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Dobutamine in Paediatric Population: A Systematic Review in Juvenile Animal Models

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Abstract

Objective: Although dobutamine is widely used in neonatal clinical practice, the evidence for its use in this specific population is not clear. We conducted a systematic review of the use of dobutamine in juvenile animals to determine whether the evidence from juvenile animal experiments with dobutamine supported the design of clinical trials in neonatal/paediatric population.

Methods: Studies were identified by searching MEDLINE (1946–2012) and EMBASE (1974–2012). Articles retrieved were independently reviewed by three authors and only those concerning efficacy and safety of the drug in juvenile animals were included. Only original articles published in English and Spanish were included.

Results: Following our literature search, 265 articles were retrieved and 24 studies were included in the review: 17 focused on neonatal models and 7 on young animal models. Although the aims and design of these studies, as well as the doses and ages analysed, were quite heterogeneous, the majority of authors agree that dobutamine infusion improves cardiac output in a dose dependent manner. Moreover, the cardiovascular effects of dobutamine are influenced by postnatal age, as well as by the dose used and the duration of the therapy. There is inadequate information about the effects of dobutamine on cerebral perfusion to draw conclusions.

Conclusion: There is enough preclinical evidence to ensure that dobutamine improves cardiac output, however to better understand its effects in peripheral organs, such as the brain, more specific and well designed studies are required to provide additional data to support the design of clinical trials in a paediatric population.

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Introduction

The synthetic catecholamine dobutamine is a relatively cardioselective agent with significant cardiac α1- and β1/β2-adrenoreceptor-mediated direct inotropic effects and limited chronotropic action [1]. Cardiovascular compromise is a frequently condition in critically ill preterm and term infants which contributes to morbidity and mortality in these population. In the diagnosis and treatment of this pathology blood pressure, blood flow and cardiac output are some of the most determinant parameters [2]. The use of inotropes is common in neonates with cardiovascular compromise, being dobutamine introduced for the management of neonatal cardiovascular compromise two decades ago [1].

Dobutamine and dopamine are the inotropes most commonly used in neonatal intensive care; however, as many medicines used in children, especially neonates, have never been tested to the level seen in adult healthcare, the dose is established by simple extrapolation from adults without taking into account age-related differences.

In order to increase availability of medicines authorised for children as well as to increase the information available on the use of medicinal products in the paediatric population, the EU established a regulation on medicinal products for paediatric use (Regulation (EC) No 1901/2006) [3]. Notably, in the European Medicines Agency priority list (EMA/480197/2010) for studies into off-patent paediatric medicinal products published in 2010, dobutamine appeared as a drug of interest [4].

Nonetheless given the difficulties of conducting pharmacological research in children and more specifically in the neonatal population, the performance of experimental studies in suitable animal species is a common practice. Preclinical findings, and especially juvenile animal data, can be useful to generate information to support the use of a specific drug in paediatric populations. Specifically, it is important that unlike models in adult animals, those based on juvenile and in particular neonatal animals allow for the fact that drug concentration (PK) and drug response (PD) may be different in immature and developing organs. In particular in this case, it is important to focus the review

on juvenile and in particular neonatal animals because there are a number of developmental variations of structure and function of the cardiovascular system that suggest a different response to the drug.

The aim of this study was to conduct a systematic review on the use of dobutamine in juvenile animal models and to summarise and assess where there is enough conclusive preclinical evidence to guide a neonatal/paediatric clinical trial to support its use in this population.

Methods

Identification of Studies

The literature search was restricted to published results of animal studies and the effects of dobutamine. An electronic search was conducted using MEDLINE (from 1946 to July 2012), and EMBASE (from 1980 to July 2012) with the following combinations of terms: "dobutamine AND different animal models (using the following strategy: pig* OR swine OR calf OR lamb OR rat OR mouse OR mice OR foal OR horse OR animal*) AND juvenile animals (using the following strategy: juvenile OR infant OR fetal OR foetal OR neonatal OR newborn OR preterm OR pup OR term OR near-term)".

The dobutamine heading included different related terms such as toxicity, pharmacology, pharmacokinetics, drug administration, adverse reactions, drug concentration, therapy, as well as various different brand and generic drug names.

Inclusion Criteria and Data Extraction

During screening, only studies reported in English or Spanish, and conducted in an "in vivo" juvenile/neonatal animal model, were included. Conference papers, book chapters and review papers were excluded, as were studies focused on adult animal models. In addition, studies were included only if the study assessed the effect of dobutamine in juvenile animal models and dobutamine was not tested in combination with other treatments.

After excluding duplicates, titles and abstracts were screened by two authors to assess whether they were relevant for this review and should be subjected to further evaluation; any disagreements were resolved by discussion and if it was not possible to reach a consensus a third author determined eligibility. Finally, the full text of articles considered relevant was evaluated by the three authors.

Relevant information such as animal model and species, age and number of animals, dose and duration of dobutamine therapy, comparison groups and outcomes, was extracted from each study entered into an electronic database and analysed. To assess the quality of the studies the following parameters were taken into account: a) randomisation of the intervention; b) blinding of the intervention; c) comparison to a control group and d) statement of compliance with animal welfare regulations. The heterogeneity of the studies included in the review precluded meta-analysis.

Results

Description of the Studies

Although the research was focused on articles in Spanish and English, none of the article retrieved was written in Spanish, so all the articles included in the review were in English.

A total of 265 articles were retrieved from the electronic search. After application of the inclusion criteria, only 24 studies were included in the systematic review; 17 focused on neonatal models and 7 on young animal models. The corresponding flow diagram is shown in Figure 1.

The characteristics of the studies focused on neonatal animal models are described in Table 1. Only one study focused on preterm animals. In the 17 articles in neonatal models included in the review, nine were performed in piglets, four in lambs, three in puppies and one in foals. A variety of animal models were used including: four studies in hypoxic animals, seven in healthy animals, two studies comparing hypoxic and normoxic conditions and the other four considering different specific conditions (pulmonary hypertension; endotoxic shock; hypotension and hypoplastic left heart syndrome). Moreover, 5 studies focused only on the effects of dobutamine whereas the other 12 studied the effects of different drugs and compared them with those of dobutamine: as a comparison drug, dopamine was used in ten studies; epinephrine in four; isoproterenol in four; norepinephrine in two; milrinone in two; nitroprusside in one and vasopressin in one. The dose range used in the studies varied from 0.5 to 80 μg/kg/min. The duration of the treatment and the infusion pattern also varied between the studies.

Table 2 summarises the characteristics of the seven studies focused on juvenile animals (infants or adolescents): six of them were in piglets and one in healthy foals. The animal models differ, using healthy animals in four studies and disease models in the other three. In five of them the effect of dobutamine was compared with that of other drugs (namely, dopamine in four studies; epinephrine in two; isoproterenol in one; norepinephrine in two; milrinone in two and phenylephrine in one), while just two articles focused on the effects of dobutamine in a model of post-resuscitation left ventricular dysfunction. The dose ranged from 2 to 32 μg/kg/min.

In general, although studies were conducted in different animal species, more than 62% of them were performed in pigs [5–19].

Only one of the studies included was blinded [6], while randomization was reported in 42% of the studies [6–9,11,13,14,16,17,20]. Similarly, 42% of the studies used a control group [5–8,12,13,15,17,21,22]. Some studies assessed the effects of dobutamine by comparison with baseline data and/or the effect of other drugs. Also, a 21% of the studies did not report any compliance with animal welfare regulations.

Cardiovascular Effects

In general, it seems that the cardiovascular effects of dobutamine are influenced by postnatal age, as well as by the dose and duration of the treatment. Although the design and aims of the studies are relatively heterogeneous, as were the doses used and the conditions, 75% of the studies report that dobutamine infusion improves cardiac output in a dose dependent-manner [6,8–13,16–21,23–27].

Some found no changes in arterial blood pressure [7–9,17,20,24,28], but in a few studies the arterial blood pressure increased at the highest dose studied [6,11,19,26,27]. Similarly, some of the studies showed an increase in heart rate in a dose-dependent manner [5,9,11–13,16,18,23,26,28]. An increase in stroke volume was mainly observed in studies using prolonged infusion (from 2 to 6 h) at doses higher than 10 μg/kg/min [6,8,9,17].

In an effort to detect any patterns in the results we looked at the studies performed in pig, since it is the specie more frequently used. In this regard, most authors agree that dobutamine infusion improves cardiac output mainly at doses higher than 10 μg/kg/min [6,8–14,16–19]. It seems that at short term infusion this improvement was mainly due to an increase in heart rate [9,11,12,16,18], whereas at long term the increment in stroke volume is more prevalent [6,8,9,17].

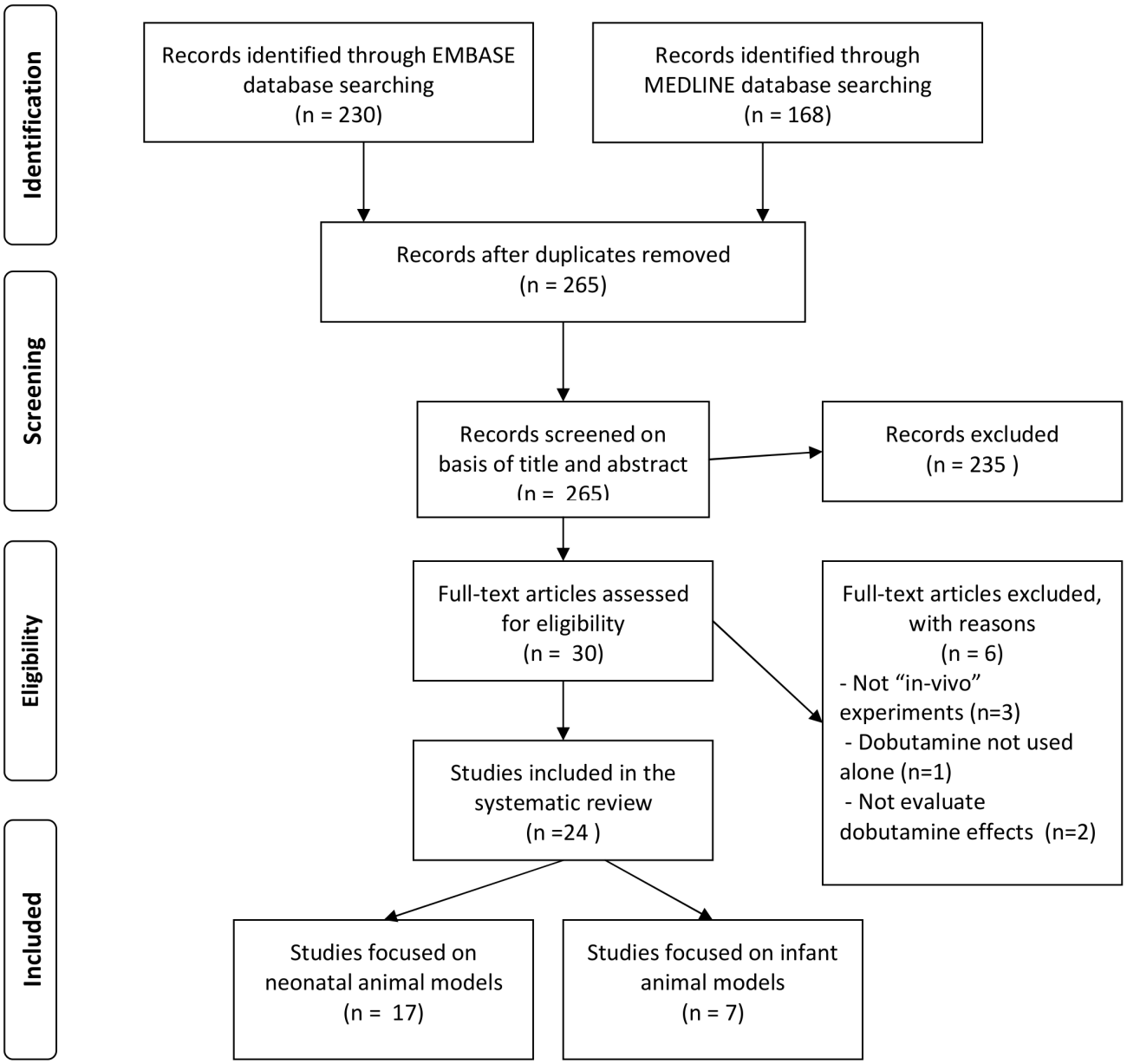

Figure 1. Flow chart of study selection. Flow chart showing the results of the search and reasons for exclusion of studies for systematic review.
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Further, it seems that the inotropic effect of dobutamine is present both during normoxia and hypoxia, but sometimes in a more attenuated way in the latter condition [12]. Only one study focused on preterm animals and in this case an increase in heart rate was observed without changes in mean arterial blood pressure or cardiac output at any of the doses used [11].

Other Organ Effects

Some studies evaluated the effects of dobutamine on other organs, mainly at renal, mesenteric and pulmonary levels, with results varying as a function of dose and duration of treatment.

There are 5 studies, all in neonatal animal models, on the effects of dobutamine on cerebral perfusion, which is mainly assessed by measurement of carotid blood flow. In this regard, two studies showed an increase in carotid blood flow at dose higher than 10 μg/kg/min, independent of the duration of the treatment [5,6] and in one study that measured cerebral blood flow through radiolabeled microspheres, a dose-dependent increase (5–15 μg/kg/min) was observed [11]. However, in another study there were no changes in carotid blood flow regardless of the dose used (5–20 μg/kg/min) [8], and other authors noted an increase in carotid vascular resistance at lowest doses (2 and 5 μg/kg/min) [12].

Some authors studied carotid oxygenation by various methods: one study found no changes at any given doses (5–20 μg/kg/min) [8], while another showed an increase at 5 and 10 μg/kg/min [12]. No follow-up studies were identified on neurodevelopment in animals treated with dobutamine.

At the renal level, two studies concluded that the renal response to dobutamine depends on maturity [12,28]. With respect to treatment duration, two studies in newborn piglets observed an increase in renal artery blood flow after 60 min of dobutamine infusion with no changes at shorter infusion times [9,19]. In most

Table 1. Characteristics of neonatal animal studies included in the systematic review.

STUDY	ANIMAL MODEL	DOBUTAMINE DOSES	NUMBER OF ANIMALS	COMPARISON GROUPS	DOBUTAMINE EFFECTS
Nachar R.A. et al. 2011 [5]	Newborn piglets (10±3 day old; 2.4±0.6 kg)	5, 10, 15, 20, 25 and 30 μg/kg/min for 15 min	N = 7/DOP, DOB and epinephrine groups; N = 6/milrinone group; N = 4/ norepinephrine group	DOP: 5–30 μg/kg/min; epinephrine: 0.25–2 μg/kg/min; norepinephrine: 0.25–1.5 μg/kg/ min; milrinone: 50 μg/kg +0.375 and 0.75 μg/kg/min.	HR increase in a dose-dependent manner. Low to moderate doses increase MABP and systemic and regional BF. At 5 and 10 μg/kg/min brain, renal and intestinal BP and O_2 saturation increase. Carotid BF and BP increase at 10 μg/kg/min.
Joynt C. et al. 2010 [6]	Hypoxic newborn piglets (1–3 days; 1.5–2.3 kg)	20 μg/kg/min for 2h	N = 6/group N = 4/sham group	Sham group; saline (hypoxic group); EP: 0.5 μg/kg/min; milrinone: 0.75 μg/kg/min	CO and SV improve without differences in SVR. MABP, carotid and intestinal BF and DO_2 increase without changes in renal perfusion. There are no differences in troponin I, lactate and histological features of ischaemia.
Al-Salam Z. et al. 2008 [7]	Hypoxic newborn piglets (1–3 days; 1.5–2.3 kg)	5, 10 or 20 μg/kg/min for 2h	N = 8/group N = 6/sham group	Sham group; saline (hypoxic group)	There are no differences between groups in HR, MABP. At 20 μg/kg/min plasma thromboxane B2 increases from baseline and a platelet aggregation dysfunction and decrease in platelet number are observed.
Al-Salam Z. et al. 2007 [8]	Hypoxic newborn piglets (1–3 days; 1.5–2.3 kg)	5, 10 or 20 μg/kg/min for 2h	N = 8/group N = 6/sham group	Sham group; saline (hypoxic group)	At 20 μg/kg/min CO and SV increase, with a moderate effect at 5 and 10 μg/kg/min, without changes in HR, MABP and SVR. The PVR decreases with a modest increase in PAP. At 20 μg/kg/min there is a transient improvement in mesenteric perfusion, with no effect on the carotid and renal BF or DO_2
Barrington K.J. 2001 [19]	Normoxic and hypoxic newborn piglets (1–3 days)			DOP; epinephrine	CO increases but BP only increases at very high doses, renal and bowel perfusion are unaffected by short term infusion, but both increase during more prolonged treatment
Cheung P-Y. et al. 1999 [9]	Newborn piglets (1–3 days; 1.2- 2.2 kg)	5, 10, 20 and 50 μg/kg/ min for 15 min (randomly given), with 15 min rests between doses+a infusion at 10 μg/kg/min for 2 h	N = 13	No	Short infusion: CO and HR increase in a dose-dependent manner, without changes in SV. MABP modestly increases at 50 μg/kg/min. At 20 and 50 μg/kg/min PAP increases and SVR decreases with no changes in PVR. Mesenteric and renal BF are not affected. Prolonged infusion: CO and SV increase with a transient tachycardia. MABP is not altered and PAP increase at 60 min but decrease towards baseline at the end. SVR and PVR decrease. Mesenteric and renal BF increase after 60 min, with a decrease in VR.
Riordan C.J. et al. 1996 [10]	Newborn piglets hypoplastic Left Heart Syndrome (1- 2 weeks)	5 and 15 μg/kg/min for at least 10 min	N = 6	DOP: 5 and 15 μg/kg/min; Epinephrine: 0.05 and 0.1 μg/kg/min	At 15 μg/kg/min the Q_p/Q_s ratio increases and DO_2 decreases. At increasing doses the A-V O_2 significantly increases. CO increases.

Table 1. Cont.

STUDY	ANIMAL MODEL	DOBUTAMINE DOSES	NUMBER OF ANIMALS	COMPARISON GROUPS	DOBUTAMINE EFFECTS
Ferrara J.J. et al. 1995 [11]	Term (1–14 days) and premature (90% of term gestation) piglets	Incremental doses: 5, 10 and 15 μg/kg/min, with 20 min rests between doses	Preterm (n = 16); 1–2 day old (n = 18); 10–14 day old (n = 16)	DOP: 5, 10 and 15 μg/kg/min	Preterm animals: HR increases moderately in a dose-dependent manner, without changes in CO, MABP or BF to the studied organs. Term animals: MABP increases at 15 μg/kg/min and CO at the highest dose. HR, brain and heart BF increase in a dose-dependent manner, without changes in renal BF and a small decrease in intestinal BF
Nudel D.B. et al. 1991 [12]	Hypoxic piglets (2–4 days and 13–17 days)	Sequential 10 min infusions of 2, 5 and 15 μg/kg/min	2–4 days (n = 21) 13–17 days (n = 27)	Sequential 10 min infusions of 2, 5 and 15 μg/kg/min of DOP or 0.05, 0.13 and 0.39 ml/min of saline	Normoxaemia: HR and CO increase in both age groups and total artery and renal resistances decrease in the youngest. Hypoxaemia: Hypoxaemia reduces HR and contractility response to DOB in older piglets with little or no effect on CO and total arterial, mesenteric and carotid resistance.
Penny D. et al. 2001 [23]	Lambs (1–2 days, 7–10 days and 6–8 weeks)	Incremental doses: 1–40 μg/kg/min	1–2 days (n = 7); 7–10 days (n = 7); 6–8 weeks (n = 8)	No	In all groups DO_2, HR and CO increase and MABP decreases. VO_2 is higher at 1–2 days old. Pulmonary artery O_2 content decreases in 1–2 day old and increases in 7–8 day old and 6–8 week old animals. At 1–2 days old the temperature increases with no changes in the other groups
Smolich J.J. et al. 2000 [24]	Lambs (1–2 days, 7–10 days and 6–8 weeks)	Incremental doses: 0.5–40 μg/kg/min	1–2 days (n = 6); 7–10 days (n = 7); 6–8 weeks (n = 6)	No	PAP increases at 1–2 and 7–10 days old, and decreases at 6–8 weeks old. In all groups there is no change in MABP with a dose-dependent increase in CO and decreases PVR and SVR.
Crowley M.R. et al. 1991 [20]	Newborn lambs with pulmonary hypertension (3–5 days)	Incremental doses: 5–20 μg/kg/min	N = 10	Isoproterenol: 0.05–1 μg/kg/min; DOP: 3–30 μg/kg/min; Nitroprusside: 0.5–10 μg/kg/min	PAP decrease at 5 and 10 μg/kg/min, with no changes at higher doses. PVR decrease. CO increase with increasing doses. At higher dose SV increase and SVR decrease. At 15 and 20 μg/kg/min HR increase. There are no changes in MABP.
OLaughlin M.P. et al. 1987 [21]	Unanaesthetized Hypoxemic Newborn Lambs	10, 20, 40 and 80 μg/kg/min	N = 15	Isoproterenol: 0.1, 0.4, 0.7 and 1 μg/kg/min; DOP: 10, 20, 40 and 80 μg/kg/min	CO and HR increase with all the dosages tested. SVR decreases between 20–80 μg/kg/min.
Goto M. et al. 1991 [22]	Newborn puppies endotoxic shock (2–10 days)	5 μg/kg/min	N = 14/LPS group; N = 9/DOP and DOB groups; N = 11/DOP+ IND and IND groups; N = 8/DOB+IND group	LPS group; DOP (15 μg/kg/min); IND (1.5 mg/kg)	HR is unchanged and SVR is maintained at the high level. MABP is stable for the first 60 min and then declines. The hypotension and CO decreases are attenuated when compared to LPS group.
Driscoll D.J. et al. 1980 [28]	Newborn puppies (0–10 days) and adults	Incremental doses: 2 to 50 μg/kg/min	N = 11 puppies; N = 5 adults	Isoproterenol: 0.05 to 1.25 μg/kg/min; DOP: 2 to 50 μg/kg/min	Adults: MABP, HR, CO and renal BF increase. Puppies: HR increases without changes in MABP, CO and renal BF.
Driscoll D.J. et al. 1979 [25]	Puppies (From 3 to 65 days)	Incremental doses: 2 to 50 μg/kg/min	N = 24	Isoproterenol: 0.05 to 1.25 μg/kg/min; DOP: 2 to 50 μg/kg/min	At 20 μg/kg/min MABP and HR increase. At 50 μg/kg/min CO increases. There are no changes in SVR and renal artery BF with an increase in renal VR at 20 and 50 μg/kg/min
Valverde A. et al. 2006 [27]	Hypotensive newborn foals (1–5 days)	4 and 8 μg/kg/min for 15 min.	N = 6	Norepinephrine: 0.3 and 1 μg/kg/min; Vasopressin: 0.3 and 1 mU/kg/min	CO, MABP and DO_2 increase and VO_2 and O_2 extraction decrease. SVR decreases at high infusion rates

Abbreviations: DOP: dopamine; LPS: lipopolysaccharide; IND: indomethacin; CO: cardiac output; HR: heart rate; SV: stroke volume; MABP: mean arterial blood pressure; (S)VR: (systemic) vascular resistance; BF: blood flow; VO_2: O_2 consumption; DO_2: O_2 delivery; PVR: pulmonary vascular resistance; PAP: pulmonary artery pressure.

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Table 2. Characteristics of young animal studies included in the systematic review.

STUDY	ANIMAL MODEL	DOBUTAMINE DOSES	NUMBER OF ANIMALS	COMPARISON GROUPS	DOBUTAMINE EFFECTS
Vasquez A. et al. 2004 [13]	Young pigs (24±0.4 kg) post-resuscitation left ventricular dysfunction	2, 5 and 7.5 μg/kg/min for 6 h	N = 20	Control group (placebo)	Ventricular systolic and diastolic function improves within minutes of infusion start and persists at 6 h for the 5 and 7.5 μg/kg/min. HR and CO increase with all doses, but only affect myocardial VO_2 at 7.5 μg/kg/min.
McGovern J.J. et al. 2000 [14]	Young pigs right ventricular injury (9–12 kg)	10 μg/kg/min for 20 min	N = 10	DOP at 10 μg/kg/min; epinephrine at 0.1 μg/kg/min	Pulmonary BF increases and PVR decreases without changes in PAP. Input resistance, right ventricle contractility and increased total hydraulic power decrease, without changes in transpulmonary vascular efficiency
Kern K.B. et al. 1997 [15]	Juvenile pigs (29±1 kg) postresuscitation left ventricular dysfunction	5 or 10 μg/kg/min	10 μg/kg/min (n = 14); 5 μg/kg/min (n = 5); controls (n = 8)	Control group	Pulmonary capillary wedge pressure, left ventricular end-diastolic pressure and time constant of left ventricular isovolumic relaxation decrease. HR and left ventricular ejection fraction increase
Cassidy S.C. et al. 1997 [16]	Pigs (3 weeks old)	20 μg/kg/min	N = 9	Epinephrine and norepinephrine: 1.5 μg/kg/min; DOP: 12 μg/kg/min; isoproterenol: 0.5 μg/kg/min and phenylephrine: 20 μg/kg +2 μg/kg/min	HR, CO, dP/dt max and preload recruitable stroke work increase, without changes in SVR, end-systolic elastance, dP/dt min and left ventricular chamber stiffness
Tighe D. et al. 1995 [17]	Adolescent pigs with sepsis (25–30 kg)	10 μg/kg/min for 6h	N = 25	Sham group; control group; dopexamine: 10 μg/kg/min; colloid - hydroxyethyl starch group	CO and SV increase and SVR decreases without changes in HR, MABP, VO2, DO_2 and O_2 extraction ratio in either whole-body or liver and splanchnic level. Dobutamine causes considerable deterioration of hepatic ultrastructure compared to other groups
Fisher D.H. et al. 1988 [18]	Healthy conscious pigs (1–2 months old)	Incremental dose: 2 to 32 μg/kg/min for 30 min each dose.	N = 12	DOP: 2 to 32 μg/kg/min	At doses >16 μg/kg/min MABP and SVR decrease and CO and HR with no changes in SV. Renal VR decreases with doses in the range of 16–32 μg/kg/min associated with an increase in renal BF. There were no changes PAP, PVR or left atrial pressure
Craig C.A. et al. 2007 [26]	Healthy foals (1–2 weeks old)	2.5, 5 and 10 μg/kg/min for a minimum of 15 min	N = 7	Norepinephrine: 0.05, 0.1, 0.2 and 0.4 μg/kg/min	HR, SV, CO, DO_2, VO_2 and ventricular stroke work increase; MABP and PAP increase slightly while preload pressure changes were variable. SVR, PVR and FTOE decrease

Abbreviations: DOP: dopamine; DOB: dobutamine; HR: heart rate; MABP: mean arterial blood pressure; CO: cardiac output; BF: blood flow; (S)VR: (systemic) vascular resistance; PAP: pulmonary artery pressure; PVR: pulmonary vascular resistance; SV: stroke volume; DO2: O2 delivery; VO2: O2 consumption; LV dp/dt: first derivative of left ventricle pressure with respect to time.

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studies there were no changes in renal blood flow after dobutamine administration [6,8,11,25], but some authors studying juvenile and adult animals observed increases in renal blood flow and decreases in renal vascular resistance, especially when the drug was infused continuously [12,18,28].

At the pulmonary level, some studies observed a decrease in pulmonary vascular resistance [6,8,9,24,26]. In contrast, however, one study in juvenile animals reported no changes in either pulmonary vascular resistance or pulmonary artery pressure [18].

Considering models of specific diseases, the effects of dobutamine are mixed, depending on the nature of the disease. For example, in a pulmonary hypertension model, dobutamine decreased the pulmonary artery pressure and pulmonary vascular resistance at 5 and 10 μg/kg/min [20]. In a neonatal piglet model of hypoplastic left heart syndrome an increase in the Qp/Qs ratio was observed, possibly due to differential effects on systemic and pulmonary vascular resistance [10], and in a model of right ventricular injury in young swine indices of pulmonary vascular impedance were found to decrease [14].

In regard to perfusion to other organs, it should be noted that an increase in mesenteric blood flow was observed with continuous dobutamine infusion over 2 hours at doses higher than 10 μg/kg/min [6,8,9,19], though there were no changes at short infusion times (10–15 min.) [9,12,19]. Moreover, in a study in newborn piglets an increase in intestinal and renal oxygen saturation was observed at 5 and 10 μg/kg/min [5], whereas in a study in adolescent pigs with sepsis a deterioration in liver function was observed at 10 μg/kg/min [17]. More specifically, one study described platelet aggregation dysfunction in hypoxic-reoxygenated newborn piglets treated with 10 and 20 μg/kg/min of dobutamine [7].

Only one study evaluated the use of dobutamine in premature animals (piglets born at 90% gestation) and no changes in specific organ perfusion were detected [11].

Considering the articles included in the review, none of them reported pharmacokinetics and pharmacodynamics (PK/PD) responses of dobutamine in neonatal and juvenile animals or focused on toxicity in immature systems.

Discussion

In the present study we focused on whether the evidence available regarding the use of dobutamine in juvenile animal was sufficient and adequate to support a clinical trial and the use of this drug in paediatric/neonatal populations.

The use of well-designed neonatal animal models, to address and predict effects of dobutamine on developing organs and therefore to obtain information on the potential different safety profile from those seen in adults, are important to support a clinical trial, due to developmental variations of structure and function of the cardiovascular system. In the context of this systematic review, although there are quite a number of studies in this field in different animal species, data from term and preterm pigs are particularly relevance due to pig is a representative model for the developmental cardiovascular physiology of humans [29–31]. However, the marked variability in the dose used, timing and duration of treatment and study design produces discrepancies between the results of studies.

Despite the heterogeneity of the studies, most of them show that dobutamine improves cardiac output in a dose-dependent manner, both in neonatal and juvenile models. As cardiac output is a crucial parameter in neonatal cardiovascular function, its improvement may be of importance in decreasing morbidity and mortality associated with cardiovascular compromise in this population.

However, precisely the variability in these studies means that the mechanism by which this improvement is achieved is not clear. Some of the studies analysed report an increase in heart rate [5,9,11–13,16,18,23,26,28], whereas others show an improvement in stroke volume [6,8,9,17] or even an increase in mean arterial pressure [6,11,19,26,27]. Focusing on studies in pigs, as an animal model, this point seems clearer, being at short term infusion tachycardia more marked [9,11,16,18,23] and at long term infusion mainly due to an increase in stroke volume than tachycardia [6,8,9,17].

The existing information about the effects on cerebral perfusion and neurodevelopmental outcomes is clearly inadequate. Although there has been some research in this area, in neonatal animal models [5,6,8,11,12], which use mainly carotid blood flow measurements to study cerebral perfusion, the results are not consistent. This is probably due to the duration of treatment, the dose regimen and the existence of differences in measurement methods (NIRS, radiolabeled microspheres, electromagnetic flow probes, ultrasonic flow probes). The variability in measurement methods used, with advantages and disadvantages between them and in many cases practical and technological limitations, make difficult to compare them and to obtain clear conclusions. Although more studies are needed to clarify the effect of dobutamine at a cerebral level to translate clear conclusions to neonatal care, some of the studies included in the review suggest a trend towards an increase in the blood flow at doses higher than 10 μg/kg/min. So in the design of future studies this point should be considered.

In addition, only one study investigated the effect of dobutamine in preterm animals [11], with insufficient power to extract reliable conclusions to predict human clinical outcomes in this particular population.

Finally, the data on adverse effects reported in some studies (such as liver damage or platelet aggregation dysfunction) related to the use of dobutamine in specific diseases [7,17] are not conclusive. These studies should be analysed carefully, suggesting that more research is needed in this area.

Limitations

Systematic reviews are vulnerable to various different forms of bias. Our search was limited to studies published in English referenced in electronic databases, while there may also be relevant studies that are unpublished or written in other languages. Moreover, the quality of any review is determined by that of the studies included, so any bias in studies included associated with a lack of randomization or blinded assessment could have an impact on the conclusions. In this review, the quality of included studies was overall poor with less than half of them randomly allocating animals to groups, and only one being a blinded study [6].

Conclusions

On the one hand there is enough preclinical evidence to conclude that dobutamine improves cardiac output. On the other hand, although there has been some research on the effects of dobutamine in juvenile animal models, the heterogeneity across studies makes it difficult to obtain clear evidence to better understand its effects in peripheral organs, above all in the brain. Hence, it is necessary to perform more standardised and higher quality studies to support a clinical trial and to allow clear conclusions to be drawn concerning the rational use of dobutamine in paediatric/neonatal population.

Moreover, it is important to conduct studies in juvenile and neonatal animals designed to address specific questions of potential toxicity in developing systems, to perform PK/PD studies, at different postnatal ages, to develop evidence for individualized dosing schemes for children and also to collect data on the long-term safety of dobutamine that cannot be obtained from clinical trials.

Author Contributions

Conceived and designed the experiments: VM AVS CRS. Performed the experiments: VM CRS. Analyzed the data: VM AVS CRS. Wrote the paper: VM CRS. Screening articles by titles and abstracts: VM CRS. Full text of articles considered relevant evaluation: VM AVS CRS.

References

1. Noori S, Friedlich P, Seri I (2004) The use of dobutamine in the treatment of neonatal cardiovascular compromise. Neoreviews 5: e22–e26.
2. Soleymani S, Borzage M, Seri I (2010) Hemodynamic monitoring in neonates: advances and challenges. J Perinatol 30: S38–S45.
3. Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use.
4. EMA (2010) Revised priority list for studies into off-patent paediatric medical products. EMA/480197/2010: 1–8.
5. Nachar RA, Booth EA, Friedlich P, Borzage M, Soleymani S, et al. (2011) Dose-dependent hemodynamic and metabolic effects of vasoactive medications in normotensive, anesthetized neonatal piglets. Pediatr Res 70: 473–479.
6. Joynt C, Bigam DL, Charrois G, Jewell LD, Korbutt G, et al. (2010) Milrinone, dobutamine or epinephrine use in asphyxiated newborn pigs resuscitated with 100% oxygen. Intensive Care Med 36: 1058–1066.
7. Al-Salam Z, Emara M, Wehlage S, Abozaid S, Johnson ST, et al. (2008) The effect of dobutamine on platelet aggregatory function in newborn piglets with hypoxia and reoxygenation. Shock 30: 293–298.
8. Al-Salam Z, Johnson ST, Abozaid S, Bigam DL, Cheung P-Y (2007) The hemodynamic effects of dobutamine during reoxygenation after hypoxia: a dose-response study in newborn pigs. Shock 28: 317–325.
9. Cheung P-Y, Barrington KJ, Bigam DL (1999) The hemodynamic effects of dobutamine infusion in the chronically instrumented newborn piglet. Crit Care Med 27: 558–564.
10. Riordan CJ, Randsbaek F, Storey JH, Montgomery WD, Santamore WP, et al. (1996) Inotropes in the hypoplastic left heart syndrome: effects in an animal model. Ann Thorac Surg 62: 83–90.
11. Ferrara JJ, Dyess L, Peeples GL, Christenberry P, Roberts WS, et al. (1995) Effects of dopamine and dobutamine on regional blood flow distribution in the neonatal piglet. Ann Surg 221: 531–542.
12. Nudel DB, Peterson BJ, Buckley BJ, Gootman N, Hoffman RG (1991) Effects of acute hypoxemia on responses to dopamine and dobutamine in neonatal swine. Meth Find Exp Clin Pharmacol 13: 111–119.
13. Vasquez A, Kern KB, Hilwig RW, Heidenreich J, Berg RA, eet al. (2004) Optimal dosing of dobutamine for treating post-resuscitation left ventricular dysfunction. Resuscitation 61: 199–207.
14. McGovern JJ, Cheifetz IM, Craig DM, Bengur AR, Quick G, et al. (2000) Right ventricular injury in young swine: effects of catecholamines on right ventricular function and pulmonary vascular mechanics. Pediatr Res 48: 763–769.
15. Kern KB, Hilwig RW, Berg RA, Rhee KH, Sanders AB, et al A (1997) Postresuscitation left ventricular systolic and diastolic dysfunction. Treatment with dobutamine. Circulation 95: 2610–2613.
16. Cassidy SC, McGovern JJ, Chan DP, Allen HD (1997) Effects of commonly used adrenergic agonists on left ventricular function and systemic vascular resistance in young piglets. Am Heart J 133: 174–183.
17. Tighe D, Moss R, Heywood G, Al-Saady N, Webb A, et al. (1995) Goal-directed therapy with dopexamine, dobutamine and volume expansion: effects of systemic oxygen transport on hepatic ultraestructure in porcine sepsis. Crit Care Med 23: 1997–2007.
18. Fiser DH, Fewell JE, Hill DE, Brown AL (1988) Cardiovascular and renal effects of dopamine and dobutamine in healthy, conscious piglets. Crit Care Med 16: 340–345.
19. Barrington KJ (2001) The effects of dopamine, epinephrine and dobutamine in the newborn piglet during normoxia and hypoxia. Cardiovasc Eng 6: 44–50.
20. Crowley MR, Fineman JR, Soifer SJ (1991) Effects of vasoactive drugs on thromboxane A_2 mimetic-induced pulmonary hypertension in newborn lambs. Pediatr Res 29: 167–172.
21. O'Laughlin MP, Fisher DJ, Dreyer WJ, Smith EO (1987) Augmentation of cardiac output with intravenous catecholamines in unanesthetized hypoxemic newborn lambs. Pediatr Res 22: 667–674.
22. Goto M, Griffin A (1991) Adjuvant effects of adrenergic drugs on indomethacin treatment of newborn canine endotoxic shock. J Pediatr Surg 26: 1156–1160.
23. Penny DJ, Sano T, Smolich JJ (2001) Increased systemic oxygen consumption offsets improved oxygen delivery during dobutamine infusion in newborn lambs. Intensive Care Med 27: 1518–1525.
24. Smolich JJ, Sano T, Penny DJ (2000) Blunting of pulmonary but not systemic vasodilator responses to dobutamine in newborn lambs. Pediatr Res 41: 107–113.
25. Driscoll DJ, Gillette PC, Lewis RM, Hartley CJ, Schwartz A (1979) Comparative hemodynamic effects of isoproterenol, dopamine and dobutamine in the newborn dog. Pediatr Res 13: 1006–1009.
26. Craig CA, Haskins SC, Hildebrand SV (2007) The cardiopulmonary effects of dobutamine and norepinephrine in isoflurane-anesthetized foals. Vet Anaesth Analg 34: 377–387.
27. Valverde A, Giguere S, Sanchez LC, Shih A, Ryan C (2006) Effects of dobutamine, norepinephrine, and vasopressin on cardiovascular function in anesthesized neonatal foals with induced hypotension. Am J Vet Res 67: 1730–1737.
28. Driscoll DJ, Gillette PC, Fukushige J, Lewis RM, Contant C, et al.(1980) Comparison of the cardiovascular action of isoproterenol, dopamine and dobutamine in the neonatal and mature dog. Ped Cardiol 1: 307–314.
29. Scheiber RA, Stiller RL, Cook R (1985) Cardiovascular and pharmacodynamic effects of high-dose of fentanyl in newborn piglets. Anesthesiology 63: 166–171.
30. Eiby YA, Wright LL, Kalanjati VP, Miller SM, Bjorkman ST, et al. (2013) A pig model of the preterm neonate: anthropometric and physiological characteristics. Plos One 8: e68763.
31. Lunney JK (2007) Advances in swine biomedical model genomics. Int J Biol Sci 3: 179–184.