JPPT | Review

Epinephrine Versus Dopamine in Children, What Is the Current Evidence and What Do We Need? A Systematic Review and Meta-analysis

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INTRODUCTION Pediatric patients often receive vasoactive agents following cardiothoracic surgery or when in shock. The use of vasoactive agents varies between different settings and has largely changed because of anecdotal observations or small observational studies. Although vasoactive agents are frequently used, there are limited studies in pediatric populations comparing them to one another. The purpose of this systematic review is to quantify the comparative effects of epinephrine and dopamine while identifying gaps in knowledge.

METHODS A systematic review of published manuscripts was completed to identify full-text manuscripts in English using PubMed, Embase, and Cochrane databases. Studies were included if they included clinical data using dopamine and epinephrine in different patients and included data for the same end points for patients receiving epinephrine or dopamine.

RESULTS A total of 5 studies with 397 patients were included. Of the included patients, 187 received epinephrine and 210 received dopamine. The mean age for all the patients was 45 months. When all patient data were pooled, a significantly lower mortality was associated with epinephrine compared with dopamine (risk ratio, 0.74; 95% CI, 0.55–0.99). When only neonatal data were pooled, epinephrine was associated with a significantly higher average heart rate (10 bpm; 95% CI, 2.0–18.7) and a significantly lower average mean arterial blood pressure (−2.5 mm Hg; 95% CI, −4.6 to −0.4).

CONCLUSION Limited data are available comparing dopamine to epinephrine in pediatric patients. The available data demonstrate an apparent mortality benefit associated with the use of epinephrine.

KEYWORDS critical care; dopamine; epinephrine; pediatrics; vasoactive agonists

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Introduction

Vasoactive agents are used in many pediatric patients with shock or pediatric patients after cardiothoracic surgery.[1–4] Practice patterns of what vasoactive agents are used has changed in these various settings over time.[4] Changes in the use of different vasoactive agents in different settings has largely changed because of anecdotal observations or small observational studies.

Dopamine is a catecholamine that is the immediate metabolic precursor of norepinephrine and epinephrine.[5] It is a central neurotransmitter with effects on the regulation of movement and the cardiovascular system. Its cardiovascular effects are mediated by both dopaminergic receptors (D1 and D2) and α- and β-adrenergic receptors. Its effects are dose dependent; at small doses (5–10 μg/kg/min) it favors an inotropic effect on β receptors, and at large doses, it predominantly acts as a vasopressor by activating α1-adrenergic receptors.[6,7]

Meanwhile, epinephrine is a catecholamine that acts on adrenergic receptors, in both α and β subsets.[8] It has a chronotropic and an inotropic effect by activating the β-adrenergic receptors of the heart and has a vasopressor effect by α-adrenergic activation on the blood vessels. Its effect on blood pressure is also dose dependent. At small doses (0.05–0.2 μg/kg/min), it may cause the blood pressure to fall due to activation of vascular β2-adrenergic receptors, but as dose increases its effect on vascular α1-adrenergic receptors becomes predominant; thus, it raises blood pressure.[7]

Both epinephrine and dopamine have agent-specific effects that go beyond simply the heart and the vasculature.[5] Epinephrine is also a potent bronchodilator, inhibits insulin secretion, stimulates the central nervous system, and increases the cellular uptake of potassium.[9] Meanwhile, dopamine also increases glomerular filtration rate, decreases tubular bicarbonate reabsorption, induces renin secretion, and inhibits secretion of prolactin.[5] All of these effects

can modify how these vasoactive agents clinically impact patients and their outcomes. A thorough understanding of the effects of each agent and proper setting-specific selection may impact patient outcome. In the context of children with septic shock, the Surviving Sepsis Pediatric Guidelines suggest using epinephrine rather than dopamine.[10] The basis of their recommendation is limited to only 2 randomized controlled studies, which showed epinephrine was associated with a lower risk of mortality and more organ failure–free days.[11,12]

Although they are frequently used in pediatrics, these vasoactive agents have not been studied at great length in comparison to one another. Therefore, the primary purpose of these pooled analyses was to conduct a systematic review of the literature and quantify the comparative effects of epinephrine and dopamine. The secondary purpose of these pooled analyses was to identify gaps in knowledge.

Methods

A systematic review of the literature was performed to identify published retrospective or prospective case series and randomized clinical studies describing the use of epinephrine or dopamine in pediatrics. This was a newly conducted review without a previously established protocol. The reporting of this systematic review was guided by the standards of the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) Statement (Supplemental Figure S1 and Supplemental Files S1 and S2).

Inclusion and Exclusion Criteria. The studies must have included patients younger than 18 years, compared a group of patients who received epinephrine and a group who received dopamine, reported data for the same end points for patients who received epinephrine or dopamine, and reported complete patient data. The studies that were published only as an abstract or published in a language other than English were excluded.

Manuscript Search and Identification Strategy. Published manuscripts were identified by searching the PubMed, Embase, and Cochrane databases. The following search terms were used in isolation and various combinations: “dopamine,” “epinephrine,” “adrenaline,” “vasoactive,” “pediatrics,” “children,” “neonates,” and “infants.” No specific restriction on the year of publication was used. Only manuscripts published in English were eligible for inclusion.

Manuscripts were initially screened by title and abstract, with full text being retrieved for select manuscripts. Full-text review of selected manuscripts was then conducted by 2 authors. These authors also assessed whether the identified studies met the inclusion criteria. Any discrepancies between the 2 authors were then reviewed by a third author and a consensus reached.

Risk of Bias Assessment. These full-text manuscripts were then reviewed by the authors for the presence of bias. Bias was assessed independently by 2 authors. Any discrepancies between the 2 authors were then reviewed by a third author and a consensus was reached. The tools suggested by the Cochrane Handbook for Systematic Reviews were used for bias evaluation; the revised tool to assess risk of bias in randomized trials (RoB 2) was used for randomized trials and the ROBINS-I tool (Risk of Bias in Non-randomized Studies–of Interventions) was used for nonrandomized studies.[13,14]

End Points. Meta-analyses were conducted to determine the effects of epinephrine or dopamine on the following end points: heart rate (bpm), mean arterial blood pressure (mm Hg), serum lactate (mg/dL), duration of vasoactive support (minutes), and mortality. Additionally, other data were collected, such as study type, setting, and patient age. Other end points were shared between studies but were excluded if data were available from 2 or fewer studies. If there was more than 1 time point of data, data were collected at the last reported time point between 30 and 360 minutes.

Data Extraction. Data were extracted using a data collection form created specifically for this study. Study-level data were extracted by 2 separate authors to confirm accuracy of the data. If no information was available for a particular outcome, this was recorded. Authors of included studies were not contacted for additional data.

Mean and SD were collected for continuous variables. If median and range or median and IQR were presented, then mean and SD were calculated for use in the pooled analyses. If studies presented data in graph form, these data were not used.

Publication Bias. Publication bias was not assessed because of the low number of included studies.

Data Analyses. Meta-analyses were conducted using Revman version 5.4 (Cochrane, London, United Kingdom). A fixed-effects model was run initially for each end point. Heterogeneity was assessed using 2 methods: 1) Q-statistics and its resulting p value, and 2) I2 value. Heterogeneity was considered statistically significant if the p value for the Q-statistic was less than 0.05 or the I2 value was greater than 50%. For end points with statistically significant heterogeneity a random effect was used for the pooled analyses. Results of pooled analyses for continuous variables are presented with mean difference and 95% CI, whereas results of binary variables are presented with risk ratio and 95% CI. Sensitivity analyses were conducted to determine the impact of time at which data were collected after initiation of epinephrine or dopamine. One pooled analysis was done including all patients, and a second analysis was done including only neonates. Figures displaying pooled effect were created using

GraphPad Prism version 9.0.1 (GraphPad Software, San Diego, CA).

Results

Study and Patient Characteristics. A total of 5 studies with 397 patients were included in the final pooled analyses (Supplemental Figure S1 and Table 1).[11,12,15–17] Of these, 187 received epinephrine, whereas 210 received dopamine. Of the 5 studies, 4 (80%) were prospective double-blind randomized controlled studies, whereas 1 (20%) was a retrospective cohort study. Four studies[11,12,15,17] were found to have low bias, and 1 study[16] was found to have moderate bias (Supplemental File 3). Four (80%) of the included studies[11,12,15,16] included patients with septic shock, and 1 of the included studies[17] included low–birth weight infants requiring vasoactive support for any indication. The mean age was 45 months (44 months for those receiving epinephrine and 46 months for those receiving dopamine). A total of 4 of the 5 studies presented contained information regarding dopamine between 2.5 and 20 mcg/kg/min and epinephrine between 0.1 and 0.5 mcg/kg/min.[11,12,15,17]

Heart Rate. A total of 3 studies were pooled for the analysis of heart rate in all patients (Tables 2 and 3).[12,15,17] This resulted in a total of 219 patients. The Q-statistic had a p value of 0.09 and the I2 value was 58%, indicating significant heterogeneity. Thus, a random-effects model was used. There was no statistically significant difference noted in heart rate between both groups. The mean difference was found to be 4.7 (−5.3 to 14.8, p = 0.36; Figure 1).

When only neonatal data were pooled, a total of 2 studies with 99 patients were included.[15,17] There was a statistically significant difference noted in heart rate between both groups. The epinephrine group was associated with a higher average heart rate, 10.4 bpm (2.0–18.7, p = 0.01; Figure 2).

Sensitivity analyses demonstrated no significant impact of time to measurements after vasoactive initiation.

Mean Arterial Blood Pressure. A total of 3 studies were pooled for the analysis of mean arterial blood pressure in all patients (Tables 2 and 3).[12,15,17] This resulted in a total of 219 patients. The Q-statistic had a p value of less than 0.01, and the I2 value was 94%, indicating significant heterogeneity. Thus, a random-effects model was used. There was no statistically significant difference noted in mean arterial blood pressure between both groups. The mean difference was found to be 1.9 mm Hg (−5.7 to 9.5, p = 0.63; Figure 1).

When only neonatal data were pooled, a total of 2 studies with 99 patients were included.[15,17] A statistically significant difference was noted in mean arterial blood pressure between both groups. The epinephrine group was associated with a lower mean arterial blood pressure, −2.5 mm Hg (−4.6 to −0.4, p = 0.02; Figure 2).

Sensitivity analyses demonstrated no significant impact of time to measurements after vasoactive initiation.

Serum Lactate. A total of 3 studies were pooled for the analysis of serum lactate in all patients (Tables 2 and 3).[12,15,17] This resulted in a total of 219 patients. The Q-statistic had a p value of 0.17, and the I2 value was 47%, indicating no significant heterogeneity. Thus, a fixed-effects model was used. There was no statistically significant difference noted in serum lactate concentration between both groups. The mean difference was found to be 0.8 mg/dL (−0.3 to 1.9, p = 0.16; Figure 1).

When only neonatal data were pooled, a total of 2 studies with 99 patients were included.[15,17] No statistically significant difference was noted in serum lactate concentration between both groups. The mean difference was found to be 1.27 mg/dL (−0.1 to 2.5, p = 0.06; Figure 2).

Sensitivity analyses demonstrated no significant impact of time to measurements after vasoactive initiation.

Duration of Vasoactive Support. A total of 3 studies were pooled for the analysis of duration of vasoactive support in all patients (Tables 2 and 3).[12,15,16] This resulted in a total of 278 patients. The Q-statistic had a p value of 0.06, and the I2 value was 63%, indicating significant heterogeneity. Thus, a random-effects model was used. There was no statistically significant difference noted in duration of vasoactive support between both groups. The mean difference was found to be 163.2 minutes (−155.6 to 482.1; Figure 1).

Sensitivity analyses demonstrated no significant impact of time to measurements after vasoactive initiation.

Mortality. A total of 5 studies were pooled for the analysis of mortality (Tables 2 and 3).[11,12,15–17] This resulted in a total of 377 patients. The Q-statistic had a p value of less than 0.44, and the I2 value was 0%, indicating no significant heterogeneity. Thus, a fixed-effects model was used. There was a statistically significant difference noted in mortality between both groups. Mortality was found to be lower in the epinephrine group, with a risk ratio of 0.74 (0.55–0.99, p = 0.04; Figure 3).

When only neonatal data were pooled, a total of 2 studies with 99 patients were included.[15,17] No statistically significant difference was noted in mortality between both groups. The risk ratio was found to be 1.01 (0.68–1.50, p = 0.95; Figure 4).

Sensitivity analyses demonstrated no significant impact of time to measurements after vasoactive initiation.

Discussion

These pooled analyses demonstrate that when all patients are considered, epinephrine is associated with lower mortality compared with dopamine. When only neonates are considered, epinephrine is associated with a statistically significantly higher heart rate and significantly lower mean arterial blood pressure. There was no difference in mortality between those

Table 1. Characteristics of Selected Studies

Source	Year	Study Type	Setting	Epinephrine, n	Dopamine, n	Epinephrine Mean Age, mo	Dopamine Mean Age, mo	Time to Repeat Data, min
Baske[15]	2018	Prospective randomized, double-blind controlled trial	Septic shock	20	20	0.1	0.1	45
Kohn-Loncarica[16]	2020	Retrospective cohort study	Septic shock	49	69	59	84	
Pellicer[17]	2005	Prospective randomized, double-blind controlled trial	Low–birth weight infants	32	27	0.1	0.1	40
Ramaswamy[11]	2016	Prospective randomized, double-blind controlled trial	Septic shock	29	31	78	50.4	
Ventura[12]	2015	Prospective randomized, double-blind controlled trial	Septic shock	57	63	56.9	39.6	360

Table 2. Outcomes Pooled for Analysis

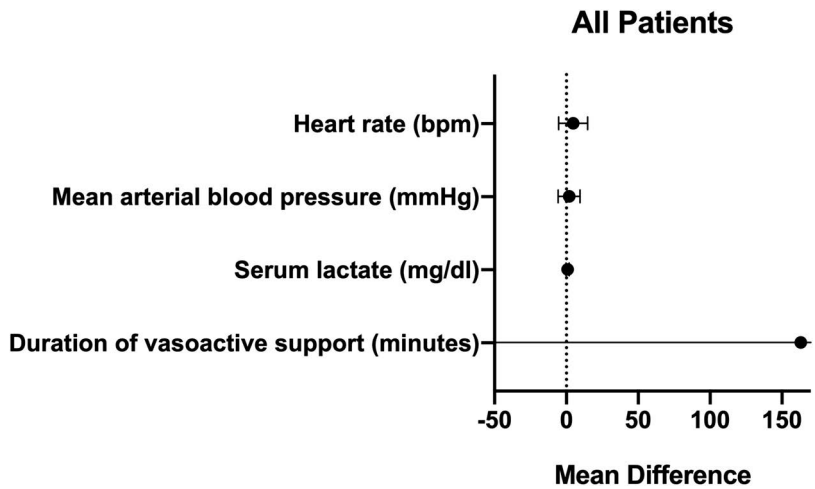
Outcomes	Total, n	Epinephrine, n	Dopamine, n	Baske[15]	Kohn-Loncarica[16]	Pellicer[17]	Ramaswamy[11]	Ventura[12]	Studies per Outcome
Heart rate (bpm)	219	109	110	X		X		X	3
Mean arterial blood pressure (mm Hg)	219	109	110	X		X		X	3
Serum lactate (mg/dL)	219	109	110	X		X		X	3
Duration of vasoactive support (min)	278	126	152	X	X			X	3
Mortality (n)	377	187	190	X	X	X	X	X	5
Neonate only	99	52	47	X		X			

Table 3. Summary of Pooled Findings*

	Studies, n	Epinephrine, n	Dopamine, n	Heterogeneity	Pooled Effect: All Patients (95% CI)	Pooled Effect: Neonates Only (95% CI)
Heart rate (bpm)	3	109	110	p = 0.09, I^2 = 58%†	4.7 (−5.3 to 14.8), p = 0.36	10.4 (2.0 to 18.7), p = 0.01†
Mean arterial blood pressure (mm Hg)	3	109	110	p < 0.01, I^2 = 94%†	1.9 (−5.7 to 9.5), p = 0.63	−2.5 (−4.6 to −0.4), p = 0.02†
Serum lactate (mg/dL)	3	109	110	p = 0.17, I^2 = 47%	0.8 (−0.3 to 1.9), p = 0.16	1.27 (−0.1 to 2.5), p = 0.06
Duration of vasoactive support (min)	3	126	152	p = 0.06, I^2 = 63%†	163.2 (−155.6 to 482.1)	-
Mortality	5	187	190	p = 0.44, I^2 = 0%	0.74 (0.55 to 0.99), p = 0.04†	1.01 (0.68 to 1.50), p = 0.95)

* *Pooled effects reported as mean difference for continuous variables and risk ratio for dichotomous variables.*
† *Statistically significant.*

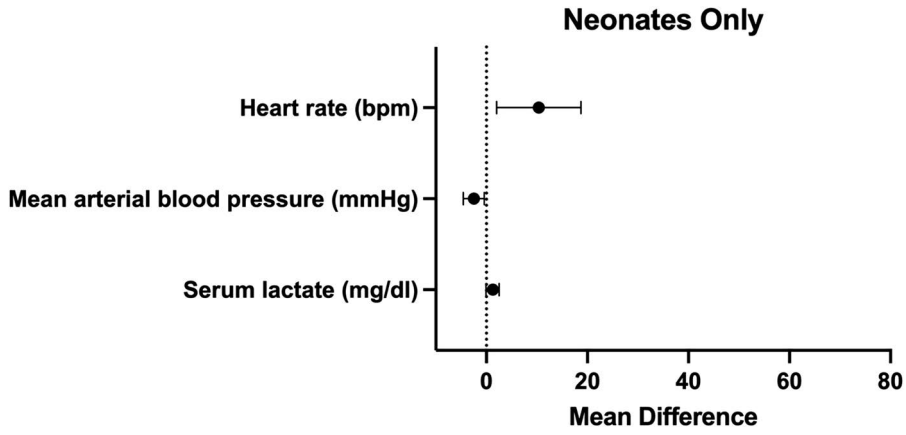
Figure 1. Forest plot displaying mean difference of heart rate, mean arterial blood pressure, serum lactate, and duration of vasoactive support in all patients.



who received epinephrine and those who received dopamine in the neonatal subset. Although there was a statistically significant difference in heart rate and blood pressure, the differences in either may not be clinically significant.

Of particular note is the fact that epinephrine was associated with lower mortality, a finding some of the source studies noted as well.[12,15] Current data do not necessarily indicate what mediates this mortality benefit, but some of the answer may lie in the mechanisms

Figure 2. Forest plot displaying mean difference of heart rate, mean arterial blood pressure, and serum lactate in neonates only.



of action. Epinephrine is a sympathomimetic catecholamine that acts directly on adrenergic receptors, of both the α and β subsets.[15] These mechanistic considerations are important to understand because they have clinical consequences. At smaller doses, epinephrine's predominantly β-adrenergic effect leads to vasodilation[11] and increased cardiac output via increased contractility. Because systemic vascular resistance is equal to the difference in mean arterial blood pressure and central venous pressure divided by systemic cardiac output, a decrease in the numerator (mean arterial blood pressure – central venous pressure) and increase in the denominator (systemic cardiac output) leads to lower systemic vascular resistance. So, although epinephrine is often considered a vasoconstrictor, this is not truly the case until larger doses (more than 0.2 mcg/kg/min). Eugene[7] performed a study that used clinical data from humans to develop a simulation of the hemodynamic effects of epinephrine and found a clear dose-dependent reduction in systemic vascular resistance with doses of epinephrine at or below 0.1 mcg/kg/min. The studies included in our meta-analysis used different dosing strategies using systolic and diastolic blood pressure increases. The Surviving Sepsis Campaign International guidelines[10] do not specifically delineate a dosing strategy. Therefore, it is in the interest of clinicians that well-designed studies be developed to assess the dose effectiveness of these vasoactives in pediatric shock. While systemic vascular resistance decreases, an increase in mean arterial blood pressure may still be noted; it is imperative to keep in mind that systemic vascular resistance and mean arterial blood pressure are not synonymous. Mean arterial blood pressure is the product of systemic cardiac output and systemic vascular resistance. Thus, it follows that mean arterial blood pressure can still increase despite decreasing systemic vascular resistance if there is an increase in cardiac output of greater magnitude. It is also important to note that mean arterial blood pressure can stay the same at a higher cardiac output and lower systemic

Figure 3. Forest plot displaying risk ratio of mortality in all patients.

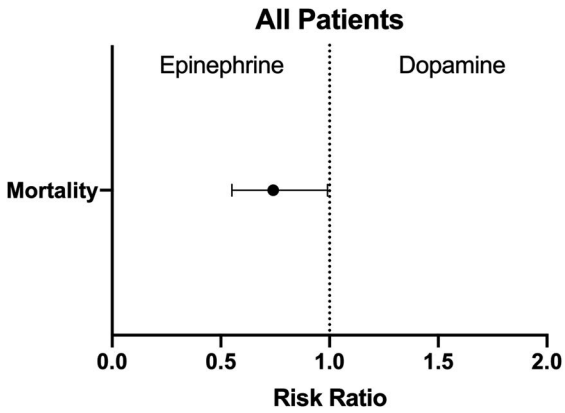
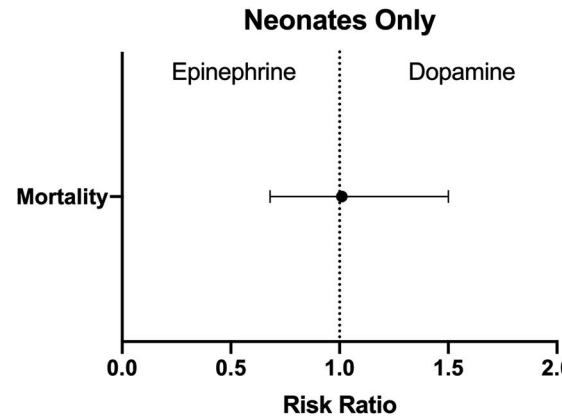


Figure 4. Forest plot displaying risk ratio of mortality in neonates only.



vascular resistance, which still represents an improvement in the hemodynamic state. This represents one of the limitations of using mean arterial pressure as the clinical target to titrate. Last, it is important to point out that on occasions a lactic acidosis can be induced by epinephrine's activation of α-adrenergic receptors, which can lead to several endocrine changes, including but not limited to suppression of insulin release, which may lead to increased serum glucose concentrations.[15,18,19] This lactic acidemia may not necessarily be a result of an inadequate oxygen supply demand balance.[17,18]

Dopamine is a dopaminergic catecholamine; it has both adrenergic and dopaminergic dose-dependent effects.[5,8] At small doses, its effect on vascular dopaminergic receptor 1 leads to vasodilation, particularly in the renal, mesenteric, and coronary beds.[6] It also activates dopaminergic 2 receptors on presynaptic nerve terminals, leading to an increase in heart rate and vascular resistance.[11,20] Its adrenergic effects are also dose dependent. At small doses, dopamine acts as an inotropic through stimulation of β-adrenergic receptors. As doses increase, it starts acting on the vascular α1-adrenergic receptor, causing vasoconstriction.[8,11] Additionally, dopamine is converted to norepinephrine by dopamine β-hydroxylase, causing an additional indirect effect on both α- and β-adrenergic receptors.[21] Therefore, similar to epinephrine, dopamine does lower systemic vascular resistance at smaller doses. Most of the dopamine's systemic vascular reduction has been demonstrated to occur at doses of 2.5 mcg/kg/min or less, although addition reduction does seem to occur until 10 mcg/kg/min.[17] Dopamine-related reduction in systemic vascular resistance is likely more related to relative increase in systemic cardiac output.[17]

Although there are some data comparing epinephrine and dopamine in pediatric patients, the available data are limited. For continuous infusions that are used with relative frequency in pediatric intensive care units, the relative effects of these vasoactive agents have not been well described. The current data tend to focus on heart, blood pressure, duration of vasoactive support, time to resolution of shock, and mortality.[18] Data on other indices, such as systemic vascular resistance, pulmonary vascular resistance, cardiac index, and systemic oxygen delivery, are not readily available. The lack of data regarding systemic oxygen delivery is particularly of note because this is the very thing that is required by the organs for function and is the basis of our therapeutic interventions. Heart rate, blood pressure, and other conventional hemodynamic parameters are simply components in the circulatory system that can impact systemic oxygen delivery. Changes in mean arterial blood pressure do not always reflect changes in systemic oxygen delivery.[22,23] It is important to point out that a previous meta-analysis on this topic showed similar heart rate response for epinephrine and dopamine in pediatric or neonatal septic shock.[24] Our study found results similar to those previously published.[24] However, when only neonatal data were assessed the epinephrine group had a higher average heart rate. These findings are consistent with the evidence that neonates increase their cardiac output primarily by raising heart rates, whereas older children do so by augmenting stroke volume.[25]

The field of pediatric critical care would benefit from data regarding the comparative effects of epinephrine and dopamine on stroke volume, cardiac output, near infrared spectroscopy, and venous saturation.

These pooled analyses add to the current literature. There is, anecdotally, misperception among pediatric intensivists that there is a wealth of information regarding vasoactive agents in children. Our systematic review of the literature and the pooled analyses highlight that this, in fact, is not the case. The finding of this meta-analysis is also in alignment with the surviving Sepsis Campaign International guidelines[10] in that epinephrine should be selected rather than dopamine, particularly in patients with septic shock and myocardial dysfunction. The pooled analyses help summarize and characterize the data that are available comparing epinephrine and dopamine in children. However, these pooled analyses are not without their limitations. The number of pooled studies and thus the number of patients across the pediatric age spectrum is low. This, however, as discussed before, highlights an important gap in knowledge in pediatrics. There are also only a few end points that could be pooled. It is important to highlight that data were pooled from a heterogenous patient population and study outcomes. Heterogeneity was present and this was accounted for by using a random-effects model for end points with significant heterogeneity. Lastly, some of the hemodynamic responses to shock may differ between neonatal and pediatric patients; therefore, some of the results should be taken in that context. Despite these limitations we believe this manuscript is a helpful addition to the shock literature.

Conclusion

There is a paucity of data comparing the effects of epinephrine and dopamine in children. The data that are available demonstrate an apparent mortality benefit associated with the use of epinephrine.

Article Information

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Data Availability Statement. The data that support the findings of this study are available from the corresponding author upon reasonable request.

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