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ORIGINAL ARTICLE

Epinephrine versus dopamine in neonatal septic shock: a double-blind randomized controlled trial

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Abstract

We compared epinephrine and dopamine as a first-line vasoactive drug in 40 neonates (enrolled in two gestational age strata ≤ $30^{6/7}$ and ≥ $31^{0/7}$ weeks) with fluid-refractory septic shock. Epinephrine or dopamine was initiated at 0.2 or 10 μg/kg/min, respectively. If shock persisted after 15 min, epinephrine or dopamine was increased to 0.3 or 15 μg/kg/min, respectively (16–30 min), and thereafter to 0.4 or 20 μg/kg/min (31–45 min). Proportion of neonates achieving 'reversal of shock' (defined as systolic and diastolic BP > fifth centile *and* capillary filling time < 3 s *and* left ventricular output ≥ 150 mL/kg/min) by 45 min [5 (25%) vs 6 (30%), RR 0.83 (95% CI 0.30, 2.29)]; haemodynamic stability (shock reversal for ≥ 120 min without escalation of vasoactive drugs) anytime during therapy [10 (50%) vs 6 (30%), RR 1.67 (95% CI 0.75, 3.71)]; and all-cause mortality by 28 days [14 (70%) vs 16 (80%), RR 0.87 (95% CI 0.61, 1.26)] were comparable in the epinephrine and dopamine groups, respectively. On stratified analysis, we observed an interaction of gestational age strata with the group of allocation favouring epinephrine in neonates ≤ $30^{6/7}$ weeks.

Conclusion: Epinephrine (0.2–0.4 μg/kg/min) and dopamine (10–20 μg/kg/min) had comparable efficacy and safety in neonatal septic shock.

Clinical Trial registry name and registration number: The study was registered with Clinical Trial Registry of India CTRI/2015/10/006285.

What is Known:
- *The choice of vasoactive drugs in neonatal septic shock is empirical and dopamine is the conventional first-line vasoactive drug.*
- *There are no randomized controlled trials comparing dopamine and epinephrine in neonatal septic shock.*

What is New:
- *In this study, epinephrine and dopamine had comparable efficacy and safety as a first-line vasoactive drug in management of neonatal septic shock.*
- *On stratified analysis in a limited sample, epinephrine was associated with better outcomes in neonates ≤ $30^{6/7}$ weeks.*

Keywords Dopamine · Epinephrine · Neonate · Septic shock · Vasoactive agents

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Abbreviations

BP	Blood pressure
BPD	Bronchopulmonary dysplasia
CFT	Capillary filling time
CO	Cardiac output
CRIB II	Clinical risk index for babies score
DBP	Diastolic blood pressure
HR	Heart rate
LVO	Left ventricular output
IVH	Intra-ventricular haemorrhage
NEC	Necrotising enterocolitis
ROP	Retinopathy of prematurity
SBP	Systolic blood pressure
SVR	Systemic vascular resistance

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Introduction

Inotropes and vasopressors are mainstay of therapy in fluid-refractory septic shock. However, the choice of vasoactive agents in neonatal septic shock is empirical and is extrapolated from adult and paediatric data [3, 24]. Vasopressors are the first-line vasoactive drugs used in the management of neonatal septic shock, as decreased systemic vascular resistance plays a major pathophysiological role [4, 21]. Both dopamine and epinephrine provide vasopressor as well as inotropic actions [19]. Conventionally, dopamine is the first-line vasoactive drug in neonatal septic shock [3, 24]. It acts mainly through the release of norepinephrine from presynaptic vesicles [16, 22]. In sick neonates, norepinephrine stores may get depleted within few hours of onset of sickness [22]. Furthermore, the conversion of dopamine to norepinephrine is decreased in hypotensive, extremely premature neonates [7]. Hence, dopamine may be ineffective in some neonates. Additionally, dopamine may lead to adverse endocrinal effects [22], and abnormal cerebral autoregulation in preterm infants [5]. In contrast, epinephrine acts directly on adrenergic receptors [19]. In animal models, it was found to decrease myocardial oxygen extraction ratio and increased the coronary sinus oxygen content [1].

There are limited studies on therapeutic use of epinephrine in neonatal shock [18]. Only two studies have compared dopamine and epinephrine in neonates. Valverde and colleagues found that in preterm neonates developing hypotension in first 24 h of life, epinephrine increased mean arterial pressure as effectively as dopamine [23]. In another unpublished trial by Phillipos and colleagues, epinephrine resulted in improved cardiac contractility compared to dopamine in sick neonates [20]. However, epinephrine and dopamine have not been compared in neonatal septic shock. We hypothesized that epinephrine, by virtue of direct actions on adrenergic receptors and other physiological advantages listed above, would result in better outcomes as compared to dopamine among neonates with fluid-refractory septic shock. We planned this study to investigate whether among neonates with fluid-refractory septic shock, an intravenous infusion of epinephrine (0.2 to 0.4 μg/kg/min) will result in 30% greater incidence of shock reversal within first 45 min of treatment as compared to an intravenous infusion of dopamine (10 to 20 μg/kg/min).

Materials and methods

We conducted this randomized, double-blind controlled trial from March 2014 to June 2015 in a Level III neonatal intensive care unit of a tertiary care Institute. The Institute Ethics Committee approved the study protocol.

Participants We enrolled neonates with fluid-refractory septic shock. We defined shock as presence of *either or both* of criteria A or B:

A) Systolic (SBP) *or* Diastolic blood pressure (DBP) < fifth centile [26]
B) Presence of two or more of following: urine output < 0.5 mL/kg/h over preceding 12 h, capillary filling time (CFT) ≥ 4 s, core to peripheral temperature difference > 3 °C (in full-term neonates), standard base excess worse than − 5.0 meq/L and serum lactate > 5 mMol/L [9, 24]. CFT was measured on sternum or forehead by applying pressure with soft pad of index finger for 5 s to blanch the area and then releasing finger to note the return of circulation with the help of wall clock.

We defined fluid-refractory shock as persistence of shock despite two normal saline boluses of 10 mL/kg, each given over 15–20 min [9, 24]. Sepsis was defined as either culture proven sepsis or septic screen positive sepsis. We defined culture proven sepsis if either blood or cerebrospinal fluid culture of a symptomatic neonate grew a microorganism within 48 h of incubation. We defined positive sepsis screen if any two out of the five components of conventional septic screen were positive: C-reactive protein (CRP) > 10 mg/L or age appropriate cut-offs of procalcitonin, microerythrocyte sedimentation rate > 10 mm after first hour, total leukocyte and absolute neutrophil counts outside the reference range, or immature to total neutrophil ratio more than 0.2. [2, 8] We excluded neonates if they had potentially lethal congenital malformations, obvious blood loss, clinical features of dehydration, clinically suspected or echocardiographically proven congenital heart disease, hypotension due to transitional circulation in very low birth weight neonates in first 12 h of life, moderate to severe hypoxic ischaemic encephalopathy [15], vasopressor drugs started prior to enrolment, or if the investigator (S.S.S.) was unavailable to perform echocardiography. We enrolled eligible subjects after obtaining written and informed consent from one of the parents.

Assessment at baseline

At baseline, we assessed vital sign parameters, arterial blood gas, score for neonatal acute physiology (SNAP-II score) score and left ventricular output (LVO). We monitored BP by intra-arterial catheters or by a non-invasive oscillometric method (if an indwelling intra-arterial catheter was not available) by IntelliVue MP80, Philips, The Netherlands. We used cuff sizes of 1 to 3 (cuff 1 for arm circumference 3.1–5.7 cm, cuff 2 for arm circumference 4.3–8.0 cm and cuff 3 for 5.8–10.9 cm) so as to cover at least 80% of arm circumference. Single investigator (S.S.S.) measured LVO using MicroMaxx® system

(SonoSite, Inc. Bothwell, WA, USA) with 8–4 MHz high-frequency phased array transducer probe using published methods [6, 21]. We derived systemic vascular resistance (SVR) index using formula: mean BP/CO [17].

Randomization The random sequence was computer generated. One of the investigators (S.D.) generated a stratified, blocked random sequence from a website (www.randomizer.org). S.D. did not participate in the patient recruitment. We recruited participants in two gestational age strata: $\leq 30^{6/7}$ and $\geq 31^{0/7}$ weeks. Each stratum had permuted, randomly varying block sizes of 4 or 6 (1:1 allocation ratio). We used serially numbered opaque sealed envelopes, bearing slips of paper with the allocated treatment, to ensure concealment of allocation.

Allocation of intervention We randomly allocated subjects to two groups: epinephrine group and dopamine group.

A. Epinephrine group: The bedside nurse diluted 0.12 mg/kg epinephrine in 10 mL normal saline and initiated infusion @ 1 mL/h (0.2 μg/kg/min).
B. Dopamine group: The nurse diluted 6 mg/kg of dopamine in 10 mL normal saline and initiated infusion at 1 mL/h (10 μg/kg/min).

Blinding All study investigators and health care personnel (except the bed side nurse and S.D.) were blinded. After a patient got enrolled, the bedside nurse opened the sealed envelope. According to the allocated intervention, she initiated the study drug at an infusion rate of 1 mL/h (either 10 μg/kg/min dopamine or 0.2 μg/kg/min epinephrine). The intervention drugs were given preferably through the central line. Peripheral line was used if the central line was either not available or could not be placed due to technical challenges. Epinephrine and dopamine solutions, once loaded in syringe, looked identical.

Monitoring and follow-up

After initiation of infusion of the study drug, we assessed the subjects at 15, 30 and 45 min for BP, CFT and LVO. If shock did not reverse at the 15-min assessment point, we increased the infusion rate to 1.5 mL/h (epinephrine 0.3 μg/kg/min or dopamine 15 μg/kg/min). If shock persisted at the 30-min assessment point, we increased the infusion rate to 2 mL/h (epinephrine 0.4 μg/kg/min or dopamine 20 μg/kg/min). If hypotension persisted beyond 45 min, then neonates were crossed over to the other drug (dopamine or epinephrine) in a blinded manner as described above. If hypotension persisted even after 90 min of vasoactive drug therapy, then further management was according to published guidelines [3, 24]. The decision to taper vasoactive drugs was taken by the treating neonatologist, if perfusion parameters remained stable on a static vasoactive drug infusion rate for ≥ 24 h. The drugs were tapered every 6 h, in steps of 5 μg/kg/min of dopamine and 0.1 μg/kg/min of epinephrine.

Outcome variables Our primary outcome variable was 'reversal of shock' during first 45 min of vasoactive drug infusion. We defined reversal of shock if a neonate satisfied all three criteria: SBP as well as DBP > fifth centile, CFT < 3 s and LVO ≥ 150 mL/kg/min. Our secondary outcome variables were (1) 'haemodynamic stability' defined as reversal of shock (as defined above) and no further escalation of vasoactive drugs for a period of ≥ 120 min thereafter; (2) requirement of additional vasoactive drugs; (3) physiological variables (HR, SBP, DBP and MAP) and acid-base status (blood pH, bicarbonate, base excess and serum lactate) at 45 min of study drug; (4) lactate clearance, as a marker of microcirculation, from baseline until 45 min, and 24 h. Lactate clearance (%) was calculated as (final serum lactate − initial serum lactate)/initial serum lactate × 100]; (5) all-cause mortality by 28 days of life; (6) incidence of medium term complications, i.e., Intraventricular haemorrhage (IVH) by 28 days of life, bronchopulmonary dysplasia (BPD) [12], necrotising enterocolitis (NEC) stage II/III until hospital discharge and retinopathy of prematurity (ROP) any stage until hospital discharge.

Sample size According to our unit data in 2013, approximately 90% neonates, who had received dopamine for treatment of septic shock, failed to achieve reversal of shock by 45 min and required a second vasoactive drug. To detect an absolute difference of 30% in the primary outcome between the dopamine group and epinephrine group, with an α-error of 0.05 and power of 80%, we had planned to recruit 64 subjects. However, due to quality improvement initiatives during the study period, less number of neonates developed sepsis. Hence, we were able to recruit 40 neonates in the given time frame.

Statistical tests We described baseline variables by standard descriptive statistics. We compared the proportion of neonates with the primary outcome, and all binary secondary outcomes by the chi-square test with Yates correction or Fisher's exact test, wherever applicable. We compared the time to event for haemodynamic stability and mortality by Kaplan–Meier survival curves and the log-rank test. We compared the change in physiological variables, and acid-base parameters over the first 45 min by RM-ANOVA or mixed linear model, wherever applicable. We studied the interaction of gestational age strata and intervention groups with the primary outcome using Cochran's and Mantel-Hansel's statistics and Brelow-Day's test of interaction. We performed analysis by intention to treat principle. We performed the data analysis with SPSS version 20.0 (IBM, New York).

Results

One hundred and seventy-six neonates developed clinical shock during the study period. We were able to enrol 40 neonates [18 (45%) in $\leq 30^{6/7}$ weeks stratum]. There were 20 subjects in each group (Fig. 1). The demographic, baseline clinical and laboratory parameters were comparable in two groups (Table 1). Out of 40 neonates, 35 had late onset neonatal sepsis [18 (90%) in epinephrine group and 17 (86%) in dopamine group]. Sixteen (40%) neonates had culture proven sepsis [7 (35%) in epinephrine group and 9 (45%) in dopamine group]. The neonates had predominantly gram-negative sepsis (*Klebsiella pneumoniae* ($n = 4$), Acinetobacter *boumanii* ($n = 4$), *E. coli* ($n = 4$), one each of Serratia, Enterobacter *faecium*, non-lactose fermenter gram-negative bacilli and methicillin-resistant *Staphylococcus aureus*). Fifteen neonates were blood culture positive and four neonates were CSF culture positive. Three neonates were positive for both blood as well as CSF cultures. Remaining 24 (60%) neonates had positive septic screen.

The proportion of neonates, who achieved reversal of shock in first 45 min [25 vs 30%; RR 0.83 (95% CI 0.30, 2.29)], haemodynamic stability during vasoactive drug infusion [50 vs 30%; RR 1.67 (95% CI 0.75, 3.71)], and mortality within first 28 days of life [70 vs 80%; RR 0.87 (95% CI 0.61, 1.26)] were comparable in the epinephrine and dopamine groups, respectively (Table 2). Using Kaplan–Meier curves, the probability of achieving haemodynamic stability during vasoactive drugs infusion and the probability of remaining alive over hospital stay were also comparable between the two groups (Log rank test, $p = 0.1$ and $p = 0.5$, respectively). Epinephrine and dopamine groups had comparable lactate clearance at 45 min and 24 h (Table 2). Neonates in epinephrine and dopamine groups had similar duration of vasoactive drugs and were comparable for requirement of additional vasoactive drugs, incidence of IVH, BPD, definite NEC and ROP (Table 2). The vital signs (HR, SBP, DBP and MAP), and acid–base parameters (pH, serum Bicarbonate, base excess and serum lactate) of study neonates changed similarly from baseline until 45 min of therapy in both the groups (Table 3). LVO also changed similarly between the two groups from baseline to 45 min (Table 3).

Stratified analysis

In both gestational age strata ($\leq 30^{6/7}$ and $\geq 31^{0/7}$ weeks), the epinephrine and dopamine groups were comparable for baseline characteristics (Table 4). We observed a significant interaction of gestational age strata with the group of

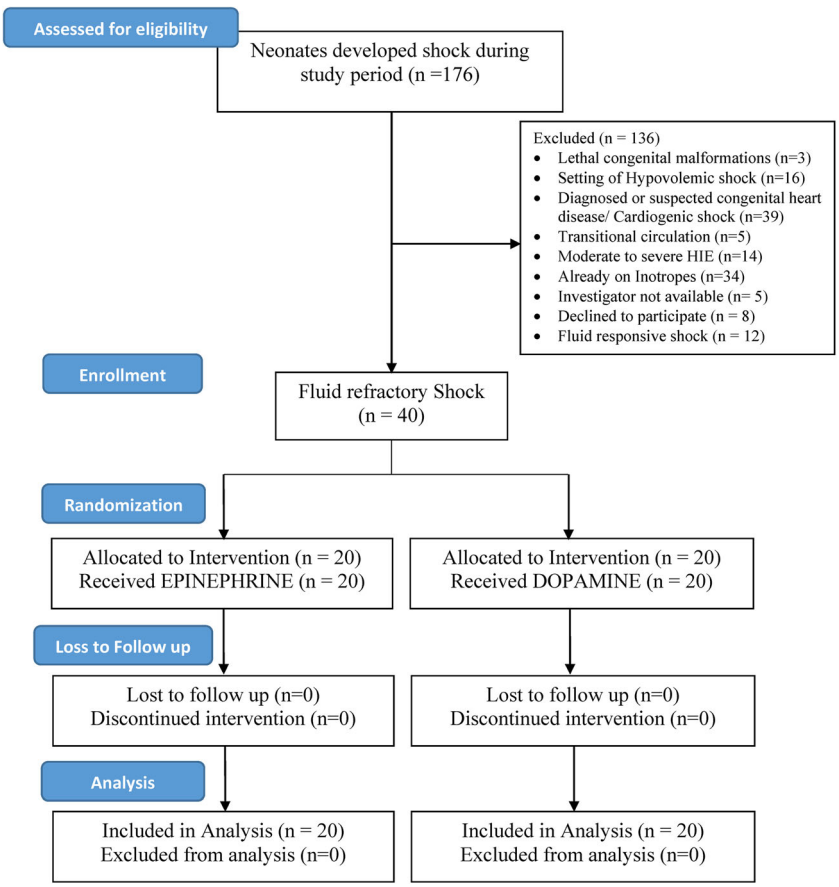

Fig. 1 Flow of study participants

Table 1 Demographic and baseline characteristics

Characteristics		Epinephrine gp ($n = 20$)	Dopamine gp ($n = 20$)
Gestation (week)		30.3 ± 3.5	30.7 ± 2.9
Birth weight (g)		1100 (926, 1400)	1181 (892, 1540)
Male gender (%)		14 (70)	13 (65)
Small for date (%)		7 (35)	9 (45)
Postnatal age (days)		7.0 (4.3, 9.0)	5.0 (4.0, 9.5)
APGAR scores at 5 min		9 (8, 9)	9 (7, 9)
Antenatal steroids (%)		14 (70)	11 (55)
Clinical chorioamnionitis (%)		0	2
Intrapartum antibiotics (%)		10 (50)	12 (60)
Caesarean section (%)		7 (35)	7 (35)
Heart rate of neonates (beats/min)		159 ± 23	153 ± 26
Blood pressure (mmHg)	Systolic	43 ± 20	43 ± 13
	Diastolic	26 ± 13	26 ± 10
	Mean	32 ± 15	32 ± 12
Capillary filling time ≥ 3 s (%)		10 (50)	8 (40)
Urine output < 0.5 mL/kg/h (%)		5 (25)	9 (45)
Left ventricular output (mL/kg/min)		299 ± 143	246 ± 116
Systemic vascular resistance index (mmHg/ml/kg/min)		0.14 ± 0.08	0.14 ± 0.08
SNAP-II score		41 (33, 55)	40 (36, 55)
Patent ductus arteriosus (%)		11 (55)	9 (45)
Required mandatory ventilation (%)		17 (85)	20 (100)
pH		7.05 ± 0.19	7.05 ± 0.15
Serum bicarbonate (mcg/ml)		13.5 ± 5.6	12.2 ± 5.5
Base excess		13.8 ± 5.4	15.0 ± 8.0
Serum lactate (mmol/L)		8.6 (5.0, 11.0)	8.1 (4.8, 11.0)

Data presented as mean ± SD, median (IQR) or proportions

SNAP Score of Neonatal Acute Physiology

allocation for reversal of shock (Breslow–Day test $p = 0.05$), as well as for haemodynamic stability (Breslow–Day test $p = 0.02$). We also observed a trend of interaction of gestational age strata with the group of allocation for all-cause mortality (Breslow–Day test, $p = 0.07$). In simple words, there was a difference in response of epinephrine and dopamine in the two gestational age strata (epinephrine performed better in $\leq 30^{6/7}$ weeks neonates).

Table 2 Outcomes

Characteristics (%)	Epinephrine gp ($n = 20$)	Dopamine gp ($n = 20$)	p value
Reversal of shock by 45 min (%)	5 (25)	6 (30)	0.6
Haemodynamic stability during vasoactive drug therapy (%)	10 (50)	6 (30)	0.3
Duration of vasoactive drugs (min)[a]	998 (709, 1675)	972 (724, 1441)	1.0
Neonates requiring additional vasoactive drugs (%)	18 (90%)	17 (85%)	0.3
Lactate clearance at 45 min (%)	20 (− 6, 48)	15 (− 1, 45)	0.4
Lactate clearance at 24 h (%)	− 3 (− 20, 80)	0 (− 22, 23)	0.3
Intra ventricular haemorrhage (any grade, %)	8 (32)	4 (16)	0.2
Necrotizing Enterocolitis (stage II/ III, %)	4 (20)	4 (20)	1.0
Retinopathy of prematurity (all stages, %)	5 (25)	2 (10)	0.4
Bronchopulmonary dysplasia (%)	1 (5)	1 (5)	1.0
All-cause mortality by 28 days (%)	14 (70)	16 (80)	0.7

[a] Median (IQR)

Table 3 Physiological variables and acid-base status in first 45 min of therapy

Variable	Epinephrine group ($n = 20$)				Dopamine group ($n = 20$)				p value
	Baseline	15 min	30 min	45 min	Baseline	15 min	30 min	45 min	
Heart rate (bpm)	159 ± 23	163 ± 22	164 ± 21	162 ± 25	153 ± 26	155 ± 27	155 ± 29	156 ± 27	0.4
Systolic BP (mmHg)	43 ± 13	48 ± 13	50 ± 21	47 ± 19	43 ± 20	48 ± 17	49±19	50±20	0.8
Diastolic BP (mmHg)	23 (20, 30)	30 (23, 38)	28 (21, 42)	27 (19, 38)	22 (17, 37)	28 (19, 40)	29 (19, 42)	31 (19, 40)	0.9
Mean BP (mmHg)	28 (23, 44)	33 (28, 46)	34 (27, 50)	36 (27, 44)	28 (23, 44)	34 (23, 47)	36 (24, 49)	39 (26, 46)	0.9
Left ventricular output (mL/kg/min)	299 ± 143	-	–	283 ± 126	246 ± 116	–	–	275 ± 71	0.8
pH	7.05 ± 0.17	–	–	7.02 ± 0.20	7.05 ± 0.15	–	–	7.03 ± 0.19	1.0
Serum Bicarbonate (mEq/L)	13.5 ± 5.6	–	–	11.2 ± 4.4	12.2 ± 5.5	–	–	11.3 ± 4.4	0.7
Base Deficit	13.8 ± 5.4	–	–	16.5 ± 6.3	15.0 ± 8.2	–	–	16.5 ± 7.7	0.3

Data presented as mean ± SD or median (IQR)

Discussion

In this study comparing epinephrine and dopamine in neonatal septic shock, a similar proportion of neonates achieved reversal of shock in the first 45 min of therapy. Other outcomes including medium-term complications and all-cause mortality were comparable between the two groups. The main strength of our study lies in its design. We evaluated an exhaustive repertoire of haemodynamic variables in our study including clinical, echocardiography and laboratory variables. We chose a combined primary outcome consisting of three variables including a marker of peripheral circulation (CFT) and cardiac output (LVO) in addition to BP. The combined outcome is likely to be a better measure of haemodynamic status as compared to BP alone.

Our population consisted mainly of inborn preterm neonates. Our neonates had decreased systemic vascular resistance suggestive of vasoregulatory failure, which is hallmark of septic shock [4, 21, 24]. Majority of our neonates had hypotensive shock. The mean systemic vascular resistance index in our neonates was 0.14 mmHg/ml/kg/min, which was lesser than the corresponding value in normal preterm neonates (0.25–0.30 mmHg/ml/kg/min) previously published by Ma et al.

Table 4 Stratified analysis: baseline and outcome variables

Variable	Stratum 1 ($\leq 30^{6/7}$ weeks)		p value	Stratum 2 ($\geq 31^{0/7}$ weeks)		p value
	Epinephrine gp ($n = 9$)	Dopamine gp ($n = 9$)		Epinephrine gp ($n = 11$)	Dopamine gp ($n = 11$)	
Gestation (week)	27.36 ± 1.1	28.19 ± 1.3	0.17	32.73 ± 2.7	32.68 ± 2.2	0.96
Birth wt (grams)	990 ± 186	932 ± 125	0.55	1434 ± 569	1664 ± 646	0.19
SNAP-II score	54 (37, 60)	39 (37, 58)	0.49	37 (28, 43)	43 (29, 51.75)	0.57
Heart rate (beats/min)	158 (138, 177)	150 (134, 172)	0.60	168 (140, 178)	163 (150, 176)	0.70
Systolic BP (mmHg)	36 (30, 42)	30 (27, 52)	0.82	46 (38, 56)	50 (32,68)	1.00
Diastolic BP (mmHg)	20 (19, 27)	19 (17, 31)	0.61	26 (21, 34)	29 (19, 37)	0.43
pH	7.03 (6.92, 7.15)	6.98 (6.89, 7.19)	0.82	7.11 (7.02, 7.21)	7.11 (6.90, 7.21)	0.80
HCO_3 (mEq/L)	12 (9.9, 14.9)	8.7 (7.2, 16.5)	0.30	14.6 (11, 15.1)	13.5 (7.30, 20.1)	1.00
Base excess	16 (13, 17)	18 (10, 22)	0.60	12 (8, 17)	12 (5, 20)	0.75
Lactate (mmol/L)	8.0 (6.3, 10.5)	6.5 (5.3, 12.8)	0.93	9 (4, 12)	7 (5, 11)	0.60
Shock reversal in 45 min (%)	2 (22)	0	0.47	3 (27)	6 (55)	0.39
Haemodynamic stability (%)	5 (56)	0	0.03*	5 (46)	6 (55)	0.67
Mortality in 28 days (%)	6 (64)	9 (100)	0.21	8 (72)	7 (64)	0.65
IVH any grade	5 (55)	4 (37)	1.00	3 (27)	0	0.21
NEC stage II/ III) (%)	2 (22)	1 (11)	1.00	2 (18)	3 (27)	1.00
Retinopathy of prematurity (%)	4 (44)	0	0.08	1 (9.1)	2 (18)	1.00
Bronchopulmonary dysplasia (%)	1	0	1.00	0	1	1.00

Data presented as mean ± SD, median (IQR) or proportions

[17]. In previous neonatal studies, BP alone was taken as primary outcome variable [20, 23]. However, BP poorly represents systemic blood flow and has several other limitations, when alone used as a marker of haemodynamic status [3, 9, 24]. To overcome these limitations, we chose a combined outcome of three variables i.e. CFT as a marker of peripheral circulation, LVO as a marker of cardiac output in addition to BP. We included only objective variables in our combined primary outcome to minimize measurement bias. Nevertheless, our primary outcome was at best an intermediate outcome, and we recognize that all-cause mortality would have been a preferred outcome measure. However, ours was a proof of concept study with a limited sample size and a limited study time frame. An RCT with all-cause mortality as an outcome would have required a much larger sample size. We did not exclude PDA in this study as infection is known to promote PDA patency by increased cyclo-oxygenase expression and prostaglandin levels [21].

In our study, efficacy and safety were comparable between epinephrine and dopamine. We understand that our study was underpowered for individual outcomes. However, we compared multiple outcomes including hard clinical outcomes (mortality, medium-term complications], intermediate clinical outcomes (incidence of shock reversal by 45 min, haemodynamic stability throughout the vasoactive drug infusion, change in vital signs in 45 min, requirements of additional vasoactive drugs), acid-base parameters, indirect markers of microcirculation (lactate clearance) and echocardiographic parameters. None of these outcomes were different in the two groups. Our study findings were in agreement with Valverde et al., who had also found these two drugs to be equally efficacious [23]. However, unlike in our study, Valverde et al. found epinephrine to be associated with hyperglycaemia and increased serum lactate levels. The difference in these outcomes could be explained by underlying pathophysiology. The neonates, in study by Valverde et al., had gestational age < 32 weeks, developed shock in first 24 h of life, and possibly had myocardial dysfunction as main underlying cause. The vasopressor actions of epinephrine could have led to these adverse effects. In contrast, our study neonates with septic shock have mainly decreased systemic vascular resistance, which require predominantly vasopressors actions. Both dopamine and epinephrine were given in vasopressor doses to our neonates and hence possibly displayed comparable safety profile.

On stratified analysis, we observed beneficial effects of epinephrine in neonates $\leq 30^{6/7}$ weeks of gestation as compared to dopamine. These findings could be related to poor conversion of dopamine to noradrenaline in ELBW neonates [7]. This difference can also be explained by differential expression of α and β receptors in preterm neonates [10, 14]. Limited data is available regarding the expression of adrenergic receptors in various degree of prematurity. Considering a small sample size, it could be just a chance finding and need more observations to evaluate the role of epinephrine in very premature and extremely premature neonates.

Our main limitation was sample size. Our primary outcome variable was an intermediate outcome. Our study results cannot be generalized to hypotension outside the setting of sepsis as well as to full-term neonates. The mortality rates of our study neonates were higher as compared to developed countries [13]. It is attributed to predominantly gram-negative sepsis in developing countries, where the case fatality rates are much higher than the developed countries [25]. It is due to the fact that in developing countries, the sepsis is predominantly gram-negative sepsis, where endotoxemia results in higher case fatality rates than gram-positive sepsis, which is predominantly observed in developed countries. Among neonates with septic shock (predominantly gram negative sepsis), 81% mortality rate was documented in a recent report from north India [21]. Recently, published Delhi Neonatal Infection Study (DeNIS) collaboration also observed a high mortality rate of 11–45% among neonates with sepsis and up to 67% in culture-proven sepsis across various centres. It is noteworthy that these neonates were older and heavier than our cohort (mean gestational age 36 weeks, birth weight 2211 g) *and* had sepsis (not septic shock in the denominator) [11]. Our LVO measurement was a single assessment. These neonates were very sick and tend to destabilize with repeated handling. Hence, we did not perform repeated measurements and hence could not check inter- or intraobserver variability.

Conclusion

Among neonates with septic shock, the reversal of shock in first 45 min of vasoactive drug therapy was comparable between epinephrine (0.2–0.4 μg/kg/min) and dopamine (10–20 μg/kg/min) groups. The secondary outcomes—haemodynamic stability anytime during vasoactive drug therapy, duration of vasoactive drugs, change in haemodynamic/acid-base parameters over first 45 min of study drugs, medium-term complications and all-cause mortality by 28 days—were also comparable between epinephrine and dopamine groups. On stratified analysis in a limited sample, epinephrine was associated with better outcomes in neonates $\leq 30^{6/7}$ weeks.

Authors' contributions • Dr. Kishore Baske: designed the data collection instruments, enrolled the patients, collected the data, drafted the initial manuscript and approved the final manuscript as submitted.
• Dr. Shiv Sajan Saini: conceptualized and designed the study, coordinated and supervised data collection, performed functional echocardiography, performed the data analysis, reviewed and revised the manuscript and approved the final manuscript as submitted
• Dr. Sourabh Dutta: critically reviewed the manuscript and approved the final manuscript as submitted
• Venkataseshan Sundaram: coordinated and supervised data collection, reviewed and revised the manuscript and approved the final manuscript as submitted

Compliance with ethical standards

Conflict of interest There is no potential, perceived, or real conflict of interest. The sponsor had no role in planning, conduct, analysis or publication of the study.

Research involving human participants and/or animals Human participants.

Informed consent Obtained from one of the parents of all neonates.

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