ORIGINAL ARTICLE

Efficacy of Epinephrine in Fluid Refractory Septic Shock in Children: A Prospective Observational Study

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Abstract

Introduction: Septic shock is a leading cause of mortality and morbidity among children globally. Although dopamine has traditionally been used, emerging evidence suggests epinephrine may be more effective. This study was conducted to identify the proportion of children responding to epinephrine and to document associated survival outcomes and side effects in a resource-limited tertiary setting.

Methods: This prospective observational study was conducted over 14 months at a tertiary care university hospital. Ethical approval was obtained from the hospital's institutional ethics committee (Reference number: 184/075/076). We enrolled 31 children aged 1 month to 16 years with fluid-refractory septic shock. Participants received epinephrine infusions at incremental doses starting at 0.1 µg/kg/min and escalating by 0.1 µg/kg/min every 10 minutes to a maximum of 0.3 µg/kg/min until shock resolution. Outcomes included the proportion of shock resolution, survival, and duration of hospital stay. Data were entered in Epidemiologic Information and Microsoft Excel.

Results: Shock resolved in 24 (77.40%) patients with epinephrine alone, while 7 (22.60%) patients achieved resolution within the first hour, and 7 (22.60%) required additional vasoactive agents, primarily noradrenaline. Side effects included feeding intolerance in 3 (9.60%) and hyperglycemia in 2 (6.40%) children. There were 7 (22.60%) deaths, and 24 (77.40%) children survived to discharge.

Conclusions: Epinephrine could be considered an effective agent for the reversal of fluid-refractory septic shock in children. It appeared to offer survival benefits with minimal life-threatening side effects in this cohort.

Keywords: *children; dopamine; epinephrine; septic shock.*

Introduction

Septic shock is defined as the presence of signs of sepsis with cardiovascular dysfunction across all ages.[1-3] The persistence of hypotension with signs of poor perfusion despite fluid resuscitation with at least 40ml/kg of isotonic saline bolus denotes fluid refractory hypotensive septic shock.[4]

The estimated global burden of 31.5 million cases of sepsis, 19.4 million cases of severe sepsis, and

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5.3 million deaths annually are data that have been extrapolated from high-income countries because of scarce data from middle and low-income countries.[5] Studies in the 1990s, using the adult sepsis definitions proposed by Bone et al. and adapted for children, reported a prevalence of septic shock in pediatric intensive care units (PICUs) of 2% to 3% in developed countries.[6] In another study done by Sáez-Llorens et al. on the application of sepsis definitions in developing countries, the prevalence of sepsis was 18% to 46%.[7] In studies conducted by Proulx et al. and Sari et al., mortality from septic shock was as high as 80%.[8,9] In South America, de Souza et al. observed that both the prevalence of severe sepsis (25.9%) and septic shock (19.80%) at admission to PICUs were high, with sepsis-related mortality at 14.20%.[10] The Sepsis Prevalence, Outcomes, and Therapies (SPROUT) study reported a severe sepsis prevalence of 8.20% in PICUs across 26 countries.[3] A study on pediatric septic shock in India reported the incidence of septic shock to be nearly 35%, with a survival of 53.30%.[11] Current guidelines recommend a 20ml/kg intravenous bolus of a crystalloid solution over 5 minutes for initial management.[12,13] However, fluid resuscitation is frequently insufficient to restore minimal organ perfusion pressure. Studies by Ventura et al. and Ramaswamy et al. have suggested that epinephrine is more effective than dopamine in achieving early shock resolution and improved survival rates.[4,14] In Nepal, dopamine remains a commonly used drug, yet there is a lack of local data regarding epinephrine's efficacy.

This study aimed to identify the proportion of children responding to epinephrine within the first hour of resuscitation and the proportion requiring additional vasoactive agents.

Methods

This prospective observational study included children aged 1 month to 16 years with fluid refractory septic shock at a tertiary-care university hospital in South Asia. Ethical approval was obtained from the Institutional Review Committee of the Institute of Medicine, Tribhuvan University Teaching Hospital (Reference number: 184/075/076).

The sample size was calculated using the single-proportion formula

$n = (Z^2 \times p \times q) / e^2$

Based on the study by Ventura et al., an expected response rate p of 0.8, q= 1-p, a 95% confidence level (Z = 1.96), and an allowable absolute error (e) of 0.14, were used, yielding a sample size of 31.4 Inclusion criteria were children aged 1 month to 16 years with fluid refractory hypotensive shock. Exclusion criteria included prior vasoactive drug use, known cardiac disease, rhythm disturbances (tachyarrhythmias), immunocompromised status, severe malnutrition, features of raised intracranial pressure, prior participation in the study during the same hospital stay, or do-not-resuscitate orders.

Septic shock was diagnosed in the presence of signs of sepsis with cardiovascular dysfunction. Cardiovascular dysfunction included hypotension (systolic blood pressure <5th percentile for age) or two or more signs of poor perfusion (e.g., capillary refill >2s, oliguria <1.0ml/kg/hr, increased lactate >2mmol/L, central - to-peripheral temperature gap greater than 3°C, mottled or cool extremities). Shock resolution was defined by achievement of therapeutic endpoints, including normalized blood pressure, heart rate, urine output, capillary refill time and mental status (except in suspected meningitis and in mechanically ventilated children on sedation). Treatment failure was defined as persistent hypotensive shock despite 10 minutes of epinephrine at 0.3µg/kg/min. Adverse events were categorized as cardiac (tachyarrhythmias), ischemic (drug extravasation), or others, including feed intolerance, hyperglycemia (blood glucose >200mg/dL), and persistently increased serum lactate (>1.46mmol/L) after the first 24 hours of treatment.

Prior to the study, all nursing staff, residents, and faculty in the pediatric department underwent standardized orientation regarding the nature of the study and the specific resuscitation protocol. For the preparation of the drug, the dose of epinephrine (1mg/1mL ampule) needed for 24 hours was calculated as: weight (kg) × dose (µg/kg/min) × 60 × 24 / 1000. This amount was diluted with normal saline to make 24mL and infused at 1mL/hr via infusion pump through a peripheral vein. If weight could not be assessed, the 50th percentile of weight for length as per the WHO growth charts was used.

Epinephrine infusion began at 0.1 µg/kg/min alongside the third fluid bolus (20ml/kg normal saline over 10 minutes), escalated by 0.1 µg/kg/min every 10 minutes up to 0.3 µg/kg/min if shock persisted. Once resolved, the infusion was tapered over 24 hours. If not, additional inotropes added. Patients were monitored via ECG, with vitals recorded every 10 minutes during resuscitation and every 4 hours for 72 hours.

Data were entered in EPI-INFO and Microsoft Excel and analyzed in EPI-INFO and Easy-Quantitative data were expressed as Mean±SD or median (IQR), while categorical variables were presented as frequencies and percentages.

Results

The mean (±SD) age was 8.71±4.82 years, and the

male-to-female ratio was 1:1.38. Most patients 26 (83.80%) were from outside the Kathmandu valley (Table 1).

Table 1: Baseline demographic characteristics (n=31)

Demographic Variables	Measures	n(%)
Age (years)		8.71±4.82*
Age categories (years)	0-<1 year	2(6.40)
	1-<10 years	11(35.40)
	≥ 10 years	18(58)
Sex	Male	13(41.90)
Residence	Outside Kathmandu	26(83.80)

*Mean±SD

Study Outcomes: Shock resolved in 7 (22.60%) patients within the first hour of resuscitation. For the remaining 17 (54.8%) responders, the mean time to resolution was 1.11±0.19 hours. 7 (22.60%) patients failed to respond to epinephrine and required additional agents, primarily noradrenaline. Among the patients, side effects included feed intolerance in 3 (9.60%) and hyperglycemia in 2 (6.50%). No cardiac side effects occurred. The final survival rate to discharge was 24 (77.40%), with a mean hospital stay of 9.48±4.59 days (Table 2).

Table 2: Study outcome of patients with fluid refractory septic shock (n=31)

Variables	n	Measures	n(%)
Shock resolution within 1 hour	31	Yes	7(22.6)
		No	24(77.4)
Use of additional vasoactive drug	31	Yes	7(22.6)
		No	24(77.4)
Side effects	31	Feed intolerance	3(9.6)
		Hyperglycemia	2(6.5)
Outcome	31	Survived (%)	24(77.4)
		Death (%)	7(22.6)
Duration of hospital stay (Days)		31	9.48±4.59*
Time taken to reach shock resolution (hour)		31	1.11±0.19*

*Mean±SD

Discussion

The mean age was 8.71 years, which was higher than the Wolfler et al. (3.25 years) and comparable international studies such as SPROUT study (3.0 years).[2,3] In our study, there were more female patients 18 (58%), with the age and sex distribution, showing a notable female preponderance in children above 10 years. This demographic profile differs from those of the SPROUT Study, Ventura et al., and Ramaswamy et al., in which male patients comprised 53.30%, 61.4%, and 51.70% of participants, respectively.[3,4,14] These variations in age and gender distribution may reflect regional differences in the epidemiology of pediatric sepsis or differences in the admission patterns of tertiary-care university hospitals in South Asia.

In this study, 24 (77.40%) of children achieved shock resolution with epinephrine, though only 7 (22.60%) did so within the first hour. The early resolution rate is lower than the 42% and 41.70% reported by Ventura et al. and Ramaswamy et al., respectively.[4,14] The relatively smaller proportion of children with early resolution of shock in our study could be explained by difficulties with the logistics in our small, non-sophisticated, and busy emergency unit. Although we followed recruitment policies of standardized guidelines, there was some degree of flexibility in adherence to treatment. Given the human, technological, and financial constraints, vasoactive agents were administered via peripheral lines in the emergency room rather than the recommended central lines.

Furthermore, although our study used clinical signs for resolution, Ventura et al.'s study included laboratory values such as central venous pressure and lactate, which may explain the variation in recorded resolution times.[4] All 7 (22.60%) deaths in our study initially presented in our emergency room and occurred later in the PICU, with 71% of these deaths occurring within the first 72 hours.

Survival in our cohort 24 (77.40%) was higher than the 48% reported by Ramaswamy et al.[14] It was lower than the 93% reported by Ventura et al.[4] These figures likely reflect differences in the clinical setting, the baseline severity of illness at admission, and the availability of advanced intensive care support. Regarding safety, side effects were minimal in our population. While Ventura et al. reported hyperglycemia in 78.90% of patients and feed intolerance in 73.70%, our study found rates of only 6.50% and 9.60%, respectively.[4] The lower incidence of hyperglycemia in our study might be linked to our titration protocol or differences in the metabolic stress response of older children compared to the younger cohorts in other studies.

This is the first study in Nepal to evaluate epinephrine's efficacy in pediatric septic shock under a standardized protocol. However, as an observational single-center study with a small sample size, the findings cannot be universally generalized. Due to

financial and technological constraints, we could not utilize the PRISM scoring system to assess illness severity or consistently monitor lactate levels and central venous oxygen saturation, which limits our ability to compare our results directly with multi-center trials in high-resource settings.

Conclusions

Based on this observational study, epinephrine could be effective and safe for the reversal of fluid-refractory septic shock in children. It appeared to provide survival benefits while avoiding life-threatening adverse effects. Further multicenter studies are suggested to confirm these findings and optimize standardized treatment protocols.

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Author's Contribution and ORCID iDs

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