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Systematic Review and Meta-Analysis

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Systematic Review and Meta-Analysis of Cardiovascular Medications in Neonatal Hypotension

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Keywords
Neonate · Arterial hypotension · Dopamine · Dobutamine

Abstract
Background: Comparative studies among the various cardiovascular medications used for the treatment of neonatal hypotension are lacking. ***Methods:*** This systematic review and pairwise meta-analysis of the anti-hypotensive treatments in preterm and term infants was conducted to evaluate efficacy and impact on outcome. Electronic databases were searched up to February 2021 for relevant articles. As an extension of the current approach for study selection, a machine learning technique was used. Only randomized controlled trials (RCTs) of inotropes, pressors, volume therapy, and corticosteroids were included. Response to treatment was the primary outcome while secondary outcomes included mortality and common morbidities. ***Results:*** Nineteen RCTs involving 758 preterm and term neonates were found, and 8 treatments were evaluated. Most studies involved subjects with early hypotension associated with prematurity. Pairwise meta-analysis among treatments showed that dopamine was more effective than dobutamine regarding the response to treatment (restoration of normotension or normalization of blood pressure) (7 trials, 286 neonates, odds ratio, 3.06 [95% CI = 1.06–8.87]; $I^2 = 49\%$, very low quality of the evidence per GRADE). Comparisons of other treatments were not significant. No differences were found among regimens regarding survival and other secondary outcomes. ***Conclusion:*** In this systematic review and pairwise meta-analysis, only the comparison of dopamine versus dobutamine provided evidence for efficacy of treatment and favored dopamine. No safe conclusions could be reached in regard to other treatments. Data regarding the management of arterial hypotension in conditions other than transition after birth in preterm newborns are sparse both in preterm and term infants.

Introduction

Arterial hypotension is a relatively common problem in critically ill infants [1–3]. Although a causal relationship between hypotension and end-organ injury has not been clearly documented, studies have shown a higher incidence of severe brain injury [4, 5], along with other important morbidities such as necrotizing enterocolitis

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[6], multiple organ failure [7], and even death [8] in infants with low blood pressure (BP). Moreover, early-onset hypotension was found to be an independent predictor of poor neurological outcome in preterm infants [9].

From the therapeutic point of view, irrespective of the long-existing controversies surrounding hypotension in neonates (definition, diagnosis, need for treatment), the restoration and maintenance of adequate organ perfusion are essential goals in the management of the sick neonate. Early cardiovascular support can improve survival and outcomes in septic children and infants [10, 11].

In this context, several cardiovascular medications have been used to treat hypotensive neonates, with dopamine and dobutamine being the most commonly used [12]. Other catecholamines (adrenaline [epinephrine], nonadrenaline [norepinephrine], phenylephrine), neuropeptides (vasopressin, terlipressin), phosphodiesterase 3 inhibitors (milrinone) [13, 14], and systemic corticosteroids (dexamethasone, hydrocortisone) have also been used, mostly as rescue therapy, along with other inotropes and pressors in neonates with refractory arterial hypotension [15].

However, after more than half a century of clinical use, there is still no clear evidence-based answer as to which vasoactive agent is most appropriate for the management of hypotension in neonates and in which clinical setting [16]. Due to the limited number of randomized controlled trials (RCTs), previous relevant systematic reviews and meta-analyses were published more than 5 years ago, and only included preterm infants with early hypotension, with dopamine being the agent to which all other interventions were compared [12, 17, 18]. Since then, more studies on neonatal hemodynamic support have been conducted, such as the "Hypotension in Preterm Infants (HIP) trial" [2]. Nevertheless, no previous study has compared the efficacy of the different cardiovascular regimens in neonatal hypotension, nor has the therapeutic role of these agents in relation to the underlying cause of hypotension or the degree of maturity (preterm vs. term infants) been evaluated. Moreover, to the best of our knowledge, there is very little evidence from clinical trials on this topic regarding term neonates.

Therefore, this systematic review and meta-analysis attempted to evaluate current evidence for the most effective vasoactive drug for the treatment of arterial hypotension in both preterm and term infants by assessing clinical benefits and outcomes. To accomplish our aim and as an extension of the current approach for study selection, a machine learning technique capable of robust automatic study selection for meta-analysis was used.

Methods

Protocol

The protocol for this review was registered with Open Science Framework (https://osf.io/b8tm2/). Minor differences from the protocol are shown in online supplementary Table 1.

Eligibility

Studies including preterm or full-term infants of less than 30 days postnatal age with arterial hypotension, treated with any of the following agents such as dopamine, dobutamine, adrenaline (epinephrine), noradrenaline (norepinephrine), vasopressin/terlipressin, levosimendan, milrinone, systemic corticosteroids (hydrocortisone, dexamethasone), or placebo were eligible for inclusion.

Outcomes

Primary outcome included response to treatment (defined as achievement of the primary outcome[s] in each study, mainly resolution of hypotension), reported as dichotomous data. The number of participants meeting the primary outcome and the number analyzed in each group were recorded. Secondary outcomes included infant survival, necrotizing enterocolitis (stage ≥2), intraventricular hemorrhage (all stages), retinopathy of prematurity (all stages), bronchopulmonary dysplasia, periventricular leukomalacia, and sepsis as well as heart function characteristics (heart rate, mean BP, left ventricular output [LVO], right ventricular output [RVO], and superior vena cava [SVC] flow).

Search

Standard Search Strategy

RCTs on cardiovascular medications used in the treatment of neonatal hypotension were identified using the standard search strategy of the Neonatal Review Group of the Cochrane Collaboration. Electronic databases (PubMed, Scopus, and the Cochrane Library) up to February 2021 were searched for potentially relevant articles using pre-defined search strategies (online suppl. Table 2). Previously published reviews were searched for references to relevant trials. The International Prospective Register of Systematic Reviews (PROSPERO) was searched periodically for relevant ongoing and completed systematic reviews. A manual search of the reference lists of all included studies was conducted to check for other possibly relevant articles. Manual searches were also conducted to capture data not reported in the main publications and data from recent studies not yet published. Furthermore, the clinical trial registry clinicaltrials.gov was also included in the search. Databases were searched using the MeSH terms "hypotension", "inotropic", "vasopressin", "levosimendan", "terlipressin", "phenylephrine", "noradrenaline", "adrenaline", "dobutamine", "dopamine", "milrinone", "infant", "newborn", NOT "animal", "humans", "groups", "randomized controlled trials", "placebo", "drug therapy". Studies included full reports in English language and were not limited by birth weight, lower gestational age threshold, or by route or duration of administration of inotropic agents. Arterial hypotension was not defined specifically but was accepted as defined in individual studies. The primary medical conditions of infants included hypotension/shock due to prematurity, neonatal sepsis, necrotizing enterocolitis, patent ductus arteriosus, post-operation complications, or perinatal asphyxia. Studies with agents used as initial treatment, as well as rescue therapy of refractory shock or prior volume expansion with crystalloids and hydrocortisone use, were also considered.

Machine Learning-Assisted Study Selection and Validation

Along with the current approach for study selection, a new method described by Xiong et al. [19] was adopted, with the aim of quickly screening abstracts for a systematic review with excellent accuracy. This approach uses modern text mining filtering techniques and is based on R [20]. Briefly, the following steps are included in the method: (i) two searches in PubMed were conducted, a general one and a target specific (a small number of abstracts from publications that were initially agreed from the reviewers that adhere to the study); (ii) the abstracts of the first search were clustered using unsupervised machine learning algorithms [21]; (iii) it was decided which cluster of abstracts should be kept and which were to be rejected by calculating the cosine similarity with the cluster of the abstracts of the second search; (iv) repeating the second step, re-clustering the remaining abstracts, and discarding the irrelevant ones, the number of abstracts eligible for manual screening was greatly reduced. Additional information on machine learning-assisted study selection is provided in online supplementary material.

Study Selection. The process was reported using the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram following the PRISMA statement (online suppl. Fig. 1) [22]. Initially, titles and abstracts of all records identified by the database searches were screened independently by two reviewers (E.V. and S.N.) against the predefined eligibility criteria to identify the subset of potentially relevant studies. To reduce the risk of missing potentially relevant studies and to resolve cases of uncertainty, a third reviewer (F.A.-K.) repeated the process of screening titles and abstracts from all potentially relevant studies. Any discrepancies were resolved by discussion. Full reports were obtained for all titles of potentially relevant studies, or where there was uncertainty. Full-text screening was also conducted by the primary researcher. Online supplementary material was consulted if the information provided in the main published article was insufficient to assess whether the inclusion criteria were met.

Data Collection. Information was extracted from all selected studies using a pre-specified data extraction form. The form was piloted on the first six selected studies and refined, as necessary. Online supplementary material was also consulted and/or authors contacted if the information provided in the original published articles was insufficient to complete the extraction. Data were extracted as counts (i.e., number of patients who responded to treatment) or as means (SD). When data were reported as medians/interquartile range/range, they were converted to means (SD) [23]. WebPlotDigitizer was used to extract numerical data if data values were given in a graphical format. As with screening, data extraction was carried out in duplicate on a subset of selected records to reduce the risk of errors and bias. Similarly, any disagreements arising between the reviewers were resolved with discussion. In the event of duplicate publications, companion documents, or multiple reports of a primary study, we maximized the yield of information by collating all available data and used the most complete dataset aggregated across all known publications. In case of doubt, the publication reporting the longest follow-up associated with our primary and secondary outcomes was given priority.

Summary Measures and Synthesis of Results. Initially, we aimed to conduct a network meta-analysis, to provide a global estimate of treatment effects for a set of multiple interventions, by combining direct and indirect evidence. This approach is particularly useful when pairwise comparisons are not available in the literature [24]. However, this was not possible due to the limited number of RCTs and the absence of closed loops in a network which resulted in violations of transitivity. Therefore, if two or more RCTs satisfying the inclusion criteria were available and reported the same outcomes in a comparable population, a pairwise meta-analysis was performed using a random effects model for each treatment. Eligibility for meta-analysis was determined by the degree of clinical and methodological heterogeneity observed between studies. Meta-analysis was conducted using a frequentist random effects inverse variance analysis using the package netmeta in R ver 4.0.0. (R Foundation of Statistical Computing, Vienna, Austria). Dichotomous outcomes are presented using the pooled odds ratios (ORs), with 95% confidence interval (95% CI). For studies with a zero cell count in one of the arms, a treatment arm continuity correction was applied [25]. Mean difference (MD) with 95% CI is presented for continuous outcomes. Effect sizes of individual studies and any pooled estimates of effect are presented in tables and graphically depicted as forest plots.

Assessment of Heterogeneity. Heterogeneity was identified by visual inspection of the forest plots and by using a standard χ^2 test with a significance level of $\alpha = 0.1$, in view of the low power of this test. Heterogeneity was examined using the I^2 statistic, which quantifies inconsistency across studies, to assess the impact of heterogeneity on the meta-analysis [26, 27]; an I^2 statistic of 75% or more indicates a considerable level of inconsistency [28]. In the case where heterogeneity was found, potential reasons for it were assessed by examining individual study and subgroup characteristics. Sensitivity analysis for the robustness of the results was not conducted due to the limited number of studies.

Quality Assessment. Two reviewers independently checked each included article to minimize bias. All selected articles were assessed for their quality based on the Cochrane Collaboration's revised risk of bias (RoB) 2.0 tool independently by the two reviewers [29]. Disagreements were resolved by consensus, or by consultation with a third reviewer.

Quality of Evidence. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) was used to rate the level of evidence of the synthesized outcomes with at least two studies in five aspects, including limitations, inconsistencies, indirectness, imprecision, and publication bias [30]. This evaluation was conducted independently by two reviewers and in case of disagreement a third reviewer was consulted.

Results

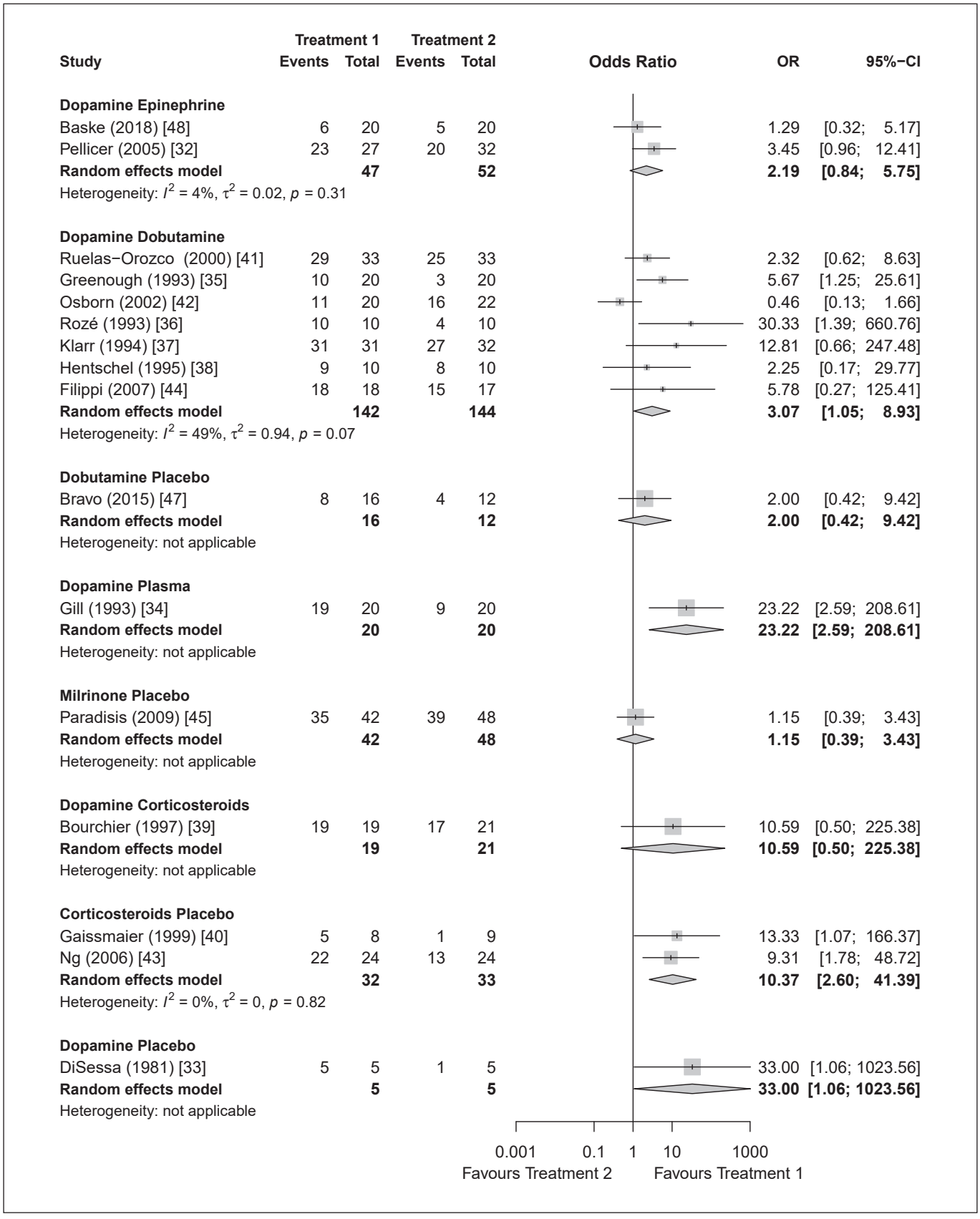
Search Results

Study Selection

Of 1,234 records identified through databases and registries, 560 were duplicates, 384 were removed using the automation tool, and a further 206 were removed as nonrelevant after the screening of title and abstract or being

Fig. 1. Forest plot displaying all pairwise comparisons for response to treatment. For each of the different pairs of treatments compared, treatment 1 refers to the first drug, while treatment 2 refers to the second one.

(For figure see next page.)


Study
Treatment 1 Events Total
Treatment 2 Events Total
Odds Ratio
OR 95%−CI
Dopamine Epinephrine
Baske (2018) [48] 6 20 5 20 1.29 [0.32; 5.17]
Pellicer (2005) [32] 23 27 20 32 3.45 [0.96; 12.41]
Random effects model 47 52 2.19 [0.84; 5.75]
Heterogeneity: I^2 = 4%, τ^2 = 0.02, p = 0.31
Dopamine Dobutamine
Ruelas−Orozco (2000) [41] 29 33 25 33 2.32 [0.62; 8.63]
Greenough (1993) [35] 10 20 3 20 5.67 [1.25; 25.61]
Osborn (2002) [42] 11 20 16 22 0.46 [0.13; 1.66]
Rozé (1993) [36] 10 10 4 10 30.33 [1.39; 660.76]
Klarr (1994) [37] 31 31 27 32 12.81 [0.66; 247.48]
Hentschel (1995) [38] 9 10 8 10 2.25 [0.17; 29.77]
Filippi (2007) [44] 18 18 15 17 5.78 [0.27; 125.41]
Random effects model 142 144 3.07 [1.05; 8.93]
Heterogeneity: I^2 = 49%, τ^2 = 0.94, p = 0.07
Dobutamine Placebo
Bravo (2015) [47] 8 16 4 12 2.00 [0.42; 9.42]
Random effects model 16 12 2.00 [0.42; 9.42]
Heterogeneity: not applicable
Dopamine Plasma
Gill (1993) [34] 19 20 9 20 23.22 [2.59; 208.61]
Random effects model 20 20 23.22 [2.59; 208.61]
Heterogeneity: not applicable
Milrinone Placebo
Paradisis (2009) [45] 35 42 39 48 1.15 [0.39; 3.43]
Random effects model 42 48 1.15 [0.39; 3.43]
Heterogeneity: not applicable
Dopamine Corticosteroids
Bourchier (1997) [39] 19 19 17 21 10.59 [0.50; 225.38]
Random effects model 19 21 10.59 [0.50; 225.38]
Heterogeneity: not applicable
Corticosteroids Placebo
Gaissmaier (1999) [40] 5 8 1 9 13.33 [1.07; 166.37]
Ng (2006) [43] 22 24 13 24 9.31 [1.78; 48.72]
Random effects model 32 33 10.37 [2.60; 41.39]
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.82
Dopamine Placebo
DiSessa (1981) [33] 5 5 1 5 33.00 [1.06; 1023.56]
Random effects model 5 5 33.00 [1.06; 1023.56]
Heterogeneity: not applicable
0.001 0.1 1 10 1000
Favours Treatment 2
Favours Treatment 1

1

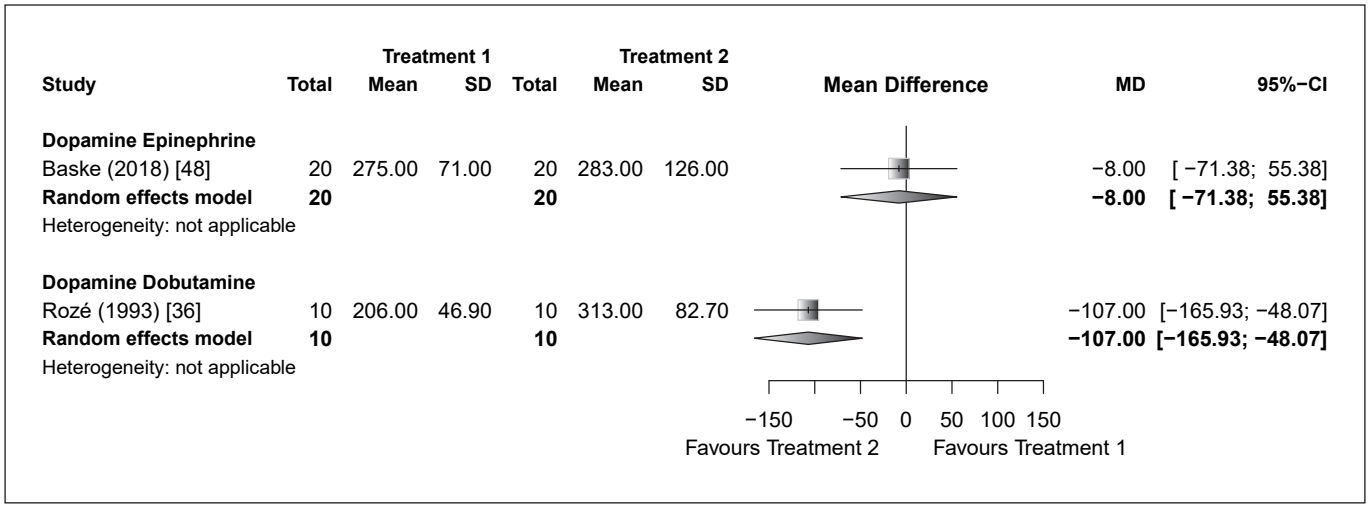


Fig. 2. Forest plot displaying all pairwise comparisons for LVO. For each of the different pairs of treatments compared, treatment 1 refers to the first drug, while treatment 2 refers to the second one.

in a non-English language. Of the remaining 84 studies, 68 were excluded following title and abstract screening, and a further one was excluded [31] because data were also used in another study [32]. In addition, of 65 records identified through citation searching, 13 were excluded after screening of title and abstract. Of the remaining 52, 48 were removed as nonrelevant after retrieval. Thus, a total of 19 studies [1, 2, 32–48] comprising 758 infants were included and provided data suitable for meta-analysis (online suppl. Fig. 2).

Contribution of Machine Learning in Study Selection

A two-step process was followed. More specifically, after the initial search in the PubMed that resulted in the clustering of 581 abstracts, the most relevant ones (n = 430) were kept while the rest were discarded (n = 88) or had to be manually inspected (n = 63). After re-clustering in the second step, only 134 abstracts were kept as the most relevant. These numbers were derived following adjustments made in terms of the number of groups and sparsity of the abstracts, so that to have the largest difference in cosine similarity between groups and, also, to be confident as to which abstract should be kept or discarded. Eventually, 197 (134 + 63) abstracts were left for manual inspection (34% of the total). This final group included all relevant articles that have been evaluated in the present study (100% accuracy).

Study Characteristics

The main characteristics of the included studies are summarized in online supplementary Table 3. All but one study included preterm infants.

Effects of Intervention

All trials included in the meta-analysis reported data on infant hypotension. Regarding response to treatment, pairwise comparisons revealed that dopamine had almost 3 times higher odds of being more effective than dobutamine for resolving hypotension (OR [95% CI] = 3.07 [1.05, 8.93], I^2 = 49%, 7 trials, 286 neonates). Similarly, dopamine was more effective than both plasma (OR [95% CI] = 23.22 [2.59, 208.61], 1 trial, 40 neonates) and placebo (OR [95% CI] = 33.00 [1.06, 1,023.66], 1 trial, 10 neonates), and systemic corticosteroids were more effective than placebo (OR [95% CI] = 10.37 [2.60, 41.39], I^2 = 0%, 2 trials, 65 neonates) (Fig. 1).

Results from the pairwise comparisons for all-cause mortality and other secondary, clinical, and cardiovascular outcomes are shown in online supplementary Figures 3–10. Most of the comparisons did not hold enough data for meta-analysis. For those outcomes where comparisons sufficed, most pooled effects were not statistically significant, with a few exceptions: dopamine when compared to dobutamine significantly reduced both LVO (MD [95% CI] = −107.0 [−165.93, −48.07] mL/kg/min) and RVO (MD [95% CI] = −125.30 [−167.03, −83.57] mL/kg/min) (Fig. 2, 3, respectively). Similarly, dopamine

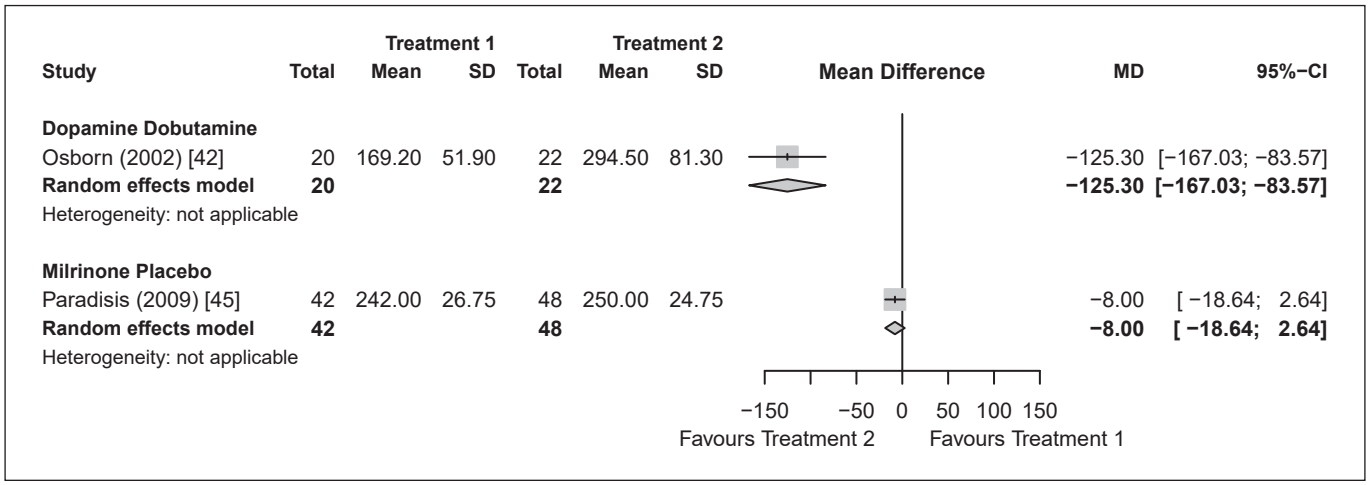


Fig. 3. Forest plot displaying all pairwise comparisons for RVO. For each of the different pairs of treatments compared, treatment 1 refers to the first drug, while treatment 2 refers to the second one.

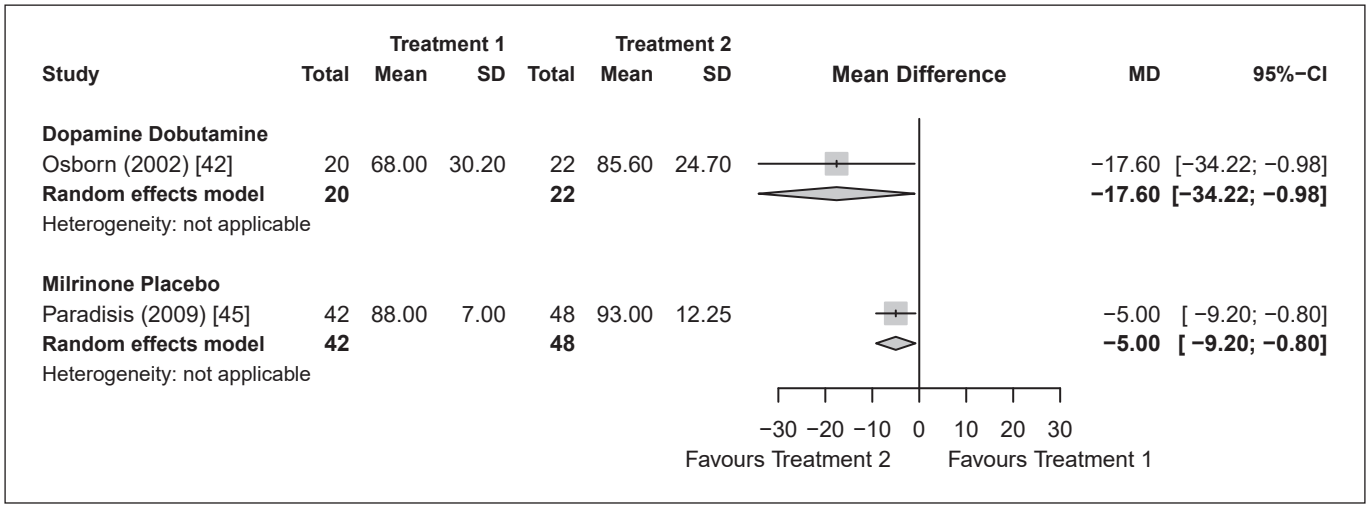


Fig. 4. Forest plot displaying all pairwise comparisons for SVC flow. For each of the different pairs of treatments compared, treatment 1 refers to the first drug, while treatment 2 refers to the second one.

when compared to dobutamine significantly reduced SVC flow (MD [95% CI] = −17.6 [−34.22, −0.98] mL/kg/min). Milrinone also reduced SVC flow when compared to placebo (MD [95% CI] = −5.00 [−9.20, −0.80] mL/kg/min) (Fig. 4). Furthermore, dobutamine and milrinone increased heart rate when compared to placebo (MD [95% CI] = 14.90 [7.65, 22.15] and 9.00 [3.39, 14.61] beats/min for dobutamine and milrinone versus placebo, respectively) (Fig. 5). However, all these estimates were derived from single trials. It is worth noting that no differences could be documented in mean BP when dopamine was compared to dobutamine or epinephrine (online suppl. Fig. 10).

Quality of Studies

Overall, the RoB was variable across comparisons. Dobutamine was compared to dopamine in seven studies. Four of them raised concerns, one was deemed of high risk, and two of low risk. Dopamine compared with placebo raised some concerns in two studies and was of low

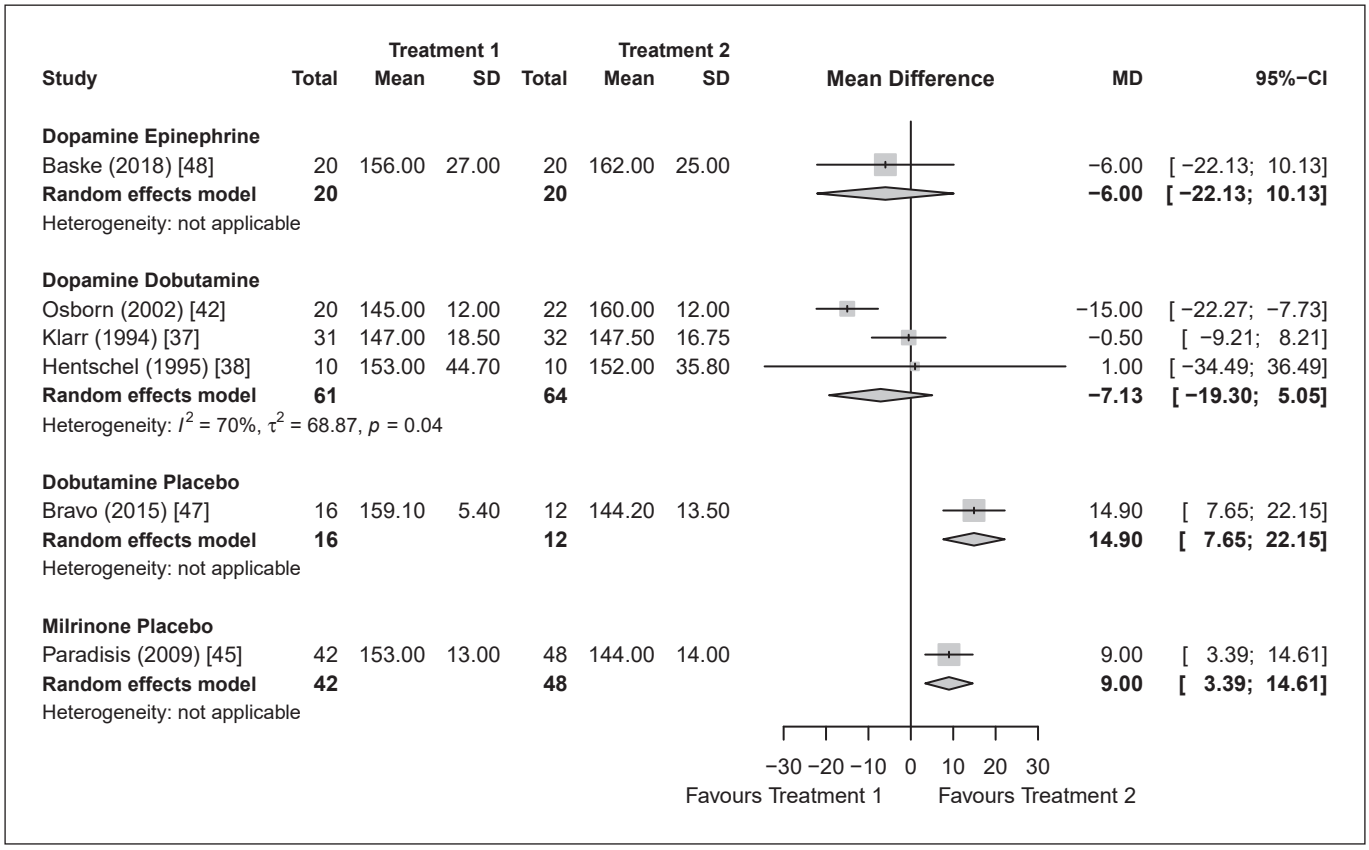


Fig. 5. Forest plot displaying all pairwise comparisons for heart rate. For each of the different pairs of treatments compared, treatment 1 refers to the first drug, while treatment 2 refers to the second one.

risk. Dopamine against no treatment or hydrocortisone was of low RoB, while when compared to epinephrine two studies were of low risk and the other was of high RoB. Dobutamine and dexamethasone against placebo were of low RoB, as was milrinone. The comparison between hydrocortisone and placebo was found to be of low RoB in one study and of high risk in the other. Plasma protein compared to dopamine as well as vasopressin against placebo raised concerns. Albumin against no treatment was tested in one study with low RoB.

Quality of Evidence

The quality of evidence according to GRADE was low to very low (online suppl.Table 4), due to the many methodological issues from the identified studies that might introduce bias.

Discussion

This systematic review and pairwise meta-analysis involving 19 RCTs and 758 neonates was conducted in order to compare the effectiveness of the vasoactive drugs used for the treatment of arterial hypotension in both preterm and term infants and to assess the overall size and quality of the existing evidence. Machine learning-assisted screening of the literature was used in the study, additionally to the current approach for study selection. There were three important findings from our analysis. First, only the comparison of dopamine versus dobutamine provided evidence for effectiveness of treatment (restoration of normal BP) and was in favor of dopamine. Second, no safe conclusions could be reached with respect to other treatments due to the limited number of RCTs and heterogeneity among them. Third, our investigation confirmed the lack of adequate data from RCTs both in preterm and term infants on the management of

hypotension in conditions other than the transition after birth in preterm newborns.

BP is determined by the cardiac output and systemic vascular resistance (SVR), so that BP = CO·SVR, and remains the most frequently monitored indicator of neonatal circulatory status. In this pairwise meta-analysis, eight treatments were compared, with dopamine being the most used in 14 of the 19 studies evaluated, followed by dobutamine in eight studies. In any case, after analyzing 7 RCTs involving 286 neonates, only the effectiveness of dopamine when compared to dobutamine for the restoration of normal BP could be documented. Still, the quality of this evidence was very low (moderate effect size, CI [1.06–8.87]), a fact that should be taken into consideration. We also found dopamine, when compared to dobutamine, to significantly reduce all three measurements of systemic perfusion such as RVO, LVO, and SVC flow. In preterm neonates during the first postnatal days, due to the presence of cardiac shunts, systemic blood flow is significantly overestimated, thus explaining the weak positive associations between BP and LVO [49]. The measurement of SVC flow has been proposed to overcome this disadvantage [50], given that the flow from the upper body and brain is evaluated without being affected by shunts. Unsurprisingly, our findings are in line with previous meta-analyses comparing dopamine to dobutamine in hypotensive preterm infants, in which dopamine was found to lead to a greater increase in mean BP (presumably secondary to an increase in SVR but not in LVO), whereas dobutamine seemed to have a greater effect on LVO [12].

In the present meta-analysis, most studies involved very premature neonates with early cardiovascular insufficiency (online suppl. Table 3), apparently due to structural and developmental aspects of the cardiovascular system and the transitional changes that occur over the first weeks of life [51]. However, RCTs on the role of cardiovascular medications in other neonatal conditions are alarmingly sparse. There is only one RCT by Baske et al. [48] (also included in the present meta-analysis), in which dopamine was compared to epinephrine in preterm neonates with fluid-refractory septic shock. Similarly, the early study by DiSessa et al. [33] comparing dopamine versus dextrose/water to treat hypotension is the only published RCT in term neonates with severe perinatal asphyxia. Interestingly, various anti-hypotensive treatments are regularly recommended by clinical guidelines for the hemodynamic support in septic [52, 53] or asphyxiated infants [54], despite the fact that there have been no comparisons between them for their effectiveness, and all recommendations were classified as "weak," based on low- or very low-quality evidence in pediatric studies. Our study further highlights the lack of strong evidence as to the most appropriate cardiovascular support in hypotensive neonates and, also, the need for disease-specific studies, despite all known difficulties in design and clinical application. Sepsis, necrotizing enterocolitis, or hypoxic-ischemic encephalopathy are conditions of great clinical interest awaiting relevant answers in the context of future RCTs. Nevertheless, the evidence for the efficacy of cardiovascular drugs should not be based solely on data derived from biomarkers (e.g., blood lactate) and surrogate (e.g., BP and other hemodynamic parameters) or hospitalization endpoints. Ideally, studies should also assess outcomes relevant to patients in the long term, such as survival at different time-points, chronic morbidities, and health-related quality of life (e.g., social functioning at school/work). As far we know, only one study by Pellicer et al. [55] assessed the impact of early cardiovascular support (dopamine or epinephrine vs. no treatment during the first 24 h of life) on the neurodevelopmental outcome of ex-preterm infants. No difference was documented between the groups at 2–3 years of age [55].

Machine learning-assisted study selection was used in the present study as it provides extra credibility of the results. More specifically, the search for abstracts-publications that adhered to the study protocol was conducted by a machine, using an automated unerring procedure to reach a result, reducing the number of abstracts for manual inspection by 66%. Moreover, contrary to the most popular programs, the use of such a flexible, user-controlled program allowed 384 abstracts to be discarded in less than 1 h. Otherwise, a manual inspection time of around 8 h would be needed (see relevant online suppl. material). Time saving on abstract screening is further improved as the number of abstracts gets larger.

The major limitation of this systematic review and meta-analysis is that, due to the small size of the evidence and its scattering across several drugs and their combinations, we have a low degree of confidence in the results. Two factors could explain this fact: the presence of many outcomes with very few studies addressing them as well as the wide and imbalanced CIs of the calculated effect estimates. This may explain why regarding BP, for instance, only its restoration and mean BP were evaluated in the outcomes and not systolic/diastolic BP.

Conclusions

In this systematic review and pairwise meta-analysis, only the comparison of dopamine versus dobutamine provided evidence for effectiveness of treatment in neonatal hypotension and was in favor of dopamine. No firm conclusions could be reached with respect to other treatments due to the limited number of RCTs and the heterogeneity among them. Moreover, the majority of the existing RCTs involve infants with transitional hypotension early after birth. These facts warrant the need for future well-designed studies in very- and late-preterm neonates as well as in term infants with common conditions associated with hypotension, including sepsis, necrotizing enterocolitis, and hypoxic-ischemic encephalopathy, to determine the optimal management of neonatal hypotension with regard to drug selection, underlying disease, and neonatal physiology.

Statement of Ethics

An ethics statement is not applicable because this study is based exclusively on published literature.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Kosmas Sarafidis and Anna-Bettina Haidich contributed to the study conception and design; Kosmas Sarafidis, Eleni Verykouki, and Fani Apostolidou-Kiouti drafted the article; Stefanos Nikopoulos, Eleni Verykouki, Eleni Agakidou, and Aggeliki Kontou collected literature; Theodoros Diakonidis evaluated the unsupervised learning techniques for automated publication selection; Eleni Verykouki, Fani Apostolidou-Kiouti, and Stefanos Nikopoulos evaluated the articles; Eleni Verykouki and Fani Apostolidou-Kiouti analyzed data and visualized the figures; Eleni Agakidou constructed the online supplementary Tables; and Kosmas Sarafidis and Anna-Bettina Haidich critically revised the article. Each author approved the article for submission.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material. Furthermore, a spreadsheet with the data extracted for the analysis can be provided by the corresponding author upon request.

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