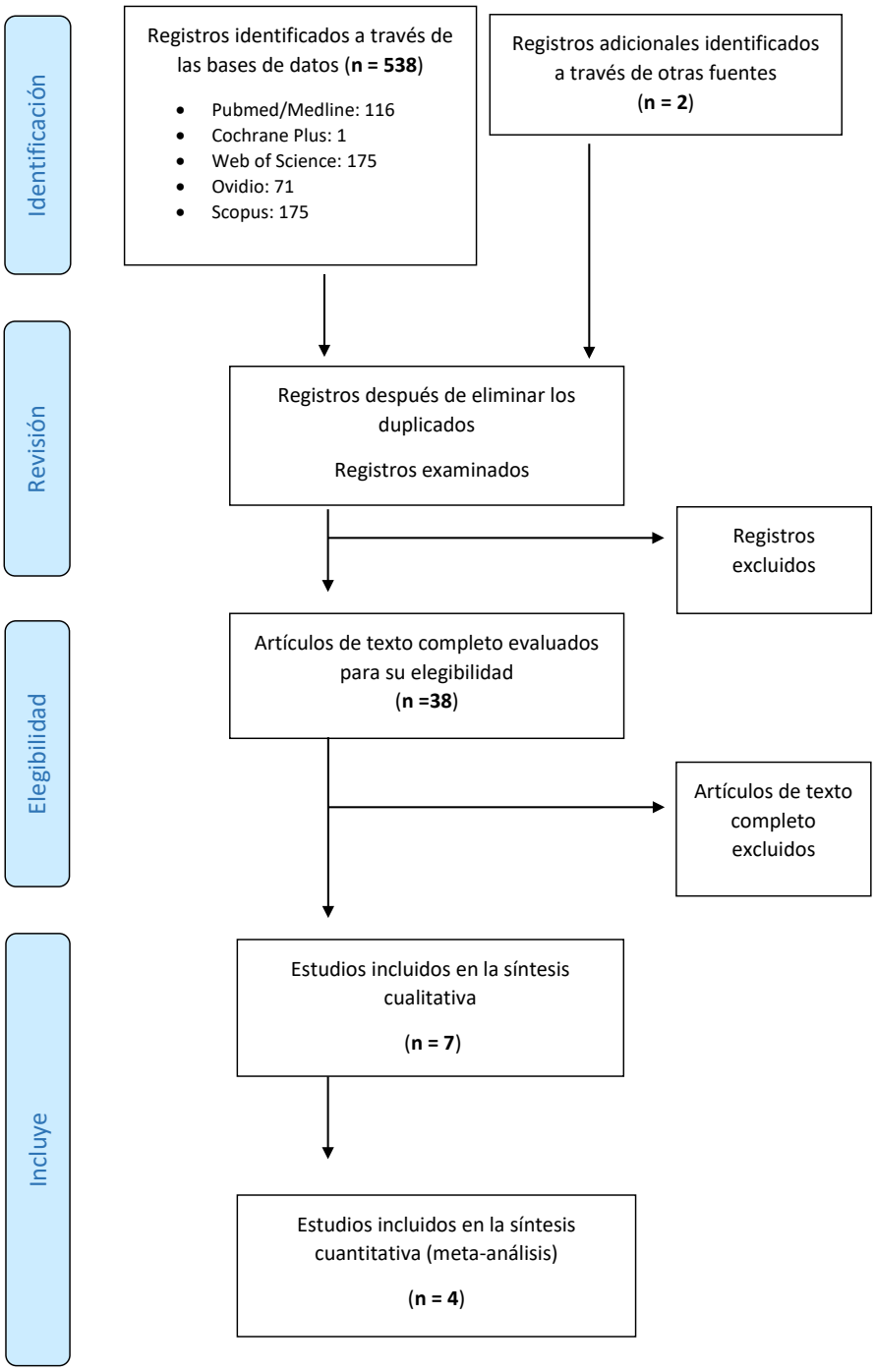


Tabla 1. Artículos de texto completo clasificados según el procedimiento quirúrgico en el que se probó la clindamicina, especificando los incluidos, los excluidos y el motivo de la exclusión.

Procedimiento quirúrgico	Autores / Año	Inclusión/exclusión
Fracturas mandibulares	Miles BA et al. 2006 [22]	Excluidos: ningún grupo de control con placebo o sin tratamiento.
Injertos óseos junto con la colocación de implantes	Lindeboom JA et al. 2005 [23]	Excluidos: ningún grupo de control con placebo o sin tratamiento.
	Lindeboom JA et al. 2006 [24]	Excluidos: ningún grupo de control con placebo o sin tratamiento.
	Klinge A et al. 2020 [25]	Excluido: Es una revisión.
Cirugía ortognática	Lindeboom JA et al. 2003 [26]	Excluidos: ningún grupo de control con placebo o sin tratamiento.
	Baqain ZH et al. 2004 [27]	Excluidos: ningún grupo de control con placebo o sin tratamiento.
	Davis CM et al. 2017 [28]	Excluidos: ningún grupo de control con placebo o sin tratamiento.
Cirugía oncológica	Righi M et al. 1995 [29]	Excluidos: ningún grupo de control con placebo o sin tratamiento.
Cirugía de cabeza y cuello	Mann W et al. 1990 [30]	Excluidos: ningún grupo de control con placebo o sin tratamiento.
	Clayman GL et al. 1993 [31]	Excluidos: ningún grupo de control con placebo o sin tratamiento.
Procedimiento de endodoncia	Raslan N et al. 2017 [32]	Excluidos: ningún grupo de control con placebo o sin tratamiento.
Cirugía endodóntica	Lindeboom JA et al. 2005 [21]	Incluido
Extracción dental	Laird WR et al. 1972 [33]	Excluidos: ningún grupo de control con placebo o sin tratamiento.
	Bystedt et al. 1980 [34]	Excluidos: no informaron de los datos en una forma adecuada para su inclusión.
	Kupfer et al. 1995 [35]	Excluido: no es un ECA
	Poeschl et al. 2003 [17]	Incluido
	Foy et al. 2003 [36]	Excluidos: no informaron de los datos en una forma adecuada para su inclusión.
	[a]Halpern et al. 2007[16]	Incluido
	Kaczmarzyk et al. 2007 [18]	Incluido
	Adde et al. 2012 [19]	Incluido
	*Hamiti-Krasniqi et al. 2014 [15]	Incluido

	Xue 2014 [37]	Excluidos: pacientes incluidos en otro estudio. No fue posible contactar con los autores.
	Xue 2015 [38]	Excluidos: no informaron de los datos en una forma adecuada para su inclusión.
	Kaposvári 2017[20]	Incluye

** clindamicina topica; ª clindamicina intravenosa*

Características de los estudios

La tabla 2 muestra las variables estudiadas de los estudios incluidos: un estudio se realizó sobre cirugía endodóntica y, seis estudios sobre cirugía de terceros molares. Hamiti-Krasniqi et al. (2014) [15], probaron la clindamicina tópica en la prevención de la alveolitis seca, mientras que Halpern y Dodson (2007) utilizaron clindamicina intravenosa (600 mg IV 1 hora antes de la cirugía) [16]. Ambos estudios mostraron menores tasas de infección en los pacientes tratados con clindamicina que en el grupo de placebo. En el resto de los ensayos clínicos, el tratamiento fue con clindamicina oral, variando en sus regímenes y dosis. El periodo de seguimiento en todos los estudios osciló entre 1 y 4 semanas.

Sólo cuatro ensayos nos permitieron agrupar la información sobre el efecto de la clindamicina oral en las extracciones de terceros molares. Por esta razón, se decidió continuar con un análisis cuantitativo que probara la hipótesis nula (H_0), con un nivel de significación de p=0,05, de que el uso preventivo de clindamicina oral no es efectivo para reducir la infección en la cirugía de terceros molares.

Tabla 2. Características de los estudios incluidos en la revisión.

Estudio	Diseño del estudio y criterios de inclusión	Antibiótico/ placebo	Post-operativo tratamiento	Variable de resultado y Período de seguimiento	Resultados	Perdido para seguir y efectos secundarios
CLINDAMICINA ORAL EN LA EXODONCIA DEL TERCER MOLAR						
Poeschl [17] 2004 Austria Fuente de financiación: sin especificar	ECA Extracción quirúrgica de terceros molares inferiores impactados Edad media 20,7 años (el rango de edad estaba entre 14 y 61 años)	Grupo experimental: 300mg de clindamicina (Dalacin) por vía oral 3 veces al día, durante 5 días post operación N=180 molares Grupo de control: nada. N=172 molares	Enjuague bucal con clorhexidina al 0,2% 1 minuto antes de la cirugía. Analgésico después de la cirugía si es necesario 500 mg de ácido mefenanimo. Cada 6h.	Alveolo seco: falta de coágulo, hueso expuesto, restos necróticos malolientes en la cavidad, paredes del alveolo extremadamente dolorosas Infección de la zona de sutura: inflamación local, hiperemia, exudado purulento y dolor en la zona de la sutura) Evaluación del dolor: Escala VAS Diferencias en la apertura de la boca Periodo de seguimiento: día 2, 10 y 4 semanas	Grupo experimental: síntomas de infección local Encaje seco 15/180 Grupo de control: síntomas de infección local Encaje seco 17/172 No se incluyó en el estudio el grupo de amoxicilina/clavulanis	2 pacientes no volvieron después de la cirugía. 4 pacientes no retiraron la sutura el día 10 7 pacientes no volvieron a la última cita a las 4 semanas de la intervención. Efectos secundarios: dolor de cabeza, debilidad, náuseas, temblores, diarrea, estreñimiento, insomnio y fiebre. Grupo experimental 22 y grupo de control 24.
Kaczmarzyk [18] 2007 Polonia Fuente de financiación: sin especificar	ECA Voluntarios sanos, extracción quirúrgica de un tercer molar inferior retenido, que requiere extracción ósea. La exclusión de los menores de 18 años o mayores de 60 significa 24 años.	Grupo experimental: (Grupo de clindamicina de 5 días): 600 mg de clorhidrato de clindamicina por vía oral 60 min antes de la operación, seguido de 300 mg de clorhidrato de clindamicina cada 8 horas durante 5 días. N=28 Grupo de control: 600 mg de placebo por vía oral 60 min antes de la cirugía, seguido de una dosis de 300 mg de placebo cada 8	Ketoprofeno 50 mg cápsulas para tomar en caso de dolor. La dosis máxima diaria era de 200 mg. Se pidió a los pacientes que no tomaran ningún otro medicamento durante el ensayo	En una escala de 4 grados, Trismus - hinchazón facial, linfadenopatía submandibular en una EAV de 100 mm de temperatura corporal, dolor Osteítis alveolar (el diagnóstico clínico de esta complicación se dio en el caso de la presencia de un coágulo gris necrótico en una cavidad ósea desnuda, el fetor ex ore, acompañado de dolor en esta zona). Periodo de seguimiento: en el primer, segundo y séptimo día postoperatorio	Grupo experimental: 2/28 Grupo de control: 4/27 No se ha incluido en el estudio Hay un grupo de dosis única: pacientes que reciben 600 mg de clorhidrato de clindamicina por vía oral 60 min antes de la operación	9 no se inscribieron en el examen de seguimiento 3 fueron descalificados debido a complicaciones 2 dimitió durante el juicio sin dar ninguna razón. Efectos secundarios El 3% de los participantes que tomaron un curso de 5 días de clindamicina desarrollaron complicaciones gástricas y fueron excluidos del ensayo

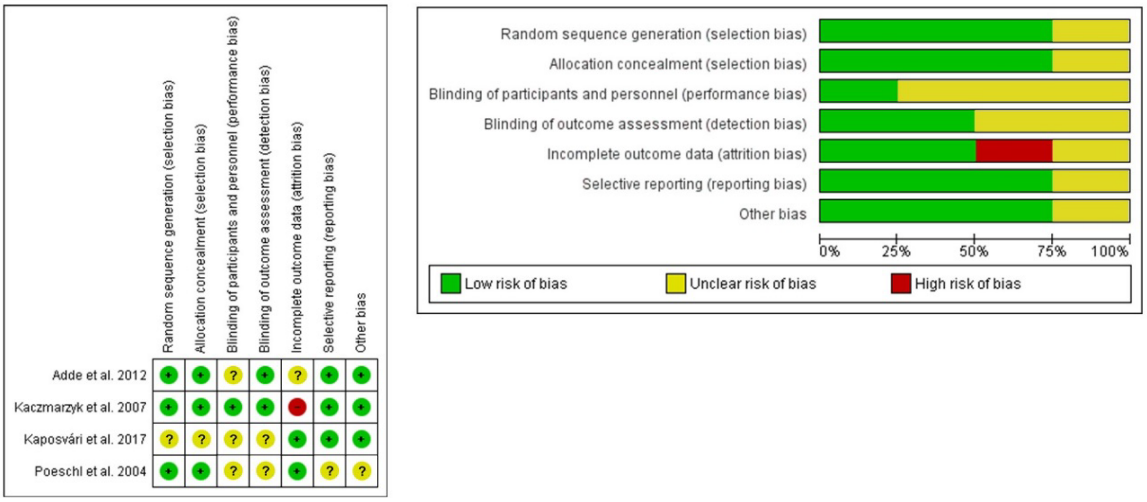
		horas durante 5 días. N=27				
Adde [19] 2012 Brasil Fuente de financiación: sin especificar	ECA Edad entre 18 y 45 años. ASA tipo I con indicación de extracción de terceros molares superiores e inferiores.	Grupo experimental: Clindamicina 300mg 4 veces al día durante 7 días. N= 23 Grupo de control: sin tratamiento. N= 24	Diclofenac 50 mg cada 8 horas durante 3 días Paracetamol 750mg al menos 1 hora antes de la cirugía y luego cada 6 horas hasta que cese el dolor.	Infección postoperatoria: temperatura corporal superior a 37,8C sin otras causas perceptibles, absceso intraoral con punto de drenaje flotante, alveolitis, dolor severo persistente o intensificado 48 horas después de la cirugía e inflamación y/o eritema, y dolor severo a partir del séptimo día acompañado de inflamación. Periodo de seguimiento: Evaluación a las 24 horas, 48 horas, 3 días y 7 días..	Grupo experimental: 0/23 infección postoperatoria Grupo de control: 0/24 de infección postoperatoria.	No hay pérdidas. Efectos secundarios No se han registrado complicaciones de ningún tipo.
Kaposvári [20] 2017 Hungría Sin financiación	Se extrajo el tercer molar inferior RCT Pacientes sanos de 18 a 35 años edad media 24,78 años	Grupo experimental: 600 mg de clindamicina una hora antes de la cirugía. N=14 (7 simples/7 complejos) Grupo de control: placebo. N=18 (8 fáciles / 10 complejos)	Diclofenaco 50 mg, máximo 3 dosis	Alveolitis Herida disecada. Periodo de seguimiento: durante una semana. hasta la retirada de la sutura	Grupo experimental: 0/14 alveolitis y herida disecada 2/14 Grupo de control: 2/18 alveolitis y 4/18 herida disecada	1 pérdida en el grupo experimental. Efectos secundarios: separación de la herida, edema y trismo.
CLINDAMICINA INTRAVENOSA EN LA EXODONCIA DEL TERCER MOLAR						
Halpern [16] 2007 EE.UU. apoyado en parte por la beca de investigación de la Fundación de Cirugía Oral y Maxilofacial y el Centro de Investigación Clínica Aplicada del Hospital General de	RCT Pacientes que requieren la extracción de terceros molares bajo sedación intravenosa o anestesia general en el ámbito ambulatorio en la oficina ' El rango de edad de los pacientes es de	Grupo experimental: solución de penicilina (15.000 unidades por kilo) o, en el caso de los sujetos alérgicos a la penicilina, clindamicina 600 mg por vía intravenosa 1 hora antes de la intervención. N=.60 N=. (clindamicina) 15 Grupo de control con placebo: solución (10 cc de solución salina al 0,9%)	Todos los sujetos recibieron dexametasona intravenosa (8 mg) antes de la operación y el 15% recibió tratamiento antiemético intravenoso (ondansetrón 2 mg))	Alveolitis seca: nueva aparición o aumento del dolor más de 36 horas después de la operación, con el coágulo de sangre en el lugar de la extracción evidenciado por el hueso expuesto, el sondeo suave o la irrigación de la herida que duplica el dolor y el alivio del dolor significativo después de la operación. Infección del sitio quirúrgico: evidencia visual de purulencia franca en uno o más de los sitios de	Grupo experimental: 0/15 infección postoperatoria. Grupo de control: 5/62 infección postoperatoria.	1 pérdida en el grupo de control 1 pérdida en el grupo experimental

Massachusetts (MGH)	17,7-31,5 años. Media de 25 años.	administrada por vía intravenosa una hora antes de la intervención. N=62	1 ó 2 comprimidos de paracetamol (500 mg) e hidrocodona (5 mg) administrados por vía oral cada 3 ó 4 horas	extracción y tinción de Gram que demuestre la presencia de glóbulos blancos. Periodo de seguimiento: Evaluado en el día postoperatorio 7 (rango 5-14).		
CLINDAMICINA TÓPICA EN LA EXODONCIA DEL TERCER MOLAR						
Hamiti-Krasniqi [15] 2012 Kosovo Fuente de financiación: sin especificar	ECA. Una boca partida. Extracción del tercer molar mandibular derecho e izquierdo. Se excluyeron los pacientes con problemas de salud y los que recibieron terapia antibiótica 14 días antes de la cirugía.	Grupo experimental: 300 mg de clindamicina mezclados con 0,2 ml de saliva. A continuación, se introduce la esponja hemostática Gelatamp N=.60 molares Grupo de control: nada. N=.60 molares Los pacientes se dividieron en fumadores y no fumadores.	La medicación analgésica se administra sólo en caso de dolor post-extracción, especificando el lado del dolor	Enchufe seco Periodo de seguimiento: al día siguiente, a los dos días y al día 5	Grupo experimental: 2/60 encaje seco. Grupo de control: 19/60 enchufes secos.	No hay que hacer un seguimiento suelto
CLINDAMICINA ORAL EN LA CIRUGÍA ENDODÓNTICA						
Lindeboom [21] 2006 Amsterdam Fuente de financiación: sin especificar	RCT Diente con periodontitis apical con cierre radicular adecuado y restauración coronal	Grupo experimental: clindamicina 600mg 1 hora antes de la incisión. N=128 dientes Grupo de control: placebo 600mg 1h antes de la incisión N=128 dientes	Solución de clorhexidina al 0,2% dos veces al día durante 1 semana.	Infección: Drenaje purulento de una incisión o drenaje, drenaje serosanguíneo y cultivo de la herida positivo para un patógeno conocido, herida dehiscada espontáneamente o abierta deliberadamente por el cirujano cuando el paciente tenía fiebre o dolor o sensibilidad localizados, con cultivo positivo de la herida. Periodo de seguimiento: los pacientes fueron evaluados en la primera, segunda y cuarta semana.	Grupo experimental: 2 dientes / 128 infecciones. Grupo de control: 4 dientes / 128 infecciones.	No hay que hacer un seguimiento suelto

Riesgo de sesgo dentro de los estudios

El riesgo de sesgo de cada estudio se presenta en la figura 2. A pesar de que algunos estudios no eran de alta calidad y de que trataban sobre diferentes dosis, el análisis cuantitativo se realizó incluyendo los cuatro artículos [17-20] en los que se estudiaba la eficacia de la clindamicina oral en la cirugía de terceros molares.

Figura 2. Gráfico y resumen del riesgo de sesgo



Medidas de resumen

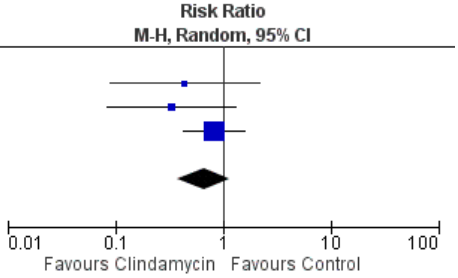
Los cuatro estudios en los que se prescribió clindamicina oral para prevenir las complicaciones infecciosas tras la extracción de terceros molares fueron los únicos incluidos. El análisis cuantitativo incluyó 486 extracciones, 245 de ellas tratadas con clindamicina y 241 del grupo de control (tratadas con placebo o sin tratamiento). Se notificaron 19 y 27 casos de infección, alveolos secos u otros eventos en los respectivos grupos.

El diagrama de Forest (Figura 3) muestra la representación gráfica de las estimaciones del RR y del IC del 95% realizadas con las muestras de los cuatro estudios incluidos. El RR global extraído de todos los estudios indicó que no había ningún beneficio estadístico, y que la clindamicina oral puede no ser eficaz en la prevención de las complicaciones infecciosas después de las extracciones de terceros molares.

Figura 3. Diagrama de Forest

Study or Subgroup	Clindamycin Events	Clindamycin Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Adde et al. 2012	0	23	0	24		Not estimable
Kaczmarzyk et al. 2007	2	26	4	23	12.1%	0.44 [0.09, 2.20]
Kaposvári et al. 2017	2	12	6	12	16.2%	0.33 [0.08, 1.33]
Poeschl et al. 2004	15	165	17	155	71.7%	0.83 [0.43, 1.60]
Total (95% CI)		**226**		**214**	**100.0%**	**0.66 [0.38, 1.16]**
Total events	19		27			

Heterogeneity: Tau² = 0.00; Chi² = 1.63, df = 2 (P = 0.44); I² = 0%
Test for overall effect: Z = 1.45 (P = 0.15)



Síntesis de los resultados

La heterogeneidad medida a partir de la prueba I2 fue de 0 (*p*=0,44), no pudiéndose rechazar la hipótesis nula de ausencia de heterogeneidad entre los resultados de los estudios incluidos en este meta-análisis. El estadístico Q también apoya la hipótesis de homogeneidad entre los estudios.

El RR global, mediante el método de Mantel-Haenszel resultó ser de 0,66, con un IC del 95% de 0,38 a 1,16, siendo no estadísticamente significativo (*p*=0,15). Este intervalo también incluía el valor 1, lo que indica que el tratamiento con clindamicina puede no prevenir el desarrollo de complicaciones infecciosas (alveolitis seca, infección o ambas condiciones al mismo tiempo) tras las extracciones de terceros molares.

Análisis de la significación clínica

El NNT fue de 29 y osciló entre 12 y -57. Esto significa que sería necesario tratar a entre 12 e infinitos pacientes con clindamicina oral para prevenir un solo caso de infección tras la extracción de terceros molares. Estos resultados indicaron que la clindamicina oral puede ser ineficaz para prevenir las infecciones tras la extracción de terceros molares.

No existen estudios sobre la eficacia de la clindamicina en la prevención de infecciones y/o fracaso de implantes orales.

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3.3.3. Clindamicina preventiva en cirugía de implantes orales. Ensayo clinico aleatorizado y controlado

RESUMEN

Objetivos: El uso profiláctico de la clindamicina en la cirugía de implantes orales no está respaldado por la evidencia, a pesar de que se prescribe con frecuencia como alternativa para los pacientes alérgicos a la penicilina. El objetivo de este estudio fue evaluar el efecto de la clindamicina preoperatoria en la reducción de las infecciones postoperatorias y los fracasos de los implantes.

Métodos: Se desarrolló un ensayo clínico prospectivo, aleatorizado, paralelo, doble ciego y controlado con placebo, de plena conformidad con los principios éticos y la declaración CONSORT. El tamaño de la muestra, calculado de antemano, fue de 62 adultos sanos, que acudieron a la Clínica Odontológica de la UPV/EHU para la colocación de un implante oral unitario sin infección previa del lecho quirúrgico y que no precisaba injerto óseo. Sesenta y dos participantes fueron asignados aleatoriamente, 31 al grupo de clindamicina: una dosis única de clindamicina oral (2 cápsulas de 300 mg) una hora antes de la cirugía. Otros 31 pacientes recibieron la misma dosis, régimen y presentación de placebo. El mismo cirujano ejecutó todos los procedimientos quirúrgicos. Un único observador entrenado evaluó a todos los pacientes en los días 1, 7, 14, 28 y 56 del postoperatorio. Se analizó la infección y el fracaso del implante. Se registraron los acontecimientos adversos y variables clínicas, radiológicas y quirúrgicas. Se calculó el número necesario de pacientes para tratar/dañar (NNT/NNH) y los riesgos relativos de infección y fracaso del implante.

Resultados: Hubo dos fracasos de implantes, ambos en pacientes tratados con clindamicina (NNH=15). No obstante, no se encontraron diferencias significativas entre los grupos (p=0,246). Tres pacientes sufrieron infecciones postoperatorias; dos pertenecían al grupo de placebo y uno al de clindamicina (RR: 0,5; IC: 0,05-5,23, RRA=0,03; IC: -0,07-0,13, NNT=31; IC: 7,2-∞). Tampoco se observaron diferencias significativas entre los grupos (p=0,5). Un paciente tratado con clindamicina tuvo trastornos gastrointestinales y diarrea, sin que hubiera diferencias significativas entre los grupos (NNH=31; p=0,5).

Conclusiones: El uso de clindamicina preoperatoria en la cirugía de implantes orales en pacientes sanos sin infección previa ni necesidad de regeneración ósea puede no ser beneficioso para reducir las infecciones postoperatorias y los fracasos de los implantes.

MÉTODOS

Diseño del ensayo y aspectos éticos

Este estudio fue diseñado como un ensayo clínico prospectivo, aleatorizado, paralelo, doble ciego y controlado con placebo. (Número EudraCT: 2017-002168-42). El ensayo fue aprobado por El Comité de Ética de Investigación con Medicamentos de Euskadi (CEIm-E) el 31/10/2018 (número de código interno: 201862) y por la Agencia Española de Medicamentos y Productos Sanitarios(AEMPS) (18/12/2018). Esta investigación se llevó a cabo en conformidad con los principios éticos, incluyendo la Declaración de Helsinki de la Asociación Médica Mundial [1]. El estudio se informó de acuerdo con la declaración CONSORT [2]. El único cambio realizado en el diseño es el momento en el que evaluamos la estabilidad del implante, se evaluó el día 56 en lugar del día 28.

Participantes

El ensayo se realizó en la Clínica Dental del Postgrado en Implantología Oral y Microcirugía de la Universidad del País Vasco (Leioa, España). La población elegible fueron todos los adultos sanos menores de 18 años, que acudieron a la Clínica Dental y en los que estaba indicada la colocación de un implante único, sin infección previa del lecho quirúrgico, ni necesidad de regeneración ósea. Se realizó un muestreo consecutivo de la población accesible.

Los pacientes fueron excluidos antes de la aleatorización por los siguientes motivos: alergia a algún fármaco utilizado en el ensayo, presencia de patologías sistémicas descompensadas (cardíacas, respiratorias, endocrinas, metabólicas, hepáticas, hematológicas, riesgo de endocarditis bacteriana, inmunodeprimidos), portador de prótesis valvulares u ortopédicas, antecedentes o uso de bifosfonatos, anticoagulantes o antiagregantes plaquetarios. También se excluyeron los pacientes que habían sido irradiados en el territorio cervical y maxilofacial, si estaban embarazadas, se sospechaba que estaban embarazadas o lactando y si tenían antecedentes de colitis ulcerosa asociada a antibióticos. A todos los pacientes se les realizó un estudio radiológico del lugar de implantación como es habitual en el protocolo de la clínica. Se excluyeron del ensayo los pacientes en los que podría ser necesario un tratamiento con injertos óseos.

Los pacientes fueron excluidos después de la aleatorización a petición del paciente, por abandono del ensayo o por pérdida de seguimiento y también si el paciente había tomado antibióticos en los últimos 15 días antes de la cirugía.

Intervenciones

Se administró una dosis única de clindamicina de 600 mg (2 cápsulas de 300 mg) una hora antes de la cirugía a los participantes del grupo experimental y el mismo régimen y presentación de placebo a los participantes incluidos en el grupo de control. Los pacientes recibieron el sobre con la medicación o el placebo en la clínica dental justo una hora antes del inicio de la cirugía.

El mismo cirujano, con gran experiencia en cirugía de implantes orales, llevó a cabo todos los procedimientos quirúrgicos. Las cirugías se iniciaron con la siguiente técnica anestésica: bloqueo anestésico de la zona, utilizando articaína 4% con epinefrina 1:1000.000, mediante una técnica de bloqueo mandibular para la colocación de implantes en la mandíbula y una técnica infiltrativa en el maxilar. Se realizó un colgajo mucoperióstico de espesor total mediante una incisión supracrestal en la sección edéntula y una incisión intrasulcular en los dientes adyacentes. Las incisiones de descarga sólo se realizaron en crestas muy reabsorbidas o en presencia de marcadas concavidades del hueso. Se colocaron implantes Straumann Roxolid® (TI-Zr) SLActive® (Sand-blasted large grift Acid-etched) (Basilea, 4002 Suiza). En las localizaciones sin compromiso estético, se colocó un implante de cuello pulido Straumann Tissue Level Standard Plus® (TL) de 1,8 mm. En las zonas estéticas, en el maxilar, se insertaron implantes Straumann Bone Level Tapered ® (BLT). Se utilizó la secuencia de fresado recomendada por el fabricante para ambos tipos de implantes. No se realizó ninguna cirugía de implantes de segunda fase en ningún paciente. La anchura del hueso y la altura ósea disponible determinaron el diámetro (3,3 o 4,1 mm), la longitud del implante (8, 10 o 12 mm) y, por tanto, la secuencia de fresado. Tras la colocación del implante, se midió el par de inserción del mismo utilizando una llave de carraca Straumann con dinamómetro (nº 046.119 y 046.049). En todos los casos se realizó un cierre primario del colgajo mediante una sutura de monofilamento de poliéster no absorbible de 5-0 con una técnica de sutura simple interrumpida.

El tratamiento antiinflamatorio consistió en Ibuprofeno 600 mg cada 12 horas, o Paracetamol 1 g a demanda.

Las cápsulas de clindamicina o placebo se presentaron en blísteres, envasados individualmente y etiquetados para mantener el ciego. Las muestras se etiquetaron con el número de muestra, el código del protocolo, el número de unidades, la forma farmacéutica, la vía de administración y la fecha de caducidad.

El antibiótico de rescate previsto era un comprimido (875/125 mg) de amoxicilina/ácido clavulánico cada 8 horas durante 7 días. Uno de los criterios de inclusión era no ser alérgico a la amoxicilina o al ácido clavulánico.

Variables respuesta

Un único observador adiestrado evaluó a todos los pacientes en los días 1, 7, 14, 28 y 56 después de la cirugía. Se registró cualquier signo clínico o radiográfico indicativo de infección o complicaciones biológicas: supuración, fístula, absceso, osteomielitis, fiebre superior a 38 °C. El dolor postoperatorio, la inflamación localizada, la hemorragia y el eritema intra y extraoral también se evaluaron con la escala visual analógica (EVA). También se registró la presencia de signos clínicos o radiológicos de fracaso del implante: radiolucidez periimplantaria en el día 56, movilidad manual y análisis de

frecuencia de resonancia de Osstell® (ISQ<60 en el día 56). También se registraron todas las reacciones adversas.

Tamaño de la muestra

El tamaño de la muestra se calculó con el programa estadístico STATA® 14. Se consideraron de relevancia clínica las diferencias de infección o fracaso del implante entre el grupo de control y el grupo de tratamiento superiores al 18%. Nolan et al. (2014) [3] informaron de una incidencia acumulada de fracaso del 18% en los pacientes tratados con placebo. Para un nivel de confianza del 95%, una potencia del 80%, una probabilidad de fracaso del implante o de infección postoperatoria del 18% con placebo y del 0% con antibióticos; se necesitaban dos grupos con 31 pacientes cada uno [3]. Por consiguiente, se consideró necesario un grupo de tratamiento (TG) con 31 implantes y un grupo de control (CG) con otros 31 implantes. La muestra se estableció en 62 pacientes, que habrían dado libremente su consentimiento informado para participar en el ensayo.

Aleatorización

A partir de la muestra total, se llevó a cabo una aleatorización restringida por bloques con una longitud de bloque de cuatro pacientes, con la misma probabilidad (0,5) de asignación a cada tratamiento dentro del bloque (dos pacientes por cada tratamiento dentro de cada bloque). La aleatorización se realizó con el programa estadístico STATA® 15.

Ocultación de la asignación

La asignación de los pacientes se realizó tras comprobar que cumplían los criterios de inclusión establecidos y una vez que dieron su consentimiento informado y por escrito para participar. Un asistente externo al estudio preparó los sobres sellados y numerados, según las instrucciones, con el antibiótico o el placebo a administrar. Cada número correspondía al tratamiento asignado en el proceso de aleatorización y a cada paciente se le asignaba sucesivamente el número de tratamiento correspondiente. Uno de los investigadores entregó el tratamiento en un sobre cerrado una hora antes de la colocación del implante. El tratamiento era desconocido tanto para los profesionales en contacto directo con el paciente como para éste.

Cegamiento

La aleatorización y el ocultamiento de la asignación se realizaron con doble cegamiento: ni el paciente ni el experto que colocó el implante conocían el tratamiento que recibió el paciente. El profesional que evaluó la infección o la pérdida del implante tampoco conocía el tratamiento que había recibido el paciente.

Análisis estadístico

Se utilizó el programa informático STATA® 15 para un análisis de datos por intención de tratar. Se calcularon las varianzas de cada variable y se evaluó la asociación entre los grupos de tratamiento y las distintas variables con la prueba t de Student para las

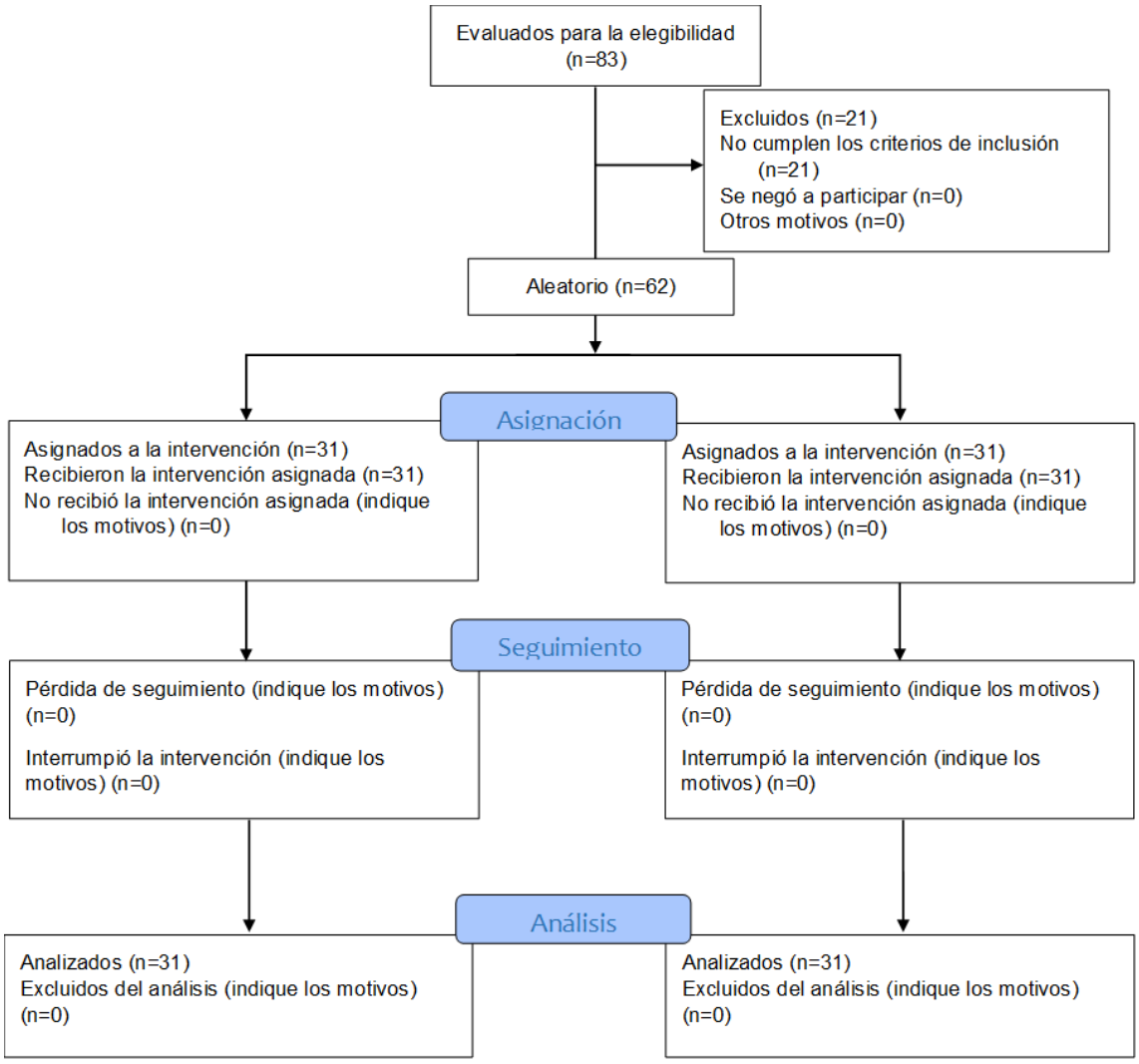
variables continuas y con la prueba exacta de Fisher para las variables categóricas. El efecto del tratamiento y su precisión se estimaron mediante intervalos de confianza (IC) del 95%. Se calcularon la reducción o el aumento del riesgo absoluto (ARR o ARI), el riesgo relativo (RR) y el número necesario para tratar o dañar (NNT o NNH) para el fracaso del implante, la infección postoperatoria, los acontecimientos adversos y las complicaciones (infecciones o fracaso del implante). Se analizaron las hipótesis de igualdad de riesgo de fracasos de implantes o infecciones postoperatorias entre los grupos experimental y placebo.

RESULTADOS

Flujo de participantes

Un diagrama de flujo muestra el número de participantes que fueron asignados al azar, recibieron el tratamiento previsto y fueron analizados para cada grupo, así como las pérdidas y exclusiones después de la aleatorización (Figura 1). Seis pacientes fueron incluidos dos veces en el ensayo después de la aleatorización y tras un periodo de al menos 2 meses entre las intervenciones. Cinco participantes recibieron placebo dos veces y el sexto recibió primero placebo y en la segunda intervención clindamicina. Ninguno de estos seis participantes sufrió una infección postoperatoria, un fallo del implante o un acontecimiento adverso.

Figura 1. Diagrama de flujo del proceso de reclutamiento



Reclutamiento

El reclutamiento comenzó en octubre de 2019 y concluyó en junio de 2021 y cada participante fue seguido hasta el día 56 después de la cirugía. El ensayo se detuvo temporalmente debido a la pandemia causada por el Covid-19 y terminó cuando todos los participantes incluidos fueron controlados en el día 56 postoperatorio (agosto de 2021).

Datos de referencia

Las características demográficas y clínicas basales de cada grupo se muestran en la Tabla 1. También se muestra la existencia o no de asociación significativa entre las variables y los grupos de tratamiento. No hubo diferencias entre el grupo de clindamicina y el de placebo, por lo que ambos grupos pueden considerarse similares y comparables en relación con la distribución de estas variables.

Tabla 1. Características de los participantes

Variable	Grupo de la clindamicina (n=31)	Grupo placebo (n=31)	En general (n=62)	Valor p
Género				0.111
Hombre	14 (45.2%)	8 (25.8%)	22 (35.5%)	
Mujer	17 (54.8%)	23 (74.2%)	40 (64.5%)	
Edad	49.7 (9.4)	47.5 (10.7)	48.6 (10.1)	0.387
Fumadores				0.755
Sí	7 (22.6%)	6 (19.4%)	13 (20.9%)	
No	24 (77.4%)	25 (80.6%)	49 (79.1%)	
Cigarrillos al día				0.677
0	24 (77.4%)	25 (80.6%)	49 (79.1%)	
<10	3 (9.6%)	4 (12.9%)	7 (11.3%)	
10 - 20	2 (6.5%)	2 (6.5%)	4 (6.4%)	
>20	2 (6.5%)	0 (0%)	2 (3.2%)	
Anticonceptivos				0.177
Sí	1 (3.3%)	4 (12.9%)	5 (8.1%)	
No	30 (99.7%)	27 (87.1%)	57 (91.9%)	
Ubicación del implante				0.526
Premolar superior	4 (12.9%)	6 (19.3%)	10 (16.1%)	
Molar superior	6 (19.3%)	6 (19.3%)	12 (19.4%)	
Premolar inferior	0	2 (6.5%)	2 (3.2%)	
Molar inferior	21 (67.8%)	17 (54.9%)	38 (61.3%)	
Tipo de implante				0.793
Nivel óseo	11 (35.5%)	12 (38.7%)	23 (37.1%)	
Nivel de tejido	20 (64.5%)	19 (61.3%)	39 (62.9%)	
Longitud del implante				
8 mm	2 (6.4%)	4 (12.9%)	6 (9.6%)	0.336
10 mm	29 (93.6%)	27 (87.1%)	56 (90.4%)	
Duración de la cirugía	14.5 (5.1)	15.3 (6.1)	14.9 (5.6)	0.339

Para las variables continuas: n (%), mientras que los valores p se obtuvieron mediante la prueba t de Student.Para las variables categóricas: media (SD), mientras que los valores p se obtuvieron mediante la prueba exacta de Fisher.

Análisis

Se incluyeron finalmente en el análisis 31 participantes en el grupo tratado con clindamicina y otros 31 participantes en el grupo placebo. El análisis fue en todos los casos por grupos asignados originalmente.

Resultados y estimación

Dos implantes fracasaron, ambos pacientes habían sido tratados con clindamicina (RR: no estimable, ARI=0,06; IC: -0,03-0,16, NNH=15,5; IC: 6-∞). El ARI señaló que el 6% de los pacientes experimentaría un fracaso del implante bajo el tratamiento con clindamicina que no tendrían si hubieran sido tratados con placebo. El NNH indicó que por cada 15 pacientes tratados con clindamicina se produciría un fracaso del implante que no se habría producido bajo tratamiento con placebo. No obstante, no se encontraron diferencias significativas entre los grupos (p=0,246).

Tres pacientes sufrieron infecciones postoperatorias y a dos de ellos se les administró el tratamiento antibiótico de rescate, mientras que el otro paciente no recibió el antibiótico de rescate porque el implante falló y fue retirado. Los dos pacientes que recibieron el antibiótico de rescate pertenecían al grupo de placebo, mientras que el otro paciente, el que sufrió el fracaso del implante pertenecía al grupo de clindamicina (RR: 0,5; IC: 0,05-5,23, ARR=0,03; IC: -0,07-0,13, NNT=31; IC: 7,2-∞). La RRA sugirió que el 3,2% de los pacientes no experimentarían infecciones postoperatorias bajo el tratamiento con clindamicina que sí tendrían con placebo. El NNT expresaba que sería necesario tratar a 31 pacientes con clindamicina para evitar que un paciente sufriera una infección postoperatoria. Sin embargo, no hubo diferencias significativas entre ambos grupos (*p*=0,554).

Considerando las complicaciones globales como la aparición de infecciones postoperatorias o fallos del implante oral por participante, hubo dos participantes en cada grupo de tratamiento que sufrieron complicaciones (RR=1; IC: 0,15-6,66, RRA=0; IC: -0,12-0,12, NNT: No estimable, *p*=0,999).

Análisis auxiliares

No hubo relaciones significativas entre ninguna variable registrada y el fracaso del implante o las reacciones adversas (Tabla 2). No se encontraron asociaciones significativas entre ninguna variable y la infección postoperatoria, excepto para el tipo de implante (*p*=0,047) y la ubicación del implante (*p*=0,048). La variable ubicación del implante no fue significativa para la infección postoperatoria (*p*=0,055). Tampoco hubo diferencias significativas (p>0,05) entre los grupos de tratamiento y las siguientes variables: supuración, fístula, absceso, osteomielitis, fiebre superior a 38 °C, dolor postoperatorio, hemorragia, inflamación localizada, eritema extraoral, eritema intraoral, radiolucencia periimplante en el día 56 y valor ISQ inferior a 60 en el día 56 (Tabla 3). La figura 2 muestra las frecuencias de la EVA registradas para cada variable en los días 1, 7, 14, 28 y 56 después de la cirugía.

Tabla 2. Variables respuesta.

Variable	Fracaso del implante			Infecciones postoperatorias			Reacciones adversas		
	Proporción de fallos	RR (IC 95%)	Valor p	Proporción de infección	RR (IC 95%)	Valor p	Proporción de reacciones adversas	RR (IC 95%)	Valor p
Grupo de tratamiento									
Clindamicina	2/31	NS	0.246	1/31	0.5 (0.05-5.23)	0.5	1/31	NS	0.5
Placebo	0/31			2/31			0/31		
Género									
Hombre	1/22	1	0.588	0/22	NS	0.261	1/22	NS	0.355
Mujer	1/40			3/40			0/40		
Tipo de implante									
Nivel óseo	2/23	NS	0.134	3/23	NS	0.047	0/23	NS	0.629
Nivel de tejido	0/39			0/39			1/39		
Longitud del implante									
8 mm	0/6	NS	0.814	1/6	4.6 (0.5-44.1)	0.267	0/6	NS	0.903
10 mm	2/56			2/56			1/56		
Ubicación del implante									
Maxilares	2/22	NS	0.048	3/22	NS	0.055	0/22	NS	0.999
Mandíbula	0/40			0/40			1/40		
Fumador									
Sí	1/13	1	0.378	0/13	NS	0.487	0/13	NS	0.790
No	1/49			4/49			1/49		
Anticonceptivos									
Sí	0/5	NS	0.844	0/5	NS	0.774	0/5	NS	0.919
No	2/57			3/57			1/57		

Los valores p se obtuvieron mediante la prueba exacta de Fisher.
IC: intervalo de confianza: NS: no estimable.

Figura 2. Gráficos de barras de las variables evaluadas con la EV

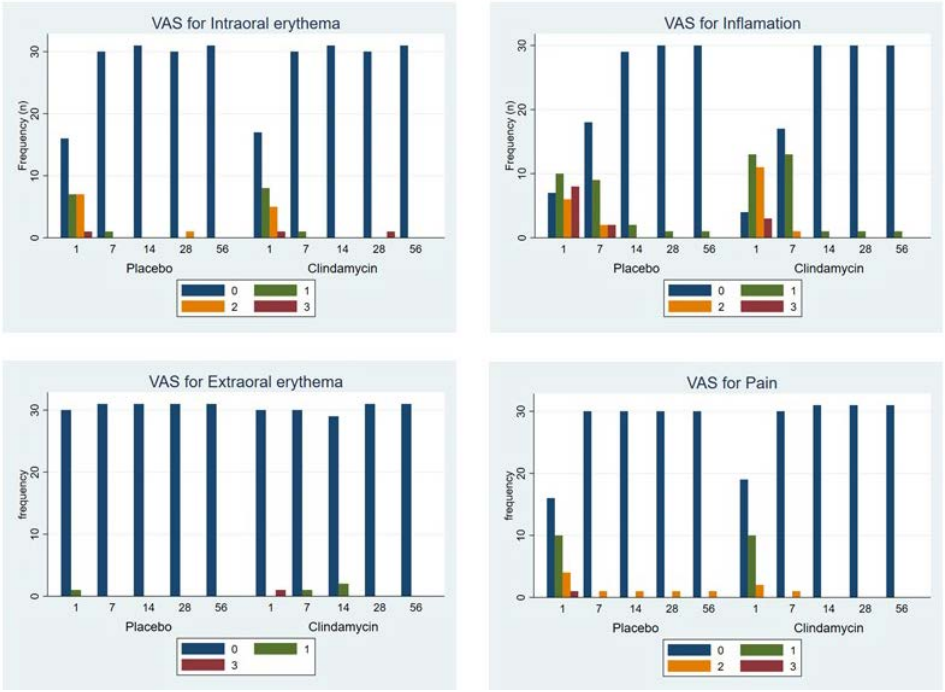


Tabla 3. Variables postoperatorias

Seguimiento	Grupo de tratamiento	Supuración	Fístula	Absceso	Osteomielitis	Fiebre >38 °C	Dolor postoperatorio	Inflamación localizada	Sangrado	Eritema extraoral	Eritema intraoral	Radiolucencia periimplantaria	Valor ISQ <60
Día 1	Clindamicina grupo	0/31	0/31	0/31	0/31	0/31	0.451	1.419	0	0.096	0.677	-	-
	Placebo grupo	0/31	0/31	0/31	0/31	0/31	0.677	1.483	0.096	0.032	0.774	-	-
	valor *p*	-	-	-	-	-	0.2315	0.7992	0.179	0.531	0.6723	-	-
Día 7	Clindamicina grupo	0/31	0/31	0/31	0/31	0/31	0.064	0.483	0	0.032	0.032	-	-
	Placebo grupo	0/31	0/31	0/31	0/31	0/31	0.064	0.612	0	0	0.032	-	-
	valor *p*	-	-	-	-	-	0.9999	0.4971	-	-	0.9999	-	-
Día 14	Clindamicina grupo	0/31	0/31	0/31	0/31	0/31	0	0.032	0	0.064	0	-	-
	Placebo grupo	0/31	0/31	0/31	0/31	0/31	0.064	0.064	0.032	0	0	-	-
	valor *p*	-	-	-	-	-	0.3213	0.5615	0.3213	0.1607	-	-	-
Día 28	Clindamicina grupo	0/31	1/31	1/31	0/31	0/31	0	0.032	0.258	0	0.096	-	-
	Placebo grupo	1/31	1/31	0/31	0/31	0/31	0.064	0.032	0	0	0.064	-	-
	valor *p*	0.5	0.754	0.5	-	-	0.3213	0.9999	0.2063	-	0.7826	-	-
Día 56	Clindamicina grupo	0/31	0/31	0/31	0/31	0/31	0	0.032	0	0	0	1/31	2/31
	Placebo grupo	0/31	0/31	0/31	0/31	0/31	0.064	0.032	0	0	0	1/31	0/31
	valor *p*	-	-	-	-	-	0.3213	0.9999	-	-	-	0.9999	0.151

Para las variables continuas: se indica la tasa, mientras que los valores p se obtuvieron mediante la prueba t de Student.

Para las variables categóricas: se indica la media, mientras que los valores p se obtuvieron mediante la prueba exacta de Fisher.

Acontecimientos adversos

Sólo un paciente tratado con clindamicina sufrió acontecimientos adversos (trastornos gastrointestinales y diarrea), sin que hubiera diferencias significativas entre los grupos (RR: No estimable, ARI=0,03; IC:-0,05-0,11, NNH=31; IC: 8,5-∞, *p*=0,5).

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3.3.4. Hábitos de prescripción antibiótica en la cirugía de implantes orales. Encuestas transversales en España, Países Bajos e Italia y meta-análisis de encuestas transversales

Hábitos de prescripción antibiótica en España

RESUMEN

Objetivos: El uso de antibióticos para prevenir los fracasos de los implantes dentales y las infecciones postoperatorias sigue siendo un tema controvertido. Los objetivos de este estudio fueron evaluar los patrones actuales de prescripción de antibióticos y la frecuencia de prescripción de antibióticos de los dentistas de Vizcaya (España) en relación con la cirugía rutinaria de implantes dentales en pacientes sanos y determinar si se ha alcanzado algún consenso por parte de dichos profesionales y se siguen las últimas evidencias publicadas.

Métodos: Estudio observacional transversal: encuesta electrónica. Este estudio se realizó de acuerdo con las directrices de STROBE. Este cuestionario anónimo contenía preguntas abiertas y cerradas. Se envió un correo electrónico el 26 de octubre de 2017 a todos los colegiados del Colegio de Odontólogos de Bizkaia (n=989). Los datos recogidos se analizaron con el programa STATA® 14 y se utilizaron intervalos de confianza (IC) del 95% para evaluar la frecuencia de prescripción de cada régimen antibiótico.

Resultados: La encuesta fue respondida por un total de 233 participantes (tasa de respuesta=23,56%). En total, 210 participantes terminaron la encuesta por completo y 23 la respondieron parcialmente. Respondieron al cuestionario 122 mujeres (58,1%) y 88 hombres (41,9%). De los participantes, el 88% (n=207) siempre prescribió antibióticos profilácticos de forma rutinaria junto con la cirugía de implantes dentales (IC 95%: 84,79-92,88%). Aproximadamente el 9% (n=22) prescribía antibióticos a veces (IC 95%: 5,68-13,19%), y sólo 4 dentistas (1,72%) no prescribían nunca antibióticos (IC 95%: 0,04-3,38%). En general, 179 de los 233 encuestados prescribieron antibióticos tanto antes como después de la operación (78,85%, IC del 95%: 72,96-83,97%), 13 prescribieron antibióticos sólo antes de la operación (5,73%, IC del 95%: 3,08-9,59%) y 35 prescribieron antibióticos exclusivamente después de la cirugía rutinaria de implantes dentales (15,42%, IC del 95%: 10,98-20,78%).

Conclusiones: La mayoría de los dentistas que trabajan en Vizcaya prescriben habitualmente antibióticos profilácticos junto con la cirugía de implantes dentales entre los pacientes sanos. Se prescribe una gran variedad de regímenes profilácticos y no se sigue la evidencia publicada más recientemente.

MÉTODOS

Este estudio observacional transversal se basó en una encuesta electrónica aprobada por el instituto de investigación BioCruces (Barakaldo, Vizcaya). Este estudio se comunicó de acuerdo con las directrices del Strengthening the Reporting of Observational studies in Epidemiology (STROBE) [1].

Diseño del estudio

Se elaboró un cuestionario validado para recoger información sobre las pautas de prescripción de antibióticos preventivos entre los dentistas en relación con la cirugía de implantes dentales. Se utilizó como base el cuestionario seguido por Deeb et al. (2015), con el permiso explícito de los autores [2]. El cuestionario ha demostrado su validez, ya que los diferentes ítems de la prueba se encontraron adecuados para medir los objetivos previstos. Este cuestionario anónimo comprendía datos en relación con lo siguiente: datos demográficos, cualificación y experiencia laboral, antibiótico más común prescrito, duración y dosis. El cuestionario contenía preguntas abiertas y cerradas. (Tabla 1)

Entorno

Vizcaya es una provincia de España situada en el País Vasco. Su población era de aproximadamente 1.148.302 habitantes en 2017 [3]. El 26 de octubre de 2017 se envió un correo electrónico a los dentistas que incluía un enlace al cuestionario web desarrollado en www.encuestafacil.com. Este correo electrónico también contenía instrucciones para responder al cuestionario si los dentistas realizaban cirugías de implantes dentales y un mensaje que describía brevemente los objetivos del estudio y el uso previsto de los datos recogidos para fines de investigación y epidemiológicos. Se hizo hincapié en que los datos eran anónimos. El 8 de noviembre de 2017 se envió un recordatorio a los participantes que no habían respondido en el plazo establecido. El cuestionario en línea se cerró al público el 2 de enero de 2018. La recogida de datos se realizó de forma automática a través del servidor www.encuestafacil.com [4].

Participantes

El cuestionario se envió a todos los colegiados del Colegio de Odontólogos de Bizkaia que no hubieran solicitado expresamente no recibir correos electrónicos. El número total de cuestionarios enviados fue de 989. Al dirigirse a toda la población de dentistas colegiados de Bizkaia, los autores entendieron que se da la misma oportunidad (probabilidad) de participar y responder al cuestionario a todos los colegiados. La participación supuso la concesión del consentimiento del participante para registrar los datos del cuestionario.

Variables

El cuestionario se muestra en la Tabla 1 con todas las variables registradas.

Fuentes de datos / medición

Cada encuestado sólo podía responder una vez exclusivamente a una encuesta electrónica, y las opciones de cada pregunta se muestran en la Tabla 1.

Sesgo

No pudo existir ningún sesgo de selección, ya que la encuesta electrónica se envió a todos los dentistas colegiados en Vizcaya, y es obligatorio estar colegiado en uno o varios colegios de dentistas para poder trabajar como dentista en España. Asimismo, los autores emplearon una encuesta electrónica realizada previamente en Estados Unidos para evitar el sesgo de información.

Tamaño del estudio

El tamaño final de la muestra estuvo compuesto por los profesionales que decidieron responder parcial o totalmente la encuesta (n=233).

Métodos estadísticos

Los datos recogidos se analizaron con el programa STATA® 14; se utilizaron intervalos de confianza (IC) del 95% para evaluar la frecuencia de prescripción de cada régimen antibiótico.

RESULTADOS

Participantes

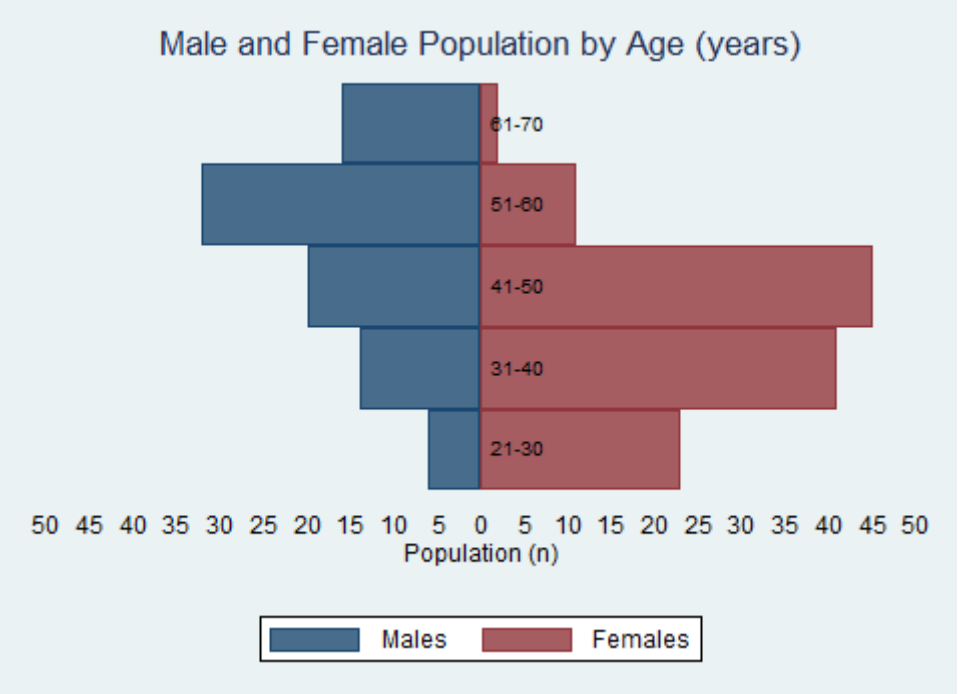
Un total de 233 participantes respondieron a la encuesta; por lo tanto, la tasa de respuesta fue del 23,56%. En total, 210 participantes terminaron la encuesta por completo, y 23 encuestas fueron contestadas sólo parcialmente. Los análisis descriptivos y estadísticos incluyeron todas las encuestas con respuestas (n=233) para realizar un análisis lo más completo posible.

Datos descriptivos

Respondieron al cuestionario 122 mujeres (58,1%) y 88 hombres (41,9%), y tenían principalmente entre 51 y 60 años (30,95%). En la Figura 1 se muestra una pirámide de población.

En general, 173 encuestados habían estudiado en la Universidad del País Vasco (82,78%), situada en Vizcaya, pero también había odontólogos que habían estudiado en otras universidades de España o de otros países (Tabla 1). Aproximadamente el 51% de los encuestados trabajaba en el área rural de la provincia, y el 43% en la capital de la provincia, Bilbao. El resto de los encuestados trabajaba en otra provincia de España (6%).

Figura1. Pirámide poblacional



Datos de los resultados

La tabla 1 muestra el porcentaje de respuesta y el IC del 95% para cada ítem. Los regímenes preoperatorios y postoperatorios seguidos se muestran en la Tabla 2 y la Tabla 3.

Tabla 1. Variables respuesta de la encuesta.

Pregunta	n	%	IC DEL 95%
INICIO DE LA ENCUESTA			
1. ¿Prescribe antibióticos antes, después o durante la colocación de un implante dental?			
Sí, siempre	207	88.84	84.79-92.88
Sí, a veces	22	9.44	5.68-13.19
No, nunca	4	1.72	0.04-3.38
Total	233	100	-
2. Su respuesta fue "Sí, a veces". Describa las situaciones en las que prescribe antibióticos.			
3.			
Injertos óseos	9	40.9	*
Paciente con antecedentes de enfermedad periodontal	7	31.81	
El paciente fuma	3	13.63	
Infección preoperatoria en el lugar del implante	14	63.63	
Perforación de los senos paranasales	13	59.09	
Colocación simultánea de más de un implante dental	7	31.81	
Cardiopatía que requiere profilaxis antibiótica	5	22.72	
Otra situación	5	22.72	
Total	*		

PATRÓN DE PRESCRIPCIÓN TEMPORAL DE ANTIBIÓTICOS

Continúe con las siguientes preguntas, asumiendo que los pacientes están sanos y no tienen alergias a los antibióticos cuando seleccione sus respuestas. Elija la respuesta más adecuada según la realidad.

4. ¿Cuándo se prescriben los antibióticos?			
Exclusivamente antes de la cirugía (preoperatorio)	13	5.73	3.08-9.59
Exclusivamente después de la cirugía (postoperatorio)	35	15.42	10.98-20.78
Antes y después de la cirugía (preoperatorio y postoperatorio)	179	78.85	72.96-83.97
Total	227	100	-

HÁBITOS DE PRESCRIPCIÓN PREOPERATORIA

5. ¿Cuándo comienza la profilaxis antibiótica antes de la inserción del implante?			
1 día antes	87	47.28	39.89-54.76
1 hora antes	47	25.54	19.41-32.48
2 días antes	43	23.37	17.45-30.15
Inmediatamente antes	7	3.80	1.54-7.68
Total	184	100	-
6. Ha seleccionado "1 o 2 días antes", seleccione entre los siguientes un solo tipo de antibiótico:			
Amoxicilina	87	66.41	57.64-74.42
Amoxicilina/ácido clavulánico	37	28.24	20.72-36.77
Otros	6	4.58	1.69-9.70
Eritromicina	1	0.76	0.01-4.17
Clindamicina	0	0	-
Penicilina V	0	0	-
Cefalexina	0	0	-
Total	131	100	-
7. Seleccione entre lo siguiente, la dosis, la posología y la vía de administración ("1 o 2 días antes"):			
7.1. Dosis (mg)			
500	53	42.06	33.32-51.18
875/125	25	19.84	13.27-27.88
800	20	15.87	9.97-23.44
1000	19	15.08	9.32-22.54
500/125	9	7.14	3.31-13.12
150	0	0	-
250	0	0	-
300	0	0	-
400	0	0	-
Total	126	100	-
7.2. Dosificación			
3 veces al día	113	90.4	83.83-94.94
2 veces al día	9	7.2	3.34-13.22
1 vez al día	2	1.6	0.19-5.66
4 veces al día	1	0.8	0.02-4.37
Total	125	100	-
7.3. Vía de administración			
Oral	125	100	97.09-1
Intramuscular	0	0	-
Intravenoso	0	0	-
8. Ha seleccionado "1 hora antes" o "Inmediatamente antes", seleccione entre los siguientes un solo tipo de antibiótico:			
Amoxicilina	46	83.64	71.19-92.23
Amoxicilina/ácido clavulánico	8	14.55	6.49-26.66
Cefazolina	1	1.82	0.04-9.71
Clindamicina	0	0	-
Penicilina V	0	0	-
Eritromicina	0	0	-
Ampicilina	0	0	-
Cefalexina	0	0	-
Otros	0	0	-

Total	55	100	-
9. Seleccione entre lo siguiente, la dosis, la posología y la vía de administración ("1 hora o Inmediatamente antes"):			
9.1. Dosis (mg)			
2000	22	40	27.02-54.09
1000	15	27.27	16.13-40.96
500	7	12.73	5.27-24.48
875/125	5	9.09	3.01-19.95
800	3	5.45	1.13-1.51
1600	1	1.82	0.04-9.71
500/125	1	1.82	0.04-9.71
600	1	1.82	0.04-9.71
Total	55	100	-
9.2. Dosificación			
1 dosis única	55	100	93.51-1
9.3. Vía de administración			
Oral	55	100	93.51-1
Intramuscular	0	0	-
Intravenoso	0	0	-

HÁBITOS DE PRESCRIPCIÓN POSTOPERATORIA

10. Seleccione de entre los siguientes un único tipo de antibiótico prescrito tras la inserción de un implante dental:			
Amoxicilina	138	67.98	61.08-74.33
Amoxicilina/ácido clavulánico	59	29.06	22.91-35.83
Otros	5	2.46	0.8-5.65
Eritromicina	1	0.49	0.01-2.71
Clindamicina	0	0	-
Penicilina V	0	0	-
Cefalexina	0	0	-
Total	203	100	-
11. Seleccione de entre los siguientes, la dosis, la posología, la vía de administración y la duración del tratamiento:			
11.1. Dosis			
500	76	38.38	31.57-45.54
800	36	18.18	13.07-24.27
875/125	36	18.18	13.07-24.27
1000	33	16.67	11.75-22.60
500/125	17	8.59	5.08-13.39
150	0	0	-
250	0	0	-
300	0	0	-
400	0	0	-
Total	198	100	-
11.2. Dosificación			
1 vez al día	2	1.01	0.12-3.60
2 veces al día	19	9.6	5.87-14.57
3 veces al día	177	89.39	84.24-93.31
4 veces al día	0	0	-
Total	198	100	-
11.3. Vía de administración			
Oral	198	100	98.15-1
Intramuscular	0	0	-
Intravenoso	0	0	-
11.4. Duración (días)			
7	91	45.96	38.87-53.16
8	38	19.19	13.95-25.37
5	25	12.63	8.34-18.07
6	17	8.59	5.08-13.39
10	13	6.57	3.54-10.96
3	6	3.03	1.12-6.47
4	4	2.02	0.05-5.09

2	2	1.01	0.12-3.60
1	1	0.51	0.01-2.78
9	1	0.51	0.01-2.78
11	0	0	-
12	0	0	-
13	0	0	-
14	0	0	-
15	0	0	-
Total	198	100	-
12. Género			
Mujer	122	58.1	51.10-64.84
Hombre	88	41.9	35.15-48.89
Total	210	100	-
13. Edad (años)			
21 - 30	29	13.81	9.44-19.22
31 - 40	55	26.19	20.38-32.68
41 - 50	65	30.95	24.77-37.68
51 - 60	43	20.48	15.23-26.57
61 - 70	18	8.57	5.15-13.20
71 años o más	0	0	-
Total	210	100	-
14. Por favor, escriba el nombre de la universidad donde estudió.			
Universidad del País Vasco (UPV/EHU)	173	82.78	76.95-87.63
Universidad Alfonso X el Sabio (UAX)	10	4.78	2.31-8.62
Universidad Complutense de Madrid	5	2.39	0.78-5.49
Universidad Europea de Madrid	3	1.44	0.29-4.13
Universidad Internacional de Cataluña (UIC) Barcelona	2	0.96	0.11-3.41
Universidad Rey juan Carlos (URJC)	2	0.96	0.11-3.41
Universidad de Granada	2	0.96	0.11-3.41
Universidad de Navarra	2	0.96	0.11-3.41
Universidad de Buenos Aires (UBA)	2	0.96	0.11-3.41
Universidad a Distancia de Madrid (UDIMA)	1	0.48	0.01-2.63
Universidad de Oviedo	1	0.48	0.01-2.63
Universidad de Valladolid (UVA)	1	0.48	0.01-2.63
Universidad de Valencia (UV)	1	0.48	0.01-2.63
"Argentina"	1	0.48	0.01-2.63
Universidad Iberoamericana (UNIBE) República Dominicana	1	0.48	0.01-2.63
Universidad Nacional de La Plata (UNLP)	1	0.48	0.01-2.63
Universidad Superior de San Andrés (UMSA)	1	0.48	0.01-2.63
Total	209	100	-

*n: frecuencia, CI: Intervalo de confianza, *: los participantes pudieron elegir mas de una opción (multirespuesta).*

Tabla 2. Regímenes preoperatorios.

TIPO DE ANTIBIÓTICO	DOSIS (mg)	N
Inmediatamente antes de la cirugía		
Amoxicilina	500	3
	2000	2
	1000	1
	800	1
*	*	8
1 hora antes de la cirugía		
Amoxicilina	2000	19
	1000	11
	500	4
	800	2
	1600	1
	600	1
Amoxicilina / ácido clavulánico	1000	2
	875/125	4
	2000	1
	500/125	1
Cefazolina	875/125	1
1 día antes de la cirugía		
Amoxicilina	500 TID	28
	800 TID	12
	1000 TID	9
	875/125 TID	3
	1000 BID	3
	500 BID	1
	800 QID	1
Amoxicilina / ácido clavulánico	875/125 TID	14
	500/125 TID	6
	500 TID	4
	875/125 BID	2
Otros	500	1
	*	3
2 días antes de la cirugía		
Amoxicilina	500 TID	17
	800 TID	6
	1000 BID	3
	1000 TID	3
Amoxicilina / ácido clavulánico	500/125 TID	3
	875/125 TID	6
	500 TID	1
	800 TID	1
Eritromicina	500 QD	1
Otros	*	2

*n: frequencia, *: los praticipantes no contestaron esta pregunta, QD: una vez al dia, BID: dos veces al día, TID: 3 veces al día, QID: 4 veces al día.*

Table 3. Regímenes postoperatorios.

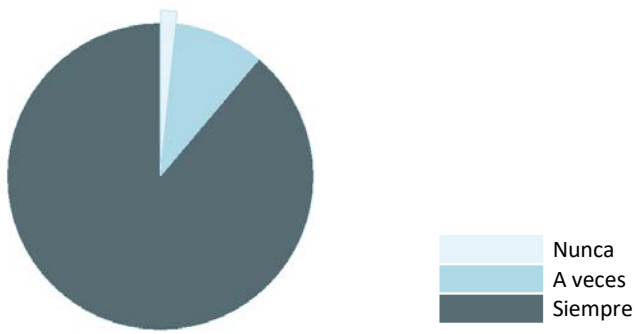
TIPO ATIBIOTICO	DURACIÓN (días)	DOSIS									
		500 mg		500/125 mg	800 mg		875/125 mg		1000 mg		
		QD	TID	TID	BID	TID	BID	TID	QD	BID	TID
Amoxicilina	2	-	1	-	-	-	-	-	-	1	-
	3	-	1	-	-	1	-	-	1	1	-
	4	-	1	-	-	1	-	-	-	1	-
	5	-	9	-	-	3	-	-	-	1	4
	6	-	7	-	-	3	-	-	-	2	2
	7	-	31	-	1	16	-	1	-	8	7
	8	-	13	1	-	7	-	1	-	1	2
	9	-	1	-	-	-	-	-	-	-	-
	10	-	4	-	-	3	-	-	-	-	1
Amoxicilina / ácido clavulánico	1	-	-	-	-	-	-	-	-	1	-
	2	-	-	-	-	-	-	-	-	-	-
	3	-	-	-	-	-	-	1	-	-	-
	4	-	-	-	-	-	-	1	-	-	-
	5	-	1	2	-	-	-	5	-	-	-
	6	-	-	1	-	-	1	1	-	-	-
	7	-	6	4	-	-	1	16	-	-	-
	8	-	1	5	-	-	-	7	-	-	-
	10	-	1	2	-	-	-	2	-	-	-
Eritromicina	3	1	-	-	-	-	-	-	-	-	-
Azitromicina	1	-	-	-	-	-	-	-	2	-	-
	3	1	-	-	-	-	-	-	-	-	-

n: frequencia de los praticipantes que contestaron esta pregunta, QD: una vez al dia, BID: dos veces al día, TID: 3 veces al día, QID: 4 veces al día; mg: miligramos.

Resultados principales

Entre todos los participantes, el 88% (n=207) siempre prescribió antibióticos profilácticos de forma rutinaria junto con una cirugía de implantes dentales (IC del 95%: 84,79-92,88%). Aproximadamente el 9% (n=22) prescribía antibióticos a veces (IC 95%: 5,68-13,19%), y sólo 4 dentistas (1,72%) no prescribían antibióticos en absoluto (IC 95%: 0,04-3,38%). Estos datos se muestran en la Figura 2.

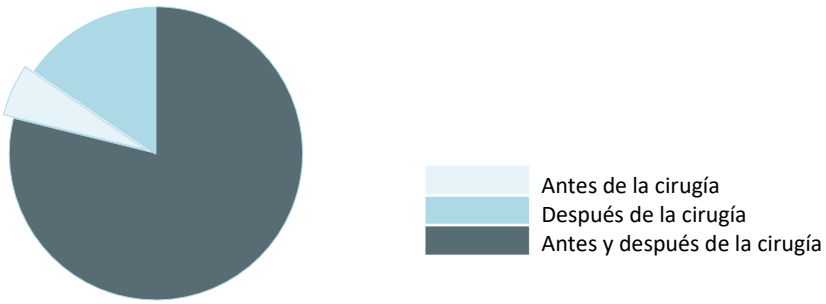
Figura 2. Frecuencia de prescripción de antibióticos profilácticos



A los 22 dentistas que prescriben antibióticos sólo "a veces" se les pidió que determinaran las situaciones en las que los prescriben. Las situaciones más elegidas fueron una infección preoperatoria del lugar del implante (n=14) y una perforación de los senos paranasales (n=13).

En general, 179 de los 233 encuestados prescribieron antibióticos tanto antes como después de la operación (78,85%, IC 95%: 72,96-83,97%), 13 prescribieron antibióticos sólo antes de la operación (5,73%, IC 95%: 3,08-9,59%) y 35 prescribieron antibióticos exclusivamente después de una operación rutinaria de implantes dentales (15,42%, IC 95%: 10,98-20,78%). Estos datos se muestran en la Figura 3.

Figura 3. Regímenes prescritos antes, durante o después de la cirugía de implantes



La única vía de administración descrita por todos los encuestados fue la oral para todos los tipos de antibióticos y regímenes.

De los 179 encuestados que indicaron que prescribían antibióticos preoperatorios y postoperatorios, el régimen preoperatorio más frecuente fue 500 mg de amoxicilina tres veces al día (TID) 1 día antes de la cirugía (n=25), y el régimen postoperatorio más frecuente fue 500 mg de amoxicilina TID por vía oral durante 7 días después de la cirugía (n=24). Este régimen pre y postoperatorio fue seguido sistemáticamente por un total de 10 dentistas.

De los 13 encuestados que prescribieron exclusivamente antibióticos preoperatorios, la pauta antibiótica más común fue 2 g de amoxicilina una vez por vía oral 1 hora antes de la cirugía (n=3) y 500 mg de amoxicilina TID 1 día antes de la cirugía (n=3).

De los 35 dentistas que prescribieron exclusivamente antibióticos postoperatorios, la pauta más frecuente fue 500 mg de amoxicilina TID durante 7 días después de la cirugía (n=7).

Después de la amoxicilina, la amoxicilina/ácido clavulánico fue el tipo de antibiótico más prescrito de forma rutinaria. La prescripción más frecuente con amoxicilina/ácido clavulánico fue pre y postoperatoria (n=49). Entre los encuestados que siguieron esta pauta de prescripción pre y postoperatoria, la pauta preoperatoria más frecuente fue

de 875/125 mg TID 1 día antes de la cirugía (n=14), y la pauta postoperatoria más frecuente fue de 875/125 mg TID por vía oral durante 7 días después de la cirugía (n=16).

Hábitos de prescripción antibiótica en Paises Bajos

RESUMEN

Objetivos: No parece haber consenso sobre la prescripción de antibióticos profilácticos en la cirugía de implantes orales. Las directrices de la Asociación Holandesa de Implantología Oral (NVOI) no incluyen una política clara sobre la prescripción de antibióticos profilácticos para la cirugía de implantes orales en pacientes sanos. El objetivo del estudio era determinar si los dentistas generales, los cirujanos maxilofaciales y los implantólogos orales prescriben habitualmente profilaxis antibiótica en los Países Bajos junto con la cirugía de implantes orales entre pacientes sanos y evaluar el tipo y la cantidad de antibiótico profiláctico prescrito.

Métodos: Este estudio observacional transversal se basa en una encuesta web. Se tradujo un cuestionario desarrollado en los Estados Unidos de América y se ajustó ligeramente para su uso en los Países Bajos. Contenía predominantemente preguntas cerradas relacionadas con la demografía, las cualificaciones, el tipo de antibiótico, la duración de la prescripción y la dosis. En febrero de 2018 se envió un correo electrónico que incluía una introducción al estudio y un enlace individual al cuestionario a una muestra de 600 odontólogos generales y a los 302 odontólogos especializados (implantólogos orales, periodoncistas y cirujanos maxilofaciales) reconocidos por el NVOI. En total, se enviaron 902 cuestionarios de forma anónima. Finalmente, se llegó a 874 participantes potenciales. Los datos recogidos se analizaron mediante estadísticas descriptivas.

Resultados: En total, 218 (24,9%) participantes respondieron al cuestionario, incluyendo 45 mujeres (20,8%) y 171 hombres (79,2%). En total, 151 (69,9%) se colocaron regularmente implantes orales. De ellos, 79 (52,7%) prescriben antibióticos sólo en situaciones puntuales, 66 (43,7%) regularmente y 5 (3,3%) no prescriben antibióticos en absoluto. En general, 83 participantes que prescriben antibióticos lo hacen tanto en el pre como en el postoperatorio (57,2%), 47 sólo en el preoperatorio (32,4%) y 12 exclusivamente en el postoperatorio (8,3%). Una dosis única de 2.000 mg de amoxicilina por vía oral una hora antes de la cirugía fue el régimen preoperatorio más prescrito. El régimen postoperatorio más frecuentemente prescrito fue 500 mg de amoxicilina tres veces al día durante cinco días después de la cirugía. De media, los participantes prescriben un total de 7.018 mg de antibióticos antes, durante o después de la cirugía de implantes orales.

Conclusiones: La profilaxis antibiótica junto con la cirugía de implantes orales se prescribe en los Países Bajos a gran escala, y con frecuencia no se siguen las recomendaciones basadas en las últimas pruebas publicadas.

MÉTODOS

Este estudio observacional transversal se basa en una encuesta web, y se informa de acuerdo con las directrices del Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) [1].

El cuestionario, desarrollado por Deeb et al. (2015) [2], se tradujo y se ajustó ligeramente para su uso en los Países Bajos con el fin de recopilar datos relativos a las tasas de prescripción de antibióticos preventivos entre los odontólogos generales, los cirujanos maxilofaciales, los periodoncistas y los implantólogos orales junto con la terapia de implantes orales. Se obtuvo la autorización explícita de Deeb y los coautores para utilizar su cuestionario. Un implantólogo oral experimentado, que participa en la formación de dentistas en los Países Bajos, evaluó la comprensión y el orden lógico del cuestionario traducido y ajustado. La formulación de las preguntas se consideró adecuada y válida para evaluar los objetivos previstos.

Entorno

Los Países Bajos son un estado miembro de la Unión Europea con, en 2018, una población de aproximadamente 17,1 millones [5]. En enero de 2018, en los Países Bajos trabajaban aproximadamente 8.800 dentistas, incluidos unos 320 implantólogos orales y 80 periodoncistas. Además, en ese momento, había unos 290 cirujanos maxilofaciales en ejercicio [6].

Participantes

En febrero de 2018, se envió un correo electrónico a una muestra representativa de 600 odontólogos generales, seleccionados aleatoriamente del registro oficial de odontólogos cualificados de la Real Asociación Odontológica Holandesa (KNMT), y a todos los 302 implantólogos orales, periodoncistas y cirujanos maxilofaciales reconocidos por el NVOI como proveedores de atención sanitaria oral que colocan implantes orales y cuyas direcciones de correo electrónico estaban disponibles públicamente.

El único criterio de elegibilidad que se tuvo en cuenta para invitar a posibles participantes al estudio fue la inclusión en las listas del NVOI y del KNMT. El KNMT mantiene un archivo actualizado de todos los dentistas con licencia en los Países Bajos, pero no sabe si los dentistas están activos en la odontología. Por este motivo, se determinó el grupo de todos los dentistas de 64 años o menos con domicilio conocido y/o dirección de trabajo en los Países Bajos, ya que se esperaba que este grupo trabajara en odontología. Se extrajo una muestra de 600 dentistas de este grupo, formado por unos 8.800 dentistas, con el procedimiento SPSS SAMPLE. Esto fue realizado por un instituto de investigación "tercero" encargado por el KNMT. Este instituto está especializado en la gestión y administración de encuestas web y ofrece apoyo en la recogida de datos. Las direcciones de correo electrónico de los miembros del NVOI están disponibles públicamente en el sitio web del NVOI.

Posteriormente, el instituto de investigación "tercero" envió la invitación por correo electrónico a todos los participantes potenciales y recogió los datos. Estos mensajes de correo electrónico contenían un enlace individual a un cuestionario basado en la web y una breve introducción a los objetivos del estudio. Se aseguraba a los participantes que los datos de la investigación se recogían de forma anónima, y se dejaba claro que, al responder al cuestionario, los participantes daban su consentimiento para el uso de los datos recogidos por la encuesta para los fines del estudio. Se hizo todo lo posible para proteger la privacidad y el anonimato de los participantes, ya que no se recogieron datos personales de los mismos (nombre, apellidos, dirección y número de teléfono). Además, los autores no almacenaron ni guardaron ninguna dirección de correo electrónico, por lo que no se pudo volver a contactar con los participantes. Por estas razones, este estudio específico no requirió una declaración ética por parte de un comité de revisión institucional (comité de ética) antes de comenzar el estudio. Se enviaron dos correos electrónicos de recordatorio a todos los posibles encuestados al cabo de dos y cuatro semanas; al cabo de seis semanas, se cerró la recogida de datos.

El instituto de investigación "Third Party" puso a disposición los datos recogidos de forma encriptada para que los autores no tuvieran acceso a ninguna información personal de los participantes, incluidas sus direcciones de correo electrónico.

No se pudo contactar con un total de 28 participantes potenciales debido a una dirección de correo electrónico incorrecta. Por lo tanto, la muestra final consistió en 874 participantes potenciales: 578 odontólogos generales y 296 implantólogos orales, periodoncistas y cirujanos maxilofaciales.

Variables

Se recopiló información sobre las cualificaciones y la experiencia laboral, los datos demográficos y el antibiótico preventivo más prescrito en caso de colocación de implantes orales, incluida la duración y la dosis. A partir de sus declaraciones sobre la dosis y el periodo de toma, se calculó el total de miligramos (mg) prescritos por profesional de la salud oral y cirugía de implantes orales.

Fuentes de datos y medición

Cada enlace que se encontraba en los mensajes de correo electrónico dirigía al usuario a un cuestionario, que sólo se podía responder una vez. El cuestionario contenía predominantemente preguntas cerradas. Los participantes podían añadir otras opciones de respuesta e información adicional.

Métodos estadísticos

Todos los datos se analizaron utilizando el paquete estadístico para ciencias sociales (SPSS) de International Business Machines Corporation (IBM) para Windows versión 24 (IBM Corporation, publicado en 2012, Armonk, Nueva York). Para empezar, mediante la estadística descriptiva, se recopiló una visión general de las características de los encuestados en términos de edad, sexo, tipo de profesional de la salud bucodental y zona geográfica. Después, el análisis descriptivo continuó sólo con los profesionales

sanitarios que habían indicado que colocaban implantes orales de forma habitual. Posteriormente, se evaluaron sus hábitos respecto a la prescripción de antibióticos antes, durante o después de la colocación de un implante oral. Se investigó si los hábitos de prescripción de antibióticos en la cirugía de implantes orales estaban relacionados con las características personales de los participantes y, en el caso de los que prescriben antibióticos, con los regímenes de prescripción utilizados (prueba de chi-cuadrado y ANOVA). En primer lugar, se investigó si la cantidad total de antibióticos prescritos variaba entre determinados grupos de participantes mediante ANOVA (prueba F) y finalmente, dado que los datos no se distribuían normalmente, se analizaron mediante la prueba de Kruskal-Wallis y la prueba U de Mann-Whitney.

RESULTADOS

Participantes

En la Tabla 1 se detallan los diferentes profesionales incluidos en el estudio. Dos participantes informaron de que no estaban trabajando actualmente, y fueron excluidos del grupo de estudio.

Tabla 1. Tipo de profesional[#1] en relación a su actividad implantologica actual.

	Colocar implantes orales		No colocar implantes orales		Total	
	n	*%*	*n*	*%*	*n*	*%*
Odontólogo generalista (GDP)	11	5.0	59	27.1	70	32.1
PIB Y OI	20	9.2			20	9.2
Implantólogo oral (OI)	67	30.7			67	30.7
OI y periodoncista (OI-PERIO)	9	4.1	1	0.5	10	4.7
Cirujano maxilofacial (MS)	44	20.2	1	0.5	45	20.6
Otro profesional de la salud bucodental [#2]			4	1.8	4	1.8
No trabajar como profesional de la salud bucodental			2	0.9	2	0.9
Total	151	69.3	67	30.7	218	100

[#1] múltiples situaciones posibles / [#2]dentista para ortodoncia (3x), prostodoncista maxilofacial

Datos descriptivos

En total, 171 hombres (79,2%) y 45 mujeres (20,8%) respondieron al cuestionario. La edad media de los participantes era de 48,6 años (DE = 11,1). El 24,1% tenía 39 años o menos, el 20,8% tenía entre 40 y 49 años y el 55,1% tenía 50 años o más.

La mayoría de los participantes (92,3%) se graduaron en una facultad de odontología de los Países Bajos: Ámsterdam (36,6%), Nimega (23,8%), Groningen (21,7%) y Utrecht (10,2%). Casi la mitad de los participantes (46,3%) estaban asentados en la parte occidental del país, con un 26,4% en el sur, un 17,6% en el este y un 9,7% en las regiones del norte.

Hábitos de colocación y prescripción de implantes orales

La tabla 1 muestra que el 69,2% de los participantes encuestados indicaron que colocaban implantes orales con regularidad. De estos 151 participantes que realizan actualmente cirugías de implantes orales, 66 (43,7%) declararon que prescriben regularmente antibióticos profilácticos, mientras que una minoría (3,3%, n = 5) informó de que nunca lo hacen. Además, 79 participantes (52,3%) indicaron que prescriben antibióticos sólo en determinadas situaciones. Estas situaciones se presentan en la Tabla 2.

Tabla 2. Situaciones en las que los participantes prescriben antibióticos[#1]

Situación	n	%
Injertos óseos	73	93.6
Perforación de los senos paranasales	33	42.2
Infección preoperatoria en el lugar del implante	29	37.2
Paciente médicamente comprometido [#2]	22	28.2
Pasado de la enfermedad periodontal	14	17.9
Hábito de fumar	13	16.7
Colocación simultánea de más de un implante dental	6	7.7
Paciente desdentado [#2]	5	6.4
Otra situación [#3]	7	9.0
Total [#4]	78	100

[#1] Múltiples situaciones posibles / [#2]Derivadas de la opción "Otra situación", según lo descrito por los participantes / [#3]Cirugía de elevación de seno (2x), complicaciones postoperatorias (2x), tratamiento bajo anestesia, ubicación específica de la colocación del implante dental, basada en la prueba microbiológica / [#4]1 participante no indicó la situación

No se encontró una relación estadísticamente significativa entre ninguna de las características de los participantes y sus hábitos de prescripción. (Tabla 3).

En la tabla 4 se recogen los horarios y regímenes de inicio de las prescripciones de antibióticos empleados por los participantes.

Tabla 3. Características personales de los participantes en relación a sus hábitos de prescripción antibiótica.

	Nunca	A veces	Siempre	En general
Mujer [#1]		13.9%	7.6%	10.7%
Edad media (años) [#2]	60.0	49.6	51.5	50.8
Tipo de especialización [#3]				
-Médico dental generalista	20.0%	5.1%	9.1%	7.3%
-Implantólogo oral y/o periodoncista	60.0%	62.0%	65.2%	63.3%
-Cirujano oral	20.0%	32.9%	25.8%	29.3%
Graduación en los Países Bajos [#4]	100%	94.9%	90.9%	93.3%
Lugar de asentamiento (parte del país) [#5]				
-Southern	60.0%	20.3%	21.2%	22.0%
-Western	40.0%	45.6%	54.5%	49.3%
-Este		17.7%	18.2%	17.3%
-Northern		16.5%	6.1%	11.3%
n [#6]	5	79	66	151

[#1] p=0,343 / [#2]p=0,071 / [#3]p=0,597 / [#4]p=0,520 / [#5]p=0,173 / 1 participante no indicó hábitos de prescripción

Tabla 4. Regímenes de prescripción antibiótica.

	n	%	n	%
Sólo el preoperatorio			47	32.4
-1 hora o inmediatamente	*43*	*29.6*		
-1 día antes	*2*	*1.4*		
-2 días antes	*2*	*1.4*		
Pre y post operatorio			83	57.2
-1 hora o inmediatamente	*60*	*41.4*		
-1 día antes	*18*	*12.4*		
-2 días antes	*5*	*3.4*		
Sólo el postoperatorio			12	8.3
Desconocido			3	2.1
Total	145	100	145	100

Antibióticos preoperatorios: tipo, dosis y posología

La mayoría de los participantes que prescriben antibióticos preoperatorios cuando se colocan implantes orales aconsejan a sus pacientes que comiencen una hora antes del tratamiento (75,2%) o inmediatamente antes del tratamiento (3,1%). Todos los demás afirmaron que aconsejan a sus pacientes empezar un día (16,3%) o dos días (5,4%) antes del tratamiento.

La mayoría de los participantes que prescriben antibióticos profilácticos una hora o inmediatamente antes de la colocación del implante prescriben 2.000 mg de amoxicilina por vía oral (70,3%). Además, el 9,9% indicó que prescribía 3.000 mg de amoxicilina, y el 9,9% indicó que prescribía 500 mg de amoxicilina, en ambos casos para tomar por vía oral.

Más de la mitad de los participantes (53,9%) que inician la profilaxis antibiótica uno o dos días antes de la intervención quirúrgica del implante prescriben 500 mg de amoxicilina por vía oral tres veces al día. Además, el 19,3% prescribe una combinación de 500/125 mg de amoxicilina/ácido clavulánico que se toma tres veces al día (Tabla 5).

Antibióticos postoperatorios: tipo, dosis y posología

De los participantes que optan por aconsejar a los pacientes que inicien una profilaxis antibiótica en el postoperatorio, el 75,1% prescriben 500 mg de amoxicilina para tomar por vía oral de una a cuatro veces al día durante un período que varía de uno a ocho días (tabla 6). Además, el 15,2% indicó que prescribía una combinación de 500/125 mg de amoxicilina/clavulánico que se tomaba tres veces al día durante un periodo de cinco o siete días.

Tabla 5. Regímenes preoperatorios

1 hora o inmediatamente antes				
Tipo de antibiótico	*Dosis(mg)*	*Administración*	*n*	*%*
Amoxicilina	2.000	oral	71	70.3
Amoxicilina	500	oral	10	9,9
Amoxicilina	3.000 [#1]	oral	10	9.9
Amoxicilina	1.000	oral	2	2.0
Amoxicilina	otros [#2]	oral	2	2.0
Amoxicilina	600	oral	1	1.0
Amoxicilina/ácido clavulánico	500 / 125	oral	3	3.0
Amoxicilina/ácido clavulánico	2.000	oral	1	1.0
Clindamicina	600	oral	1	1.0
Total [#3]			101	100.0
1 o 2 días antes				
Tipo de antibiótico	*Dosis(mg)*	*Dosificación*	*n*	*%*
Amoxicilina	500	TID oral	14	53.9
Amoxicilina	400	TID oral	1	3.8
Amoxicilina	500	BID oral	1	3.8
Amoxicilina	otros [#4]	TID oral	1	3.8
Amoxicilina/ácido clavulánico	500 / 125	TID oral	5	19.3
Clindamicina	300	BID oral	1	3.8
Clindamicina	300	QID oral	1	3.8
Eritromicina (forma de etilsuccinato)	150	TID oral	1	3.8
Otros [#5]	500	QD oral	1	3.8
Total [#6]			26	100.0
QD: una vez al día, BID: dos veces al día, TID: 3 veces al día, QID: 4 veces al día / [#1]mencionado espontáneamente / variable /[#2] [#3]2 participantes no declararon el régimen preoperatorio prescrito / [#4]375mg, se trata de un tratamiento antibiótico y no de profilaxis antibiótica / Zithromax /[#5] [#6]1 participante no declaró el régimen preoperatorio prescrito				

Tabla 6. Regímenes postoperatorios

Tipo de antibiótico	Dosis (mg)	Dosificación	Duración	n	%
Amoxicilina	250	TID oral	5 días	1	1.1
Amoxicilina	400	TID oral	5 días	1	1.1
Amoxicilina	500	QD oral	3 días	1	1.1
Amoxicilina	500	BID oral	7 días	1	1.1
Amoxicilina	500	TID oral	1 día	4	4.3
Amoxicilina	500	TID oral	3 días	2	2.2
Amoxicilina	500	TID oral	5 días	29	31.5
Amoxicilina	500	TID oral	6 días	1	1.1
Amoxicilina	500	TID oral	7 días	24	26.1
Amoxicilina	500	TID oral	8 días	1	1.1
Amoxicilina	500	TID oral	otros [#1]	2	`2.2
Amoxicilina	500	QID oral	2 días	1	1.1
Amoxicilina	500	QID oral	4 días	1	1.1
Amoxicilina	500	QID oral	5 días	2	2.2
Amoxicilina/ácido clavulánico	500/125	TID oral	7 días	1	1.1
Amoxicilina/ácido clavulánico	500/125	TID oral	1 día	1	1.1
Amoxicilina/ácido clavulánico	500/125	TID oral	5 días	6	6.5
Amoxicilina/ácido clavulánico	500/125	TID oral	7 días	7	7.6
Amoxicilina/ácido clavulánico	500/125	QID oral	6 días	1	1.1
Amoxicilina/ácido clavulánico	500/125	QID oral	7 días	1	1.1
Clindamicina	300	TID oral	7 días	1	1.1
Clindamicina	300	QID oral	5 días	1	1.1
Clindamicina	300	QID oral	7 días	1	1.1
otros [#4]	500	QD oral	2 días	1	1.1
total [#5]				92	100.0
QD: una vez al día, BID: dos veces al día, TID: 3 veces al día, QID: 4 veces al día / desconocido / 2[#1#2].000 mg / 3[#3].000 mg / Zithromax / [#4]3 [#5]participantes no declararon el régimen postoperatorio prescrito					

Cantidades de antibióticos prescritos

Por término medio, los participantes declararon que prescribían un total de 7.018 mg (SD = 4.325 mg) de antibióticos profilácticos antes, durante o después de la cirugía de implantes orales, variando entre 500 mg y 14.600 mg, con una mediana de 8.000 mg. Tres participantes no indicaron sus regímenes de prescripción, y seis no declararon el número de miligramos prescritos (Tabla 7).

Tabla 7. Cantidad total (mg) de antibióticos pescritos en relación al tipo de profesional

	Media	Desviación estándar	Mediana	Valor *P*
Tipo de profesional de la salud bucodental				0,032
-Médico dental generalista (GDP) [#1]	4,150	3,705	2,000	
-Implantólogo oral (OI)	7,969	4,179	9,500	
-Cirujano oral (OS)	6,883	4,195	8,000	
Hábitos de prescripción de antibióticos				0.004
-a veces	7,799	4,173	9,500	
-siempre	5,913	4,059	4,750	
Régimen de prescripción de antibióticos				0.000
-Sólo preoperatorio [#1]	2,060	463	2,000	
-Sólo en el postoperatorio	9,250	1,545	10,500	
-Pre y post operatorio	9,598	2,963	9,500	
Total	7,018	4,235	8,000	
n = 136 [#2]				
[#1] Comparación múltiple post hoc de Bonferroni / [#2]3 participantes no indicaron los regímenes de prescripción y 6 participantes no declararon completamente el número de mg o no lo declararon en absoluto.				

En particular, los cirujanos maxilofaciales prescriben significativamente más antibióticos que los implantólogos orales y los médicos generales (7.969 mg frente a 6.883 mg y 4.150 mg; *p*=0,03).

En particular, la diferencia entre los cirujanos maxilofaciales y los médicos generales fue estadísticamente significativa (*p*=0,02). Los participantes que sólo optaron por los antibióticos antes del tratamiento informaron de la prescripción de cantidades significativamente menores que sus colegas que optaron por los antibióticos sólo después del tratamiento y tanto antes como después del tratamiento (2.060 mg frente a 9.250 mg y 9.598 mg; p < 0,001). Además, parece que los participantes que prescriben regularmente una profilaxis antibiótica junto con la cirugía de implantes orales prescriben cantidades significativamente menores de antibióticos que los participantes que prescriben antibióticos profilácticos sólo en determinadas circunstancias. Por el contrario, los participantes que prescriben antibióticos profilácticos sólo en determinadas circunstancias al colocar implantes orales indicaron que prescriben regímenes más largos (antes y después de la operación) que los participantes que indicaron que prescriben regularmente antibióticos profilácticos (*p*=0,04).

Hábitos de prescripción antibiótica en Italia

RESUMEN

Objetivos: La prescripción de antibióticos profilácticos en conjunción con la cirugía de implantes orales sigue siendo inconsistente entre las diferentes poblaciones de dentistas. El objetivo principal de este estudio fue evaluar los hábitos actuales de prescripción de antibióticos por parte de los dentistas junto con la cirugía de implantes orales en Italia. El objetivo secundario fue evaluar la naturaleza y la cantidad (mg) de las prescripciones de antibióticos para evaluar si se ha alcanzado algún consenso y si se cumplen las recomendaciones actuales.

Métodos: Estudio observacional transversal basado en una encuesta web reportada según las directrices de STROBE. Se envió un cuestionario por correo electrónico a cada miembro registrado de la Academia Italiana de Osteointegración (n=400). El correo electrónico incluía un enlace al cuestionario web anónimo desarrollado en www.encuestafacil.com. Contenía preguntas cerradas y algunas abiertas relativas a los datos demográficos, el tipo de antibiótico, la duración de la prescripción y la dosis. Los datos recogidos se analizaron con el programa STATA® 14.

Resultados: 160 participantes respondieron a la encuesta (tasa de respuesta=40%). Aproximadamente el 84% prescribió antibióticos profilácticos de forma rutinaria junto con la cirugía de implantes orales, el 15,6% prescribió antibióticos en determinadas situaciones y sólo 1 no prescribió antibióticos en absoluto. En total, 116 encuestados prescribieron antibióticos tanto antes como después de la operación, 29 prescribieron antibióticos sólo antes de la operación y 14 prescribieron antibióticos exclusivamente después de la operación. Los dentistas italianos prescribieron una cantidad media de 10.331 mg de antibióticos antes, durante o después de la cirugía de implantes orales. Aproximadamente, sólo el 17% (n=27) de los participantes que prescribieron antibióticos antes de la cirugía de implantes orales cumplieron las recomendaciones propuestas por las últimas publicaciones (no más de 3 g de amoxicilina preoperatoria antes de la cirugía de implantes orales).

Conclusiones: Los dentistas en Italia prescriben a gran escala la profilaxis antibiótica junto con la cirugía de implantes orales entre los pacientes sanos. Se prescribe una gran variedad de regímenes profilácticos que no se ajustan a las nuevas especificaciones de base científica. Se necesitan directrices centradas en las indicaciones de los antibióticos profilácticos entre los pacientes sanos para evitar la resistencia bacteriana, los efectos secundarios y los costes causados por el sobretratamiento y el uso irracional de los antibióticos.

MÉTODOS

Este estudio observacional transversal se basa en una encuesta web y se comunica de acuerdo con las directrices del Strengthening the Reporting of Observational studies in Epidemiology (STROBE) [1].

Diseño del estudio

El cuestionario desarrollado por Deeb et al. (2015) se adaptó a las circunstancias de Italia con el propósito de recoger datos relativos a los hábitos de prescripción de antibióticos preventivos entre los profesionales de la odontología junto con la terapia de implantes orales [2]. Se obtuvo el permiso de Deeb y los coautores para utilizar su cuestionario. Tras ser ajustado y traducido, el cuestionario fue revisado en cuanto a su comprensibilidad y orden lógico por un implantólogo oral italiano con experiencia. La forma en que se formularon las preguntas se consideró adecuada para evaluar los objetivos previstos.

Entorno

Italia es un estado miembro de la Unión Europea, que en 2018 tenía una población de aproximadamente 60,3 millones de habitantes [7]. En marzo de 2018, el número de dentistas inscritos en el registro de la Federación Nacional de Órdenes de Médicos y Odontólogos (FNOMCeO) era de 61.586 [8].

Participantes

En abril de 2018, la IAO envió un correo electrónico a todos los miembros de la asociación (400 odontólogos) con un enlace a un cuestionario basado en la web y una breve introducción relativa a los objetivos del estudio. Todos los potenciales encuestados recibieron un correo electrónico de recordatorio de la IAO después de cuatro semanas, y dos semanas más tarde el acceso al cuestionario ya no era posible. Además, se garantizó a los participantes que los datos de la investigación se recogerían de forma anónima y que los participantes habían dado su consentimiento para el uso de los datos para el estudio.

De todos los miembros de la IAO, 36 son mujeres y el 20% de todos los miembros son realmente dentistas especializados en cirugía oral.

Variables

Se recogieron datos relativos a los siguientes puntos: datos demográficos, formación, experiencia laboral y antibiótico preventivo prescrito en caso de colocación de implantes orales (incluida la dosis y la duración). A partir de las respuestas de los participantes sobre la dosis y el periodo de toma, se calculó la cantidad total de antibióticos prescritos (mg).

Fuentes de datos / medición

Cada enlace se dirigía a un cuestionario que sólo se podía responder una vez. El cuestionario contenía principalmente preguntas cerradas y algunas preguntas abiertas.

Sesgo

Se minimizó la posibilidad de cualquier sesgo de selección, ya que se abordó una muestra de dentistas que se sabe que realizan regularmente implantes orales.

Tamaño del estudio

El tamaño final del estudio incluyó sólo a los dentistas, entre los abordados, que habían decidido responder parcial o totalmente a la encuesta.

Métodos estadísticos

Todos los datos se analizaron con el programa informático STATA® 14. Se realizó una evaluación estadística en función de la edad, el sexo y la ubicación. Posteriormente, se evaluó el uso de la prescripción de antibióticos profilácticos y sus cantidades (mg) antes, después o durante la cirugía de implantes orales.

Las variables binomiales correspondientes a cada una de las preguntas se evaluaron mediante proporciones (porcentaje) de las respuestas al cuestionario. Se realizaron las pruebas de chi-cuadrado y exacta de Fisher para evaluar las diferencias en el régimen de antibióticos adoptado por los participantes según su sexo, edad, educación, ubicación y experiencia laboral.

Finalmente, se calculó la dosis total de antibióticos en mg prescrita por cada participante y se utilizó la media (mg) como valor principal de evaluación. Se seleccionó la media como valor principal de evaluación debido a la homogeneidad de la muestra y a su validez, así como a su frecuente empleo en la investigación sanitaria. Sin embargo, también se proporcionó información sobre la mediana y el rango intercuartil. Se realizó un ANOVA (prueba t de Student) para evaluar las diferencias en el total de antibióticos (mg) prescritos en concomitancia con la cirugía de implantes dentales. Se determinó así la desviación estándar (Std. Dev.) y los valores *p*.

RESULTADOS

Participantes

Ciento sesenta participantes devolvieron la encuesta, lo que supone una tasa de respuesta del 40%.

Datos descriptivos

Ciento cuarenta y seis hombres (93,6%) y diez mujeres (6,4%) respondieron al cuestionario, y la mayoría tenía entre 51 y 60 años (30,1%).

La mayoría de los participantes (97,4%) se graduó en una facultad de odontología de Italia. La mayoría de los participantes se graduaron en la Facultad de Odontología de Milán (26,9%), otros en la Facultad de Odontología de Padua (8,3%) y en la Facultad de Odontología Sapienza - Universidad de Roma (6,4%). Casi dos tercios de los participantes (60,9%) llevaban más de 20 años trabajando como proveedores de salud bucodental,

casi un tercio tenía entre 10 y 20 años de experiencia (30,1%) y el resto de los encuestados llevaba menos de 10 años (9%). La mayoría de los encuestados trabajaban en la región de Lombardía (30,7%), y otros en Véneto (10,9%), Lacio (9,6%), Piamonte (7%) y Toscana (7%).

Datos sobre los resultados

Aproximadamente el 84% de los participantes (n=134), que realizan actualmente cirugía de implantes orales, declararon que siempre prescriben antibióticos profilácticos junto con la cirugía de implantes orales, sólo uno de los participantes (0,6%) no los prescribe nunca.

Además, el 15,6% adoptó los antibióticos sólo en casos particulares (n=25). Como cardiopatía que requiere profilaxis antibiótica (24,2%), injerto óseo (23,1%); perforación de seno (13,7%); infección preoperatoria del sitio del implante (11,6%); fumadores (9,5%); enfermedad periodontal previa (8,4%); inserción de múltiples implantes (3,1%); pacientes médicamente comprometidos (3,1%) y colocación inmediata de implantes (1%). No se encontraron diferencias estadísticamente significativas en relación con las prescripciones de antibióticos de los dentistas respecto a algunas características generales (Tabla 1).

Tabla 1. Características personales de los dentistas relacionadas con sus hábitos de prescripción de antibióticos en la cirugía de implantes orales

Características personales	Hábitos de prescripción de antibióticos			Total
	Nunca	*A veces*	*Siempre*	
Mujer [a]		8%	6.15%	6.4%
Edad (años) [b]				
- 21-30		12%	3.0%	4.5%
- 31-40		20%	19.2%	19.2%
- 41-50		24%	30%	28.9%
- 51-60	100%	24%	30.7%	30.1%
- 61-70		16%	14.6%	14.7%
- 71 o más		4%	2.3%	2.6%
Graduación en Italia [c]	100%	100%	96.1%	96.8%
Experiencia (años) [d]				
- Menos del 10		16%	7.7%	8.9%
- Entre 11 y 20	100%	52%	62.3%	60.9%
- Más de 20		32%	30%	30.1%
Lugar de asentamiento (macrorregiones) [e]				
-Noroeste		36%	43.1%	41.7%
-North-East	100%	24%	20%	21.1%
-Centro		16%	23.1%	21.8%
-Sur		16%	10.8%	11.5%
- Islas		4%	2.3%	2.6%
- Otros		4%	0.7%	1.3%
n [f]	1	25	130	156

[a] p=0.910
[b] p=0.735
[c] p=0.597
[d] p=0.618
[e] p=0.718
[f] *4 encuestados no respondieron a estas preguntas o lo hicieron de forma incompleta*

La mayoría de los encuestados afirmaron que optaban por una combinación de un régimen pre y postoperatorio (72,9%), mientras que el 18,2% sólo utiliza el régimen preoperatorio y el 8,8% sólo el postoperatorio (Tabla 2).

Tabla 2. Regímenes de prescripción de antibióticos y hora de inicio de las prescripciones

Régimen y hora de inicio de la prescripción	n	%	n	%
Sólo el preoperatorio			29	18.2
-Inmediatamente antes	2	6.9		
-1 hora antes	26	89.6		
-1 día antes	0	0		
-2 días antes	1	3.4		
Pre y post operatorio [#1]			114	72.9
-Inmediatamente antes	1	0.8		
-1 hora antes	59	51.7		
-1 día antes	49	42.98		
-2 días antes	5	4.39		
Sólo el postoperatorio			14	8.8
Total			157	100.0
[#1] 2 encuestados no declararon la hora de inicio de la prescripción o lo hicieron de forma incompleta				

Principales resultados

Antibióticos preoperatorios

La mayoría de los 143 dentistas que prescriben antibióticos preoperatorios cuando se colocan implantes orales aconsejan a sus pacientes que empiecen 1 hora antes de la cirugía (59,4%) o 1 día antes de la cirugía (34,2%). Los demás participantes que prescriben antibióticos preoperatorios aconsejan empezar dos días (4,2%) o inmediatamente (2,1%) antes de la cirugía. La tabla 3 muestra el tipo de antibióticos, su dosis y su régimen.

Se encontró que la amoxicilina/ácido clavulánico oral era el antibiótico más frecuentemente prescrito cuando se administraba 1 o 2 días antes de la operación (80,7%) y 1 hora o inmediatamente antes de la cirugía (71,6%). En general, el régimen preoperatorio más frecuente fue 2 g de amoxicilina/ácido clavulánico oral 1 hora antes de la cirugía (n=31, 21,6%).

Tabla 3. Regímenes antibióticos preoperatorios prescritos por los dentistas.

1 hora o inmediatamente antes				
Tipo de antibiótico	*Dosis (mg)*	*Administración*	*n*	*%*
Amoxicilina/ácido clavulánico	*2000*	*oral*	*32*	*36.3*
Amoxicilina/ácido clavulánico	*875/125*	*oral*	*22*	*25*
Amoxicilina	*2000*	*oral*	*17*	*19.3*
Amoxicilina/ácido clavulánico	*1000*	*oral*	*9*	*10.2*
Amoxicilina	*1000*	*oral*	*4*	*4.5*
Amoxicilina	*500*	*oral*	*1*	*1.1*
Penicilina V	*1.000*	*oral*	*1*	*1.1*
otros [#1]			*2*	*2.2*
Total			*88*	*100.0*
1 o 2 días antes				
Tipo de antibiótico	*Dosis (mg)*	*Dosificación*	*n*	*%*
Amoxicilina/ácido clavulánico	*875/125*	*BID oral*	*27*	*49.0*
Amoxicilina/ácido clavulánico	*1000*	*BID oral*	*14*	*25.4*
Amoxicilina	*1000*	*BID oral*	*8*	*14.5*
Amoxicilina/ácido clavulánico	*1000*	*TID oral*	*2*	*3.6*
Amoxicilina/ácido clavulánico	*800*	*BID oral*	*1*	*1.8*
Amoxicilina/ácido clavulánico	*875/125*	*TID oral*	*1*	*1.8*
Amoxicilina	*875/125*	*BID oral*	*1*	*1.8*
otros [#2]	*500*	*QD oral*	*1*	*1.8*
Total			*55*	*100.0*

[#1] 1 "Claritromicina" y 1 "Zithromax PD durante 3 días" mencionados espontáneamente

[#2] "Azitromicina 500 mg 1 cpr cada 24 horas durante 3 días" mencionado espontáneamente

QD: una vez al día, BID: dos veces al día, TID: 3 veces al día, QID: 4 veces al día

[*] 2 encuestados no declararon la hora de inicio de las prescripciones o lo hicieron de forma incompleta, por lo que sus datos no pudieron incluirse en esta tabla.

Antibióticos postoperatorios

Casi tres cuartas partes (70,6%) de los dentistas que aconsejan a los pacientes iniciar el tratamiento antibiótico en el postoperatorio, prescriben 875/125 mg de amoxicilina/ácido clavulánico oral dos veces al día durante un periodo que varía entre cinco y seis días (Tabla 4). En general, la pauta postoperatoria más frecuentemente prescrita fue 875/125 mg de amoxicilina/ácido clavulánico oral dos veces al día durante 6 días después de la cirugía (n=43, 32,5%). La tabla 4 muestra el tipo de antibióticos, su dosis y su régimen.

Tabla 4. Regímenes antibióticos postoperatorios prescritos por los dentistas.

Tipo de antibiótico	Dosis (mg)	Dosificación	Duración (días)	n	%
Amoxicilina	1000	QD oral	1	1	0.7
Amoxicilina	1000	BID oral	2	1	0.7
Amoxicilina	1000	BID oral	3	1	0.7
Amoxicilina	1000	BID oral	4	3	2.2
Amoxicilina	1000	BID oral	5	6	4.5
Amoxicilina	1000	BID oral	6	8	6.0
Amoxicilina	1000	BID oral	7	2	1.5
Amoxicilina	500	BID oral	5	1	0.7
Amoxicilina/ácido clavulánico	500/125	BID oral	5	1	0.7
Amoxicilina/ácido clavulánico	500/125	TID oral	6	1	0.7
Amoxicilina/ácido clavulánico	875/125	BID oral	2	3	2.2
Amoxicilina/ácido clavulánico	875/125	BID oral	3	3	2.2
Amoxicilina/ácido clavulánico	875/125	BID oral	4	8	6.0
Amoxicilina/ácido clavulánico	875/125	BID oral	5	28	21.2
Amoxicilina/ácido clavulánico	875/125	BID oral	6	43	32.5
Amoxicilina/ácido clavulánico	875/125	BID oral	7	4	3.0
Amoxicilina/ácido clavulánico	875/125	BID oral	[#1]	1	0.7
Amoxicilina/ácido clavulánico	875/125	TID oral	3	1	0.7
Amoxicilina/ácido clavulánico	875/125	TID oral	4	2	1.5
Amoxicilina/ácido clavulánico	875/125	TID oral	5	3	2.2
Amoxicilina/ácido clavulánico	875/125	TID oral	6	1	0.7
Amoxicilina/ácido clavulánico	875/125	TID oral	7	1	0.7
Penicilina V	875/125	BID oral	7	1	0.7
otros [#2]				4	3.0
Total				128	100.0

[#1] no ha respondido

[#2] 1 "Azitromicina 500 mg", 1 "Claritromicina", 1 "Claritromicina x2 250 mg x5 al día por os" y 1 "Zitromax PD durante 3 días"

QD: una vez al día, BID: dos veces al día, TID: 3 veces al día, QID: 4 veces al día

Cantidad de antibióticos prescritos

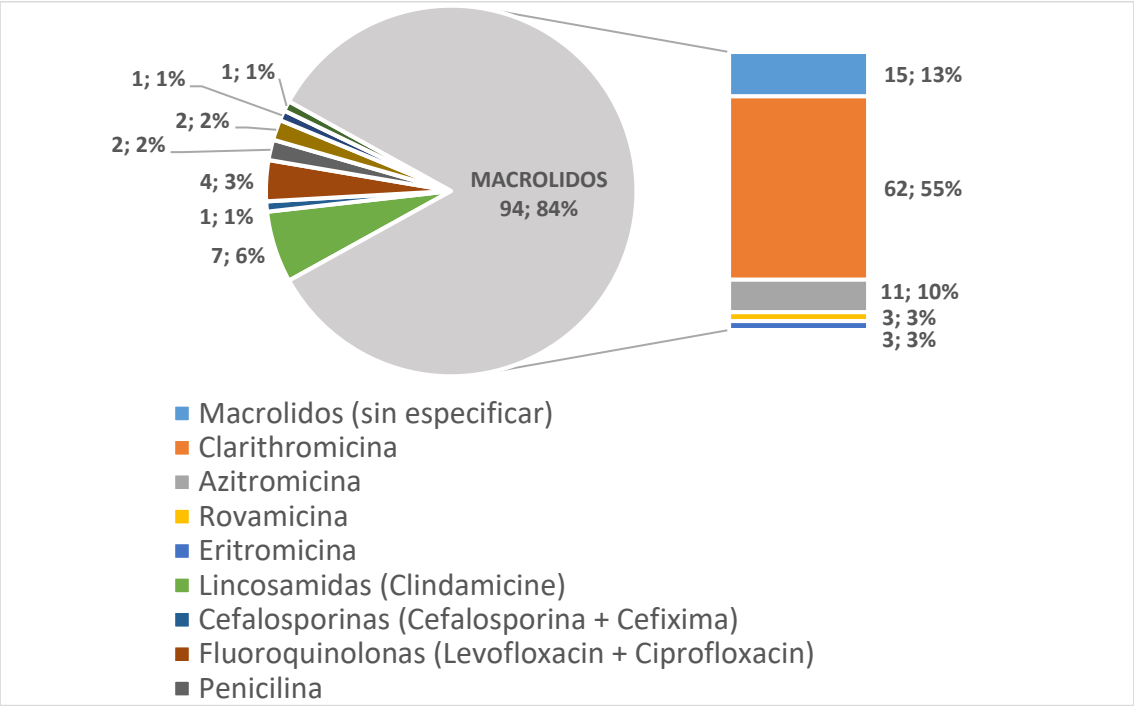
Por término medio, los dentistas prescribieron un total de 10.331 mg de antibióticos (desviación estándar=4.973 mg) antes, después o durante la colocación de los implantes orales, variando de 1.000 mg a 22.000 mg. Los dentistas que prescribieron sólo antibióticos preoperatorios administraron, de media, significativamente (p=0,000) menos mg (2.241 mg) que sus colegas que prescribieron antibióticos sólo después de la cirugía (10.404 mg), o antes y después de la cirugía (12.436 mg).

No se encontraron diferencias estadísticamente significativas (p=0,176) en los valores medios de la cantidad total de antibióticos prescritos (mg) por los dentistas que prescribían antibióticos profilácticos de forma rutinaria en comparación con los que prescribían antibióticos de forma no regular.

Regímenes de antibióticos en caso de alergia a la penicilina

Los participantes prescribieron una gran variedad de antibióticos profilácticos diferentes a los pacientes alérgicos a la penicilina. En total, se recetaron 12 tipos de antibióticos diferentes; 94 participantes recetaron macrólidos y un participante no recetó ninguno. La mayoría de los participantes (n=62, 52,9%) recetaron Claritromicina en su lugar (Figura 1).

Figura 1. Antibióticos prescritos en pacientes alérgicos a la amoxicilina



Cumplimiento de los últimos estudios publicados

Aproximadamente, sólo el 17% (n=27) de los participantes que prescribieron antibióticos antes de la cirugía de implantes orales se adhirieron a las recomendaciones propuestas por las últimas publicaciones (no más de 3 g de amoxicilina preoperatoria antes de la cirugía de implantes orales) [2,7]. De ellos, 25 comenzaron a prescribir antibióticos 1 hora antes de la intervención y prescribieron amoxicilina (n=11) o amoxicilina/ácido clavulánico (n=14). Las prescripciones realizadas inmediatamente antes de la intervención siempre contenían amoxicilina/ácido clavulánico. En general, la pauta más prescrita entre estos participantes fue amoxicilina 2 g 1 hora antes de la intervención (n=10).

Hábitos de prescripción antibiótica en cirugía de implates orales. Meta-análisis de encuestas transversales

RESUMEN

Objetivos: Este estudio tenía como objetivo evaluar la dosis y los tipos de antibióticos prescritos en la cirugía de implantes orales, compararlos entre las diferentes subpoblaciones (país y regímenes de prescripción) y compararla con la dosis recomendada con mayor frecuencia en la literatura: una dosis única preoperatoria de 2 gramos de amoxicilina.

Métodos: Se realizó un meta-análisis de encuestas transversales, que informa sobre la dosis global y el tipo de antibióticos prescritos en combinación con la colocación de implantes. Se realizaron búsquedas en PubMed, Cochrane, Science, Direct y EMBASE a través de OVID hasta abril de 2019. Tres revisores realizaron de forma independiente la extracción de datos y la evaluación del riesgo de sesgo. La variable de resultado se estableció en el promedio de antibióticos profilácticos prescritos por cirugía de implante oral.

Resultados: Se incluyeron finalmente 726 participantes de cinco encuestas transversales, que representaban a cinco países diferentes. La amoxicilina fue el antibiótico más prescrito. Por término medio, se prescribieron 10.724 mg de antibióticos por cirugía de implantes. Esta media fue significativamente (p<0,001) superior a los 2.000 mg. En general, las dosis de amoxicilina fueron significativamente superiores a los 2.000 mg (9.700 mg, p<0,001). Todos los regímenes de amoxicilina prescritos contenían independientemente más de 2.000 mg, incluidos los que comprendían sólo amoxicilina preoperatoria (2.175 mg, p=0,006).

Los regímenes de antibióticos preoperatorios exclusivos fueron el único subgrupo con dosis de prescripción inferiores a este umbral (p=0,091). Se encontraron variaciones significativas en las prescripciones de antibióticos entre los distintos países y regímenes antibióticos (p<0,001).

Conclusiones: La dosis media de antibióticos prescrita por cirugía de implantes orales fue mayor que la dosis recomendada basada en la evidencia en pacientes sanos y en condiciones ordinarias. Además, se encontraron variaciones en las dosis medias de antibióticos entre los diferentes países y regímenes de prescripción.

MÉTODOS

El estudio se llevó a cabo y se informó de acuerdo con el grupo de Meta-análisis de Estudios Observacionales en Epidemiología [9]. Los detalles del protocolo de este meta-análisis se registraron en el Registro Internacional Prospectivo de Revisiones Sistemáticas (PROSPERO) con la siguiente identificación de registro: CRD42020156885. Acesible en: https://www.crd.york.ac.uk/prospero/#recordDetails

Los estudios elegibles incluyeron todos los artículos que evaluaban la prescripción de antibióticos en asociación con la cirugía de implantes orales y en cumplimiento con el siguiente marco de Participantes; Intervención; Comparación; Resultado y Tipo de estudio (PICOS):

Participantes: Odontólogos generales o especialistas que colocan implantes orales.

Intervención: Prescripciones de antibióticos en asociación con la cirugía de implantes orales.

Comparaciones:

1. Dosis recomendada por la evidencia en pacientes sanos y en condiciones rutinarias: dosis única preoperatoria de 2.000 mg [10].

2. Comparaciones entre diferentes subpoblaciones (países, tipos de antibióticos y regímenes de prescripción).

Resultados: Dosis media y tipos de antibióticos prescritos por cirugía de implantes orales.

Tipo de estudio: Encuesta transversal.

Se excluyeron las publicaciones que eran ensayos clínicos, series de casos o estudios retrospectivos. No hubo restricciones en cuanto al idioma o al año de publicación. También se excluyeron las publicaciones que no aportaban suficiente información para calcular la dosis total de antibióticos contenida en las prescripciones de sus participantes.

Se realizaron búsquedas en las siguientes bases de datos electrónicas hasta el 4 de junio de 2020: Embase, PubMed, Ovid Medline, Scopus, Science-Direct, Web of Knowledge, así como la base de datos de tesis doctorales del Consejo General de Universidades de España, las bases de datos bibliográficas del Consejo Superior de Investigaciones Científicas y el Índice Médico Español.

Tres investigadores independientes realizaron la búsqueda en las bases de datos. Los términos buscados fueron descriptores de los componentes PICO: antibióticos, cirugía de implantes orales, cirugía de implantes dentales, colocación de implantes orales, colocación de implantes dentales y encuesta transversal.

Como palabras clave para la búsqueda electrónica se utilizaron MeSH y algoritmos de búsqueda conectados con operadores booleanos. No se aplicaron filtros en la búsqueda

en Ovid Medline y PubMed: (antibiotic) AND (((oral OR dental) implant AND surgery) OR ((oral OR dental) implant AND placement)) AND (survey). En Scopus, la búsqueda se limitó a "Dentistry" y "Article" para el área temática y el tipo de documento: (antibiotic) AND (((oral OR dental) implant AND surgery) OR ((oral OR dental) implant AND placement)) AND (survey) AND (LIMIT-TO (DOCTYPE , "ar")) AND (LIMIT-TO (SUBJAREA , "DENT")). La búsqueda en In Web of Knowledge se filtró por "Artículo": TS=(antibiotic "AND" oral implant surgery "OR" dental implant surgery "AND" survey). En Science Direct, se filtró la búsqueda por "Artículos de investigación": (antibiotic) AND (((oral OR dental) implant AND surgery) OR ((oral OR dental) implant AND placement)) AND (survey).

La búsqueda en Embase se limitó a "Article", "Short Survey", "Article in Press" y "Questionnaire": (antibiotic) AND (((oral OR dental) implant AND surgery) OR ((oral OR dental) implant AND placement)) AND (survey) AND ('article'/it OR 'article in press'/it OR 'short survey'/it) AND 'questionnaire'/de.

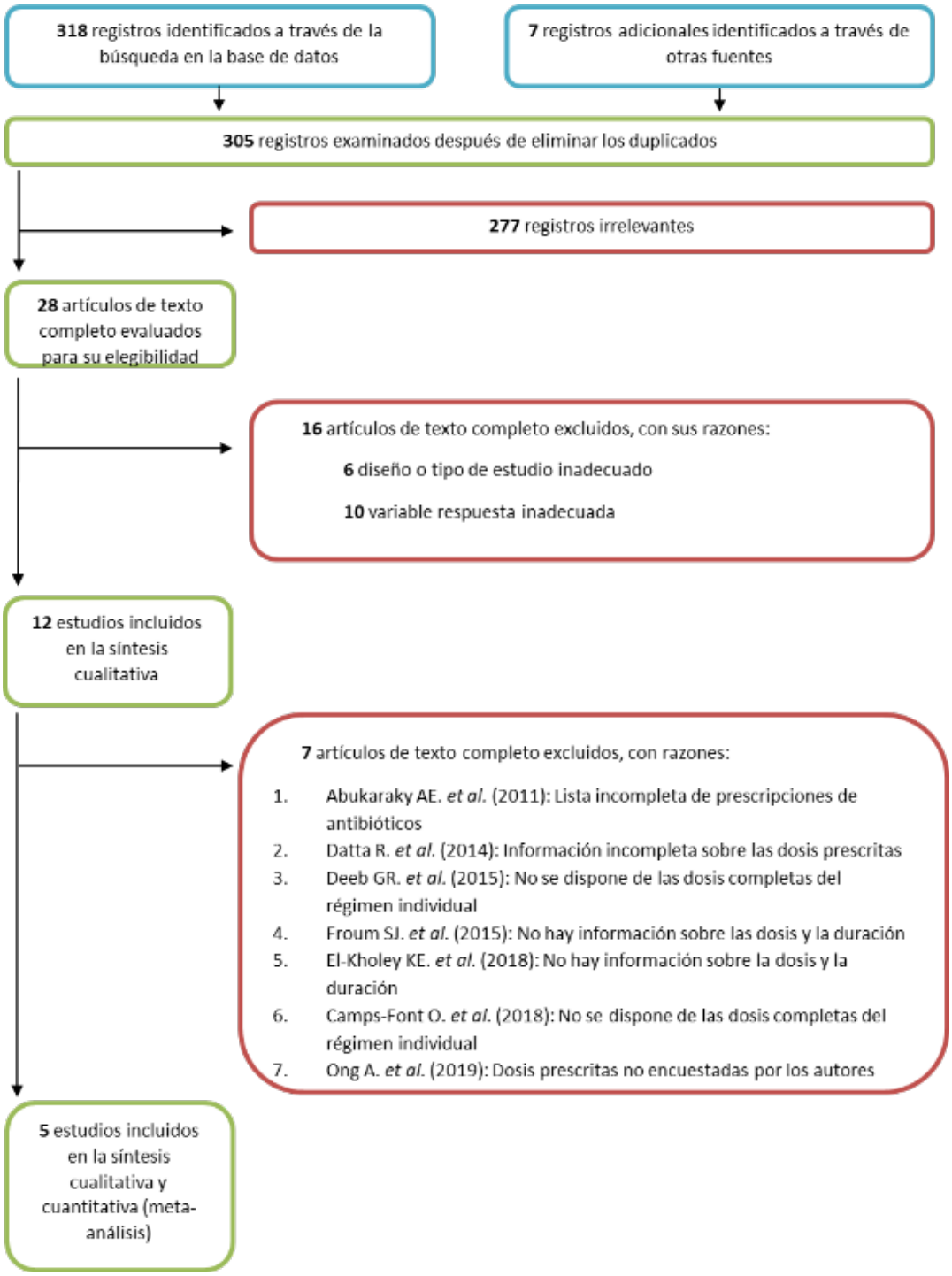
Para las bases de datos en español, se utilizaron los siguientes términos: (antibióticos) AND (implante dental O implante oral) AND (encuesta).

También se revisaron las referencias de todos los artículos recuperados. No se pudo identificar ningún material potencialmente inédito.

Dos revisores independientes (F.R.S. y C.R.A.) examinaron los títulos y los resúmenes de los registros identificados a partir de la búsqueda mediante el software en línea de Cochrane [35]. Se adquirieron los artículos de texto completo de los registros que cumplían los criterios de inclusión. Los investigadores se pusieron en contacto con cada autor correspondiente cuando se necesitaba información adicional en el proceso de selección. Todas las discrepancias se discutieron con un tercer investigador (I.A.). Se informaron los motivos de exclusión (Figura 1).

Los datos registrados incluían lo siguiente: tipo de antibiótico, régimen (preoperatorio, postoperatorio o ambos), dosis, duración del tratamiento y país. Si no se podía obtener el conjunto de datos original de un estudio incluido, la información relativa al tipo de antibiótico, el régimen profiláctico (preoperatorio, postoperatorio o ambos), la dosis y la duración del tratamiento fueron extraídos del artículo publicado por dos investigadores independientes (F.R.S. y C.R.A.). Se consultó a un tercero para resolver cualquier desacuerdo (I.A.). Se realizaron cálculos a partir de los datos de las tablas si los datos de alguna variable no se indicaban explícitamente en el texto. Se contactó con los autores correspondientes de 8 estudios diferentes porque la información necesaria de sus estudios no estaba clara [2, 11-17].

Figura 1. Diagrama de flujo.



Un estudio encuestó a 133 profesionales dentales suecos [18]. De ellos, 98 prescribían antibióticos, mientras que 35 no prescribían ningún antibiótico profiláctico. Este estudio describió completamente 85 regímenes antibióticos; sin embargo, lamentablemente faltaban 13 regímenes antibióticos. Tras contactar con los autores, no se obtuvo ninguna información adicional. Por lo tanto, se incluyeron los 85 dentistas que prescribieron

antibióticos con un número proporcional de profesionales no prescriptores (n = 22) en lugar de los 35 del principio.

El mismo ajuste se aplicó a otros estudios incluidos con 29 participantes que, lamentablemente, fueron excluidos por no proporcionar una descripción de sus regímenes de prescripción (14 de España, 6 de Italia y 9 de los Países Bajos). Los nuevos números calculados y proporcionados de profesionales no prescriptores en estos casos fueron 3,75; 0,96 y 4,7 respectivamente, mientras que los números originales eran 4, 1 y 5 respectivamente. Como los valores calculados eran muy próximos a los originales, se decidió mantener las cifras iniciales para realizar un análisis lo más conservador posible [17, 19, 20].

Se contactó sin éxito con los autores de los otros cinco artículos para recabar los datos necesarios para su inclusión en el metaanálisis [4, 6-8]. Se contactó con los autores de dos artículos con éxito; sin embargo, los datos solicitados sobre la dosis de prescripción fueron insuficientes para su inclusión en el metaanálisis porque sus encuestas no recogían esta información [11, 16].

Dos revisores independientes (F.R.S. y C.R.A.) evaluaron la calidad de los estudios incluidos utilizando la Herramienta de Evaluación de la Calidad del Instituto Nacional del Corazón, los Pulmones y la Sangre para Estudios Transversales y de Cohortes Observacionales [6]. Todas las discrepancias se discutieron con un tercer investigador (I.A.). Los estudios se clasificaron como de calidad baja, moderada o alta si el porcentaje de respuestas afirmativas a la lista de comprobación era inferior al 50%, entre el 50% y el 80% o superior al 80%, respectivamente.

Cada estudio incluido presentó diferentes conjuntos de datos y codificaciones de datos. Esta presentación heterogénea de los datos supuso una limitación para realizar un análisis cuantitativo adecuado (meta-análisis). Para superar esta limitación y cumplir los objetivos del estudio, se creó una base de datos uniforme con el conjunto de datos original de cada estudio. Se utilizó el programa informático STATA® versión 15 para generar esta base de datos y realizar todos los análisis estadísticos.

Se calculó la dosis media (mg) de antibióticos profilácticos prescritos por cirugía de implante según los regímenes de prescripción individuales (multiplicando la dosis de tratamiento, la dosis y la duración correspondiente) con una estimación de la desviación estándar (DE). También se incluyeron en este análisis los participantes que nunca prescribieron antibióticos profilácticos para la cirugía de implantes orales. La distribución normal de los datos de los resultados se evaluó gráficamente mediante gráficos de cuantiles (gráficos Q-Q).

Se utilizó la prueba t de Student para comparar las medias de los antibióticos profilácticos prescritos por estudio, país y régimen de prescripción frente al régimen recomendado basado en la evidencia: dosis única preoperatoria de 2.000 mg. En este análisis, las prescripciones se incluyeron sólo si contenían antibióticos con una Dosis Diaria Definida (DDD) igual al régimen recomendado basado en la evidencia (2.000 mg)

o igual a la DDD de amoxicilina (1.500 mg) según el sistema químico terapéutico anatómico de la Organización Mundial de la Salud [22].

Se utilizaron pruebas f múltiples para comparar las variaciones en los distintos grupos. Dependiendo del análisis de la varianza, se realizaron múltiples pruebas t para varianzas iguales o desiguales para comparar las medias de los antibióticos prescritos en los estudios incluidos. Se realizaron correcciones estándar de Bonferroni tanto en las pruebas f como en las t. En ambas pruebas, el valor α se calculó dividiendo 0,05 por el número total de comparaciones realizadas.

RESULTADOS

Finalmente se incluyeron en este meta-análisis cinco estudios transversales [18-20, 23, 24]. La tabla 1 muestra la información descriptiva de cada estudio incluido en el análisis cuantitativo. Un diagrama de flujo describe el proceso de selección, los registros y las exclusiones de texto completo con sus justificaciones (Figura 1).

Tabla 1. Información descriptiva de cada estudio incluido

Estudio (año)	País	n	Tipo de profesionales	Régimen más frecuentemente prescrito (n)	Participantes que prescriben antibióticos profilácticos de forma rutinaria (n)
Khalil *et al.* (2012) [18]	Suecia	133	Dentistas generals	2 g de amoxicilina oral en el preoperatorio (27)	74% (98)
Ireland *et al.* (2012) [24]	Reino Unido	109	Dentistas generals	3 g de amoxicilina oral una hora antes de la operación (54)	72% (76)
Arteagoitia *et al.* (2018) [16]	España	233	Dentistas generals	500 mg de amoxicilina oral TID 1 día antes de la operación y durante 7 días después de la misma (10)	89% (207)
Rodríguez Sánchez *et al.* (2019) [20]	Italia	160	Dentistas generales y cirujanos orales	875/125 mg de amoxicilina/ácido clavulánico oral BID 1 día antes de la operación y durante 5 días después de la misma (15)	84% (134)
Rodríguez Sánchez *et al* (2019) [19]	Países Bajos	151	Odontólogos generales, implantólogos orales, periodoncistas y cirujanos maxilofaciales	2 g de amoxicilina oral 1 hora o inmediatamente antes de la cirugía (35)	44% (66)

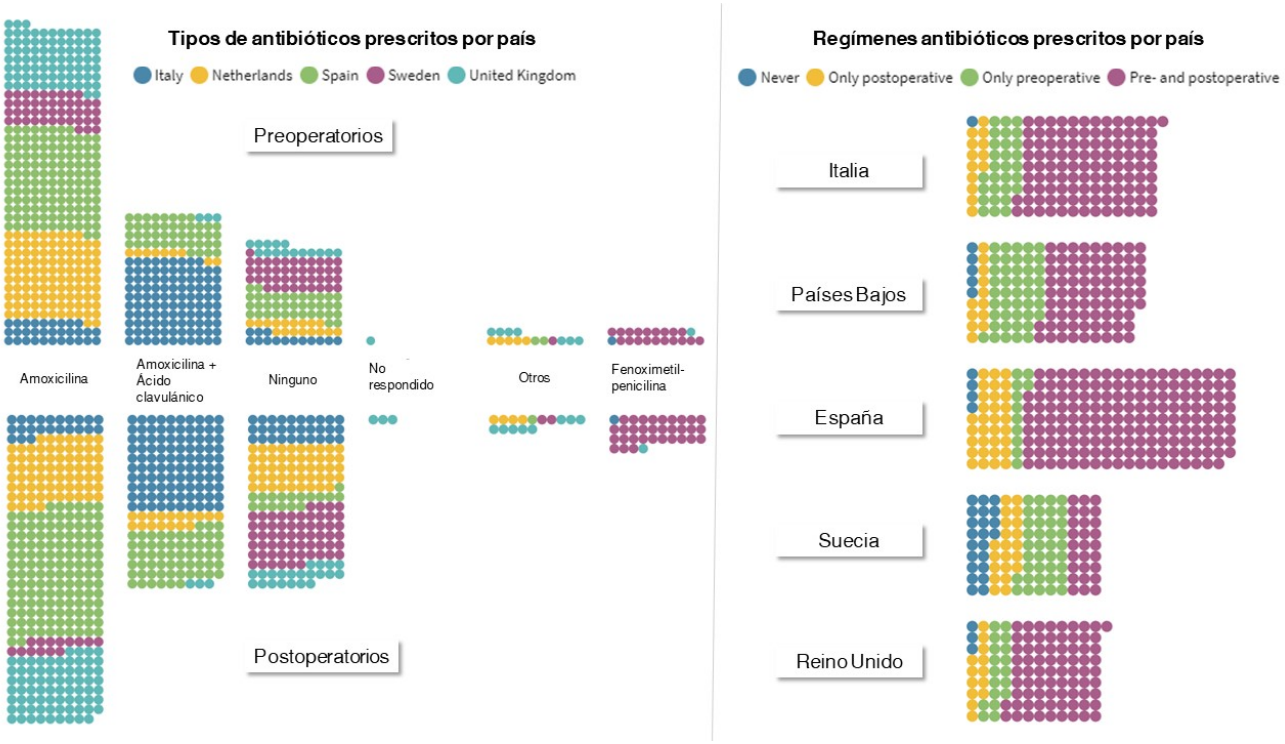
BID: Dos veces al día; TID: Tres veces al día.

Cuatro estudios fueron considerados de calidad moderada [18,19,20,23] y uno de baja calidad [24]. El porcentaje de respuestas afirmativas a la lista de comprobación del Índice Nacional de Salud fue del 75% para el estudio realizado en Suecia, del 54,5% para los otros 3 estudios (España, Países Bajos e Italia) y del 45,5% para el estudio realizado

en el Reino Unido. La distribución de los datos de la variable de resultado se muestra en los gráficos Q-Q.

En total, se incluyeron 726 participantes en este meta-análisis. Todas las prescripciones profilácticas consistieron en antibióticos orales. La Figura 2 ilustra los tipos de antibióticos y los regímenes prescritos por país. Cada punto representa un participante incluido en el meta-análisis.

Figura 2. Tipos de antibióticos y regímenes prescritos por país.



Por término medio, se prescribieron 10.724 mg de antibióticos profilácticos por cirugía de implante oral. Esta dosis media de antibióticos resultó ser significativamente mayor ($p<0,001$) que la dosis recomendada por la evidencia (2.000 mg).

La tabla 2 muestra la dosis media de antibióticos profilácticos prescritos por tipo de antibiótico y país. La amoxicilina fue el tipo de antibiótico más frecuentemente prescrito, seguido de la amoxicilina en asociación con el ácido clavulánico. La mayoría de los profesionales de la encuesta italiana, seguidos por los participantes de la encuesta española, prescribieron ácido clavulánico (Tabla 2).

Tabla 2. Dosis media de antibióticos profilácticos (mg) prescritos por país y tipo de antibiótico.

Tipo de antibiótico / País		España	Italia	Países Bajos	Suecia	Reino Unido	En general	Código ATC	DDD
Amoxicilina	Media *SD* n	1,5047 *6,829* 150	8,672 *5,180* 32	6,561 *4,207* 111	4,642 *5,325* 44	7,399 *3,676* 86	9,700 *6,726* 423	J01CA04	1,500
Amoxicilina / ácido clavulánico	Media *SD* n	19,178 *8,228* 56	10,685 *4,839* 117	7,600 *4,029* 10	- - 0	17,494 *14,946* 4	13,208 *7,472* 187	J01CR02	1,500
Penicilina V	Media *SD* n	- - 0	15,000 0 1	- - 0	18,079 *17,197* 38	3,000 0 1	17,625 *16,925* 40	J01CE02	2,000
Amoxicilina / Amoxicilina + Ácido Clavulánico	Media *SD* n	25,166 *763* 3	11,000 *7550* 3	10,296 *1,406* 8	- - 0	8,812 *265* 2	13,031 6,726 16	J01CA04 / J01CR02	1,500 / 1,500
Azitromicina	Media *SD* n	- - 0	- - 0	11,000 *3,869* 3	- - 0	10,100 *1,732* 3	10,550 *2,726* 6	J01FA10	300
Clindamicina	Media *SD* n	- - 0	- - 0	11,000 *3,869* 1	600 *0* 1	12,600 *0* 1	6,600 *6,600* 3	J01FF01	1,200
Clindamicina / Amoxicilina + Ácido Clavulánico	Media *SD* n	- - 0	- - 0	11,200 *2,687* 2	- - 0	- - 0	11,200 *2,687* 2	J01FF01 / J01CR02	1,200 / 1,500
Amoxicilina / Penicilina V	Media *SD* n	- - 0	- - 0	- - 0	24,000 *0* 1	8,000 *0* 1	16,000 *11,314* 2	J01CA04 / J01CE02	1,500 / 2,000
Metronidazol	Media *SD* n	- - 0	- - 0	- - 0	6,000 - 1	25,200 *0* 1	15,600 *13,576* 2	J01XD01	1,500
Eritromicina	Media *SD* n	3,000 0 1	- - 0	- - 0	- - 0	6,500 *0* 1	4,750 *2,475* 2	J01FA01	2,000

Amoxicilina / Metronidazol	Media *SD* n	- - 0	- - 0	- - 0	- - 0	24,000 *0* 1	24,000 *0* 1	J01CA04 / J01XD01	1,500 / 1,500
Primcillin	Media *SD* n	- - 0	- - 0	- - 0	- - 0	18,400 *0* 1	18,400 *0* 1	J01CE02	2,000
Cefazolina	Media *SD* n	- - 0	- - 0	- - 0	- - 0	8,250 *0* 1	8,250 *0* 1	J01DC02	3,000
Cefuroxima / Amoxicilina + Ácido Clavulánico	Media *SD* n	- - 0	- - 0	- - 0	- - 0	14,375 *0* 1	14,375 *0* 1	J01DC04 / J01CR02	500 / 1,500
Cefazolina / Amoxicilina + Ácido Clavulánico	Media *SD* n	25,000 0 1	- - 0	- - 0	- - 0	- - 0	25,000 *0* 1	J01DB04 / J01CR02	3,000 / 1,500
No respondió	Media *SD* n	- - 0	- - 0	2,000 0 1	- - 0	10,500 0 2	7,667 4,907 3	-	-
Ninguno	Media *SD* n	0 *0* 4	0 *0* 1	0 *0* 5	0 *0* 22	0 *0* 3	0 *0* 35	-	-
En general	Media *SD* n	15,974 *7,764* 215	10,231 *5,044* 154	6,742 *4,310* 141	8,615 *13,103* 107	8,216 *5,426* 109	10,713 *8,315* 726	-	-

En esta tabla se ha utilizado el nombre de Penicilina V en lugar de Fenoximetilpenicilina, siendo ambos nombres diferentes para el mismo fármaco. SD: desviación estándar; DDD: dosis diaria definida; ATC: sustancia química anatómica terapéutica

La dosis global de amoxicilina prescrita fue significativamente superior a 2.000 mg (9.700 mg, *p*<0,001). Todos los regímenes con sólo amoxicilina comprendían de forma independiente una dosis significativamente superior a la referencia de 2.000 mg, incluidos los que sólo tenían amoxicilina preoperatoria (2.175 mg, *p*=0,006). Sin embargo, los participantes del Reino Unido que prescribían exclusivamente amoxicilina preoperatoria fueron los únicos que lo hicieron significativamente (*p*<0,001) por encima del nivel de 2.000 mg por cirugía de implante oral (Tabla 3).

Tabla 3. Dosis media de amoxicilina (mg) prescrita por país y régimen de prescripción.

Régimen de prescripción / País		España	Italia	Países Bajos	Suecia	Reino Unido	General
Sólo el preoperatorio	Media	2,182†	1,900‡	2,042¶	2,025††	2,926*	2,175‡‡
	SD	*1,401*	*316*	*462*	*211*	*528*	*655*
	n	11	10	42	30	17	110
Sólo el postoperatorio	Media	13,433	1,0667	9,300	-	6,675	10,769*
	SD	*4,603*	*2,309*	*1,549*	-	*1,390*	*4,345*
	n	21	3	10	0	10	44
Pre y post operatorio	Media	16,534	11,921	9,314	10,250	8,810	12,603*
	SD	*6,111*	*2,878*	*3,042*	*6,635*	*3,384*	*6,012*
	n	118	19	59	14	59	269
En general	Media	15,047*	8,672*	6,561*	4,642**	7,399*	9,700*
	SD	*6,829*	*5,180*	*4,207*	*5,325*	*3,676*	*6,726*
	n	150	32	111	44	86	423

*Prueba T bilateral que contrasta la media=2.000 mg: *p<0,001; **p=0,002; †p=0,676; ‡p=0,343; ¶p=0,561; ††p=0,521; ‡‡p=0,006*
SD: desviación estándar

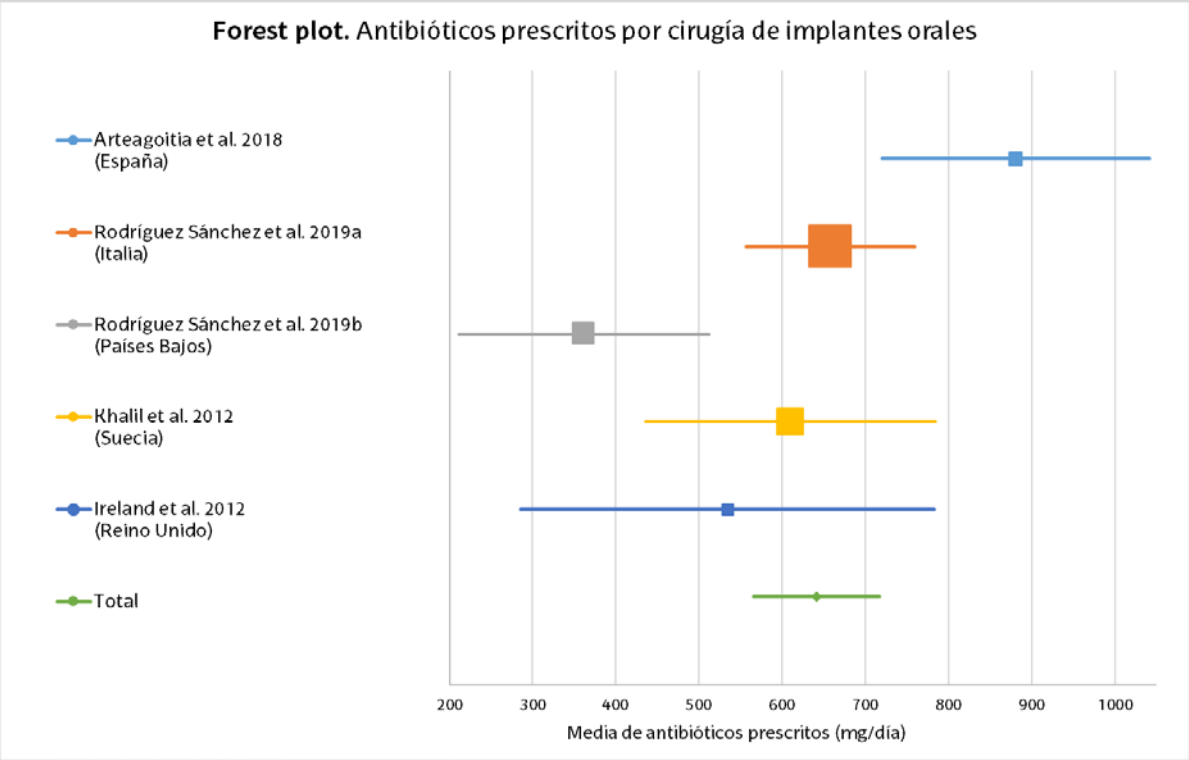
Entre las diferentes subpoblaciones (país y régimen de prescripción), los profesionales que prescribían exclusivamente antibióticos preoperatorios eran los únicos cuyas prescripciones de antibióticos (2.110 mg) no estaban significativamente (*p*=0,091) por encima de este umbral (Tabla 4). En la Figura 3 se muestra un diagrama de Forest teniendo en cuenta la variable de resultado. (Figura 3).

Tabla 4. Dosis media de antibióticos profilácticos (mg) prescritos por país y régimen de prescripción.

Régimen de prescripción / País		España	Italia	Países Bajos	Suecia	Reino Unido	General
Nunca	Media	-	-	-	-	-	-
	SD	-	-	-	-	-	-
	n	4	1	5	22	3	35
Sólo el preoperatorio	Media	2,182**	1,786††	2,037‡‡	2,020¶	2,930*	2,110¶¶
	SD	*1,401*	*630*	*451*	*302*	*513*	*676*
	n	11	28	44	37	18	138
Sólo el postoperatorio	Media	13,210	10,404	9,156	31,600	6,579	15,593*
	SD	*5,988*	*2,440*	*1,495*	*13,003*	*1,356*	*11,490*
	n	32	13	12	20	11	88
Pre y post operatorio	Media	17,830	12,414	9,413	7,327	9,992	13,282*
	SD	*6,782*	*3,254*	*2,937*	*5,770*	*5,672*	*6,480*
	n	166	112	73	26	67	444
En general	Media	15,993*	10,231*	6,617*	8,545*	8,025*	10,724*
	SD	*7,725*	*5,044*	*4,287*	*13,119*	*5,614*	*8,377*
	n	213	154	134	105†	99	705‡

† 13 participantes con regímenes ausentes no pudieron ser incluidos. Para mantener un número proporcional de participantes no prescriptores, solo se incluyeron 22 de los 35 participantes originales que nunca prescriben antibióticos profilácticos.
‡ 21 participantes excluidos porque sus prescripciones incluían tipos de antibióticos con DDD diferentes a 2.000 mg o del valor de DDD de la amoxicilina (1.500 mg).
*Prueba T bilateral que contrasta la media=2.000 mg: *p<0,001; **p<0,676; ††p=0,083; ‡‡p=0,590; ¶p=0,781; ¶p=0,091*
SD: desviación estándar

Figura 3. Diagrama de Forest



El gráfico de bosque representa las estimaciones de los valores medios y los intervalos de confianza del 95% para cada variable de resultado. El área de los cuadrados alrededor de los valores medios es proporcional al peso del estudio en el análisis. Una línea horizontal continua indica los intervalos de confianza del 95%, mientras que un rombo y una línea de puntos indican el valor medio global.

La prueba de Bartlett resultó ser estadísticamente significativa (p<0,001) entre los diferentes países y regímenes de prescripción profiláctica. Además, se encontró que el I^2 era bajo (18,7%). Por lo tanto, se encontró una baja heterogeneidad entre los países (Tabla 5).

El análisis de comparación múltiple de varianzas mostró que todas las comparaciones de varianzas eran estadísticamente significativas, excepto tres: Italia contra los Países Bajos, Italia contra el Reino Unido y el Reino Unido contra los Países Bajos. Por lo tanto, en cada una de estas comparaciones se encontró que ambos países eran homogéneos, en relación con las dosis de antibióticos prescritas.

Además, las comparaciones de medias resultaron ser estadísticamente significativas, excepto en el caso de Italia frente a Suecia, los Países Bajos frente a Suecia, el Reino Unido frente a los Países Bajos, Suecia frente al Reino Unido y sólo el postoperatorio frente al pre y postoperatorio. En consecuencia, se comprobó que ambos países, en cada una de estas comparaciones, prescribían una dosis media similar de antibióticos profilácticos (Tabla 5).

Tabla 5. Comparación múltiple de medias y varianzas de los antibióticos profilácticos prescritos (mg).

Comparaciones de grupos	Contraste de medias†	IC DEL 95%	*Valor p‡*	*Valor p§*
España contra Italia	5,743	4,430 - 7,056	<0.001	<0.001
España contra Holanda	9,232	7,969 - 10,495	<0.001	<0.001
Italia contra Holanda	3,489	2,409 - 4,569	0.058	<0.001
España contra Suecia	7,436	4,740 - 1,032	<0.001	<0.001
Italia contra Suecia	1,693	-922 - 4,307	<0.001	0.202
Holanda contra Suecia	-1,796	-4,386 - 794	<0.001	0.172
España contra el Reino Unido	7,758	6,298 - 9,219	<0.001	<0.001
Italia contra el Reino Unido	2,015	732 - 3,298	0.405	0.002
Reino Unido contra Holanda	1,473	261 - 2,686	0.011	0.017
Suecia contra el Reino Unido	323	-2,367 - 3,012	<0.001	0.813
Pre y post operatorio vs. Sólo el preoperatorio	11,022	10,402 - 11,641	<0.001	<0.001
Sólo el postoperatorio frente a la Pre y post operatorio	2,122	-329 - 4,573	<0.001	0.089
Sólo el preoperatorio frente a la Sólo el postoperatorio	13,144	10,756 - 15,531	<0.001	<0.001

† Las diferencias se calcularon deduciendo el valor medio del segundo grupo del del primero.

‡ Pruebas F bilaterales que contrastan H0: varianzas iguales. El valor α se calculó dividiendo 0,05 por el número total de comparaciones realizadas, 10 al comparar países (valor α=0,005) y 3 al comparar regímenes de prescripción (valor α=0,016)

§ Prueba t de dos muestras que contrasta las medias con varianzas iguales o desiguales en función de las varianzas Pruebas F. El valor α se calculó dividiendo 0,05 por el número total de comparaciones realizadas: 10 al comparar países (valor α=0,005) y 3 al comparar regímenes de prescripción (valor α=0,016)

IC: intervalo de confianza.

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3.4. Discusión

Los resultados obtenidos tras realizar la revisión sistemática y el meta-análisis sugieren que el uso rutinario de una dosis única de amoxicilina oral preoperatoria parece ser el único régimen favorable para prevenir los fracasos de los implantes tras la cirugía de implantes orales en pacientes sanos en condiciones ordinarias. Sin embargo, los regímenes de amoxicilina oral postoperatoria no parecen prevenir significativamente los fracasos de los implantes orales o las infecciones postoperatorias. En consecuencia, el uso adicional de amoxicilina oral postoperatoria no parece añadir ningún beneficio y podría considerarse como un sobretratamiento.

El análisis de efectividad de la amoxicilina sugirió que sería necesario tratar a 67 pacientes con una única dosis preoperatoria de amoxicilina oral para evitar la pérdida de un implante en un paciente. Además, también indicó que 77 implantes orales deberían ser tratados con una única dosis preoperatoria de amoxicilina oral para prevenir el fracaso del implante. Esto podría suponer una ligera reducción de casi el 1,3% del riesgo de fracaso del implante.

Además, ninguno de los estudios incluidos en este meta-análisis mostró por sí solo beneficios significativos de la amoxicilina en la prevención de los fracasos de los implantes dentales y las infecciones postoperatorias. Este hecho se observó tanto considerando los implantes como unidad experimental en el análisis como considerando a los pacientes como unidad experimental.

Este estudio demostró que el uso postoperatorio de amoxicilina no aporta ningún beneficio en la prevención del fracaso de los implantes. Posteriormente, otro artículo ha confirmado nuestros hallazgos [1].

Además, investigaciones anteriores sugerían que la administración postoperatoria de amoxicilina provocaba un aumento del número de anaerobios resistentes y una disminución del número de bacterias facultativas sensibles y cocos facultativos Gram positivos alrededor del implante oral [2]. Además, el uso prolongado de amoxicilina tendría un efecto negativo en la formación de hueso alrededor de los implantes, según una investigación realizada en un modelo animal [3].

La efectividad y la eficacia no pudieron evaluarse con otro tipo de antibiótico que no fuera la amoxicilina debido a la ausencia de ensayos clínicos al respecto.

Los pacientes sanos alérgicos a la amoxicilina son tratados frecuentemente de forma preventiva con clindamicina en cirugía oral. En el meta-análisis que hemos realizado no se ha encontrado ningún ensayo que estudiara este antibiótico en la cirugía de implantes orales. Los resultados encontrados en la exodoncia de terceros molares indican que la clindamicina oral no sólo puede ser ineficaz para prevenir las infecciones después de la cirugía, sino que incluso puede tener un efecto negativo.

Los pacientes alérgicos a la penicilina y el uso alternativo de clindamicina se han considerado recientemente factores de riesgo de fracasos de implantes [4-6] e infecciones tras cirugías orales y maxilofaciales [7], técnicas de preservación alveolar, y aumento óseo [8]. Este hecho, junto con la ausencia de ensayos clínicos (sólo se habían publicado estudios observacionales utilizando la clindamicina como segunda opción en caso de alergia a las penicilinas) impulsó la realización a través de este proyecto de investigación de un ensayo clínico controlado y aleatorizado que evaluara por primera vez la clindamicina en la cirugía de implantes orales.

El presente ensayo clínico demostró que una dosis única preoperatoria de 600 mg de clindamicina oral no difiere del placebo en la prevención de los fracasos de los implantes orales o de las infecciones postoperatorias tras la cirugía de implantes orales en pacientes sanos y en condiciones ordinarias. En cambio, hubo una tendencia no significativa a desarrollar una mayor incidencia de fracasos de los implantes cuando se administró clindamicina oral en el preoperatorio.

Además, la controversia sobre la asociación entre los fracasos de los implantes orales, los pacientes alérgicos a la penicilina y el uso de la clindamicina también pudo investigarse mediante este ensayo clínico [4,5]. Al excluir del ensayo a todos los participantes alérgicos a la penicilina, esta investigación podría delimitar la relación entre la posible mayor incidencia de fracasos de los implantes y el uso de clindamicina. Excluyendo hipotéticamente de la ecuación el papel de factores genéticos desconocidos de los pacientes alérgicos a la penicilina. Sin embargo, los pacientes no se sometieron a ninguna prueba de alergia a la penicilina, por lo que podrían ser alérgicos a la misma sin conocer esta condición.

La baja tasa de incidencia de infecciones postoperatorias notificada en este ensayo clínico puede haber sido el resultado de las medidas quirúrgicas antisépticas-estériles estándar, en combinación con la actuación de un cirujano experto y la duración limitada de la cirugía. No obstante, las tasas de infección postoperatoria reportadas en este ensayo clínico (3,2% para el grupo de clindamicina y 6,4% para el grupo de placebo) son bastante más elevadas pero similares a las encontradas en otros ensayos clínicos realizados con otro antibiótico (2,2% para el grupo de amoxicilina y 3,1% para el grupo de placebo).

Los resultados de este estudio son aplicables a la población de la que proceden los individuos incluidos en el ensayo y podrían generalizarse a otras poblaciones similares. Los autores no encontraron ninguna razón para creer que existan limitaciones en la validez externa y la aplicabilidad de este estudio a dichas poblaciones y en estas condiciones específicas: cirugía de implantes orales realizada por un cirujano experto y llevada a cabo en pacientes sanos con sitios de implantes completamente curados, sin infecciones preoperatorias ni necesidad de procedimientos de aumento óseo.

Los hayadgos de esta investigación no permiten recomendar el uso de clindamicina oral preoperatoria en la cirugía de implantes orales. Además, el diseño del estudio permite relacionar este tipo de antibiótico como el factor de riesgo y no la posible predisposición genética presente en los pacientes alérgicos a la penicilina, como algunos estudios habían hipotetizado [4,5].

Debe considerarse seriamente la relación riesgo-beneficio asociada al uso de antibióticos profilácticos, ya que el uso de amoxicilina preoperatoria puede prevenir un porcentaje moderado de fracasos de los implantes.

Debido a la alarma que suscita el desarrollo de resistencias bacterianas, los costes y los beneficios deben evaluarse siempre cuidadosamente en relación con la gravedad de la afección que se desea prevenir. Por lo tanto, el hallazgo de que la profilaxis antibiótica preoperatoria con amoxicilina reduce los fracasos de los implantes orales no debe llevar necesariamente a la conclusión de que esta práctica deba adoptarse sistemáticamente [9]. Desgraciadamente, las encuestas realizadas y el meta-análisis de encuestas, demostraron lo contrario.

La encuesta realizada en España mostró que la mayoría de los dentistas encuestados en Vizcaya prescribían habitualmente antibióticos profilácticos (aproximadamente el 88%) junto con la cirugía de implantes orales. También se descubrió que se prescribía una amplia gama de regímenes profilácticos que ilustraban la enorme variedad de tratamientos de profilaxis antibiótica prescritos por los dentistas. En consecuencia, esto reveló una falta de consenso entre los profesionales.

Al mismo tiempo, las recomendaciones formuladas en los últimos artículos publicados no se siguieron con frecuencia, ya que aproximadamente el 93% de los que prescriben antibiótico, lo hacían con un régimen postoperatorio [10]. Por lo tanto, los hábitos de prescripción de la mayoría de los dentistas encuestados en Vizcaya podrían considerarse como sobretratamiento.

Los resultados de esta encuesta también contrastan con las recomendaciones realizadas por el boletín INFAC en el volumen 29, número 1 del año 2021, dirigidas al uso racional de los antibióticos en los procedimientos dentales. El Boletín INFAC es un boletín farmacoterapéutico cuyo objetivo es actualizar los conocimientos farmacoterapéuticos de los profesionales sanitarios del País Vasco. Ofrece revisiones de tratamientos farmacológicos para diferentes patologías, revisiones de fármacos, noticias breves sobre medicamentos, etc. Está elaborada por un comité multidisciplinar en el que participan profesionales sanitarios del Departamento de Sanidad, Osakidetza y la Universidad del País Vasco [11].

En el citado volumen se afirma que no hay evidencia para el uso rutinario de la profilaxis antibiótica para prevenir las infecciones post-implante en pacientes sanos. La profilaxis antibiótica para prevenir el fracaso de los implantes sólo se recomendaría en casos complejos (implantes inmediatos con infecciones periapicales previas, necesidad de injertos óseos, etc.) y en pacientes inmunodeprimidos. Además, se recomienda una dosis única de amoxicilina 2 g por vía oral administrada 30-60 minutos antes del procedimiento, y en pacientes alérgicos a los betalactámicos, clindamicina 600 mg [11].

Por otra parte, los profesionales encuestados en los Países Bajos parecen ser más cautelosos a la hora de prescribir antibióticos en las cirugías de implantes dentales, y sólo el 44% lo hace de forma rutinaria.

Sin embargo, más de dos tercios de los profesionales encuestados en los Países Bajos tampoco siguieron un régimen antibiótico profiláctico adecuado y prescribieron antibióticos profilácticos en muchas situaciones no definidas por las directrices propuestas por el NVOI. Este hecho implicaría una falta de consenso en cuanto a las indicaciones para prescribir antibióticos profilácticos junto con la cirugía de implantes orales entre pacientes sanos, así como en cuanto al antibiótico de elección y la selección del régimen [12].

Siguiendo las directrices de la NVOI, los antibióticos preoperatorios sólo estaban indicados como profilaxis de la endocarditis bacteriana, en pacientes con implantes ortopédicos o cirugías realizadas en lugares infectados. La primera opción de tratamiento sugerida por el NVOI en estas situaciones debería ser una dosis única de amoxicilina y ácido clavulánico orales (1000/250 mg) una hora antes de la cirugía o clindamicina oral (600 mg) en caso de pacientes alérgicos a las penicilinas. Sin embargo, estas recomendaciones se hicieron con una ausencia total de pruebas que apoyaran la eficacia de estos dos regímenes antibióticos y los autores pedían la realización de nuevas investigaciones al respecto [12].

La mayoría de los dentistas encuestados en Italia tampoco cumplían las recomendaciones publicadas en los últimos artículos científicos y prescribían sistemáticamente varios tipos de antibióticos y regímenes profilácticos sin ninguna base científica. La encuesta descubrió que se prescribían sistemáticamente antibióticos a pacientes sanos, a menudo con tratamientos postoperatorios prolongados tras la cirugía de implantes orales.

La ausencia de directrices estandarizadas por parte de los organismos oficiales podría considerarse una de las razones del desacuerdo entre los profesionales sobre el tipo de antibiótico y el régimen seleccionado, especialmente cuando se trata de pacientes alérgicos a la penicilina. Además, la falta de pruebas científicas sobre el uso de otros

tipos de antibióticos distintos de la amoxicilina podría ser otra de las razones de la gran variación en el tratamiento de los pacientes alérgicos a la penicilina.

El meta-análisis de encuestas realizadas en diferentes países indica que la cantidad media de antibióticos profilácticos prescritos junto con la cirugía de implantes orales es aproximadamente cinco veces mayor que las recomendaciones basadas en la evidencia para pacientes sanos y condiciones ordinarias. Incluso en el caso de las prescripciones de antibióticos preoperatorios únicamente, la dosis media fue superior a la recomendada por la evidencia [5]. Los países presentaron una gran variabilidad en sus prescripciones y regímenes de antibióticos. También se observa que los facultativos de los países del norte de Europa tienden a prescribir con más cautela (un porcentaje menor de facultativos en los Países Bajos prescribió antibióticos de forma rutinaria) y a utilizar más antibióticos con un menor espectro antimicrobiano (fenoximetilpenicilina en el caso de Suecia). Estos factores pueden ser de vital importancia para evitar la resistencia bacteriana.

Los resultados del meta-análisis sugieren que un número significativo de prescripciones de antibióticos puede no estar basado en pruebas científicas. Este hecho puede llevar a que se prescriba un volumen significativo de antibióticos de forma irracional para la profilaxis en la cirugía de implantes orales.

Esta situación puede aumentar injustificadamente el riesgo de reacciones adversas y el desarrollo de resistencias bacterianas. La existencia de un mayor porcentaje de bacterias resistentes y de valores más altos de concentración mínima inhibitoria para diferentes antibióticos en España en comparación con los Países Bajos se ha relacionado previamente con un mayor consumo de antibióticos en España [13].

Además, el coste económico de la profilaxis antibiótica para el paciente es relativamente bajo, pero los costes potenciales para el sistema sanitario pueden ser importantes y expresamente infundados si se hicieran por medio de prescripciones irracionales [14].

Hasta la fecha de su publicación, éste fue el primer meta-análisis que evaluó cuantitativamente la prescripción de antibióticos profilácticos junto con la cirugía de implantes orales y la contrastó con las recomendaciones científicas existentes. Posteriormente, otro estudio similar ha corroborado estos resultados [15]. En consecuencia, este estudio podría revelar información clínicamente relevante para los profesionales que colocan implantes orales, con el fin de aumentar el cumplimiento de las recomendaciones a la hora de prescribir antibióticos profilácticos y evitar su mal uso.

3.4.1. Vacío de conocimiento

A pesar de los avances en el conocimiento logrados con la realización de este proyecto de investigación, todavía hay muchas incógnitas en cuanto a la profilaxis antibiótica en la cirugía de implantes orales.

El uso preoperatorio de amoxicilina resultó ser eficaz para prevenir el fracaso del implante, pero no para prevenir las infecciones postoperatorias. Sin embargo, se encontró que tres dosis preoperatorias diferentes de amoxicilina eran eficaces: 1, 2 o 3 gramos 1 hora antes de la cirugía. Esposito y colaboradores (2013) sugirieron que el uso rutinario de una simple dosis preoperatoria de 2 gramos podría ser sensato. Posteriormente, Romandini y colaboradores (2019) continuaron las recomendaciones de Esposito et al. (2013), pero sugirieron que la dosis preoperatoria de 3 gramos parecía ser la mejor.

Sin embargo y a pesar de las sugerencias de Esposito et al. (2013), el número relativamente alto de pacientes que deben ser tratados con amoxicilina para prevenir una sola pérdida de implante plantea el dilema de si su uso rutinario en es efectivo y debe ser indicado en pacientes sanos y condiciones ordinarias.

Por otra parte, un estudio prospectivo analizó la concentración plasmática de amoxicilina en la sangre venosa y del lecho del implante después de una cirugía de implante oral. Sus resultados mostraron que las concentraciones plasmáticas tras una dosis profiláctica de 1 gramo de amoxicilina preoperatoria eran superiores a la concentración inhibitoria mínima necesaria para prevenir las bacterias dentales más comunes implicadas en la periimplantitis y las enfermedades periodontales [16]. Por lo tanto, existe incertidumbre sobre la elección de la dosis de amoxicilina preoperatoria en caso de que su uso rutinario se considere indicado en la cirugía de implantes orales.

Por otro lado, teniendo en cuenta la amenaza de la resistencia bacteriana y la gran variabilidad en la efectividad de la amoxicilina preoperatoria (el NNT varía entre 25 y 77), lo más prudente sería no recomendar la prescripción rutinaria de antibióticos en la cirugía de implantes orales en pacientes sanos en condiciones ordinarias.

Hasta que se realizó el ensayo clínico incluido en esta tesis doctoral, la única evidencia existente sobre la profilaxis antibiótica en la cirugía de implantes orales se limitaba a la amoxicilina. Desgraciadamente, aún se carece de conocimiento científico sobre la eficacia y efectividad de otros tipos de antibióticos que se prescriben con frecuencia en este entorno, como la combinación de amoxicilina con ácido clavulánico o la claritromicina en pacientes alérgicos a la penicilina.

Además, la falta de evidencia que apoye el uso de clindamicina en pacientes alérgicos a la penicilina plantea la cuestión del tipo de antibiótico indicado en estos casos.

Naturalmente, todas estas limitaciones de conocimiento se refieren a la cirugía de implantes orales en condiciones ordinarias y en pacientes sanos. Sin embargo, en las cirugías de implantes orales realizadas con aumento o injerto óseo la falta de evidencia sobre el uso de antibióticos profilácticos también es un problema [17].

3.4.2. Perspectivas futuras

Esta tesis doctoral, ha servido para aclarar algunos aspectos de la profilaxis antibiótica en la cirugía de implantes orales, pero también ha descubierto muchas preguntas nuevas que carecen de una respuesta clara en este momento. Por este motivo, se debe seguir investigando a nivel clínico, farmacoepidemiológico y del sistema sanitario.

En primer lugar, se necesitan nuevos ensayos clínicos aleatorizados y controlados con placebo que contrasten diferentes dosis preoperatorias de amoxicilina oral entre sí. Debe hacerse hincapié en la comparación de dosis de 1 y 2 gramos administradas 1 hora antes de la cirugía de implantes.

En segundo lugar, sería necesario evaluar la eficacia y efectividad de otros tipos de antibióticos distintos a la amoxicilina mediante ensayos clínicos controlados y aleatorizados.

En tercer lugar, es necesario diseñar programas de difusión del conocimiento científico a los clínicos para adecuar el resultado de las investigaciones a la práctica diaria. Sería necesario adaptar las recomendaciones del uso de clindamicina properatoria en casos de alergia a los antibióticos beta-lactámicos y confeccionarnuevas encuestas transversales que corroboren este cambio de actitud en la prescripción de antibióticos en conjunción con la cirugía de implantes orales.

Nuevas investigaciones son necesarias para concretar las indicaciones del uso profiláctico de antibióticos en la cirugía de implantes orales en pacientes con patologías sistémicas y optimizar las recomendaciones existentes al respecto.

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4. Conclusiones

4.2. Conclusiones específicas

Antibióticos preventivos en cirugía de implantes orales. Revisión sistemática y meta-análisis

Una dosis única preoperatoria de 1, 2 o 3 gramos de amoxicilina oral puede ser eficaz y efectiva para prevenir los fracasos de los implantes dentales. La amoxicilina oral postoperatoria (exclusivamente postoperatoria o asociada a la amoxicilina oral preoperatoria) podría no ser beneficiosa en la profilaxis de los fracasos de los implantes dentales en conjunción con la cirugía de implantes orales en pacientes sanos y en cirugías no complejas. No existe evidencia que ampare la utilización de amoxicilina oral para prevenir el desarrollo de infecciones postoperatorias.

Clindamicina preventiva en cirugía oral. Revisión sistemática y meta-análisis

No hay estudios suficientes sobre la eficacia de la clindamicina preventiva en intervenciones quirúrgicas orales que no sea la extracción de terceros molares. Se puede aceptar la hipótesis nula de que la clindamicina oral no es eficaz para prevenir la infección en la cirugía de terceros molares, independientemente de la dosis utilizada. No existen ensayos clínicos aleatorios y controlados sobre la eficacia de la clindamicina para prevenir la infección y/o el fracaso en la cirugía de implantes dentales.

Clindamicina preventiva en la cirugía de implantes orales. Ensayo clínico aleatorizado y controlado

En la cirugía de colocación de implantes dentales en pacientes sanos y cuando no hay infección previa en el lecho implantarlo ni se necesita injerto óseo, una dosis única de 600 mg de clindamicina administrada una hora antes de la cirugía por vía oral, no se muestra eficaz ni en la disminución de la incidencia de infección ni en la posibilidad de pérdida del implante.

Hábitos de prescripción antibiótica en cirugía de implantes orales. Encuestas transversales en España, Países Bajos e Italia y meta-análisis de encuestas transversales

La prescripción de antibióticos preventivos es muy habitual en la cirugía de implantes orales en pacientes sanos en cirugías no complicadas por los profesionales actualmente activos en España, Países Bajos e Italia. Los clínicos prescriben una gran variedad de regímenes profilácticos, demostrando una falta de consenso en sus hábitos de prescripción.

Los profesionales que realizan cirugía de implantes orales suelen recetar en promedio más antibióticos preventivos que la dosis recomendada basada en la evidencia. Se observó una gran variación en la cantidad media de antibióticos prescritos entre los diferentes países, así como una gran diversidad en los regímenes empleados.

4.3. Conclusiones generales

La prescripción rutinaria de antibióticos preventivos en implantología debe considerarse con cautela. La decisión de utilizar un antibiótico debe juzgarse de forma individual para cada paciente en función de su estado de salud y de las posibles complicaciones de contraer una infección. No disponemos de información sobre la eficacia de la profilaxis antibiótica en pacientes con enfermedades de base y mayor riesgo de infección.

En pacientes sanos no alérgicos a la amoxicilina, el empleo de una dosis única preoperatoria de 1, 2 ó 3 gramos de amoxicilina oral parece ser eficaz en la prevención del fracaso de los implantes orales. Sin embargo, debemos tener en cuenta que sería necesario tratar entre 33 y 167 pacientes para evitar la pérdida de un implante. Por lo tanto, al decidir utilizar profilaxis antibiótica para prevenir las complicaciones infecciosas y/o el fracaso del implante en pacientes sanos, el profesional debe tener en cuenta el posible aumento del riesgo de efectos adversos leves, la baja tasa de complicaciones y la ausencia de complicaciones graves incluso en ausencia de profilaxis. Otro aspecto importante que debe considerarse es la necesidad de limitar el uso de antibióticos para frenar la creciente resistencia microbiana a los fármacos.

En pacientes sanos alérgicos a la amoxicilina, el análisis de la literatura nos permitió comprobar que no existía ningún ensayo clínico que avalara la eficacia de la clindamicina en la prevención de la infección y/o el fracaso en la cirugía de implantes. Los resultados del ensayo clínico aleatorizado y cegado que se realizó con una dosis preoperatoria de 600 mg de clindamicina oral, no muestra que la clindamicina sea eficaz en la cirugía de implantes orales en comparación con el placebo, para prevenir la infección y/o el fracaso de los implantes. La clindamicina podría incluso ser responsable de un mayor riesgo de pérdida del implante.

Por otro lado, hemos corroborado y analizado como los profesionales de la implantología, mayoritariamente no siguen las recomendaciones publicadas en la literatura, empleando todo tipo de antibióticos con pautas y posologías muy dispares. En general, se puede afirmar que en la mayor parte de los casos los implantólogos emplean antibióticos preventivos con dosis muy superiores a las que los estudios consideran eficaces.

5. Anexo

5.2. Lista de publicaciones e indicios de calidad

Rodríguez Sánchez F, Rodríguez Andrés C, Arteagoitia I. Which antibiotic regimen prevents implant failure or infection after dental implant surgery? A systematic review and meta-analysis. J Craniomaxillofac Surg. 2018 Apr;46(4):722-736. doi: 10.1016/j.jcms.2018.02.004. Epub 2018 Feb 26. PMID: 29550218.

Factor de impacto de la revista

- Journal of Citation Reports: 1.960
- Scimago Journal: 1.96

Posición de la revista por categoría

- Journal of Citation Reports:

Surgery; 90/200 (Q2)

Dentistry, Oral Surgery & Medicine; 31/91 (Q2)

- Scimago Journal:

Oral Surgery (Q1), Otorhinolaryngology (Q1), Surgery (Q1)

Número de citas

- Web of Science: 19
- Scopus: 23
- Google Scholar: 46

Índice H de revistas

- Scimago Journal: 77

Arteagoitia I, Rodríguez-Andrés C, Rodríguez-Sánchez F. Antibiotic prophylaxis habits in dental implant surgery among dentists in Spain. A cross-sectional survey. Med Oral Patol Oral Cir Bucal. 2018 Sep 1;23(5):e608-e618. doi: 10.4317/medoral.22626. PMID: 30148475; PMCID: PMC6167099.

Factor de impacto de la revista

- Journal of Citation Reports: 1.284
- Scimago Journal: 0.623

Posición de la revista por categoría

- Journal of Citation Reports:

Dentistry, Oral Surgery & Medicine; 65/91 (Q3)

- Scimago Journal:

Dentistry (Q2), Medicine (Q2), Otorhinolaryngology (Q2), Surgery (Q2)

Número de citas

- Web of Science: 9
- Scopus: 9
- Google Scholar: 13

Índice H de revistas

- Scimago Journal: 56

Rodríguez Sánchez F, Arteagoitia I, Rodríguez Andrés C, Bruers J. Antibiotic prophylaxis prescribing habits in oral implant surgery in the Netherlands: a cross-sectional survey. BMC Oral Health. 2019 Dec 12;19(1):281. doi: 10.1186/s12903-019-0981-4. PMID: 31830979; PMCID: PMC6909651.

Factor de impacto de la revista

- Journal of Citation Reports: 1.911
- Scimago Journal: 0.731

Posición de la revista por categoría

- Journal of Citation Reports:

Dentistry, Oral Surgery & Medicine; 38/91 (Q2)

- Scimago Journal:

Dentistry (Q1)

Número de citas

- Web of Science: 7
- Scopus: 6
- Google Scholar: 9

Índice H de revistas

- Scimago Journal: 50

Rodríguez Sánchez F, Arteagoitia I, Rodríguez Andrés C, Caiazzo A. Antibiotic prophylaxis habits in oral implant surgery among dentists in Italy: a cross-sectional survey. BMC Oral Health. 2019 Dec 2;19(1):265. doi: 10.1186/s12903-019-0943-x. PMID: 31791306; PMCID: PMC6889412.

Factor de impacto de la revista

- Journal of Citation Reports: 1.911
- Scimago Journal: 0.731

Posición de la revista por categoría

- Journal of Citation Reports:

Dentistry, Oral Surgery & Medicine; 38/91 (Q2)

- Scimago Journal:

Dentistry (Q1)

Número de citas

- Web of Science: 8
- Scopus: 8
- Google Scholar: 10

Índice H de revistas

- Scimago Journal: 50

Rodríguez Sánchez F, Arteagoitia I, Teughels W, Rodríguez Andrés C, Quirynen M. Antibiotic dosage prescribed in oral implant surgery: A meta-analysis of cross-sectional surveys. PLoS One. 2020 Aug 18;15(8):e0236981. doi: 10.1371/journal.pone.0236981. PMID: 32810135; PMCID: PMC7446810.

Factor de impacto de la revista

- Journal of Citation Reports: 3.240
- Scimago Journal: 0.990

Posición de la revista por categoría

- Journal of Citation Reports:

Biology (n/a)

Multidisciplinary Sciences; 26/72 (Q2)

- Scimago Journal:

Multidisciplinary (Q1)

Número de citas

- Web of Science: 4
- Scopus: 3
- Google Scholar: 6

Índice H de revistas

- Scimago Journal: 332

Arteagoitia I, Rodríguez Sánchez F, Figueras A, Arroyo-Lamas N. Is clindamycin effective in preventing infectious complications after oral surgery? Systematic review and meta-analysis of randomized controlled trials. Clinical Oral Investigations.

Bajo revisión

Factor de impacto de la revista

- Journal of Citation Reports: 3.573 (2020)
- Scimago Journal: 1.088 (2020)

Posición de la revista por categoría

- Journal of Citation Reports (2020):

Dentistry, Oral Surgery & Medicine; 21/92 (Q1)

- Scimago Journal (2020):

Dentistry (miscellaneous) (Q1)

Número de citas

- Web of Science: 4
- Scopus: 3
- Google Scholar: 6

Índice H de revistas

- Scimago Journal: 82

Santamaría G, Rodríguez Sánchez F, Rodriguez C, Barbier L Arteagoitia I, Effect of Preoperative Clindamycin Preventing Implant Failures and Postoperative Infections after Oral Implant Surgery: a Randomized Placebo-controlled Clinical Trial. Clinical oral implants research.

Enviado a la revista

Factor de impacto de la revista

- Journal of Citation Reports: 5.977
- Scimago Journal: 2.407

Posición de la revista por categoría

- Journal of Citation Reports (2020):

Dentistry, Oral Surgery & Medicine; 6/92 (Q1)

Engineering, Biomedical; 17/89 (Q1)

- Scimago Journal (2020):

Dentistry; oral Surgery (Q1)

Índice H de revistas

- Scimago Journal: 161

5.3. Artículos publicados

Véase a partir de la página numero 326.

Antibiotic prophylaxis in oral implant surgery

Fabio Rodríguez Sánchez

Promotor: María Iciar Arteagoitia Calvo

Co-promotor: Carlos Rodríguez Andrés

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This project would not have been possible without the unconditional help of my thesis directors Dr. Iciar Arteagoitica Calvo and Dr. Carlos Rodríguez Andrés. Undoubtedly, a great part of the merit belongs to you too. It has been several years of unsuspected patience and tenacity also bathed in tints of drama with a pandemic in the middle. Without your effort and support I am sure that this project would not have been possible. Thank you.

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I could not forget the great collaboration provided by a long list of colleagues, who over the years have become my friends, and who have enriched me personally and professionally: Dr. Martine Pauwels, Dr. Tim Verspecht, Drs. Wannes Van Holm, Drs. Naiera Zayed, Drs. Mihai Tarce, Drs. Manoetjer Siawasch, Moaad Alami, Nina Sidiropoulou and Nikolaos Ntovas.

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3. Contents

LIST OF ABBREVIATIONS

AEMPS: Spanish Agency of Medicines and Medical Devices

AMX: Amoxicillin

ARI: Absolute Risk Increase

ARR: Absolute Risk Reduction

BID: twice a day

BL: Bone Level

CG: Control Group

CI: Confidence Interval

CLX: Chlorhexidine

CONSORT: Consolidated Standards of Reporting Trials

CSIC: Spanish National Research Council

DDD: Defined Daily Dose

EU: European Union

FNOMCeO: National Federation of the Orders of Physicians and Dentists

GRADE: Grading of Recommendations, Assessment, Development and Evaluations

IAO: Italian Academy of Osseointegration

IBM: International Business Machines Corporation

KNMT: Royal Dutch Dental Association

MA: Mean Age

mg: milligram

MH: Mantel-Haenszel

N: Newton's

n: Sample size

NNH: Number needed to harm

NNT: Number needed to treat

NS: Not estimable

NVOI: Dutch Association of Oral Implantology

OR: Odds Ratio

PICOS: Patient, Intervention, Comparison, Outcome and Study type

POA: Postoperative oral amoxicillin

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

PROA: Spanish Antimicrobial Stewardship Program in Primary Care

QD: once a day

QID: Four times daily

Q-Q plots: Quantile-quantile plots

RCT: Randomized clinical trial

RevMan: Review Manager

RR: Relative Risk

SD: Standard Deviation

SDOAP: Single-dose oral amoxicillin preoperatively

SICOI: Society of Oral Surgery and Implant Dentistry

SIO: Italian Society of Osseointegration

SPSS: Statistical Package for Social Sciences

STROBE: Strengthening the Reporting of Observational studies in Epidemiology

TG: Test Group

TID: 3 times daily

TL: Tissue Leven

VAS: Visual Analogue Scale

EU: European Union

5. Synthesis

5.1. Summary

INTRODUCTION

After the loss of one or more teeth, the placement of an oral implant to restore this absence is becoming more frequent. In Spain, approximately 1.2 to 1.4 million implants are placed every year, being one of the countries with the highest frequency of such treatment. Prophylactic antibiotics are prescribed to prevent implant failures and postoperative infections. However, this treatment remains controversial and there is uncertainty about its indication and the most appropriate dosing regimen.

OBJECTIVES

The aim of this doctoral thesis is to provide information on the indication of antibiotic prophylaxis in oral implant surgery in healthy patients and ordinary conditions. In addition, to analyze the prescription guidelines made by clinicians and the existence of consensus in different countries to perform this prophylaxis.

METHODS

The scientific literature was analysed by means of three meta-analyses aimed at determining the level of evidence and clarifying the existing consensus in the literature. A clinical trial was conducted to study the efficacy and effectiveness of oral clindamycin and the prescription of prophylactic antibiotics by clinicians in three different countries was evaluated by means of a cross-sectional survey: Spain, Italy and the Netherlands.

RESULTS

A single preoperative dose of 1, 2 or 3 grams of amoxicillin one hour before surgery could be effective in preventing oral implant failure. In cases of allergy to amoxicillin, clindamycin is usually recommended, but in the clinical trial conducted it has not been shown to be effective in preventing either failure or infection. The doses and dosing schedules of prophylactic antibiotics used in clinical practice identified by the surveys are very different from the consensus reached, being possible to observe a probable overtreatment of patients.

CONCLUSIONS

The routine prescription of preventive antibiotics in implant dentistry should be judged on an individual patient basis. In healthy patients not allergic to amoxicillin, a single preoperative dose of 1, 2 or 3 grams could be used. In patients allergic to beta-lactam antibiotics, the administration of 600 mg of oral clindamycin does not show efficacy or effectiveness in the prevention of failures and infections and it could be a risk factor for implant loss. In addition, most practitioners do not follow the advice of the literature on oral implant surgery in healthy patients and straightforward conditions, using very varied regimens and doses of antibiotics much higher than those recommended in the scientific literature.

5.2. Introduction

5.2.1. Oral implants

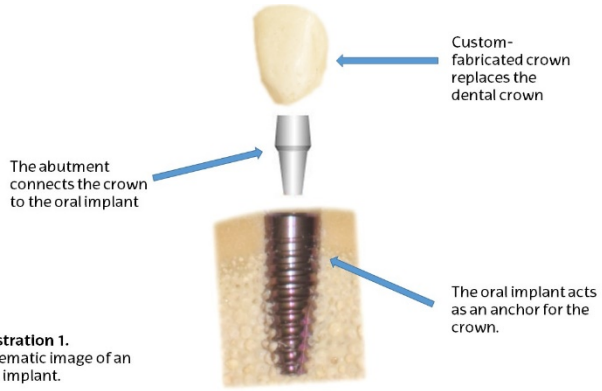


Illustration 1.
Schematic image of an oral implant.

After the loss of a tooth there is a lack of both, its visible part called crown, as well as its root that is hidden by the gum and alveolar bone. Tooth loss is a very common phenomenon and is usually the result of caries, periodontal disease, an endodontic (pulp) problem or trauma. In 2010, approximately 2.3% of the world's population, representing 158 million people worldwide, suffered severe tooth loss [1]. According to a press release from the General Council of Dentists of Spain dated October 28, 2021, 25 million inhabitants have lost at least one tooth in our country.

Oral implants, also known as dental implants, are medical devices that serve as artificial tooth root replacements. An oral implant is placed in the maxillary, mandibular or zygomatic bone in such a way that it fuses with the patient's natural bone. This phenomenon is called osseointegration. In this way, the oral implant becomes a strong and robust base or abutment for subsequent tooth replacement [2].

Oral implants can serve to replace an individual tooth with a single crown, several teeth at once with a bridge, or all the teeth in an arch with a prosthesis or overdenture. Oral implants can also serve as anchorage and force transmission in orthodontic treatment [3].

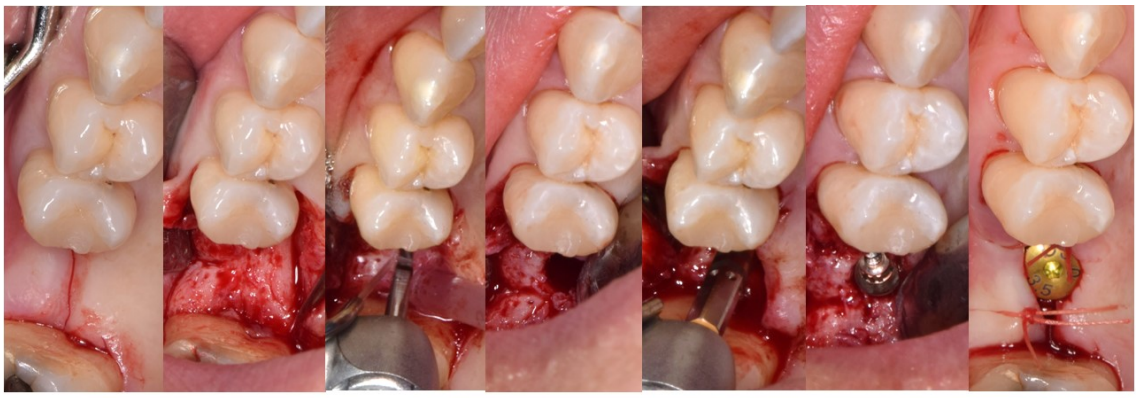


Illustration 2.
Surgical procedure performed for the insertion of an oral implant in the right upper arch: crestal incision of the gingiva and intrasulcular incision of the adjacent teeth (a), elevation of a muco-periosteal flap (b), drilling of the alveolar bone according to the manufacturer's protocol (c), ostectomy completed (d), insertion of the implant according to the torque and speed indicated by the manufacturer (e), bone level implant positioned in the alveolar bone (f), insertion of the healing abutment and closure of the flap by means of a four-zero resorbable suture (g).

Most dental implants usually require five basic steps for their placement: incision in the soft tissue and elevation of a mucoperiosteal flap, preparation of the implant bed by drilling the alveolar bone, placement of the implant and adaptation of the soft tissue by placing a healing abutment on the implant, also called a "healing abutment".

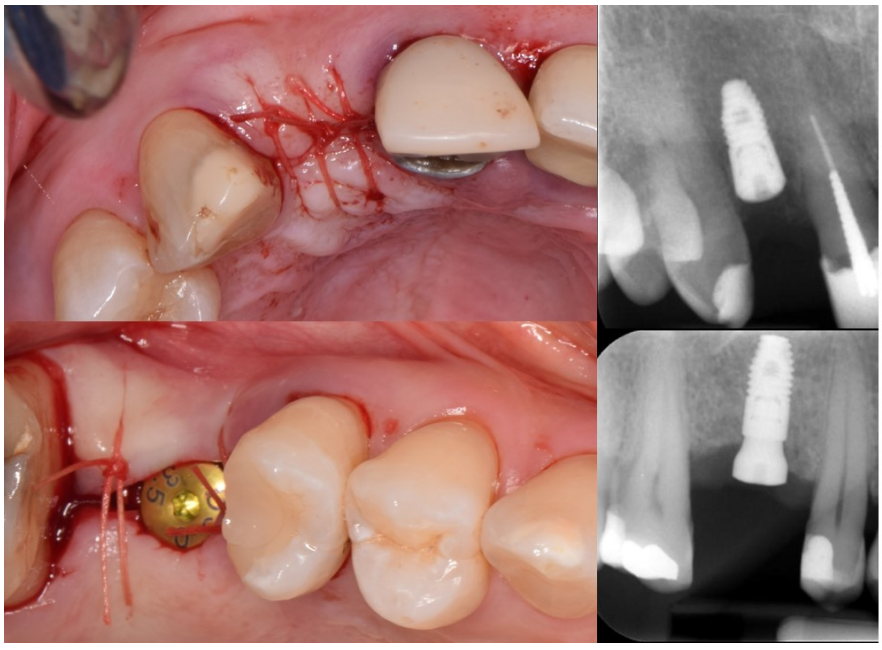
Alternatively, a cover screw can be placed and the flap closed [4].

There are also different sequences of implant placement after tooth extraction. An implant can be placed immediately after extraction, two weeks to two months after extraction, or three or more months after extraction [5].

When residual bone volume is insufficient, it is common to perform bone augmentation procedures before or in conjunction with oral implant placement, a term also known as guided bone regeneration [6].

There are also several options when it comes to restoring the crown of the missing tooth with a prosthesis or "loading" the implant. Immediate loading after the surgical procedure, early loading two weeks after surgery or late loading up to three months after oral implant surgery can be performed [7].

Survival of dental implants is described in several longitudinal studies and varies between 90-95% [8]. Despite the high survival rate, implant failures and other postoperative complications can occur [9].



a **Illustration 3.**
Bone level implant positioned in the maxilla and submerged under the gingiva after placement of a cover screw and a four-zero resorbable suture (a).

b Bone-level implant positioned in the maxilla and connected to the oral cavity by a healing abutment (b).
To the right of the clinical photographs, the respective radiographs.

These failures and complications are very poorly tolerated by both patients and professionals.

After the insertion of a dental implant, peri-implant infections are one of the most frequent complications. They are called mucositis if there are signs of inflammation in the absence of bone loss around the implant, or peri-implantitis if there is bone loss along with the typical signs of soft tissue inflammation. The prevalence of mucositis and peri-implantitis varies between 1% and 63.4% depending on the studies [10]. When peri-implantitis is established, its treatment is complex, the peri-implant bone is resorbed and may lead to implant loss. One of the causes related to peri-implant infections has been the inoculation of bacteria during the surgical procedure [9].

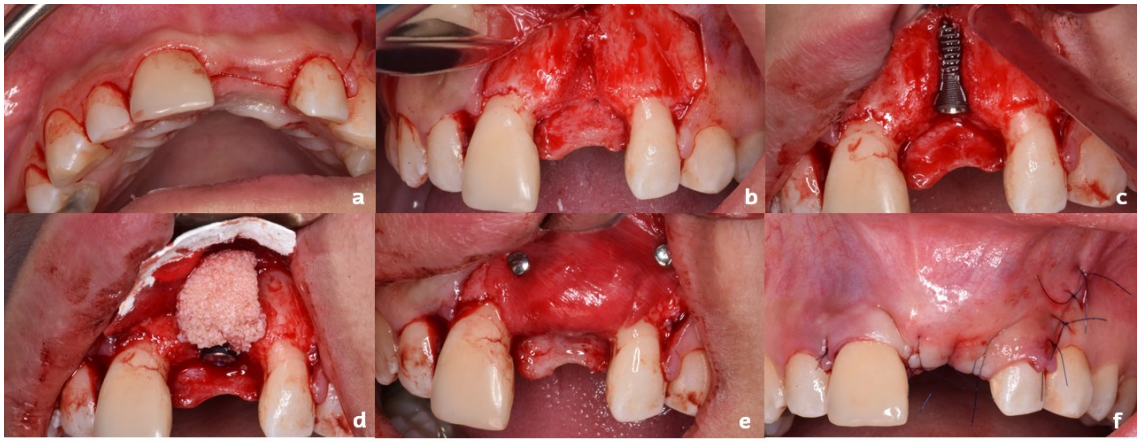


Illustration 4.
Surgical procedure performed for the insertion of an oral implant in the left upper arch by means of a concomitant bone augmentation procedure: crestal incision of the gingiva and intrasulcular incision of the adjacent teeth and unloading incision (a), elevation of a mucoperiosteal flap and exposure of the bone defect (b), drilling of the alveolar bone according to the manufacturer's protocol and insertion of the implant (c), covering of the defect and the implant with a bone xenograft (d), covering of the bone substitute by means of a resorbable collagen membrane and fixation with pins (e), closure of the mucoperiosteal flap (g).

5.2.2. Prophylaxis in oral implantology

The term "prophylaxis" comes from Ancient Greek; from *pro* (Modern Greek: προ, romanization: *pro*) meaning "before" and from *phulaxis* (Modern Greek: φύλαξις, romanization: *phýas*), meaning literally "guardian". According to the Royal Academy of the Spanish Language "prophylaxis" means preservation from disease. It could also be defined as the set of measures taken to protect or preserve someone from disease.

In this project, prophylactic antibiotics were defined as those antibiotics prescribed in the perioperative period in conjunction with oral implant surgery to prevent postoperative infections and oral implant failures [11,12].

Due to the potential complications related to oral implant surgery, several antimicrobial peri-surgical treatments based on antiseptics and antibiotics have been studied for the prophylaxis of post-implant infections and oral implant failures.

Chlorhexidine may be a relevant and low-risk option, as it alters the bacterial biofilm (colony of bacteria adhering to each other and to the surfaces of the implant, dental tissue or gingiva) and reduces inflammation of the peri-implant tissues [13,14].

The use of prophylactic antibiotics in oral implant surgery dates back to the early years of oral implantology. In early publications, penicillin was routinely administered 1 hour preoperatively and the following 10 postoperative days after oral implant surgery to promote osseointegration [15]. Shortly afterwards this practice has been refuted by other publications [16].

Currently, there appears to be no established consensus on the use and indications for antibiotic prophylaxis at oral implant placement in healthy patients under straightforward conditions [17]. A systematic review conducted by Cochrane concluded that it might be sensible to suggest the routine use of a single dose of 2 g of prophylactic amoxicillin just before oral implant placement. However, it could not be clarified whether the adjunctive use of postoperative antibiotics was beneficial, nor which antibiotic would be the most effective [9].

Similarly, scientific evidence regarding the prophylactic use of antibiotics to reduce the risk of infection in guided bone regeneration procedures prior to or in conjunction with oral implant placement is very limited [6]. However, practitioners are more likely to prescribe antibiotics with the use of bone grafts and as the complexity of the procedure increases to decrease the chances of developing an infection [18].

The choice of antibiotic, dosage and dosing regimen vary according to the studies. The beta-lactam group has been the most commonly used antibiotic for prophylaxis in dentistry. Within this group, amoxicillin is frequently the first choice due to its efficacy against *streptococci* and oral anaerobes. If the patient has a history of anaphylactic reactions to the penicillin group, amoxicillin is commonly substituted for clindamycin [19]. This also seems to occur with oral implant surgeries [20, 21].

The prophylactic use of antibiotics in dentistry does seem to be well documented to prevent complications in patients who are at risk of developing infectious endocarditis or immunocompromised patients [22]. According to other authors, the placement of dental implants after performing a mucoperiosteal flap does not reveal a significant risk of bacteremia, so its prophylactic use, even in patients at risk, would be questionable [23].

There are several clinical trials using amoxicillin with different dosing regimens in healthy patients and straightforward conditions (1 hour preoperatively, two days postoperatively or one week after implant placement) and doses (1, 2 or 3 grams) for the prophylaxis of postoperative complications such as infection, inflammation and dental implant failure [24-30].

However, clindamycin being one of the commonly prescribed antibiotics in patients allergic to amoxicillin [31,32], there are no clinical trials available evaluating its effect in preventing postoperative failures or infections after oral implant surgery in healthy patients and in whom bone regeneration or augmentation was not performed. For this reason, further clinical investigations with antibiotics other than amoxicillin were required to augment the limited evidence for alternative antibiotics in penicillin-allergic patients [12]. Although several earlier studies concluded that both penicillin and clindamycin were effective in reducing infections in bone beds where bone regeneration has been performed for oral implant placement [33, 34], new retrospective research indicates that penicillin allergy and alternative use of clindamycin may be associated with increased failure of oral implants and bone regeneration itself [35-38].

Several systematic reviews and meta-analyses studying the prophylactic effect of amoxicillin in oral implant surgery have been published in the past [9, 11, 39-41]. However, there is still insufficient evidence and it is unclear whether the use of antibiotics is beneficial and what and how the most effective antibiotic treatment would be to prevent infection or loss of the oral implant after surgery [27, 29, 30]. In the absence of protocols, the prophylactic prescription of antibiotics after dental implant placement has become a very common practice.

On the other hand, the use of antibiotics prescribed by dentists has increased in recent years [42] and the estimated costs, in the USA alone, for antibiotics used for prophylaxis in dental treatment exceed $145 billion annually [43].

Similarly, dental implant therapy is also on the rise. In the USA alone approximately 500,000 dental implants are placed every year [44]. In addition, the global market for dental implants is growing steadily and is expected to grow to about $13 billion by 2023 [45].

The evolution in the number of dental implants used in Spain has undergone an enormous progression. In 2004, 400,000 implants were placed, in 2008 there were 813,000 and in 2016 the figure reached 1,076,000, according to the "*Implant Flash Analysis*" project, carried out by the company KeyStone®. Spain is probably the country with the highest ratio of implants per inhabitant in Europe, and perhaps in the world. With approximately one million patients undergoing oral implant treatment each year, it ranks third in volume of people treated with this therapy, behind only Germany and Italy. Considering 2012 as the base year, the number of implants sold, and probably placed, has increased by 35% [46]. According to a press release from the General Council of Dentists of Spain dated 28 October 2021, between 1.2 and 1.4 million implants are placed annually in Spain.

Given the large number of dental implants that are placed worldwide, the amount of antibiotics used to prevent complications can be a relevant data at epidemiological and public health level. In addition, the General Council of Dentists of Spain reported in a

press release dated 29 October 2021 that about 10% of antibiotic prescriptions in Spain come from dentists, "so the profession must take urgent measures, since its misuse is increasing resistance to infections and, therefore, poses a threat to health".

5.2.3. Adverse reactions to antibiotic therapy

Irrational use of antibiotics can lead to unjustified increase in costs and adverse reactions such as allergies, toxicity, gastrointestinal disorders and bacterial resistances [47, 48]. The latter condition has recently become a major threat worldwide. Epidemiological studies have shown a direct relationship between antibiotic consumption and the emergence and spread of resistant bacterial strains [49].

Concern about the increasing emergence of new bacterial strains resistant to all types of antibiotics and superinfections continues to rise. Drug-resistant diseases already cause at least 700,000 deaths per year worldwide, and in the most alarming scenario, the figure could rise to 10 million deaths per year by 2050 if no action is taken [50].

The economic damage caused by uncontrolled antimicrobial resistance could be comparable to that of the 2008-2009 global financial crisis due to the dramatic increase in health-care costs, impact on food and feed production, trade and livelihoods. By 2030, antimicrobial resistance could push 24 million people into extreme poverty [50].

Many professionals and patients do not see antibiotic resistance as a reason to abstain from antibiotic use. Furthermore, data provided by the Special Eurobarometer in April 2016 on antimicrobial resistance indicate that neither European nor Spanish society has adequate knowledge about the purpose and mechanism of action of antibiotics [51].

One of the initiatives developed in Spain during 2015 proposed by the Ministry of Health, Social Services and Equality in its strategic and action plan to reduce the risk of selection and dissemination of antibiotic resistance was to limit the prophylactic use of antibiotics to cases with defined clinical needs in Human Health. To this end, it was proposed to design and disseminate tools for the promotion of the prudent use of antibiotics. During 2016, the goal was set to develop documentation concerning the limitation of prophylactic antibiotic use [52].

5.2.4. Theoretical framework

For antibiotic prophylaxis in oral implant surgery, each professional may be using the drug and dosage they consider most appropriate, but it is not known how often prophylactic antibiotics are actually prescribed in implant placement in Spain and whether this is similar to that of other countries in our environment. It is also unknown which antibiotics and dosage are being prescribed more frequently, as well as the evidence that supports these antibiotic prescriptions to prevent infection and failure of oral implants. As published by Deeb and colleagues in a study of U.S. practitioners, the lack of consensus may result in practitioners not using antibiotic prophylaxis in

accordance with evidence-based recommendations published in the scientific literature [17].

This project aims to find out whether the prophylactic use of antibiotics in oral implant surgery is effective in the prevention of postoperative infections and oral implant failure. To this end, a systematic review and meta-analysis of the scientific literature was carried out. Subsequently, a survey was performed among oral health professionals in our country and other surrounding countries to evaluate their antibiotic prophylaxis habits in oral implantology, to assess the level of clinical consensus and to determine whether they follow the latest recommendations published in the scientific literature. Subsequently, a systematic review and meta-analysis of all the cross-sectional surveys that had the same objective was accomplished in order to compare different populations and their prescriptions. Because patients allergic to beta-lactam antibiotics were often treated preventively with clindamycin, a systematic review and meta-analysis was performed to check the efficacy of clindamycin in oral surgery. Finally, and after demonstrating the lack of evidence in this regard, a randomized, double-blind, placebo-controlled clinical trial was designed and carried out to provide new scientific evidence on the effect of clindamycin in antibiotic prophylaxis in oral implant surgery performed on healthy patients without the need for bone regeneration, in an implant bed without previous infection.

5.2.5. Justification of the thematic unit

The thematic unity of all these studies is based on three fundamental lines of research of the PhD program in public health of the University of the Basque Country: clinical epidemiology, health services research and pharmacoepidemiology. The use of prophylactic antibiotics in oral implantology can be a major problem at the epidemiological level due to the apparent lack of clinical consensus in their prescription and the increasing number of oral implant surgeries performed. The appearance of bacterial resistance is an increasingly frequent complication due mainly to the irrational use of antibiotics and has serious consequences of great relevance at the pharmacoepidemiological level. Research in oral health services carried out in this sense is essential to detect, prevent and avoid unjustified risks and costs for the health system, the economy and society.

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3.3. Objectives and Hypotheses

3.3.1. General objectives

The main objective of this project is to provide information to the clinician on what should be his attitude about the preventive prescription of antibiotics to a patient who is going to be implanted whether the patient is allergic to beta-lactam antibiotics or not.

We also want to know if the preventive prescription of antibiotics in implant surgery is the same in different countries and if the recommendations provided by the literature are followed.

Our aim is to provide answers to the following questions:

1: Should we prescribe antibiotics to prevent infection and/or failure of these implants in this patient who is going to receive an implant? If so, what should our preventive treatment be? We conducted a systematic review and meta-analysis to know the available evidence.

2: What if this patient is allergic to beta-lactam antibiotics? We found that the efficacy of preventive treatments proposed in patients allergic to this group of antibiotics is not based on clinical trials that support their efficacy. In our environment one of the most commonly used is clindamycin, so we conducted a systematic review on the efficacy of preventive clindamycin in oral surgery and when we found that there is no information on its use in implantology, we designed and conducted a randomized, blinded clinical trial with placebo.

3: We asked ourselves whether implant dentists prescribe preventive antibiotics following the guidelines published in the literature. We conducted three different surveys, in Spain, in the Netherlands and in Italy, so that together with other surveys published in other countries we could conclude what attitudes are currently held about preventive antibiotic prescribing in implant dentistry.

3.3.2. Specific objectives and hypotheses

Preventive antibiotics in oral implant surgery. Systematic review and meta-analysis

Objectives To analyze the available scientific evidence on the efficacy of systemic antibiotic prophylaxis to prevent infection and/or failure in the placement of dental implants. To subsequently evaluate whether any antibiotic regimen prevents dental implant failures and/or postoperative infections.

Null hypothesis The prescription of peri-operative antibiotics in the placement of oral implants is neither efficient nor effective in the prophylaxis of postoperative infection and/or implant failure. There are no statistically significant differences in the incidences of implant failure and/or postoperative infection between patients treated with peri-implant antibiotic prophylaxis and those who do not receive any type of antibiotic prophylaxis.

Rodríguez Sánchez F, Rodríguez Andrés C, Arteagoitia I. Which antibiotic regimen prevents implant failure or infection after dental implant surgery? A systematic review and meta-analysis. J Craniomaxillofac Surg. 2018 Apr;46(4):722-736. doi: 10.1016/j.jcms.2018.02.004. Epub 2018 Feb 26. PMID: 29550218.

Preventive clindamycin in oral surgery. Systematic review and meta-analysis

Objectives To assess the effect of clindamycin (with any type of route of administration, regimen or dose) for preventing infectious complications in patients undergoing any type of oral surgery, including dental implant placement.

Null hypothesis Clindamycin, with any type of administration route, regimen or dose, is not effective in preventing infectious complications in patients submitted to any type of oral surgery, neither is it effective in implant placement surgery.

Arteagoitia I, Rodríguez Sánchez F, Figueras A, Arroyo-Lamas N. Is clindamycin effective in preventing infectious complications after oral surgery? Systematic review and meta-analysis of randomized controlled trials. Clinical Oral Investigations.

Under Review

Preventive clindamycin in oral implant surgery. Randomized and controlled clinical trial

Objectives To analyze the efficacy versus placebo of a systemic prophylactic antibiotic regimen (a single 600 mg dose of clindamycin administered orally one hour before surgery) in reducing the incidence of infection and/or implant loss after oral implant surgery in healthy patients when implants are placed in sites with no previous infection and no bone regeneration required.

Null hypothesis There is no difference in the cumulative incidence of implant failure and/or infection in oral implant insertion when using a systemic antibiotic regimen of clindamycin, (600 mg one hour before surgery) versus the same regimen of placebo.

Santamaría G, Rodríguez Sánchez F, Rodriguez C, Barbier L Arteagoitia I, Effect of Preoperative Clindamycin Preventing Implant Failures and Postoperative Infections after Oral Implant Surgery: a Randomized Placebo-controlled Clinical Trial. Clinical oral implants research.

Sent to Journal

Antibiotic prescribing habits in oral implant surgery. Cross-sectional surveys in Spain, the Netherlands and Italy, and meta-analysis of cross-sectional surveys

Objectives To identify the systemic antibiotic prescribing patterns used in oral implant surgeries in healthy patients by practitioners in Spain, the Netherlands and Italy. To assess the dose and types of antibiotics prescribed and to contrast the mean dose of antibiotics prescribed with the recommended evidence-based regimen in healthy patients under simple conditions: a single preoperative dose of 2 g amoxicillin. An additional aim of this study was to assess differences in antibiotic dose and type of antibiotic between countries and prescribing regimens.

Null hypotheses were postulated as follows: (1) the mean dose of prophylactic antibiotics prescribed per oral implant surgery is equal to a single dose of 2,000 mg and (2) there is no variation in the mean dose of antibiotics prescribed between different countries and prescribing regimens.

Arteagoitia I, Rodríguez-Andrés C, Rodríquez-Sánchez F. Antibiotic prophylaxis habits in dental implant surgery among dentists in Spain. A cross-sectional survey. Med Oral Patol Oral Cir Bucal. 2018 Sep 1;23(5):e608-e618. doi: 10.4317/medoral.22626. PMID: 30148475; PMCID: PMC6167099.

Rodríguez Sánchez F, Arteagoitia I, Rodríguez Andrés C, Bruers J. Antibiotic prophylaxis prescribing habits in oral implant surgery in the Netherlands: a cross-sectional survey. BMC Oral Health. 2019 Dec 12;19(1):281. doi: 10.1186/s12903-019-0981-4. PMID: 31830979; PMCID: PMC6909651.

Rodríguez Sánchez F, Arteagoitia I, Rodríguez Andrés C, Caiazzo A. Antibiotic prophylaxis habits in oral implant surgery among dentists in Italy: a cross-sectional survey. BMC Oral Health. 2019 Dec 2;19(1):265. doi: 10.1186/s12903-019-0943-x. PMID: 31791306; PMCID: PMC6889412.

Rodríguez Sánchez F, Arteagoitia I, Teughels W, Rodríguez Andrés C, Quirynen M. Antibiotic dosage prescribed in oral implant surgery: A meta-analysis of cross-sectional surveys. PLoS One. 2020 Aug 18;15(8):e0236981. doi: 10.1371/journal.pone.0236981. PMID: 32810135; PMCID: PMC7446810.

3.4. Methodological Tools and Results

3.4.1. Preventive antibiotics in oral implant surgery. Systematic review and meta-analysis

SUMMARY

Objectives: To evaluate which antibiotic regimen prevents dental implant failures or postoperative infections after implant placement.

Methods: Systematic review and meta-analysis. Data sources: Pubmed, Cochrane, Science Direct, and EMBASE were searched through OVID until August 2017. Only randomized controlled clinical trials (RCTs) using antibiotics were included. Outcomes were established on dental implant failures or incidence of postoperative infection after dental implant surgery. Three review authors independently performed risk of bias assessment and data extraction. Stratified meta-analyses of binary data were performed using fixed-effect models with STATA® 14. The risk ratio (RR) and 95% confidence interval (CI) were estimated.

Results: Nine articles corresponding to 15 RCTs were included. All RCTs tested oral amoxicillin only. Analysis of implant failure: overall RR=0.53 (*p=0.*005, 95% CI 0.34-0.82) and overall NNT=55 (95% CI 33-167). Preoperative single dose oral amoxicillin (SDOAP) is beneficial (RR=0.50, CI: 0.29-0.86. *p=0.*012) compared to postoperative oral amoxicillin (POA: RR= 0.60, CI: 0.28-1.30. P=.197). Analysis of postoperative infection: overall RR=0.76 (*p=0.*250, 95% CI: 0.47-1.22). Neither SDOAP (RR=0.82, CI=0.46-1.45, *p=0.*488) nor POA (RR=0.64, CI=0.27-1.51, *p=0.*309) are beneficial. I2=0.0%, chi-square *p≈1* tests.

Conclusions: Only SDOAP is effective and efficient in preventing implant failures, but it was not significant for postoperative infections after dental implant surgeries.

METHODS

Protocol and registration

To address the purpose of the research, the authors designed and implemented a systematic review and meta-analysis. The research was conducted and is reported in accordance with the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [1].

Details of the protocol for this systematic review were recorded in PROSPERO (CRD42017054364) and can be found at: https://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42017054364.

Eligibility Criteria

The target sample consisted of all published articles presenting an assessment of the efficacy of antibiotics in preventing postoperative infection or failure of dental implants after placement.

For inclusion in the study, publications had to be RCTs (with or without placebo) involving patients of any age or sex undergoing dental implant surgery. Studies had to have examined the efficacy of any antibiotic at any dose or treatment regimen (preoperative, postoperative, or both) in preventing postoperative infection or failure of dental implants after placement.

Publications were excluded if they were case series, retrospective studies or were not randomized clinical trials. We also excluded articles that did not assess the postoperative incidence of implant site infection or dental implant failure, or if they did, but the implant was placed in beds with periradicular infection or apical pathology. The authors did not use restrictive criteria to define postoperative infection or dental implant failure. There were no restrictions by language or year of publication.

Sources of information

The following electronic databases were searched until August 2017: Medline/PubMed, Scopus, Science-Direct, Web of Science, Evidence-Based Dentistry, ClinicalTrials.gov, the EU Clinical Trials Register and the Cochrane Central Register of Controlled Trials, as well as the database of doctoral theses of the Consejo General de Universidades de España (TESEO), the bibliographic databases of the Consejo Superior de Investigaciones Científicas (CSIC) and the Índice Médico Español (IME).

Search

The terms searched were descriptors for each of the Patient, Intervention, Comparison, and Outcome (PICO) components: dental implant surgery, dental implant placement, antibiotics, amoxicillin, implant failure, implant loss, and postoperative infection. The following filters were applied: human, clinical trials, meta-analysis and randomised controlled trials. The electronic search of the Medline/PubMed database was performed using MeSH and linked search algorithms with Boolean operators as keywords for titles and abstracts: ((randomized controlled trials OR controlled clinical trial OR randomized controlled trials OR random allocation OR double-blind method OR single-blind method OR clinical trial OR clinical trials OR clinical trials OR ("clinical trial") OR ((singl* OR doubl* OR trebl* OR trebl* OR tripl*) AND (mask* OR blind*)) OR ("latin square") OR placebos OR placebo* OR random* OR research design OR comparative study OR evaluation studies OR follow-up studies OR prospective studies OR cross-over studies OR control* OR prospective* OR volunteer*) NOT animal) AND (amoxicillin) AND (dental implant failure OR dental implant loss OR postoperative infection) AND (dental implant placement OR dental implant surgery)).

For the Spanish databases, the following terms were used: (antibiotics OR amoxicillin) AND (implant failure OR implant loss) AND (dental implant).

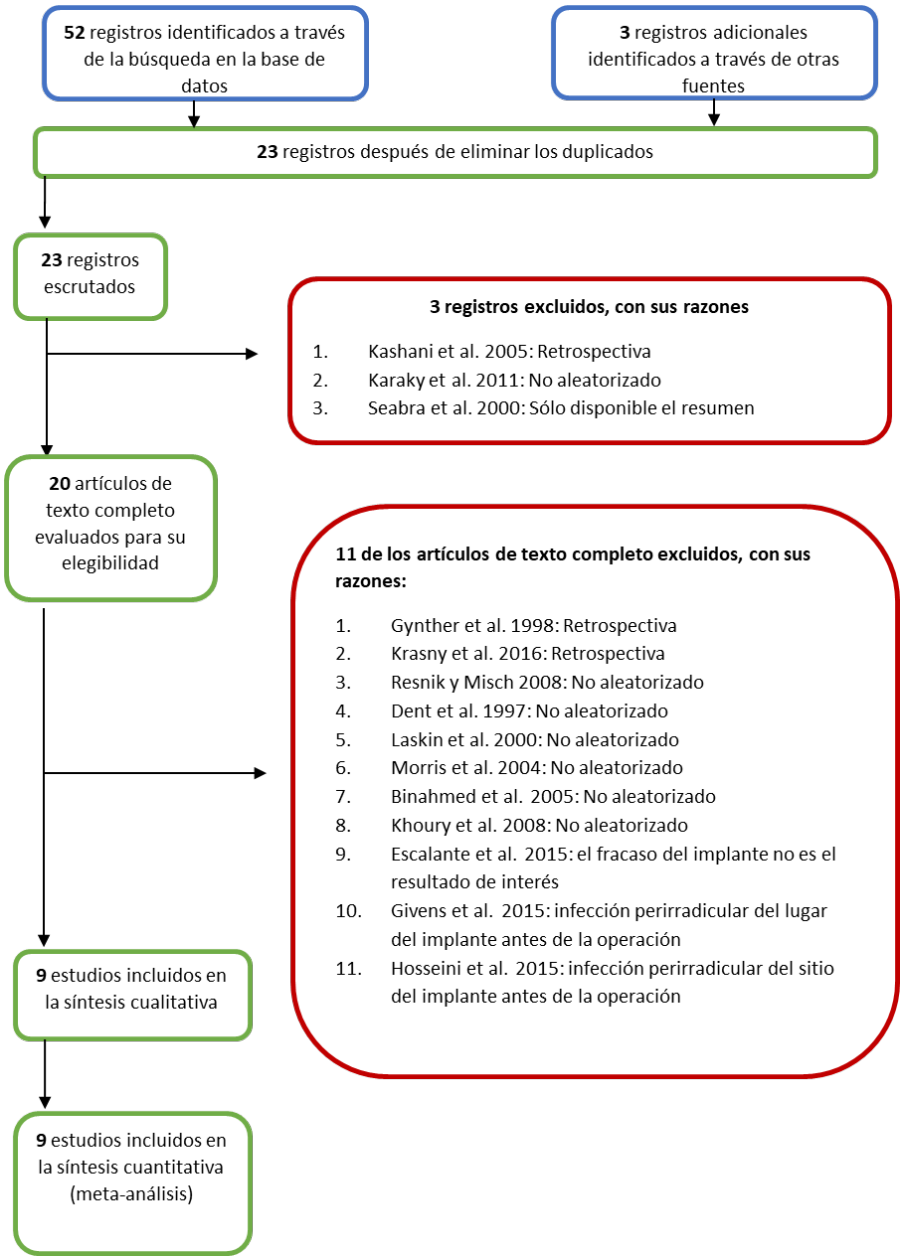
The authors reviewed the references of all retrieved papers, and when they identified potentially unpublished papers, they contacted the corresponding authors to request a copy of the study report.

Selection of studies

Three researchers independently searched the databases using the above criteria.

Three records were excluded after removal of duplicates as their titles specified that they were retrospective and not randomized [2, 3]. The third was a conference abstract with insufficient information to assess randomization and risk of bias [4]. From there, 20 full-text articles were assessed for eligibility and 11 were excluded. Two were excluded because they were retrospective studies, 6 because no randomization method was performed, one because it was an abstract article, one because implant failure was not the outcome of interest, and 2 articles because they used implants placed in beds with periradicular infection and apical pathology [4-15] (Figure 1).

Figure 1. Flow Diagram



Data collection process

All selected studies were independently reviewed by two researchers who extracted data from each article. Where explicit data for some variables were not stated in the text, they were calculated using data from the tables where possible. In case of uncertainty, authors were contacted to obtain the necessary information. A third researcher was consulted in case of disagreement.

Postoperative infection:

The authors of the studies included in this meta-analysis applied different diagnostic criteria for the definition of postoperative infection. The most commonly used terms to define this outcome were the presence of suppuration, fistula and abscess or pus exudation with pain, tenderness, edema, swelling, erythema and warmth at the implant site or fever.

The terms suppuration and pus exudation were considered as postoperative infection during the data collection process. Four studies reported the term suppuration [16-19]. The RCT by Tan et al. (2014) reported the percentage of patients with suppuration at weeks 1, 2, 4, and 8 after surgery [19]. However, it was not made explicit whether the data for each week were reported independently. Therefore, it was impossible to distinguish whether a patient who had signs of infection in one week was the same person with the same signs in another week in the same treatment group. The authors were contacted and the doubt was resolved, as it was found that the percentage of patients with suppuration in each week was reported independently. The study by Arduino et al. (2015) used the term pus exudation [20].

Implant failure:

The outcome of implant failure was essentially defined as a mobile implant that had to be mechanically removed due to lack of osseointegration. The study by Arduino et al. (2015) did not report the total number of implants analyzed in each group (test and control) after loss to follow-up and exclusions [20]. In addition, the RCT by Caiazzo et al. (2011) did not report the total number of patients who had implant failures in each group [21]. For this reason, we contacted the authors of both RCTs, who successfully provided these data (Table 1).

The article published by Nolan et al. (2014) [18] did not report the total number of implants inserted in each group, and the corresponding author was also contacted, but in this case, unfortunately, the raw data were not available. For this reason, this study was excluded from the analysis performed for the number of implant failures. However, the authors used the data available in this study for the analyses for the number of patients who had an implant failure and the number of patients who had a postoperative infection.

The articles by Caiazzo et al. (2011) and Tan et al. (2014) included 3 amoxicillin treatment groups and a control group. In this meta-analysis, each treatment group was included as a separate RCT using the same control group provided by the investigators [21,19].

In 2 articles, patients in the control group were also treated with amoxicillin with a different dosing regimen than the treatment group [20, 22]. These control groups could be considered as treatment groups in different RCTs, for which a new control group would be necessary.

To do this, the authors constructed a new control group for each analysis. The new control groups were based on the calculation of the mean number of subjects who had the outcome variables (patients who had an implant failure, total number of implant failures, and patients who had a postoperative infection) in the control groups of the other RCTs included in each analysis [16- 19, 21, 23, 24]. Similarly, we also calculated the mean number of subjects who did not have the outcome variables (successful implants, patients who had no implant failures, and patients who had no postoperative infections) in the control groups of the other RCTs [16-19, 21, 23, 24].

These newly constructed control groups were composed of 4 patients who had an implant failure and 94 patients who had no implant failure for the first analysis (implant failure per patient), 4 implant failures and 130 successful implants for the second analysis (implant failure per implant), and 2 patients who had a postoperative infection and 76 patients with no postoperative infections for the last analysis.

The authors imputed data from these newly constructed control groups for the 2 aforementioned studies [20, 22].

Data elements and analysis

The predictor variable was the use or non-use of antibiotics in each RCT. The data recorded included the following: type of antibiotic, route of administration and treatment regimen (before or after implant placement). In all studies, the only type of antibiotic used was oral amoxicillin.

The authors performed a stratified meta-analysis with 3 different outcome variables: 1.-Number of patients who had an implant failure; 2.-Number of implant failures; and 3.-Number of patients who had a postoperative infection. A stratified analysis was conducted to contrast the effect of preoperative-only oral antibiotics versus postoperative antibiotics (used either exclusively postoperatively or as an adjunct to a perioperative regimen).

The authors did not use restrictive criteria to define postoperative infection and implant failure.

The authors also recorded the presence or absence of adverse effects.

The remaining variables described the characteristics of the sample in each article (sample size, sex, mean age of patients, number of smokers, and contraceptive use) and the characteristics of the study design in each article (type of study, number of treatment groups, randomization process, secret allocation, blinding, loss to follow-up, test materials, control materials, co-treatment materials, type of implant, and type of surgery). The data collected are listed in Table 1.

Risk of bias in individual studies

The Cochrane Collaboration tool was used in order to assess the individual risk of bias of each included RCT at the study level. The risk of bias graph (Figure 2) and risk of bias summary (Figure 3) were generated using Review Manager 5.3 (The Cochrane Collaboration 2014). We collected quantitative and qualitative data on loss to follow-up, the randomization process, blinding, and other factors that could be potential sources of bias (Table 1).

Overview measure

Treatment efficacy was assessed by relative risk (RR) (Figure 4). Antibiotic treatment efficacy was assessed using the number needed to treat (NNT). Overall weight-adjusted NNTs were estimated for each study for all analyses.

Summary of results

All analyses were performed with STATA® 14 (StataCorp LP, College Station, TX) [25]. The authors assessed heterogeneity between the different studies using the I2 statistic, and graphically with l'Abbé plots (Figure 5). The overall RR, resulting from the combination of different studies, was calculated with a fixed-effect model with weights calculated using the Mantel-Haenszel method [26].

Risk of bias in studies

Publication bias was assessed graphically using funnel plots (Figure 6).

The quality of evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system, considering each outcome variable independently (Table 2 and 3). The GRADE system was developed to grade the quality of evidence and strength of recommendations [27-28].

RESULTS

Selection of studies

In total, 9 articles published since 2008 were included in this meta-analysis. Figure 1 presents a flow chart of the study selection process with a list of excluded studies and the reasons for their exclusion.

The final analyses, by the number of patients who had implant failure and by the number of postoperative infections, were performed in 15 RCTs corresponding to 9 articles [16-19, 20, 21, 23, 24].

In addition, 14 RCTs corresponding to 8 articles were finally included in the meta-analysis because of the number of implant failures [16-19, 21, 23, 24].

Characteristics of the studies

In the studies reviewed, only one type of antibiotic was evaluated: amoxicillin. It is used in various doses and therapeutic regimens. Preoperative regimens were as follows: single dose of 1 gram [22, 24], 2 grams [16, 17, 19, 20, 21, 23] or 3 grams 1 hour before surgery [18]. Postoperative regimens were as follows: 2 grams immediately after surgery [19], 1 gram two/three times daily for one week [21] or for two days after implant placement [20], and 500 mg three times daily for two [24] or three days after surgery [19, 22]. Several studies combined preoperative and postoperative antibiotics [19, 21, 22, 24]. Table 1 presents the main characteristics of the 9 RCTs included in the meta-analysis.

Table 1. Characteristics of the studies

Study, Year and Country	Type of study	Method of randomization	Blinding	Test material (which and dosage)	Control material	Co-treatment materials	Test group patients	Control group patients	Diagnostic criteria	Quantitative outcome measure & LTF	Follow up period	Adverse reactions
Abu-Ta'a et al. 2008 Belgium	ECA of parallel groups	Random sampling	Double blind	AMX 1 g per os, 1 h before the operation and 500 mg 4 times a day, 2 days after the operation.	No antibiotics	Post-operative rinse with 0.12% CLX for 1 minute. for 7-10 days	n=40 male= 23 female= 17 MA= 60 Range= 27-82 n implants= 128	n=40 man= 20 female= 20 MA= 57 Range= 26-88 n implants= 119	**Postoperative infection:** purulent drainage (pus) or fistula in the operated region, with pain or tenderness, localized swelling, redness, and warmth or fever. **Implant failure:** Signs of infection and/or radiographic peri-implant radiolucencies and/or judging a failure to perform exploratory flap surgery	**Test group:** Patients with infection: 1/40 Survival rate (implants): 128/128 (100%) Patients who had implant failure: 0/40 **Control group:** Patients with infection: 4/40 Survival rate (implants): 114/119 (96%) Patients who had implant failures: 3/40 **LTF:** 0	5 months after implant placement	No side effects of the antibiotic were reported

Esposito et al. 2008 Italy	ECA of parallel groups	Twelve computer-generated restricted randomization lists	Double blind	2 g of AMX orally (2 x 1 g tablets) 1 hour prior to implant placement	2 identical placebo tablets 1 hour prior to implant placement	Postoperative rinse with 0.2% CLX for 1 min. twice a day for at least 1 week. In the control group, 1 patient was treated with antibiotics due to flu 2 days after implant placement.	n= 158 Women= 78 (49.4%) MA (range)= 47.8 (18-78) Non-smokers=99 (62.7%) Duration (range)= 27 m (3-130) Total number of implants= 341 Took postoperative antibiotics= 2	n= 158 Women: 96 (60.8%) MA (range)= 47.9 (19-76) Non-smokers= 108 (68.4%) Duration (range)= 26.5 m (4-125) Total number of implants=: 355 Took postoperative antibiotics= 1	**Postoperative infection:** suppuration, fistula, abscess. **Implant failures:** Mobility of the implant and/or any infection that forces its removal.	**Test group:** Implant failures: 2/341 Patients with infection: 3/158 Implant failure patients: 2/158 LTF: 0, Excluded patients: 7 **Control group:** Implant failures: 9/355 Patients with infection: 2/158 Patients with implant failures: 8/158 LTF: 0, Excluded patients: 7	4 months after implant placement	There was 1 adverse event in the placebo group (itching for 1 day) and 1 in the AMX group (diarrhea and drowsiness).
Anitua et al. 2009 Spain	ECA of parallel groups	Random Number Table	Double blind	2 g of oral AMX 1 hour prior to implant surgery	2 placebo tablets administered orally 1 hour prior to implant surgery	Rinse with 0.2% CLX for 1 minute prior to surgery. Immediately after surgery and the following 3 days	n= 52 Women= 37 (71%) Men= 15 (29%) MA= 49 (±12) Smokers= 10 (19%)	n= 53 Women= 33 (62%) Men= 20 (38%) MA= 47 (±12) Smokers= 8 (15%)	**Postoperative infection:** Inflammation, pain, heat fever and discharge. Implant **survival:** Implant	**Test group:** Postoperative infections: 6/52 Implant failures: 2/52 LTF: 0 **Control group:**	3 months after implant placement	NR

						intravenous or intramuscular dexamethasone. Acetaminophen as rescue medication (maximum 1 g/8 hours). Metamizole (575 mg, 1 or two tablets/8 hours) was also allowed.	Non-smokers= 42 (81%) Duration (mean value ±SD)= 41.03 m (±29) Maxillae= 26 (51%) Mandibular= 25 (49%) Previous zone= 11 (22%) Rear area= 39 (78%) Immediate loading type= 1 (2%)	Non-smokers= 45 (85%) Duration (mean value ±SD)= 41.71 m (±27) Maxillae= 21 (40%) Mandibular = 32 (60%) Previous zone= 12 (23%) Rear= 40 (77%) Immediate loading type= 1 (2%)	stability **was** tested with Osstell (Ostell, Göteborg, Sweden).	Postoperative infections: 6/53 Implant failures: 2/53 LTF: 1		
Esposito et al. 2010 Italy	ECA of parallel groups	Computer-generated restricted randomization list	Triple blind	2 g of AMX orally (two 1 g tablets) 1 hour prior to implant placement	2 identical placebo tablets one hour prior to implant placement	0.2% CLX mouth rinse for 1 minute prior to implant placement and 0.2% CLX mouth rinse for 1 minute twice daily for at least 1 week postoperatively	n= 252 Women= 138 (54.8%) MA (range)= 49.1 (18-85) Non-smokers= 171 (67.9%) Smoking up to 10 cigarettes/day= 55 (21.8%) Smoking more than 10 cigarettes/day= 26 (10.3%) Duration (range)= 32 m (4-190)	n= 254 Women 132 (52.0%) MA (range) 47.6 (18-86) Non-smokers 166 (65.4%) Smoking up to 10 cigarettes/day 60 (23.6%) Smoking more than 10 cigarettes/day 28 (11%)	**Postoperative infection:** suppuration, fistula, abscess. **Implant failures:** Measured implant mobility and/or any infection that dictates implant removal.	**Test group:** Implant failures: 7/489 Patients who had implant failures: 5/252 Patients who had postoperative infections: 4/252 LTF: 0, Excluded patients: 2 **Control group:**	4 months after implant placement	No adverse effects of antibiotics were observed in any group.

							n implants= 489 Immediate loading rate= 60 Took postoperative antibiotics 2 (0.8%)	Duration (range) 31 m (5-180) Total number of implants 483 Immediate loading type= 76 6 (2.4%) took postoperative antibiotics		Implant failures: 13/483 Patients who had implant failures: 12/254 Patients who had postoperative infections: 8/254 LTF: 0, Excluded: 1		
Caiazzo et al. 2011 Italy	ECA of parallel groups	Computer-generated randomization lists	NR	**Group 1:** Single dose of prophylactic antibiotic consisting of AMX 2 g 1 hour prior to surgery **Group 2:** Preoperative and postoperative antibiotic treatment consisting of AMX 2 g 1 hour before surgery and 1 g twice daily for 7 days after surgery. **Group 3:**	**Group 4:** No antibiotic treatment	Rinse with 0.2% CLX gluconate solution for 1 minute before each procedure and twice daily for 15 days after surgery.	**Group 1:** n= 25 Women: 12 Men: 13 MA=52 n implants= 35 **Group 2:** n= 25 Women: 13 Men: 12 MA=45 n implants= 36 **Group 3:** n= 25 Women: 18 Men: 7 MA=42 n implants= 48	**Group 4:** n= 25 Women: 15 Men: 10 MA=43 n implants= 29	**Postoperative infection:** Internal and external edema, internal and external erythema, pain, heat and exudates. **Implant failure**: Mechanical implant removal due to lack of osseointegration	**Group 1:** Infections: 0/35 Implant failures: 0/35 Patients who had implant failures: 0/25 **Group 2:** Infections: 0/36 Implant failures: 0/36 Patients who had implant failures: 0/25 **Group 3:** Infections: 0/48 Implant failures: 0/48	3 months after implant placement	No adverse effects of antibiotics were observed in any group.

				Postoperative antibiotic coverage consisting of AMX 1 g twice daily initiated after surgery and continued for 1 week after surgery.						Patients who had implant failures: 0/25 **Group 4:** Infections: 0/29 Implant failures: 2/29 Patients who had implant failures: 2/25 LTF= NR		
K. E. El-Kholey 2014 Saudi Arabia	ECA of parallel groups	Computer-generated list of random numbers	NR	**Group 1:** single dose of 1 g oral AMX 1 h before surgery, and no antibiotic postoperatively **Group 2:** 1 g oral AMX 1 h before surgery followed by postoperative oral AMX, 500 mg every 8 h for 3 days	*	Mouthwash with CLX 0.12% for 1 minute before surgery and for 5 days postoperatively. Paracetamol 500 mg four times a day as needed.	**Group 1:** n=40 Women=4 Men=16 MA (±SD)= 32,2 ±7,7 Number of maxillary implants= 23 Number of mandibular implants= 24 Total implants= 47 **Group 2:** n=40 Women:26 Men:14 MA (±SD)= 30 ±6,8 Maxillary implants= 20 Mandibular implants= 23 n implants= 43	*	**Postoperative infection:** Swelling, pain, erythema, tenderness, or pus formation at the surgical site **Successful osseointegration:** Good implant stability at 25 N cm with absence of any clinical or radiographic signs of infection.	**Group 1:** Wound infections: 0/47 Implant failures: 0/47 Patients who had implant failure: 0/40 LTF= 0 **Group 2:** Wound infections: 0/43 Implant failures: 0/43 Patients who had implant failure: 0/40 LTF= 0	3 months after implant placement	NR

Nolan et al. 2014 Ireland	ECA of parallel groups	NR	Double blind	3 g of AMX orally, 1 hour before surgery.	Placebo capsules (with sugar) by mouth, 1 hour before surgery	CLX 0.2% mouthwash for at least 60 seconds before surgery and 4-5 times daily for the first postoperative week.	n= 27 Female= 16 Male= 11 <40 years= 16 40-60 years=7 >60 years= 4 Non smokers= 20 Smokers=7	n= 28 Female= 20 Male= 8 <40 years= 15 40-60 years=10 >60 years= 3 Non-smokers= 22 Smokers=6	Osseointegration recorded by 2 independent examiners: Success = Immobile Failure = Mobile	**Test group:** Patients who had an implant failure= 0/27 Patients with infection = 0/27 **Control group:** Number of patients who have had an implant failure= 5/28 Number of patients with infection= 2/28 LTF= 16, Exclusions after randomization= 12	4 months after implant placement	NR Only VAS and bruising, but no quantitative data.
Tan et al. 2014	ECA of parallel groups	Randomization tables. Randomization in blocks of eight, whereby in each block of eight enrolments, there were two subjects randomly assigned to one of the	A single blind man	**Group 1:** 2 g of amoxicillin in the preoperative period, 1 h before the placement of conventional implant. **Group 2:** 2 g of AMX immediately after surgery.	**Group 4:** 2 g of a preoperative placebo, 1 h before implant placement without any antibiotics	Pre-rinse with 0.2 % CLX for 1 min.	**Group 1 (PC)** n = 81 Women = 49.4%. Males = 50.6%. MA= 48.8 Non-smoker 81.5% Non-smoker 81.5% Non-smoker 81.5% Non-smoker	**Group 4 (NC)** n = 80 Women = 44.7%. Males = 55.3%. MA= 45,1 Non-smoker 80.0% Non-smoker 80.0% Non-smoker	**Postoperative infection:** Suppuration **Implant failure:** Unstable implant that was lost	**Group 1:** Implant failures: 0/81 Patients with implant failure: 0/81 Patients with postoperative infections: 2/81 **Group 2:** Implant failures: 0/82	2 months after implant placement	There are no statistically significant differences between the four treatment groups in terms of bleeding, swelling, pain and bruising.

		four intervention groups.		**Group 3:** 2 g amoxicillin preoperatively, 1 h before implant placement and 500 mg three times a day (every 8 hours) on days 2 and 3.			Smoker 18.5% Smoking **Group 2 (T1)** n = 82 Women = 42.7%. Male= 57,3% Male= 57,3% Male= 57,3% Male= 57,3% Male= 57,3% MA= 47.8 Non-smoker 80.5% Non-smoker 80.5% Non-smoker 80.5% Non-smoker Smoker 19.5%. **Group 3 (T2)** n = 86 Female= 45.3% Female= 45.3% Female= 45.3% Female= 45.3% Female= 45.3% Males = 54.7%. MA= 46.9	80.0% Non-smoker Smoker 20 % Smoking Width of alveolar bone B-L (average, mm): 7.91 Alveolar bone width M-D (average, mm) 11.33		Patients with implant failures: 0/82 Patients with postoperative infections: 0/82 **Group 3:** Implant failures: 0/86 Implant failure patients: 0/86 Patients with postoperative infections: 2/86 **Group 4:** Implant failures: 1/80 Patients with implant failures: 1/80 Patients with postoperative infections: 0/80 LTF: NR for any group		Other adverse events NR.

							Non-smoker 80.2% Non-smoker 80.2% Smoker 19.8%.					
Arduino et al. 2015 Italy	ECA of parallel groups	Two computer-generated randomization lists	Double blind	**Group 1:** 2 g of AMX orally (2 x 1 g tablets) 1 hour before surgery **Group 2:** 2 g of AMX orally (2 x 1 g tablets) 1 hour before surgery and 1 g on the evening of the day of surgery and 1 g twice daily for 2 days after surgery	*	Rinse with 0.2% CLX 1 min immediately prior to surgery.	**Group 1:** n= 180 MA (SD)= 49.3 (13.9) Female= 101 Male= 79 Smokers= 57 (31.7%) Mandibular implants= 202 Maxillary implants= 76 Number of implants= 278 **Group 2:** n= 180 MA (SD)= 51.6 (14.4) Female= 88 Male= 92 Smokers= 37 (20.6%) Mandibular implants= 173 Maxillary implants= 116	*	**Implant failure:** Implant mobility or removal due to pain or infection **Postoperative infection:** Suppuration, fistula, abscess	**Group 1:** Implant failures: 5/244 Patients with implant failure: 5/166 (3%) Patients with postoperative infections: 2/166 LTF: 9 Loss of all data=5 Patients excluded from analysis= 14 **Group 2:** Implant failures: 8/285 Patients with implant failure: 5/177 (2.8%) Patients with postoperative infections:	10 months after implant placement	**Group 1:** No adverse events **Group 2:** 3 adverse events: 2 men with abdominal swelling, 1 woman with rash and laryngeal oedema with a severe reaction requiring discontinuation of treatment and temporary admission to hospital. There are no statistically significant differences between the two groups.

							Number of implants= 289			2/177 LTF: 1 Loss of all data= 2 Excluded patients = 3		

*AMX: Amoxicillin; CLX: Chlorhexidine; N: Newton's, n: population; RCT: Randomized Controlled Trial; n: sample size; MA: mean age; SD: standard derivation; NR: Not reported; LTF: Lost to follow-up; *Indicates studies whose data have been imputed from the calculated control group.*

Risk of bias in studies

The risk of bias graph (Figure 2) illustrates the proportion of studies with each of the judgements (low risk, high risk, unclear risk). The risk of bias summary (Figure 3) presents all judgments in a cross-tabulation of study by entry.

Figure 2. Risk of Bias Graph

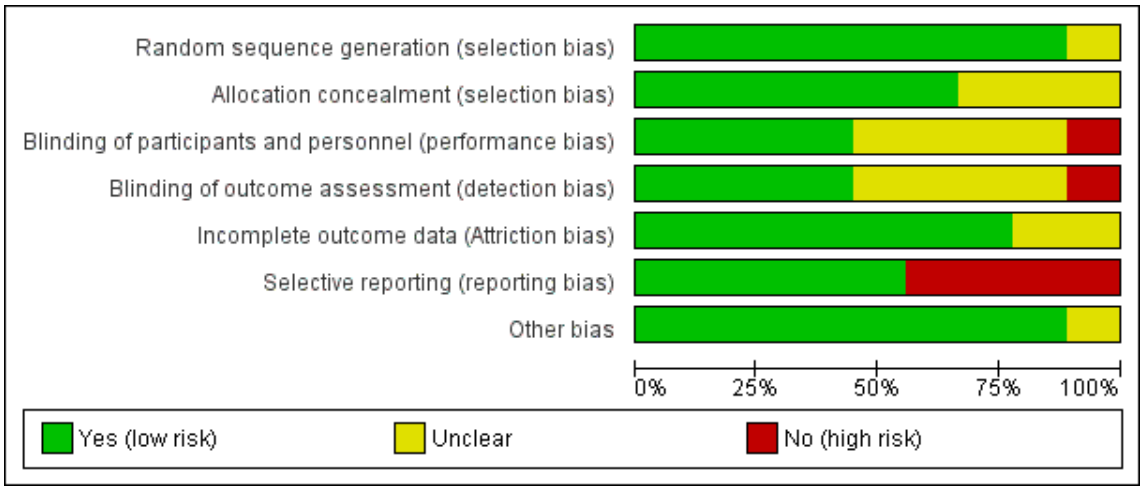
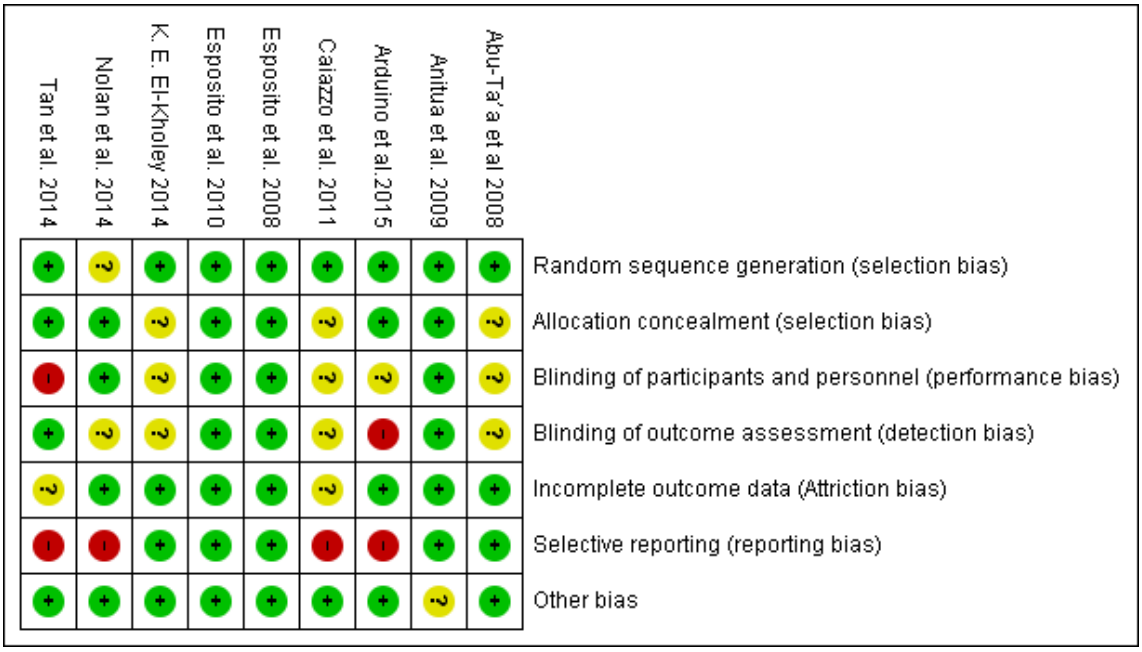


Figure 3. Risk of Bias Summary



The RCT conducted by Anitua et al. (2009) could present a possible risk of reporting bias, since the Instituto de Biotecnología (BTI®, Vitoria, Spain) provided the funding and controlled the analysis and results of the trial.

Table 2. Table of Evidence

Quality assessment							Summary of results				
Participants (studies)	Risk of Bias	Inconsistency	Indirect	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative effect (95% CI)	Expected absolute effects	
							Control group (without AMX)	Treatment Group (with AMX)		Risk without antibiotics	Risk difference with antibiotics
Implant failure by patients (follow-up: median 4 months)											
2982 (15 ECA)	not serious	not serious	not serious	serious [a]	none	⨁⨁⨁◯ MODERATE	56/1469 (3.8%)	31/1513 (2.0%)	Overall RR 0.53 (0.34 to 0.82)	38 per 1,000	18 less per 1,000 (25 less to 7 less)
Failure of dental implants (follow-up: median 4 months)											
3870 (14 ECA)	not serious	not serious	not serious	serious [b]	none	⨁⨁⨁◯ MODERATE	54/1873 (2.9%)	33/1997 (1.7%)	Overall RR 0.54 (0.35 to 0.85)	29 per 1,000	13 less per 1,000 (19 less to 4 less)
Postoperative infection (follow-up: median 4 months)											
2500 (15 ECA)	not serious	not serious	not serious	very serious [c,d,e]	none	⨁⨁◯◯ LOW	36/1172 (3.1%)	29/1328 (2.2%)	Overall RR 0.76 (0.47 to 1.22)	31 per 1,000	7 less per 1,000 (16 less to 7 more)

CI: confidence interval; RR: risk ratio; RCT: randomised controlled clinical trial; AMX: Amoxicillin Explanations:

a. Less than 300-400 events (patients who had an implant failure) b. Less than 300-400 events (implant failures) c. 95% CIs include null effect, but also include benefit. d. Lower 95% CI (0.47) < 0.75 e. Less than 300-400 events (patients who had a postoperative infection).

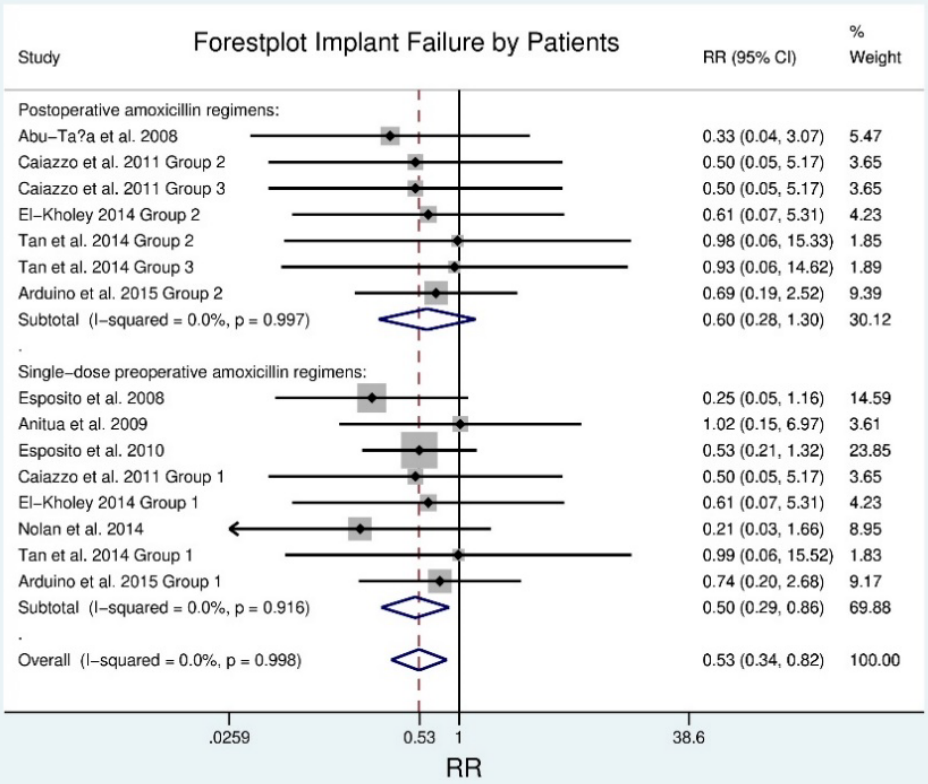
Table 3: Quality Grades of Evidence

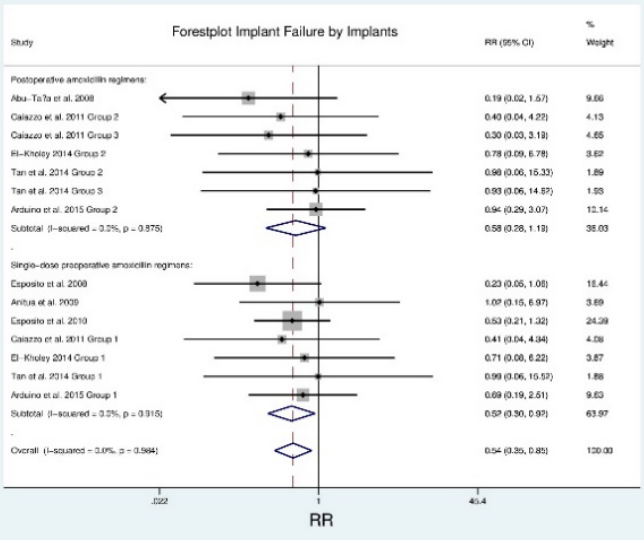
Grade	Definition
High	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Under	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very low	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

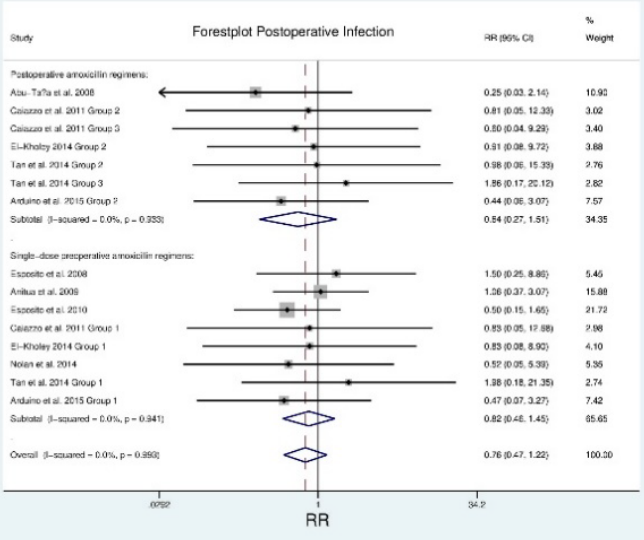
Results of the individual studies

The forest plots presented in Figure 4 are graphical representations of the RR estimates and 95% confidence intervals (CI) obtained with samples from each of the studies. The area of grey squares around the RR is proportional to the weight of the study in the analysis. The CIs, indicated by a solid horizontal line crossing the vertical line at an RR equal to one, correspond to studies with non-significant results. The graph also indicates the overall RR based on all studies with a diamond and a dotted line.

Figure 4. Forest Plots







Summary of results

Analysis of implant failure per patient:

We observed that a single dose of oral amoxicillin preoperatively (SDOAP) before implant surgery significantly (*p*=0.012) prevented patients from developing dental implant failures (RR = 0.50, CI: 0.29-0.86), while postoperative use of oral amoxicillin (exclusively postoperatively and as an adjunct to preoperative amoxicillin) did not significantly (*p*=0.197) achieve a prophylactic effect (RR=0.60, CI: 0.28-1.30).

The overall RR of the analysis by the number of patients who had an implant failure was 0.53 (95% CI 0.34 to 0.82), which is significantly different from 1 (*p*=0.005).

The estimated overall NNT for the analysis performed by the number of patients who had an implant failure was 55. Considering the 95% CI, it would be necessary to treat between 33 and 167 patients with amoxicillin to prevent a single patient having an implant failure. The NNT for SDOAP was 67 (95% CI 26 to 125), and the NNT for postoperative use of oral amoxicillin was 53 (95% CI 30 to 200).

Implant failure analysis per implant:

SDOAP before implant surgery was significantly (*p*=0.024) effective in preventing dental implant failures (RR = 0.52, CI 0.30-0.92). However, postoperative use of oral amoxicillin (exclusively postoperatively and as an adjunct to preoperative amoxicillin) was not significant (*p*=0.137) in preventing dental implant failures (RR = 0.58 CI 0.28-1.19).

The overall RR of the analysis by number of implant failures was 0.54 (95% CI 0.35 to 0.85), which is also significantly different from 1 (*p*=0.007).

The overall NNT of the analysis by number of implant failures was estimated to be 77. If its 95% CI is also taken into account, 43 to 250 dental implants would need to be treated with amoxicillin to prevent 1 implant failure. The NNT for SDOAP was 77 (95% CI 32 to 250), and the NNT for postoperative use of oral amoxicillin was also 77 (95% CI 42 to 500).

Analysis of postoperative infection:

Neither postoperative oral amoxicillin (RR=0.64, CI 0.27-1.51) nor SDOAP (RR=0.82, CI 0.46-1.45) were found to significantly prevent (*p*=0.309 and *p=0.*488, respectively) postoperative infections after dental implant surgery.

The overall RR of the analysis by number of postoperative infections was 0.76 (95% CI 0.47 to 1.22), which is not significantly different from 1 (*p*=0.250).

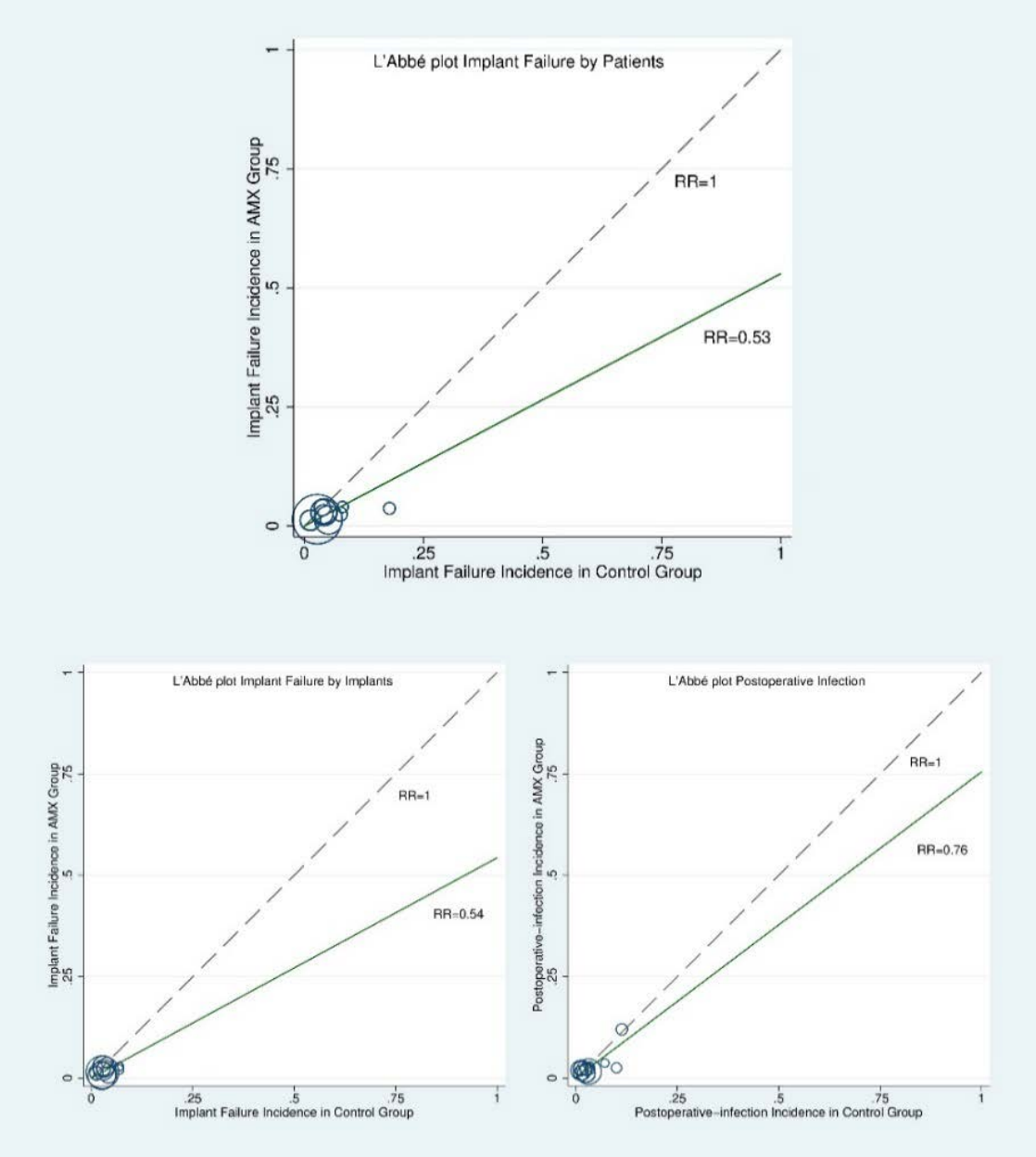
The overall NNT calculated for the analysis by the number of patients presenting with postoperative infection was 143. The 95% CI reveals that it would take 50 to 200 patients to be treated with amoxicillin to prevent only one case of postoperative infection. The

NNT for SDOAP was 100 (95% CI 32 to 100), and the NNT for postoperative use of oral amoxicillin was 143 (95% CI 50 to 200).

Heterogeneity analysis:

Heterogeneity, indicated by the I statistic^2, was 0.0 for the 3 analyses, since the *p* values were close to 1. This fact provides sufficient evidence to accept the null hypothesis of absence of heterogeneity among the results of the studies included in this meta-analysis. In the l'Abbé graphs (Figure 5), each circle corresponds to each study included in the analyses, the area of the circle being proportional to the weight of the study. In the graphs, the authors did not observe any relevant pattern of heterogeneity, with all circles clustered in the same region, regardless of their size and baseline risk.

Figure 5. Combined l'Abbé plots



Adverse reactions:

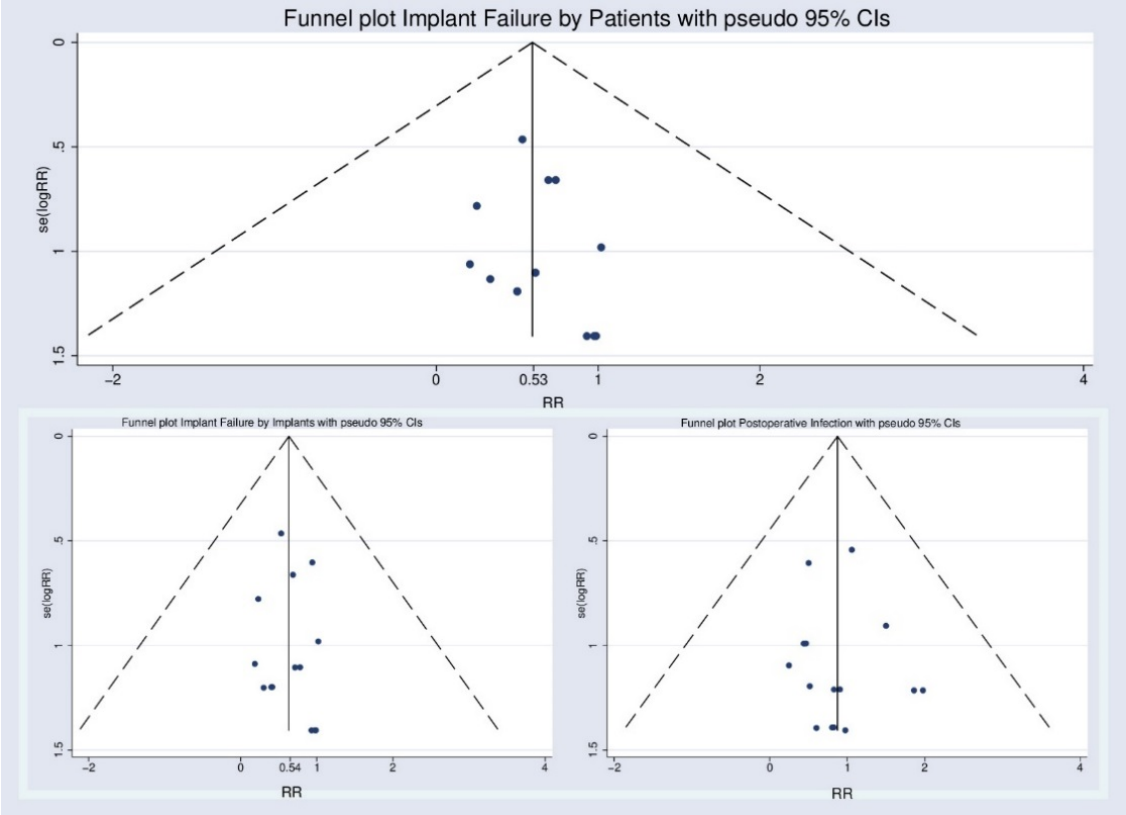
The study by Esposito et al. (2008) reported 1 adverse event occurring in the placebo group (itching for 1 day) and 1 in the antibiotic group (diarrhea and drowsiness), but the difference was not significant (p=1). Research by Arduino et al. (2015) reported no adverse events in group 1. However, in group 2, 2 men (aged 53 and 73 years) reported abdominal bloating with bloating and heartburn and 1 female patient (aged 78 years) reported rash and laryngeal oedema. This patient, who did not report any possible allergy to any type of antibiotic in the anamnesis, experienced a profoundly severe reaction requiring discontinuation of treatment and temporary admission to hospital. The authors found no significant differences between the two groups.

In the 3 included articles [16, 21, 24] no adverse reactions to amoxicillin were reported, and in 4 of the included articles [18, 19, 23, 22] there is no information on adverse reactions to amoxicillin.

Risk of bias in studies

The funnel plots (Figure 6) suggest an absence of publication bias considering the symmetrical dispersion of the points in reference to a RR equal to 0.53, 0.54 and 0.74, respectively.

Figure 6. Combined Funnel plots



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3.4.2. Preventive clindamycin in oral surgery. Systematic review and meta-analysis

SUMMARY

Objectives: Patients allergic to amoxicillin are frequently treated in our setting with clindamycin. In cases in which preventive amoxicillin is prescribed in oral surgery procedures, as in the case of implant surgery, the use of preventive clindamycin is common. Our objective is to determine the effect of clindamycin in the prevention of infection after oral surgery.

Methods: This systematic review and meta-analysis followed the PRISMA statement, the PICO framework and included only randomized controlled clinical trials. In all studies clindamycin was administered to prevent infections in patients undergoing oral surgery. Search, data extraction and assessment of risk of bias were performed by two independent investigators. Included studies were classified according to the type of oral surgery. In addition, data on patients, procedures and outcome variables were collected. We calculated risk ratios (RR) and 95% confidence intervals (CI) using the Mantel-Haenszel model and the number needed to treat (NNT). Finally, we estimated possible sources of heterogeneity.

Results: Seven trials out of 540 articles met the inclusion criteria and were included in the qualitative synthesis. Four articles evaluating the effect of oral clindamycin in third molar surgery were quantitatively analysed. The overall RR was 0.66 (95% CI=0.38-1.16), not statistically significant (p=0.15). There was no heterogeneity between studies I^2=0, p=0.44. The NNT was 29 (95% CI=12- -57).

Conclusions: The effectiveness of clindamycin could not be evaluated except in third molar extraction. Oral clindamycin is ineffective in preventing infection in third molar surgery. There are no studies on the efficacy of clindamycin in routine implant placement to prevent infectious complications and/or implant failure.

METHODS

This study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). Before conducting the review, its methods were established. The protocol registration number was CRD42021226241. Accessible at: https://www.crd.york.ac.uk/prospero/#recordDetails

The null hypothesis (H_0) was tested at a significance level of $p=0.05$, that preventive use of clindamycin is not effective in reducing infection in oral surgery.

Eligibility Criteria

Only randomised clinical trials (RCTs) controlled with placebo or no treatment were included, regardless of whether they were double-blind or not. At least patients in one of the groups had to have received preventive clindamycin (with any type of route of administration, regimen or dose) to prevent infectious complications after any type of oral surgery procedure. The articles were classified according to the type of oral surgery in which the efficacy of clindamycin was tested.

We excluded all studies that did not meet the inclusion criteria; of particular note were trials in which the control group received antibiotic treatment.

Sources of information

The following electronic databases were used for the search: Pubmed/Medline, Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science, Embase Ovid and Scopus. A handsearch was also performed. All databases were searched until January 2021.

Search

The search strategy was based on the PICO framework. Population (P): Patients were assessed for inclusion in the analysis regardless of age, sex, previous pathologies or habits, such as smoking. All studies evaluating any type of oral surgical procedure were included. Intervention (I): Antibiotic prophylaxis with clindamycin administered orally, intravenously or topically and prescribed before, during and/or after oral surgery. Comparison (C): Placebo or no treatment administered perioperatively. Outcome (O): Outcome variables included all signs of postoperative infection (pain, fever, swelling, trismus and wound or surgical site infection), dry socket, other related complications and adverse events. Two independent investigators performed study selection until January 2021.

The electronic search in the PubMed/Medline database was performed using the MeSH thesaurus and search algorithms connected with Boolean operators as keywords for titles and abstracts. These are some of the different search strategies used:

("clindamycin"[MeSH Terms] OR "clindamycin"[All Fields] OR "clindamycine"[All Fields]) AND ("surgery, oral" [MeSH Terms] OR ("surgery" [All Fields] AND "oral" [All Fields]) OR "oral surgery" [All Fields] OR ("oral" [All Fields] AND "surgery" [All Fields]) OR "oral

surgery" [All Fields] OR "oral surgical procedures" [MeSH Terms] OR ("oral" [All Fields] AND "surgical" [All Fields] AND "procedures" [All Fields]) OR "oral surgical procedures" [All Fields] OR ("oral" [All Fields] AND "surgery" [All Fields]).

("clindamycin" [MeSH Terms] OR "clindamycin" [All Fields] OR "clindamycine" [All Fields]) AND ("dental implants" [MeSH Terms] OR ("dental" [All Fields] AND "implants" [All Fields]) OR "dental implants" [All Fields]).

("clindamycin" [MeSH Terms] OR "clindamycin" [All Fields] OR "clindamycine" [All Fields]) AND ("tooth extraction" [MeSH Terms] OR ("tooth" [All Fields] AND "extraction" [All Fields]) OR "tooth extraction" [All Fields] OR ("dental" [All Fields] AND "extraction" [All Fields]) OR "dental extraction" [All Fields]).

("clindamycin" [MeSH Terms] OR "clindamycin" [All Fields] OR "clindamycine" [All Fields]) AND (("mouth" [MeSH Terms] OR "mouth" [All Fields] OR "oral" [All Fields]) AND ("biopsie" [All Fields] OR "biopsy" [MeSH Terms] OR "biopsy"[All Fields] OR "biopsied"[All Fields] OR "biopsies"[All Fields] OR "biopsy s"[All Fields] OR "biopsying"[All Fields] OR "biopsys"[All Fields] OR "pathology"[MeSH Subheading] OR "pathology"[All Fields]).

No restrictions on language or date of publication were used. The filters activated were: human and clinical trials.

Selection of studies

The search strategy produced the results shown in Figure 1. Databases not shown in this figure did not contribute any relevant publications. Two independent investigators performed the selection of studies (IA and AF), a third investigator was requested in case of conflict (FR). Included and excluded articles with reasons for exclusion were recorded in Table 1.

Data collection process

A data collection protocol was designed, in which each selected study was reviewed independently by two investigators (IA and NAL), and differences were resolved by consulting a third analyst (FR). Where no explicit data were available in the main text, calculations were performed using results in tables or figures, where possible. In case of missing or doubt about data of interest in the article, the authors were contacted.

Data

Table 2 included all the data recorded in each study. The studies were classified according to the type of oral surgery performed. In addition, when more than one antibiotic was tested in the same study, only information regarding patients who were treated with clindamycin and those who belonged to the control groups was collected.

Risk of bias in individual studies

The Cochrane Collaboration tool was used to assess the individual risk of bias of each RCT included in the quantitative analysis (Figure 2). The bias of each study was analysed

using the recommended approach for assessing risk of bias in studies included in Cochrane reviews.

Overview Measures

Treatment efficacy was assessed by considering relative risk (RR). Differences in incidences between treatment and control groups or attributable risk were used to assess the clinical significance of clindamycin treatment. In addition, the number needed to treat (NNT) was calculated.

Summary of results

The analysis was performed using STATA® IC 13 and Review Manager (RevMan) 5.2 version software (Copenhagen: The Cochrane Collaboration, 2012). Heterogeneity of the different studies was assessed using the I2 statistic. The overall relative risk, resulting from combining the results of the different studies, was calculated with the variance-weighted inverse Mantel-Haenszel (MH) model. An empirical correction was used for studies with null effect sizes in one of their arms, and studies with a null effect size in both arms were excluded from the analysis.

RESULTS

Selection of studies

We identified 540 records from both databases and handsearching (Figure 1). After removing duplicates, 38 articles were selected for full-text assessment. Following full text assessment, seven were included in the qualitative synthesis. First, all articles that did not analyze infection clinically were excluded. Nine articles [1-9] studied bacteraemia, three articles [10-12] studied the influence of clindamycin on the oral microbiome. Bulut et al. (2001) [13] studied acute phase protein levels. One article [14] could not be found and was excluded. Subsequently, the articles were classified according to the type of oral surgery in which the efficacy of clindamycin was tested. Table 1 shows the studies that were included and those that were excluded with their reasons.

Figure 1: PRISMA Flow Diagram

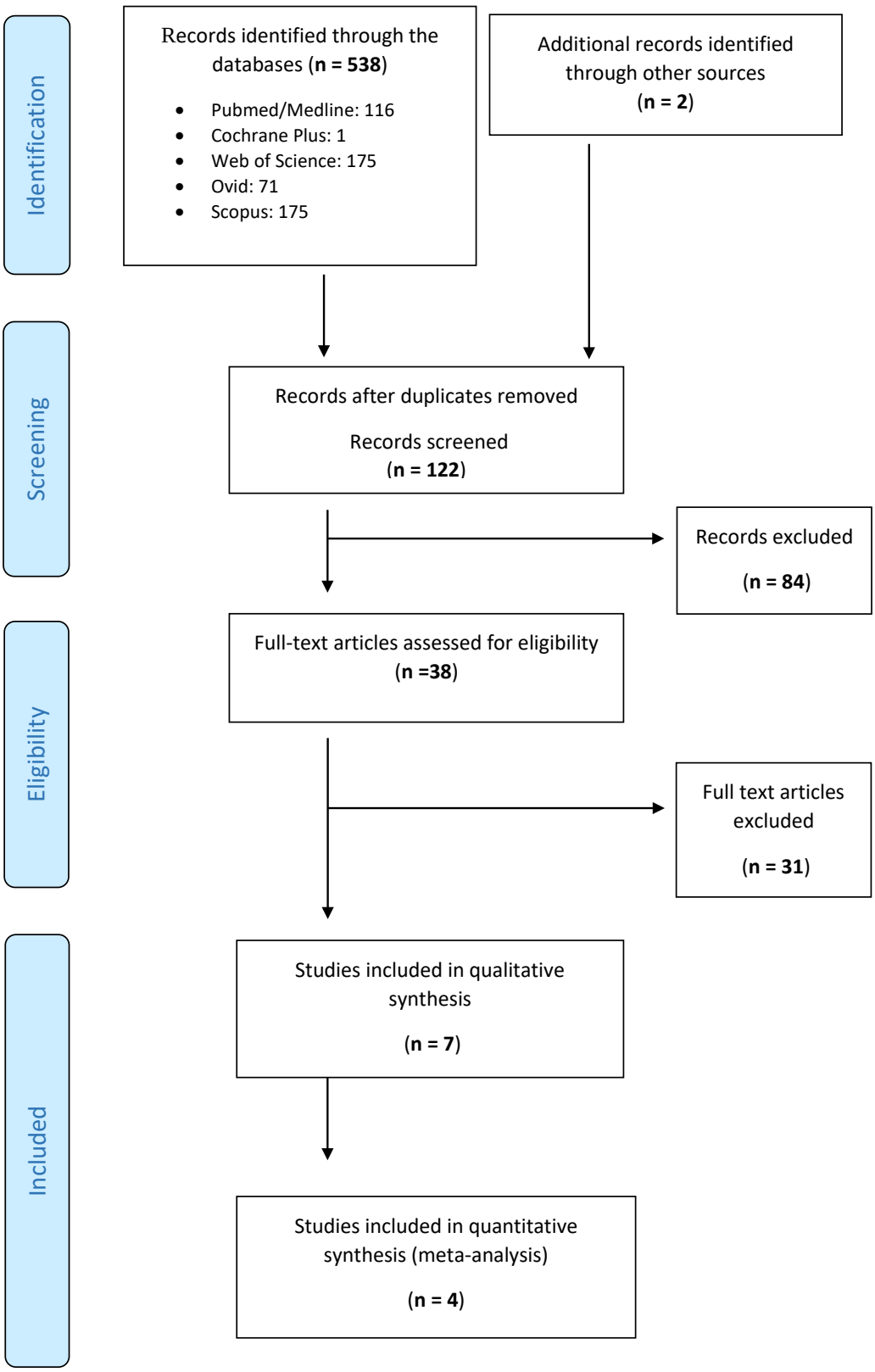


Table 1. Full-text articles classified according to the surgical procedure in which clindamycin was tested, specifying those included, those excluded and the reason for exclusion.

Surgical procedure	Authors / Year	Inclusion/exclusion
Mandibular Fractures	Miles BA et al. 2006 [22].	Excluded: no placebo or no treatment control group.
Bone grafting in conjunction with implant placement	Lindeboom JA et al. 2005 [23].	Excluded: no placebo or no treatment control group.
	Lindeboom JA et al. 2006 [24].	Excluded: no placebo or no treatment control group.
	Klinge A et al. 2020 [25].	Excluded: This is a revision.
Orthognathic surgery	Lindeboom JA et al. 2003 [26].	Excluded: no placebo or no treatment control group.
	Baqain ZH et al. 2004 [27].	Excluded: no placebo or no treatment control group.
	Davis CM et al. 2017 [28].	Excluded: no placebo or no treatment control group.
Oncological surgery	Righi M et al. 1995 [29].	Excluded: no placebo or no treatment control group.
Head and neck surgery	Mann W et al. 1990 [30]	Excluded: no placebo or no treatment control group.
	Clayman GL et al. 1993 [31].	Excluded: no placebo or no treatment control group.
Endodontic procedure	Raslan N et al. 2017 [32].	Excluded: no placebo or no treatment control group.
Endodontic surgery	Lindeboom JA et al. 2005 [21].	Including
Tooth extraction	Laird WR et al. 1972 [33].	Excluded: no placebo or no treatment control group.
	Bystedt et al. 1980 [34].	Excluded: did not report data in a form suitable for inclusion.
	Kupfer et al. 1995 [35].	Excluded: not an ECA
	Poeschl et al. 2003 [17].	Including
	Foy et al. 2003 [36]	Excluded: did not report data in a form suitable for inclusion.
	[a]Halpern et al. 2007[16].	Including
	Kaczmarzyk et al. 2007 [18].	Including
	Adde et al. 2012 [19].	Including
	*Hamiti-Krasniqi et al. 2014 [15].	Including
	Xue 2014 [37]	Excluded: patients included in another study. It was not possible to contact the authors.

	Xue 2015 [38]	Excluded: did not report data in a form suitable for inclusion.
	Kaposvári 2017[20]	Includes

** clindamycin topical;[a] intravenous clindamycin*

Characteristics of the studies

Table 2 shows the variables studied from the included studies: one study was conducted on endodontic surgery and six studies on third molar surgery. Hamiti-Krasniqi et al. (2014) [15], tested topical clindamycin in the prevention of dry alveolitis, while Halpern and Dodson (2007) used intravenous clindamycin (600 mg IV 1 hour before surgery) [16]. Both studies showed lower infection rates in patients treated with clindamycin than in the placebo group. In the remaining clinical trials, treatment was with oral clindamycin, varying in regimens and doses. The follow-up period in all studies ranged from 1 to 4 weeks.

Only four trials allowed us to pool information on the effect of oral clindamycin on third molar extractions. For this reason, we decided to proceed with a quantitative analysis testing the null hypothesis (H_0), at a significance level of $p=0.05$, that preventive use of oral clindamycin is not effective in reducing infection in third molar surgery.

Table 2. Characteristics of the studies included in the review.

Study	Study design and inclusion criteria	Antibiotic/ placebo	Post-operative treatment	Outcome variable and Follow-up period	Results	Lost to follow and side effects
ORAL CLINDAMYCIN IN THIRD MOLAR EXODONTIA						
Poeschl [17] 2004 Austria Source of funding: unspecified	RCT Surgical extraction of impacted lower third molars Mean age 20.7 years (age range was 14-61 years)	Experimental group: 300mg clindamycin (Dalacin) orally 3 times a day for 5 days post-operatively N=180 molars. Control group: none. N=172 molars	Mouthwash with 0.2% chlorhexidine 1 minute before surgery. Analgesic after surgery if necessary 500 mg mefenanimo acid. Every 6 hours.	Dry socket: lack of clot, exposed bone, foul-smelling necrotic debris in the cavity, extremely painful socket walls Infection of the suture site: local inflammation, hyperemia, purulent exudate and pain at the suture site) Pain assessment: VAS Scale Differences in opening the mouth Follow-up period: day 2, 10 and 4 weeks	Experimental group: symptoms of local infection Dry socket 15/180 Control group: symptoms of local infection Dry Socket 17/172 The amoxicillin/clavulanis group was not included in the study.	2 patients did not return after surgery. 4 patients did not remove suture on day 10 7 patients did not return to the last appointment 4 weeks after surgery. Side effects: headache, weakness, nausea, tremor, diarrhea, constipation, insomnia and fever. Experimental group 22 and control group 24.
Kaczmarzyk [18] 2007 Poland Source of funding: unspecified	RCT Healthy volunteers, surgical removal of a retained lower third molar, requiring bone extraction. Exclusion of those under 18 years of age or over 60 years of age. means 24 years.	Experimental group: (5-day clindamycin group): 600 mg clindamycin hydrochloride orally 60 min before surgery, followed by 300 mg clindamycin hydrochloride every 8 hours for 5 days. N=28 Control group: 600 mg placebo orally 60 min before surgery, followed by a dose of 300 mg placebo every 8 hours for 5 days. N=27	Ketoprofen 50 mg capsules to take in case of pain. The maximum daily dose was 200 mg. Patients were asked not to take any other medicines during the trial.	On a scale of 4 degrees, Trismus - facial swelling, submandibular lymphadenopathy in a VAS of 100 mm of body temperature, pain Alveolar osteitis (the clinical diagnosis of this complication was given in the case of the presence of a necrotic gray clot in a bare bone cavity, the fetor ex ore, accompanied by pain in this area). Follow-up period: on the first, second and seventh postoperative day.	Experimental group: 2/28 Control group: 4/27 Not included in the study There is a single-dose group: patients receiving 600 mg clindamycin hydrochloride orally 60 min before surgery	9 did not register for the follow-up review 3 were disqualified due to complications 2 resigned during the trial without giving any reason. Side effects 3% of participants who took a 5-day course of clindamycin developed gastric complications and were excluded from the trial

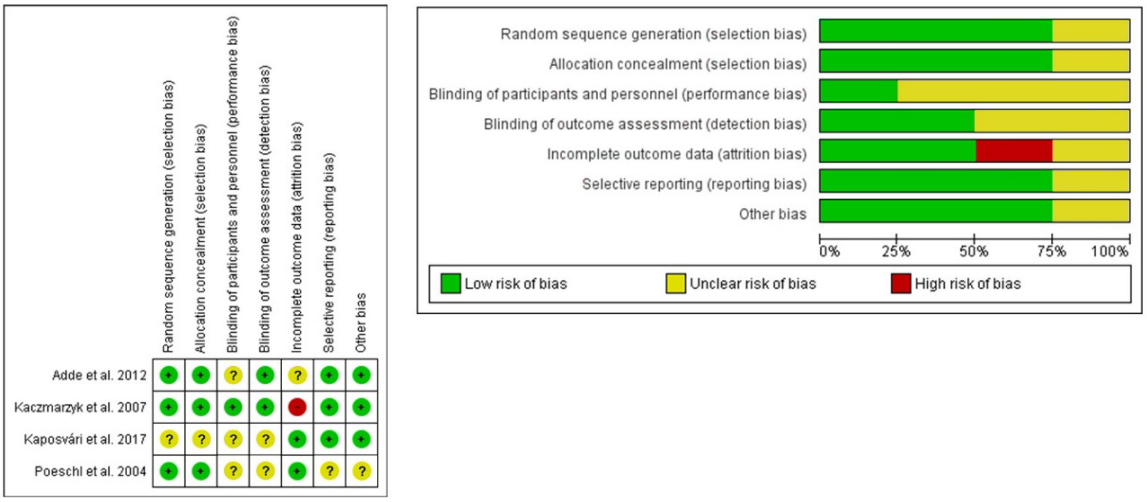
Adde [19] 2012 Brazil Source of funding: unspecified	ECA Age between 18 and 45 years. ASA type I with indication for extraction of upper and lower third molars.	Experimental group: Clindamycin 300mg 4 times a day for 7 days. N= 23 Control group: no treatment. N= 24	Diclofenac 50 mg every 8 hours for 3 days Paracetamol 750mg at least 1 hour before surgery and then every 6 hours until the pain stops.	Postoperative infection: body temperature above 37.8C without other discernible causes, intraoral abscess with floating drainage point, alveolitis, persistent or intensified severe pain 48 hours after surgery and swelling and/or erythema, and severe pain from the seventh day onwards accompanied by swelling. Follow-up period: Assessment at 24 hours, 48 hours, 3 days and 7 days.	Experimental group: 0/23 postoperative infection Control group: 0/24 postoperative infection.	No losses. Side effects No complications of any kind have been reported.
Kaposvári [20] 2017 Hungary Unfinanced	Third lower molar RCT was extracted Healthy patients aged 18 to 35 years mean age 24.78 years	Experimental group: 600 mg clindamycin one hour before surgery. N=14 (7 simple/7 complex) Control group: placebo. N=18 (8 easy / 10 complexes)	Diclofenac 50 mg, maximum 3 doses	Alveolitis Dissected wound. Follow-up period: for one week until suture removal.	Experimental group: 0/14 alveolitis and dissected wound 2/14 Control group: 2/18 alveolitis and 4/18 dissected wound	1 loss in the experimental group. Side effects: wound separation, edema and trismus.
INTRAVENOUS CLINDAMYCIN IN THIRD MOLAR EXODONTIA						
Halpern [16] 2007 USA supported in part by the research grant of the Oral and Maxillofacial Surgery Foundation and the Center for Applied Clinical Research at Massachusetts General Hospital (MGH)	RCT Patients requiring third molar extraction under intravenous sedation or general anesthesia in the outpatient office setting. The age range of the patients is 17.7-31.5 years. Mean age was 25 years.	Experimental group: penicillin solution (15,000 units per kilo) or, in the case of penicillin-allergic subjects, clindamycin 600 mg intravenously 1 hour before surgery. N=.60 N=. (clindamycin) 15 Placebo control group: solution (10 cc of 0.9% saline) administered intravenously one hour before surgery. N=62	All subjects received intravenous dexamethasone (8 mg) preoperatively and 15% received intravenous antiemetic treatment (ondansetron 2 mg). 1 or 2 tablets of paracetamol (500 mg) and hydrocodone (5	Dry alveolitis: new onset or increased pain more than 36 hours postoperatively, with blood clot at the extraction site evidenced by exposed bone, mild probing or irrigation of the wound doubling the pain and significant pain relief postoperatively. Surgical site infection: visual evidence of frank purulence at one or more of the extraction sites and Gram stain demonstrating the presence of white blood cells. Follow-up period: Assessed on postoperative day 7 (range 5-14).	Experimental group: 0/15 postoperative infection. Control group: 5/62 postoperative infection.	1 loss in the control group 1 loss in the experimental group

			mg) taken orally every 3 to 4 hours			
TOPICAL CLINDAMYCIN IN THIRD MOLAR EXODONTIA						
Hamiti-Krasniqi [15]. 2012 Kosovo Source of funding: unspecified	ECA. A split mouth. Extraction of the right and left mandibular third molar. Patients with health problems and those who received antibiotic therapy 14 days before surgery were excluded.	Experimental group: 300 mg of clindamycin mixed with 0.2 ml of saliva. Then the Gelatamp haemostatic sponge is introduced N=.60 molar Control group: none. N=.60 molars Patients were divided into smokers and non-smokers.	Analgesic medication is administered only in case of post-extraction pain, specifying the side of the pain.	Dry plug Follow-up period: the next day, two days and day 5	Experimental group: 2/60 dry socket. Control group: 19/60 dry sockets.	No loose tracking
ORAL CLINDAMYCIN IN ENDODONTIC SURGERY						
Lindeboom [21] 2006 Amsterdam Source of funding: unspecified	RCT Apical periodontitis tooth with adequate root closure and coronal restoration	Experimental group: clindamycin 600mg 1 hour before the incision. N=128 teeth Control group: placebo 600mg 1h before the incision. N=128 teeth	Chlorhexidine solution 0.2% twice a day for 1 week.	Infection: Purulent drainage from an incision or drainage, serosanguineous drainage and wound culture positive for a known pathogen, wound spontaneously dehisced or deliberately opened by the surgeon when the patient had fever or localized pain or tenderness, with positive wound culture. Follow-up period: patients were evaluated at the first, second and fourth week.	Experimental group: 2 teeth / 128 infections. Control group: 4 teeth / 128 infections.	No loose tracking

Risk of bias within studies

The risk of bias of each study is presented in Figure 2. Although some studies were not of high quality and dealt with different doses, the quantitative analysis was performed including the four articles [17-20] studying the efficacy of oral clindamycin in third molar surgery.

Figure 2. Risk of Bias Graph and Summary

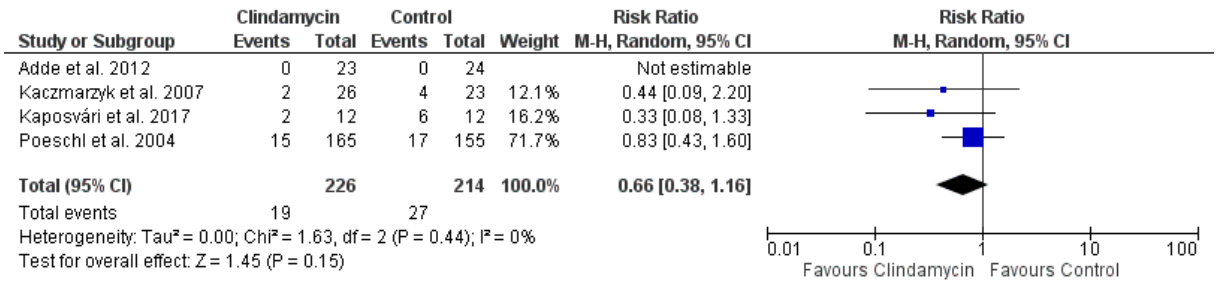


Overview Measures

The four studies in which oral clindamycin was prescribed to prevent infectious complications after third molar extractions were the only ones included. The quantitative analysis included 486 extractions, 245 of which were treated with clindamycin and 241 in the control group (treated with placebo or no treatment). Nineteen and 27 cases of infection, dry sockets or other events were reported in the respective groups.

The Forest plot (Figure 3) shows the graphical representation of the RR and 95% CI estimates made using the samples from the four included studies. The overall RR extracted from all studies indicated that there was no statistical benefit, and that oral clindamycin may not be effective in preventing infectious complications following third molar extractions.

Figure 3. Forest Plot



Summary of results

The heterogeneity measured from the I2 test was 0 (*p=0*.44), and the null hypothesis of absence of heterogeneity among the results of the studies included in this meta-analysis could not be rejected. The Q statistic also supports the hypothesis of homogeneity among the studies.

The overall RR using the Mantel-Haenszel method was 0.66, with a 95% CI of 0.38 to 1.16, which was not statistically significant (*p=0.*15). This interval also included the value 1, indicating that clindamycin treatment may not prevent the development of infectious complications (dry alveolitis, infection or both conditions at the same time) after third molar extractions.

Analysis of clinical significance

The NNT was 29 and ranged from 12 to -57. This means that it would be necessary to treat between 12 and an infinite number of patients with oral clindamycin to prevent a single case of infection after third molar extraction. These results suggested that oral clindamycin may be ineffective in preventing infections after third molar extractions.

There are no studies on the efficacy of clindamycin in the prevention of infections and/or oral implant failure.

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3.4.3. Preventive clindamycin in oral implant surgery. Randomized and controlled clinical trial

SUMMARY

Objectives: The prophylactic use of clindamycin in oral implant surgery is not supported by evidence, although it is frequently prescribed as an alternative for penicillin-allergic patients. The aim of this study was to evaluate the effect of preoperative clindamycin in reducing postoperative infections and implant failures.

Methods: A prospective, randomized, parallel, double-blind, placebo-controlled clinical trial was conducted in full compliance with ethical principles and the CONSORT declaration. The sample size, calculated in advance, was 62 healthy adults, who attended the UPV/EHU Dental Clinic for the placement of a single oral implant without previous infection of the surgical site and not requiring bone grafting. Sixty-two participants were randomly assigned, 31 to the clindamycin group: a single dose of oral clindamycin (2 capsules of 300 mg) one hour before surgery. Another 31 patients received the same dose, regimen and placebo presentation. The same surgeon performed all surgical procedures. A single trained observer evaluated all patients on postoperative days 1, 7, 14, 28, and 56. Infection and implant failure were analysed. Adverse events and clinical, radiological and surgical variables were recorded. The number needed to treat/harm (NNT/NNH) and the relative risks of infection and implant failure were calculated.

Results: There were two implant failures, both in patients treated with clindamycin (NNH=15). However, no significant differences were found between groups (p=0.246). Three patients suffered postoperative infections; two were in the placebo group and one in the clindamycin group (RR: 0.5, CI: 0.05-5.23, ARR=0.03, CI: -0.07-0.13, NNT=31, CI: 7.2-∞). There was also no significant difference between groups (p=0.5). One patient treated with clindamycin had gastrointestinal disturbances and diarrhea, with no significant difference between groups (NNH=31; p=0.5).

Conclusions: Preoperative clindamycin use in oral implant surgery in healthy patients without prior infection or need for bone regeneration may not be beneficial in reducing postoperative infections and implant failures.

METHODS

Trial design and ethical issues

This study was designed as a prospective, randomized, parallel, double-blind, placebo-controlled clinical trial. (EudraCT number: 2017-002168-42). The trial was approved by El Comité de Ética de Investigación con Medicamentos de Euskadi (CEIm-E) on 31/10/2018 (internal code number: 201862) and by the Spanish Agency of Medicines and Medical Devices (AEMPS) (18/12/2018). This research was conducted in accordance with ethical principles, including the Declaration of Helsinki of the World Medical Association [1]. The study was reported in accordance with the CONSORT statement [2]. The only change made to the design is the timing at which we assessed implant stability, it was assessed on day 56 instead of day 28.

Participants

The trial was conducted at the Dental Clinic of the Postgraduate Program in Oral Implantology and Microsurgery of the University of the Basque Country (Leioa, Spain). The eligible population was all healthy adults under 18 years of age who attended the Dental Clinic and in whom the placement of a single implant was indicated, without previous infection of the surgical site or need for bone regeneration. Consecutive sampling of the accessible population was carried out.

Patients were excluded before randomization for the following reasons: allergy to any drug used in the trial, presence of decompensated systemic pathologies (cardiac, respiratory, endocrine, metabolic, hepatic, hematological, risk of bacterial endocarditis, immunocompromised), carrying valvular or orthopedic prostheses, history or use of bisphosphonates, anticoagulants or antiplatelet agents. We also excluded patients who had been irradiated in the cervical and maxillofacial territory, if they were pregnant, suspected of being pregnant or breastfeeding, and if they had a history of ulcerative colitis associated with antibiotics. All patients underwent a radiological study of the implantation site as per clinic protocol. Patients in whom bone graft treatment might be necessary were excluded from the trial.

Patients were excluded after randomization at the patient's request, by dropping out of the trial or loss to follow up and also if the patient had taken antibiotics in the last 15 days before surgery.

Interventions

A single dose of clindamycin 600 mg (2 capsules of 300 mg) was administered one hour before surgery to participants in the experimental group and the same regimen and placebo presentation to participants in the control group. The patients received the envelope with the medication or placebo at the dental clinic just one hour before the start of surgery.

The same surgeon, with extensive experience in oral implant surgery, performed all surgical procedures. The surgeries were started with the following anesthetic technique: anesthetic block of the area, using articaine 4% with epinephrine 1:1000,000, using a mandibular block technique for implant placement in the mandible and an infiltrative technique in the maxilla. A full-thickness mucoperiosteal flap was made through a supracrestal incision in the edentulous section and an intrasulcular incision in the adjacent teeth. Unloading incisions were only made in very resorbed ridges or in the presence of marked bone concavities. Straumann Roxolid® (TI-Zr) SLActive® (Sand-blasted large grift Acid-etched) implants (Basel, 4002 Switzerland) were placed. In the non-esthetic sites, a 1.8 mm Straumann Tissue Level Standard Plus® (TL) polished collar implant was placed. In the esthetic sites, Straumann Bone Level Tapered® (BLT) implants were inserted in the maxilla. The drilling sequence recommended by the manufacturer for both implant types was used. No second stage implant surgery was performed in any patient. The bone width and available bone height determined the diameter (3.3 or 4.1 mm), the implant length (8, 10 or 12 mm) and thus the drilling sequence. After implant placement, the insertion torque of the implant was measured using a Straumann ratchet wrench with dynamometer (No. 046.119 and 046.049). In all cases, primary flap closure was performed using a 5-0 nonabsorbable polyester monofilament suture with an interrupted single suture technique.

Anti-inflammatory treatment consisted of Ibuprofen 600 mg every 12 hours, or Paracetamol 1g on demand.

Clindamycin capsules or placebo were presented in blister packs, individually packaged and labelled to maintain the blind. Samples were labelled with sample number, protocol code, number of units, dosage form, route of administration and expiry date.

The intended rescue antibiotic was one tablet (875/125 mg) of amoxicillin/clavulanic acid every 8 hours for 7 days. One of the inclusion criteria was not being allergic to amoxicillin or clavulanic acid.

Response variables

A single trained observer assessed all patients on days 1, 7, 14, 28 and 56 after surgery. Any clinical or radiographic signs indicative of infection or biological complications were recorded: suppuration, fistula, abscess, osteomyelitis, fever greater than 38 °C. Postoperative pain, localized swelling, bleeding, intraoral and extraoral erythema were also assessed with the visual analogue scale (VAS). The presence of clinical or radiological signs of implant failure were also recorded: peri-implant radiolucency at day 56, manual mobility and Osstell® resonance frequency analysis (ISQ<60 at day 56). All adverse reactions were also recorded.

Sample Size

The sample size was calculated using STATA® 14 statistical software. Differences in infection or implant failure between the control and treatment groups of more than 18%

were considered clinically relevant. Nolan et al. (2014) [3] reported a cumulative incidence of failure of 18% in placebo-treated patients. For a 95% confidence level, 80% power, a probability of implant failure or postoperative infection of 18% with placebo and 0% with antibiotics; two groups with 31 patients each were required [3]. Therefore, a treatment group (TG) with 31 implants and a control group (CG) with another 31 implants were considered necessary. The sample was set at 62 patients, who would have freely given informed consent to participate in the trial.

Randomization

From the total sample, a restricted block randomization was performed with a block length of four patients, with the same probability (0.5) of allocation to each treatment within the block (two patients for each treatment within each block). Randomization was performed with the statistical program STATA® 15.

Assignment concealment

Patients were assigned after verifying that they met the established inclusion criteria and once they had given their written informed consent to participate. An external study assistant prepared the sealed and numbered envelopes, according to the instructions, with the antibiotic or placebo to be administered. Each number corresponded to the treatment assigned in the randomization process and each patient was successively assigned the corresponding treatment number. One of the investigators delivered the treatment in a sealed envelope one hour before implant placement. The treatment was unknown to both the professionals in direct contact with the patient and the patient.

Blinding

Randomization and allocation concealment were performed with double blinding: neither the patient nor the expert who placed the implant was aware of the treatment the patient received. The professional who assessed the infection or loss of the implant was also unaware of the treatment the patient had received.

Statistical analysis

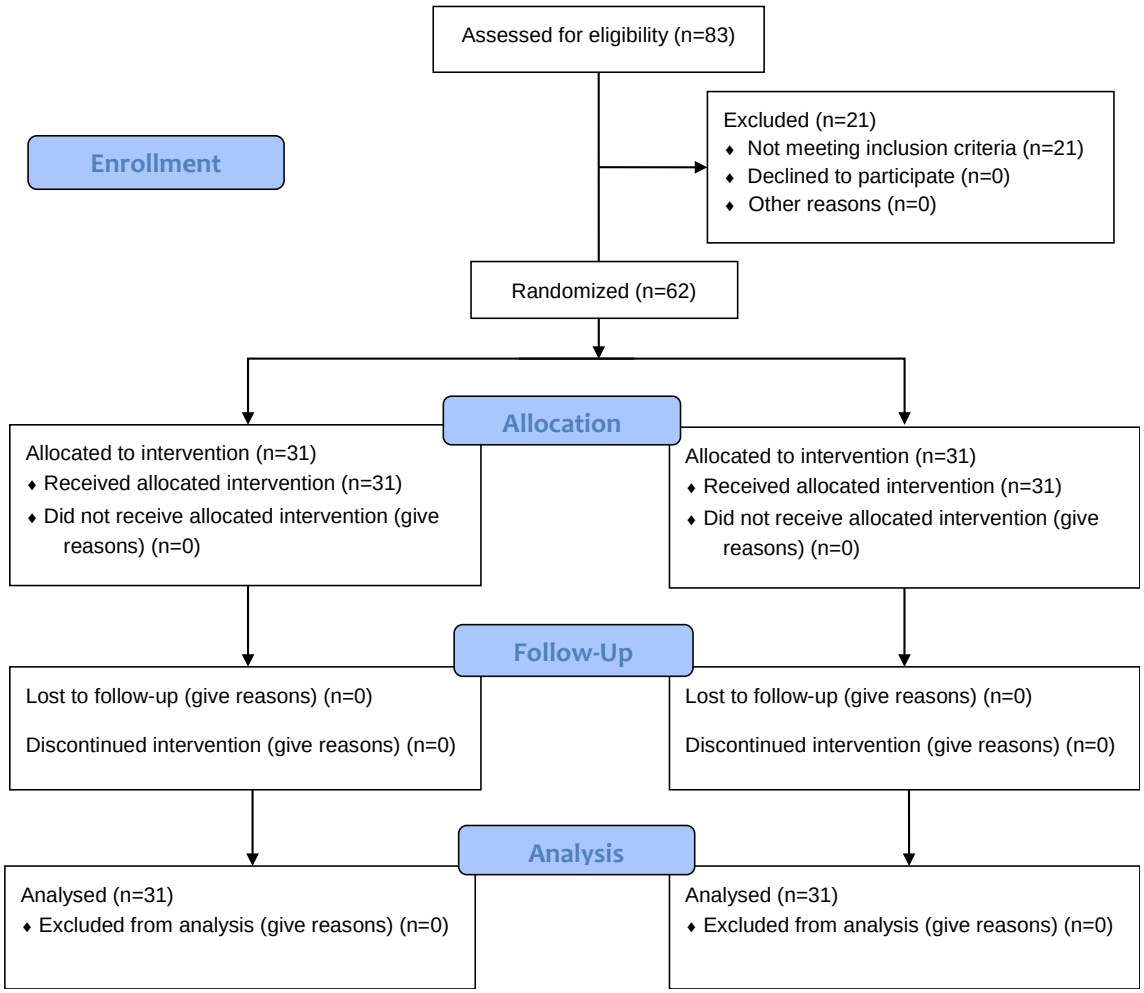
We used STATA® 15 software for intention-to-treat data analysis. The variances of each variable were calculated and the association between the treatment groups and the different variables was assessed using Student's t-test for continuous variables and Fisher's exact test for categorical variables. Treatment effect and precision were estimated using 95% confidence intervals (CI). Absolute risk reduction or increase (ARR or ARI), relative risk (RR) and number needed to treat or harm (NNT or NNH) were calculated for implant failure, postoperative infection, adverse events and complications (infections or implant failure). Hypotheses of equal risk of implant failure or postoperative infection between the experimental and placebo groups were tested.

RESULTS

Participant flow

A flow chart shows the number of participants who were randomized, received the intended treatment, and were analyzed for each group, as well as losses and exclusions after randomization (Figure 1). Six patients were included twice in the trial after randomization and after a period of at least 2 months between interventions. Five participants received placebo twice and the sixth received placebo first and clindamycin in the second intervention. None of these six participants had a postoperative infection, implant failure or adverse event.

Figure 1. Recruitment Process Flowchart



Recruitment

Recruitment began in October 2019 and ended in June 2021 and each participant was followed until day 56 after surgery. The trial was temporarily halted due to the pandemic caused by Covid-19 and ended when all included participants were monitored at day 56 post-surgery (August 2021).

Reference data

The baseline demographic and clinical characteristics of each group are shown in Table 1. The existence or not of significant association between the variables and the treatment groups is also shown. There were no differences between the clindamycin and placebo groups, so both groups can be considered similar and comparable in relation to the distribution of these variables.

Table 1. Characteristics of the participants

Variable	Clindamycin group (n=31)	Placebo group (n=31)	Overall (n=62)	p-value
Genre				0.111
Man	14 (45.2%)	8 (25.8%)	22 (35.5%)	
Woman	17 (54.8%)	23 (74.2%)	40 (64.5%)	
Age	49.7 (9.4)	47.5 (10.7)	48.6 (10.1)	0.387
Smokers				0.755
Yes	7 (22.6%)	6 (19.4%)	13 (20.9%)	
No	24 (77.4%)	25 (80.6%)	49 (79.1%)	
Cigarettes per day				0.677
0	24 (77.4%)	25 (80.6%)	49 (79.1%)	
<10	3 (9.6%)	4 (12.9%)	7 (11.3%)	
10 - 20	2 (6.5%)	2 (6.5%)	4 (6.4%)	
>20	2 (6.5%)	0 (0%)	2 (3.2%)	
Contraceptives				0.177
Yes	1 (3.3%)	4 (12.9%)	5 (8.1%)	
No	30 (99.7%)	27 (87.1%)	57 (91.9%)	
Implant Location				0.526
Upper Premolar	4 (12.9%)	6 (19.3%)	10 (16.1%)	
Upper molar	6 (19.3%)	6 (19.3%)	12 (19.4%)	
Lower Premolar	0	2 (6.5%)	2 (3.2%)	
Lower molar	21 (67.8%)	17 (54.9%)	38 (61.3%)	
Type of implant				0.793
Bone level	11 (35.5%)	12 (38.7%)	23 (37.1%)	
Fabric level	20 (64.5%)	19 (61.3%)	39 (62.9%)	
Implant length				
8 mm	2 (6.4%)	4 (12.9%)	6 (9.6%)	0.336
10 mm	29 (93.6%)	27 (87.1%)	56 (90.4%)	
Duration of surgery	14.5 (5.1)	15.3 (6.1)	14.9 (5.6)	0.339

For continuous variables: n (%), while p-values were obtained using Student's t-test. For categorical variables: mean (SD), while p-values were obtained using Fisher's exact test.

Analysis

Thirty-one participants in the clindamycin-treated group and 31 participants in the placebo group were finally included in the analysis. The analysis was in all cases by originally assigned groups.

Results and estimation

Two implants failed, both patients had been treated with clindamycin (RR: not estimable, ARI=0.06, CI: -0.03-0.16, NNH=15.5, CI: 6-∞). The ARI indicated that 6% of patients would experience implant failure under clindamycin treatment that they would not have if they had been treated with placebo. The NNH indicated that for every 15 patients treated with clindamycin, one implant failure would occur that would not have occurred under placebo treatment. However, no significant differences were found between the groups (p=0.246).

Three patients suffered postoperative infections and two of them were given rescue antibiotic treatment, while the other patient did not receive rescue antibiotic because the implant failed and was removed. The two patients who received the rescue antibiotic belonged to the placebo group, while the other patient, the one who suffered implant failure belonged to the clindamycin group (RR: 0.5, CI: 0.05-5.23, ARR=0.03, CI: -0.07-0.13, NNT=31, CI: 7.2-∞ 7.2-∞). The ARR suggested that 3.2% of patients would not experience postoperative infections under clindamycin treatment that they would have with placebo. The NNT stated that 31 patients would need to be treated with clindamycin to prevent one patient from having a postoperative infection. However, there was no significant difference between the two groups (p=0.554).

Considering overall complications such as occurrence of postoperative infections or oral implant failure per participant, there were two participants in each treatment group who experienced complications (RR=1, CI: 0.15-6.66, ARR=0, CI: -0.12-0.12, NNT: Not estimable, p=0.999).

Auxiliary analyses

There were no significant relationships between any variable recorded and implant failure or adverse reactions (Table 2). No significant associations were found between any variable and postoperative infection, except for implant type (p=0.047) and implant location (p=0.048). The variable implant location was not significant for postoperative infection (p=0.055). There were also no significant differences (p>0.05) between the treatment groups and the following variables: suppuration, fistula, abscess, osteomyelitis, fever over 38°C, postoperative pain, bleeding, localized inflammation, extraoral erythema, intraoral erythema, peri-implant radiolucency on day 56 and ISQ value less than 60 on day 56 (Table 3). Figure 2 shows the VAS frequencies recorded for each variable on days 1, 7, 14, 28 and 56 after surgery.

Table 2. Response variables.

Variable	Implant failure			Postoperative infections			Adverse reactions		
	Failure rate	RR (95% CI)	p-value	Infection rate	RR (95% CI)	p-value	Proportion of adverse reactions	RR (95% CI)	p-value
Treatment group									
Clindamycin	2/31	NS	0.246	1/31	0.5 (0.05-5.23)	0.5	1/31	NS	0.5
Placebo	0/31			2/31			0/31		
Genre									
Man	1/22	1	0.588	0/22	NS	0.261	1/22	NS	0.355
Woman	1/40			3/40			0/40		
Type of implant									
Bone level	2/23	NS	0.134	3/23	NS	0.047	0/23	NS	0.629
Fabric level	0/39			0/39			1/39		
Implant length									
8 mm	0/6	NS	0.814	1/6	4.6 (0.5-44.1)	0.267	0/6	NS	0.903
10 mm	2/56			2/56			1/56		
Implant Location									
Maxillae	2/22	NS	0.048	3/22	NS	0.055	0/22	NS	0.999
Jaw	0/40			0/40			1/40		
Smoker									
Yes	1/13	1	0.378	0/13	NS	0.487	0/13	NS	0.790
No	1/49			4/49			1/49		
Contraceptives									
Yes	0/5	NS	0.844	0/5	NS	0.774	0/5	NS	0.919
No	2/57			3/57			1/57		

P-values were obtained using Fisher's exact test.

CI: confidence interval: NS: not estimable.

Figure 2. Bar graphs of the variables evaluated with the VE

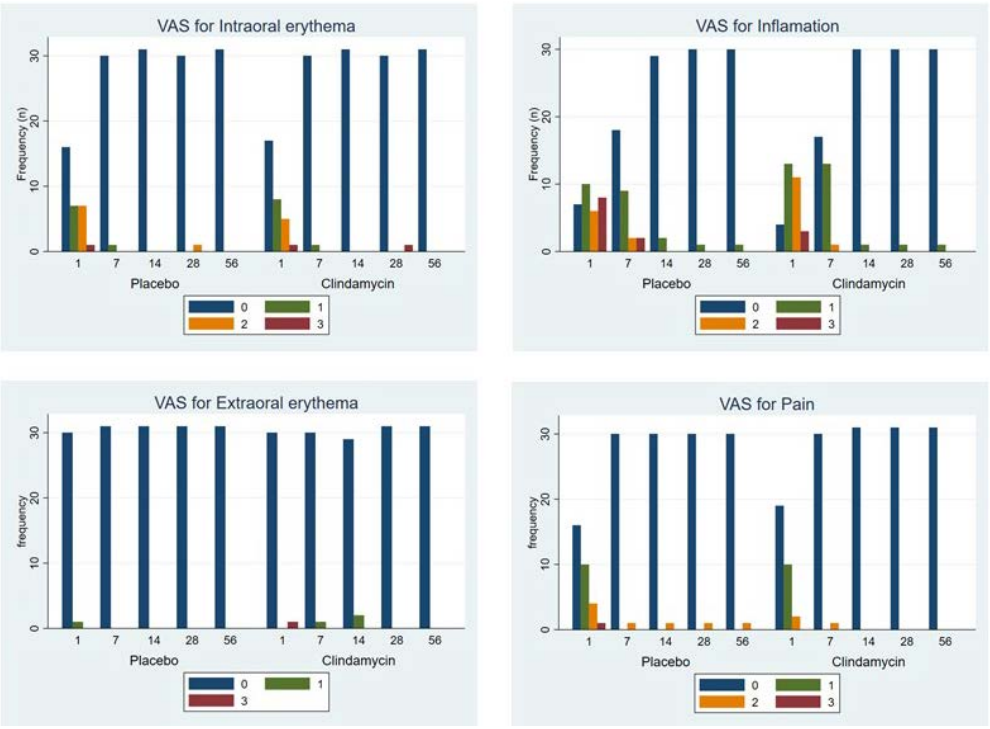


Table 3. Postoperative variables

Follow up	Treatment group	Suppuration	Fistula	Abscess	Osteomyelitis	Fever >38 °C	Postoperative pain	Localized inflammation	Bleeding	Extraoral erythema	Intraoral erythema	Peri-implant radiolucency	ISQ value <60
Day 1	Clindamycin group	0/31	0/31	0/31	0/31	0/31	0.451	1.419	0	0.096	0.677	-	-
	Placebo group	0/31	0/31	0/31	0/31	0/31	0.677	1.483	0.096	0.032	0.774	-	-
	p-value	-	-	-	-	-	0.2315	0.7992	0.179	0.531	0.6723	-	-
Day 7	Clindamycin group	0/31	0/31	0/31	0/31	0/31	0.064	0.483	0	0.032	0.032	-	-
	Placebo group	0/31	0/31	0/31	0/31	0/31	0.064	0.612	0	0	0.032	-	-
	p-value	-	-	-	-	-	0.9999	0.4971	-	-	0.9999	-	-
Day 14	Clindamycin group	0/31	0/31	0/31	0/31	0/31	0	0.032	0	0.064	0	-	-
	Placebo group	0/31	0/31	0/31	0/31	0/31	0.064	0.064	0.032	0	0	-	-
	p-value	-	-	-	-	-	0.3213	0.5615	0.3213	0.1607	-	-	-
Day 28	Clindamycin group	0/31	1/31	1/31	0/31	0/31	0	0.032	0.258	0	0.096	-	-
	Placebo group	1/31	1/31	0/31	0/31	0/31	0.064	0.032	0	0	0.064	-	-
	p-value	0.5	0.754	0.5	-	-	0.3213	0.9999	0.2063	-	0.7826	-	-
Day 56	Clindamycin group	0/31	0/31	0/31	0/31	0/31	0	0.032	0	0	0	1/31	2/31
	Placebo group	0/31	0/31	0/31	0/31	0/31	0.064	0.032	0	0	0	1/31	0/31
	p-value	-	-	-	-	-	0.3213	0.9999	-	-	-	0.9999	0.151

For continuous variables: the rate is indicated, while p-values were obtained using Student's t-test.

For categorical variables: the mean is indicated, while p-values were obtained using Fisher's exact test.

Adverse events

Only one patient treated with clindamycin suffered adverse events (gastrointestinal disorders and diarrhea), with no significant differences between groups (RR: Not estimable, ARI=0.03, CI:-0.05-0.11, NNH=31, CI: 8.5-∞, *p*=0.5).

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3.4.4. Antibiotic prescribing habits in oral implant surgery. Cross-sectional surveys in Spain, the Netherlands and Italy, and meta-analysis of cross-sectional surveys.

Antibiotic prescribing habits in Spain

SUMMARY

Objectives: The use of antibiotics to prevent dental implant failures and postoperative infections remains a controversial topic. The aims of this study were to evaluate the current antibiotic prescribing patterns and the frequency of antibiotic prescribing by dentists in Vizcaya (Spain) in relation to routine dental implant surgery in healthy patients and to determine whether any consensus has been reached by these professionals and the latest published evidence is followed.

Methods: Cross-sectional observational study: electronic survey. This study was conducted according to STROBE guidelines. This anonymous questionnaire contained open and closed questions. An email was sent on 26 October 2017 to all the members of the College of Dentists of Bizkaia (n=989). The data collected were analyzed with STATA® 14 software and 95% confidence intervals (CI) were used to assess the frequency of prescription of each antibiotic regimen.

Results: A total of 233 participants responded to the survey (response rate=23.56%). In total, 210 participants completed the survey completely and 23 partially completed the survey. A total of 122 females (58.1%) and 88 males (41.9%) responded to the questionnaire. Of the participants, 88% (n=207) always prescribed prophylactic antibiotics routinely in conjunction with dental implant surgery (95% CI 84.79-92.88%). Approximately 9% (n=22) prescribed antibiotics sometimes (95% CI: 5.68-13.19%), and only 4 dentists (1.72%) never prescribed antibiotics (95% CI: 0.04-3.38%). Overall, 179 of the 233 respondents prescribed antibiotics both preoperatively and postoperatively (78.85%, 95% CI 72.96-83.97%), 13 prescribed antibiotics only preoperatively (5.73%, 95% CI 3.08-9.59%), and 35 prescribed antibiotics exclusively after routine dental implant surgery (15.42%, 95% CI 10.98-20.78%).

Conclusions: Most dentists working in Biscay routinely prescribe prophylactic antibiotics in conjunction with dental implant surgery among healthy patients. A wide variety of prophylactic regimens are prescribed and the most recent published evidence is not followed.

METHODS

This cross-sectional observational study was based on an electronic survey approved by the BioCruces research institute (Barakaldo, Vizcaya). This study was reported according to the guidelines of the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) [1].

Study design

A validated questionnaire was developed to collect information on preventive antibiotic prescribing patterns among dentists in relation to dental implant surgery. The questionnaire followed by Deeb et al. (2015) was used as a basis, with the explicit permission of the authors [2]. The questionnaire has proven its validity, as the different test items were found adequate to measure the intended objectives. This anonymous questionnaire comprised data in relation to the following: demographic data, qualification and work experience, most common antibiotic prescribed, duration and dosage. The questionnaire contained both open and closed questions. (Table 1)

Environment

Vizcaya is a province of Spain located in the Basque Country. Its population was approximately 1,148,302 in 2017 [3]. An email was sent to dentists on 26 October 2017 that included a link to the web questionnaire developed at www.encuestafacil.com. This email also contained instructions for answering the questionnaire if dentists performed dental implant surgeries and a message briefly describing the aims of the study and the intended use of the data collected for research and epidemiological purposes. It was emphasized that the data were anonymous. A reminder was sent on 8 November 2017 to participants who had not responded by the deadline. The online questionnaire was closed to the public on 2 January 2018. Data collection was done automatically through the server www.encuestafacil.com [4].

Participants

The questionnaire was sent to all the members of the College of Dentists of Bizkaia who had not expressly requested not to receive e-mails. The total number of questionnaires sent was 989. By addressing the entire population of registered dentists in Bizkaia, the authors understood that all members were given the same opportunity (probability) to participate and answer the questionnaire. Participation implied the granting of the participant's consent to record the questionnaire data.

Variables

The questionnaire is shown in Table 1 with all the variables recorded.

Data sources / measurement

Each respondent could only answer an electronic survey once exclusively, and the options for each question are shown in Table 1.

Bias

There could be no selection bias, since the electronic survey was sent to all dentists registered in Vizcaya, and it is compulsory to be registered with one or more dental associations in order to work as a dentist in Spain. Likewise, the authors used an electronic survey previously carried out in the United States to avoid information bias.

Study size

The final sample size was composed of the professionals who decided to respond partially or completely to the survey (n=233).

Statistical methods

The collected data were analysed using STATA® 14 software; 95% confidence intervals (CI) were used to assess the frequency of prescribing each antibiotic regimen.

RESULTS

Participants

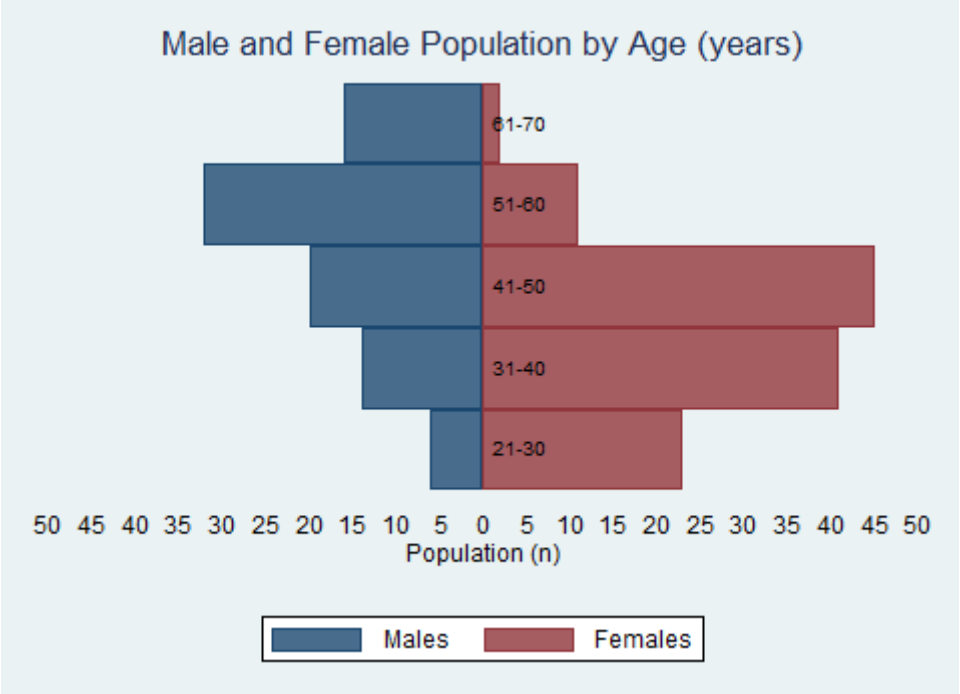
A total of 233 participants responded to the survey; therefore, the response rate was 23.56%. In total, 210 participants completed the survey completely, and 23 surveys were only partially answered. Descriptive and statistical analyses included all surveys with responses (n=233) for the most complete analysis possible.

Descriptive data

A total of 122 women (58.1%) and 88 men (41.9%) responded to the questionnaire, and they were mainly between 51 and 60 years old (30.95%). A population pyramid is shown in Figure 1.

Overall, 173 respondents had studied at the University of the Basque Country (82.78%), located in Biscay, but there were also dentists who had studied at other universities in Spain or other countries (Table 1). Approximately 51% of the respondents worked in the rural area of the province, and 43% in the provincial capital, Bilbao. The rest of the respondents worked in another province of Spain (6%).

Figure 1. Population pyramid



Results data

Table 1 shows the response rate and 95% CI for each item. The preoperative and postoperative regimens followed are shown in Table 2 and Table 3.

Table 1. Survey response variables.

Ask	n	%	95% CI
START OF THE SURVEY			
15. Do you prescribe antibiotics before, after or during dental implant placement?			
Yes, always	207	88.84	84.79-92.88
Yes, sometimes	22	9.44	5.68-13.19
No, never	4	1.72	0.04-3.38
Total	233	100	-
16. Your answer was "Yes, sometimes". Describe the situations in which you prescribe antibiotics.			
17.			
Bone grafts	9	40.9	
Patient with a history of periodontal disease	7	31.81	
Patient smokes	3	13.63	
Preoperative infection at the implant site	14	63.63	
Sinus perforation	13	59.09	*
Simultaneous placement of more than one dental implant	7	31.81	
Heart disease requiring antibiotic prophylaxis	5	22.72	
Another situation	5	22.72	
Total	*		

TEMPORARY ANTIBIOTIC PRESCRIBING PATTERN

Continue with the following questions, assuming patients are healthy and have no allergies to antibiotics when selecting your answers. Choose the most appropriate answer based on reality.

18. When are antibiotics prescribed?			
Exclusively before surgery (preoperative)	13	5.73	3.08-9.59
Exclusively after surgery (postoperative)	35	15.42	10.98-20.78
Before and after surgery (preoperative and postoperative)	179	78.85	72.96-83.97
Total	227	100	-

PREOPERATIVE PRESCRIBING HABITS

19. When does antibiotic prophylaxis begin before implant insertion?			
1 day before	87	47.28	39.89-54.76
1 hour before	47	25.54	19.41-32.48
2 days before	43	23.37	17.45-30.15
Immediately before	7	3.80	1.54-7.68
Total	184	100	-
20. You have selected "1 or 2 days before", select only one type of antibiotic from the following:			
Amoxicillin	87	66.41	57.64-74.42
Amoxicillin/clavulanic acid	37	28.24	20.72-36.77
Other	6	4.58	1.69-9.70
Erythromycin	1	0.76	0.01-4.17
Clindamycin	0	0	-
Penicillin V	0	0	-
Cephalexin	0	0	-
Total	131	100	-
21. Select from the following, the dose, dosage and route of administration ("1 or 2 days before"):			
21.1. Dosage (mg)			
500	53	42.06	33.32-51.18
875/125	25	19.84	13.27-27.88
800	20	15.87	9.97-23.44
1000	19	15.08	9.32-22.54
500/125	9	7.14	3.31-13.12
150	0	0	-
250	0	0	-
300	0	0	-
400	0	0	-
Total	126	100	-
21.2. Dosage			
3 times a day	113	90.4	83.83-94.94
2 times a day	9	7.2	3.34-13.22
1 time per day	2	1.6	0.19-5.66
4 times a day	1	0.8	0.02-4.37
Total	125	100	-
21.3. Route of administration			
Oral	125	100	97.09-1
Intramuscular	0	0	-
Intravenous	0	0	-
22. You have selected "1 hour before" or "Immediately before", select from the following only one type of antibiotic:			
Amoxicillin	46	83.64	71.19-92.23
Amoxicillin/clavulanic acid	8	14.55	6.49-26.66
Cefazolin	1	1.82	0.04-9.71
Clindamycin	0	0	-
Penicillin V	0	0	-
Erythromycin	0	0	-
Ampicillin	0	0	-
Cephalexin	0	0	-
Other	0	0	-

Total	55	100	-
23. Select from the following, the dose, dosage and route of administration ("1 hour or Immediately Before"):			
23.1. Dosage (mg)			
2000	22	40	27.02-54.09
1000	15	27.27	16.13-40.96
500	7	12.73	5.27-24.48
875/125	5	9.09	3.01-19.95
800	3	5.45	1.13-1.51
1600	1	1.82	0.04-9.71
500/125	1	1.82	0.04-9.71
600	1	1.82	0.04-9.71
Total	55	100	-
23.2. Dosage			
1 single dose	55	100	93.51-1
23.3. Route of administration			
Oral	55	100	93.51-1
Intramuscular	0	0	-
Intravenous	0	0	-

POSTOPERATIVE PRESCRIPTION HABITS

24. Select from the following only one type of antibiotic prescribed after dental implant insertion:			
Amoxicillin	138	67.98	61.08-74.33
Amoxicillin/clavulanic acid	59	29.06	22.91-35.83
Other	5	2.46	0.8-5.65
Erythromycin	1	0.49	0.01-2.71
Clindamycin	0	0	-
Penicillin V	0	0	-
Cephalexin	0	0	-
Total	203	100	-
25. Select from the following, the dose, dosage, route of administration and duration of treatment:			
25.1. Dose			
500	76	38.38	31.57-45.54
800	36	18.18	13.07-24.27
875/125	36	18.18	13.07-24.27
1000	33	16.67	11.75-22.60
500/125	17	8.59	5.08-13.39
150	0	0	-
250	0	0	-
300	0	0	-
400	0	0	-
Total	198	100	-
25.2. Dosage			
1 time per day	2	1.01	0.12-3.60
2 times a day	19	9.6	5.87-14.57
3 times a day	177	89.39	84.24-93.31
4 times a day	0	0	-
Total	198	100	-
25.3. Route of administration			
Oral	198	100	98.15-1
Intramuscular	0	0	-
Intravenous	0	0	-
25.4. Duration (days)			
7	91	45.96	38.87-53.16
8	38	19.19	13.95-25.37
5	25	12.63	8.34-18.07
6	17	8.59	5.08-13.39
10	13	6.57	3.54-10.96
3	6	3.03	1.12-6.47
4	4	2.02	0.05-5.09

2	2	1.01	0.12-3.60
1	1	0.51	0.01-2.78
9	1	0.51	0.01-2.78
11	0	0	-
12	0	0	-
13	0	0	-
14	0	0	-
15	0	0	-
Total	198	100	-
26. Genre			
Woman	122	58.1	51.10-64.84
Man	88	41.9	35.15-48.89
Total	210	100	-
27. Age (years)			
21 - 30	29	13.81	9.44-19.22
31 - 40	55	26.19	20.38-32.68
41 - 50	65	30.95	24.77-37.68
51 - 60	43	20.48	15.23-26.57
61 - 70	18	8.57	5.15-13.20
71 years of age or older	0	0	-
Total	210	100	-
28. Please write the name of the university where you studied.			
University of the Basque Country (UPV/EHU)	173	82.78	76.95-87.63
Alfonso X el Sabio University (UAX)	10	4.78	2.31-8.62
Complutense University of Madrid	5	2.39	0.78-5.49
European University of Madrid	3	1.44	0.29-4.13
International University of Catalonia (UIC) Barcelona	2	0.96	0.11-3.41
King Juan Carlos University (URJC)	2	0.96	0.11-3.41
University of Granada	2	0.96	0.11-3.41
University of Navarra	2	0.96	0.11-3.41
University of Buenos Aires (UBA)	2	0.96	0.11-3.41
Distance University of Madrid (UDIMA)	1	0.48	0.01-2.63
University of Oviedo	1	0.48	0.01-2.63
University of Valladolid (UVA)	1	0.48	0.01-2.63
University of Valencia (UV)	1	0.48	0.01-2.63
"Argentina"	1	0.48	0.01-2.63
Universidad Iberoamericana (UNIBE) Dominican Republic	1	0.48	0.01-2.63
National University of La Plata (UNLP)	1	0.48	0.01-2.63
Higher University of San Andrés (UMSA)	1	0.48	0.01-2.63
Total	209	100	-

*n: frequency, CI: confidence interval, *: participants were able to choose more than one option (multi-response).*

Table 2. Preoperative regimens.

TYPE OF ANTIBIOTIC	DOSAGE (mg)	N
Immediately before surgery		
Amoxicillin	500	3
	2000	2
	1000	1
	800	1
*	*	8
1 hour before surgery		
Amoxicillin	2000	19
	1000	11
	500	4
	800	2
	1600	1
	600	1
Amoxicillin/clavulanic acid	1000	2
	875/125	4
	2000	1
	500/125	1
Cefazolin	875/125	1
1 day before surgery		
Amoxicillin	500 TID	28
	800 TID	12
	1000 TID	9
	875/125 TID	3
	1000 BID	3
	500 BID	1
	800 QID	1
Amoxicillin/clavulanic acid	875/125 TID	14
	500/125 TID	6
	500 TID	4
	875/125 BID	2
Other	500	1
	*	3
2 days before surgery		
Amoxicillin	500 TID	17
	800 TID	6
	1000 BID	3
	1000 TID	3
Amoxicillin/clavulanic acid	500/125 TID	3
	875/125 TID	6
	500 TID	1
	800 TID	1
Erythromycin	500 QD	1
Other	*	2

*n: frequency, *: participants did not answer this question, QD: once a day, BID: twice a day, TID: 3 times a day, QID: 4 times a day.*

Table 3. Postoperative regimens.

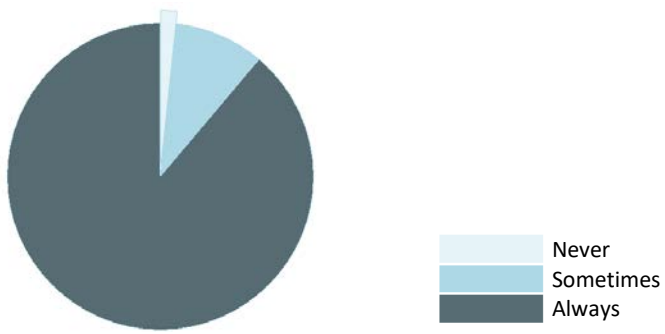
ATIBIOTIC TYPE	DURATION (days)	DOSAGE									
		500 mg		500/125 mg	800 mg		875/125 mg		1000 mg		
		QD	TID	TID	IDB	TID	IDB	TID	QD	IDB	TID
Amoxicillin	2	-	1	-	-	-	-	-	-	1	-
	3	-	1	-	-	1	-	-	1	1	-
	4	-	1	-	-	1	-	-	-	1	-
	5	-	9	-	-	3	-	-	-	1	4
	6	-	7	-	-	3	-	-	-	2	2
	7	-	31	-	1	16	-	1	-	8	7
	8	-	13	1	-	7	-	1	-	1	2
	9	-	1	-	-	-	-	-	-	-	-
	10	-	4	-	-	3	-	-	-	-	1
Amoxicillin/clavulanic acid	1	-	-	-	-	-	-	-	-	1	-
	2	-	-	-	-	-	-	-	-	-	-
	3	-	-	-	-	-	-	1	-	-	-
	4	-	-	-	-	-	-	1	-	-	-
	5	-	1	2	-	-	-	5	-	-	-
	6	-	-	1	-	-	1	1	-	-	-
	7	-	6	4	-	-	1	16	-	-	-
	8	-	1	5	-	-	-	7	-	-	-
	10	-	1	2	-	-	-	2	-	-	-
Erythromycin	3	1	-	-	-	-	-	-	-	-	-
Azithromycin	1	-	-	-	-	-	-	-	2	-	-
	3	1	-	-	-	-	-	-	-	-	-

n: frequency of participants who answered this question; QD: once a day; BID: twice a day; TID: three times a day; QID: four times a day; mg: milligrams.

Main results

Among all participants, 88% (n=207) always prescribed prophylactic antibiotics routinely in conjunction with dental implant surgery (95% CI 84.79-92.88%). Approximately 9% (n=22) prescribed antibiotics sometimes (95% CI: 5.68-13.19%), and only 4 dentists (1.72%) did not prescribe antibiotics at all (95% CI: 0.04-3.38%). These data are shown in Figure 2.

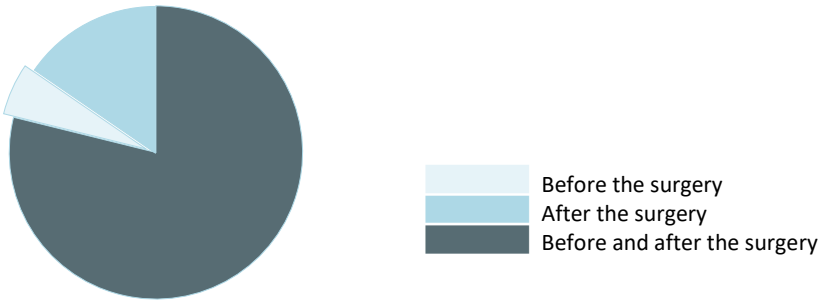
Figure 2. Frequency of prescription of prophylactic antibiotics



The 22 dentists who prescribe antibiotics only "sometimes" were asked to determine the situations in which they prescribe antibiotics. The most frequently chosen situations were preoperative implant site infection (n=14) and sinus perforation (n=13).

Overall, 179 of the 233 respondents prescribed antibiotics both preoperatively and postoperatively (78.85%, 95% CI 72.96-83.97%), 13 prescribed antibiotics only preoperatively (5.73%, 95% CI 3.08-9.59%), and 35 prescribed antibiotics exclusively after routine dental implant surgery (15.42%, 95% CI 10.98-20.78%). These data are shown in Figure 3.

Figure 3. Prescribed regimens before, during, or after implant surgery



The only route of administration described by all respondents was oral for all antibiotic types and regimens.

Of the 179 respondents who indicated that they prescribed preoperative and postoperative antibiotics, the most frequent preoperative regimen was 500 mg amoxicillin three times daily (TID) 1 day before surgery (n=25), and the most frequent postoperative regimen was 500 mg amoxicillin TID orally for 7 days after surgery (n=24). This preoperative and postoperative regimen was consistently followed by a total of 10 dentists.

Of the 13 respondents who prescribed preoperative antibiotics exclusively, the most common antibiotic regimen was 2 g amoxicillin once orally 1 hour before surgery (n=3) and 500 mg amoxicillin TID 1 day before surgery (n=3).

Of the 35 dentists who exclusively prescribed postoperative antibiotics, the most frequent regimen was 500 mg amoxicillin TID for 7 days after surgery (n=7).

After amoxicillin, amoxicillin/clavulanic acid was the most routinely prescribed type of antibiotic. The most frequent prescription with amoxicillin/clavulanic acid was pre- and post-operative (n=49). Among the respondents who followed this preoperative and postoperative prescribing pattern, the most frequent preoperative guideline was 875/125 mg TID 1 day before surgery (n=14), and the most frequent postoperative guideline was 875/125 mg TID orally for 7 days after surgery (n=16).

Antibiotic prescribing habits in the Netherlands

SUMMARY

Objectives: There seems to be no consensus on the prescription of prophylactic antibiotics in oral implant surgery. The guidelines of the Dutch Association of Oral Implantology (NVOI) do not include a clear policy on the prescription of prophylactic antibiotics for oral implant surgery in healthy patients. The aim of the study was to determine whether general dentists, maxillofacial surgeons and oral implantologists routinely prescribe antibiotic prophylaxis in the Netherlands in conjunction with oral implant surgery among healthy patients and to assess the type and amount of prophylactic antibiotic prescribed.

Methods: This cross-sectional observational study is based on a web survey. A questionnaire developed in the United States of America was translated and slightly adjusted for use in the Netherlands. It contained predominantly closed questions related to demographics, qualifications, type of antibiotic, duration of prescription and dosage. An email including an introduction to the study and an individual link to the questionnaire was sent in February 2018 to a sample of 600 general dentists and the 302 specialist dentists (oral implantologists, periodontists and maxillofacial surgeons) recognised by the NVOI. A total of 902 questionnaires were sent out anonymously. In the end, 874 potential participants were reached. The collected data were analysed using descriptive statistics.

Results: In total, 218 (24.9%) participants responded to the questionnaire, including 45 women (20.8%) and 171 men (79.2%). In total, 151 (69.9%) had regular oral implants. Of these, 79 (52.7%) prescribed antibiotics only in occasional situations, 66 (43.7%) regularly and 5 (3.3%) did not prescribe antibiotics at all. Overall, 83 participants who prescribe antibiotics do so both preoperatively and postoperatively (57.2%), 47 only preoperatively (32.4%) and 12 exclusively postoperatively (8.3%). A single dose of 2,000 mg amoxicillin orally one hour before surgery was the most frequently prescribed preoperative regimen. The most frequently prescribed postoperative regimen was 500 mg amoxicillin three times daily for five days after surgery. On average, participants prescribed a total of 7,018 mg of antibiotics before, during or after oral implant surgery.

Conclusions: Antibiotic prophylaxis in conjunction with oral implant surgery is prescribed in the Netherlands on a large scale, and recommendations based on the latest published evidence are often not followed.

METHODS

This cross-sectional observational study is based on a web survey, and is reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [1].

The questionnaire, developed by Deeb et al. (2015) [2], was translated and slightly adjusted for use in the Netherlands to collect data regarding preventive antibiotic prescribing rates among general dentists, maxillofacial surgeons, periodontists and oral implantologists along with oral implant therapy. Explicit permission was obtained from Deeb and coauthors to use their questionnaire. An experienced oral implantologist, involved in the training of dentists in the Netherlands, assessed the comprehension and logical order of the translated and adjusted questionnaire. The wording of the questions was considered adequate and valid for assessing the intended objectives.

Environment

The Netherlands is a member state of the European Union with, in 2018, a population of approximately 17.1 million [5]. In January 2018, approximately 8,800 dentists were working in the Netherlands, including about 320 oral implantologists and 80 periodontists. In addition, at that time, there were about 290 practicing maxillofacial surgeons [6].

Participants

In February 2018, an email was sent to a representative sample of 600 general dentists, randomly selected from the official register of qualified dentists of the Royal Dutch Dental Association (KNMT), and to all 302 oral implantologists, periodontists and maxillofacial surgeons recognized by the NVOI as oral healthcare providers who place oral implants and whose email addresses were publicly available.

The only eligibility criterion taken into account for inviting potential participants to the study was inclusion on the lists of the NVOI and the KNMT. The KNMT keeps an up-to-date file of all licensed dentists in the Netherlands, but does not know whether dentists are active in dentistry. For this reason, the group of all dentists aged 64 years or younger with a known address and/or working address in the Netherlands was determined, as this group was expected to be working in dentistry. A sample of 600 dentists was drawn from this group, consisting of about 8,800 dentists, with the SPSS SAMPLE procedure. This was carried out by a "third party" research institute commissioned by the KNMT. This institute specialises in the management and administration of web surveys and offers support in data collection. The email addresses of the NVOI members are publicly available on the NVOI website.

Subsequently, the "third party" research institute sent the email invitation to all potential participants and collected the data. These emails contained an individual link to a web-based questionnaire and a brief introduction to the aims of the study. Participants were assured that the research data were collected anonymously, and it was made clear that by responding to the questionnaire, participants consented to the

use of the data collected by the survey for the purposes of the study. Every effort was made to protect the privacy and anonymity of the participants, as no personal data (first name, surname, address and telephone number) were collected from the participants. In addition, no email addresses were stored or saved by the authors, so participants could not be contacted again. For these reasons, this specific study did not require an ethics statement from an institutional review board (ethics committee) prior to commencing the study. Two reminder emails were sent to all potential respondents after two and four weeks; after six weeks, data collection was closed.

The research institute "Third Party" made the collected data available in encrypted form so that the authors would not have access to any of the participants' personal information, including their email addresses.

A total of 28 potential participants could not be contacted due to an incorrect e-mail address. Therefore, the final sample consisted of 874 potential participants: 578 general dentists and 296 oral implantologists, periodontists and maxillofacial surgeons.

Variables

Information was collected on qualifications and work experience, demographics, and the most commonly prescribed preventive antibiotic for oral implant placement, including duration and dose. From their statements on dosage and period of intake, we calculated the total milligrams (mg) prescribed per oral health professional and oral implant surgery.

Data sources and measurement

Each link in the e-mail messages directed the user to a questionnaire, which could only be answered once. The questionnaire contained predominantly closed questions. Participants could add additional response options and additional information.

Statistical methods

All data were analyzed using the International Business Machines Corporation (IBM) Statistical Package for Social Sciences (SPSS) for Windows version 24 (IBM Corporation, released 2012, Armonk, New York). To begin with, using descriptive statistics, an overview of the respondents' characteristics in terms of age, gender, type of oral health professional and geographical area was collected. Then, the descriptive analysis continued only with those health professionals who had indicated that they placed oral implants on a regular basis. Subsequently, their antibiotic prescribing habits before, during or after oral implant placement were assessed. We investigated whether antibiotic prescribing habits in oral implant surgery were related to the personal characteristics of the participants and, in the case of those prescribing antibiotics, to the prescribing regimens used (chi-square test and ANOVA). Firstly, we investigated whether the total amount of antibiotics prescribed varied between particular groups of participants using ANOVA (F-test) and finally, as the data were not normally distributed, they were analysed using the Kruskal-Wallis test and the Mann-Whitney U-test.

RESULTS

Participants

Table 1 details the different professionals included in the study. Two participants reported that they were not currently working, and were excluded from the study group.

Table 1. Type of professional[#1] in relation to their current implantological activity.

	Placing oral implants		Do not place oral implants		Total	
	n	*%*	*n*	*%*	*n*	*%*
General Dentist (GDP)	11	5.0	59	27.1	70	32.1
GDP & IO	20	9.2			20	9.2
Oral Implantologist (OI)	67	30.7			67	30.7
OI and Periodontist (OI-PERIO)	9	4.1	1	0.5	10	4.7
Maxillofacial Surgeon (MS)	44	20.2	1	0.5	45	20.6
Other oral health professional [#2]			4	1.8	4	1.8
Not working as an oral health professional			2	0.9	2	0.9
Total	151	69.3	67	30.7	218	100
[#1] multiple situations possible / [#2]dentist for orthodontics (3x), maxillofacial prosthodontist						

Descriptive data

In total, 171 men (79.2%) and 45 women (20.8%) responded to the questionnaire. The mean age of the participants was 48.6 years (SD = 11.1). 24.1% were aged 39 years or younger, 20.8% were aged 40-49 years and 55.1% were aged 50 years or older.

The majority of the participants (92.3%) graduated from a dental school in the Netherlands: Amsterdam (36.6%), Nijmegen (23.8%), Groningen (21.7%) and Utrecht (10.2%). Almost half of the participants (46.3%) were based in the western part of the country, with 26.4% in the south, 17.6% in the east and 9.7% in the northern regions.

Oral implant placement and prescription habits

Table 1 shows that 69.2% of the surveyed participants indicated that they regularly placed oral implants. Of these 151 participants currently performing oral implant surgeries, 66 (43.7%) stated that they regularly prescribe prophylactic antibiotics, while a minority (3.3%, n = 5) reported that they never do. In addition, 79 participants (52.3%) indicated that they prescribe antibiotics only in certain situations. These situations are presented in Table 2.

Table 2. Situations in which participants prescribe antibiotics [#1]

Situation	n	%
Bone grafts	73	93.6
Sinus perforation	33	42.2
Preoperative infection at the implant site	29	37.2
Medically Compromised Patient [#2]	22	28.2
Past of periodontal disease	14	17.9
Smoking	13	16.7
Simultaneous placement of more than one dental implant	6	7.7
Toothless patient [#2]	5	6.4
Another situation [#3]	7	9.0
Total [#4]	78	100

[#1] Multiple possible scenarios /[#2] Derived from "Other scenario" option, as described by participants / [#3]Sinus lift surgery (2x), postoperative complications (2x), treatment under anaesthesia, specific location of dental implant placement, based on microbiological testing / [#4]1 participant did not indicate the scenario

No statistically significant relationship was found between any of the participants' characteristics and their prescribing habits. (Table 3).

Table 4 shows the starting times and regimens of antibiotic prescriptions used by the participants.

Table 3. Personal characteristics of the participants in relation to their antibiotic prescription habits.

	Never	Sometimes	Always	Overall
Woman [#1]		13.9%	7.6%	10.7%
Average age (years) [#2]	60.0	49.6	51.5	50.8
Type of specialization [#3]				
-General Dental Practitioner	20.0%	5.1%	9.1%	7.3%
-Oral implantologist and/or periodontist	60.0%	62.0%	65.2%	63.3%
-Oral Surgeon	20.0%	32.9%	25.8%	29.3%
Graduation in the Netherlands [#4]	100%	94.9%	90.9%	93.3%
Place of settlement (part of the country) [#5]				
-Southern	60.0%	20.3%	21.2%	22.0%
-Western	40.0%	45.6%	54.5%	49.3%
-This		17.7%	18.2%	17.3%
-Northern		16.5%	6.1%	11.3%
n [#6]	5	79	66	151

[#1] p=0.343 /[#2] p=0.071 /[#3] p=0.597 / [#4]p=0.520 /[#5] p=0.173 / 1 participant reported no prescription habits

Table 4. Antibiotic prescription regimens.

	n	%	n	%
Pre-op only			47	32.4
-1 hour or immediately	*43*	*29.6*		
-1 day before	*2*	*1.4*		
-2 days before	*2*	*1.4*		
Pre and post operative			83	57.2
-1 hour or immediately	*60*	*41.4*		
-1 day before	*18*	*12.4*		
-2 days before	*5*	*3.4*		
Post-operative only			12	8.3
Unknown			3	2.1
Total	145	100	145	100

Preoperative antibiotics: type, dosage and posology

The majority of participants who prescribe preoperative antibiotics when placing oral implants advise their patients to start one hour before treatment (75.2%) or immediately before treatment (3.1%). All others stated that they advise their patients to start one day (16.3%) or two days (5.4%) before treatment.

The majority of participants prescribing prophylactic antibiotics one hour or immediately prior to implant placement prescribed 2,000 mg of amoxicillin orally (70.3%). In addition, 9.9% indicated prescribing 3,000 mg of amoxicillin, and 9.9% indicated prescribing 500 mg of amoxicillin, both to be taken orally.

More than half of the participants (53.9%) who initiate antibiotic prophylaxis one or two days before implant surgery prescribe 500 mg amoxicillin orally three times daily. In addition, 19.3% prescribe a 500/125 mg amoxicillin/clavulanic acid combination taken three times daily (Table 5).

Postoperative antibiotics: type, dose and posology

Of the participants who choose to advise patients to initiate antibiotic prophylaxis postoperatively, 75.1% prescribe 500 mg of amoxicillin to be taken orally one to four times daily for a period varying from one to eight days (table 6). In addition, 15.2% indicated prescribing a 500/125 mg amoxicillin/clavulanic combination to be taken three times daily for a period of five to seven days.

Table 5. Preoperative regimens

1 hour or immediately before				
Type of antibiotic	*Dose(mg)*	*Administration*	*n*	*%*
Amoxicillin	2.000	oral	71	70.3
Amoxicillin	500	oral	10	9,9
Amoxicillin	3.000 [#1]	oral	10	9.9
Amoxicillin	1.000	oral	2	2.0
Amoxicillin	other [#2]	oral	2	2.0
Amoxicillin	600	oral	1	1.0
Amoxicillin/clavulanic acid	500 / 125	oral	3	3.0
Amoxicillin/clavulanic acid	2.000	oral	1	1.0
Clindamycin	600	oral	1	1.0
Total [#3]			101	100.0
1 or 2 days before				
Type of antibiotic	*Dose(mg)*	*Dosage*	*n*	*%*
Amoxicillin	500	Oral TID	14	53.9
Amoxicillin	400	Oral TID	1	3.8
Amoxicillin	500	Oral BID	1	3.8
Amoxicillin	other [#4]	Oral TID	1	3.8
Amoxicillin/clavulanic acid	500 / 125	Oral TID	5	19.3
Clindamycin	300	Oral BID	1	3.8
Clindamycin	300	Oral QID	1	3.8
Erythromycin (ethylsuccinate form)	150	Oral TID	1	3.8
Other [#5]	500	Oral QD	1	3.8
Total [#6]			26	100.0
QD: once a day, BID: twice a day, TID: 3 times a day, QID: 4 times a day / [#1]mentioned spontaneously / variable / [#2#3]2 participants did not state the prescribed preoperative regimen / [#4]375mg, this is an antibiotic treatment and not antibiotic prophylaxis / Zithromax / [#5#6]1 participant did not state the prescribed preoperative regimen				

Table 6. Postoperative regimens

Type of antibiotic	Dosage (mg)	Dosage	Duration	n	%
Amoxicillin	250	Oral TID	5 days	1	1.1
Amoxicillin	400	Oral TID	5 days	1	1.1
Amoxicillin	500	Oral QD	3 days	1	1.1
Amoxicillin	500	Oral BID	7 days	1	1.1
Amoxicillin	500	Oral TID	1 day	4	4.3
Amoxicillin	500	Oral TID	3 days	2	2.2
Amoxicillin	500	Oral TID	5 days	29	31.5
Amoxicillin	500	Oral TID	6 days	1	1.1
Amoxicillin	500	Oral TID	7 days	24	26.1
Amoxicillin	500	Oral TID	8 days	1	1.1
Amoxicillin	500	Oral TID	other [#1]	2	`2.2
Amoxicillin	500	Oral QID	2 days	1	1.1
Amoxicillin	500	Oral QID	4 days	1	1.1
Amoxicillin	500	Oral QID	5 days	2	2.2
Amoxicillin/clavulanic acid	500/125	Oral TID	7 days	1	1.1
Amoxicillin/clavulanic acid	500/125	Oral TID	1 day	1	1.1
Amoxicillin/clavulanic acid	500/125	Oral TID	5 days	6	6.5
Amoxicillin/clavulanic acid	500/125	Oral TID	7 days	7	7.6
Amoxicillin/clavulanic acid	500/125	Oral QID	6 days	1	1.1
Amoxicillin/clavulanic acid	500/125	Oral QID	7 days	1	1.1
Clindamycin	300	Oral TID	7 days	1	1.1
Clindamycin	300	Oral QID	5 days	1	1.1
Clindamycin	300	Oral QID	7 days	1	1.1
other [#4]	500	Oral QD	2 days	1	1.1
total [#5]				92	100.0
QD: once daily, BID: twice daily, TID: 3 times daily, QID: 4 times daily / unknown / 2[#1#2],000 mg / 3[#3],000 mg / Zithromax / [#4]3 [#5]participants did not declare the prescribed postoperative regimen.					

Amounts of antibiotics prescribed

On average, participants reported prescribing a total of 7,018 mg (SD = 4,325 mg) of prophylactic antibiotics before, during, or after oral implant surgery, ranging from 500 mg to 14,600 mg, with a median of 8,000 mg. Three participants did not indicate their prescription regimens, and six did not state the number of milligrams prescribed (Table 7).

Table 7. Total amount (mg) of antibiotics fished in relation to type of practitioner

	Media	Standard deviation	Medium	*P-value*
Type of oral health professional				0,032
-General Dental Practitioner (GDP) [#1]	4,150	3,705	2,000	
-Oral Implantologist (OI)	7,969	4,179	9,500	
-Oral Surgeon (OS)	6,883	4,195	8,000	
Antibiotic prescribing habits				0.004
-sometimes	7,799	4,173	9,500	
-always	5,913	4,059	4,750	
Antibiotic prescribing regimen				0.000
-Pre-operative only [#1]	2,060	463	2,000	
-Only in the postoperative period	9,250	1,545	10,500	
-Pre and post operative	9,598	2,963	9,500	
Total	7,018	4,235	8,000	
n = 136 [#2]				
[#1] Bonferroni's post hoc multiple comparison /[#2] 3 participants did not state prescription regimens and 6 participants either did not state the number of mg completely or not at all.				

In particular, maxillofacial surgeons prescribe significantly more antibiotics than oral implantologists and general practitioners (7,969 mg vs. 6,883 mg and 4,150 mg; p=0.03).

In particular, the difference between maxillofacial surgeons and general practitioners was statistically significant (p=0.02). Participants who only opted for pre-treatment antibiotics reported prescribing significantly lower amounts than their colleagues who opted for antibiotics only after treatment and both pre- and post-treatment (2,060 mg vs. 9,250 mg and 9,598 mg; $p < 0.001$). In addition, it appears that participants who regularly prescribe antibiotic prophylaxis in conjunction with oral implant surgery prescribe significantly lower amounts of antibiotics than participants who prescribe prophylactic antibiotics only in certain circumstances. Conversely, participants who prescribe prophylactic antibiotics only in certain circumstances when placing oral implants indicated that they prescribe longer regimens (pre- and post-operatively) than participants who indicated that they regularly prescribe prophylactic antibiotics (p=0.04).

Antibiotic prescribing habits in Italy

SUMMARY

Objectives: The prescription of prophylactic antibiotics in conjunction with oral implant surgery remains inconsistent among different populations of dentists. The primary objective of this study was to assess the current antibiotic prescribing habits of dentists in conjunction with oral implant surgery in Italy. The secondary objective was to evaluate the nature and quantity (mg) of antibiotic prescriptions to assess whether any consensus has been reached and whether current recommendations are adhered to.

Methods: Cross-sectional observational study based on a web survey reported according to STROBE guidelines. A questionnaire was sent by email to each registered member of the Italian Academy of Osseointegration (n=400). The email included a link to the anonymous web questionnaire developed at www.encuestafacil.com. It contained closed and some open questions regarding demographic data, type of antibiotic, duration of prescription and dosage. The data collected were analysed using STATA® 14 software.

Results: 160 participants responded to the survey (response rate=40%). Approximately 84% prescribed prophylactic antibiotics routinely in conjunction with oral implant surgery, 15.6% prescribed antibiotics in certain situations and only 1 did not prescribe antibiotics at all. In total, 116 respondents prescribed antibiotics both preoperatively and postoperatively, 29 prescribed antibiotics only preoperatively, and 14 prescribed antibiotics exclusively postoperatively. Italian dentists prescribed an average amount of 10,331 mg of antibiotics before, during or after oral implant surgery. Approximately, only 17% (n=27) of the participants who prescribed antibiotics before oral implant surgery complied with the recommendations proposed by the latest literature (no more than 3 g of preoperative amoxicillin before oral implant surgery).

Conclusions: Dentists in Italy prescribe antibiotic prophylaxis in conjunction with oral implant surgery on a large scale among healthy patients. A wide variety of prophylactic regimens are prescribed that do not conform to new science-based specifications. Guidelines focusing on the indications for prophylactic antibiotics among healthy patients are needed to avoid bacterial resistance, side effects and costs caused by overtreatment and irrational use of antibiotics.

METHODS

This cross-sectional observational study is based on a web survey and reported according to the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) guidelines [1].

Study design

The questionnaire developed by Deeb et al. (2015) was adapted to the circumstances of Italy for the purpose of collecting data regarding preventive antibiotic prescribing habits among dental professionals in conjunction with oral implant therapy [2]. Permission was obtained from Deeb and co-authors to use their questionnaire. After being adjusted and translated, the questionnaire was reviewed for comprehensibility and logical order by an experienced Italian oral implantologist. The way the questions were formulated was considered adequate to assess the intended objectives.

Environment

Italy is a member state of the European Union, which in 2018 had a population of approximately 60.3 million [7]. In March 2018, the number of dentists registered in the register of the National Federation of Orders of Doctors and Dentists (FNOMCeO) was 61,586 [8].

Participants

In April 2018, the IAO sent an email to all association members (400 dentists) with a link to a web-based questionnaire and a brief introduction regarding the aims of the study. All potential respondents received a reminder email from the IAO after four weeks, and two weeks later access to the questionnaire was no longer possible. In addition, participants were assured that the research data would be collected anonymously and that participants had given their consent to the use of the data for the study.

Of all IAO members, 36 are women and 20% of all members are actually dentists specializing in oral surgery.

Variables

Data were collected regarding the following items: demographics, education, work experience and preventive antibiotic prescribed in case of oral implant placement (including dose and duration). From the participants' responses on dosage and period of intake, the total amount of antibiotic prescribed (mg) was calculated.

Data sources / measurement

Each link led to a questionnaire that could only be answered once. The questionnaire contained mainly closed questions and some open questions.

Bias

The possibility of any selection bias was minimised as we approached a sample of dentists known to regularly perform oral implants.

Study size

The final study size included only those dentists, among those approached, who had chosen to respond partially or fully to the survey.

Statistical methods

All data were analyzed using STATA® 14 software. Statistical evaluation was performed according to age, sex and location. Subsequently, the use of prophylactic antibiotic prescription and its amounts (mg) before, after or during oral implant surgery were evaluated.

Binomial variables corresponding to each of the questions were assessed as proportions (percentage) of the responses to the questionnaire. Chi-square and Fisher's exact tests were performed to evaluate the differences in the antibiotic regimen adopted by the participants according to their sex, age, education, location and work experience.

Finally, the total antibiotic dose in mg prescribed by each participant was calculated and the mean (mg) was used as the primary endpoint. The mean was selected as the primary endpoint due to the homogeneity of the sample and its validity, as well as its frequent use in health research. However, information on median and interquartile range was also provided. An ANOVA (Student's t-test) was performed to assess differences in total antibiotics (mg) prescribed concomitant with dental implant surgery. The standard deviation (Std. Dev.) and *p-values* were determined.

RESULTS

Participants

One hundred and sixty participants returned the survey, a response rate of 40%.

Descriptive data

One hundred and forty-six men (93.6%) and ten women (6.4%) responded to the questionnaire, and the majority were between 51 and 60 years of age (30.1%).

The majority of the participants (97.4%) graduated from a dental school in Italy. Most of the participants graduated from the Faculty of Dentistry of Milan (26.9%), others from the Faculty of Dentistry of Padua (8.3%) and from the Sapienza Faculty of Dentistry - University of Rome (6.4%). Almost two thirds of the participants (60.9%) had been working as oral health care providers for more than 20 years, almost one third had between 10 and 20 years of experience (30.1%) and the rest of the respondents had been working for less than 10 years (9%). The majority of respondents worked in the Lombardy region (30.7%), with others in Veneto (10.9%), Lazio (9.6%), Piedmont (7%) and Tuscany (7%).

Performance data

Approximately 84% of the participants (n=134), who currently perform oral implant surgery, stated that they always prescribe prophylactic antibiotics in conjunction with oral implant surgery, only one participant (0.6%) never prescribes them.

In addition, 15.6% adopted antibiotics only in particular cases (n=25). Such as heart disease requiring antibiotic prophylaxis (24.2%), bone grafting (23.1%); sinus perforation (13.7%); preoperative implant site infection (11.6%); smokers (9.5%); previous periodontal disease (8.4%); multiple implant insertion (3.1%); medically compromised patients (3.1%) and immediate implant placement (1%). No statistically significant differences were found in relation to dentists' antibiotic prescriptions with respect to some general characteristics (Table 1).

Table 1. Personal characteristics of dentists related to their antibiotic prescribing habits in oral implant surgery.

Personal Characteristics	Antibiotic prescribing habits			Total
	Never	*Sometimes*	*Always*	
Woman [a]		8%	6.15%	6.4%
Age (years) [b]				
- 21-30		12%	3.0%	4.5%
- 31-40		20%	19.2%	19.2%
- 41-50		24%	30%	28.9%
- 51-60	100%	24%	30.7%	30.1%
- 61-70		16%	14.6%	14.7%
- 71 or more		4%	2.3%	2.6%
Graduation in Italy [c]	100%	100%	96.1%	96.8%
Experience (years) [d]				
- Less than 10		16%	7.7%	8.9%
- Between 11 and 20	100%	52%	62.3%	60.9%
- More than 20		32%	30%	30.1%
Place of settlement (macro-regions) [e]				
-Northwest		36%	43.1%	41.7%
-North-East	100%	24%	20%	21.1%
-Center		16%	23.1%	21.8%
-South		16%	10.8%	11.5%
- Islands		4%	2.3%	2.6%
- Other		4%	0.7%	1.3%
n [f]	1	25	130	156

[a] p=0.910
[b] p=0.735
[c] p=0.597
[d] p=0.618
[e] p=0.718
[f] *4 respondents did not answer these questions or answered incompletely.*

The majority of respondents stated that they opted for a combination of a preoperative and postoperative regimen (72.9%), while 18.2% only use the preoperative regimen and 8.8% only the postoperative regimen (Table 2).

Table 2. Antibiotic prescribing regimens and start time of prescriptions

Prescription start time and regimen	n	%	n	%
Pre-op only			29	18.2
-Immediately before	2	6.9		
-1 hour before	26	89.6		
-1 day before	0	0		
-2 days before	1	3.4		
Pre and post operative [#1]			114	72.9
-Immediately before	1	0.8		
-1 hour before	59	51.7		
-1 day before	49	42.98		
-2 days before	5	4.39		
Post-operative only			14	8.8
Total			157	100.0
[#1] 2 respondents did not state the start time of the prescription or stated it incompletely				

Main results

Preoperative antibiotics

The majority of the 143 dentists who prescribe preoperative antibiotics when placing oral implants advise their patients to start 1 hour before surgery (59.4%) or 1 day before surgery (34.2%). The remaining participants prescribing preoperative antibiotics advise starting 2 days (4.2%) or immediately (2.1%) before surgery. Table 3 shows the type of antibiotics, their dose and regimen.

Oral amoxicillin/clavulanic acid was found to be the most frequently prescribed antibiotic when given 1-2 days preoperatively (80.7%) and 1 hour or immediately before surgery (71.6%). Overall, the most frequent preoperative regimen was 2 g of oral amoxicillin/clavulanic acid 1 hour before surgery (n=31, 21.6%).

Table 3. Preoperative antibiotic regimens prescribed by dentists.

1 hour or immediately before				
Type of antibiotic	*Dosage (mg)*	*Administration*	*n*	*%*
Amoxicillin/clavulanic acid	*2000*	*oral*	*32*	*36.3*
Amoxicillin/clavulanic acid	*875/125*	*oral*	*22*	*25*
Amoxicillin	*2000*	*oral*	*17*	*19.3*
Amoxicillin/clavulanic acid	*1000*	*oral*	*9*	*10.2*
Amoxicillin	*1000*	*oral*	*4*	*4.5*
Amoxicillin	*500*	*oral*	*1*	*1.1*
Penicillin V	*1.000*	*oral*	*1*	*1.1*
other [#1]			*2*	*2.2*
Total			*88*	*100.0*
1 or 2 days before				
Type of antibiotic	*Dosage (mg)*	*Dosage*	*n*	*%*
Amoxicillin/clavulanic acid	*875/125*	*Oral BID*	*27*	*49.0*
Amoxicillin/clavulanic acid	*1000*	*Oral BID*	*14*	*25.4*
Amoxicillin	*1000*	*Oral BID*	*8*	*14.5*
Amoxicillin/clavulanic acid	*1000*	*Oral TID*	*2*	*3.6*
Amoxicillin/clavulanic acid	*800*	*Oral BID*	*1*	*1.8*
Amoxicillin/clavulanic acid	*875/125*	*Oral TID*	*1*	*1.8*
Amoxicillin	*875/125*	*Oral BID*	*1*	*1.8*
other [#2]	*500*	*Oral QD*	*1*	*1.8*
Total			*55*	*100.0*

[#1] 1 "Clarithromycin" and 1 "Zithromax PD for 3 days" mentioned spontaneously
[#2] "Azithromycin 500 mg 1 cpr every 24 hours for 3 days" mentioned spontaneously
QD: once a day, BID: twice a day, TID: 3 times a day, QID: 4 times a day
[*] 2 respondents did not state the start time of prescriptions or did so incompletely, so their data could not be included in this table.

Postoperative antibiotics

Almost three quarters (70.6%) of dentists advising patients to start antibiotic treatment postoperatively prescribed 875/125 mg of oral amoxicillin/clavulanic acid twice daily for a period varying between five and six days (Table 4). Overall, the most frequently prescribed postoperative regimen was 875/125 mg oral amoxicillin/clavulanic acid twice daily for 6 days after surgery (n=43, 32.5%). Table 4 shows the type of antibiotics, their dose and regimen.

Table 4. Postoperative antibiotic regimens prescribed by dentists**.**

Type of antibiotic	Dosage (mg)	Dosage	Duration (days)	n	%
Amoxicillin	1000	Oral QD	1	1	0.7
Amoxicillin	1000	Oral BID	2	1	0.7
Amoxicillin	1000	Oral BID	3	1	0.7
Amoxicillin	1000	Oral BID	4	3	2.2
Amoxicillin	1000	Oral BID	5	6	4.5
Amoxicillin	1000	Oral BID	6	8	6.0
Amoxicillin	1000	Oral BID	7	2	1.5
Amoxicillin	500	Oral BID	5	1	0.7
Amoxicillin/clavulanic acid	500/125	Oral BID	5	1	0.7
Amoxicillin/clavulanic acid	500/125	Oral TID	6	1	0.7
Amoxicillin/clavulanic acid	875/125	Oral BID	2	3	2.2
Amoxicillin/clavulanic acid	875/125	Oral BID	3	3	2.2
Amoxicillin/clavulanic acid	875/125	Oral BID	4	8	6.0
Amoxicillin/clavulanic acid	875/125	Oral BID	5	28	21.2
Amoxicillin/clavulanic acid	875/125	Oral BID	6	43	32.5
Amoxicillin/clavulanic acid	875/125	Oral BID	7	4	3.0
Amoxicillin/clavulanic acid	875/125	Oral BID	[#1]	1	0.7
Amoxicillin/clavulanic acid	875/125	Oral TID	3	1	0.7
Amoxicillin/clavulanic acid	875/125	Oral TID	4	2	1.5
Amoxicillin/clavulanic acid	875/125	Oral TID	5	3	2.2
Amoxicillin/clavulanic acid	875/125	Oral TID	6	1	0.7
Amoxicillin/clavulanic acid	875/125	Oral TID	7	1	0.7
Penicillin V	875/125	Oral BID	7	1	0.7
other [#2]				4	3.0
Total				128	100.0

[#1] has not responded
[#2]1 "Azithromycin 500 mg", 1 "Clarithromycin", 1 "Clarithromycin x2 250 mg x5 per day per os" and 1 "Zitromax PD for 3 days".
QD: once a day, BID: twice a day, TID: 3 times a day, QID: 4 times a day

Number of antibiotics prescribed

On average, dentists prescribed a total of 10,331 mg of antibiotics (standard deviation=4,973 mg) before, after, or during oral implant placement, ranging from 1,000 mg to 22,000 mg. Dentists who prescribed only preoperative antibiotics administered, on average, significantly (p=0.000) fewer mg (2,241 mg) than their colleagues who

prescribed antibiotics only after surgery (10,404 mg), or before and after surgery (12,436 mg).

No statistically significant differences (p=0.176) were found in the mean values of the total amount of antibiotics prescribed (mg) by dentists who routinely prescribed prophylactic antibiotics compared to those who prescribed antibiotics on a non-regular basis.

Antibiotic regimens in case of penicillin allergy

Participants prescribed a wide variety of different prophylactic antibiotics to penicillin-allergic patients. In total, 12 different types of antibiotics were prescribed; 94 participants prescribed macrolides and one participant prescribed none. Most participants (n=62, 52.9%) prescribed Clarithromycin instead (Figure 1).

Figure 1. Antibiotics prescribed in patients allergic to amoxicillin

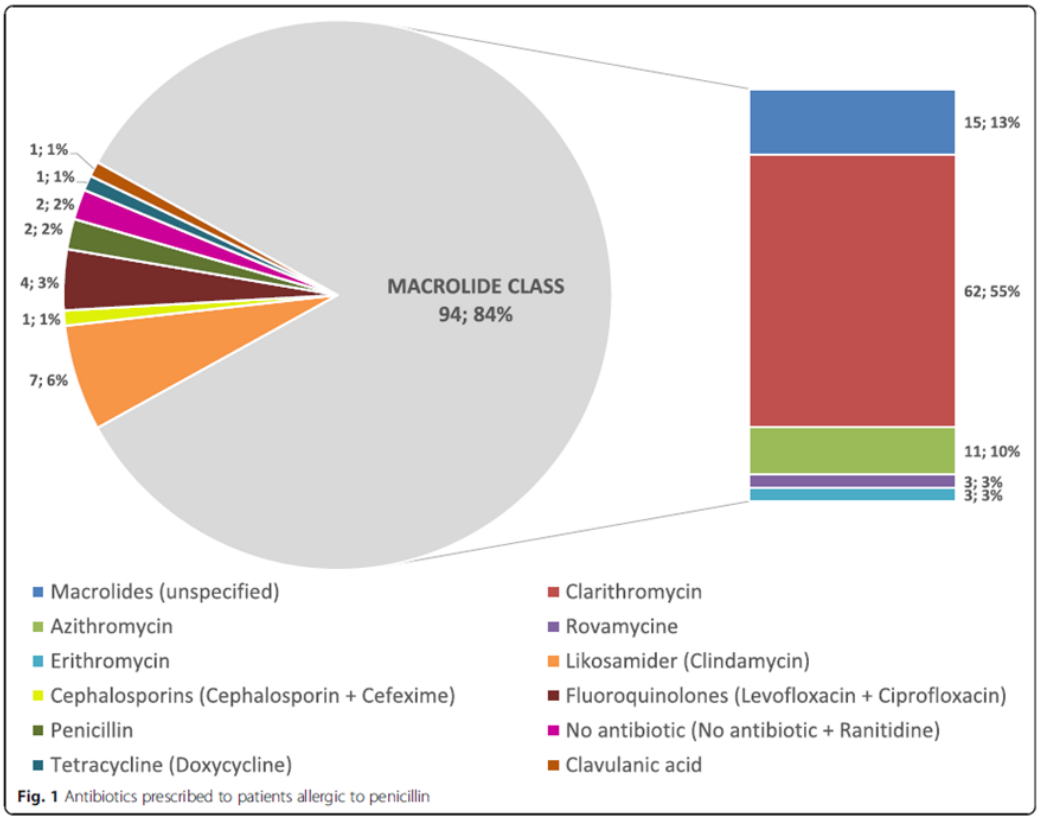


Fig. 1 Antibiotics prescribed to patients allergic to penicillin

Compliance with the latest published studies

Approximately, only 17% (n=27) of the participants who prescribed antibiotics before oral implant surgery adhered to the recommendations proposed by the latest publications (no more than 3 g of preoperative amoxicillin before oral implant surgery) [2,7]. Of these, 25 started prescribing antibiotics 1 hour before surgery and prescribed amoxicillin (n=11) or amoxicillin/clavulanic acid (n=14). Prescriptions immediately prior to surgery always contained amoxicillin/clavulanic acid. Overall, the most commonly prescribed regimen among these participants was amoxicillin 2 g 1 hour before surgery (n=10).

Antibiotic prescribing habits in oral implant surgery. Meta-analysis of cross-sectional surveys

SUMMARY

Objectives: This study aimed to evaluate the dose and types of antibiotics prescribed in oral implant surgery, compare them between different subpopulations (country and prescription regimens) and compare it with the most frequently recommended dose in the literature: a single preoperative dose of 2 grams of amoxicillin.

Methods: A meta-analysis of cross-sectional surveys was conducted, reporting the overall dose and type of antibiotics prescribed in combination with implant placement. PubMed, Cochrane, Science, Science, Direct and EMBASE were searched through OVID until April 2019. Three reviewers independently performed data extraction and risk of bias assessment. The outcome variable was set at the mean number of prophylactic antibiotics prescribed per oral implant surgery.

Results: 726 participants from five cross-sectional surveys, representing five different countries, were finally included. Amoxicillin was the most prescribed antibiotic. On average, 10,724 mg of antibiotics were prescribed per implant surgery. This mean was significantly ($p<0.001$) higher than 2,000 mg. Overall, amoxicillin doses were significantly higher than 2,000 mg (9,700 mg, $p<0.001$). All prescribed amoxicillin regimens independently contained more than 2,000 mg, including those comprising preoperative amoxicillin alone (2,175 mg, $p=0.006$).

Exclusive preoperative antibiotic regimens were the only subgroup with prescription doses below this threshold ($p=0.091$). Significant variations in antibiotic prescriptions were found between countries and antibiotic regimens ($p<0.001$).

Conclusions: The mean antibiotic dose prescribed per oral implant surgery was higher than the evidence-based recommended dose in healthy patients under straightforward conditions. In addition, variations in mean antibiotic doses were found between different countries and prescribing regimens.

METHODS

The study was conducted and reported in accordance with the Meta-analysis of Observational Studies in Epidemiology group [9]. The protocol details of this meta-analysis were registered with the Prospective International Registry of Systematic Reviews (PROSPERO) with the following registration ID: CRD42020156885. Accessible at: https://www.crd.york.ac.uk/prospero/#recordDetails

Eligible studies included all articles evaluating antibiotic prescribing in association with oral implant surgery and in compliance with the following framework of Participants; Intervention; Comparison; Outcome and Study Type (PICOS):

Participants: General dentists or specialists who place oral implants.

Intervention: Antibiotic prescriptions in association with oral implant surgery.

Comparisons:

Evidence-recommended dose in healthy patients under routine conditions: single preoperative dose of 2,000 mg [10].

2. Comparisons between different subpopulations (countries, types of antibiotics and prescribing regimens).

Results: Mean doses and types of antibiotics prescribed for oral implant surgery.

Type of study: Cross-sectional survey.

Publications that were clinical trials, case series or retrospective studies were excluded. There were no restrictions on language or year of publication. We also excluded publications that did not provide sufficient information to calculate the total antibiotic dose contained in their participants' prescriptions.

The following electronic databases were searched until 4 June 2020: Embase, PubMed, Ovid Medline, Scopus, Science-Direct, Web of Knowledge, as well as the database of doctoral theses of the Consejo General de Universidades de España, the bibliographic databases of the Consejo Superior de Investigaciones Científicas and the Índice Médico Español.

Three independent investigators searched the databases. The searched terms were PICO component descriptors: antibiotics, oral implant surgery, dental implant surgery, oral implant placement, dental implant placement and cross-sectional survey.

MeSH and search algorithms connected with Boolean operators were used as keywords for the electronic search. No filters were applied in the search in Ovid Medline and PubMed: (antibiotic) AND (((oral OR dental) implant AND surgery) OR ((oral OR dental) implant AND placement) AND (survey). In Scopus, the search was limited to "Dentistry" and "Article" for subject area and document type: ((antibiotic) AND (((oral OR dental) implant AND surgery) OR ((oral OR dental) implant AND placement)) AND (survey) AND (LIMIT-TO (DOCTYPE , "ar")) AND (LIMIT-TO (SUBJAREA , "DENT")). The search in In Web

of Knowledge was filtered by "Article": TS=(antibiotic "AND" oral implant surgery "OR" dental implant surgery "AND" survey). In Science Direct, the search was filtered by "Research articles": (antibiotic) AND (((oral OR dental) implant AND surgery) OR ((oral OR dental) implant AND placement)) AND (survey).

The Embase search was limited to "Article", "Short Survey", "Article in Press" and "Questionnaire": (antibiotic) AND ((((oral OR dental) implant AND surgery) OR (((oral OR dental) implant AND placement)) AND (survey) AND ('article'/it OR 'article in press'/it OR 'short survey'/it) AND 'questionnaire'/de.

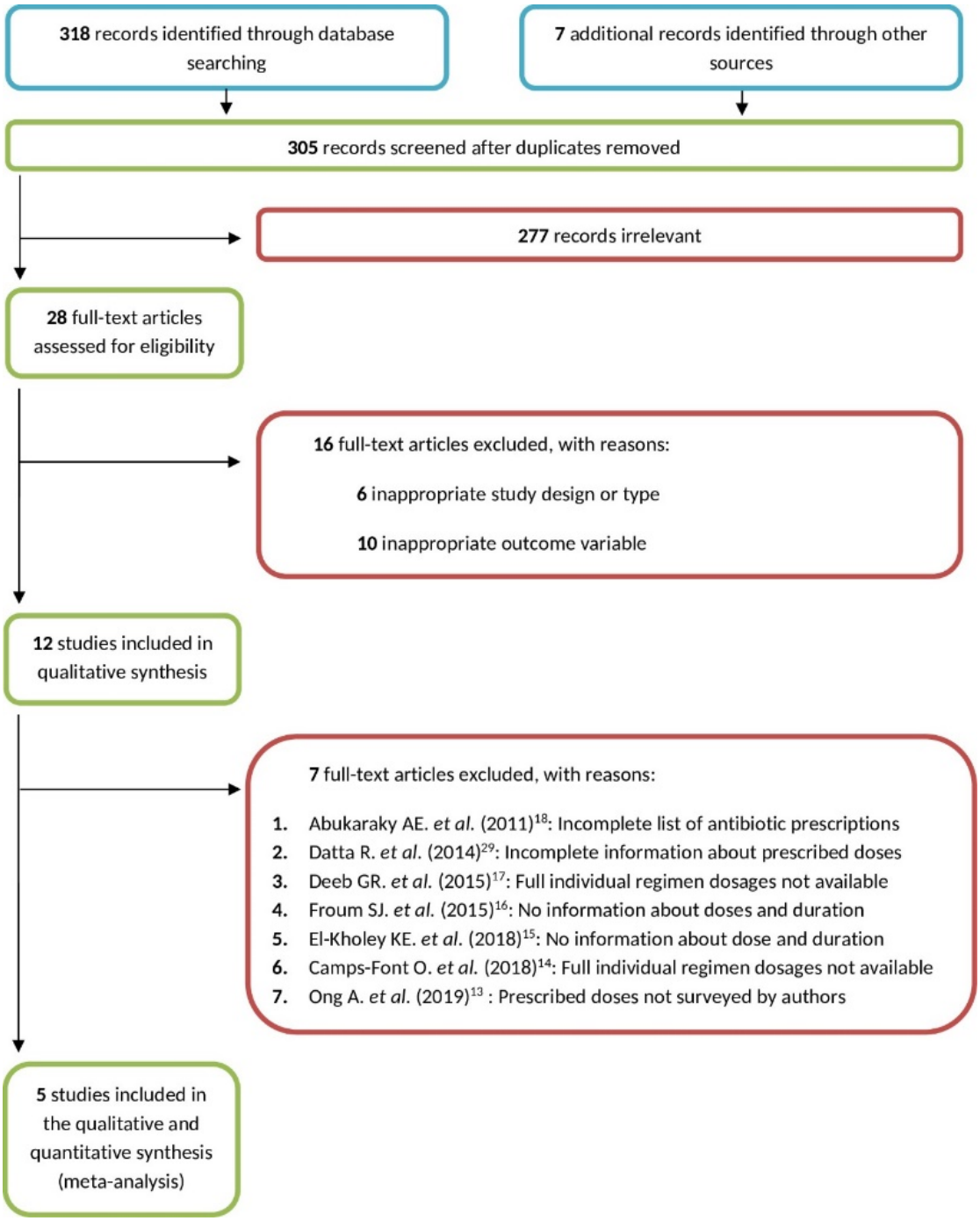
For the Spanish databases, the following terms were used: (antibiotics) AND (dental implant OR oral implant) AND (survey).

The references of all retrieved articles were also reviewed. No potentially unpublished material could be identified.

Two independent reviewers (F.R.S. and C.R.A.) reviewed titles and abstracts of records identified from the search using Cochrane online software [35]. Full text articles were acquired from records that met the inclusion criteria. The investigators contacted each corresponding author when additional information was needed in the selection process. All discrepancies were discussed with a third investigator (AI). Reasons for exclusion were reported (Figure 1).

The data recorded included the following: type of antibiotic, regimen (preoperative, postoperative or both), dose, duration of treatment and country. If the original data set could not be obtained from an included study, information regarding antibiotic type, prophylactic regimen (preoperative, postoperative, or both), dose, and duration of treatment were extracted from the article published by two independent investigators (F.R.S. and C.R.A.). A third party was consulted to resolve any disagreement (A.I.). Calculations were made from the data in the tables if data for any variable were not explicitly stated in the text. Corresponding authors of 8 different studies were contacted because the necessary information from their studies was unclear [2, 11-17].

Figure 1. Flowchart.



A study surveyed 133 Swedish dental professionals [18]. Of these, 98 prescribed antibiotics, while 35 did not prescribe any prophylactic antibiotics. This study fully described 85 antibiotic regimens; however, 13 antibiotic regimens were unfortunately missing. After contacting the authors, no additional information was obtained. Therefore, we included the 85 dentists who prescribed antibiotics with a proportionate number of non-prescribing practitioners (n = 22) instead of the 35 at the beginning.

The same adjustment was applied to other included studies with 29 participants who were unfortunately excluded for not providing a description of their prescribing regimens (14 from Spain, 6 from Italy and 9 from the Netherlands). The newly calculated and provided numbers of non-prescribing professionals in these cases were 3.75, 0.96 and 4.7 respectively, whereas the original numbers were 4, 1 and 5 respectively. As the calculated values were very close to the original ones, it was decided to keep the initial numbers in order to make the analysis as conservative as possible [17, 19, 20].

We unsuccessfully contacted the authors of the other five articles to collect the necessary data for inclusion in the meta-analysis [4, 6-8]. The authors of two articles were successfully contacted; however, the requested data on prescription dose were insufficient for inclusion in the meta-analysis because their surveys did not collect this information [11, 16].

Two independent reviewers (F.R.S. and C.R.A.) assessed the quality of the included studies using the National Heart, Lung, and Blood Institute Quality Assessment Tool for Cross-sectional and Observational Cohort Studies [6]. All discrepancies were discussed with a third investigator (AI). Studies were classified as low, moderate, or high quality if the percentage of affirmative responses to the checklist was less than 50%, between 50% and 80%, or greater than 80%, respectively.

Each included study presented different data sets and data coding. This heterogeneous presentation of data was a limitation to perform a proper quantitative analysis (meta-analysis). To overcome this limitation and meet the objectives of the study, a uniform database was created with the original dataset of each study. STATA® version 15 software was used to generate this database and perform all statistical analyses.

We calculated the mean dose (mg) of prophylactic antibiotics prescribed per implant surgery according to individual prescribing regimens (multiplying treatment dose, dose and corresponding duration) with an estimate of the standard deviation (SD). Participants who never prescribed prophylactic antibiotics for oral implant surgery were also included in this analysis. The normal distribution of outcome data was assessed graphically using quantile plots (Q-Q plots).

Student's t-test was used to compare the means of prophylactic antibiotics prescribed by study, country and prescribing regimen against the recommended evidence-based regimen: single preoperative dose of 2,000 mg. In this analysis, prescriptions were included only if they contained antibiotics with a Defined Daily Dose (DDD) equal to the recommended evidence-based regimen (2,000 mg) or equal to the DDD of amoxicillin (1,500 mg) according to the World Health Organization anatomical chemical therapeutic system [22].

Multiple f-tests were used to compare variances across groups. Depending on the analysis of variance, multiple t-tests for equal or unequal variances were performed to compare the means of antibiotics prescribed in the included studies. Standard Bonferroni corrections were performed for both f-tests and t-tests. In both tests, the α value was calculated by dividing 0.05 by the total number of comparisons performed.

RESULTS

Finally, five cross-sectional studies were included in this meta-analysis [18-20, 23, 24]. Table 1 shows descriptive information for each study included in the quantitative analysis. A flow chart describes the selection process, registrations and full-text exclusions with their justifications (Figure 1).

Table 1. Descriptive information for each study included

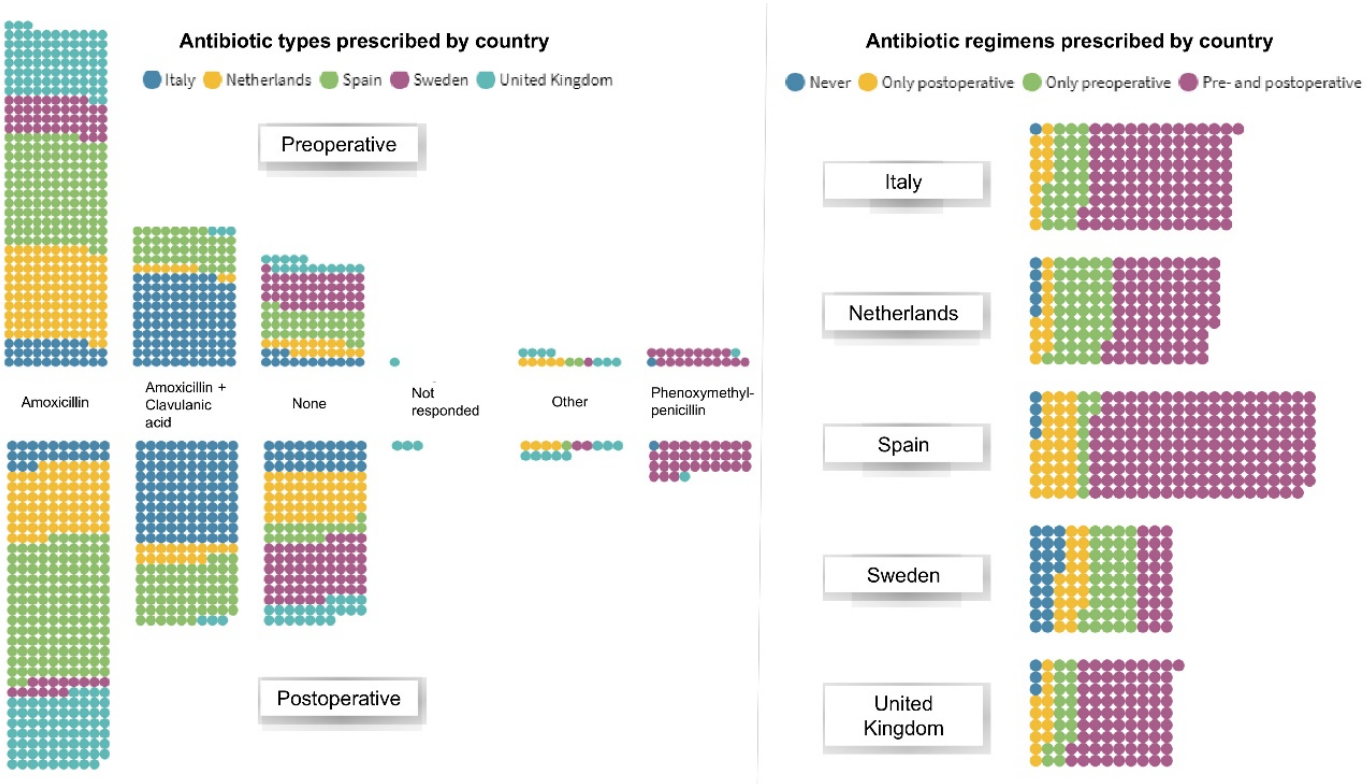
Study (year)	Country	n	Type of professionals	Most frequently prescribed regimen (n)	Participants who routinely prescribe prophylactic antibiotics (n)
Khalil *et al.* (2012) [18].	Sweden	133	General Dentists	2 g oral amoxicillin preoperatively (27)	74% (98)
Ireland *et al.* (2012) [24].	United Kingdom	109	General Dentists	3 g of oral amoxicillin one hour before surgery (54)	72% (76)
Arteagoitia *et al.* (2018) [16].	Spain	233	General Dentists	500 mg oral amoxicillin TID 1 day before surgery and for 7 days after surgery (10).	89% (207)
Rodriguez Sanchez *et al.* (2019) [20].	Italy	160	General dentists and oral surgeons	875/125 mg amoxicillin/clavulanic acid oral BID 1 day preoperatively and for 5 days postoperatively (15)	84% (134)
Rodriguez Sanchez *et al* (2019) [19].	Netherlands	151	General dentists, oral implantologists, periodontists, and maxillofacial surgeons	2 g oral amoxicillin 1 hour or immediately before surgery (35)	44% (66)

BID: Twice a day; TID: Three times a day.

Four studies were considered to be of moderate quality [18,19,20,23] and one of low quality [24]. The percentage of affirmative responses to the National Health Index checklist was 75% for the Swedish study, 54.5% for the other 3 studies (Spain, Netherlands and Italy) and 45.5% for the UK study. The distribution of the outcome variable data is shown in the Q-Q graphs.

In total, 726 participants were included in this meta-analysis. All prophylactic prescriptions consisted of oral antibiotics. Figure 2 illustrates the types of antibiotics and regimens prescribed by country. Each dot represents one participant included in the meta-analysis.

Figure 2. Types of antibiotics and prescribed regimens by country



On average, 10,724 mg of prophylactic antibiotics were prescribed per oral implant surgery. This mean antibiotic dose was significantly higher ($p<0.001$) than the evidence-recommended dose (2,000 mg).

Table 2 shows the mean dose of prophylactic antibiotics prescribed by type of antibiotic and country. Amoxicillin was the most frequently prescribed type of antibiotic, followed by amoxicillin in association with clavulanic acid. Most practitioners in the Italian survey, followed by participants in the Spanish survey, prescribed clavulanic acid (Table 2).

Table 2. Mean dose of prophylactic antibiotics (mg) prescribed by country and type of antibiotic.

Type of antibiotic / Country		Spain	Italy	Netherlands	Sweden	United Kingdom	Overall	ATC Code	DDD
Amoxicillin	Media	1,5047	8,672	6,561	4,642	7,399	9,700	J01CA04	1,500
	SD	*6,829*	*5,180*	*4,207*	*5,325*	*3,676*	*6,726*		
	n	150	32	111	44	86	423		
Amoxicillin/clavulanic acid	Media	19,178	10,685	7,600	-	17,494	13,208	J01CR02	1,500
	SD	*8,228*	*4,839*	*4,029*	-	*14,946*	*7,472*		
	n	56	117	10	0	4	187		
Penicillin V	Media	-	15,000	-	18,079	3,000	17,625	J01CE02	2,000
	SD	-	0	-	*17,197*	0	*16,925*		
	n	0	1	0	38	1	40		
Amoxicillin / Amoxicillin + Amoxicillin + Clavulanic Acid	Media	25,166	11,000	10,296	-	8,812	13,031	J01CA04 / J01CR02	1,500 / 1,500
	SD	*763*	*7550*	*1,406*	-	*265*	6,726		
	n	3	3	8	0	2	16		
Azithromycin	Media	-	-	11,000	-	10,100	10,550	J01FA10	300
	SD	-	-	*3,869*	-	*1,732*	*2,726*		
	n	0	0	3	0	3	6		
Clindamycin	Media	-	-	11,000	600	12,600	6,600	J01FF01	1,200
	SD	-	-	*3,869*	*0*	*0*	*6,600*		
	n	0	0	1	1	1	3		
Clindamycin / Amoxicillin + Clavulanic Acid	Media	-	-	11,200	-	-	11,200	J01FF01 / J01CR02	1,200 / 1,500
	SD	-	-	*2,687*	-	-	*2,687*		
	n	0	0	2	0	0	2		
Amoxicillin / Penicillin V	Media	-	-	-	24,000	8,000	16,000	J01CA04 / J01CE02	1,500 / 2,000
	SD	-	-	-	*0*	*0*	*11,314*		
	n	0	0	0	1	1	2		
Metronidazole	Media	-	-	-	6,000	25,200	15,600	J01XD01	1,500
	SD	-	-	-	-	*0*	*13,576*		
	n	0	0	0	1	1	2		
Erythromycin	Media	3,000	-	-	-	6,500	4,750	J01FA01	2,000
	SD	0	-	-	-	*0*	*2,475*		
	n	1	0	0	0	1	2		
Amoxicillin / Metronidazole	Media	-	-	-	-	24,000	24,000	J01CA04 / J01XD01	1,500 / 1,500
	SD	-	-	-	-	*0*	*0*		

	n	0	0	0	0	1	1		
Primcillin	Media *SD* n	- - 0	- - 0	- - 0	- - 0	18,400 *0* 1	18,400 *0* 1	J01CE02	2,000
Cefazolin	Media *SD* n	- - 0	- - 0	- - 0	- - 0	8,250 *0* 1	8,250 *0* 1	J01DC02	3,000
Cefuroxime / Amoxicillin + Amoxicillin + Clavulanic Acid	Media *SD* n	- - 0	- - 0	- - 0	- - 0	14,375 *0* 1	14,375 *0* 1	J01DC04 / J01CR02	500 / 1,500
Cefazolin / Amoxicillin + Clavulanic Acid	Media *SD* n	25,000 0 1	- - 0	- - 0	- - 0	- - 0	25,000 *0* 1	J01DB04 / J01CR02	3,000 / 1,500
No response	Media *SD* n	- - 0	- - 0	2,000 0 1	- - 0	10,500 0 2	7,667 4,907 3	-	-
None	Media *SD* n	0 *0* 4	0 *0* 1	0 *0* 5	0 *0* 22	0 *0* 3	0 *0* 35	-	-
Overall	Media *SD* n	15,974 *7,764* 215	10,231 *5,044* 154	6,742 *4,310* 141	8,615 *13,103* 107	8,216 *5,426* 109	10,713 *8,315* 726	-	-

In this table the name Penicillin V has been used instead of Phenoxymethylpenicillin, both names being different for the same drug. SD: standard deviation; DDD: defined daily dose; ATC: anatomical therapeutic chemical substance.

The overall dose of amoxicillin prescribed was significantly higher than 2,000 mg (9,700 mg, *p<0*.001). All amoxicillin-only regimens independently comprised a significantly higher dose than the baseline of 2,000 mg, including those with only preoperative amoxicillin (2,175 mg, *p=0.*006). However, UK participants prescribing preoperative amoxicillin only were the only ones prescribing significantly (*p<0*.001) above the 2,000 mg level per oral implant surgery (Table 3).

Table 3. Mean dose of amoxicillin (mg) prescribed by country and prescription regimen.

Prescription regime / Country		Spain	Italy	Netherlands	Sweden	United Kingdom	General
Pre-op only	Media	2,182†	1,900‡	2,042¶	2,025††	2,926*	2,175‡‡
	SD	*1,401*	*316*	*462*	*211*	*528*	*655*
	n	11	10	42	30	17	110
Post-operative only	Media	13,433	1,0667	9,300	-	6,675	10,769*
	SD	*4,603*	*2,309*	*1,549*	-	*1,390*	*4,345*
	n	21	3	10	0	10	44
Pre and post operative	Media	16,534	11,921	9,314	10,250	8,810	12,603*
	SD	*6,111*	*2,878*	*3,042*	*6,635*	*3,384*	*6,012*
	n	118	19	59	14	59	269
Overall	Media	15,047*	8,672*	6,561*	4,642**	7,399*	9,700*
	SD	*6,829*	*5,180*	*4,207*	*5,325*	*3,676*	*6,726*
	n	150	32	111	44	86	423

*Bilateral t-test contrasting mean=2,000 mg: *p<0.001; **p=0.002; †p=0.676; ‡p=0.343; ¶p=0.561; †††p=0.521; ‡‡‡p=0.006.*
SD: standard deviation

Among the different subpopulations (country and prescribing regimen), practitioners prescribing exclusively preoperative antibiotics were the only ones whose antibiotic prescriptions (2,110 mg) were not significantly (*p=0.*091) above this threshold (Table 4). A Forest plot taking into account the outcome variable is shown in Figure 3. (Figure 3).

Table 4. Mean doses of prophylactic antibiotics (mg) prescribed by country and prescription regimen.

Prescription regime / Country		Spain	Italy	Netherlands	Sweden	United Kingdom	General
Never	Media	-	-	-	-	-	-
	SD	-	-	-	-	-	-
	n	4	1	5	22	3	35
Pre-op only	Media	2,182**	1,786††	2,037‡‡	2,020¶	2,930*	2,110¶¶
	SD	*1,401*	*630*	*451*	*302*	*513*	*676*
	n	11	28	44	37	18	138
Post-operative only	Media	13,210	10,404	9,156	31,600	6,579	15,593*
	SD	*5,988*	*2,440*	*1,495*	*13,003*	*1,356*	*11,490*
	n	32	13	12	20	11	88
Pre and post operative	Media	17,830	12,414	9,413	7,327	9,992	13,282*
	SD	*6,782*	*3,254*	*2,937*	*5,770*	*5,672*	*6,480*
	n	166	112	73	26	67	444
Overall	Media	15,993*	10,231*	6,617*	8,545*	8,025*	10,724*
	SD	*7,725*	*5,044*	*4,287*	*13,119*	*5,614*	*8,377*
	n	213	154	134	105†	99	705‡

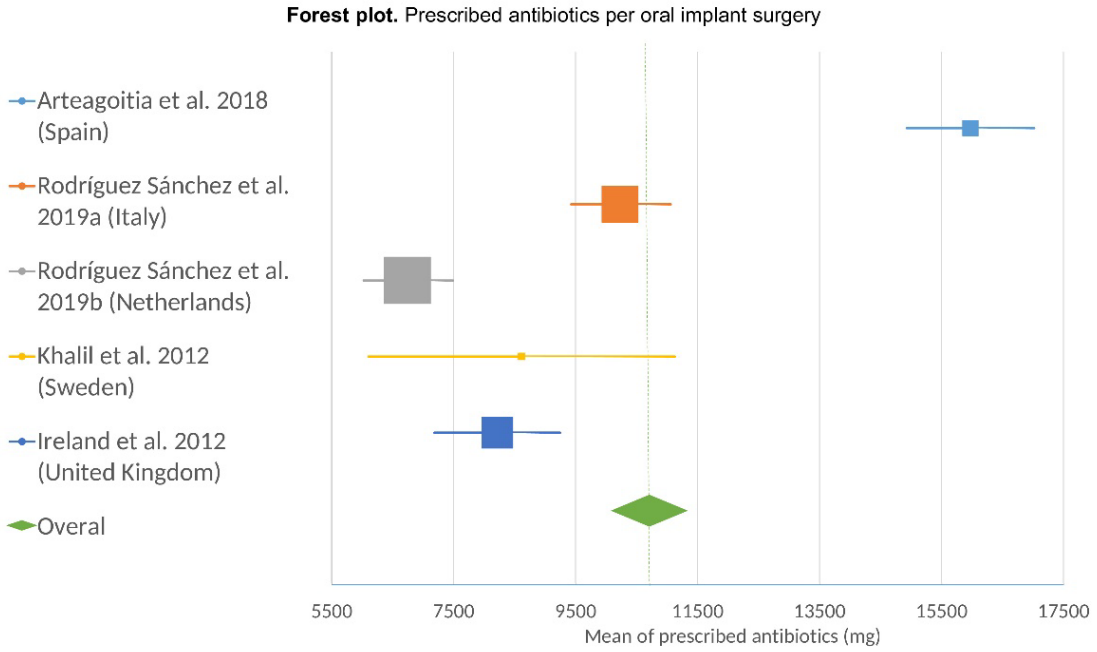
† 13 participants with absent regimens could not be included. To maintain a proportional number of nonprescribing participants, only 22 of the original 35 participants who never prescribe prophylactic antibiotics were included.

‡ 21 participants excluded because their prescriptions included antibiotic types with DDD other than 2,000 mg or the DDD value of amoxicillin (1,500 mg).

*Bilateral t-test contrasting mean=2,000 mg: *p<0.001; **p<0.676; ††p=0.083; ‡‡‡p=0.590; ¶p=0.781; ¶¶p=0.091.*

SD: standard deviation

Figure 3. Forest Diagram



The forest plot represents the estimates of the mean values and 95% confidence intervals for each outcome variable. The area of the squares around the mean values is proportional to the weight of the study in the analysis. A solid horizontal line indicates the 95% confidence intervals, while a diamond and dotted line indicate the overall mean value.

Bartlett's test was found to be statistically significant ($p<0.001$) between the different countries and prophylactic prescribing regimens. In addition, the I^2 was found low (18.7%). Therefore, low heterogeneity between countries was found (Table 5).

Multiple comparison analysis of variances showed that all but three comparisons of variances were statistically significant: Italy versus the Netherlands, Italy versus the UK and the UK versus the Netherlands. Therefore, in each of these comparisons both countries were found to be homogeneous, in relation to antibiotic doses prescribed.

Furthermore, mean comparisons were found to be statistically significant except for Italy versus Sweden, the Netherlands versus Sweden, the UK versus the Netherlands, Sweden versus the UK and only postoperative versus preoperative and postoperative. Consequently, both countries, in each of these comparisons, were found to prescribe a similar mean dose of prophylactic antibiotics (Table 5).

Table 5. Multiple comparison of means and variances of prophylactic antibiotics prescribed (mg).

Group comparisons	Contrast of means†	95% CI	*Value p‡*	*p§ value*
Spain vs Italy	5,743	4,430 - 7,056	<0.001	<0.001
Spain vs Netherlands	9,232	7,969 - 10,495	<0.001	<0.001
Italy vs Netherlands	3,489	2,409 - 4,569	0.058	<0.001
Spain vs Sweden	7,436	4,740 - 1,032	<0.001	<0.001
Italy vs Sweden	1,693	-922 - 4,307	<0.001	0.202
Netherlands v Sweden	-1,796	-4,386 - 794	<0.001	0.172
Spain v. United Kingdom	7,758	6,298 - 9,219	<0.001	<0.001
Italy v. United Kingdom	2,015	732 - 3,298	0.405	0.002
United Kingdom v. Netherlands	1,473	261 - 2,686	0.011	0.017
Sweden v. United Kingdom	323	-2,367 - 3,012	<0.001	0.813
Pre and post operative vs. Pre-op only	11,022	10,402 - 11,641	<0.001	<0.001
Only the postoperative period vs. Pre and post operative	2,122	-329 - 4,573	<0.001	0.089
Only the preoperative vs. Post-operative only	13,144	10,756 - 15,531	<0.001	<0.001

† Differences were calculated by deducting the mean value of the second group from that of the first group.

‡ Bilateral F tests that contrast H0: equal variances. The α value was calculated by dividing 0.05 by the total number of comparisons made, 10 when comparing countries (value α=0.005) and 3 when comparing prescribing regimens (value α=0.016)

§ The α value was calculated by dividing 0.05 by the total number of comparisons made: 10 when comparing countries (value α=0.005) and 3 when comparing prescribing regimens (value α=0.016).

CI: confidence interval.

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3.5. Discussion

The results obtained from the systematic review and meta-analysis suggest that routine use of a single dose of preoperative oral amoxicillin appears to be the only favourable regimen for preventing implant failures after oral implant surgery in healthy patients under straightforward conditions. However, postoperative oral amoxicillin regimens do not appear to significantly prevent oral implant failures or postoperative infections. Consequently, the additional use of postoperative oral amoxicillin does not seem to add any benefit and could be considered as overtreatment.

The amoxicillin effectiveness analysis suggested that 67 patients would need to be treated with a single preoperative dose of oral amoxicillin to prevent implant loss in one patient. In addition, it also suggested that 77 oral implants should be treated with a single preoperative dose of oral amoxicillin to prevent implant failure. This could lead to a slight reduction of almost 1.3% in the risk of implant failure.

Furthermore, none of the studies included in this meta-analysis alone showed significant benefits of amoxicillin in the prevention of dental implant failures and postoperative infections. This was observed both considering implants as the experimental unit in the analysis and considering patients as the experimental unit.

This study showed that postoperative use of amoxicillin does not provide any benefit in preventing implant failure. Subsequently, another article has confirmed our findings [1].

In addition, previous research suggested that postoperative administration of amoxicillin resulted in an increase in the number of resistant anaerobes and a decrease in the number of sensitive facultative bacteria and Gram-positive facultative cocci around the oral implant [2]. In addition, prolonged use of amoxicillin would have a negative effect on bone formation around implants, according to research in an animal model [3].

Effectiveness and efficacy could not be assessed with antibiotics other than amoxicillin due to the absence of clinical trials.

Healthy patients allergic to amoxicillin are frequently treated with prophylactic clindamycin in oral surgery. In the meta-analysis that we have carried out, we have not found any trial that studied this antibiotic in oral implant surgery. The results found in third molar extractions indicate that oral clindamycin may not only be ineffective in preventing infections after surgery, but may even have a negative effect.

Penicillin-allergic patients and the alternative use of clindamycin have recently been considered risk factors for implant failures [4-6] and infections after oral and maxillofacial surgery [7], alveolar preservation techniques, and bone augmentation [8]. This fact, together with the absence of clinical trials (only observational studies had been

published using clindamycin as a second option in case of penicillin allergy) prompted the realization through this research project of a randomized controlled clinical trial to evaluate clindamycin in oral implant surgery for the first time.

The present clinical trial demonstrated that a single preoperative dose of 600 mg of oral clindamycin did not differ from placebo in the prevention of oral implant failures or postoperative infections after oral implant surgery in healthy patients under straightforward conditions. In contrast, there was a non-significant trend to develop a higher incidence of implant failures when oral clindamycin was administered preoperatively.

In addition, the controversy about the association between oral implant failures, penicillin-allergic patients and clindamycin use could also be investigated by this clinical trial [4, 5]. By excluding all penicillin-allergic participants from the trial, this investigation could delimitate the relationship between the possible increased incidence of implant failures and clindamycin use. Hypothetically excluding the role of unknown genetic factors in penicillin-allergic patients from the equation. However, the patients did not undergo any penicillin allergy testing, so they could be allergic to penicillin without knowing this condition.

The low incidence rate of postoperative infections reported in this clinical trial may have been the result of standard antiseptic-sterile surgical measures in combination with the performance of a skilled surgeon and the limited duration of surgery. However, the postoperative infection rates reported in this clinical trial (3.2% for the clindamycin group and 6.4% for the placebo group) are significantly higher but similar to those found in other clinical trials conducted with another antibiotic (2.2% for the amoxicillin group and 3.1% for the placebo group).

The results of this study are applicable to the population from which the individuals included in the trial were drawn and could be generalized to other similar populations. The authors found no reason to believe that there are any limitations in the external validity and applicability of this study to such populations and under these specific conditions: oral implant surgery performed by an experienced surgeon and conducted in healthy patients with fully healed implant sites, with no preoperative infections and no need for bone augmentation procedures.

The findings of this research do not allow us to recommend the use of preoperative oral clindamycin in oral implant surgery. In addition, the study design allows relating this type of antibiotic as the risk factor and not the possible genetic predisposition present in patients allergic to penicillin, as some studies had hypothesized [4,5].

The risk-benefit ratio associated with the use of prophylactic antibiotics should be seriously considered, as the use of preoperative amoxicillin may prevent a moderate percentage of implant failures.

Because of the alarm raised by the development of bacterial resistance, the costs and benefits should always be carefully evaluated in relation to the severity of the condition to be prevented. Therefore, the finding that preoperative antibiotic prophylaxis with amoxicillin reduces oral implant failures should not necessarily lead to the conclusion that this practice should be adopted routinely [9]. Unfortunately, surveys and meta-analysis of surveys have shown otherwise.

The survey conducted in Spain showed that the majority of dentists surveyed in Biscay routinely prescribed prophylactic antibiotics (approximately 88%) in conjunction with oral implant surgery. It was also found that a wide range of prophylactic regimens was prescribed illustrating the enormous variety of antibiotic prophylaxis treatments prescribed by dentists. Consequently, this revealed a lack of consensus among practitioners.

At the same time, the recommendations made in the latest published articles were not frequently followed, as approximately 93% of those prescribing antibiotics did so with a postoperative regimen [10]. Therefore, the prescribing habits of most of the dentists surveyed in Vizcaya could be considered as overtreatment.

The results of this survey also contrast with the recommendations made by the INFAC bulletin in volume 29, number 1 of the year 2021, aimed at the rational use of antibiotics in dental procedures. The INFAC Bulletin is a pharmacotherapeutic bulletin whose aim is to update the pharmacotherapeutic knowledge of healthcare professionals in the Basque Country. It offers reviews of pharmacological treatments for different pathologies, drug reviews, brief news on medicines, and so on. A multidisciplinary committee in which health professionals from the Department of Health, Osakidetza and the University of the Basque Country participated on it [11].

This volume states that there is no evidence for the routine use of antibiotic prophylaxis to prevent post-implant infections in healthy patients. Antibiotic prophylaxis to prevent implant failure would only be recommended in complex cases (immediate implants with previous periapical infections, need for bone grafting, etc.) and in immunocompromised patients. In addition, a single dose of amoxicillin 2 g orally administered 30-60 minutes before the procedure is recommended, and in patients allergic to beta-lactam antibiotics, clindamycin 600 mg [11].

On the other hand, practitioners surveyed in the Netherlands appear to be more cautious about prescribing antibiotics in dental implant surgeries, with only 44% doing so routinely.

However, more than two thirds of the surveyed practitioners in the Netherlands also failed to follow an adequate prophylactic antibiotic regimen and prescribed prophylactic antibiotics in many situations not defined by the proposed NVOI guidelines. This fact would imply a lack of consensus on the indications for prescribing prophylactic antibiotics in conjunction with oral implant surgery among healthy patients, as well as on the antibiotic of choice and regimen selection [12].

Following the NVOI guidelines, preoperative antibiotics were only indicated as prophylaxis for bacterial endocarditis, in patients with orthopedic implants or surgeries performed in infected sites. The first treatment option suggested by the NVOI in these situations should be a single dose of oral amoxicillin and clavulanic acid (1000/250 mg) one hour before surgery or oral clindamycin (600 mg) in case of patients allergic to penicillins. However, these recommendations were made in the complete absence of evidence to support the efficacy of these two antibiotic regimens and the authors called for further research [12].

Most of the dentists surveyed in Italy also did not comply with the recommendations published in the latest scientific articles and systematically prescribed various types of antibiotics and prophylactic regimens without any scientific basis. The survey found that antibiotics were routinely prescribed to healthy patients, often with prolonged postoperative treatment after oral implant surgery.

The absence of standardized guidelines by official agencies could be considered one of the reasons for disagreement among professionals on the type of antibiotic and regimen selected, especially when it comes to penicillin-allergic patients. In addition, the lack of scientific evidence on the use of other types of antibiotics than amoxicillin could be another reason for the large variation in the treatment of penicillin-allergic patients.

Meta-analysis of surveys conducted in different countries indicates that the mean amount of prophylactic antibiotics prescribed in conjunction with oral implant surgery is approximately five times higher than evidence-based recommendations for healthy patients and straightforward conditions. Even for preoperative antibiotic prescriptions alone, the mean dose was higher than the evidence-based recommendations [5]. Countries showed great variability in their antibiotic prescriptions and regimens. It is also noted that practitioners in Northern European countries tend to prescribe more cautiously (a lower percentage of practitioners in the Netherlands prescribed antibiotics routinely) and to use more antibiotics with a narrower antimicrobial spectrum

(phenoxymethylpenicillin in the case of Sweden). These factors may be of vital importance to avoid bacterial resistance.

The results of the meta-analysis suggest that a significant number of antibiotic prescriptions may not be based on scientific evidence. This fact may lead to a significant volume of antibiotics being prescribed irrationally for prophylaxis in oral implant surgery.

This situation may unjustifiably increase the risk of adverse reactions and the development of bacterial resistance. The existence of a higher percentage of resistant bacteria and higher values of minimum inhibitory concentration for different antibiotics in Spain compared to the Netherlands has previously been related to higher antibiotic consumption in Spain [13].

Furthermore, the economic cost of antibiotic prophylaxis to the patient is relatively low, but the potential costs to the health care system may be substantial and expressly unfounded if they were to be made through irrational prescribing [14].

At the time of publication, this was the first meta-analysis that quantitatively evaluated the prescription of prophylactic antibiotics in conjunction with oral implant surgery and contrasted it with existing scientific recommendations. Subsequently, another similar study has corroborated these results [15]. Consequently, this study could reveal clinically relevant information for practitioners who place oral implants, in order to increase compliance with recommendations when prescribing prophylactic antibiotics and to avoid their misuse.

3.5.1. Knowledge gap

Despite the advances in knowledge achieved with the completion of this research project, there are still many unknowns regarding antibiotic prophylaxis in oral implant surgery.

Preoperative use of amoxicillin was effective in preventing implant failure, but not in preventing postoperative infections. However, three different preoperative doses of amoxicillin were found to be effective: 1, 2, or 3 grams 1 hour before surgery. Esposito et al (2013) suggested that routine use of a simple preoperative dose of 2 grams might be sensible. Subsequently, Romandini et al. (2019) continued the recommendations of Esposito et al. (2013), but suggested that the preoperative dose of 3 grams appeared to be best.

However and despite the suggestions of Esposito et al. (2013), the relatively high number of patients who must be treated with amoxicillin to prevent a single implant

loss raises the dilemma of whether its routine use in is effective and should be indicated in healthy patients and straightforward conditions.

On the other hand, a prospective study analysed the plasma concentration of amoxicillin in venous and implant bed blood after oral implant surgery. Their results showed that plasma concentrations after a prophylactic dose of 1 gram of amoxicillin preoperatively were higher than the minimum inhibitory concentration necessary to prevent the most common dental bacteria implicated in peri-implantitis and periodontal diseases [16]. Therefore, there is uncertainty about the choice of preoperative amoxicillin dosage in case its routine use is considered indicated in oral implant surgery.

On the other hand, considering the threat of bacterial resistance and the great variability in the effectiveness of preoperative amoxicillin (NNT varies between 25 and 77), it would be wiser not to recommend the routine prescription of antibiotics in oral implant surgery in healthy patients under straightforward conditions.

Until the clinical trial included in this doctoral thesis was performed, the only existing evidence on antibiotic prophylaxis in oral implant surgery was limited to amoxicillin. Unfortunately, there is still a lack of scientific knowledge on the efficacy and effectiveness of other types of antibiotics that are frequently prescribed in this setting, such as the combination of amoxicillin with clavulanic acid or clarithromycin in patients allergic to penicillin.

In addition, the lack of evidence to support the use of clindamycin in penicillin-allergic patients raises the question of the type of antibiotic indicated in these cases.

Naturally, all these knowledge limitations refer to oral implant surgery in straightforward conditions and in healthy patients. However, in oral implant surgeries performed with augmentation or bone grafting the lack of evidence on the use of prophylactic antibiotics is also a problem [17].

3.5.2. Future perspectives

This doctoral thesis has served to clarify some aspects of antibiotic prophylaxis in oral implant surgery, but it has also uncovered many new questions that lack a clear answer at this time. For this reason, further research is needed at the clinical, pharmacoepidemiological and health system levels.

First, new randomized, placebo-controlled clinical trials contrasting different preoperative doses of oral amoxicillin with each other are needed. Emphasis should be placed on comparing doses of 1 and 2 grams administered 1 hour before implant surgery.

Secondly, the efficacy and effectiveness of other types of antibiotics other than amoxicillin would need to be evaluated in randomised controlled clinical trials.

Thirdly, it is necessary to design programs to disseminate scientific knowledge to clinicians in order to adapt the results of research to daily practice. It would be necessary to adapt the recommendations for the use of properatory clindamycin in cases of allergy to beta-lactam antibiotics and to carry out new cross-sectional surveys to corroborate this change of attitude in the prescription of antibiotics in conjunction with oral implant surgery.

Further research is needed to specify the indications for prophylactic use of antibiotics in oral implant surgery in patients with systemic pathologies and to optimize the existing recommendations in this regard.

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4. Conclusions

4.1. Specific conclusions

Preventive antibiotics in oral implant surgery. Systematic review and meta-analysis

A single preoperative dose of 1, 2 or 3 grams of oral amoxicillin may be effective and efficient in preventing dental implant failures. Postoperative oral amoxicillin (exclusively postoperative or in association with preoperative oral amoxicillin) may not be beneficial in the prophylaxis of dental implant failures in conjunction with oral implant surgery in healthy patients and in non-complex surgeries. There is no evidence to support the use of oral amoxicillin to prevent the development of postoperative infections.

Preventive clindamycin in oral surgery. Systematic review and meta-analysis

There are insufficient studies on the efficacy of preventive clindamycin in oral surgery other than third molar extraction. The null hypothesis that oral clindamycin is not effective in preventing infection in third molar surgery, irrespective of the dose used, can be accepted. There are no randomised controlled clinical trials on the efficacy of clindamycin in preventing infection and/or failure in dental implant surgery.

Preventive clindamycin in oral implant surgery. Randomized and controlled clinical trial

In dental implant surgery in healthy patients and when there is no previous infection in the implant site and no need for bone grafting, a single dose of 600 mg of clindamycin administered orally one hour before surgery is not effective in reducing either the incidence of infection or the possibility of implant loss.

Antibiotic prescribing habits in oral implant surgery. Cross-sectional surveys in Spain, the Netherlands and Italy, and meta-analysis of cross-sectional surveys.

The prescription of preventive antibiotics is very common in oral implant surgery in healthy patients in uncomplicated surgeries by currently active practitioners in Spain, the Netherlands and Italy. Clinicians prescribe a wide variety of prophylactic regimens, demonstrating a lack of consensus in their prescribing habits.

Practitioners performing oral implant surgery often prescribe on average more preventive antibiotics than the evidence-based recommended dose. There was a large variation in the average amount of antibiotics prescribed between countries, as well as great diversity in the regimens used.

4.2. General conclusions

The routine prescription of preventive antibiotics in implant dentistry should be considered with caution. The decision to use an antibiotic should be judged individually for each patient based on their health status and the potential complications of acquiring an infection. We have no information on the efficacy of antibiotic prophylaxis in patients with underlying disease and increased risk of infection.

In healthy patients not allergic to amoxicillin, the use of a single preoperative dose of 1, 2 or 3 grams of oral amoxicillin appears to be effective in preventing oral implant failure. However, we must take into account that it would be necessary to treat between 33 and 167 patients to prevent the loss of an implant. Therefore, when deciding to use antibiotic prophylaxis to prevent infectious complications and/or implant failure in healthy patients, the practitioner should take into account the possible increased risk of mild adverse effects, the low complication rate and the absence of serious complications even in the absence of prophylaxis. Another important aspect to consider is the need to limit the use of antibiotics to curb the increasing microbial drug resistance.

In healthy patients allergic to amoxicillin, the analysis of the literature allowed us to verify that there was no clinical trial that supported the efficacy of clindamycin in the prevention of infection and/or failure in implant surgery. The results of the randomized, blinded clinical trial conducted with a preoperative dose of 600 mg of oral clindamycin do not show that clindamycin is effective in oral implant surgery compared to placebo in preventing infection and/or implant failure. Clindamycin might even be responsible for an increased risk of implant loss.

On the other hand, we have corroborated and analyzed how implantology professionals, for the most part, do not follow the recommendations published in the literature, using all types of antibiotics with very different guidelines and doses. Overall, it can be stated that in most cases implantologists use preventive antibiotics with doses much higher than those considered effective by studies.

5. Appendices

5.1. List of publications and quality indicators

Rodríguez Sánchez F, Rodríguez Andrés C, Arteagoitia I. Which antibiotic regimen prevents implant failure or infection after dental implant surgery? A systematic review and meta-analysis. J Craniomaxillofac Surg. 2018 Apr;46(4):722-736. doi: 10.1016/j.jcms.2018.02.004. Epub 2018 Feb 26. PMID: 29550218.

Journal Impact Factor

- Journal of Citation Reports: 1.960
- Scimago Journal: 1.96

Journal position per cathegory

- Journal of Citation Reports:

Surgery; 90/200 (Q2)

Dentistry, Oral Surgery & Medicine; 31/91 (Q2)

- Scimago Journal:

Oral Surgery (Q1), Otorhinolaryngology (Q1), Surgery (Q1)

Number of citations

- Web of Science: 19
- Scopus: 23
- Google Scholar: 46

Journal H-Index

- Scimago Journal: 77

Arteagoitia I, Rodríguez-Andrés C, Rodríguez-Sánchez F. Antibiotic prophylaxis habits in dental implant surgery among dentists in Spain. A cross-sectional survey. Med Oral Patol Oral Cir Bucal. 2018 Sep 1;23(5):e608-e618. doi: 10.4317/medoral.22626. PMID: 30148475; PMCID: PMC6167099.

Journal Impact Factor

- Journal of Citation Reports: 1.284
- Scimago Journal: 0.623

Journal position per cathegory

- Journal of Citation Reports:

Dentistry, Oral Surgery & Medicine; 65/91 (Q3)

- Scimago Journal:

Dentistry (Q2), Medicine (Q2), Otorhinolaryngology (Q2), Surgery (Q2)

Number of citations

- Web of Science: 9
- Scopus: 9
- Google Scholar: 13

Journal H-Index

- Scimago Journal: 56

Rodríguez Sánchez F, Arteagoitia I, Rodríguez Andrés C, Bruers J. Antibiotic prophylaxis prescribing habits in oral implant surgery in the Netherlands: a cross-sectional survey. BMC Oral Health. 2019 Dec 12;19(1):281. doi: 10.1186/s12903-019-0981-4. PMID: 31830979; PMCID: PMC6909651.

Journal Impact Factor

- Journal of Citation Reports: 1.911
- Scimago Journal: 0.731

Journal position per cathegory

- Journal of Citation Reports:

Dentistry, Oral Surgery & Medicine; 38/91 (Q2)

- Scimago Journal:

Dentistry (Q1)

Number of citations

- Web of Science: 7
- Scopus: 6
- Google Scholar: 9

Journal H-Index

- Scimago Journal: 50

Rodríguez Sánchez F, Arteagoitia I, Rodríguez Andrés C, Caiazzo A. Antibiotic prophylaxis habits in oral implant surgery among dentists in Italy: a cross-sectional survey. BMC Oral Health. 2019 Dec 2;19(1):265. doi: 10.1186/s12903-019-0943-x. PMID: 31791306; PMCID: PMC6889412.

Journal Impact Factor

- Journal of Citation Reports: 1.911
- Scimago Journal: 0.731

Journal position per cathegory

- Journal of Citation Reports:

Dentistry, Oral Surgery & Medicine; 38/91 (Q2)

- Scimago Journal:

Dentistry (Q1)

Number of citations

- Web of Science: 8
- Scopus: 8
- Google Scholar: 10

Journal H-Index

- Scimago Journal: 50

Rodríguez Sánchez F, Arteagoitia I, Teughels W, Rodríguez Andrés C, Quirynen M. Antibiotic dosage prescribed in oral implant surgery: A meta-analysis of cross-sectional surveys. PLoS One. 2020 Aug 18;15(8):e0236981. doi: 10.1371/journal.pone.0236981. PMID: 32810135; PMCID: PMC7446810.

Journal Impact Factor

- Journal of Citation Reports: 3.240
- Scimago Journal: 0.990

Journal position per cathegory

- Journal of Citation Reports:

Biology (n/a)

Multidisciplinary Sciences; 26/72 (Q2)

- Scimago Journal:

Multidisciplinary (Q1)

Number of citations

- Web of Science: 4
- Scopus: 3
- Google Scholar: 6

Journal H-Index

- Scimago Journal: 332

Arteagoitia I, Rodríguez Sánchez F, Figueras A, Arroyo-Lamas N. Is clindamycin effective in preventing infectious complications after oral surgery? Systematic review and meta-analysis of randomized controlled trials. Clinical Oral Investigations.

Under Review

Journal impact factor

- Journal of Citation Reports: 3,573 (2020)
- Scimago Journal: 1,088 (2020)

Position of the magazine by category

- Journal of Citation Reports (2020):

Dentistry, Oral Surgery & Medicine; 21/92 (Q1)

- Scimago Journal (2020):

Dentistry (miscellaneous) (Q1)

Number of appointments

- Web of Science: 4
- Scopus: 3
- Google Scholar: 6

Journal H-index

- Scimago Journal: 82

Santamaría G, Rodríguez Sánchez F, Rodriguez C, Barbier L Arteagoitia I, Effect of Preoperative Clindamycin Preventing Implant Failures and Postoperative Infections after Oral Implant Surgery: a Randomized Placebo-controlled Clinical Trial. Clinical oral implants research.

Sent to Journal

Journal impact factor

- Journal of Citation Reports: 5,977
- Scimago Journal: 2,407

Position of the magazine by category

- Journal of Citation Reports (2020):

Dentistry, Oral Surgery & Medicine; 6/92 (Q1)

Engineering, Biomedical; 17/89 (Q1)

- Scimago Journal (2020):

Dentistry; Oral Surgery (Q1)

Journal H-index

- Scimago Journal: 161

5.2. Published articles

Journal of Cranio-Maxillo-Facial Surgery 46 (2018) 722–736

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journal homepage: www.jcmfs.com

Review

Which antibiotic regimen prevents implant failure or infection after dental implant surgery? A systematic review and meta-analysis

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ABSTRACT

Objective: To assess which antibiotic regimen prevents dental implant failures or postoperative infections following dental implant placement.
Materials and methods: Systematic review and meta-analysis. Data sources: Pubmed, Cochrane, Science Direct, and EMBASE via OVID were searched up to August 2017. Only randomized controlled clinical trials (RCT) using antibiotics were included. Outcome measures were set on dental implant failures or postoperative infection incidence after dental implant surgery. Three reviewers independently undertook risk of bias assessment and data extraction. Stratified meta-analyses of binary data using fixed-effects models were performed using Stata 14.0. The risk ratio (RR) and 95% confidence interval (CI) were estimated.
Results: Nine articles were included corresponding to 15 RCTs. All RCTs tested only oral amoxicillin. Implant-failure analysis: overall RR = 0.53 (P = .005, 95% CI: 0.34–0.82) and overall NNT = 55 (95% CI, 33 –167). Single-dose oral amoxicillin preoperatively (SDOAP) is beneficial (RR = 0.50, CI: 0.29–0.86. P = .012), when compared to postoperative oral amoxicillin (POA): RR = 0.60, CI: 0.28–1.30. P = .197. Postoperative-infection analysis: overall RR = 0.76 (P = 0.250, 95% CI: 0.47–1.22). Neither SDOAP (RR = 0.82, CI = 0.46–1.45, P = .488) nor POA (RR = 0.64, CI = 0.27–1.51, P = .309) are beneficial. I^2 = 0.0%, chi-squared tests P ≈ 1.
Conclusion: Only SDOAP is effective and efficacious at preventing implant failures, but it was not significant for postoperative infections following dental implant surgeries.

1. Introduction

The insertion of dental implants is a routine treatment in the rehabilitation of partially and completely edentulous jaws (American Academy of Implant Dentistry, 2017 December 12). Treatment with dental implants is expected to have a high success rate: implant survival rates of 90–95% have been reported in longitudinal studies with long-term follow-up (Hee-Won et al., 2011).

Despite the high success rates, failures do occur and may be classified as either early failures, occurring prior to prosthetic restoration, or late failures, post-prosthesis placement (Koldsland et al., 2009). Bacterial contamination at implant insertion may be one cause of infection and early implant failure (Pye et al., 2009; Esposito et al., 2013).

In spite of the fact that there are different therapeutic options, if an infection has been established, infected implants usually have to be removed. Both patients and professionals poorly tolerate complications and failures in implantology. For this reason, diverse strategies to prevent implant infection and failure in healthy subjects, such as antiseptic dilutions and oral

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antibiotics, have been studied (Lambert et al., 1997; Piñeiro et al., 2010; Pedrazzi et al., 2014).

Antibiotic prophylaxis in oral and dental surgery is usually recommended for patients at risk of infectious endocarditis, patients with reduced host response, and when surgery is performed in infected sites (Gould et al., 2006; Wilson et al., 2007; Resnik and Misch, 2008). However, the evidence of antimicrobial protocols in order to prevent implant failure or infection in healthy subjects is limited. In spite of the fact that there are some published articles (Dent et al., 1997; Laskin et al., 2000; Seabra et al., 2000; Morris et al., 2004; Binahmed et al., 2005; Schwartz and Larson, 2007; Abu-Ta'a et al., 2008; Esposito et al., 2008, 2010; Khoury et al., 2008; Anitua et al., 2009; Caiazzo et al., 2011; Givens et al., 2013; El-Kholey, 2014; Hosseini et al., 2014; Tan et al., 2014; Nolan et al., 2014; Arduino et al., 2015; Escalante et al., 2015) and review papers (Ahmad, 2012; Esposito et al., 2013; Ata-Ali et al., 2014; Chrcanovic et al., 2014; Lund et al., 2015; Surapaneni et al., 2016; Park et al., 2017) with different antibiotic regimens for preventing dental implant failures or postoperative infections, their results remain inconclusive.

Unfortunately, there is still no consensus among professionals about the use and indications of antibiotics for preventing failures or postoperative infections in these surgeries in healthy patients under normal circumstances (Caiazzo et al., 2011; Arduino et al., 2015; Lund et al., 2015). Additionally, it remains unclear whether an adjunct use of postoperative antibiotics is beneficial after the use of single preoperative doses of antibiotics (Esposito et al., 2013; Park et al., 2017). Therefore, the widespread use of perioperative antibiotics to prevent such an infrequent complication remains controversial.

The irrational use of antibiotics could potentially cause adverse reactions, and this risk should be seriously considered. Adverse events related to the use of antibiotics range from diarrhea to life-threatening allergic reactions. Another current concern of antibiotic use is the development of bacterial resistance and the risk of superinfection (Resnik and Misch, 2008; Surapaneni et al., 2016).

A rather alarming increased rate of the prescribing of antibiotics by dental practitioners has been documented (Marra et al., 2016). Moreover, there is a significant cost for antibiotic prophylaxis in the dental practice setting, and evidence-based recommendations concerning this practice are needed (Lockhart et al., 2013).

Consequently, the authors considered it important to analyze all of the quality evidence published and to try to keep it up-to-date to support the clinician's evidenced-based decisions.

The purpose of this systematic review and meta-analysis was to assess the efficacy and effectiveness of antibiotics in preventing dental implant failure or postoperative infection, compared to a control group, among patients undergoing dental implant placements under ordinary conditions. The second purpose was to evaluate which was the most effective and efficacious antibiotic regimen preventing dental implant failure or postoperative infection.

The investigators hypothesize that the use of antibiotics, in any regimen, is neither effective nor efficacious in preventing dental implant failures or postoperative infections after a dental implant placement. The authors also hypothesize that the use of a postoperative antibiotic regimen, used either exclusively postoperatively or in conjunction with a preoperative regimen (adjunct use), is neither more effective nor more efficacious than a solely preoperative antibiotic regimen.

The specific aims of the research were as follows:

- To assess the incidence rate of dental implant failures and postoperative infections after dental implant placements among healthy patients who were treated with or without antibiotics (in any regimen and dosage).
- To contrast the benefits of postoperative antibiotics orally (exclusively postoperative and adjunctive to preoperative antibiotics) versus only preoperative antibiotics orally.

2. Materials and methods

2.1. Protocol and registration

To address the research purpose, the authors designed and implemented a systematic review and meta-analysis. The research was conducted and is reported in accordance with the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Liberati et al., 2009).

Details of the protocol for this systematic review were registered on PROSPERO (CRD42017054364) and can be accessed at (https://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42017054364).

2.2. Eligibility criteria

The target sample was composed of all published articles presenting an evaluation of the efficacy of antibiotics for preventing postoperative infection or dental implant failure after a dental implant placement.

For inclusion in the study, publications had to be RCTs (with or without placebo) that included patients of any age or gender who underwent a dental implant surgery. Studies were required to have analyzed the efficacy of any antibiotic in any treatment dose or regimen (preoperatively, postoperatively or both) for preventing postoperative infection or dental implant failure after dental implant placement.

Publications were excluded if they were case series, retrospective studies or not randomized clinical trials. Articles were also excluded if they did not assess the postoperative incidence of implant-site infection or dental implant failure, or if they did but the implant was inserted into sites with periradicular infection or with apical pathology. The authors did not use restrictive criteria for defining postoperative infection or dental implant failure. There was no restriction by language or year of publication.

2.3. Information sources

Searches were conducted in the following electronic databases up to August 2017: Medline/PubMed, Scopus, Science-Direct, Web of Science, Evidence-Based Dentistry, ClinicalTrials.gov, the EU Clinical Trials Register, and the Cochrane Central Register of Controlled Trials, as well as the Spanish General University Board database of doctoral theses in Spain (TESEO), the Spanish National Research Council (CSIC) bibliographic databases, and the Spanish Medical Index (IME).

2.4. Search

The searched terms were descriptors of each of the Patient, Intervention, Comparison, and Outcome (PICO) components: dental implant surgery, dental implant placement, antibiotics, amoxicillin, implant failure, implant loss, and postoperative infection. The following filters were applied: humans, clinical trials, meta-analysis, and randomized controlled trials. The electronic search in the Medline/PubMed database was carried out using MeSH and search algorithms connected with Boolean operators as key words for titles and abstracts (Robinson and Dickersin, 2002): ((randomized controlled trials OR controlled clinical trial OR randomized controlled trials OR random allocation OR double-blind method OR single-blind method OR clinical trial OR clinical trials

OR ("clinical trial") OR ((singl* OR doubl* OR trebl* OR tripl*) AND (mask* OR blind*)) OR ("latin square") OR placebos OR placebo* OR random* OR research design OR comparative study OR evaluation studies OR follow-up studies OR prospective studies OR cross-over studies OR control* OR prospective* OR volunteer*) NOT animal) AND (amoxicillin) AND (dental implant failure OR dental implant loss OR postoperative infection) AND (dental implant placement OR dental implant surgery)).

For databases in Spanish, we used the following terms: (antibioticos O amoxicilina) AND (fracaso implante O pérdida implante) AND (implante dental).

The authors reviewed the references of all papers retrieved, and when they identified potentially unpublished work, they contacted the corresponding authors to request a copy of the study report.

2.5. Study selection

Three researchers independently carried out the search on the databases applying the aforementioned criteria.

Three records were excluded after the duplicates were removed, since their titles specified that they were retrospective and not randomized (Kashani et al., 2005; Karaky et al., 2011). The third one was a congress abstract without enough information to assess randomization and risk of bias (Seabra et al., 2000). Thereafter, 20 full text articles were assessed for eligibility and 11 were excluded. Two of these were excluded because they were retrospective studies, 6 because no randomization method was performed, one for being an abstract article, another because the implant failure was not the outcome of interest, and 2 articles because they used implants placed in sites with periradicular infection and apical pathology (Fig. 1).

2.6. Data collection process

All selected studies were independently examined by 2 researchers who extracted data from each article. When explicit data on some variables were not stated in the text, they were calculated using data from tables when possible. In the event of uncertainty, the authors were contacted to obtain the necessary information. A third researcher was consulted in cases of disagreement.

2.6.1. Postoperative infection

The authors of the studies included in this meta-analysis applied different diagnostic criteria for the definition of postoperative infection. The most used terms to define this outcome were the presence of suppuration, fistula and abscess or pus exudation with pain, tenderness, edema, swelling, erythema, and heat in the implant site or fever.

The terms suppuration and pus exudation were considered as postoperative infection during the data collection process. The study conducted by Arduino et al. (2015) used the term pus exudation, and 4 studies reported the term suppuration (Esposito et al., 2008, 2010; Nolan et al., 2014; Tan et al., 2014). The RCT implemented by Tan et al. (2014) reported the percentage of patients with suppuration at weeks 1, 2, 4 and 8 after the surgery intervention. Nevertheless, it was not explicit if the data from each week were independently reported. Therefore, it was impossible to distinguish if one patient who had infection signs at one week was the same person with the same signs at another week in the same treatment group. The authors were contacted, and the doubt was resolved, as the percentage of patients with suppuration at each week was found to be independently reported.

2.6.2. Implant failure

Implant failure outcome was essentially defined as a mobile implant that had to be mechanically removed due to lack of osseointegration. The study performed by Arduino et al. (2015) did not report the total number of implants analyzed in each group (test and control) after losses to follow-up and exclusions. Additionally, the RCT carried out by Caiazzo et al. (2011) did not report the total number of patients who had implant failures in each group. For this reason, the authors from both RCTs were contacted and they successfully provided these data (Table 1).

The article published by Nolan et al. (2014) did not report the total number of implants inserted in each group, and the corresponding author was also contacted, but in this case, the raw data were unfortunately not available. For this reason, this study was excluded from the analysis carried out by the number of implant failures. Nevertheless, the authors used the data available in this study for the analyses by the number of patients who had an implant failure and the number of patients who suffered a postoperative infection.

The articles conducted by Caiazzo et al. (2011) and Tan et al. (2014) included 3 treatment groups using amoxicillin and 1 control group. In this meta-analysis, each treatment group was included as an independent RCT using the same control group provided by the researchers.

In 2 articles, patients in the control group were also treated with amoxicillin with a different dose regimen from the treatment group (El-Kholey, 2014; Arduino et al., 2015). These control groups might be considered as treatment groups in different RCTs, for which a new control group would be necessary.

To this end, the authors constructed a new control group for each analysis. The new control groups were based on calculating the mean number of subjects presenting the outcome variables (patients who had an implant failure, total number of implant failures and patients who had a postoperative infection) in the control groups from the other RCTs included in each analysis (Abu-Ta'a et al., 2008; Esposito et al., 2008, 2010; Anitua et al., 2009; Caiazzo et al., 2011; Nolan et al., 2014; Tan et al., 2014). Similarly, the mean number of subjects not presenting the outcome variables (successful implants, patients who had no implant failures and patients who had no postoperative infections) in the control groups from the other RCTs was also calculated (Abu-Ta'a et al., 2008; Esposito et al., 2008, 2010; Anitua et al., 2009; Caiazzo et al., 2011; Nolan et al., 2014; Tan et al., 2014).

These newly constructed control groups were composed of 4 patients who had an implant failure and 94 patients who had no implant failure for the first analysis (implant failure by patients), 4 implant failures and 130 successful implants for the second analysis (implant failure by implants), and 2 patients who had a postoperative infection and 76 patients without postoperative infections for the last analysis.

The authors imputed the data of these newly constructed control groups for the 2 aforementioned studies (El-Kholey, 2014; Arduino et al., 2015).

2.7. Data items and analysis

The predictor variable was whether or not antibiotics were used in each RCT. The recorded data included the following: type of antibiotic, administration route and treatment regimen (before or after the implant placement). In all studies, the only antibiotic type used was oral amoxicillin.

The authors performed a stratified meta-analysis with 3 different outcome variables: 1.-Number of patients who had an implant failure; 2.- Number of implant failures; and 3.-Number of patients who suffered a postoperative infection. Stratified analysis

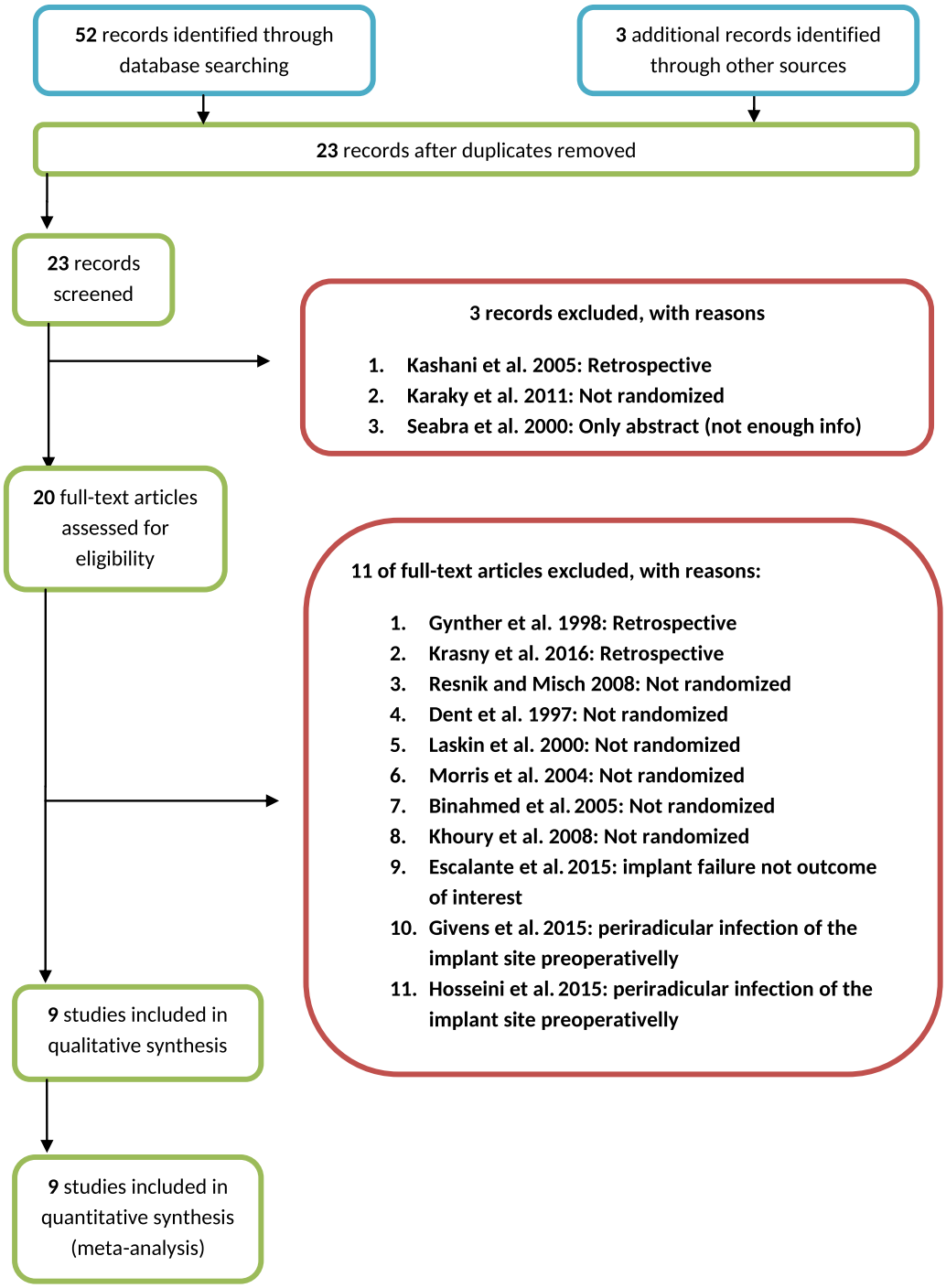


Fig. 1. Flow chart.

was carried out in order to contrast the effect of solely preoperative oral antibiotics versus postoperative antibiotics (used both exclusively postoperatively and as adjunct use in a perioperative regimen).

The authors did not use restrictive criteria for defining postoperative infection and implant failure.

The authors also recorded the presence or absence of adverse effects.

The remaining variables described the characteristics of the sample of each article (sample size, gender, mean age of the patients, number of smokers, and use of contraceptives) and the characteristics of the study design in each article (study type, number of treatment groups, randomization process, secret assignment, blinding, losses to follow-up, test materials, control materials, co-treatment materials, type of implant and type of surgery). The data collected are listed in Table 1.

2.8. Risk of bias in individual studies

The Cochrane Collaboration's tool was used in order to assess the individual risk of bias of each included RCT at the study level (Higgins and Green, 2011). The risk of bias graph (Fig. 2) and the risk

Table 1
Study characteristics.

Study, Year and Country	Type of study	Method of randomization	Blinding	Test material (which and dosage)	Control material	Co-treatment materials	Test group patients	Control group patients	Diagnostic criteria	Quantitative outcome measure & LTF	Follow up period	Adverse reactions
Abu-Taa et al., 2008, Belgium	Parallel-group RCT	Random sampling	Double-blinded	AMX 1 g per os, 1 h preoperatively and 500 mg 4 times per day, 2 days postoperatively	No antibiotics	Postoperative rinse with 0.12% CLX for 1 min for 7–10 days	n=40 male= 23 female= 17 MA= 60 Range= 27–82 n implants= 128	n = 40 male = 20 female = 20 MA = 57 Range = 26–88 n implants = 119	**Postoperative infection:** Purulent drainage (pus) or fistula in the operated region, with pain or tenderness, localized swelling, redness and heat or fever **Implant failure:** Signs of infection and/or radiographic peri-implant radiolucencies and/or judged a failure after performing an explorative flap surgery	**Test group:** Patients with infection: 1/40 Survival rate (implants): 128/128 (100%) Patients who had implant failures: 0/40 **Control group:** Patients with infection: 4/40 Survival rate (implants): 114/119 (96%) Patients who had implant failures: 3/40 **LTF:** 0	5 months after implant placement	No side effects of the antibiotic were reported
Esposito et al., 2008, Italy	Parallel-group RCT	Twelve computers-generated restricted randomization list	Double-blinded	2 g AMX orally (2 tablets of 1 g) 1 h prior to implant placement	2 identical placebo tablets 1 h prior to implant placement	Postoperative rinse with 0.2% CLX for 1 min twice a day for at least 1 week In the control group 1 patient was treated with antibiotics because of influenza 2 days after implant placement	n = 158 Female = 78 (49.4%) MA (range) = 47.8 (18–78) Non-smokers = 99 (62.7%) Duration (range) = 27 m (3–130) Total number of implants = 341 Took postoperative antibiotics = 2	n = 158 Female: 96 (60.8%) MA (range) = 47.9 (19–76) Non-smokers = 108 (68.4%) Duration (range) = 26.5 m (4–125) Total number of implants = : 355 Took postoperative antibiotics = 1	**Postoperative infection:** Suppuration, fistula, abscess. **Implant failures:** Implant mobility and/or any infection dictating implant removal	**Test group:** Implant failures: 2/341 Patients with infection: 3/158 Patients with implant failures: 2/158 LTF: 0, Patients Excluded: 7 **Control Group:** Implant failures: 9/355 Patients with infection: 2/158 Patients with implant failures: 8/158 LTF: 0, Patients Excluded: 7	4 months after implant placement	1 adverse event occurred in the placebo group (itching for 1 day) and 1 in the AMX group (diarrhea and somnolence).
Anitua et al., 2009, Spain	Parallel-group RCT	Random numbers table	Double-blinded	2 g oral AMX 1 h before implant surgery	2 placebo tablets administered orally 1 h before implant surgery	0.2% CLX rinse for 1 min preoperatively. Immediately after the surgery and the following 3 days intravenous or intramuscular dexamethasone. Acetaminophen as rescue medication (maximum 1 g/8 h). Metamizol (575 mg, 1 or two tablets/8 h) was also allowed	n = 52 Females = 37 (71%) Males = 15 (29%) MA = 49 (±12) Smokers = 10 (19%) Non-smokers = 42 (81%) Duration (mean value ± SD) = 41.03 m (±29) Maxillary = 26 (51%) Mandibular = 25 (49%) Anterior Zone = 11 (22%) Posterior Zone = 39 (78%) Immediate Loading type = 1 (2%)	n = 53 Females = 33 (62%) Males = 20 (38%) MA = 47 (±12) Smokers = 8 (15%) Non-smokers = 45 (85%) Duration (mean value ± SD) = 41.71 m (±27) Maxillary = 21 (40%) Mandibular = 32 (60%) Anterior Zone = 12 (23%) Posterior = 40 (77%) Immediate Loading type = 1 (2%)	**Postoperative infection:** Inflammation, pain, heat fever and discharge. **Implant survival:** Measured by testing the stability of the implants with Osstell (Ostell, Göteborg, Sweden) Implant failure was defined as an implant loss	**Test Group:** Postoperative infections: 6/52 Implant failures: 2/52 LTF: 0 **Control Group:** Postoperative infections: 6/53 Implant failures: 2/53 LTF: 1	3 months after implant placement	NR
Esposito et al., 2010, Italy	Parallel-group RCT	Computer generated restricted randomization list	Triple-blinded	2 g AMX orally (two tablets of 1 g) 1 h prior to implant placement	2 identical placebo tablets 1 h prior to implant placement	CLX mouthwash 0.2%for 1 min prior to implant placement and CLX mouthwash 0.2% for 1 min twice a day for at least 1 week postoperatively	n = 252 Female = 138 (54.8%) MA (range) = 49.1 (18–85) Non-smokers = 171 (67.9%) Smoking up to 10 cigarettes/day = 55 (21.8%)	n = 254 Female 132 (52.0%) MA (range) 47.6 (18–86) Non-smokers 166 (65.4%) Smoking up to 10 cigarettes/day 60 (23.6%) Smoking more than 10 cigarettes/day 28 (11%)	**Postoperative infection:** Suppuration, fistula, abscess. **Implant failures:** Implant Mobility measured and/or any infection	**Test group:** Implant failures: 7/489 Patients who had implant failures: 5/252 Patients who had postoperative infections: 4/252 LTF: 0, Patients Excluded: 2	4 months after implant placement	No antibiotic adverse events were noted in any group

							Smoking more than 10 cigarettes/day = 26 (10.3%) Duration (range) = 32 m (4–190) n implants = 489 Immediate Loading type = 60 Took postoperative antibiotics 2 (0.8%)	Duration (range) 31 m (5–180) Total number of implants 483 Immediate Loading type = 76 Took postoperative antibiotics 6 (2.4%)	dictating implant removal	**Control Group:** Implant failures: 13/483 Patients who had implant failures: 12/254 Patients who had postoperative infections: 8/254 LTF: 0, Excluded: 1		
Caiazzo et al., 2011, Italy	Parallel-group RCT	Computer-generated randomization lists	NR	**Group 1:** Single prophylactic antibiotic dose consisting of AMX 2 g 1 h before surgery **Group 2:** Preoperative and postoperative antibiotic treatment consisting of AMX 2 g 1 h before surgery and 1 g twice a day for 7 days following surgery **Group 3:** Postoperative antibiotic coverage consisting of AMX 1 g twice a day started after surgery and continued for 1 week after surgery	**Group 4:** No antibiotic treatment	Rinse with CLX gluconate 0.2% solution for 1 min before each procedure and twice daily for 15 days following surgery	**Group 1:** n = 25 Females: 12 Males: 13 MA = 52 n implants = 35 **Group 2:** n = 25 Females: 13 Males: 12 MA = 45 n implants = 36 **Group 3:** n = 25 Females: 18 Males: 7 MA = 42 n implants = 48	**Group 4:** n = 25 Females: 15 Males: 10 MA = 43 n implants = 29	**Postoperative infection:** Internal and external edema, internal and external erythema, pain, heat, and exudates. **Implant failure**: Mechanical implant removal because of lack of osteointegration	**Group 1:** Infections: 0/35 Implant failures: 0/35 Patients who had implant failures: 0/25 **Group 2:** Infections: 0/36 Implant failures: 0/36 Patients who had implant failures: 0/25 **Group 3:** Infections: 0/48 Implant failures: 0/48 Patients who had implant failures: 0/25 **Group 4:** Infections: 0/29 Implant failures: 2/29 Patients who had implant failures: 2/25 LTF = NR	3 months after implant placement	No antibiotic adverse events were noted in any group
El-Kholey, 2014, Saudi Arabia	Parallel-group RCT	Computer-generated list of random numbers	NR	**Group1:** single dose of 1 g oral AMX 1 h preoperatively, and no postoperative antibiotics **Group 2:** 1 g oral AMX 1 h preoperatively followed by postoperative oral AMX, 500 mg every 8 h for 3 days	*	0.12% CLX mouth wash for 1 min before the procedure and for 5 days postoperatively. Paracetamol 500 mg four times daily as needed.	**Group 1:** n = 40 Females = 4 Males = 16 MA (±SD) = 32.2 ± 7.7 Number implants maxilla = 23 Number implants mandible = 24 Total implants = 47 **Group 2:** n = 40 Females:26 Males:14 MA (±SD) = 30 ± 6.8 Implants maxilla = 20 Implants mandible = 23 n implants = 43	*	**Postoperative infection**: Swelling, pain, erythema, tenderness, or pus for- mation at the site of surgery **Successful osseointegration:** Good implant stability at 25 N cm with the absence of any clinical or radiographic sign of infection	**Group1:** Wound infections: 0/47 Implant failures: 0/47 Patients who had implant failures: 0/40 LTF = 0 **Group 2:** Wound infections: 0/43 Implant failures: 0/43 Patients who had implant failures: 0/40 LTF = 0	3 months after implant placement	NR
Nolan et al., 2014, Ireland	Parallel-group RCT	NR	Double-blinded	3 g AMX orally, 1 h prior to the surgery.	Placebo capsules (containing sugar) orally, 1 h prior to the surgery	0.2% CLX mouthrinse for at least 60 s prior to the surgery and 4–5 times daily for the first postoperative week	n = 27 Female = 16 Male = 11 <40 years old = 16 40-60 years old = 7 >60 years old = 4 Non smokers = 20 Smokers = 7	n = 28 Female = 20 Male = 8 <40 years old = 15 40-60 years old = 10 >60 years old = 3 Non smokers = 22 Smokers = 6	Osseointegration recorded by 2 independent examiners: Success = Immobile Failure = Mobile	**Test group:** Patients who had an implant failure = 0/27 Patients with infection = 0/27 **Control Group:** Number of patients who had an implant failure = 5/28 Number of patients with infection = 2/28 LTF = 16, Exclusions after randomization = 12	4 months after implant placement	NR Only VAS and bruising but no quantitative data.

(*continued on next page*)

Table 1 (*continued*)

Study, Year and Country	Type of study	Method of randomization	Blinding	Test material (which and dosage)	Control material	Co-treatment materials	Test group patients	Control group patients	Diagnostic criteria	Quantitative outcome measure & LTF	Follow up period	Adverse reactions
Tan et al., 2014	Parallel-group RCT	Randomization tables. Blocked randomization in blocks of eight, whereby at every block of eight enrollments, there were two subjects randomly assigned to one of the four intervention groups	Single-blinded	**Group 1:** 2 g of amoxycillin preoperatively, 1 h prior to conventional implant placement. **Group 2:** 2 g of AMX immediately postoperatively. **Group 3:** 2 g of amoxycillin preoperatively, 1 h prior to implant placement and 500 mg three times a day (8 hourly) on days 2 and 3	**Group 4:** 2 g of a placebo preoperatively, 1 h prior to implant placement without any antibiotics	Preoperation 0.2 % CLX rinse for 1 min	**Group 1 (PC)** n = 81 Female = 49.4% Male = 50.6% MA = 48.8 Non-smoker 81.5% Smoker 18.5% **Group 2(T1)** n = 82 Female = 42.7% Male = 57.3% MA = 47.8 Non-smoker 80.5% Smoker 19.5% **Group 3 (T2)** n = 86 Female = 45.3% Male = 54.7% MA = 46.9 Non-smoker 80.2% Smoker 19.8%	**Group 4 (NC)** n = 80 Female = 44.7% Male = 55.3% MA = 45.1 Non-smoker 80.0% Smoker 20% Alveolar Bone Width B-L (Mean, mm): 7.91 Alveolar Bone Width M-D (Mean, mm) 11.33	**Postoperative infection:** Suppuration **Implant failure:** Unstable implant that was lost	**Group 1: I**mplant failures: 0/81 Patients with implant failures: 0/81 Patients with postoperative infections: 2/81 **Group 2:** Implant failures: 0/82 Patients with implant failures: 0/82 Patients with postoperative infections: 0/82 **Group 3:** Implant failures: 0/86 Patients with implant failures: 0/86 Patients with postoperative infections: 2/86 **Group 4:** Implant failures: 1/80 Patients with implant failures: 1/80 Patients with postoperative infections: 0/80 LTF: NR for any group	2 months after implant placement	No statistically significant difference between the 4 treatment groups for bleeding, swelling, pain, and bruising. Other adverse events NR.
Arduino et al., 2015, Italy	Parallel-group RCT	Two computer-generated randomization lists	Double-blinded	**Group1:** 2 g of AMX orally (2 tablets of 1 g) 1 h prior to surgery **Group 2:** 2 g of AMX orally (2 tablets of 1 g) 1 h prior to surgery and 1 g the evening of the day of surgery and 1 g twice a day for 2 days following surgery	*	Rinse with 0.2% CLX 1 min immediately prior to surgery	**Group 1:** n = 180 MA (SD) = 49.3 (13.9) Female = 101 Male = 79 Smokers = 57 (31.7%) Mandibular Implants = 202 Maxillary implants = 76 Number of implants = 278 **Group 2:** n = 180 MA (SD) = 51.6 (14.4) Female = 88 Male = 92 Smokers = 37 (20.6%) Mandibular Implants = 173 Maxillary implants = 116 Number of implants = 289	*	**Implant failure:** Implant mobility or implant removal due to pain or infection **Postoperative infection:** Suppuration, fistula, abscess	**Group 1:** Implant failures: 5/244 Patients with implant failures: 5/166 (3%) Patients with postoperative infections: 2/166 LTF: 9 Lost all data = 5 Patients excluded from analysis = 14 **Group 2:** Implant failures: 8/285 Patients with implant failures: 5/177 (2.8%) Patients with postoperative infections: 2/177 LTF: 1 Lost all data = 2 Patients Excluded = 3	10 months after implant placement	**Group1:** No adverse events **Group 2:** 3 adverse events: 2 men with abdominal swelling, 1 female with skin rash and laryngeal edema with a severe reaction requiring discontinuation of therapy and temporary hospital admission. No statistically significant differences between both groups

AMX: Amoxicillin; CLX: Chlorhexidine; N: Newton's, n: population; RCT: Randomized Controlled Trial; n: sample size; MA: mean age; SD: standard derivation; NR: Not reported; LTF: Lost to follow-up. *Indicates studies whose data have been imputated from the calculated control group.

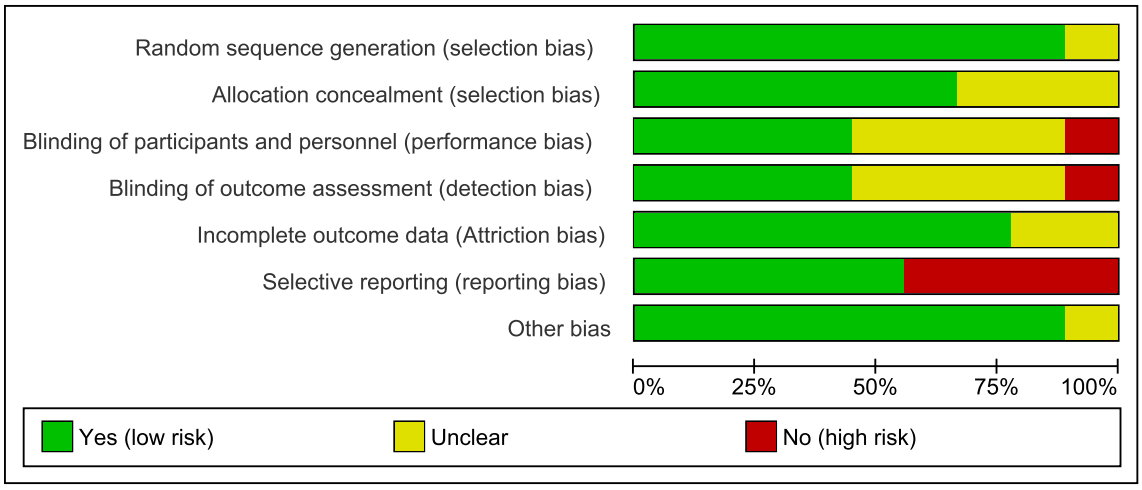


Fig. 2. Risk of bias graph.

of bias summary (Fig. 3) were generated using Review Manager 5.3 (The Cochrane Collaboration, 2014). Quantitative and qualitative data were collected on losses to follow-up, the randomization process, blinding and other factors that could be potential sources of bias (Table 1).

2.9. Summary measure

The efficacy of the treatment was assessed using Risk Ratio (RR) (Fig. 4). The effectiveness of the treatment with antibiotics was assessed using the number needed to treat (NNT). The overall NNTs adjusted for the weight of each study for all analyses were estimated.

2.10. Synthesis of results

All analyses were carried out using STATA 14 (StataCorp LP, College Station, TX) (Sterne, 2009). The authors assessed the heterogeneity among different studies using the I^2 statistic, and graphically with the l'Abbé plots (Fig. 5). The overall RR, resulting from combining different studies, was calculated with a fixed-effects model with weights calculated using the Mantel–Haenszel method (Delgado, 2015).

2.11. Risk of bias across the studies

Publication bias was assessed graphically using funnel plots (Fig. 6).

The quality of the evidence was assessed with the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system, considering each outcome variable independently (Tables 2 and 3). GRADE was developed for rating the quality of evidence and strength of recommendations (Guyatt et al., 2008, 2011).

3. Results

3.1. Study selection

Overall, 9 articles published since 2008 were included in this meta-analysis. Fig. 1 presents a flow diagram of the study selection process with a list of the excluded studies and the reasons for their exclusion.

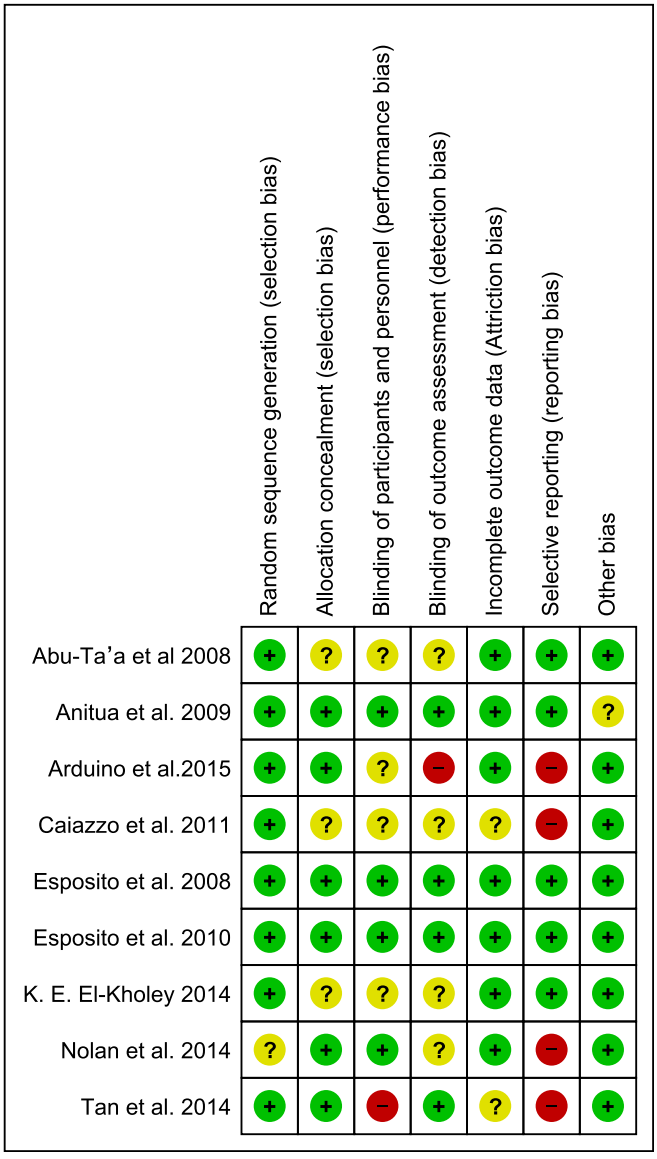
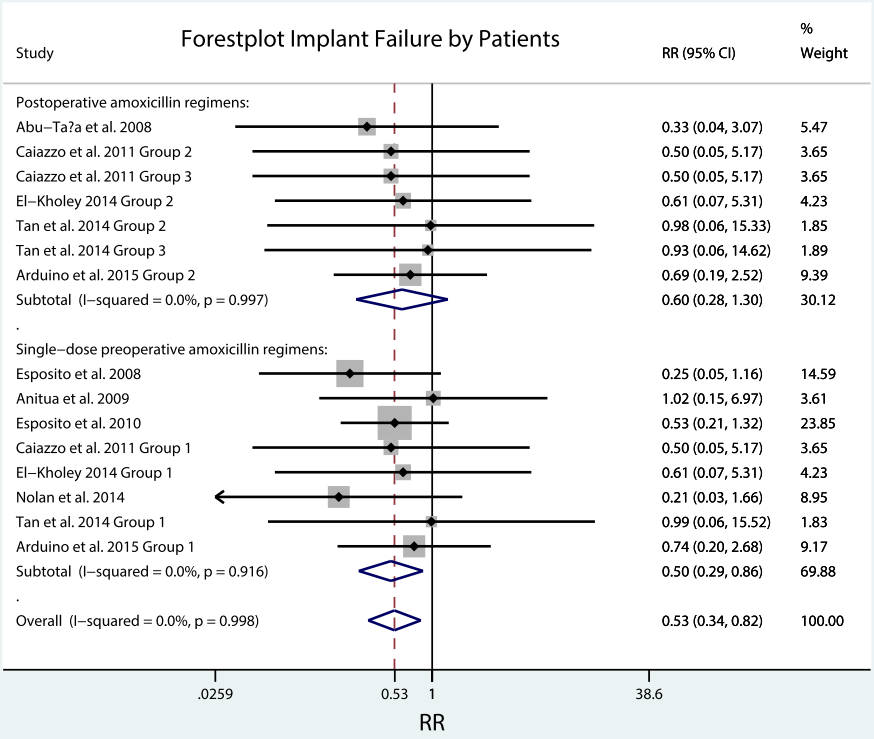
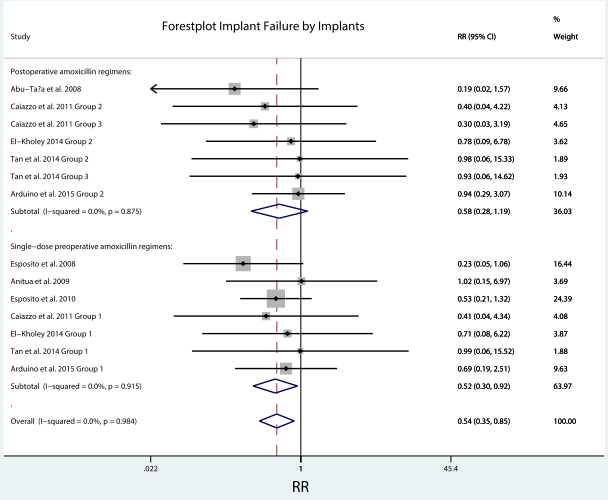


Fig. 3. Risk of bias summary.





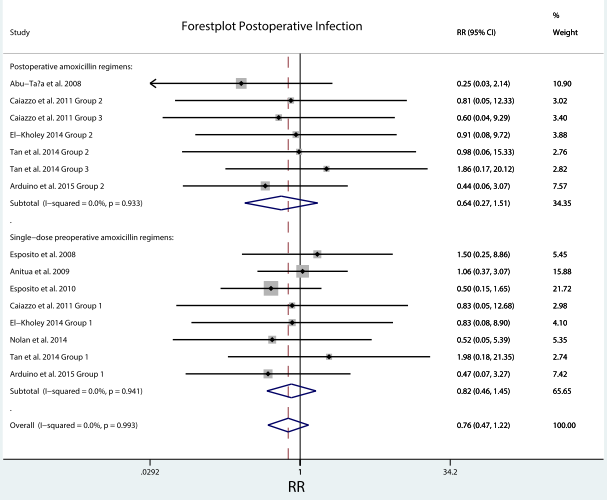


Fig. 4. Combined Forest plots. RR: Risk Ratio, CI: Confidence Interval.

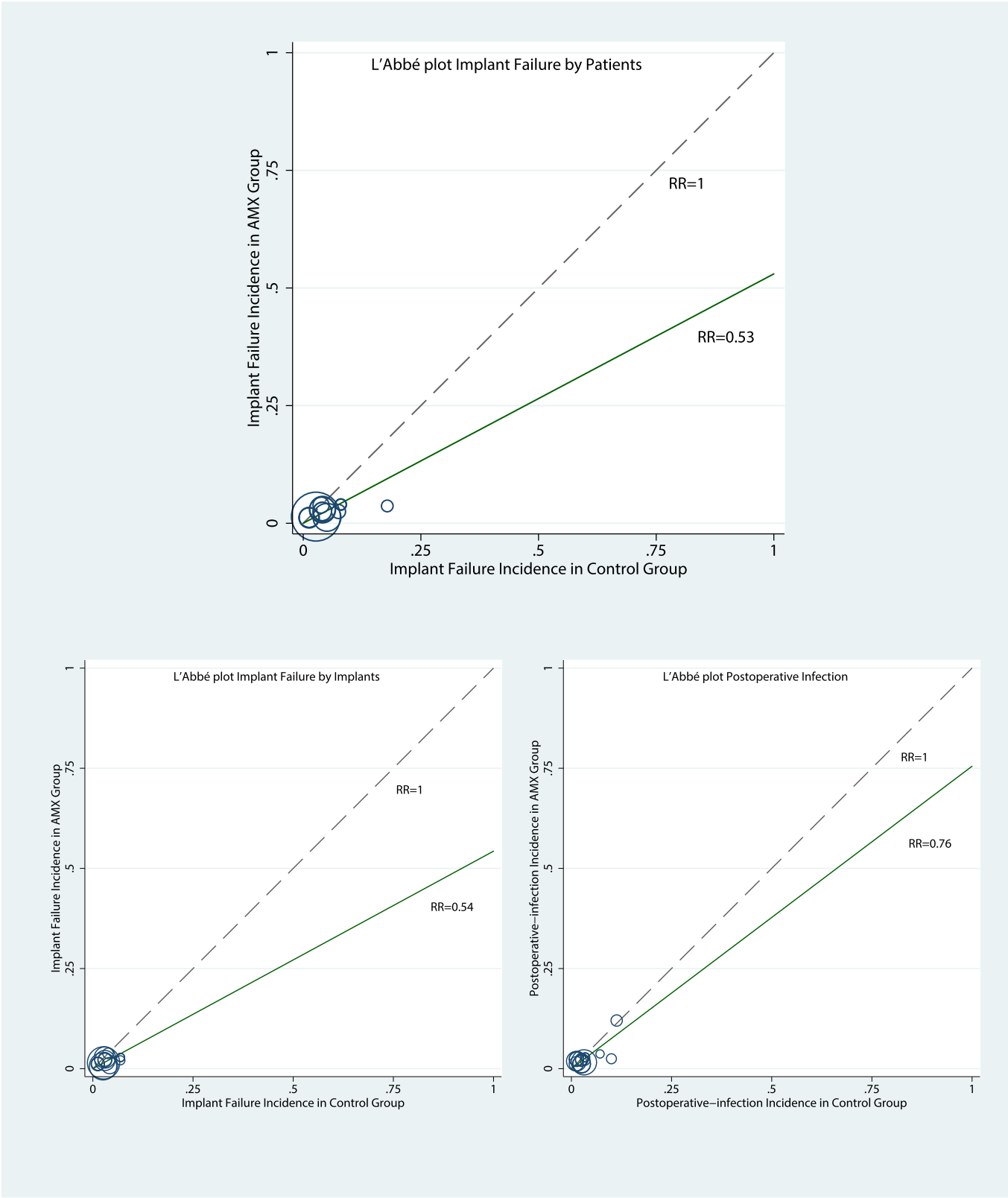


Fig. 5. Combined l'Abbé plots. RR: Risk Ratio; AMX: amoxicillin.

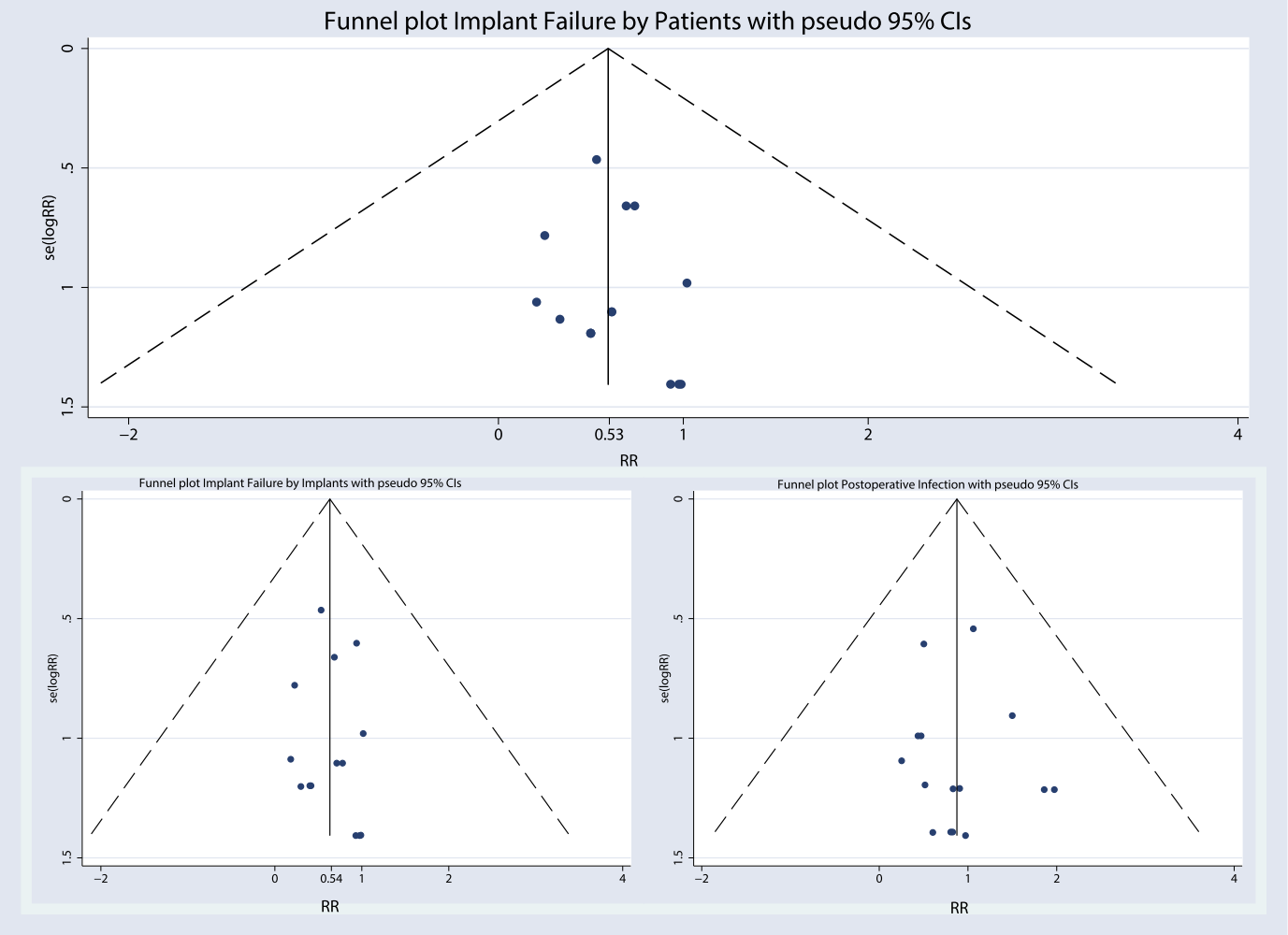


Fig. 6. Combined funnel plots. RR: Risk Ratio, CI: Confidence Interval.

The final analyses, by the number of patients who had an implant failure and by the number of postoperative infections, were performed on 15 RCTs corresponding to 9 articles (Abu-Ta'a et al., 2008; Esposito et al., 2008, 2010; Anitua et al., 2009; Caiazzo et al., 2011; Nolan et al., 2014; Tan et al., 2014; Arduino et al., 2015).

Furthermore, 14 RCTs corresponding to 8 articles were finally included in the meta-analysis by the number of implant failures (Abu-Ta'a et al., 2008; Esposito et al., 2008, 2010; Anitua et al., 2009; Caiazzo et al., 2011; Nolan et al., 2014; Tan et al., 2014).

3.2. Study characteristics

In the studies reviewed, only one antibiotic type was assessed: amoxicillin. It is used in various dosages and therapeutic regimens. Preoperative regimens were as follows: single dose of 1 g (Abu-Ta'a et al., 2008; El-Kholey, 2014), 2 g (Esposito et al., 2008, 2010; Caiazzo et al., 2011; Nolan et al., 2014; Tan et al., 2014; Arduino et al., 2015), or 3 g 1 h before surgery (Nolan et al., 2014). Postoperative regimens were as follows: 2 g immediately after the surgery (Tan et al., 2014), 1 g two/three times a day for one week (Caiazzo et al., 2011) or for two days after implant placement (Arduino et al., 2015), and 500 mg three times a day for two (Abu-Ta'a et al., 2008) or three days after surgery (El-Kholey, 2014; Tan et al., 2014). Several studies combined preoperative and postoperative antibiotics (Abu-Ta'a et al., 2008; Caiazzo et al., 2011; El-Kholey, 2014; Tan et al., 2014; Arduino et al., 2015).

Table 1 presents the main characteristics of the 9 RCTs included in the meta-analysis.

3.3. Risk of bias within the studies

The risk of bias graph (Fig. 2) illustrates the proportion of studies with each of the judgments (*Low risk, High risk, Unclear* risk of bias). The risk of bias summary (Fig. 3) presents all of the judgments in a cross-tabulation of study by entry.

The RCT carried out by Anitua et al. (2009) might present a possible risk of information bias, as the Biotechnology Institute (BTI®, Vitoria, Spain) provided funding and controlled the analysis and results of the trial.

3.4. Results of individual studies

The forest plots presented in Fig. 4 are graphical representations of the estimates of the RR and 95% confidence intervals (CIs) obtained using the samples from each of the studies. The area of gray squares around the RR is proportional to the weight of the study in the analysis. CIs, indicated by a continuous horizontal line that crosses the vertical line at a RR equal to 1, correspond to studies with non-significant results. The graph also indicates the overall RR based on all the studies with a rhombus and a dotted line.

Table 2
Evidence table.

Quality assessment						Summary of findings				
No. of participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							Control Group (without AMX)	Treatment Group (with AMX)		Risk without antibiotics	Risk difference with antibiotics
Implant failure by patients (follow up: median 4 months)											
2982 (15 RCTs)	not serious	not serious	not serious	serious[a]	none	⊕⊕⊕◯ MODERATE	56/1469 (3.8%)	31/1513 (2.0%)	Overall RR 0.53 (0.34–0.82)	38 per 1,000	18 fewer per 1,000 (25 fewer to 7 fewer)
Implant failure by dental implants (follow up: median 4 months)											
3870 (14 RCTs)	not serious	not serious	not serious	serious[b]	none	⊕⊕⊕◯ MODERATE	54/1873 (2.9%)	33/1997 (1.7%)	Overall RR 0.54 (0.35–0.85)	29 per 1,000	13 fewer per 1,000 (19 fewer to 4 fewer)
Postoperative infection (follow up: median 4 months)											
2500 (15 RCTs)	not serious	not serious	not serious	very serious[c,d,e]	none	⊕⊕◯◯ LOW	36/1172 (3.1%)	29/1328 (2.2%)	Overall RR 0.76 (0.47–1.22)	31 per 1,000	7 fewer per 1,000 (16 fewer to 7 more)

CI: Confidence interval; RR: Risk ratio; RCT: Randomize controlled Clinical Trial; AMX: Amoxicillin.
Explanations.
[a] Less than 300–400 events (patients who had an implant failure).
[b] Less than 300–400 events (implant failures).
[c] The 95% CIs include null effect but they also include benefit.
[d] The lower 95% CI (0.47) < 0.75.
[e] Less than 300–400 events (patients who suffered a postoperative infection).

Table 3
Quality of evidence grades.

Grade	Definition
High	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very Low	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

3.5. Synthesis of results

3.5.1. Implant failure analysis by patients

A single dose of oral amoxicillin preoperatively (SDOAP) before implant surgery was found to significantly ($P = .012$) prevent patients from developing dental implant failures (RR = 0.50, CI: 0.29–0.86), while the postoperative use of oral amoxicillin (exclusively postoperative and adjunct with preoperative amoxicillin) did not significantly ($P = .197$) achieve a prophylactic effect (RR = 0.60, CI: 0.28–1.30).

The overall RR from the analysis carried out by the number of patients who had an implant failure was 0.53 (95% CI, of 0.34–0.82), which is significantly different from 1 ($P = .005$).

The overall NNT estimated for the analysis carried out by the number of patients who had an implant failure was 55. Considering the 95% CI, 33 to 167 patients would need to be treated with amoxicillin to prevent just 1 patient from suffering an implant failure. The NNT for SDOAP was 67 (95% CI, of 26–125), and the NNT for the postoperative use of oral amoxicillin was 53 (95% CI, of 30–200).

3.5.2. Implant failure analysis by implants

SDOAP before implant surgery was found to be significantly ($P = .024$) effective at preventing dental implant failures (RR = 0.52, CI: 0.30–0.92). However, the postoperative use of oral amoxicillin (exclusively postoperative and adjunct with preoperative amoxicillin) was not found to significantly ($P = .137$) prevent dental implant failures (RR = 0.58, CI: 0.28–1.19).

The overall RR from the analysis performed by the number of implant failures was 0.54 (95% CI, of 0.35–0.85), which is also significantly different from 1 ($P = .007$).

The overall NNT from the analysis by the number of implant failures was estimated to be 77. If its 95% CI is also considered, 43 to 250 dental implants would need to be treated with amoxicillin to prevent 1 implant failure. The NNT for SDOAP was 77 (95% CI, of 32–250), and the NNT for the postoperative use of oral amoxicillin was also 77 (95% CI, of 42–500).

3.5.3. Postoperative infection analysis

Neither postoperative oral amoxicillin (RR = 0.64, CI 0.27–1.51) nor SDOAP (RR = 0.82, CI: 0.46–1.45) was found to significantly ($P = .309$ and $P = .488$, respectively) prevent postoperative infections after dental implant surgery.

The overall RR from the analysis carried out by the number of postoperative infections was 0.76 (95% CI, of 0.47–1.22), which is not significantly different from 1 ($P = .250$).

The overall NNT calculated for the analysis performed by the number of patients who had postoperative infection was 143. The 95% CI reveals that 50 to 200 patients would need to be treated with amoxicillin to prevent just 1 case of postoperative infection. The

NNT for SDOAP was 100 (95% CI, of 32–100), and the NNT for the postoperative use of oral amoxicillin was 143 (95% CI, of 50–200).

3.5.4. Heterogeneity analysis

The heterogeneity, as indicated by the I^2 statistic, was 0.0 for the 3 analyses, as the *P* values were next to 1. This fact provides sufficient evidence to accept the null hypothesis of a lack of heterogeneity among the results of the studies included in this meta-analysis. In the l'Abbé plots (Fig. 5), each circle corresponds to each study included in the analyses, with the area of the circle being proportional to the weight of the study. In the graphics, the authors did not observe any relevant pattern of heterogeneity, with all the circles being grouped in the same region, regardless of their size and baseline risk.

3.5.5. Adverse reactions

The study conducted by Esposito et al. (2008) reported 1 adverse event that occurred in the placebo group (itching for 1 day) and 1 in the antibiotic group (diarrhea and somnolence), but the difference was not significant ($P = 1$). The research performed by Arduino et al. (2015) reported no adverse events in group 1. However, in group 2, two men (aged 53 and 73) reported abdominal swelling with bloating and heartburn and 1 female patient (aged 78) reported skin rash and laryngeal edema. This patient, who did not report in the anamnesis any possible allergy to any type of antibiotic, experienced a profoundly severe reaction requiring discontinuation of therapy and temporary hospital admission. The authors found no significant differences between the two groups.

No adverse reactions to amoxicillin were reported in the 3 included articles (Abu-Ta'a et al., 2008; Esposito et al., 2010; Caiazzo et al., 2011), and there is no information on adverse reactions to amoxicillin in 4 of the included articles (Anitua et al., 2009; El-Kholey, 2014; Nolan et al., 2014; Tan et al., 2014).

3.6. Risk of bias across the studies

The funnel plots (Fig. 6) suggest a lack of publication bias considering the symmetrical dispersion of the points in reference to a RR equal to 0.53, 0.54 and 0.74, respectively.

The results of the quality of the evidence (GRADE) analysis are presented in Table 2.

4. Discussion

4.1. Summary of evidence

This systematic review and meta-analysis suggests that the use of SDOAP might be the only beneficial regimen for preventing dental implant failures after a dental implant placement. The use of postoperative oral amoxicillin regimens might not significantly prevent dental implant failures or postoperative infections after dental implant surgeries. For this reason, the use of postoperative amoxicillin orally might not add any benefits to SDOAP and may be considered overtreatment.

The effectiveness analysis suggests that 67 patients would need to be treated with a SDOAP to prevent 1 patient from suffering an implant loss. Additionally, the effectiveness analysis also suggests that 77 dental implants would need to be treated with preoperative amoxicillin orally to prevent 1 implant failure. This might result in a slight reduction of almost 1.30% in the risk for implant failure.

Unfortunately, there is still no consensus on the use of antibiotics in healthy patients in order to prevent dental implant failures and complications or which prophylactic regimen should be used. Several of the last published reviews and meta-analyses are chronologically listed below.

The systematic literature review conducted by Ahmad (2012) found no significant difference between the success rate of implants with and without the use of antibiotics. Implants performed with the use of antibiotics had a success rate of 96.5%, while surgeries performed without antibiotics had a slightly lower success rate of 92%. This review concluded that there is no clear evidence pointing to the need for prophylaxis antibiotics in conjunction with dental implant surgery.

The Cochrane systematic review and meta-analysis conducted by Esposito et al. (2013) included 6 RCTs and suggested that short-term antibiotics, e.g., 2 g or 3 g of amoxicillin administered 1 h prior to implant placement or 1 g of amoxicillin administered 1 h prior to implant placement and 500 mg four times a day for two days postoperatively, significantly decrease early implant failures in ordinary conditions (RR = 0.33; 95%CI 0.16 to 0.67). The use of antibiotics in this way would prevent one person from experiencing an early implant loss for every 25 people receiving antibiotics. There were no significant differences for any of the other outcomes: infections (RR 0.69; 95% CI 0.36 to 1.35) or adverse events (RR = 1; 95% CI 0.06 to 15.85). However, it remained unclear whether an adjunct use of postoperative antibiotics is beneficial and which antibiotic is the most effective.

The systematic review and meta-analysis performed by Ata-Ali et al. (2014) included 4 RCTs, and the results showed that antibiotic treatment significantly reduced the risk of implant failure (OR = 0.331, 95% CI 0.157–0.696) (P = 0.003, QA = 8.49). The NNT to prevent one patient from having an implant failure was 48 (95% CI 31–109). The result of the X^2 test applied to the four included RCTs showed antibiotic administration not to be associated with a decrease in the incidence of postoperative infection (OR = 1.091, 95% CI 0.629–1.893), and this result failed to reach significance (P = 0.754, QA = 8.49) (Ata-Ali et al., 2014).

The systematic review and meta-analysis conducted by Chrcanovic et al. (2014) included 6 RCTs rated as low risk of bias assessing the event "implant failure" and 7 RCTs rated as low risk of bias assessing the postoperative infections. The results showed that the difference between the procedures (use versus non-use of antibiotics) significantly reduced (P = 0.003) the implant failure rates in ordinary conditions (RR = 0.37, 95% CI 0.19–0.72). On the other hand, the meta-analysis showed that there were no apparent significant effects of prophylactic antibiotics on the occurrence of post-operative infections in healthy patients receiving implants (RR = 0.72, 95% CI 0.38–1.39; P = 0.66). The overall NNT to prevent one patient from having an implant failure was 50 (95% CI 33–100).

The complex systematic review and meta-analysis carried out by Lund et al. (2015) showed that preoperative antibiotic prophylaxis reduced the risk of implant loss (pooled RR 0.39, 95% CI 0.18–0.84; P = 0.02) (pooled RD 0.02, 95% CI 0.04–0.00; P = 0.02). A risk difference of 2% yielded an NNT of 50 to prevent one patient from experiencing implant loss. They concluded that preoperative antibiotics give a modest reduction of 2% for the risk for implant loss, and the results suggested that there was no benefit of antibiotic prophylaxis in uncomplicated implant surgery in healthy patients, while a beneficial effect in complicated cases could not be excluded.

The systematic review implemented by Surapaneni et al. (2016) concluded that prophylactic antibiotics for each implant surgery are not mandatory but that antibiotics are, however, useful in preventing postoperative infections after implant placement and that antibiotic prophylaxis is required to achieve high long-term survival and success rates of dental implants.

The systematic review reported by Park et al. (2017) concluded that the routine use of systemic antibiotics to accompany dental implant placement in healthy patients is not supported. It also suggested that antibiotic use at the time of surgery does not appear to play a major

role in influencing the early incidence of prosthesis failure, implant failure, adverse events or postoperative complications.

The last published systematic reviews and meta-analyses differ in their results. The variation among their conclusions is related to their inclusion criteria, the RCTs available on that date and the outcome variable analyzed. This systematic review and meta-analysis presented similar results, compared to past meta-analyses, associated with the efficacy of preoperative oral amoxicillin for preventing dental implant failures but not postoperative infections. Nevertheless, the present study is the first publication achieving conclusive results over the inefficacy and ineffectiveness of postoperative regimens using oral amoxicillin.

4.2. Limitations

In spite of the fact that the objective of this systematic review and meta-analysis was to assess the effect of overall antibiotics preventing dental implant failures and post-operative infections, only 1 antibiotic type could be assessed. For this reason, the results can only be applied to the use of amoxicillin.

The effect of perioperative amoxicillin should be considered cautiously, due to the imprecision (wide range in the confidence intervals) of statistical analysis results. Moreover, none of the studies included in this meta-analysis showed, on its own, significant benefits of perioperative amoxicillin in the prevention of dental implant failures and postoperative infections, neither considering implants as the experimental unit in the analysis nor considering patients as the experimental unit.

This meta-analysis presented no statistical or graphical heterogeneity among the included studies. However, there are some differences to be considered in the study design, implant placement procedure (flapless, immediate implants, conventional approach, etc.), implant system, type, brand, diameter, length, healing period (immediate, early or conventional loading) and type of restoration among the included studies.

The main differences in the study design are related to the duration of the follow-up period, the antibiotic dose, the antibiotic regimen, and the 2 studies that included only patients who underwent a single implant placement (Anitua et al., 2009; Tan et al., 2014). These 2 studies also included a lower proportion of smokers than the other studies. No great differences were found in relation to the criteria used in the definition of dental implant failure and postoperative infection cases.

In the US only, 3 million people have dental implants, and that number is increasing by 500,000 a year. Additionally, 10 percent of all US dentists place implants, but this is also increasing and the estimated US and European market for dental implants is expected to reach $4.2 billion by 2022 (Hee-Won et al., 2011).

Establishing a protocol for the prophylaxis of dental implant failures and postoperative infections in ordinary conditions and healthy patients has great clinical and economic importance because of the cost for antibiotic prophylaxis in dental practice and the increasing antibiotic prescription frequency of dental practitioners (Lockhart et al., 2013; Marra et al., 2016).

For these reasons, and due to the development of adverse reactions and bacterial resistance (including at the peri-implant sulcus), the use of antibiotics should be measured carefully (Moslemi et al., 2016; Resnik and Misch, 2008; Surapaneni et al., 2016). The risk–benefit equation associated with the use of prophylactic antibiotics should be seriously considered, as the use of preoperative amoxicillin may prevent a moderate percentage of implant failures (approximately 1.30%, data yielded from the NNT).

5. Conclusion

A single preoperative dose of 1 g, 2 g, or 3 g of oral amoxicillin may be efficacious and effective at preventing dental implant failures, while postoperative oral amoxicillin (exclusively postoperative and adjunct with preoperative oral amoxicillin) might not be beneficial in the prophylaxis of dental implant failures in conjunction with dental implant surgery among healthy patients and in ordinary conditions.

However, there is not enough evidence to support the use of perioperative amoxicillin orally in order to prevent the development of postoperative infections.

New clinical trials comparing the efficacy of different antibiotic types, preoperative dosages and regimens are needed to improve clinical application guidelines in preventing dental implant failures and postoperative infections.

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Antibiotic prophylaxis habits in dental implant surgery among dentists in Spain. A cross-sectional survey

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Abstract

Background: The use of antibiotics to prevent dental implant failures and postoperative infections remains a controversial issue. The objectives of this study were to assess the current antibiotic prescribing patterns and antibiotic prescribing frequency of dentists in Biscay (Spain) in conjunction with routine dental implant surgery among healthy patients and to determine whether any consensus has been reached by such practitioners and last published evidence was being followed.

Material and Methods: Observational cross-sectional study: electronic survey. This study was reported according to the STROBE guidelines. This anonymous questionnaire contained open-ended and close-ended questions. An email was sent 26 October 2017 to all the registered members of the Biscay dentists' College (n=989). The collected data were analyzed using STATA® 14 software, and 95% confidence intervals (CI) were used to assess the frequency of prescription for each antibiotic regimen.

Results: The survey was responded to by a total of 233 participants (response rate=23.56%). Overall, 210 participants finished the survey completely, and 23 surveys were answered partially. The questionnaire was responded to by 122 females (58.1%) and 88 males (41.9%). Of the participants, 88% (n=207) always routinely prescribed prophylactic antibiotics in conjunction with dental implant surgery (95% CI: 84.79-92.88%). Approximately 9% (n=22) prescribed antibiotics sometimes (95% CI: 5.68-13.19%), and only 4 dentists (1.72%) never prescribed antibiotics (95% CI: 0.04-3.38%). Overall, 179 of 233 respondents prescribed both pre- and postoperative antibiotics (78.85%, 95% CI: 72.96-83.97%), 13 prescribed antibiotics only preoperatively (5.73%, 95% CI: 3.08-9.59%), and 35 prescribed antibiotics exclusively after routine dental implant surgery (15.42%, 95% CI: 10.98-20.78%).

Conclusions: Most of the dentists working in Biscay routinely prescribe prophylactic antibiotics in conjunction with dental implant surgery among healthy patients. A large range of prophylactic regimens are prescribed and the most recently published evidence is not being followed.

Key words: *Clinical decision making, epidemiology, infection control, dental implants, antibiotics.*

Introduction

Dental implant placement is a routine surgery to replace a lost tooth (1). Despite the fact that dental implants routinely have a high rate of success, dental implant failures occur (2). Bacterial contamination at implant placement might be one of the causes of postoperative infections and early implant failures (3). Infected implants usually have to be removed, and this complication is highly undesirable, both for patients and professionals. For this reason, several prophylactic methods, such as antibiotics, have been used (4).

Nevertheless, the use of antibiotics to prevent dental implant failures and postoperative infections remains a controversial issue (5-7) Unfortunately, there is no consensus among oral health professionals over the use and indications of prophylactic antibiotics in conjunction with dental implant surgeries (8-12).

The use of antibiotics has been the subject of special monitoring since the beginning of the project called European Surveillance of Antimicrobial Consumption (ESAC) in 2001 (13). Spain is actively involved in this project through the Spanish Agency of Medicines and Medical Devices (AEMPS). The latest consumer data on human health, reported in 2016, described Spain as the country with the highest consumption of antibiotics in primary care among the European Union. This high use of antibiotics is also related to a high rate of bacterial resistance. To improve these data, the Spanish Government and the different communities from the Interterritorial Council of the National Health System developed the Spanish Antimicrobial Stewardship Program in Primary Care (PROA) (14). After the implementation of these programs in the hospital, reducing the consumption of antibiotics for 2017-2018 was established as one of the priority objectives. Moreover, a recent review on the antimicrobial prophylaxis in dentistry concluded that antibiotic prophylaxis in healthy patients, for minor oral surgeries, third molar surgeries, implant placement and periodontal surgeries, is not necessary (15).

The use of antibiotics is not indicated in all oral infections, and preventive antibiotics are frequently prescribed to healthy patients (12). The prophylactic use of antibiotics in conjunction with dental implant surgery may be one of these situations (7).

As a result of the present condition, many questions remain, and we asked ourselves what dentists actually do in our province, Biscay: Do they prescribe antibiotics in conjunction with a dental implant surgery? When? Are they following any kind of guidelines? For this reason, we decided to carry out a survey aimed at the total population of registered dentists in Biscay (members of the Colegio Oficial de Dentistas de Bizkaia), a province of the Basque Country in Spain.

The objective of this study is to assess the current antibiotic prescribing frequency and the antibiotic prescribing patterns of dentists in Biscay in conjunction with routine dental implant surgery among healthy patients to determine whether any consensus has been reached by such practitioners and last published evidence is being followed.

Material and Methods

This observational cross-sectional study was based on an electronic survey approved by the research institute BioCruces (Barakaldo, Biscay). This study was reported according to the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) guidelines (16). Due to the anonymous cross-sectional nature of this study and as it was aimed to professionals instead of real patients, it was granted an exemption in writing by the University of the Basque Country Institutional Review Board (IRB).

-Study Design

A validated questionnaire was prepared to collect information regarding the prescribing patterns of preventive antibiotics among dentists in conjunction with dental implant surgery. The questionnaire followed by Deeb *et al*. was used as a basis, with the explicit permission of the authors (12). The questionnaire has proved its validity, as the different items of the test were found adequate to measure the intended objectives. This anonymous questionnaire comprised data in relation to the following: demographic details, qualification and work experience, most common antibiotic prescribed, duration and dosage. The questionnaire contained both open-ended and close-ended questions (Table 1, 1 continue, 1 continue-1).

-Setting

Biscay is a province of Spain located in the Basque Country. Its population was approximately 1,148,302 inhabitants in 2017. An email was sent on 26 October 2017 to dentists including a link to the web questionnaire developed on www.encuestafacil.com. This email also contained instructions to answer the questionnaire if dentists performed dental implant surgeries and a message briefly describing the objectives of the study and the intended use of the collected data for research and epidemiological purposes. It was emphasized that the data were anonymized. A reminder was forwarded on 8 November 2017 to participants who had not responded within the deadline. The online questionnaire was closed to the public on 2 January 2018. Data collection was carried out automatically via the www.encuestafacil.com server.

-Participants

The questionnaire was sent to all the registered members of the Biscay dentists' College who had not expressly requested not to receive emails. The total number of sent questionnaires was 989. When addressing the entire population of registered dentists of Biscay,

Table 1: Survey outcome variables: n: Frequency, CI: Confidece Interval, *: respondents could choose more than one option (multianswer).

Question	n	%	95% CI
BEGINNING OF THE SURVEY			
1. Do you prescribe antibiotics before, after or during a dental implant placement?			
Yes, always	207	88.84	84.79-92.88
Yes, sometimes	22	9.44	5.68-13.19
No, never	4	1.72	0.04-3.38
Total	233	100	-
2. Your answer was "Yes, sometimes". Describe the situations when you prescribe antibiotics.			
Bone grafting	9	40.9	*
Patient with a past of periodontal disease	7	31.81	
Patient smokes	3	13.63	
Preoperative implant-site infection	14	63.63	
Sinus perforation	13	59.09	
Simultaneous placement of more than one dental implant	7	31.81	
Cardiopathy requiring antibiotic prophylaxis	5	22.72	
Other situation	5	22.72	
Total	*		
TEMPORARY ANTIBIOTIC PRESCRIPTION PATTERN Continue with the following questions, assuming that patients are healthy and have no antibiotic allergies when selecting your responses. Choose the most proper answer according to reality.			
3. When do you prescribe antibiotics?			
Exclusively before surgery (Pre-operative)	13	5.73	3.08-9.59
Exclusively after surgery (Post-operative)	35	15.42	10.98-20.78
Before and after surgery (Pre-operative and Post-operative)	179	78.85	72.96-83.97
Total	227	100	-
PRE-OPERATIVE PRESCRIPTION HABITS			
4. When does the antibiotic prophylaxis begin prior to implant insertion?			
1 day prior	87	47.28	39.89-54.76
1 hour prior	47	25.54	19.41-32.48
2 days prior	43	23.37	17.45-30.15
Immediately prior	7	3.80	1.54-7.68
Total	184	100	-
5. You have selected "1 or 2 days prior", select from the following a single antibiotic type:			
Amoxicillin	87	66.41	57.64-74.42
Amoxicillin/Clavulanic acid	37	28.24	20.72-36.77
Other	6	4.58	1.69-9.70
Erythromycin	1	0.76	0.01-4.17
Clindamycin	0	0	-
Penicillin V	0	0	-
Cephalexin	0	0	-
Total	131	100	-
6. Select from the following, the dose, dosage and administration route ("1 or 2 days prior"):			
6.1. Dose (mg)			
500	53	42.06	33.32-51.18
875/125	25	19.84	13.27-27.88
800	20	15.87	9.97-23.44
1000	19	15.08	9.32-22.54
500/125	9	7.14	3.31-13.12
150	0	0	-
250	0	0	-
300	0	0	-
400	0	0	-
Total	126	100	-
6.2. Dosage			
3 times daily	113	90.4	83.83-94.94
2 times daily	9	7.2	3.34-13.22
1 time daily	2	1.6	0.19-5.66

Table 1 continue: Survey outcome variables: n: Frequency, CI: Confidece Interval, *: respondents could choose more than one option (multianswer).

4 times daily	1	0.8	0.02-4.37
Total	125	100	-
6.3. Administration route			
Oral	125	100	97.09-1
Intramuscular	0	0	-
Intravenous	0	0	-
7. You have selected "1 hour prior" or "Immediately prior", select from the following a single type of antibiotic:			
Amoxicillin	46	83.64	71.19-92.23
Amoxicillin/Clavulanic acid	8	14.55	6.49-26.66
Cefazolin	1	1.82	0.04-9.71
Clindamycin	0	0	-
Penicillin V	0	0	-
Erythromycin	0	0	-
Ampicillin	0	0	-
Cephalexin	0	0	-
Other	0	0	-
Total	55	100	-
8. Select from the following, the dose, dosage and administration route ("1 hour or Immediately prior"):			
8.1. Dose (mg)			
2000	22	40	27.02-54.09
1000	15	27.27	16.13-40.96
500	7	12.73	5.27-24.48
875/125	5	9.09	3.01-19.95
800	3	5.45	1.13-1.51
1600	1	1.82	0.04-9.71
500/125	1	1.82	0.04-9.71
600	1	1.82	0.04-9.71
Total	55	100	-
8.2. Dosage			
1 single dose	55	100	93.51-1
8.3. Administration route			
Oral	55	100	93.51-1
Intramuscular	0	0	-
Intravenous	0	0	-
POST-OPERATIVE PRESCRIPTION HABITS			
9. Select from the following a single antibiotic type prescribed after dental implant insertion:			
Amoxicillin	138	67.98	61.08-74.33
Amoxicillin/Clavulanic acid	59	29.06	22.91-35.83
Other	5	2.46	0.8-5.65
Erythromycin	1	0.49	0.01-2.71
Clindamycin	0	0	-
Penicillin V	0	0	-
Cephalexin	0	0	-
Total	203	100	-
10. Select from the following, the dose, dosage, administration route and treatment duration:			
10.1.Dose			
500	76	38.38	31.57-45.54
800	36	18.18	13.07-24.27
875/125	36	18.18	13.07-24.27
1000	33	16.67	11.75-22.60
500/125	17	8.59	5.08-13.39
150	0	0	-
250	0	0	-
300	0	0	-
400	0	0	-
Total	198	100	-
10.2.Dosage			
1 time daily	2	1.01	0.12-3.60
2 times daily	19	9.6	5.87-14.57
3 times daily	177	89.39	84.24-93.31

Table 1 continue-1: Survey outcome variables: n: Frequency, CI: Confidece Interval, *: respondents could choose more than one option (multianswer).

4 times daily	0	0	-
Total	198	100	-
10.3.Administration route			
Oral	198	100	98.15-1
Intramuscular	0	0	-
Intravenous	0	0	-
10.4.Duration (days)			
7	91	45.96	38.87-53.16
8	38	19.19	13.95-25.37
5	25	12.63	8.34-18.07
6	17	8.59	5.08-13.39
10	13	6.57	3.54-10.96
3	6	3.03	1.12-6.47
4	4	2.02	0.05-5.09
2	2	1.01	0.12-3.60
1	1	0.51	0.01-2.78
9	1	0.51	0.01-2.78
11	0	0	-
12	0	0	-
13	0	0	-
14	0	0	-
15	0	0	-
Total	198	100	-
11. Genre			
Female	122	58.1	51.10-64.84
Male	88	41.9	35.15-48.89
Total	210	100	-
12. Age (years)			
21 - 30	29	13.81	9.44-19.22
31 - 40	55	26.19	20.38-32.68
41 - 50	65	30.95	24.77-37.68
51 - 60	43	20.48	15.23-26.57
61 - 70	18	8.57	5.15-13.20
71 or older	0	0	-
Total	210	100	-
13. Please, write the name of the university where you studied.			
University of the Basque Country (UPV/EHU)	173	82.78	76.95-87.63
Alfonso X el Sabio University (UAX)	10	4.78	2.31-8.62
Complutense University of Madrid	5	2.39	0.78-5.49
Universidad Europea de Madrid	3	1.44	0.29-4.13
Universitat Internacional de Catalunya (UIC) Barcelona	2	0.96	0.11-3.41
Universidad Rey juan Carlos (URJC)	2	0.96	0.11-3.41
University of Granada	2	0.96	0.11-3.41
University of Navarra	2	0.96	0.11-3.41
University of Buenos Aires (UBA)	2	0.96	0.11-3.41
Universidad a Distancia de Madrid (UDIMA)	1	0.48	0.01-2.63
University of Oviedo	1	0.48	0.01-2.63
University of Valladolid (UVA)	1	0.48	0.01-2.63
University of Valencia (UV)	1	0.48	0.01-2.63
“Argentina”	1	0.48	0.01-2.63
Universidad Iberoamericana (UNIBE) Dominican Republic	1	0.48	0.01-2.63
National University of La Plata (UNLP)	1	0.48	0.01-2.63
Higher University of San Andrés (UMSA)	1	0.48	0.01-2.63
Total	209	100	-

the authors understood that the same chance is given (probability) to participate and answer the questionnaire for all members of the association. Participation meant granting the consent of the participant to record the data from the questionnaire.

-Variables

The questionnaire is shown in the Table 1 with all variables registered.

-Data sources / measurement

Each respondent could only exclusively answer one

electronic survey once, and the options for each question are shown in Table 1.

-Bias

There could not be any selection bias as the electronic survey was sent to all registered dentist in Biscay dentists' college, and it is mandatory to be registered in one or more dentists' colleges to work as a dentist in Spain. Similarly, the authors employed an electronic survey previously performed in the United States to avoid information bias.

-Study size

The final sample size comprised the professionals who decided to partially or completely respond the survey (n=233).

-Statistical methods

The collected data were analyzed using Stata 14 software (StataCorp, College Station, Texas, USA); 95% confidence intervals (CI) were used to assess frequency of prescription for each antibiotic regimen.

Results

-Participants

The survey was responded to by a total number of 233 participants; thus, the response rate was 23.56%. Overall, 210 participants finished the survey completely, and 23 surveys were answered just partially. The descriptive and statistical analyses included all surveys with responses (n=233) to perform as comprehensive an analysis as possible.

-Descriptive data

The questionnaire was responded to by 122 females (58.1%) and 88 males (41.9%), and they were principally aged between 51 and 60 years old (30.95%). A population pyramid is shown in Figure 1.

Overall, 173 respondents had studied in the University of the Basque Country (82.78%) located in Biscay but there were also dentists who had studied at other universities in Spain or in other countries (Table 1). Approximately 51% of the respondents were working in the rural area of the province, and 43% were working in the capital city of the province, Bilbao. The rest of the respondents were working in another province of Spain (6%).

-Outcome data

Table 1 shows the percentage of response and the 95% CI for each item. The preoperative and postoperative regimens being followed are shown in Table 2 and Table 3.

-Main results

Among all participants, 88% (n=207) always routinely prescribed prophylactic antibiotics in conjunction with a dental implant surgery (95% CI: 84.79-92.88%). Approximately 9% (n=22) prescribed antibiotics sometimes (95% CI: 5.68-13.19%), and only 4 dentists (1.72%) did not prescribe antibiotics at all (95% CI: 0.04-3.38%), (Fig. 2).

The 22 dentists prescribing antibiotics only "sometimes" were asked to determine the situations when they do prescribe them. The most-often selected conditions were a preoperative implant-site infection (n=14) and sinus perforation (n=13).

Overall, 179 of 233 respondents prescribed both pre- and postoperative antibiotics (78.85%, 95% CI: 72.96-83.97%), 13 prescribed antibiotics only preoperatively (5.73%, 95% CI: 3.08-9.59%), and 35 prescribed antibiotics exclusively after a routine dental implant surgery (15.42%, 95% CI: 10.98-20.78%), (Fig. 3).

The only route of administration described by all re-

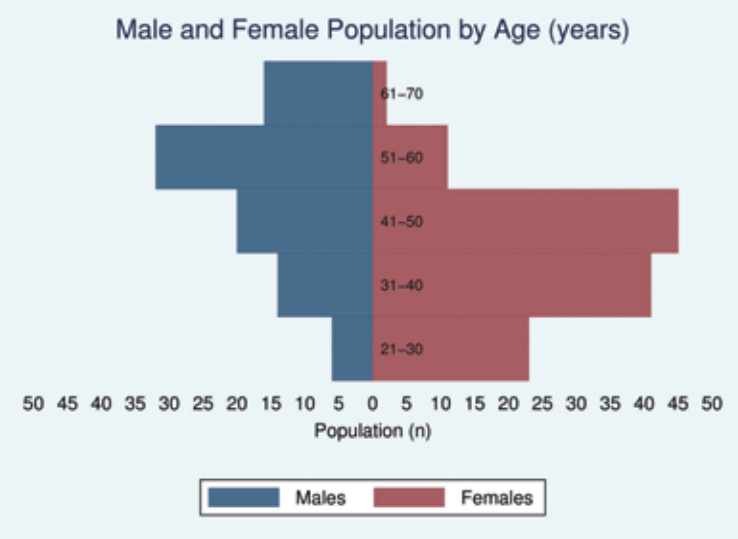

Fig. 1. Population Pyramid: No necessary captions.

Table 2: Preoperative regimens: n: frequency, *: the respondents did not answer this question, QD: once a day, BID: twice a day, TID: 3 times daily, QID: 4 times daily.

ANTIBIOTIC TYPE	DOSE (mg)	n
Inmediately before surgery		
Amoxicillin	500	3
	2000	2
	1000	1
	800	1
*	*	8
1 hour before surgery		
Amoxicillin	2000	19
	1000	11
	500	4
	800	2
	1600	1
	600	1
Amoxicillin / Clavulanic acid	1000	2
	875/125	4
	2000	1
	500/125	1
Cefazolin	875/125	1
1 day before surgery		
Amoxicillin	500 TID	28
	800 TID	12
	1000 TID	9
	875/125 TID	3
	1000 BID	3
	500 BID	1
	800 QID	1
Amoxicillin / Clavulanic acid	875/125 TID	14
	500/125 TID	6
	500 TID	4
	875/125 BID	2
Other	500	1
	*	3
2 days before surgery		
Amoxicillin	500 TID	17
	800 TID	6
	1000 BID	3
	1000 TID	3
Amoxicillin / Clavulanic acid	500/125 TID	3
	875/125 TID	6
	500 TID	1
	800 TID	1
Erythromycin	500 QD	1
Other	*	2

Table 3: Postoperative regimens: n: frequency of respondents choosing this answer, mg: milligrams, QD: once a day, BID: twice a day, TID: 3 times daily, QID: 4 times daily.

ATIBIOTIC TYPE	DURATION (days)	FREQUENCY (n)									
		DOSE									
		500 mg		500/125 mg	800 mg		875/125 mg		1000 mg		
		QD	TID	TID	BID	TID	BID	TID	QD	BID	TID
Amoxicillin	2	-	1	-	-	-	-	-	-	1	-
	3	-	1	-	-	1	-	-	1	1	-
	4	-	1	-	-	1	-	-	-	1	-
	5	-	9	-	-	3	-	-	-	1	4
	6	-	7	-	-	3	-	-	-	2	2
	7	-	31	-	1	16	-	1	-	8	7
	8	-	13	1	-	7	-	1	-	1	2
	9	-	1	-	-	-	-	-	-	-	-
	10	-	4	-	-	3	-	-	-	-	1
Amoxicillin / Clavulanic acid	1	-	-	-	-	-	-	-	-	1	-
	2	-	-	-	-	-	-	-	-	-	-
	3	-	-	-	-	-	-	1	-	-	-
	4	-	-	-	-	-	-	1	-	-	-
	5	-	1	2	-	-	-	5	-	-	-
	6	-	-	1	-	-	1	1	-	-	-
	7	-	6	4	-	-	1	16	-	-	-
	8	-	1	5	-	-	-	7	-	-	-
	10	-	1	2	-	-	-	2	-	-	-
Erythromycin	3	1	-	-	-	-	-	-	-	-	-
Azithromycin	1	-	-	-	-	-	-	-	2	-	-
	3	1	-	-	-	-	-	-	-	-	-

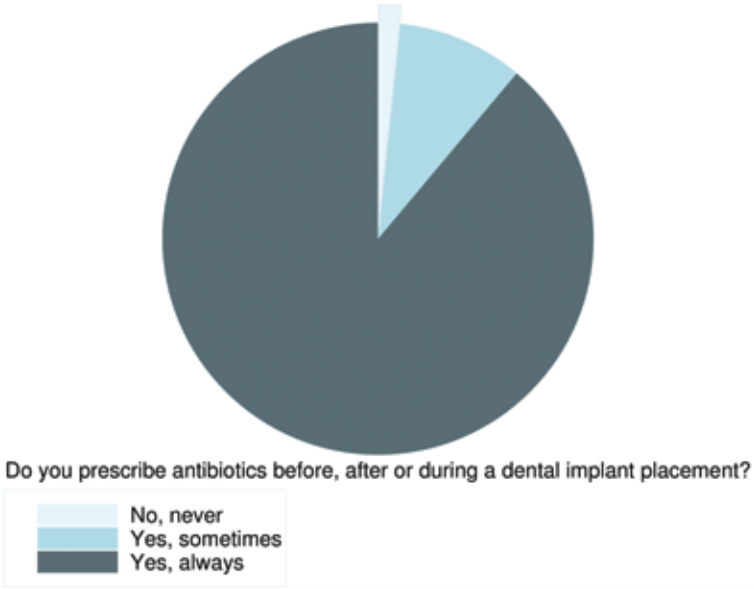

Fig. 2. Prophylactic-antibiotics prescription frequency: No necessary captions.

spondents was orally for all antibiotic types and regimens.

Of the 179 respondents who indicated that they prescribed preoperative and postoperative antibiotics, the most common preoperative regimen was 500 mg amoxicillin three times a day (TID) 1 day before surgery (n=25), and the most frequent postoperative regimen was 500 mg amoxicillin TID orally for 7 days after surgery (n=24). This pre- and postoperative regimen was consistently followed by a total of 10 dentists.

Of the 13 respondents who prescribed exclusively preoperative antibiotics, the most common antibiotic regi-

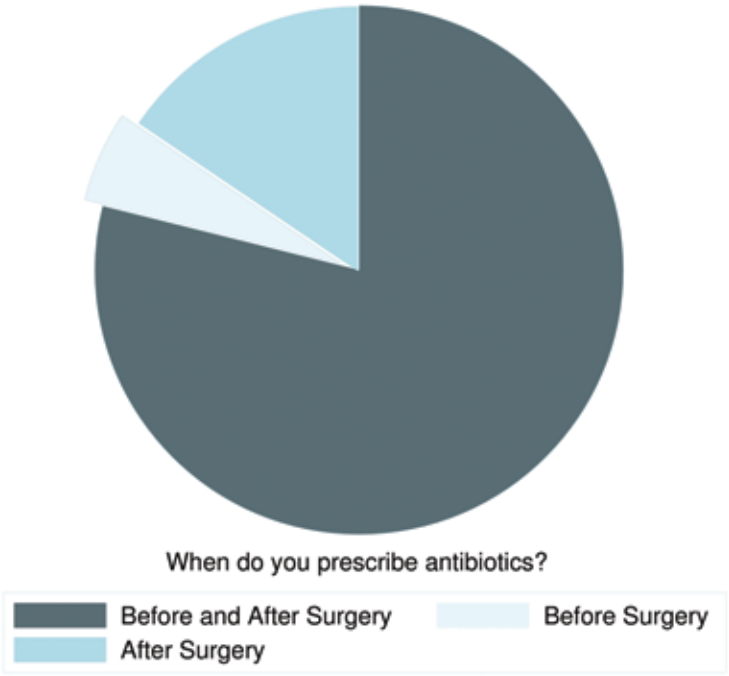

Fig. 3. Time patterns of antibiotics prescription: No necessary captions.

men was 2 g amoxicillin once orally 1 hour before surgery (n=3) and 500 mg amoxicillin TID 1 day before surgery (n=3).

Of the 35 dentists who exclusively prescribed postoperative antibiotics, the most frequent regimen was 500 mg amoxicillin TID for 7 days after surgery (n=7).

After amoxicillin, amoxicillin/clavulanic acid was the most routinely prescribed antibiotic type. The most frequent prescription with amoxicillin/clavulanic acid was pre- and postoperative (n=49). Among the respondents who followed this pre- and postoperative prescription pattern, the most common preoperative regimen was 875/125 mg TID 1 day before surgery (n=14), and the most frequent postoperative regimen was 875/125 mg TID orally for 7 days after surgery (n=16).

Discussion

-Key results

Most dentists in Biscay routinely prescribe prophylactic antibiotics in conjunction with dental implant surgery. Approximately 88% of the respondents always prescribed prophylactic antibiotics. A large range of prophylactic regimens is followed, which demonstrates the substantial variety of choices made by dentists. This fact also reveals a lack of consensus among professionals. In addition, recommendations made in the last published evidence are not being followed.

The review performed by Exposito *et al.* suggested that a single dose of 2 or 3 g amoxicillin 1 hour preoperatively significantly reduces dental implant failures (2). Moreover, the review conducted by Rodríguez Sánchez *et al.* concluded that postoperative amoxicillin (associated or not with preoperative amoxicillin) might not be beneficial preventing dental implant failures and postoperative infections (7). Therefore, the prescription habits of most of the dentists might be considered overtreatment, as approximately 93% of the respondents prescribed some kind of postoperative regimen after surgery. Furthermore, only 3 dentists (1.28%) exclusively prescribed 2 g amoxicillin 1 hour before surgery.

-Limitations

This survey was sent to all dentists registered in Biscay, and it was focused on the antibiotic prescription patterns involving dental implant surgery among health patients without any allergies.

To assure the confidence of the respondents, the authors and institution were precisely introduced, and the objectives were explained in the email with the link. This introduction message sent with the link to the questionnaire stated that the survey should only be answered by dentists performing dental implant surgeries. However, the electronic survey could have been responded to by professionals who do not perform dental implant surgeries. Unfortunately, there is no possible way to avoid and control this fact, but this number is assumed to be low.

It is also not possible to know the total number of dentists who perform dental implant surgeries in Biscay; however, the percentage of response seems to be coherent with the professionals carrying out dental implant surgeries in the province.

The survey could only be answered exclusively by a single respondent. The authors consider the response percentage high. Nevertheless, there are some aspects that cannot be controlled, such as the reliability and authenticity of the answers obtained.

-Interpretation

The lack of standardized protocols may be the reason for the routine and systematic prescription of antibiotic regimens without enough scientific evidence supporting a beneficial effect (especially for postoperative regimens) (2,7). The current situation might increase the incidence of the adverse effects associated with the overtreatment with antibiotics, such as bacterial resistance and other systemic disorders. Therefore, this condition must be considered of interest to the dentistry community and national health systems because of epidemiological and economic reasons.

This fact has encouraged the development of many other surveys in the last years performed in very diverse countries, such as Jordan, the United Kingdom (UK), Sweden, and the United States (US) (8,9,10,12).

Although there is limited evidence supporting antibiotic prophylaxis, the high percentage of professionals in other countries prescribing prophylactic antibiotics routinely in conjunction with a dental implant placement is remarkable. The prescription percentages among professionals range from almost 50% to 75% among the respondents in these other studies. However, in Biscay this statistic reaches 88%.

The results suggested by the present survey of dentists from Biscay are similar to those reported by other authors, who also found great variation in antibiotic prescribing regimens with respect to types, dose and treatment duration. Amoxicillin was found to be the most frequently prescribed antibiotic type in other survey studies, except in Jordan, which favors amoxicillin with clavulanic acid. Similar to the habits in Biscay, the practice of prescribing amoxicillin 2 g preoperatively was also found in Sweden and the US as the most common preoperative regimen. On the other hand, professionals from the UK and the US were aligned on the most frequently prescribed postoperative regimen, as they prescribed 500 mg amoxicillin 3 times daily for 5 days. However, dentists from Biscay lengthen this postoperative prescription pattern until 7 days after surgery.

-Generalizability

This survey was carried out among respondents registered as dentists in the College of Biscay, and most of them had studied at the University of the Basque Country (UPV/EHU). Consequently, other professionals who had been trained in other institutions in Spain may generate other patterns of prescription regarding the use of prophylactic antibiotics in dental implant surgeries. Nevertheless, the systematic use of prophylactic antibiotics among dentists and the large variation in the prescription regimens being used, most of them based on no scientific evidence, may be generalized.

In conclusion, dentists in Biscay routinely use prophylactic antibiotic in conjunction with a dental implant placement among healthy patients. A large range of prophylactic regimens is followed, and high variability among the prescribed regimens is shown. However, a consecutive pre- and postoperative regimen with amoxicillin is the most frequently prescribed.

Unfortunately, recommendations made by the most recent published evidence are not being followed. Protocols and guidelines are needed to define the indications for prophylactic antibiotic prescription in dental implant surgery to avoid overtreatment with antibiotics and the associated risks and economic costs.

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Conflict of interest and Aknowledgements
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RESEARCH ARTICLE Open Access

Antibiotic prophylaxis prescribing habits in oral implant surgery in the Netherlands: a cross-sectional survey

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Abstract

Background: There seems to be no consensus on the prescription of prophylactic antibiotics in oral implant surgery. The Dutch Association of Oral Implantology (NVOI) guidelines do not include a clear policy on prophylactic antibiotic prescriptions for oral implant surgery among healthy patients. The purpose of the study was to determine whether antibiotic prophylaxis is commonly prescribed in the Netherlands by general dentists, maxillofacial surgeons and oral implantologists in conjunction with oral implant surgery among healthy patients and to assess the type and amount of prophylactic antibiotic prescribed.

Methods: This observational cross-sectional study is based on a web survey. A questionnaire developed in the United States of America was translated and slightly adjusted for use in the Netherlands. It contained predominantly close-ended questions relating to demographics, qualifications, antibiotic type, prescription duration and dosage. An email including an introduction to the study and an individual link to the questionnaire was sent in February 2018 to a sample of 600 general dental practitioners and all 302 specialized dentists (oral implantologists, periodontists and maxillofacial surgeons) recognized by the NVOI. Overall, 902 questionnaires were anonymously sent. Finally, 874 potential participants were reached. Collected data were analyzed through descriptive statistics.

Results: In total, 218 (24.9%) participants responded to the questionnaire, including 45 females (20.8%) and 171 males (79.2%). Overall, 151 (69.9%) regularly placed oral implants. Of them, 79 (52.7%) prescribe antibiotics only in specific situations, 66 (43.7%) regularly, and 5 (3.3%) did not prescribe antibiotics at all. Overall, 83 participants who prescribe antibiotics did so both pre- and postoperatively (57.2%), 47 only preoperatively (32.4%) and 12 exclusively postoperatively (8.3%). A single dose of 2000 mg of amoxicillin orally one hour prior to surgery was the most prescribed preoperative regimen. The most frequently prescribed postoperative regimen was 500 mg of amoxicillin three times daily for five days after surgery. On average, participants prescribe a total of 7018 mg of antibiotics before, during or after oral implant surgery.

Conclusions: Antibiotic prophylaxis in conjunction with oral implant surgery is prescribed in the Netherlands on a large scale, and recommendations based on the last published evidence are frequently not followed.

Keywords: Antibiotic prophylaxis prescribing habits, Oral implant surgery, Postoperative infection, Bacterial resistance

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Background

Oral implant surgery is a routine treatment to replace lost teeth [1]. Although oral implants are expected to have a high rate of success, implant failures do occur [2].

Implant failures can be classified as early failures or late failures. Early implant failures occur before the prosthetic restoration, and one of their possible causes might be postoperative infection because of bacterial contamination during the implant insertion [3]. For this reason, the use of perioperative antibiotics has been suggested to prevent postoperative infections and oral implant failures [4].

However, the use of prophylactic antibiotics to reduce the incidence of postoperative infections and oral implant failures remains a controversial issue [5, 6]. Some reviews recommended a single dose of 1 g, 2 g or 3 g of amoxicillin preoperatively but found no evidence to support the postoperative use of a prophylactic antibiotic after oral implant surgery among healthy patients [2, 7].

Markedly, there seems to be no consensus among dentists, oral implantologists, periodontists and maxillofacial surgeons over the use of antibiotics to prevent post-implant infections and oral implant failures [8–12].

The inconsistent use of antibiotics has become an important epidemiologic problem due to the development of bacterial resistance and the risk of superinfection [13], resulting in considerable human and economic costs [14]. Other adverse effects, such as secondary infections, interactions with other medications, gastro-intestinal discomfort, toxicity and allergic reactions, should also be considered [7].

The government and healthcare services of the Netherlands are pursuing several strategies against antibiotic resistance, which include encouraging health professionals to comply with strict guidelines when prescribing antibiotics in an effort to reduce inappropriate antibiotic prescriptions by at least 50% in 2019 [15].

In the Netherlands, oral implant surgery is mainly performed by maxillofacial surgeons and oral implantologists, i.e. dentists who completed a three-year master's qualification. Antibiotics are the most prescribed drugs in dentistry in the Netherlands. National data revealed that 41.0% of all prescriptions written by dentists during 2015 in the Netherlands were for amoxicillin. Metronidazole and clindamycin accounted for 2.5% of all medications prescribed by dentists [16]..

Nevertheless, the guidelines used in the Netherlands for oral implant surgery do not include a clear policy on the use of prophylactic antibiotics among healthy patients. The Dutch Association of Oral Implantology (NVOI), recommending new publications on this topic in the future, proposed amendments to these guidelines [17].

New research assessing the effectiveness of prophylactic antibiotics for oral implant surgery has been performed in recent years [7, 18, 19].

Moreover, several studies focused on antibiotic prescribing habits in conjunction with oral implant surgeries in different countries have been published recently [8–12]. Markedly, no data were available concerning the situation in the Netherlands. Consequently, it is imperative to assess the current situation in the Netherlands and compare it with similar conditions in other countries.

Therefore, the primary aim of this study was to determine whether antibiotic prophylaxis is commonly prescribed in the Netherlands by general dentists, maxillofacial surgeons and oral implantologists in conjunction with oral implant surgery among healthy patients. The secondary aim was to assess the type and amount (expressed in milligrams: mg) of antibiotics prescribed to evaluate whether any consensus has been reached and the current recommendations made by the last published evidence have been followed [2, 7].

Methods

This observational cross-sectional study is based on a web survey, and it is reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [20].

The questionnaire, developed by Deeb et al. (2015) [12], was translated and slightly adjusted for use in the Netherlands to collect data concerning the prescription rates of preventive antibiotics among general dental practitioners, maxillofacial surgeons, periodontists and oral implantologists in conjunction with oral implant therapy. The explicit authorization of Deeb and the co-authors was obtained to use their questionnaire. The translated and adjusted questionnaire was evaluated for comprehensibility and logical order by an experienced oral implantologist, who is involved in the training of dentists in the Netherlands. The formulation of the questions was found adequate and valid to assess the intended objectives.

Setting

The Netherlands is a member state of the European Union with, in 2018, a population of approximately 17.1 million [21]. In January 2018, roughly 8800 dentists were employed in the Netherlands, including about 320 oral implantologists and 80 periodontists. In addition, at that time, there were about 290 practicing maxillofacial surgeons [22].

Participants

In February 2018, an email was sent to a representative sample of 600 general dental practitioners, randomly selected from the official register of qualified dentists of the Royal Dutch Dental Association (KNMT), and to all 302 oral implantologists, periodontists and maxillofacial surgeons recognized by the NVOI as oral health care providers who place oral implants and whose email addresses were publicly available.

The only eligibility criteria considered for inviting potential participants to the study was inclusion in the NVOI and KNMT lists. The KNMT maintains an updated file of all licensed dentists in the Netherlands, but does not know whether dentists are active in dentistry. For this reason, it was determined the group of all dentists aged 64 years or less with a known domicile and/or work address in the Netherlands because this group was expected to work in dentistry. A sample of 600 dentists from this group, consisting of about 8800 dentists, was drawn with the SPSS SAMPLE procedure. This was performed by a "Third Party" research institute commissioned by the KNMT. This institute specialized in the management and administration of web surveys and offers support in data collection. The email addresses of NVOI members are publicly available on the NVOI website.

Subsequently, the "Third Party" research institute sent the invitation by e-mail to all potential participants and collected the data. These email messages contained an individual link to a web-based questionnaire and a brief introduction to the study objectives. The participants were assured that the research data were collected anonymously, and it was made clear that by answering the questionnaire, participants consented to the use of the data collected by the survey for the study purpose. All efforts were made to protect the participants' privacy and anonymity as no personal data of the participants (name, surname, address and telephone number) were collected. In addition, no email addresses were stored or saved by the authors so the participants could not be contacted again. For these reasons, this specific study did not require an ethics statement by an institutional review board (ethics committee) before the study began. Two reminder emails were sent to all potential respondents after two and four weeks; after six weeks, the data collection was closed.

The "Third Party" research institute made the collected data available for use in an encrypted manner so that the authors did not have access to any personal information of the participants, including their email addresses.

A total of 28 potential participants could not be reached because of an incorrect email address. Therefore, the final sample consisted of 874 potential participants: 578 general dental practitioners and 296 oral implantologists, periodontists and maxillofacial surgeons.

Variables

Information was gathered regarding qualifications and work experience, demographic details and most commonly prescribed preventive antibiotic in case of oral implant placement, including duration and dosage. Based on their statements regarding dosage and period of intake, the total milligrams (mg) prescribed per oral health professional and oral implant surgery was calculated.

Data sources and measurement

Each link found in the email messages directed the user to a questionnaire, which could only be answered once. The questionnaire contained predominantly close-ended questions. Participants were allowed to add other answer options and additional information (Additional file 1).

Statistical methods

All data were analyzed using International Business Machines Corporation (IBM) Statistical Package for Social Sciences (SPSS) for Windows Version 24 (IBM Corporation, released 2012, Armonk, New York). To begin, by means of descriptive statistics, an overview was compiled of the respondents' characteristics in terms of age, sex, type of oral health professional and geographical area. After that, the descriptive analysis continued with only those care providers who had indicated that they place oral implants on a regular basis. Subsequently, their habits regarding prescribing antibiotics before, during or after an oral implant placement were assessed. It was investigated whether antibiotic prescribing habits in oral implant surgery were related to personal characteristics of participants and, for those who prescribe antibiotics, prescription regimens used (chi-squared test and ANOVA). Whether the total amount of prescribed antibiotics varied among certain groups of participants was first investigated by means of ANOVA (F-test) and finally, because the data were not normally distributed, analyzed by means of the Kruskal-Wallis test and Mann-Whitney U test.

Results

Participants

Table 1 details the different professionals included in the study. Two participants reported that they were not currently working, and they were excluded from the study group.

Descriptive data

In total, 171 males (79.2%) and 45 females (20.8%) responded to the questionnaire. The mean age of the participants was 48.6 years ($SD = 11.1$). While 24.1% were 39 years or younger, 20.8% were between 40 and 49 years old, and 55.1% were 50 years of age or older.

Most participants (92.3%) graduated from a dental school in the Netherlands: Amsterdam (36.6%), Nijmegen (23.8%), Groningen (21.7%) and Utrecht (10.2%). Almost half of the participants (46.3%) were settled in the western part of the country, with 26.4% in the southern, 17.6% in the eastern and 9.7% in the northern regions.

Oral implant placement and prescribing habits

Table 1 depicts that 69.2% of the participants surveyed indicated that they regularly place oral implants. Of these 151 participants currently performing oral implant surgeries, 66 (43.7%) stated that they regularly prescribe

Table 1 Professional specializations of participants[#1] and current activity in oral implant surgery

professional specialization	Do place oral implants		Do not place oral implants		Overall	
	n	%	n	%	n	%
General dental practitioner (GDP)	11	5.0	59	27.1	70	32.1
GDP & OI	20	9.2			20	9.2
Oral implantologist (OI)	67	30.7			67	30.7
OI & periodontist (OI-PERIO)	9	4.1	1	0.5	10	4.7
Maxillofacial surgeon (MS)	44	20.2	1	0.5	45	20.6
Other oral health professional[#2]			4	1.8	4	1.8
Not working as oral health professional[#3]			2	0.9	2	0.9
Total	151	69.2	67	30.8	218	100

[#1] multiple situations possible / [#2] dentist for orthodontics (3x), maxillofacial prosthodontist /[#3] the 2 participants who are not working as oral health professional were excluded from the further analysis of the data

prophylactic antibiotics, while a minority (3.3%, $n = 5$) reported they never do so. In addition, 79 participants (52.3%) indicated they prescribe antibiotics only in certain situations. These situations are presented in Table 2.

No statistically significant relationship was found between any of the participants' characteristics and their prescribing habits. (Table 3).

Table 4 reports the starting times and regimens of the antibiotic prescriptions employed by the participants.

Preoperative antibiotics: type, dose and dosage

The majority of participants who prescribe preoperative antibiotics when placing oral implants advise their patients to start one hour prior to treatment (75.2%) or immediately prior to treatment (3.1%). All others stated that they advise their patients to start one day (16.3%) or two days (5.4%) prior to treatment.

Most participants who prescribe prophylactic antibiotics one hour or immediately prior to implant placement prescribe 2000 mg of amoxicillin to be taken orally (70.3%). Furthermore, 9.9% indicated they prescribe 3000 mg of amoxicillin, and 9.9% indicated they prescribe 500 mg of amoxicillin, in both instances to be taken orally.

More than half of the participants (53.9%) who start antibiotic prophylaxis one or two days prior to implant surgery prescribe 500 mg of amoxicillin to be taken orally three times a day. In addition, 19.3% prescribe a combination of 500/125 mg amoxicillin/clavulanic acid to be taken three times a day (Table 5).

Table 2 Situations in which participants prescribed antibiotics before, after or during oral implant placement[#1]

	n	%
Bone grafting	73	93.6
Sinus perforation	33	42.2
Preoperative implant-site infection	29	37.2
Medically compromised patient[#2]	22	28.2
Past of periodontal disease	14	17.9
Smoking habit	13	16.7
Simultaneous placement of more than 1 dental implant	6	7.7
Dentulous patient[#2]	5	6.4
Other situation[#3]	7	9.0
Total[#4]	78	100

[#1] multiple situations possible / [#2] derived from the option 'Other situation', as described by participants / [#3] sinus lift surgery (2x), post-operative complications (2x), treatment under anaesthesia, specific location of dental implant placement, based on microbiological test / [#4] 1 participant did not indicate situation

Postoperative antibiotics: type, dose and dosage

Of the participants who opt to advise patients to start antibiotic prophylaxis postoperatively, 75.1% prescribe 500 mg of amoxicillin to be taken orally one to four times a day for a period varying from one to eight days (Table 6). Furthermore, 15.2% indicated they prescribe a combination of 500/125 mg amoxicillin/clavulanic to be taken three times a day for a period of five or seven days.

Amounts of prescribed antibiotics

On average, participants stated that they prescribe a total of 7018 mg ($SD = 4325$ mg) of prophylactic antibiotics before, during or after oral implant surgery, varying from 500 mg to 14,600 mg with the median lying at 8000 mg. Three participants did not indicate their prescribing regimens, and six did not declare the number of milligrams prescribed (Table 7).

Notably, maxillofacial surgeons prescribe significantly more antibiotics than oral implantologists and general practitioners (7969 mg versus 6883 mg and 4150 mg; $p = 0.03$).

In particular, the difference between maxillofacial surgeons and general practitioners was statistically significant ($p = 0.02$). Participants who only opted for antibiotics prior to treatment reported prescribing significantly smaller amounts than their colleagues who opted for antibiotics only after treatment and prior to as well as after treatment

Table 3 Personal characteristics of participants related to antibiotic prescription habits in oral implant surgery

	Never	Some-times	Always	Overall
Female[#1]		13.9%	7.6%	10.7%
Mean (SD) age in years[#2]	60.0 (4.8)	49.6 (10.1)	51.5 (10.8)	50.8 (10.4)
Type of specialization[#3]				
-General dental practitioner	20.0%	5.1%	9.1%	7.4%
-Oral implantologist and/or periodontist	60.0%	62.0%	65.2%	63.3%
-Oral surgeon	20.0%	32.9%	25.7%	29.3%
Graduation in the Netherlands[#4]	100%	94.9%	90.9%	93.3%
Place of settlement (part of the country)[#5]				
-Southern	60.0%	20.3%	21.2%	22.0%
-Western	40.0%	45.6%	54.5%	49.3%
-Eastern		17.6%	18.2%	17.3%
-Northern		16.5%	6.1%	11.4%
n [#6]	5	79	66	150

[#1] p 0.343 / [#2] p 0.071 / [#3] p 0.597 / [#4] p 0.520 / [#5] p 0.173 / [#6] 1 participant did not indicate prescription habits
SD: Standard deviation

(2060 mg versus 9250 mg and 9598 mg; $p < 0.001$). Furthermore, it appears that participants who regularly prescribe an antibiotic prophylaxis in conjunction with oral implant surgery prescribe significantly smaller amounts of antibiotics than participants who prescribe prophylactic antibiotics only in certain circumstances. Conversely, participants who prescribe prophylactic antibiotics only in certain circumstances when inserting oral implants indicated they prescribe longer regimens (pre- and postoperatively) than participants who indicated they regularly prescribe prophylactic antibiotics ($p = 0.04$).

Discussion

Key results

Considering the latest evidence published on this topic, more than two-thirds of the participants in this study do not follow an adequate prophylactic antibiotic regimen. They prescribe prophylactic antibiotics in many situations not defined by the guidelines proposed by the NVOI [17]. Moreover, there appears to be a lack of consensus regarding the indications for prescribing prophylactic antibiotics in conjunction with oral implant surgery among healthy patients as well as regarding the antibiotic of choice and the regimen selection.

Table 4 Antibiotic prescribing regimens and starting time of the prescriptions employed by participants

	n	%	n	%
Only pre-operative			47	32.4
-1 h or immediately	43	29.6		
-1 day prior	2	1.4		
-2 days prior	2	1.4		
Pre- and post-operative			83	57.2
-1 h or immediately	60	41.4		
-1 day prior	18	12.4		
-2 days prior	5	3.4		
Only post-operative			12	8.3
Unknown			3	2.1
Total	145	100	145	100

Limitations

Before the start of the study, it was unclear how many dentists and maxillofacial surgeons insert oral implants in the Netherlands. For that reason, the research group was composed of all maxillofacial surgeons, periodontists and oral implantologists who are recognized to routinely perform oral implant surgery and an additional random sample of general dental practitioners, who are also qualified to perform this treatment. In this way, the chance of any selection bias was minimized.

Overall, the response rate of 24.9% was not high, but it was considered adequate for a web questionnaire [23]. While there was no certainty that all dentists, maxillofacial surgeons, periodontists and oral implantologists placing oral implants in the Netherlands were reached, it was considered that the participants in this study properly represented the target population.

The questionnaire was completely anonymous to encourage respondents to answer the questions as truthfully as possible to avoid risk of bias. Nevertheless, the authenticity of the answers obtained was difficult to control. Moreover, as in most survey studies, it is uncertain whether respondents' statements about their behavior match their behavior in practice.

Table 5 Pre-operative antibiotic regimens prescribed before surgery by participants

1 h or immediately prior				
Antibiotic type	Dose (mg)	Administration	n	%
Amoxicillin	2.000	oral	71	70.3
Amoxicillin	500	oral	10	9,9
Amoxicillin	3.000[#1]	oral	10	9.9
Amoxicillin	1.000	oral	2	2.0
Amoxicillin	other[#2]	oral	2	2.0
Amoxicillin	600	oral	1	1.0
Amoxicillin/Clavulanic acid	500 / 125	oral	3	3.0
Amoxicillin/Clavulanic acid	2.000	oral	1	1.0
Clindamycin	600	oral	1	1.0
Total[#3]			101	100
1 or 2 days prior				
Antibiotic type	Dose (mg)	Dosage	n	%
Amoxicillin	500	oral TID	14	53.9
Amoxicillin	400	oral TID	1	3.8
Amoxicillin	500	oral BID	1	3.8
Amoxicillin	other[#4]	oral TID	1	3.8
Amoxicillin/Clavulanic acid	500 / 125	oral TID	5	19.3
Clindamycin	300	oral BID	1	3.8
Clindamycin	300	oral QID	1	3.8
Erythromycin (ethylsuccinate form)	150	oral TID	1	3.8
Other[#5]	500	oral QD	1	3.8
Total[#6]			26	100

QD: once a day, BID: twice a day, TID: 3 times daily, QID: 4 times daily / [#1] mentioned spontaneously / [#2] varying / [#3] 2 participants did not declare the pre-operative regimen prescribed / [#4] 375 mg, it concerns an antibiotic treatment and not antibiotic prophylaxis / [#5] Zithromax / [#6] 1 participant did not declare the pre-operative regimen prescribed

Table 6 Post-operative antibiotic regimens prescribed after surgery by participants

Antibiotic type	Dose (mg)	Dosage	Duration	n	%
Amoxicillin	250	oral TID	5 days	1	1.1
Amoxicillin	400	oral TID	5 days	1	1.1
Amoxicillin	500	oral QD	3 days	1	1.1
Amoxicillin	500	oral BID	7 days	1	1.1
Amoxicillin	500	oral TID	1 day	4	4.2
Amoxicillin	500	oral TID	3 days	2	2.2
Amoxicillin	500	oral TID	5 days	29	31.4
Amoxicillin	500	oral TID	6 days	1	1.1
Amoxicillin	500	oral TID	7 days	24	26.1
Amoxicillin	500	oral TID	8 days	1	1.1
Amoxicillin	500	oral TID	other[#1]	2	`2.2
Amoxicillin	500	oral QID	2 days	1	1.1
Amoxicillin	500	oral QID	4 days	1	1.1
Amoxicillin	500	oral QID	5 days	2	2.2
Amoxicillin/Clavulanic acid	500/125	oral TID	1 day	1	1.1
Amoxicillin/Clavulanic acid	500/125	oral TID	5 days	6	6.5
Amoxicillin/Clavulanic acid	500/125	oral TID	7 days	8	8.7
Amoxicillin/Clavulanic acid	500/125	oral QID	6 days	1	1.1
Amoxicillin/Clavulanic acid	500/125	oral QID	7 days	1	1.1
Clindamycin	300	oral TID	7 days	1	1.1
Clindamycin	300	oral QID	5 days	1	1.1
Clindamycin	300	oral QID	7 days	1	1.1
Other[#2]	500	oral QD	2 days	1	1.1
Total[#3]				92	100

QD: once a day, BID: twice a day, TID: 3 times daily, QID: 4 times daily / [#1] unknown /[#2] Zithromax / [#3] 3 participants did not declare the postoperative regimen prescribed

Interpretation

In accordance with Esposito et al. [2], the NVOI guidelines acknowledge that a single preoperative dose of oral antibiotics may slightly decrease implant failures. Nevertheless, standard antibiotic prophylaxis in conjunction with oral implant placement among healthy patients is not recommended. The last published reviews stress the lack of evidence supporting the use of postoperative antibiotics exclusively after surgery or as a combination with preoperative antibiotics [2, 7]. Preoperative antibiotics are only indicated as bacterial endocarditis prophylaxis for patients with orthopedic implants or in implant surgeries performed on infected sites. Following the NVOI guidelines, the first treatment choice in these situations should be a single dose of oral amoxicillin and clavulanic acid (1000/250 mg) one hour before surgery or, in the event of allergies, oral clindamycin (600 mg) one hour prior to treatment [17]. However, the last published evidence recommends a single preoperative dose of 1 g, 2 g or 3 g of amoxicillin [2, 7]. It has also been described recently that penicillin-allergic patients treated with clindamycin may present more risk of suffering oral implant failures [24].

This study confirms a lack of agreement on the prescription of prophylactic antibiotics in oral implant surgery, as already demonstrated in many other medical situations in which this treatment is an option [25]. However, in comparison with their colleagues in other countries, dentists, maxillofacial surgeons, periodontists and oral implantologists in the Netherlands seem to prescribe a smaller range of antibiotic types and regimens and seem more cautious in prescribing prophylactic antibiotics. In the UK, a study revealed that approximately 72% of dentists prescribe antibiotics for all oral implant surgery procedures [9], while a Swedish study revealed that 74% of dentists routinely prescribe antibiotics in conjunction with oral implant surgery [10].

Table 7 Total amount of antibiotics (mg) prescribed by participants related to their type of working situation and prescription habits

	Mean	SD	Mean Rank [#1]	P
Type of oral health professional				0.029
-General dental practitioner (GDP)	4150	3705	39.3	
-Maxillofacial surgeon (MS)	6883	4195	68.3	
-Oral implantologist (OI)	7969	4179	75.8	
Antibiotic prescription habits				0.003
-Sometimes	7799	4173	77.9	
-Always	5913	4059	57.9	
Antibiotic prescription regimen				< 0.0001
-Only pre-operative	2060	463	24.9	
-Only post-operative	9250	1545	84.1	
-Pre- and post-operative	9598	2963	91.8	
Total	7018	4235		
n = 136 [#2]				

[#1] Kruskal-Wallis test or Mann-Whitney test / [#2] 3 participants did not indicate prescribing regimens and 6 participants did not completely declare the number of mg or did not declare it at all

The prescription patterns of maxillofacial surgeons in the USA revealed that 96% prescribe prophylactic antibiotics for healthy patients [12], and similar research in Spain found that almost 90% of the dentists studied regularly prescribe antibiotics among healthy patients [11]. Conversely, it was found that the proportion of dentists in Jordan who prescribe antibiotics in all implant surgeries was around 50% [8].

The present study found differences in the prescription duration between participants who prescribe prophylactic antibiotics systematically (more often opting for short-term regimens) and those professionals who prescribe prophylactic antibiotics only in certain instances (more often opting for long-term regimens). This is probably related to the fact that the latter more often prescribe prophylactic antibiotics for a particular reason after reflection and a decision-making process.

The discrepancies in the average amount of prophylactic antibiotics prescribed by maxillofacial surgeons and general dentists in the Netherlands might be explained by the relative contrast in the complexity of the surgeries executed by each group. Maxillofacial surgeons may face more complicated treatments than general dentists, which could generate the prescription of heavier prophylactic regimens.

Similar to health care professionals worldwide, oral health professionals performing implant surgery in the Netherlands prescribe too often and too many prophylactic antibiotics. This may lead to an alarming risk of bacterial resistance and the development of other adverse reactions to antibiotics, which potentially generates a serious public health problem and consequently, high societal and economic costs.

Generalisability

This survey was conducted among oral healthcare professionals in the Netherlands registered as general dental practitioners, oral implantologists or maxillofacial surgeons who graduated in representative proportions from various dental schools. Combined with the fact that a substantial proportion of the oral health professionals who perform oral implant surgeries participated in this study, it is plausible that the results of the survey broadly reflect the national situation in the Netherlands.

Conclusions

Antibiotic prophylaxis in conjunction with oral implant surgery among healthy patients is prescribed in the Netherlands on a large scale by general dentists, maxillofacial surgeons, periodontists and oral implantologists. In addition, recommendations based on the last published evidence are frequently not being followed. For this reason, more attention should be paid to the implementation of existing guidelines. New research assessing the effects of different prophylactic antibiotic types, dosages and regimens in healthy patients is also necessary to update evidence-based guidelines.

Supplementary information

Supplementary information accompanies this paper at https://doi.org/10.1186/s12903-019-0981-4.

Additional file 1. Questionnaire. This file contains the English version of the survey sent to participants.

Abbreviations

GDP: General dental practitioner; IBM: International Business Machines Corporation; KNMT: Royal Dutch Dental Association; Mg: Milligrams; MS: Maxillofacial surgeon; NVOI: Dutch Association of Oral Implantology; OI: Oral implantologist; OI-PERIO: Oral implantologist and periodontist; SPSS: Statistical Package for Social Sciences; STROBE: Strengthening the Reporting of Observational Studies in Epidemiology

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Endnotes

Not applicable.

Authors' contributions

All authors have read and approved the manuscript, Conceptualization, F. R. S., I. A. and C. R. A, Formal Analysis, F. R. S., C. R. A. and J. B, Methodology, R. S., I. A. and C. R. A, Supervision, C. R. A. and J. B, Writing – Original Draft Preparation, R. S., I. A. and C. R. A, Writing – Review & Editing, R. S. and J. B.

Authors' information

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Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate
Ethical approval was waived because this study did not perform any intervention in humans and it did not use any personal data or biological samples of human origin. All collected data were completely anonymized. The informed consent obtained from study participants was written [26].

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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Antibiotic prophylaxis habits in oral implant surgery among dentists in Italy: a cross-sectional survey

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Abstract

Background: The prescription of prophylactic antibiotics in conjunction with oral implant surgery remains inconsistent among different populations of dentists. The main objective of this study was to assess the current antibiotic prescribing habits of dentist in conjunction with oral implant surgery in Italy. The secondary objective was to assess the nature and amount (mg) of antibiotics prescriptions in order to evaluate whether any consensus has been reached and if the current recommendations are complied.

Methods: Observational cross-sectional study based on a web-survey reported according to the STROBE guidelines. A questionnaire was sent via email to each registered member of the Italian Academy of Osseointegration ($n = 400$). The email included a link to the anonym web questionnaire developed on www.encuestafacil.com. It contained close-ended and some open-ended questions concerning demographics, antibiotic type, prescription duration and dosage. Collected data were analyzed using STATA® 14 software.

Results: 160 participants responded the survey (response rate = 40%). Approximately 84% routinely prescribed prophylactic antibiotics in conjunction with oral implant surgery, 15.6% prescribed antibiotics in certain situations and only 1 did not prescribe antibiotics at all. Overall, 116 respondents prescribed both pre- and postoperative antibiotics, 29 prescribed antibiotics only preoperatively and 14 prescribed antibiotics exclusively after surgery. Italian dentists prescribed an average amount of 10,331 mg antibiotics before, during or after oral implant surgery. Approximately, only 17% ($n = 27$) of the participants who prescribed antibiotics before oral implant surgery complied with the recommendations proposed by the latest publications (no more than 3 g of preoperative amoxicillin before oral implant surgery).

Conclusions: Dentists in Italy on a large scale prescribe antibiotic prophylaxis in conjunction with oral implant surgery among healthy patients. A high range of prophylactic regimens is prescribed and they are not adhering to the new science-based specifications. Guidelines focused on the indications for prophylactic antibiotics among healthy patients are required to prevent bacterial resistance, side effects and costs caused by overtreatment and the irrational use of antibiotics.

Keywords: Antibiotic prophylaxis habits, Oral implant surgery, Postoperative infection, Bacterial resistance

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Background

Oral implant surgery is a routine treatment from which both dentists and patients expect high success rate, but often this is not the case [1, 2]. Bacterial contamination at implant surgery has been related to early implant failures [3]. Therefore, different prophylactic treatments such as the use of perioperative antibiotics have been studied [4].

Nevertheless, the use of prophylactic antibiotics to reduce the incidence of postoperative infections and oral implant failures in healthy patients is still controversial [5, 6]. Several reviews have found no evidence supporting the prophylactic effect of antibiotics on postoperative infections, and they have remained inconclusive on the prevention of oral implant failures [2, 7–12]. Consequently, many professionals disagree on the utility of antibiotics and which is the most suitable regimen to adopt [13–18].

The inadequate use of antibiotics must be seriously taken into consideration as it could cause bacterial resistance and other important adverse effects, such as secondary infections, interactions with other medications, gastro-intestinal discomfort, toxicity and allergic reactions [7, 18]. The consequences are substantially human and economic [19].

Owing to this, the use of antibiotics has been the subject of a special monitoring in the European Union (EU) and the main topic of public awareness campaigns [20]. Italy was the ninth country with more systemic consumption of antimicrobials in the EU community (primary care sector) in 2017 [21]. Moreover, Italy was one of the countries with the highest levels of bacterial resistance in most pathogenic species monitored [22].

There is evidence showing that dental practitioners have over prescribed large numbers of systemic antibiotics and that their number has even increased in the last years [23]. In addition, a recent survey involving more than one thousand Italian dentists found that the use of systemic antibiotics is frequent and excessive [24].

In Italy, dental practitioners whether specialized or not in periodontics or oral surgery routinely perform oral implant surgery. Implant training is part of the basic training as dentists as well as part of the postgraduate in oral surgery and periodontology.

There used to be two scientific bodies related to oral implatology: the Italian Society of Oral Surgery and Implant Dentistry (SICOI) and the Italian Society of Osseointegration (SIO). In 2015, they merged into a new entity called the Italian Academy of Osseointegration (IAO). Unfortunately, there is still no guideline available regrading antibiotic prophylaxis in oral implant surgery in Italy. Nevertheless, new research assessing the effectiveness of prophylactic antibiotics for oral implant surgery among healthy patients has been published. They recommended a single dose (1 g, 2 g or 3 g) of oral Amoxicillin preoperatively [2, 7]. Moreover, several studies assessed the antibiotic prescribing patterns in conjunction with oral implant surgeries in different countries [13–18].

However, in Italy this issue has yet to be addressed. Therefore, it is currently important to evaluate the different regimens adopted among oral health professionals in Italy in comparison to other countries.

The primary aim of this study was to determine whether antibiotic prophylaxis is a common treatment in Italy among dentists in conjunction with oral implant placement in healthy patients. The secondary aim was to assess the nature and amount (mg) of antibiotics prescriptions in order to evaluate whether any consensus has been reached and if the current recommendations supported by last published evidence are complied [2, 7].

Methods

This observational cross-sectional study is based on a web survey and it is reported according to the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) guidelines [25].

Study design

The questionnaire developed by Deeb et al. (2015) was adapted to the circumstances in Italy with the purpose of collecting data concerning the prescription habits of preventive antibiotics among dental practitioners in conjunction with oral implant therapy [17]. The permission of Deeb and co-authors was obtained to use their questionnaire. After being adjusted and translated, the questionnaire was reviewed on comprehensibility and logical order by an experienced Italian oral implantologist. The way the questions were formulated was found appropriate to assess the intended objectives (Additional file 1).

Setting

Italy is a member state of the European Union, which in 2018 had a population of approximately 60.3 million inhabitants [26]. In March 2018, the number of dentists enrolled with the register held by the National Federation of the Orders of Physicians and Dentists (FNOMCeO) was 61,586 [27].

Participants

In April 2018, the IAO sent an email to all members of the association (400 dental practitioners) containing a link to a web based questionnaire and a brief introduction regarding the study objectives. All potential respondents received a reminder-email from the IAO after 4 weeks, and 2 weeks later the access to the questionnaire was no longer possible. Furthermore, the participants were guaranteed that the research data would be

collected anonymously and the participants had consented the use of the data for the study.

Among all members of the IAO, 36 are female and 20% of all members are actually dentists specialized in oral surgery.

Variables

Data regarding the following items: demographic details, education, work experience and preventive antibiotic prescribed in case of oral implant placement (including dosage and duration) was gathered. Based on the participants' answers regarding dosage and period of intake, the total prescribed amount of antibiotics was calculated (mg).

Data sources / measurement

Each link was directed to a questionnaire that could only be answered once. The questionnaire contained mainly close-ended questions and some open-ended questions.

Bias

The chance of any bias selection was minimized, since a sample of dentists who are known to regularly carry out oral implants were approached.

Study size

The final study size included only the dentists, among the ones approached, who had decided to respond partially or completely to the survey.

Statistical methods

All data was analyzed using STATA® 14 software (StataCorp, College Station, Texas, USA). A statistical evaluation in terms of age, gender and location was carried out. Subsequently, the use of prescribing prophylactic antibiotics and its quantities (mg) before, after or during oral implant surgery was assessed.

The binomial variables corresponding to each of the questions were assessed using proportions (percentage) of the answers to the questionnaire. The chi-squared and Fisher's exact test were run to evaluate the differences in the antibiotics regimen adopted by the participants according to their gender, age, education, location and work experience.

Eventually, the total dosage of antibiotics in mg being prescribed by each participant was calculated and the mean (mg) was used as the main assessing value. The mean was selected as the main assessing value because of the homogeneity of the sample and its validity and its frequent employment in health research. However, information regarding the median and interquartile range was also provided. ANOVA (Student's t-test) was run to assess the differences in the total antibiotics (mg) prescribed in concomitance to dental implant surgery. Standard deviation (Std. Dev.) and *P* values were determined in this way.

Results

Participants

One hundred and sixty participants returned the survey, resulting in a response rate of 40%.

Descriptive data

One hundred and forty-six males (93.6%) and ten females (6.4%) answered the questionnaire, who were mostly between 51 and 60 years old (30.1%).

The majority of the participants (97.4%) graduated from a dental school in Italy. Most of the participants graduated from the School of dentistry of Milan (26.9%), others from the School of dentistry of Padova (8.3%) and from the School of dentistry Sapienza - University of Rome (6.4%). Almost two-thirds of the participants (60.9%) had been working as oral health providers for more than 20 years, almost one-third had between 10 and 20 years of experience (30.1%) and the rest of the respondents had been working for less than 10 years (9%). Most of respondents were working in the Lombardia region (30.7%), others in Veneto (10.9%), Lazio (9.6%), Piemonte (7%) and Toscana (7%).

Outcome data

Approximately 84% of the participants ($n = 134$), currently performing oral implant surgery, stated that they always prescribe prophylactic antibiotics in conjunction with oral implant surgery, only one of the participants (0.6%) never prescribe them.

In addition, 15.6% adopted antibiotics only in particular cases ($n = 25$). Such as cardiopathy requiring antibiotic prophylaxis (24.2%), bone grafting (23.1%); sinus perforation (13.7%); preoperative implant-site infection (11.6%); smokers (9.5%); previous periodontal disease (8.4%); multiple implant insertion (3.1%); medically compromised patients (3.1%) and immediate implant placement (1%). No statistically significant differences were found related to the antibiotic prescriptions of dentists regarding some general characteristics (Table 1).

Most respondents stated that they opt for a combination of a pre- and postoperative regimen (72.9%), while 18.2% only use preoperative regime and 8.8% only postoperative (Table 2).

Main results

Pre-operative antibiotics

The majority of the 143 dentists who prescribe preoperative antibiotics when placing oral implants advise their patients to start 1 h prior to surgery (59.4%) or 1 day prior to surgery (34.2%). The other participants prescribing preoperative antibiotics advise starting 2 days

Table 1 Personal characteristics of dentists related to their antibiotic prescription habits in oral implant surgery

Personal characteristics	Antibiotic prescription habits			Total
	Never	*Sometimes*	*Always*	
Female [a]		8%	6.15%	6.4%
Age (years) [b]				
21–30		12%	3.0%	4.5%
31–40		20%	19.2%	19.2%
41–50		24%	30%	28.9%
51–60	100%	24%	30.7%	30.1%
61–70		16%	14.6%	14.7%
71 or more		4%	2.3%	2.6%
Graduation in Italy[c]	100%	100%	96.1%	96.8%
Experience (years) [d]				
Less than 10		16%	7.7%	8.9%
Between 11 and 20	100%	52%	62.3%	60.9%
More than 20		32%	30%	30.1%
Place of settlement (macroregions) [e]				
North-West		36%	43.1%	41.7%
North-East	100%	24%	20%	21.1%
Centre		16%	23.1%	21.8%
South		16%	10.8%	11.5%
Islands		4%	2.3%	2.6%
Other		4%	0.7%	1.3%
n[f]	1	25	130	156

[a] $P = 0.910$
[b] $P = 0.735$
[c] $P = 0.597$
[d] $P = 0.618$
[e] $P = 0.718$
[f] 4 respondents did not or incompletely answer these questions

Table 2 Antibiotic prescribing regimens and starting time of the prescriptions

Regimen and prescription starting time	*n*	%	*n*	%
Only pre-operative			29	18.2
Immediately prior	2	6.9		
1 h prior	26	89.6		
1 day prior	0	0		
2 days prior	1	3.4		
Pre- and post-operative[a]			116	72.9
Immediately prior	1	0.8		
1 h prior	59	51.7		
1 day prior	49	42.98		
2 days prior	5	4.39		
Only post-operative			14	8.8
Total			157	100.0

[a]2 respondents did not or incompletely declare their prescriptions starting time

(4.2%) or immediately (2.1%) prior to surgery. Table 3 shows the type of antibiotics, its dosage and its regimen.

Oral Amoxicillin/Clavulanic acid was found to be the most frequently prescribed antibiotic when administered 1 or 2 days preoperatively (80.7%) and 1 h or immediately prior to surgery (71.6%). Overall, the most frequently preoperative regimen was 2 g of oral Amoxicillin/Clavulanic acid 1 h prior to surgery ($n = 31$, 21.6%).

Post-operative antibiotics

Almost three quarters (70.6%) of the dentists who advise patients to start the antibiotics treatment post-operatively, prescribe oral 875/125 mg Amoxicillin/Clavulanic acid twice a day for a period varying from five to six days (Table 4). Overall, The most frequently postoperative regimen prescribed was 875/125 mg oral Amoxicillin/Clavulanic acid twice daily for 6 days after surgery ($n = 43$, 32.5%). Table 4 shows the type of antibiotics, its dosage and its regimen.

Amount of prescribed antibiotics

On average, dentists prescribed a total of 10,331 mg of antibiotics (Standard deviation = 4973 mg) before, after

Table 3 Preoperative antibiotic regimens prescribed by dentists

1 h or immediately prior				
Antibiotic type	*Dose (mg)*	*Administration*	n	%
Amoxicillin/Clavulanic acid	2.000	oral	32	36.3
Amoxicillin/Clavulanic acid	875/125	oral	22	25
Amoxicillin	2.000	oral	17	19.3
Amoxicillin/Clavulanic acid	1.000	oral	9	10.2
Amoxicillin	1.000	oral	4	4.5
Amoxicillin	500	oral	1	1.1
Penicillin V	1.000	oral	1	1.1
other[a]			2	2.2
Total			88	100.0
1 or 2 days prior				
Antibiotic type	*Dose (mg)*	*Dosage*	n	%
Amoxicillin/Clavulanic acid	875/125	oral BID	27	49.0
Amoxicillin/Clavulanic acid	1000	oral BID	14	25.4
Amoxicillin	1000	oral BID	8	14.5
Amoxicillin/Clavulanic acid	1000	oral TID	2	3.6
Amoxicillin/Clavulanic acid	800	oral BID	1	1.8
Amoxicillin/Clavulanic acid	875/125	oral TID	1	1.8
Amoxicillin	875/125	oral BID	1	1.8
other[b]	500	oral QD	1	1.8
Total			55	100.0

QD once a day, BID twice a day, TID 3 times daily, QID 4 times daily
[a]*1 "Clarithromycin" and 1 "Zithromax PD for 3 days" mentioned spontaneously*
[b]*"Azithromycin 500 mg 1 cpr every 24 h for 3 days" mentioned spontaneously*
[*]2 respondents did not or incompletely declare their prescriptions starting time and their data could not be included in this table

Table 4 Postoperative antibiotic regimens prescribed by dentists

Antibiotic type	Dose (mg)	Dosage	Duration (days)	n	%
Amoxicillin	1000	oral QD	1	1	0.7
Amoxicillin	1000	oral BID	2	1	0.7
Amoxicillin	1000	oral BID	3	1	0.7
Amoxicillin	1000	oral BID	4	3	2.2
Amoxicillin	1000	oral BID	5	6	4.5
Amoxicillin	1000	oral BID	6	8	6.0
Amoxicillin	1000	oral BID	7	2	1.5
Amoxicillin	500	oral BID	5	1	0.7
Amoxicillin/Clavulanic acid	500/125	oral BID	5	1	0.7
Amoxicillin/Clavulanic acid	500/125	oral TID	6	1	0.7
Amoxicillin/Clavulanic acid	875/125	oral BID	2	3	2.2
Amoxicillin/Clavulanic acid	875/125	oral BID	3	3	2.2
Amoxicillin/Clavulanic acid	875/125	oral BID	4	8	6.0
Amoxicillin/Clavulanic acid	875/125	oral BID	5	28	21.2
Amoxicillin/Clavulanic acid	875/125	oral BID	6	43	32.5
Amoxicillin/Clavulanic acid	875/125	oral BID	7	4	3.0
Amoxicillin/Clavulanic acid	875/125	oral BID	a	1	0.7
Amoxicillin/Clavulanic acid	875/125	oral TID	3	1	0.7
Amoxicillin/Clavulanic acid	875/125	oral TID	4	2	1.5
Amoxicillin/Clavulanic acid	875/125	oral TID	5	3	2.2
Amoxicillin/Clavulanic acid	875/125	oral TID	6	1	0.7
Amoxicillin/Clavulanic acid	875/125	oral TID	7	1	0.7
Penicillin V	875/125	oral BID	7	1	0.7
other[b]				4	3.0
Total				128	100.0

QD once a day, BID twice a day, TID 3 times daily, QID 4 times daily
[a]*not responded*
[b]*1 "Azithromycin 500 mg", 1"Clarithromycin", 1 "Clarithromycin ×2 250 mg ×5 a day* per os*" and 1 "Zithromax PD for 3 days"*

or during oral implant placement, varying form 1000 mg to 22,000 mg. Dentists who prescribed only preoperative antibiotics administered, on average, significantly (p = 0.000) less mg (2241 mg) than their colleagues who prescribed antibiotics only after surgery (10,404 mg), or prior and after surgery (12,436 mg).

No statistically significant differences (p = 0.176) were found in the mean values of the total amount of antibiotics prescribed (mg) by dentists who routinely prescribed prophylactic antibiotics compared to those who prescribed antibiotics not on a regular basis.

Antibiotic regimens in case of penicillin allergies

Participants prescribed a large range of different prophylactic antibiotics to patients allergic to penicillin. Overall, 12 different antibiotics types were prescribed; 94 participants prescribed macrolides, and one participant prescribed none at all. The majority of participants (n = 62, 52.9%) prescribed Clarithromycin instead (Fig. 1).

Compliance with last published evidence

Approximately, only 17% (n = 27) of the participants who prescribed antibiotics before oral implant surgery adhered to recommendations proposed by the latest publications (no more than 3 g of preoperative amoxicillin before oral implant surgery) [2, 7]. Of these, 25 began prescribing antibiotics 1 h before the intervention prescribing Amoxicillin (n = 11) or Amoxicillin/Clavulanic (n = 14). Prescriptions made immediately before the intervention always contained Amoxicillin/Clavulanic. Overall, the most commonly prescribed regimen among these participants was 2 g of oral Amoxicillin 1 h before surgery (n = 10).

Discussion

Key results

Bearing in mind the last published evidence on this topic, most of the dentists surveyed in this study did not comply with their recommendations [2, 7]. They systematically

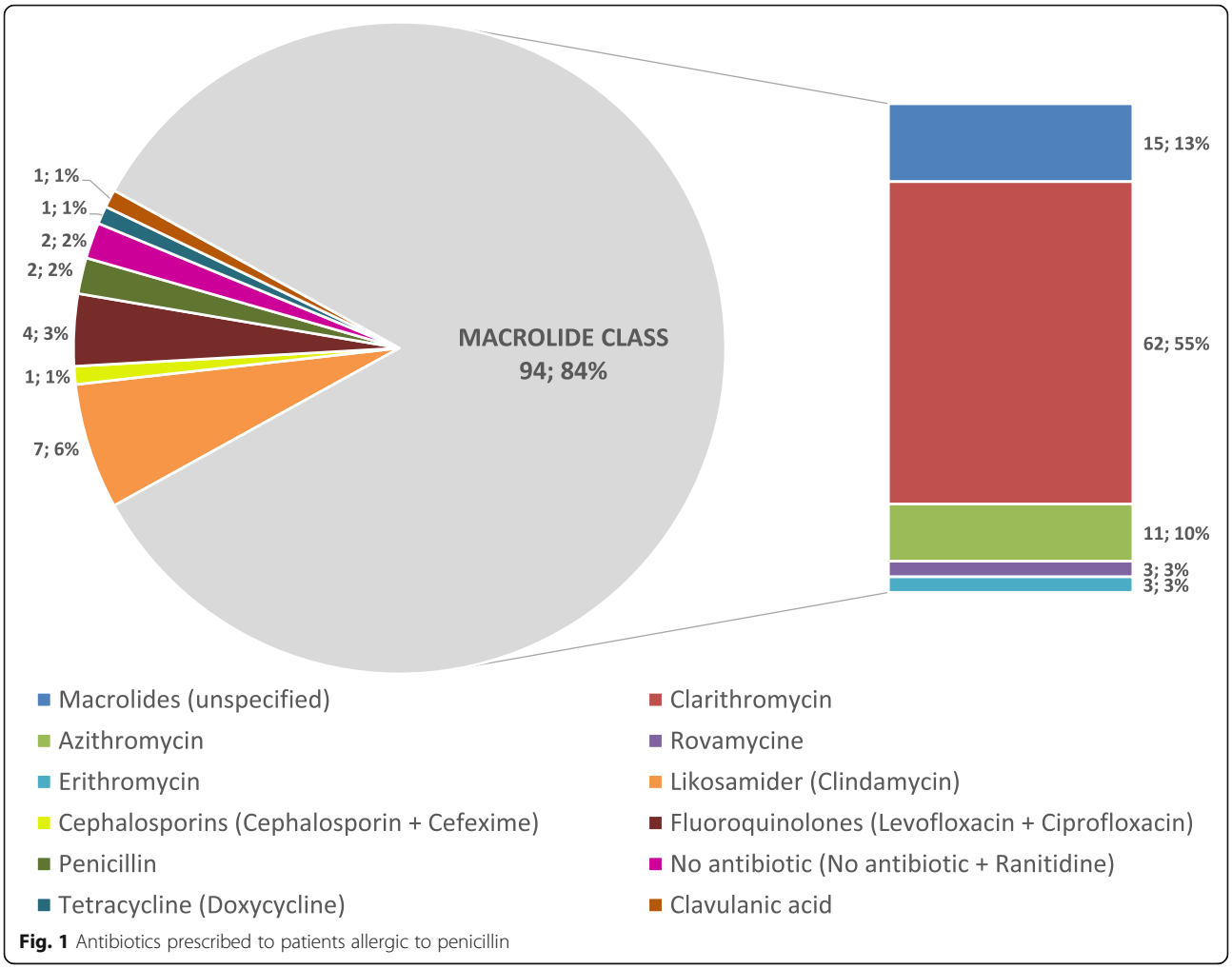

Fig. 1 Antibiotics prescribed to patients allergic to penicillin

prescribed antibiotics in oral implant surgery to healthy patients, frequently using extended postoperative treatments. In addition, there is currently in Italy a discordance about the antibiotic type and regimen selected, especially when treating patients allergic to penicillin.

Limitations

It is unknown as such the number of dentists placing implants in Italy. Therefore, this sample is based on dentists acknowledged as dental practitioners performing oral implant surgery in Italy. The large differences shown in the gender of participants may be related to the low rate of IAO female members. The response rate of 40% was quite low but it was retained satisfactory for a web survey [28]. Nevertheless, this fact could be a potential risk of bias because it is unknown whether the drop-outs are over-prescribing professionals or they are just uninterested in this topic.

Despite being uncertain whether all dentists placing oral implants in Italy were reached, the study sample could not be considered unrepresentative of the target population (members of the IAO).

The survey was completely anonymous to protect the participants' privacy as well as to insure sincere answers. However, truthful answers are not always possible. As in most cross-sectional surveys, what participants declare about their therapies is not always in accordance with their authentic treatment.

In order to favor comparability, this survey was based on a questionnaire performed in the USA. A specialized translation company translated that questionnaire from English to Italian but it was not translated back to English to check correct phrasing order. Instead, an experienced Italian implantologist checked its comprehensively and logical order. Before translation, the original questionnaire was adjusted to circumstances in Italy but it was not validated.

Interpretation

The large range of different regimens prescribed by dentists in this study confirmed that there is not a standard

prophylactic antibiotic regimen prescribed to healthy patients undergoing oral implant surgery in Italy. This has already been shown in other medical procedures where the antibiotic prophylaxis is elective according to each physician [29]. This is also being the case among oral health professionals in other countries [13–18].

Despite having no guidelines available in Italy validating the regular prescription of prophylactic antibiotics in oral implant surgery to healthy patients, this study has shed light on the fact that the majority of dentists in Italy are routinely prescribing long antibiotic treatments to healthy patients without a substantial indication.

Regarding the most recent reviews published on this topic, prophylactic antibiotics have not been found beneficial in preventing postoperative infections. Just a single preoperative dose of amoxicillin (1 g, 2 g or 3 g) prior to oral implant placement might prevent oral implant failure among healthy patients [2, 7]. Consequently, the prescription of postoperative antibiotics in healthy patients could be considered overtreatment and it could lead to potential adverse reactions and unnecessary costs.

Unfortunately, most of dentists surveyed in this study commonly prescribed longer regimens including postoperative antibiotics instead. Most participants consistently prescribed various types of antibiotics and prophylactic regimens without any scientific-based support. The absence of standardized guidelines could be considered an important reason for the discretional use of antibiotics. Moreover, a lack of scientific evidence on the use of further antibiotic types (different to amoxicillin) might be the reason of such large variation when treating patients allergic to penicillin.

A similar survey performed among 109 dentists in UK found that approximately 72% of dentists prescribed antibiotics for all oral implant surgeries [14]. Other analogous study performed among 133 dentists in Sweden showed nearly the same data (74%) [15]. This percentage was considerably lower among 176 dentists in Jordan (50%) [13]. On the other hand, the percentage prescribing prophylactic antibiotics for healthy patients among 217 maxillofacial surgeons in the USA (96%) and among 233 dentists in Spain (90%) was slightly higher than in Italy [17, 18].

In Italy, significant differences in the means of prescribed antibiotics (mg) were found between dentists prescribing only preoperative antibiotics and those prescribing only postoperative or pre- and postoperative regimens. This may be due to the dispersion of the variables (difference in variances), or a real statistically significant difference in their means. The analysis of variance did not offer an explanation but the durations of exclusive preoperative regimens were frequently shorter and this might be a plausible explanation.

The current condition described on this cross-sectional survey may produce a negative discrepancy in the risk-benefit ratio concerning the use of prophylactic antibiotics because of a reduction of their positive effects and an increasing incidence of adverse reactions such as bacterial resistance, patient risk and societal costs.

Generalizability

This cross-sectional survey was performed among dentists acknowledge in Italy as professionals who carry out oral implant surgery and who have graduated in representative proportions from different Italian dental schools. The survey has an internal validity (lack of bias in estimating the dentist's current antibiotic prescribing habits in combination with oral implant surgery) for its target population (members of the IAO). Furthermore, this study has also an external validity (lack of bias to extrapolate its estimations) for an external population (all dentists placing oral implants in Italy). The authors found no epidemiological reason indicating that our target population differs from all dentists' population currently placing oral implants in Italy. Therefore, the authors assumed that the estimates from this survey could be extrapolated to all dentists currently performing oral implant surgery in Italy.

Conclusions

Dentists in Italy on a large scale prescribe antibiotic prophylaxis in conjunction with oral implant surgery among healthy patients. A high range of prophylactic regimens is prescribed and they are not adhering to the science-based recommendations [2, 7]. Guidelines based on last published evidence and focused on the indications for prophylactic antibiotics among healthy patients (also for those allergic to penicillin) are required to prevent bacterial resistance, side effects and costs caused by overtreatment and the irrational use of antibiotics.

Abbreviations

EU: European Union; FNOMCeO: Orders of Physicians and Dentists; g: Grams; IAO: Italian Academy of Osseointegration; mg: Milligrams; SICOI: Italian Society of Oral Surgery and Implant Dentistry; SIO: Italian Society of Osseointegration; Std. Dev: Standard deviation; STROBE: Strengthening the Reporting of Observational studies in Epidemiology; UK: United Kingdom; USA: United States of America

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Authors' contributions

All authors have read and approved the manuscript. Conceptualization: F. R. S. Formal Analysis: F. R. S., C. R. A. Investigation: F. R. S., I. A., A. C. Methodology: F. R. S., C. R. A., A. C. Project Administration: I. A. Resources: C. R. A., A. C. Software: F. R. S., C. R. A. Writing – Original Draft: F. R. S., I. A., C. R. A. Writing – Review & Editing: A. C., F. R. S.

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Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate
Ethical approval was waived because this study did not perform any intervention in humans and it did not use any personal data or biological samples of human origin. All collected data were completely anonymized. The informed consent obtained from study participants was written.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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Additional file 1. Questionnaire. This file contains the English version of the survey sent to IAO members.

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RESEARCH ARTICLE

Antibiotic dosage prescribed in oral implant surgery: A meta-analysis of cross-sectional surveys

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Abstract

This study aimed to assess the dosage and types of antibiotics prescribed in oral implant surgery, compare them among the different subpopulations (country and prescription regimens) and against the evidence-based recommended dosage: a 2-gram single preoperative dose of amoxicillin. A meta-analysis of cross-sectional surveys was conducted, which reports the overall dosage (and type) of antibiotics prescribed in combination with implant placement. PubMed, Cochrane, Science, Direct, and EMBASE via OVID were searched until April 2019. Three reviewers independently undertook data extraction and risk of bias assessment. The outcome variable was set on the average of prophylactic antibiotics prescribed per oral implant surgery. Overall, 726 participants from five cross-sectional surveys, representing five different countries were finally included. Amoxicillin was the most prescribed antibiotic. On average, 10,724 mg of antibiotics were prescribed per implant surgery. This average was significantly ($p<0.001$) higher than 2,000 mg. Overall, amoxicillin doses were significantly higher than 2,000 mg (9,700 mg, $p<0.001$). All prescribed amoxicillin regimens independently contained more than 2,000 mg, including those comprising only preoperative amoxicillin (2,175 mg, $p = 0.006$). Exclusive preoperative antibiotic regimens were the only subgroup with prescription dosages below this threshold ($p = 0.091$). Significant variations in antibiotic prescriptions were found among different countries and antibiotic regimens ($p<0.001$). In conclusion, the average dose of antibiotics prescribed per oral implant surgery was larger than the evidence-based recommended dose in healthy patients and straightforward conditions. In addition, variations in the average antibiotic dosages were found among different countries and prescription regimens.

Introduction

Oral implant therapy has developed into a very predictable treatment for the rehabilitation of a partial or complete edentulous oral cavity [1–3]. Nevertheless, oral implant failures do occur [4]. Postoperative infection after bacterial contamination of the surgical site is believed to be one of the main sources of early implant failures; however, it is also known to be associated to certain delayed implant failures [5]. Therefore, perioperative antibiotics have been studied and recommended to prevent these complications [6–11].

Reviews published in this field found that antibiotics were not effective in reducing the incidence of post-operative infections; nonetheless, preoperative antibiotics were found to be beneficial in preventing oral implant failures [8,9,12]. Esposito et al. [9] suggested that routinely prescribing a single pre-operative dose of 2,000 mg of amoxicillin might prevent implant failures in healthy patients and in straightforward conditions. However, 25 patients would need to receive this treatment in order to prevent just one patient from having an implant failure [9].

The prescription of prophylactic antibiotics in oral implant surgery remains controversial [13]. Numerous cross-sectional surveys have been conducted to assess prescription habits in oral implant surgery among dental professionals in different countries [14–26]. These studies reported a wide range of different antibiotic prescriptions and a wide selection of antibiotic types. Recommendations published in recent meta-analyses are often not followed. This emphasizes the need to establish standardized guidelines to support clinicians' decision-making practices [15,22–25].

Irrational use of antibiotics may lead to an unjustified increase in economic costs and adverse reactions such as allergies, toxicity, gastrointestinal disorders and bacterial resistance [27,28]. The latter condition has become a major threat worldwide. Recent studies have shown a direct relationship between antibiotic consumption and the emergence and dissemination of resistant bacterial strains [29].

This alarming situation, coupled with the substantial growth of the oral implant market in recent years [30], predicates an important public health concern. The prescription of antibiotics in dentistry is still rising despite many campaigns to prevent their excessive use [31,32]. Moreover, additional studies have been requested to better assess antibiotic prescription behaviors in dentistry [33]. Consequently, it was deemed necessary to evaluate the prophylactic antibiotic treatments prescribed in oral implant therapy and to determine the quantity of antibiotics that may be considered as overtreatment. As a result, this would permit us to estimate the potential risk caused by the irrational use of prophylactic antibiotics in this situation.

This meta-analysis of cross-sectional surveys primarily aimed to assess the dosage and types of antibiotics prescribed per oral implant surgery. The secondary aim was to contrast the average dosage of prescribed antibiotics against the evidence-based recommended regimen in healthy patients and in straightforward conditions: a single 2-g preoperative dose of amoxicillin [9].

An additional aim of this study was to assess the differences in dosage and antibiotic type between countries and prescription regimens.

The null hypotheses were postulated as follows: (1) the average dosage of prophylactic antibiotics prescribed per oral implant surgery is equal to a single dose of 2,000 mg and (2) there are no variations in the average dosage of prescribed antibiotics among the different countries and prescription regimens.

Methods

The study was conducted and reported in accordance with the Meta-analysis of Observational Studies in Epidemiology group [34]. Details of the protocol for this meta-analysis were registered on the International Prospective Register of Systematic Reviews (PROSPERO) with the following register identification: CRD42020156885.

Eligible studies included all articles evaluating antibiotic prescriptions in association with oral implant surgery and in adherence with the following Participants; Intervention; Comparison; Outcome and Study type (PICOS) framework:

Participants: General dental practitioners or specialists placing oral implants.

Intervention: Antibiotic prescriptions in association with oral implant surgery.

Comparisons:

1. Evidence-based recommended dosage in healthy patients and in routine conditions: single pre-operative dose of 2,000 mg [9].
2. Comparisons among different subpopulations (countries, antibiotic types and prescription regimens).

Outcomes: Average dosage and types of antibiotics prescribed per oral implant surgery.

Study type: Cross-sectional survey.

Publications were excluded if they were clinical trials, case series or retrospective studies. There were no restrictions on language or publication year. Publications that did not report enough information to calculate the total dosage of antibiotics contained in their participants' prescriptions were also excluded.

Searches were conducted in the following electronic databases up to June 4, 2020: Embase, PubMed, Ovid Medline, Scopus, Science-Direct, Web of Knowledge, as well as the Spanish General University Board database of doctoral theses in Spain, the Spanish National Research Council bibliographic databases, and the Spanish Medical Index.

Three independent investigators carried out the search in the databases. The searched terms were descriptors of the PICO components: antibiotics, oral implant surgery, dental implant surgery, oral implant placement, dental implant placement, and cross-sectional survey.

MeSH and search algorithms connected with Boolean operators were used as keywords for the electronic search. No filters were applied in the Ovid Medline and PubMed search: (antibiotic) AND (((oral OR dental) implant AND surgery) OR ((oral OR dental) implant AND placement)) AND (survey). In Scopus, the search was limited to "Dentistry" and "Article" for subject area and document type: (antibiotic) AND (((oral OR dental) implant AND surgery) OR ((oral OR dental) implant AND placement)) AND (survey) AND (LIMIT-TO (DOCTYPE, "ar")) AND (LIMIT-TO (SUBJAREA, "DENT")). The search in In Web of Knowledge was filtered by "Article": TS = (antibiotic "AND" oral implant surgery "OR" dental implant surgery "AND" survey). In Science Direct, "Research articles" filtered the search: (antibiotic) AND (((oral OR dental) implant AND surgery) OR ((oral OR dental) implant AND placement)) AND (survey).

The search in Embase was limited to "Article", "Short Survey", "Article in Press" and "Questionnaire": (antibiotic) AND (((oral OR dental) implant AND surgery) OR ((oral OR dental) implant AND placement)) AND (survey) AND ('article'/it OR 'article in press'/it OR 'short survey'/it) AND 'questionnaire'/de.

For databases in Spanish, the following terms were used: (antibioticos) AND (implante dental O implante oral) AND (encuesta).

The references of all retrieved papers were reviewed as well. No potentially unpublished material could be identified.

Two independent reviewers (F.R.S. and C.R.A.) screened the titles and abstracts from the records identified from the search by using Cochrane's online software [35]. Full-text articles were acquired for records that fulfilled the inclusion criteria. The researchers contacted every corresponding author when extra information was required in the selection process. All discrepancies were discussed with a third researcher (I.A.). The reasons for exclusion were reported (Fig 1).

The recorded data included the following: antibiotic type, regimen (preoperative, postoperative or both), dose, treatment duration and country. If the original dataset of an included study could not be obtained, information relating to the antibiotic type, prophylactic regimen (preoperative, postoperative or both), dose and treatment duration were extracted from the published paper by two independent researchers (F.R.S. and C.R.A.). A third party was consulted to resolve any disagreement (I.A.). Calculations using data from tables were performed if the data on any variable were not explicitly stated in the text. The corresponding authors of 8 different studies were contacted because the necessary information from their studies were unclear [14–20,26].

One study surveyed 133 Swedish dental professionals [21]. Of these, 98 prescribed antibiotics while 35 did not prescribe any prophylactic antibiotics. This study completely described 85 antibiotic regimens; however, there were unfortunately 13 missing antibiotic regimens. After contacting the authors, no extra information was obtained. Therefore, the 85 dentists who prescribed antibiotics were included with a proportionate number of non-prescribing professionals (n = 22) in place of the 35 at the beginning.

The same adjustment was applied to other included studies with 29 participants who were unfortunately excluded because they did not provide a description of their prescription regimens (14 from Spain, 6 from Italy and 9 from the Netherlands). The newly calculated and proportionate numbers of non-prescribing professionals in these cases were 3.75, 0.96 and 4.7 respectively, while the original numbers were 4, 1 and 5 respectively. As the calculated values were very close to the original ones, it was decided to keep the initial numbers in order to perform the most conservative analysis possible [24–26].

The authors of the other five articles were unsuccessfully contacted in order to collect necessary data for inclusion in the meta-analysis [15,17–19]. The authors of two articles were successfully contacted; however, data requested on prescription dosage was insufficient for inclusion in the meta-analysis because their surveys did not collect this information [14,20].

Two independent reviewers (F.R.S. and C.R.A.) assessed the quality of the included studies using the National Heart, Lung, and Blood Institute Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies [36]. All discrepancies were discussed with a third researcher (I.A.). The studies were categorized as low, moderate or high quality if the percentage of affirmative answers to the checklist was less than 50%, between 50% and 80% or more than 80% respectively.

Each included study presented different datasets and data codifications. This heterogeneous presentation of data was for a limitation to performing a proper quantitative analysis (meta-analysis). To overcome this limitation and accomplish the study objectives, a uniform database with the original dataset from each study was created. The software STATA version 15 (StataCorp LLC, College Station, TX, USA) was used to generate this database and to perform all statistical analyses.

The average dosage (mg) of prophylactic antibiotics prescribed per implant surgery was calculated according to the individual prescription regimens (multiplying the treatment dose, dosage and the corresponding duration) with an estimation of the standard deviation (SD).

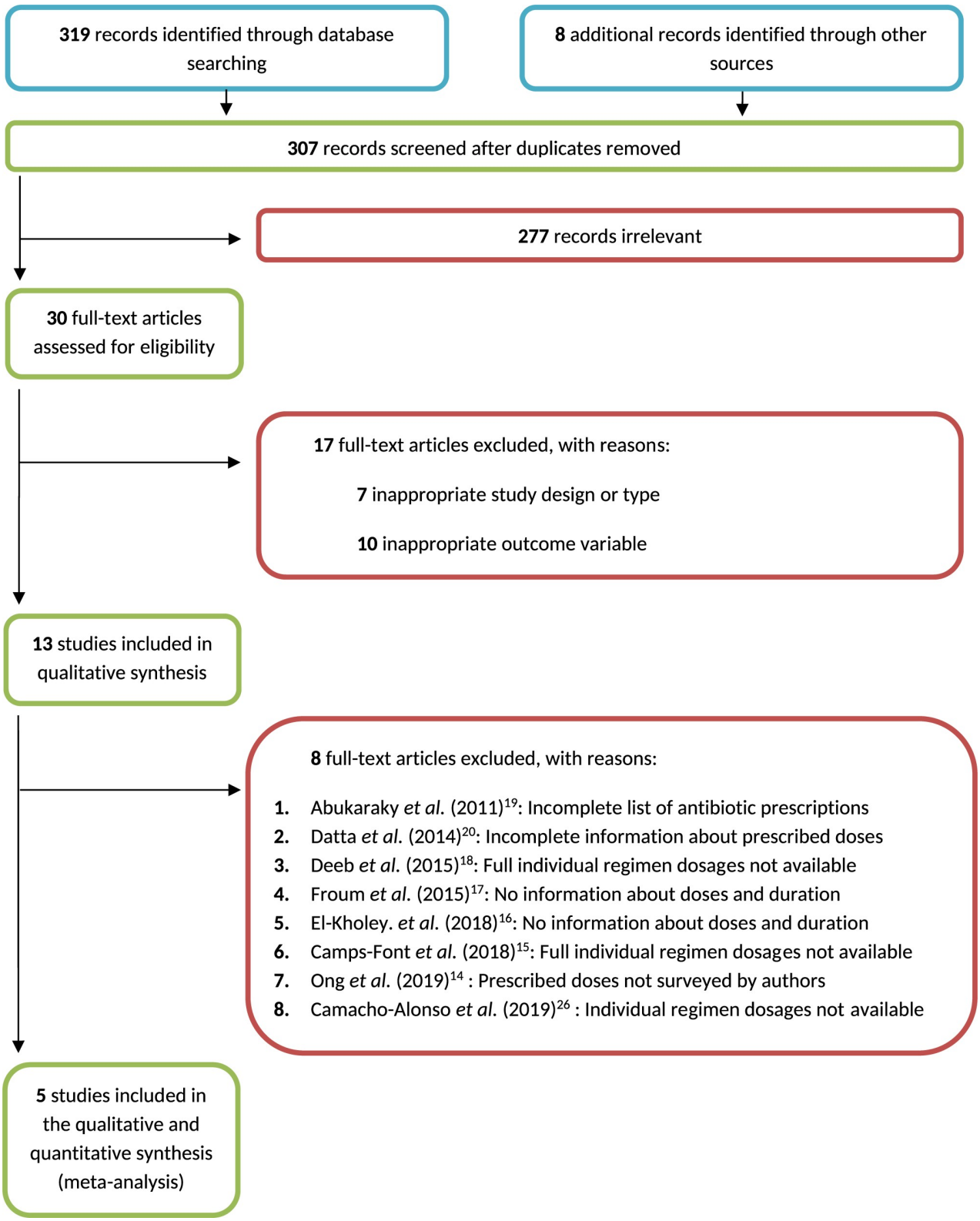

Fig 1. Flow diagram. This diagram describes the study selection process.

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Participants who never prescribe prophylactic antibiotics for oral implant surgery were also included in this analysis. The normal distribution of the outcome data was graphically assessed using quantile-quantile plots (Q-Q plots).

Student's t-test was used to compare the means of the prophylactic antibiotics prescribed per study, country and prescription regimen against the evidence-based recommended regimen: single pre-operative dose of 2,000 mg. In this analysis, prescriptions were included only if they contained antibiotics with a Defined Daily Dose (DDD) equal to the evidence-based recommended regimen (2,000 mg) or equal to the DDD of amoxicillin (1,500 mg) according to the Anatomical Therapeutic Chemical system of the World Health Organization [37].

Multiple f-tests were used to compare the variations in different groups. Depending on the variance analysis, multiple t-tests for equal or unequal variances were performed to compare the means of the antibiotics prescribed in the included studies. Bonferroni standard corrections were performed in both, f- and t-tests. In both tests, the α-value was calculated by dividing 0.05 by the total number of performed comparisons.

Results

Five cross-sectional surveys were finally included in this meta-analysis [21–25]. Table 1 shows the descriptive information for of each study included in the quantitative analysis. A flow chart describes the selection process, records and full-text exclusions with their justifications (Fig 1).

Four studies were judged as being of moderate quality [21–25] and one of low quality [22]. The percentage of affirmative answers to the National Health Index checklist was 75% for the study performed in Sweden, 54.5% for the other 3 studies (Spain, the Netherlands and Italy) and 45.5% for the study performed in the United Kingdom. The data distribution of the outcome variable is shown in the Q–Q plots (S1 Fig).

Overall, 726 participants were enrolled in this meta-analysis. All prophylactic prescriptions consisted of oral antibiotics. Fig 2 illustrates the antibiotic types and regimens prescribed per country (Fig 2).

On average, 10,724 mg of prophylactic antibiotics were prescribed per oral implant surgery. This average dose of antibiotics was found to be significantly higher ($p<0.001$) than the evidence-based recommended dose (2,000 mg).

Table 1. Descriptive information of each included study.

Study (year)	Country	n	Type of professionals	Most frequently prescribed regimen (n)	Participants routinely prescribing prophylactic antibiotics (n)
Khalil et al., (2012) [21]	Sweden	133	General dentists	2 g of oral amoxicillin pre-operatively (27)	74% (98)
Ireland et al., (2012) [22]	United Kingdom	109	General dentists	3 g of oral amoxicillin one hour pre-operatively (54)	72% (76)
Arteagoitia et al., (2018)[23]	Spain	233	General dentists	500 mg of oral amoxicillin TID 1 day pre-operatively and for 7 days post-operatively (10)	89% (207)
Rodríguez Sánchez et al., (2019)[24]	Netherlands	151	General dentists, oral implantologists, periodontists and maxillofacial surgeons	2 g of oral amoxicillin 1 hour or immediately prior to surgery (35)	44% (66)
Rodríguez Sánchez et al., (2019)[25]	Italy	160	General dentists and oral surgeons	875/125 mg of oral amoxicillin/clavulanic acid BID 1 day pre-operatively and for 5 days post-operatively (15)	84% (134)

BID: Two times daily; TID: Three times daily.

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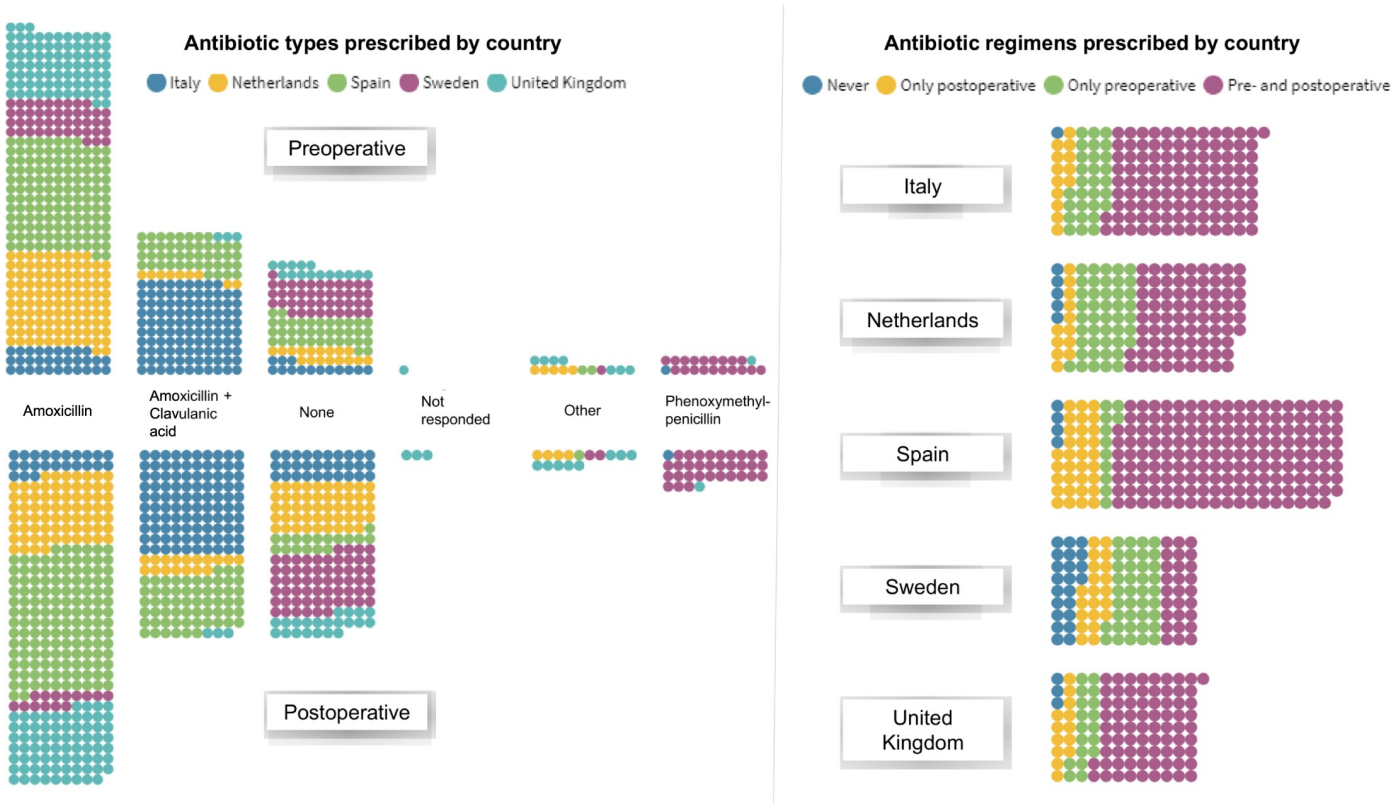

Fig 2. Antibiotic types and regimens prescribed per country. Each dot represents one participant included in the meta-analysis.

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Table 2 shows the average dose of prophylactic antibiotics prescribed per antibiotic type and country. Amoxicillin was the most frequently prescribed antibiotic type, followed by amoxicillin in association with clavulanic acid. Most professionals from the Italian survey, followed by the participants from the Spanish survey prescribed clavulanic acid (Table 2).

The overall dose of the prescribed amoxicillin was significantly higher than 2,000 mg (9,700 mg, $p<0.001$). All the regimens with only amoxicillin independently comprised a significantly higher dose than the reference of 2,000 mg, including those with only pre-operative amoxicillin (2,175 mg, $p = 0.006$). Nevertheless, the participants from United Kingdom prescribing exclusively pre-operative amoxicillin were the only ones that significantly ($p<0.001$) did it above the level of 2,000 mg per oral implant surgery (Table 3).

Among the different subpopulations (country and prescription regimen), professionals prescribing only pre-operative antibiotics were the only ones whose antibiotic prescriptions (2,110 mg) were not significantly ($p = 0.091$) above this threshold (Table 4). A forest plot taking the outcome variable into account is shown in Fig 3 (Fig 3).

Bartlett's test was found to be statistically significant ($p<0.001$) among the different countries and prophylactic prescription regimens. Moreover, I^2 was found to be low (18.7%). Therefore, low heterogeneity was found between countries (Table 5).

The multiple-comparison analysis of variances showed that all comparisons of variances were statistically significant, except for three: Italy against the Netherlands, Italy against the United Kingdom, and the United Kingdom against the Netherlands. Therefore, both countries in each of these comparisons were found to be homogeneous, relating to the dosages of prescribed antibiotics.

Table 2. Average dosage of prophylactic antibiotics (mg) prescribed per country and antibiotic type.

Antibiotic type / Country		Spain	Italy	Netherlands	Sweden	United Kingdom	Overall	ATC code	DDD
Amoxicillin	Mean	1,5047	8,672	6,561	4,642	7,399	9,700	J01CA04	1,500
	SD	*6,829*	*5,180*	*4,207*	*5,325*	*3,676*	*6,726*		
	n	150	32	111	44	86	423		
Amoxicillin / Clavulanic Acid	Mean	19,178	10,685	7,600	-	17,494	13,208	J01CR02	1,500
	SD	*8,228*	*4,839*	*4,029*	-	*14,946*	*7,472*		
	n	56	117	10	0	4	187		
Penicillin V	Mean	-	15,000	-	18,079	3,000	17,625	J01CE02	2,000
	SD	-	0	-	*17,197*	0	*16,925*		
	n	0	1	0	38	1	40		
Amoxicillin / Amoxicillin + Clavulanic Acid	Mean	25,166	11,000	10,296	-	8,812	13,031	J01CA04 / J01CR02	1,500 / 1,500
	SD	*763*	*7550*	*1,406*	-	*265*	6,726		
	n	3	3	8	0	2	16		
Azithromycin	Mean	-	-	11,000	-	10,100	10,550	J01FA10	300
	SD	-	-	*3,869*	-	*1,732*	*2,726*		
	n	0	0	3	0	3	6		
Clindamycin	Mean	-	-	11,000	600	12,600	6,600	J01FF01	1,200
	SD	-	-	*3,869*	*0*	*0*	*6,600*		
	n	0	0	1	1	1	3		
Clindamycin / Amoxicillin + Clavulanic Acid	Mean	-	-	11,200	-	-	11,200	J01FF01 / J01CR02	1,200 / 1,500
	SD	-	-	*2,687*	-	-	*2,687*		
	n	0	0	2	0	0	2		
Amoxicillin / Penicillin V	Mean	-	-	-	24,000	8,000	16,000	J01CA04 / J01CE02	1,500 / 2,000
	SD	-	-	-	*0*	*0*	*11,314*		
	n	0	0	0	1	1	2		
Metronidazole	Mean	-	-	-	6,000	25,200	15,600	J01XD01	1,500
	SD	-	-	-	-	*0*	*13,576*		
	n	0	0	0	1	1	2		
Erythromycin	Mean	3,000	-	-	-	6,500	4,750	J01FA01	2,000
	SD	0	-	-	-	*0*	*2,475*		
	n	1	0	0	0	1	2		
Amoxicillin / Metronidazole	Mean	-	-	-	-	24,000	24,000	J01CA04 / J01XD01	1,500 / 1,500
	SD	-	-	-	-	*0*	*0*		
	n	0	0	0	0	1	1		
Primcillin	Mean	-	-	-	-	18,400	18,400	J01CE02	2,000
	SD	-	-	-	-	*0*	*0*		
	n	0	0	0	0	1	1		
Cefazolin	Mean	-	-	-	-	8,250	8,250	J01DC02	3,000
	SD	-	-	-	-	*0*	*0*		
	n	0	0	0	0	1	1		
Cefuroxime / Amoxicillin + Clavulanic Acid	Mean	-	-	-	-	14,375	14,375	J01DC04 / J01CR02	500 / 1,500
	SD	-	-	-	-	*0*	*0*		
	n	0	0	0	0	1	1		
Cefazolin / Amoxicillin + Clavulanic Acid	Mean	25,000	-	-	-	-	25,000	J01DB04 / J01CR02	3,000 / 1,500
	SD	0	-	-	-	-	*0*		
	n	1	0	0	0	0	1		

(*Continued*)

Table 2. (Continued)

Antibiotic type / Country		Spain	Italy	Netherlands	Sweden	United Kingdom	Overall	ATC code	DDD
Not responded	Mean	-	-	2,000	-	10,500	7,667	-	-
	SD	-	-	0	-	0	4,907		
	n	0	0	1	0	2	3		
None	Mean	0	0	0	0	0	0	-	-
	SD	*0*	*0*	*0*	*0*	*0*	*0*		
	n	4	1	5	22	3	35		
Overall	Mean	15,974	10,231	6,742	8,615	8,216	10,713	-	-
	SD	*7,764*	*5,044*	*4,310*	*13,103*	*5,426*	*8,315*		
	n	215	154	141	107	109	726		

The name Penicillin V was used in this table instead of Phenoxymethylpenicillin, being both different names for the same drug.

SD: standard deviation; DDD: defined daily dose; ATC: Anatomical Therapeutic Chemical

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In addition, mean comparisons were found to be statistically significant, except for Italy against Sweden, the Netherlands against Sweden, the United Kingdom against the Netherlands, Sweden against the United Kingdom and only post-operative against pre- and postoperative. Consequently, both countries in each of these comparisons were found to prescribe a similar average dosage of prophylactic antibiotics (Table 5).

Discussion

This meta-analysis quantitatively assessed the prescriptions of prophylactic antibiotics in association with oral implant surgery and compared them to the existing scientific

Table 3. Average dosage of amoxicillin (mg) prescribed per country and prescription regimen.

Prescription regimen / Country		Spain	Italy	Netherlands	Sweden	United Kingdom	Overall
Only pre-operative	Mean	2,182†	1,900‡	2,042¶	2,025††	2,926*	2,175‡‡
	SD	*1,401*	*316*	*462*	*211*	*528*	*655*
	n	11	10	42	30	17	110
Only post-operative	Mean	13,433	1,0667	9,300	-	6,675	10,769*
	SD	*4,603*	*2,309*	*1,549*	-	*1,390*	*4,345*
	n	21	3	10	0	10	44
Pre- & post-operative	Mean	16,534	11,921	9,314	10,250	8,810	12,603*
	SD	*6,111*	*2,878*	*3,042*	*6,635*	*3,384*	*6,012*
	n	118	19	59	14	59	269
Overall	Mean	15,047*	8,672*	6,561*	4,642**	7,399*	9,700*
	SD	*6,829*	*5,180*	*4,207*	*5,325*	*3,676*	*6,726*
	n	150	32	111	44	86	423

Bilateral T-test contrasting mean = 2,000 mg

*$p<0.001$

**$p = 0.002$

†$p = 0.676$

‡$p = 0.343$

¶$p = 0.561$

††$p = 0.521$;

‡‡$p = 0.006$

SD: Standard deviation

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Table 4. Average dose of prophylactic antibiotics (mg) prescribed per country and prescription regimen.

Prescription regimen / Country		Spain	Italy	Netherlands	Sweden	United Kingdom	Overall
Never	Mean	-	-	-	-	-	-
	SD	-	-	-	-	-	-
	n	4	1	5	22	3	35
Only pre-operative	Mean	2,182**	1,786††	2,037‡‡	2,020¶	2,930*	2,110¶¶
	SD	*1,401*	*630*	*451*	*302*	*513*	*676*
	n	11	28	44	37	18	138
Only post-operative	Mean	13,210	10,404	9,156	31,600	6,579	15,593*
	SD	*5,988*	*2,440*	*1,495*	*13,003*	*1,356*	*11,490*
	n	32	13	12	20	11	88
Pre- & post-operative	Mean	17,830	12,414	9,413	7,327	9,992	13,282*
	SD	*6,782*	*3,254*	*2,937*	*5,770*	*5,672*	*6,480*
	n	166	112	73	26	67	444
Overall	Mean	15,993*	10,231*	6,617*	8,545*	8,025*	10,724*
	SD	*7,725*	*5,044*	*4,287*	*13,119*	*5,614*	*8,377*
	n	213	154	134	105†	99	705‡

† 13 participants with missing regimens could not be included. To keep a proportional number of non-prescribing participants, only 22 out of the original 35 participants who never prescribe prophylactic antibiotics were included.

‡ 21 participants excluded because their prescriptions included antibiotic types with DDDs different to 2,000 mg or from the DDD value of amoxicillin (1,500 mg).

Bilateral T-test contrasting mean = 2,000 mg

*$p<0.001$

**$p<0.676$

††$p = 0.083$

‡‡$p = 0.590$

¶$p = 0.781$

¶¶$p = 0.091$

SD: standard deviation

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recommendations. In addition, this study provides quantitative comparisons of the average dosage of antibiotics and the regimens prescribed in oral implant surgery by professionals from different countries.

This meta-analysis indicates that the average dosage of prophylactic antibiotics prescribed in conjunction with oral implant surgery is approximately five times larger than the evidence-based recommendations for healthy patients and straightforward conditions: a 2-gram single preoperative dose. Even for prescriptions of only pre-operative antibiotics, the average dosage was higher than the evidence-based recommended dose [9]. Countries presented great variability in their average dosage of prescribed antibiotics and prescription regimens. These findings may be the consequence of a lack of consensus on the use of antibiotics in oral implant surgery among clinicians. Furthermore, the prescription variances found among the different countries included in this meta-analysis may be attributed to this clinician's disagreement coupled with the idiosyncratic and cultural prescription habits of each country.

Cross-sectional studies may be the most appropriate study design to estimate the antibiotics prescribed in oral implant surgery, due to the lack of official records. Nevertheless, participants' statements in this kind of study may differ from their real behavior and the included participants may have changed their conduct over time, since the included surveys were performed over the past years. In addition, patient interviews are required to measure the real drug intake at the patient level because they do not always follow the prescriptions.

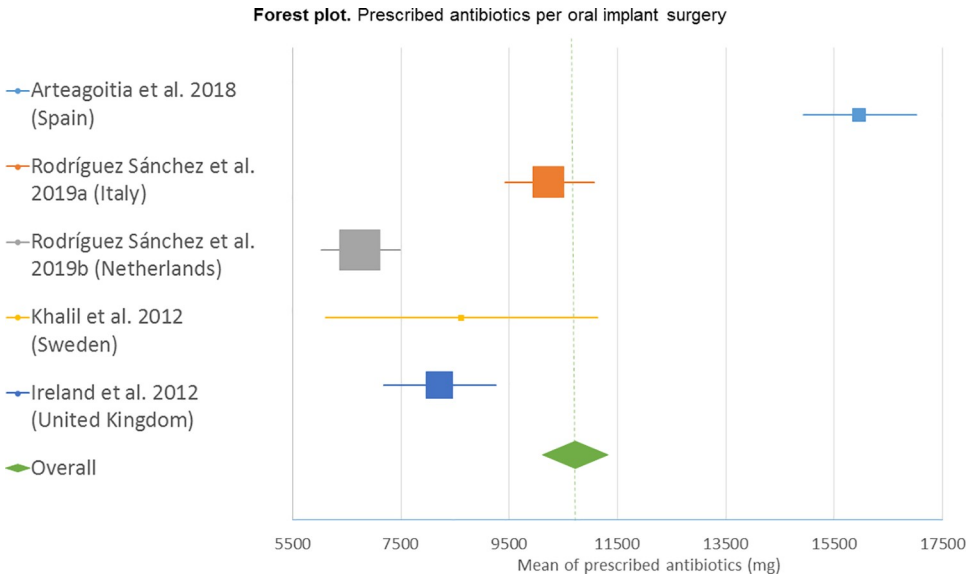

Fig 3. Forest plot. The forest plot represents the estimates of the mean values and 95% confidence intervals for each outcome variable. The area of the squares around the mean values is proportional to the weight of the study in the analysis. A continuous horizontal line indicates the 95% confidence intervals, while a rhombus and a dotted line indicate the overall mean value.

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Despite all the efforts made to include the largest number of cross-sectional surveys in this meta-analysis, only five studies from five countries could be included. Moreover, the cross-sectional surveys did not reach all practitioners placing oral implants in each country, which may

Table 5. Multiple comparison of means and variances of prescribed prophylactic antibiotics (mg).

Group comparisons	Contrast of means†	95% CI	*P*-value‡	*p*-value§
Spain vs. Italy	5,743	4,430–7,056	<0.001	<0.001
Spain vs. Netherlands	9,232	7,969–10,495	<0.001	<0.001
Italy vs. Netherlands	3,489	2,409–4,569	0.058	<0.001
Spain vs. Sweden	7,436	4,740–1,032	<0.001	<0.001
Italy vs. Sweden	1,693	-922–4,307	<0.001	0.202
Netherlands vs. Sweden	-1,796	-4,386–794	<0.001	0.172
Spain vs. United Kingdom	7,758	6,298–9,219	<0.001	<0.001
Italy vs. United Kingdom	2,015	732–3,298	0.405	0.002
United Kingdom vs. Netherlands	1,473	261–2,686	0.011	0.017
Sweden vs. United Kingdom	323	-2,367–3,012	<0.001	0.813
Pre- & post-operative vs. Only pre-operative	11,022	10,402–11,641	<0.001	<0.001
Only post-operative vs. Pre- & post-operative	2,122	-329–4,573	<0.001	0.089
Only pre-operative vs. Only post-operative	13,144	10,756–15,531	<0.001	<0.001

† Differences were calculated by deducting the mean value in the second group from that of the first.

‡ Bilateral F-tests contrasting H_0: equal variances. The α-value was calculated by dividing 0.05 by the total number of performed comparisons, 10 when comparing countries (α-value = 0.005) and 3 when comparing prescription regimens (α-value = 0.016)

§ Two-sample t-test contrasting means with equal or unequal variances depending on the variances F-tests. The α-value was calculated by dividing 0.05 by the total number of performed comparisons: 10 when comparing countries (α-value = 0.005) and 3 when comparing prescription regimens (α-value = 0.016)

CI: confidence interval.

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represent a source of bias. The combined analysis of all included studies in this meta-analysis increased the sample size and consequently, the power of the planned hypothesis analysis. The variability found among the surveys did not cause heterogeneity in the results. The quality analysis performed through each of the included surveys suggests that the quality of this meta-analysis may be moderate, which could represent an important limitation. Consequently, the findings of this study must be considered cautiously due to the inherent limitations of any cross-sectional survey and the intrinsic weakness of the included papers, coupled with the limitations of this meta-analysis. These facts must be contemplated with utmost care to correctly interpret the outcomes of this meta-analysis.

Regardless of the determination of the authors, not all participants of the included surveys could be enrolled in this meta-analysis because of missing information. This may represent only a minor limitation in the data collection procedure as this problem was later solved by including a proportionated sample of non-prescribing professionals.

The average dosage of prescribed antibiotics was compared against a single pre-operative dose of 2,000 mg, which was considered the evidence-based recommendation in healthy patients and straightforward conditions despite its relative effectiveness [9]. This recommended dose was suggested for amoxicillin; however, but other antibiotic types have different assumed maintenance dosages for their main indications for adults. This could represent significant limitation when contrasting the prescriptions against this recommendation, despite the fact that most majority of the prescriptions included in this meta-analysis involved amoxicillin with or without clavulanic acid or antibiotic types coming from the family of penicillin.

Therefore, only antibiotics types with equal DDDs to amoxicillin or the evidence-based recommendations were included in this comparison. The DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults. The DDDs for anti-infectives are the main rule based on their use in infections of moderate severity [37].

In addition, two cross-sectional surveys (Sweden and the United Kingdom) were performed before these recommendations were published [21,22]. The time lapse since the publication of these studies may have increased the possibilities of changes in the participants' antibiotic prescription habits for oral implant surgery. This means that the current prescriptions could have varied over time and, therefore, the results of this study should be considered cautiously.

The professionals included in this study may present differences in their makeup, with possible variations in the proportion of specialists and general dentists between each country. This could lead to the presence of longer and more frequent antibiotic prescriptions among participants depending on their degree of specialization and the complexity of the surgeries performed.

Nonetheless, three of the cross-sectional surveys, comprising the majority of the participants included in this meta-analysis (70%), contained prescriptions exclusively made for oral implant surgery in healthy patients and straightforward conditions [23–25]. Although the other two surveys may have included some prescriptions based on different circumstances, the majority of their participants (72% and 74% respectively) reported that they routinely prescribed antibiotics regardless of any specific conditions [21,22]. Despite these limitations, the lack of a clinical consensus, rather than the performance of complex surgeries or in patients with compromised health, is most likely the reason for the large differences found between prescribed antibiotics and scientific recommendations.

The findings reported by this meta-analysis suggest that an important number of antibiotic prescriptions might not be based on scientific evidence. This situation may unreasonably increase the risk of adverse events such as allergies, toxicity, gastrointestinal disorders and the development of bacterial resistance [27,28]. This last consequence must be regarded as an

extraordinary concern as drug-resistant diseases already cause at least 700,000 deaths a year worldwide [38]. In the most alarming scenario, this figure could rise to 10 million deaths a year by 2050 if no action is taken. The economic damage caused by uncontrolled antimicrobial resistance could be devastating, as it could drive 24 million people into extreme poverty [38]. Moreover, the economic cost of antibiotic prophylaxis for an individual is low but the potential costs for the healthcare system may be substantial and definitely groundless if they are made through irrational prescriptions [39].

Consequently, this study might reveal clinically relevant information for professionals placing oral implants in order to increase their adherence to recommendations when prescribing prophylactic antibiotics and preventing their misuse. The present meta-analysis should inspire new clinical research to improve the guidelines on this topic. This study could also encourage the dissemination of methodologically strong evidence-based guidelines over antibiotic prophylaxis in oral implant surgery, as this may induce behavioral changes in professionals that may eventually correct their prescription patterns [40].

Conclusions

In conclusion, the average dose of antibiotics prescribed per oral implant surgery was higher than that of the evidence-based recommended regimen in healthy patients and in straightforward conditions. Additionally, there were variances in the average dose of prescribed antibiotics among different countries and prescription regimens.

Supporting information

S1 Checklist. MOOSE (Meta-analyses Of Observational Studies in Epidemiology) checklist.
(PDF)

S2 Checklist. PRISMA 2009 checklist.
(DOC)

S1 Fig. Q-Q plots. A dot on the plot corresponds to one of the quantiles of the outcome data distribution (y-coordinate) plotted against the same quantile of the normal distribution (x-coordinate). *Antibiotic types in which DDD is equal to the evidence-based recommended regimen (2,000 mg) or to the DDD of amoxicillin (1,500 mg).
(TIF)

S1 Dataset.
(XLSX)

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