Double-Blind Prospective Randomized Controlled Trial of Dopamine Versus Epinephrine as First-Line Vasoactive Drugs in Pediatric Septic Shock

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Objectives: The primary outcome was to compare the effects of dopamine or epinephrine in severe sepsis on 28-day mortality; secondary outcomes were the rate of healthcare–associated infection, the need for other vasoactive drugs, and the multiple organ dysfunction score.

Design: Double-blind, prospective, randomized controlled trial from February 1, 2009, to July 31, 2013.

Setting: PICU, Hospital Universitário da Universidade de São Paulo, Brazil.

Patients: Consecutive children who are 1 month to 15 years old and met the clinical criteria for fluid-refractory septic shock. Exclusions were receiving vasoactive drug(s) prior to hospital admission, having known cardiac disease, having already participated in the trial during the same hospital stay, refusing to participate, or having do-not-resuscitate orders.

Interventions: Patients were randomly assigned to receive either dopamine (5–10 μg/kg/min) or epinephrine (0.1–0.3 μg/kg/min) through a peripheral or intraosseous line. Patients not reaching predefined stabilization criteria after the maximum dose were classified as treatment failure, at which point the attending physician gradually stopped the study drug and started another catecholamine.

Measurements and Main Results: Physiologic and laboratory data were recorded. Baseline characteristics were described as proportions and mean (± SD) and compared using appropriate statistical tests. Multiple regression analysis was performed, and statistical significance was defined as a p value of less than 0.05. Baseline characteristics and therapeutic interventions for the 120 children enrolled (63, dopamine; 57, epinephrine) were similar. There were 17 deaths (14.2%): 13 (20.6%) in the dopamine group and four (7%) in the epinephrine group ($p = 0.033$). Dopamine was associated with death (odds ratio, 6.5; 95% CI, 1.1–37.8; $p = 0.037$) and healthcare–associated infection (odds ratio, 67.7; 95% CI, 5.0–910.8; $p = 0.001$). The use of epinephrine was associated with a survival odds ratio of 6.49.

Conclusions: Dopamine was associated with an increased risk of death and healthcare–associated infection. Early administration of peripheral or intraosseous epinephrine was associated with increased survival in this population. Limitations should be observed while interpreting these results. (*Crit Care Med* 2015; 43:2292–2302)

Key Words: children; dopamine; epinephrine; mortality; septic shock; vasoactive drug

Severe sepsis continues to be recognized as a significant healthcare problem worldwide. The prevalence of sepsis in critically ill children is expected to increase as more children survive diseases that were previously considered uniformly fatal. In children, the case-fatality rate in developed countries is around 10% (1), and it is 18% in developing nations (2). If septic shock is present, the mortality can be as high as 50% (3).

International collaborative efforts to improve the diagnosis and treatment of sepsis in children and neonates have been in place for more than a decade (4, 5). Adherence to guideline recommendations has decreased mortality in developed (survival odds ratio, 6.81; 95% CI, 1.26–36.80) (6) and developing countries (mortality odds ratio, 0.33; 95% CI, 0.13–0.85) (7). Nevertheless, some aspects of the guidelines are still a matter of debate. One of these, thanks to a paucity of research, is which first-line vasoactive drug is the best choice for children with fluid-refractory septic shock. Because myocardial dysfunction is well documented in adults (8) and children with severe

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sepsis (9, 10), we hypothesized that children with fluid-refractory septic shock would benefit from a potent inotrope.

To address this hypothesis, we conducted a single-center, prospective, randomized, double-blind trial involving children with fluid-refractory septic shock to determine whether dopamine or epinephrine decreases 28-day mortality. Secondary outcomes were the rate of healthcare–associated infection (HAI), the need for other vasoactive drugs, and multiple organ dysfunction score.

METHODS

Study Design

The study protocol and the informed-consent process were approved by the ethics committee at the Hospital Universitário da Universidade de São Paulo, Brazil. During a training period of 3 months, we validated the software that was used to allocate patients to group A (dopamine) or group B (epinephrine) and to calculate the volume of the vasoactive drug, the volume of crystalloids used for dilution, and the flow rate. Written informed consent was obtained from all patients, their next of kin, or another surrogate decision maker, as appropriate. Randomization was performed with the use of a computer-generated assignment sequence. A registered nurse was responsible for checking the randomization code and accessing password-protected software for the drug prescription. The nurse entered the patient's weight (in kg), initials, hospital record number, and case number. After preparation of the nonidentified vials, the printed prescription was kept in a sealed opaque envelope. Nurses were not involved in the decision-making process for the protocol or in reassessment of patients. The attending physician and fellows were responsible for obtaining informed consent, reassessing patients, and the protocol decision-making process.

Posters illustrating the flow chart of the study and the normal range of vital signs were placed in the emergency department and PICU. Continuous training for residents, nurses, and doctors was provided throughout the study period.

Children who were 1 month to 15 years old and met the clinical criteria for fluid-refractory septic shock (4) were enrolled in the study after being screened for eligibility criteria. Patients were excluded if they were receiving vasoactive drug(s) prior to hospital admission, had known cardiac disease, had already participated in the trial during the same hospital stay, refused to participate, or had do-not-resuscitate orders.

Definitions

We adopted the recommendations of the American College of Critical Care Medicine/Pediatric Advanced Life Support guidelines for defining severe sepsis (sepsis with signs of hypoperfusion) (4, 5). Clinical signs of hypoperfusion included abnormal heart rate (HR) for age, altered/decreased mental status, altered capillary refill time (CRT) (> 2 s or flash), diminished or impalpable or bounding peripheral pulses, mottled cool extremities, and urine output (UO) below 1 mL/kg/hr. Fluid-refractory septic shock was defined as persistence of clinical signs of hypoperfusion in spite of a fluid bolus of at least 40 mL/kg of crystalloids or colloids. Response to treatment included all of the following: normal HR for age, normal mental status, systolic blood pressure (SBP) more than 5th percentile for age, CRT less than 2 s, palpable peripheral pulses with no difference between central and peripheral, warm extremities, and UO more than 1 mL/kg/hr. Once a central catheter was in place, we also targeted central venous oxygen saturation ($ScvO_2$) higher than 70% and mean arterial pressure (MAP) minus central venous pressure (CVP) according to age (4, 5). The resuscitation period was defined as the period during which the dose of any vasoactive drug was increased or the child was given a bolus of 20 mL/kg of crystalloids or colloids.

Preparation of the Drug

The computer software used for allocation and drug prescription was developed for the trial by one of the authors with expertise in computer system analysis and development. The software adjusted the volume of either drug by using the patient's weight in kilograms and the desired initial dose, which was 5 μg/kg/min for dopamine and 0.1 μg/kg/min for epinephrine. The volume of crystalloid was calculated to maintain a maximum concentration of 4 μg/mL for epinephrine and 1,600 μg/mL for dopamine. Physicians were aware of the flow rate. The first flow rate corresponded to 5 μg/kg/min for dopamine and 0.1 μg/kg/min for epinephrine (X dose). The second flow rate corresponded to 7.5 μg/kg/min for dopamine and 0.2 μg/kg/min for epinephrine (Y dose). The third flow rate corresponded to 10 μg/kg/min for dopamine and 0.3 μg/kg/min for epinephrine (Z dose). Increases in flow rate occurred in 20-minute intervals. We used an infusion pump (Colleague 3; Baxter, Deerfield, IL) and light-protected IV infusion sets for both groups. The solutions were changed every 24 hours to guarantee stability at room temperature.

Clinical and Laboratory Data

Acquisition of clinical data for all patients occurred at baseline, after each fluid bolus, and before randomization. After randomization, each patient was reassessed at 20-minute intervals until reaching the above-defined criteria for response to treatment, then hourly for 6 hours, and then every 6 hours until at least 72 hours from treatment initiation or until vasoactive drug discontinuation. Clinical data included HR, blood pressure (BP), shock index (SI = HR/SBP), UO, CRT, arterial oxygen saturation (So_2), MAP-CVP, and $ScvO_2$ for those with a central venous catheter. Clinical data (HR, SBP, SI, and MAP-CVP) were compared at baseline, before randomization, at 6 hours after randomization, and at the end of resuscitation. The clinical profile of patients during the use of the study drug was described as cold or warm shock, defined as follows: cold shock as the presence of cool, clammy and/or cyanotic extremities, CRT more than 2 s, weak and feeble peripheral pulses, tachycardia or bradycardia according to age, and narrowed pulse pressure; and warm shock as the presence of warm and/or flushed extremities, CRT less than 2 s, bounding peripheral pulses, tachycardia according to age, and widened pulse pressure. Laboratory data were collected at baseline and at 6, 12, 24,

and 48 hours and at the end of resuscitation (if different from the precedents) and included serum blood lactate (mmol/L), troponin (ng/mL), and D-dimer (ng/mL).

Study Interventions

Patients were randomly assigned to receive either dopamine or epinephrine through a peripheral or intraosseous catheter (EZ-IO; Vidacare, San Antonio, TX) if clinical signs of hypoperfusion did not improve after 40 mL/kg of crystalloids (**Fig. 1**). After randomization, patients received a third fluid bolus of 20 mL/kg of crystalloids or colloids along with a starting dose of 5 μg/kg/min of dopamine or 0.1 μg/kg/min of epinephrine (X dose) through an exclusive peripheral or intraosseous catheter. If there was no response to the initial dose, two dose increments of the vasoactive drugs were allowed and accomplished by increasing the flow rate (Y and Z doses, respectively). With no response to the highest possible study drug dose, the selection of the vasoactive drug was left to the physician's discretion. A known dose and drug were started while the infusion of the study drug was gradually diminished until discontinuation.

Study Outcomes

The primary outcome was death from any cause by 28 days after inclusion. Secondary outcomes were HAI, the need for other vasoactive drugs, and multiple organ dysfunction score (11). HAI was defined according to the U.S. Centers for Disease Control and Prevention (12) and included central catheter–associated bloodstream infection, catheter-associated urinary tract infection, ventilator-associated pneumonia, surgical site infection, and nosocomial pneumonia. The need for another vasoactive drug was analyzed as "yes" or "no," and we calculated the amount of vasoactive drug used by calculating the vasopressor inotropic score (VIS) during the first 48 hours (VIS 24 hr and VIS 48 hr) (13). We used the mean Pediatric Logistic Organ Dysfunction (PELOD) score (11) for the first five hospital days to analyze differences in multiple organ dysfunctions between groups.

Adverse Events

Serious adverse events were recorded during infusion of the study drugs and were classified as cardiac, ischemic, or other. Cardiac events were defined as rhythm disturbances (tachyarrhythmia). Tachyarrhythmia was defined as abnormally high HR according to age (4, 5) and could include atrial fibrillation, atrial flutter, supraventricular tachycardia, or ventricular tachycardia. We analyzed only those ischemic events arising from drug extravasation. Other events monitored were feeding intolerance, blood glucose concentration, and persistently increased serum lactate levels. Feeding intolerance was defined, according to the Institution's protocol, as any of the following: increased gastric residual volumes (above 50% of the volume infused in the previous 3 hr), abdominal distention, emesis, changes in stool patterns, fasting for more than 72 hours, or the need for exclusive or supplemental parenteral nutrition. Blood glucose levels were monitored every 6 hours during the first 72 hours of the PICU stay. Hyperglycemia was defined as a blood glucose level above 126 mg/dL, and severe hyperglycemia was defined as a blood glucose level above 200 mg/dL at any time during the first 72 hours. Serum lactate was collected with the goal of controlling for adverse events, not as a resuscitation target. Normal values ranged from 0.33 to 1.46 mmol/L, using a lactate oxidase automated measuring method. If any value was above the higher limit after the first 24 hours of treatment, we classified it as an adverse event if the patient was already considered resuscitated.

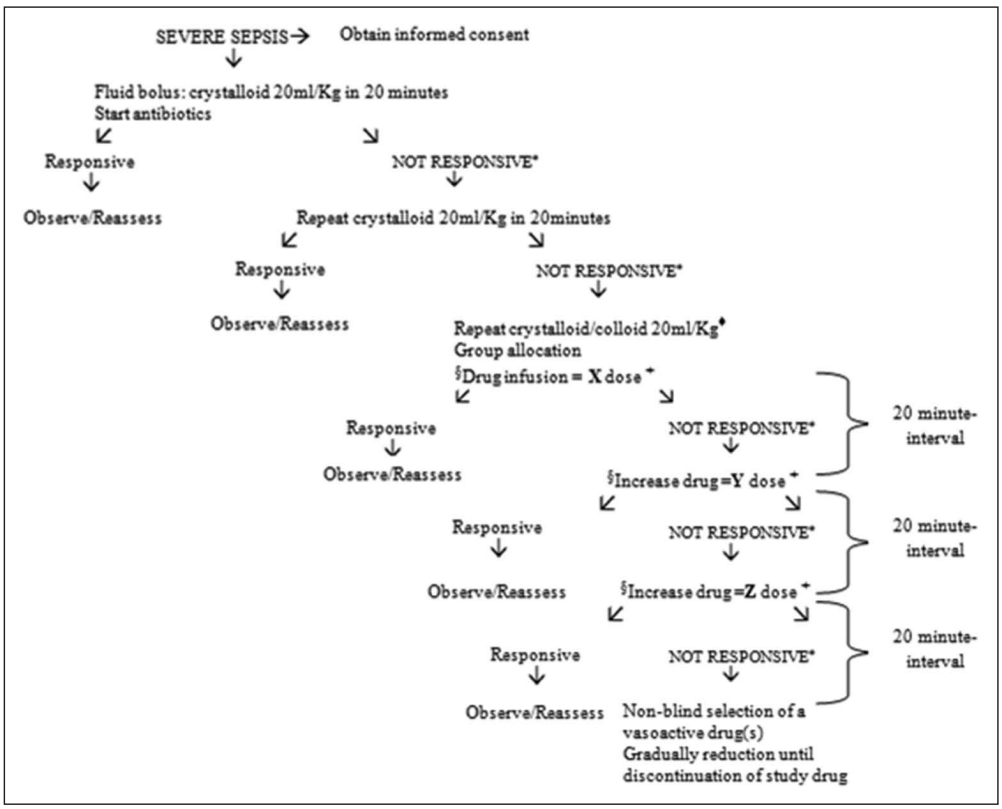

Figure 1. Study protocol. *Response to treatment include all of the following: Normal heart rate/age, normal mental status, systolic blood pressure > 5th percentile for age, capillary refill time < 2 s, palpable peripheral pulses with no difference between central and peripheral, urine output > 1 mL/kg/hr; •Observe signs of fluid overload: hepatomegaly, crackles, increased work of breathing or gallop rhythm; §Consider endotracheal intubation/nasal continuous positive airway pressure (CPAP), +**X** dose: dopamine = 5 μg/kg/min and epinephrine = 0.1 μg/kg/min, **Y** dose: dopamine = 7.5 μg/kg/min and epinephrine = 0.2 μg/kg/min, **Z** dose: dopamine = 10 μg/kg/min and epinephrine = 0.3 μg/kg/min.

Statistical Analysis

We determined that a sample of 152 patients would provide the study with 80% power to detect a 15% absolute reduction in mortality at 28 days, on the basis of an estimated baseline mortality of 25% for the control group (dopamine group), with a one-sided α value of less than 0.05 indicating statistical significance. To assure safety, we increased the sample size to 180 patients with two interim analyses for the primary outcome after enrollment of 60 and 120 patients. The first analysis identified a nonsignificant increase in mortality between groups A and B (22.6% × 6.9%; $p = 0.15$; respectively). The protocol was stopped with 120 patients because of differences in mortality. There were 17 deaths (14.2%): 13 (20.6%) in the dopamine group and four (7%) in the epinephrine group ($p = 0.033$).

All analyses were conducted on an intention-to-treat basis and performed by two independent statisticians who were not part of the study group and before the randomization code was broken. Quantitative variables were expressed as mean (± SD) and were compared using the Mann–Whitney test or Student *t* test. Qualitative variables were expressed as absolute and relative frequencies and tested with the chi-square test, Fisher exact test, or the likelihood ratio test, as appropriate.

The measures of association with the risk of death at 28 days, need for other vasoactive drugs, and rate of HAI (in percentages) were obtained using the odds ratio and respective 95% CI in a simple logistic regression model. Multivariate linear models were estimated for each outcome, and we included the variables that showed levels of significance smaller than 0.20 in bivariate tests. Time to death was calculated using the Kaplan-Meier function, and comparisons between groups were performed with the log-rank test.

Because of the asymmetrical distribution of the mean PELOD in the first five PICU days, we used generalized linear models to compare values between categories of qualitative variables and to calculate Spearman coefficient for quantitative explanatory variables. A multivariate linear model was developed for the mean PELOD in the first five PICU days using the generalized linear model with variables that in bivariate tests showed levels of significance smaller than 0.20. The level of significance was defined as a p value of less than 0.05.

All analyses were performed with the use of SPSS software, version 20.0 (SPSS Statistics for Windows, V20; Chicago, IL) and PASS 13 (power analysis and sample size software) (NCSS, Kaysville, UT).

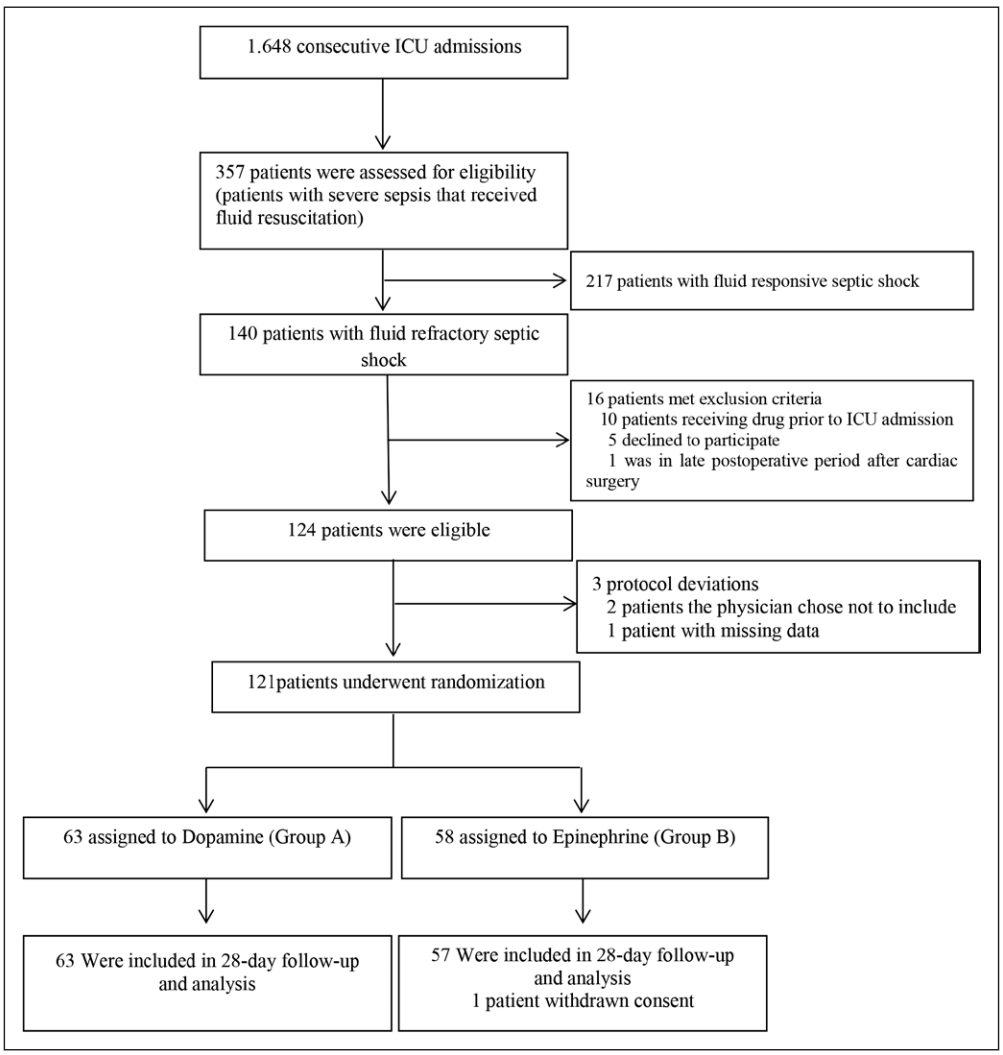

Figure 2. Screening, randomization, and follow-up of the study patients.

RESULTS

Over 4.5 years (February 1, 2009, to July 31, 2013), there were 1,648 admissions at the PICU of the Hospital Universitário, and 357 patients received fluid resuscitation because of sepsis with signs of hypoperfusion (severe sepsis = 21.7%). A total of 217 patients improved with fluids; therefore, 140 patients were classified as having fluid-refractory septic shock. Exclusion criteria were present in 16 excluded patients. Three protocol deviations occurred, and one patient withdrew consent, so that the study population ultimately consisted of 120 patients (**Fig. 2**).

At baseline, patients were similar according to age ($p = 0.145$), percent males ($p = 0.516$), nutritional status ($p = 0.142$), disease severity (Pediatric Risk of Mortality

TABLE 1. Characteristics of 120 Children With Septic Shock at Baseline

Characteristic	Dopamine (*n* = 63)	Epinephrine (*n* = 57)	*p*
Age, mo (± SD)	39.6 (46.3)	56.9 (58.2)	0.145[a]
Male gender, *n* (%)	35.0 (55.6)	35.0 (61.4)	0.516[b]
Body mass index/age *z* score (± SD)	0.16 (1.5)	−0.08 (1.9)	0.142[a]
Pediatric Risk of Mortality (± SD)	15.7 (10.4)	14.4 (9.9)	0.527[a]
Pediatric Logistic Organ Dysfunction (1st day) (± SD)	15.5 (6.5)	14.7 (6.3)	0.582[a]
Underlying disease, yes, *n* (%)	13 (20.6)	12 (21.1)	0.955[b]
Cold shock during use of study drug, yes, *n* (%)	43 (88.3)	40 (70.2)	0.818[b]
Community-acquired infection, yes, *n* (%)	59 (93.6)	51 (89.4)	0.563[b]
Source of infection, *n* (%)			
Respiratory	41	36	0.788[c]
Intra-abdominal	12	7	
Skin/soft tissue	3	3	
CNS	7	5	
Urinary tract	1	2	
Others	19	10	
Etiology, *n* (%)	40 (63.4)	40 (70)	0.735[c]
Streptococcus pneumoniae	9 (22.5)	8 (20)	
Methicillin-sensitive *Staphylococcus aureus*	7 (17.5)	5 (12.5)	
Neisseria meningitidis	4 (10)	7 (17.5)	
Streptococcus pyogenes	4 (10)	3 (7.5)	
Haemophilus influenzae	4 (10)	3 (7.5)	
Methicillin-resistant *S. aureus*	1 (2.5)	4 (10)	
Others	15 (37.5)	13 (32.5)	

[a]Mann-Whitney test.
[b]Chi-square test.
[c]Fisher exact test.

[PRISM] II and PELOD scores: $p = 0.527$ and 0.582, respectively), presence of underlying disease ($p = 0.955$), source of infection ($p = 0.788$), and etiology ($p = 0.735$) (**Table 1**). At presentation and during the protocol (use of the study drug), the clinical profile of patients was similar, with 88.3% and 70.2% in the dopamine and epinephrine groups having presented with cold shock, respectively ($p = 0.818$).

Treatment interventions were also similar for both groups (**Table 2**). Fluids used for resuscitation were mainly crystalloids (normal saline in all patients in the first hour); 5% albumin was responsible for 22.4 and 20.5 mL/kg of volume received in the first 6 hours in the dopamine and epinephrine groups, respectively. Packed RBCs were administered in two children in dopamine group (3.2%) and three children in epinephrine group prior to randomization (5.3%) ($p = 0.567$). All children received antibiotics in the first 6 hours, and the majority received antibiotics in the first hour of treatment in both groups. Children in the dopamine group had a significantly longer resuscitation period ($p = 0.024$), and a higher percentage in this group required renal replacement therapy compared with the epinephrine group ($p = 0.001$).

Table 3 provides a comparison of the use of vasoactive drugs according to study group. We observed that the duration of the use of dopamine was significantly the shorter of the two ($p = 0.003$); half of the children in the dopamine group required other vasoactive drugs (not significant) and had significantly fewer vasoactive-free days ($p = 0.028$). The VIS category was similar between groups in the first 24 and 48 hours. None of the children in the dopamine group had received dopamine after being considered nonresponsive to study drug. On the other hand, epinephrine was chosen as the sole or one of the vasoactive drugs in 36.5% of patients in the dopamine group and in 33.3% of patients in epinephrine group who were considered nonresponsive to the study drug.

TABLE 2. Treatment Administered

Interventions	Dopamine (*n* = 63)	Epinephrine (*n* = 57)	*p*
Time to fluids, hr[a]	0.4 (0.6)	0.4 (0.8)	0.344[b]
Fluids 1st hr, mL/kg[a]	49.7 (18.1)	50.7 (10.9)	0.114[b]
Fluids 1st 6 hr, mL/kg[a]	90.3 (33.9)	86.9 (23.4)	0.787[b]
Antibiotics 1st hr, yes, *n* (%)	53 (84)	47 (82.5)	0.167[c]
Time to study drug, hr[a]	3.2 (3.1)	2.4 (1.9)	0.441[b]
Duration of resuscitation, hr[a]	33.6 (57)	16.1 (23.6)	0.024[b]
MV, yes, *n* (%)	62 (98.4)	51 (89.5)	0.052[c]
MV-free days[a]	16.3 (10.6)	18.6 (10.3)	0.174[b]
Hydrocortisone for shock, yes, *n* (%)	21 (33.3)	17 (29.8)	0.680[c]
Renal replacement therapy, yes, *n* (%)	11 (17.4)	6 (10.5)	0.001[c]

MV = mechanical ventilation.
[a]Values are expressed as mean ± SD.
[b]Mann-Whitney test.
[c]Chi-square test.

TABLE 3. Profile of Use of Vasoactive Drugs According to Study Group

Interventions	Dopamine (*n* = 63)	Epinephrine (*n* = 57)	*p*
Duration of the use of study drug, hr, mean (± SD)	20.4 (21.4)	36.5 (46.3)	0.003[a]
Need for other drugs, yes, *n* (%)	33 (52.4)	22 (38.6)	0.130[b]
VIS category 1st day, *n* (%)			
< 10	30 (47.6)	1 (1.8)	0.078[a]
10–14	1 (1.6)	21 (36.8)	
15–19	1 (1.6)	9 (15.8)	
20–24	0 (0)	4 (7)	
≥ 25	31 (49.2)	22 (38.6)	
VIS category 2nd day, *n* (%)			
< 5	13 (21.7)	21 (37.5)	0.769[a]
5–9	21 (35)	1 (1.8)	
10–14	5 (8.3)	14 (25)	
15–19	2 (3.3)	5 (8.9)	
≥ 20	19 (31.7)	15 (26.8)	
Other vasoactive drugs used, yes, *n* (%)			
Dopamine	0 (0)	0 (0)	NA
Epinephrine	23 (36.5)	19 (33.3)	0.08[b]
Dobutamine	14 (22.2)	8 (14)	0.247[b]
Milrinone	3 (4.8)	3 (5.3)	> 0.999[c]
Vasopressin	2 (3.2)	2 (3.5)	> 0.999[c]
Norepinephrine	19 (30.2)	13 (22.8)	0.363[c]
Vasoactive drug–free days	18.9 (11.3)	23.7 (9)	0.028[a]

VIS = vasoactive inotropic score, NA = not applicable.
[a]Mann-Whitney test.
[b]Chi-square test.
[c]Fisher exact test.

TABLE 4. Vital Signs According to Group

Variable	Baseline	Before Randomization	6 Hr After Randomization	At the End of Resuscitation
Heart rate (beats/min)				
Dopamine	159 ± 25 (108–204)	154 ± 23 (96–206)	145 ± 27 (98–207)	142 ± 26 (81–201)
Epinephrine	149 ± 31 (76–205)	143 ± 28 (74–190)	142 ± 25 (81–188)	140 ± 23 (86–185)
p	0.047[a]	0.02[a]	0.50[a]	0.67[a]
Systolic blood pressure (mm Hg)				
Dopamine	85 ± 22 (40–135)	85 ± 18 (43–144)	92 ± 19 (55–161)	96 ± 18 (53–143)
Epinephrine	87 ± 19 (56–143)	80 ± 15 (52–120)	99 ± 17 (52–150)	104 ± 19 (53–169)
p	0.59[a]	0.13[a]	0.03b	0.01[b]
Shock index				
Dopamine	1.9 ± 0.6 (1–4.3)	1.9 ± 0.6 (0.9–3.6)	1.7 ± 0.6 (0.9–3.4)	1.5 ± 0.4 (0.7–2.6)
Epinephrine	1.7 ± 0.5 (0.7–3)	1.8 ± 0.6 (0.7–4.t5)	1.5 ± 0.4 (0.6–2.4)	1.3 ± 0.4 (0.6–2.9)
p	0.12[b]	0.87[b]	0.02[a]	0.07[a]
Mean arterial pressure and central venous pressure (cm H_2O)				
Dopamine	47 ± 10 (33–56)	54 ± 13 (35–75)	55 ± 14 (25–87)	57 ± 11 (26–76)
Epinephrine	49 ± 19 (35–77)	53 ± 10 (35–77)	66 ± 10 (46–88)	68 ± 13 (41–93)
p	0.99[b]	0.86[a]	0.003[a]	0.007[a]
$Scvo_2$ (%)				
Dopamine	72 ± 8 (59–81)	67 ± 8 (54–80)	74 ± 10 (38–91)	76 ± 8 (42–89)
Epinephrine	67 ± 3 (64–74)	66 ± 8 (50–80)	77 ± 5 (64–89)	79 ± 5 (69–89)
p	0.24[a]	0.70[a]	0.31[b]	0.18[b]

$Scvo_2$ = central venous oxygen saturation.
[a]Student *t* test.
[b]Mann-Whitney test.
Values are expressed as mean ± SD (limits).

Patients in the dopamine group had a significantly higher HR at baseline and before randomization. Patients in the epinephrine group had higher SBP and MAP-CVP at 6 hours after randomization and at the end of resuscitation. The SI was higher in the epinephrine group at 6 hours after randomization. The $Scvo_2$ was similar between groups at all times (**Table 4**).

Table 5 gives the laboratory data. We observed that mean lactate, troponin, and D-dimer values were high at baseline with a tendency to increase during resuscitation. Groups did not differ in any laboratory test results.

Variables independently associated with outcomes are outlined in **Table 6**. The chance of death increased 22% with each unit increase in the PELOD score ($p < 0.001$). Patients who received dopamine had a 6.51-fold increased chance of death in comparison with patients who received epinephrine ($p = 0.037$). Renal replacement therapy increased the chance of dying in all patient ($p < 0.001$). Variables associated with the development of HAI were use of dopamine ($p = 0.001$), renal replacement therapy ($p = 0.004$), and ICU length of stay. For each day that the patient stayed in the ICU, there was a 13% increased chance of acquiring a HAI ($p = 0.001$). HAI occurred in 18 of 63 patients in the dopamine group (28.5%) and four of 57 patients in the epinephrine group (2.3%). Ventilator-associated pneumonia was the main site of infection and was diagnosed in 11 of 18 patients in the dopamine group and two of four patients in the epinephrine group.

The use of hydrocortisone for refractory shock ($p < 0.001$) was an independent predictor of the need for other vasoactive drugs. Every hour increment in the duration of resuscitation was associated with a 10% increase in the risk of needing other vasoactive drugs ($p = 0.004$).

The need for other vasoactive drugs was associated with a 60% increase in the PELOD score. In addition, for every 1% in the PRISM risk value, there was a 0.6% increase in the mean PELOD score, and for every hour of resuscitation, there was a 0.2% increase in the PELOD value.

Children who received epinephrine had a survival odds ratio of 6.49 versus that of those who were treated with dopamine as the first-line vasoactive drug. Patients in the dopamine group also died significantly earlier during the course of the disease than those in the epinephrine group ($p = 0.047$) (**Fig. 3**).

TABLE 5. Laboratory Tests According to Group

Variable	Baseline	6 Hr After Randomization	At the End of Resuscitation	12 Hr After Randomization	24 Hr After Randomization	48 Hr After Randomization
Lactate (mmol/L)						
Dopamine	1.9 ± 1.6 (0.3–9.7)	2.6 ± 3.6 (0.4–21.4)	2.3 ± 4.1 (0.4–21.4)	2.2 ± 4.3 (0.3–28.4)	2.4 ± 5.1 (0.4–28.4)	2.0 ± 3.9 (0.4–22.1)
Epinephrine	2.4 ± 2.6 (0.4–15)	2.6 ± 2.7 (0.4–15.2)	2.3 ± 3.1 (0.6–19.3)	2.3 ± 3.0 (0.4–19.3)	1.6 ± 2.1 (0.3–14)	1.3 ± 0.8 (0.5–5.1)
p	0.55[a]	0.35[a]	0.57[a]	0.06[a]	0.22[a]	0.56[a]
Troponin (ng/mL)						
Dopamine	0.45 ± 2.1 (0.006–14.9)	0.53 ± 2.2 (0.006–15.2)	0.74 ± 2.9 (0.006–2.1)	0.45 ± 1.1 (0.006–6.3)	0.37 ± 0.7 (0.006–3.1)	0.39 ± 0.7 (0.006–3.6)
Epinephrine	0.44 ± 1.4 (0.006–8.2)	0.67 ± 1.8 (0.006–8.6)	0.69 ± 1.6 (0.006–8.6)	0.5 ± 0.8 (0.006–3.7)	2.1 ± 7.1 (0.006–42.1)	2.4 ± 7.2 (0.006–41.3)
p	0.41[a]	0.16[a]	0.57[a]	0.22[a]	0.23[a]	0.18[a]
D-Dimer (ng/mL)						
Dopamine	3,859 ± 3,070 (213–1,000)	4,452 ± 3,326 (227–10,000)	5,200 ± 3,242 (593–10,000)	5,467 ± 3,233 (300–10,000)	6,128 ± 3,224 (565–10,000)	5,274 ± 3,079 (539–10,000)
Epinephrine	4,378 ± 3,502 (340–10,000)	4,284 ± 3,433 (363–10,000)	5,081 ± 3,187 (407–10,000)	6,104 ± 3,446 (955–10,000)	6,018 ± 3,307 (1,210–10,000)	6,222 ± 2,808 (1,395–10,000)
p	0.5[a]	0.49[a]	0.89[a]	0.43[b]	0.84[b]	0.24[b]

[a]Mann-Whitney test.
[b]Student *t* test.
Values are expressed as mean ± SD (limits).

TABLE 6. Multiple Logistic Regression Analyses: Outcomes Odds Ratios or Relative Risk With 95% CI

	OR (95% CI); *p*			Relative Risk (95% CI); *p*
Variable	Death at 28 D	Healthcare-Associated Infection	Need for Other Vasoactive Drugs	Multiple Organ Dysfunction Score (PELOD)
Dopamine	6.51 (1.12–37.80); 0.037	67.74 (5.04–910.87); 0.001	–	–
PELOD	1.22 (1.09–1.36); < 0.001	–	–	–
Renal replacement therapy	38.89 (7.39–204.80); < 0.001	12.57 (2.28–69.40); 0.004	–	
Hydrocortisone for shock	–	–	42.85 (7.86–233.78); < 0.001	2.31 (1.23–1.55); < 0.001
Duration of resuscitation	–	–	1.10 (1.03–1.17); 0.004	1.002 (1.0–1.01); < 0.001
ICU length of stay	–	1.13 (1.06–1.21); 0.001	–	–
Pediatric Risk of Mortality (risk)	–	–	–	1.006 (1.001–1.003); < 0.001
Need for other vasoactive drugs	–	–	–	1.60 (1.25–1.30); 0.037

OR = odds ratio, PELOD = Pediatric Logistic Organ Dysfunction.

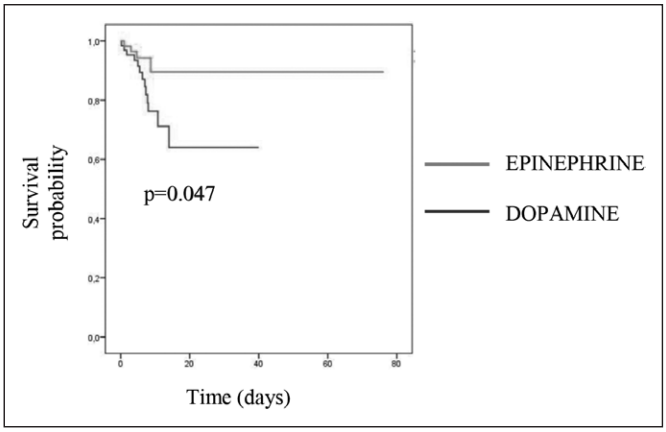

Figure 3. Kaplan-Meyer survival function according to group.

The frequency of adverse events was similar between groups (**Table 7**). An exception was hyperglycemia, which was significantly higher in patients in the epinephrine group ($p = 0.017$). Nevertheless, the prevalence of moderate and severe hyperglycemia was similar in both groups ($p = 0.07$ and $p = 0.26$, respectively). No ischemic events related to drug infusion were observed in this population.

DISCUSSION

As far as we are aware, this is the first prospective, controlled, randomized trial to compare the effect of two first-line vasoactive drugs in children with septic shock. In this population, we observed that the use of epinephrine compared with dopamine was independently associated with better survival and lower HAI rates.

If they are reproduced, these results could be important for treating children in resource-limited settings where mortality rates are higher. We demonstrated an improvement in mortality with early initiation of peripheral IV or intraosseous infusion of epinephrine. Whenever a guideline is published, it must be adapted to ensure adherence (14), and a delay in administration of a vasoactive drug until central venous (15) or peripheral access (16) is obtained has been noted as a barrier to adherence. This gap is important; for example, a delay in vasoactive drug start has been associated with increased mortality in pediatric meningococcal sepsis in the United Kingdom (17). In our hospital and perhaps in the majority of the emergency departments in Brazil, a central venous catheter is rarely placed before PICU admission. The main reason is that physicians working in pediatric emergency departments in Brazil are usually generalists and not always familiarized with central venous catheterization. Ultrasound-guided cannulation of central veins in children is an interesting alternative because it is likely to be associated with improvement in success rates in the emergency department and PICU (18); however, ultrasound technology is not available worldwide.

Studies comparing first-line inotropes have not been conducted in children with septic shock. In adults with septic shock, studies analyzing the impact of first-line vasopressors (dopamine or norepinephrine) on morbidity or mortality have conflicting outcomes (19–21), as do investigations involving newborns, including studies of dopamine administration in infants (22–24).

Both children and adults with septic shock present with myocardial dysfunction (8–10, 25), but children with community-acquired septic shock appear to present predominantly with a low cardiac output state in the first hours of treatment (10), which can persist longer in some patients (25). Infants and children differ developmentally from adults in ways that explain the differences in the hemodynamic response to sepsis, as well as the response to therapeutic agents (26). Some of these differences include preexisting elevated HR, a relatively decreased left ventricular mass in comparison to the adult myocardium (27), an increased ratio of type I collagen (decreased elasticity) to type III collagen (increased elasticity) (28), increased connective tissue content in the infant heart, and diminished actin and myosin content (29). Therefore, in this population, it is reasonable to consider an inotrope as a first-line vasoactive drug until a central venous access is obtained.

Dopamine and epinephrine are complex vasoactive drugs that exert their effects through increases in cyclic-adenosine-monophosphate, with dose-dependent sympathomimetic actions along with metabolic, endocrine, and immunomodulatory effects (30–32). Epinephrine infusion has been associated with improvements in cardiac performance in experimental models (33) and in neonates (34) and adults with septic shock (35). Transient increases in blood lactate levels and decreases in arterial pH without compromised tissue oxygenation have been described with

TABLE 7. Adverse Event Comparison

Adverse Event Category, *n* (%)	Dopamine (*n* = 63)	Epinephrine (*n* = 57)	*p*[a]
Cardiac events	1 (1.6)	0	0.339
Ischemic events[b]	0	0	NA
Feeding intolerance	45 (71.4)	42 (73.7)	0.782
Hyperglycemia	37 (58.7)	45 (78.9)	0.017
Persistently high lactate levels	5 (7.9)	10 (17.5)	0.112

NA = not applicable.

[a]Chi-square test.

[b]There were 61 patients in the dopamine and 55 patients in the epinephrine group included for this adverse event analysis.

epinephrine infusion in critically ill adults (36–38) and in animal models (39). Exaggerated aerobic glycolysis mediated by Na+K+ ATPase stimulation within the muscles is probably responsible for these metabolic effects (37). The metabolic effects of epinephrine are described across all ranges of doses. We observed a transient increase in lactate levels in children treated with epinephrine, although not sustained longer than 24 hours, and mild hyperglycemia. Epinephrine may have a deleterious effect on oxygen use (increases in oxygen consumption and decreases in blood flow in the splanchnic circulation), possibly by causing misdistribution of blood flow and worsening of tissue hypoxia (36–40). We did not measure splanchnic blood flow or Co_2 production through gastric tonometry but instead used feeding intolerance as a surrogate marker of regional hypoperfusion. We observed a high rate of feeding intolerance, probably because of the broad definition applied, but children treated with epinephrine had no more feeding intolerance events than those treated with dopamine. We note that the effects of epinephrine on splanchnic blood flow have been described at epinephrine doses that were much higher (36, 40) than those used in our population.

We cannot confirm that the study doses of each vasoactive drug were comparable. Hypoxia (41), potential differences in drug metabolism, the number, affinity, and maturation of adrenergic receptors, and cardiovascular reflexes during sepsis can all modify the drug action profile. Sepsis down-regulates β-adrenoceptors by phosphorylation and internalization, reducing the density of receptors on the cell (41). Some of the patients would have benefited from an α agonist effect early if vasodilation were the main issue related to shock. Dopamine usually exerts a vasopressor effect because of α adrenergic stimulation at higher doses (above 15 μg/kg/min). The clinical profile, defined as cold or warm shock at presentation, has limitations in defining the cardiac output and peripheral vascular resistance. We observed that the majority of patients presented with cold shock, which could have influenced the negative outcome observed with the use of dopamine.

Before randomization, patients in the dopamine group had a significantly higher HR for those with warm shock. Tachycardia could have been due to several factors (anemia and pain) but also to underresuscitation, although patients received similar amounts of fluids during the first and sixth hours.

According to other vital signs, we could infer that resuscitation with epinephrine was more effective: The duration of the use of dopamine was probably shorter because patients were considered nonresponsive; the majority of children who received dopamine required other vasoactive drugs; and BP, SI, and MAP-CVP were higher in the epinephrine group at 6 hours after randomization.

We can infer that physicians were not aware of the study drugs because they continued to choose epinephrine as the only or one of the vasoactive drugs in 36.5% of patients in the dopamine group and in 33.3% of patients in the epinephrine group after a patient was considered nonresponsive to the study drug. Also, because once a patient was considered nonresponsive, dopamine was not the drug of choice in this population treated by this specific group of physicians.

The focus of the study was on early initiation of a potent inotrope; thus, we cannot extrapolate the results for patients who receive a vasoactive drug later during the course of the disease. The decision to start the drug along with the third fluid bolus, that is, before 60 mL/kg, was made because children frequently arrive at the hospital long after the beginning of the process as a result of delayed parental recognition (42), treatment is delayed because of a lack of recognition of sepsis and its severity (43), and management in a busy emergency department can be difficult (7, 44). Children in the dopamine group received the drug around an hour later than those in epinephrine group. Although this lag in time did not reach statistical significance, it could have influenced the outcome for an individual patient.

Dopamine use was associated with higher HAI rates. Although there is a plausible physiopathological explanation (29, 45), we could not investigate the immunological status of our population to confirm this association.

Limitations of our study should be considered when analyzing the results. Its single-center nature limits its external validity, and the population consisted mainly of previously healthy infants. Results from single-center studies are infrequently reproduced, and the choice of patient, treatment endpoints, protocol compliance, and potential antagonism, or synergism with one or more treatment procedures unique to a particular ICU could explain these differences. The initial assessment of the patient and decision to start, stop, or increase the study drug were based solely on clinical variables, which are highly sensitive but lack specificity. Other possible limitations include a detrimental effect of other catecholamines used in patients who initially received dopamine and did not respond (i.e., the VIS score at 24 and 48 hr was higher in the dopamine group although not statistically significant) or potential antagonism or synergism with one or more treatment procedures that we did not include in the analysis (e.g., fluid balance).

Further multicenter trials or single-center studies are necessary to verify the reproducibility of our results. The best research scenario would be to control the initial as well as the subsequent catecholamines with priority given to those that do not increase cAMP. The results of our investigation could be useful for countries with similar mortality rates, but if local outcomes are already superior to those observed in our single-center trial, the observed results may not apply.

The use of dopamine in this population was associated with increased death and HAI odds ratios. Early administration of peripheral or intraosseous epinephrine was safe and associated with increased survival rates compared with dopamine. Limitations should be observed while interpreting these results.

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