e-ISSN: 0976-822X, p-ISSN:2961-6042

Available online on http://www.ijcpr.com/

International Journal of Current Pharmaceutical Review and Research 2026; 18(3); 664-667

Original Research Article

Comparative Evaluation of Epinephrine and Norepinephrine in Fluid-Refractory Septic Shock in Children: A Randomized Clinical Study in a Tertiary Care Centre

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Received: 01-12-2025 / Revised: 15-01-2026 / Accepted: 21-02-2026

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Conflict of interest: Nil

Abstract

Background: Fluid-refractory septic shock remains a major cause of morbidity and mortality among children, particularly in low- and middle-income countries. Current paediatric sepsis guidelines recommend early initiation of vasoactive agents such as epinephrine or norepinephrine when shock persists despite adequate fluid resuscitation. However, comparative regarding the efficacy and safety of these agents in children remains limited.

Objectives: To compare the efficacy and safety of epinephrine and norepinephrine in children with fluid-refractory septic shock.

Methods: This open-label randomized clinical study was conducted in the paediatric intensive care unit of a tertiary care hospital. Children aged 2 months to 12 years with fluid-refractory septic shock, defined according to international paediatric sepsis consensus criteria[8], were randomized to receive either epinephrine or norepinephrine as the initial vasoactive agent. The primary outcome was resolution of shock at one hour. Secondary outcomes included achievement of therapeutic endpoints at 6, 24, 48, and 72 hours, adverse events, duration of hospital stay, and in-hospital mortality.

Results: A total of 54 children were enrolled, with 27 patients in each group. Shock resolution at one hour was achieved in 59.2% of children in the norepinephrine group and 51.8% in the epinephrine group, with no statistically significant difference. There were no significant differences between the groups in achievement of therapeutic endpoints, incidence of adverse events, duration of hospital stay, or mortality. Tachycardia was the most commonly observed adverse event in both groups.

Conclusion: Epinephrine and norepinephrine demonstrated comparable efficacy and safety in the management of paediatric fluid-refractory septic shock. These findings support current guideline recommendations endorsing the use of either agent as first-line vasoactive therapy[3], with selection guided by clinical context and resource availability.

Keywords: Fluid-Refractory Septic Shock; Epinephrine; Norepinephrine; Paediatric Intensive Care; Vasopressors.

DOI: 10.25258/ijcpr.18.3.105

Introduction

Septic shock remains one of the leading causes of morbidity and mortality among children worldwide, with a higher burden reported in low- and middle-income countries. Despite advances in paediatric critical care, outcomes remain poor when shock is not recognized early and promptly managed. International estimates indicate that sepsis and septic shock account for a significant proportion of paediatric intensive care unit admissions and deaths [1]. Initial management of septic shock focuses on early fluid resuscitation to restore intravascular volume and improve tissue perfusion. However, a considerable number of children fail to respond adequately to fluid therapy alone and progress to fluid-refractory septic shock, necessitating the initiation of vasoactive agents

[2,3]. Early initiation of appropriate vasoactive support has been shown to improve hemodynamic stability and clinical outcomes. Historically, dopamine was widely used as the first-line vasoactive agent in paediatric septic shock. However, emerging evidence has demonstrated higher rates of adverse effects and inferior outcomes associated with dopamine use when compared to other catecholamines [2]. Consequently, current paediatric sepsis guidelines recommend epinephrine or norepinephrine as first-line vasoactive agents once shock persists despite adequate fluid resuscitation [3].

Epinephrine exerts both inotropic and vasoconstrictive effects through stimulation of alpha and beta adrenergic receptors, making it useful in states of myocardial dysfunction. Norepinephrine predominantly acts on alpha-adrenergic receptors, resulting in increased systemic vascular resistance with modest inotropic effects [4]. Although both agents are commonly used in clinical practice, data comparing their efficacy and safety in children remain limited, particularly from Indian and other resource-constrained settings [5,7].

Given these considerations, the present study was undertaken to compare the efficacy and safety of epinephrine and norepinephrine in children with fluid-refractory septic shock admitted to a tertiary care centre.

Materials and Methods

Study design and setting: This randomized clinical study was conducted in the Paediatric Intensive Care Unit of a tertiary care teaching hospital in South India over a two-year period.

Study population: Children aged 2 months to 12 years admitted with septic shock who continued to have hypotension or signs of impaired perfusion despite receiving at least 60 mL/kg of isotonic fluid resuscitation were eligible for inclusion. Fluid-refractory septic shock was defined in accordance with international paediatric sepsis consensus definitions [8].

Children who were already receiving vasoactive medications prior to admission and those with known congenital or acquired cardiac disease or chronic kidney disease were excluded from the study.

Randomization and Intervention: After obtaining written informed consent from parents or legal guardians, eligible children were randomly allocated into two groups using a computer-generated randomization sequence. One group received epinephrine and the other received norepinephrine as the initial vasoactive agent. Due to the nature of the intervention, the study was conducted in an open-label manner.

The study drugs were initiated at a dose of 0.1 µg/kg/min and titrated at regular intervals up to a maximum of 0.3 µg/kg/min until predefined therapeutic endpoints were achieved. Children who failed to respond to the maximum dose were managed with additional vasoactive agents based on their physiological shock profile, as recommended by standard paediatric sepsis guidelines [3].

Outcome Measures: The primary outcome was resolution of shock within one hour of initiation of vasoactive therapy.

Secondary outcomes included achievement of therapeutic endpoints at 6, 24, 48, and 72 hours, occurrence of drug-related adverse events, duration of hospital stay, and in-hospital mortality.

Statistical Analysis: Statistical analysis was performed using SPSS software. Continuous variables were expressed as mean ± standard deviation, and categorical variables were expressed as frequencies and percentages. Comparisons between groups were performed using appropriate statistical tests. A p value <0.05 was considered statistically significant.

Results

Table 1: Demographic and baseline clinical characteristics

Parameter	Norepinephrine (n=27)	Epinephrine (n=27)	p value
Age (months), mean ± SD	38.4 ± 42.1	35.3 ± 39.6	0.78
Age <1 year, n (%)	10 (37.0)	11 (40.7)	0.78
Male gender, n (%)	15 (55.6)	16 (59.3)	0.79
Duration of illness (days), mean ± SD	8.6 ± 9.6	7.7 ± 4.7	0.66
Hypotension at admission, n (%)	22 (81.5)	26 (96.3)	0.08
Cold shock physiology, n (%)	20 (74.1)	23 (85.2)	0.32

Table 1 summarizes the demographic profile and baseline clinical characteristics of children in the norepinephrine and epinephrine groups. Both groups were comparable with respect to age, gender distribution, duration of illness, and hemodynamic status at admission.

Table 2: Primary efficacy outcome – shock resolution at 1 hour

Outcome	Norepinephrine n (%)	Epinephrine n (%)	p value
Shock resolved	16 (59.2)	14 (51.8)	0.78
Shock not resolved	11 (40.8)	13 (48.2)	Not applicable

Table 2 shows the proportion of children who achieved resolution of shock within one hour of initiation of vasoactive therapy. There was no statistically significant difference between the norepinephrine and epinephrine groups in early shock reversal.

Table 3: Comparison of therapeutic response over time

Time interval	Norepinephrine n (%)	Epinephrine n (%)	p value
6 hours	18 (66.7)	18 (66.7)	1.00
24 hours	18 (66.7)	16 (59.3)	0.77
48 hours	15 (55.6)	14 (51.9)	0.78
72 hours	16 (59.3)	15 (55.6)	1.00

Table 3 compares the achievement of therapeutic endpoints at 6, 24, 48, and 72 hours following initiation of vasoactive therapy. Both treatment groups demonstrated comparable clinical responses at all assessed time points.

Table 4: Drug-related adverse events

Adverse effect	Norepinephrine n (%)	Epinephrine n (%)	p value
Tachycardia	18 (66.7)	22 (81.5)	0.35
Arrhythmia	2 (7.4)	1 (3.7)	1.00

Table 4 presents the incidence of adverse events observed during vasoactive therapy in both groups. Tachycardia was the most common adverse event, while serious arrhythmias were infrequent and comparable between the two groups.

Table 5: Clinical outcomes

Outcome	Norepinephrine (n=27)	Epinephrine (n=27)	p value
Discharged, n (%)	18 (66.7)	16 (59.3)	0.78
Mortality, n (%)	9 (33.3)	11 (40.7)	0.78
Hospital stay (days), mean ± SD	19.8 ± 4.8	20.9 ± 5.4	0.54

Table 5 outlines the final clinical outcomes, including discharge status, mortality, and duration of hospital stay. No statistically significant differences were observed between the norepinephrine and epinephrine groups with respect to these outcomes.

Discussion

The present randomized clinical study compared the efficacy and safety of epinephrine and norepinephrine as first-line vasoactive agents in children with fluid-refractory septic shock and demonstrated no statistically significant difference between the two drugs in terms of early shock resolution, achievement of therapeutic endpoints, adverse events, or in-hospital mortality. These findings are in accordance with current paediatric sepsis literature, which supports the use of either agent based on clinical context and availability. [1,3]. Resolution of shock at one hour was achieved in a slightly higher proportion of children receiving norepinephrine compared to epinephrine; however, this difference did not reach statistical significance. Similar observations have been reported in previous paediatric studies, including the work by Deep et al., who demonstrated comparable improvement in cardiac index and systemic vascular resistance with both agents in fluid-refractory septic shock[7]. Adult studies have also shown no significant difference between epinephrine and norepinephrine in achieving target mean arterial pressure or short-term outcomes [4].

The pharmacological actions of epinephrine and norepinephrine differ and may influence clinician preference in specific physiological states. Epinephrine provides combined inotropic and vasoconstrictive effects, whereas norepinephrine primarily increases systemic vascular resistance with modest inotropic activity [4]. In paediatric vasodilatory shock, norepinephrine has been shown to improve preload and reduce fluid requirements, as demonstrated in studies from resource-limited settings [5]. However, such hemodynamic advantages did not translate into superior clinical outcomes in the present study.

Tachycardia was the most frequently observed adverse event in both groups and was more common among children receiving epinephrine. This finding is consistent with the known beta-adrenergic effects of epinephrine and has been reported in both paediatric and adult studies [2,4]. Importantly, serious arrhythmias were uncommon and comparable between the two groups,

suggesting that both agents are relatively safe when used with appropriate monitoring. Meta-analyses evaluating vasopressor use in septic shock have similarly reported no significant difference in serious adverse events between epinephrine and norepinephrine [9].

The mortality rates observed in this study were comparable between the two groups and are similar to those reported in other paediatric studies from low- and middle-income countries [5,7]. Factors such as delayed presentation, severity of illness at admission, and ongoing sepsis may have contributed to the overall mortality observed. Adult trials, including the CENSER study, have also demonstrated that early norepinephrine improves shock control without significantly reducing mortality [6], supporting the notion that early hemodynamic stabilization alone may not be sufficient to alter survival outcomes.

The strengths of this study include its randomized design and the use of clinically relevant bedside parameters to assess shock resolution, making the findings applicable to real-world clinical settings. However, the study has limitations, including its single-centre design and lack of advanced hemodynamic monitoring, which may have provided more detailed physiological insights. Additionally, the open-label nature of the study may have introduced treatment bias.

Overall, the findings of this study reinforce existing guideline recommendations endorsing the use of either epinephrine or norepinephrine as first-line vasoactive therapy in paediatric fluid-refractory septic shock [1,3]. Selection of the agent should therefore be individualized based on patient physiology, clinician experience, institutional protocols, and resource availability

Conclusion

In this randomized clinical study, epinephrine and norepinephrine demonstrated comparable efficacy and safety profiles in children with fluid-refractory septic shock. There was no statistically significant difference between the two agents in terms of early shock resolution, achievement of therapeutic endpoints, adverse events, or clinical outcomes. These findings support current guideline recommendations endorsing the use of either epinephrine or norepinephrine as first-line vasoactive therapy in paediatric septic shock [3]. Selection of the vasoactive agent may therefore be guided by patient physiology, clinician experience, drug availability, and resource considerations.

Ethical Approval: The study protocol was approved by the Institutional Ethics Committee of Karnataka Medical College and research institute, Hubballi.

Informed Consent: Written informed consent was obtained from parents or legal guardians of all participants prior to enrolment.

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