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Efficacy of Epinephrine in Fluid Refractory Hypotensive Septic Shock in Children

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ABSTRACT

Background: Sepsis remains a significant health burden worldwide, especially among children, with an estimated annual incidence of 1.2 million cases. Mortality rates for sepsis range from 1% to 5%, while severe sepsis has a higher mortality of 9% to 20%. Early initiation of appropriate treatment, especially for children in septic shock, is crucial. This study focuses on the effectiveness of epinephrine, an agent known for its potent inotropic effects and minimal impact 'on systemic vascular resistance, in managing fluid-refractory hypotensive septic shock in pediatric patients'. The study aims to evaluate the efficacy of 'epinephrine in treating fluid-refractory hypotensive septic shock' in children at Lady Reading Hospital, Peshawar.

Methodology: This was a descriptive study, was conducted in the Department of Pediatrics at Lady Reading Hospital, Peshawar and was carried out from August 20, 2022, to February 20, 2023. A total of 146 'children with fluid-refractory hypotensive septic shock', of both genders, were included. Each child received an epinephrine infusion at a dosage of 0.1–0.3 µg/kg/min. The infusion rate was adjusted every 10 minutes, increasing by 0.5 mL/hr, with a 'maximum limit of 1.5 mL/hr, until shock resolution'. The efficacy of treatment was assessed based on clinical resolution of shock.

Results: The study included children aged 1 to 12 years, 'with a mean age of' 7.35±1.75 'years'. The mean duration of complaints was 7.54±2.03 days. Males comprised 58.9% of the sample, while females accounted for 41.1%. Epinephrine demonstrated efficacy in 51.4% of the cases.

Conclusion: The findings suggest that epinephrine is effective in achieving early resolution of fluid-refractory hypotensive septic shock in children.

Keywords: Pediatric sepsis, Epinephrine, Hypotensive septic shock, Fluid-refractory shock, Efficacy

Introduction

Sepsis continues to be a global health challenge, particularly for pediatric populations. It is estimated that sepsis affects 1.2 million children annually, with mortality rates varying from 1% for uncomplicated cases to 20% for severe sepsis (1, 2). Various factors contribute to poor outcomes, including age, vaccination status, delays in recognizing sepsis, and inadequate adherence to treatment protocols (3). Children with underlying cardiovascular conditions or multiple organ dysfunction face higher risks of mortality (4).

Though case-fatality rates for pediatric sepsis have shown a declining trend over the years, significant disparities exist between low- and middle-income countries (LMICs) and high-income countries (5, 6). Studies from regions South America highlight a disproportionately high rate of sepsis-related mortality, especially during the first 24 hours of PICU admission (7).

Prompt identification of sepsis and timely administration of appropriate fluids antibiotics and are critical for effective intervention. When fluid resuscitation fails to restore adequate tissue perfusion, vasoactive agents such as epinephrine become necessary. Epinephrine is widely used for its predictable effects on cardiac output and mean arterial pressure, making it an ideal first-line treatment in septic shock (8).

Epinephrine, when administered in 'low doses (0.05–0.2 µg/kg/min), provides predominantly inotropic support by stimulating β1 receptors while promoting vasodilation through β2 receptors' (9). At higher doses, it increases systemic vascular resistance due to α1-mediated vasoconstriction. Studies have demonstrated epinephrine's efficacy in pediatric septic shock, particularly in cases where fluid resuscitation alone is insufficient (10). This study aims to assess the efficacy of epinephrine as a first-line treatment for fluid-refractory hypotensive septic shock in children.

Materials and Methods

This was a descriptive study conducted in the Department of Pediatrics at Lady Reading Hospital, Peshawar and was carried out from August 20, 2022, to February 20, 2023. Non-probability consecutive sampling was used to recruit participants. The sample size for the study was determined using the WHO 'sample size calculation tool, incorporating a 95% confidence' level, an 8% margin of error, and an anticipated efficacy rate of 41%, derived from prior studies on the impact of epinephrine in treating fluid-refractory hypotensive septic shock. This resulted in the enrollment of 146 children in the study.

The inclusion criteria was children aged 1 to 12 years, regardless of gender, who presented 'with fluid-refractory hypotensive septic shock', as defined by the study's operational criteria, were included. And the exclusion criteria was children with preexisting heart conditions, rhythm disturbances, those already on vasoactive agents, those with raised intracranial pressure, immunocompromised states, or severe acute malnutrition were excluded from the study.

After obtaining ethical approval and informed consent from the parents or guardians, baseline demographic information, including age, gender, and the duration of complaints, was recorded. The epinephrine infusion (0.1–0.3 µg/kg/min) was administered via infusion pumps. Infusions began at 0.5 mL/hr and were 'increased by 0.5 mL/hr every 10 minutes to a maximum of 1.5 mL/hr until the resolution of shock was achieved'. The efficacy of the treatment was documented based on predefined criteria.

Data was analyzed using IBM-SPSS version 22. Descriptive statistics were used to summarize quantitative variables such as age and duration of complaints, while frequencies and

percentages were calculated for categorical variables like gender and efficacy. Efficacy was stratified by age, gender, socioeconomic status, and duration of complaints, and 'a post-stratification chi-square test was applied, with' a p-value of ≤0.05 considered statistically significant.

Results

Table 1 the average age of the patients included in the study was 7.349 years, with a relatively narrow standard deviation, indicating that most patients were in a similar age range. The average duration of complaints was 7.541 days, which suggests that children with fluid-refractory hypotensive septic shock had symptoms for approximately a week before being treated. The standard deviation of 2.03 days shows that there was some variation in how long the symptoms persisted before treatment.

Table 1: Demographics of Patients (Age, Duration of Complaints)

Variable	**Mean ± SD**	**n**
Age (years)	7.349 ± 1.75	146
Duration of Complaints (days)	7.541 ± 2.03	146

Table 2 there were more male patients (58.9%) compared to female patients (41.1%). This suggests a higher prevalence of fluid-refractory hypotensive septic shock in males in this specific sample.

The majority of patients came from a middle socioeconomic background (67.8%), followed by those from a poor background (22.6%), and the smallest group was from the rich socioeconomic group (9.6%). This distribution may reflect the overall demographic composition of the population served by the hospital, or it could suggest that middle-income families had greater access to healthcare facilities.

Epinephrine was effective in 51.4% of the patients, indicating a little over half of the children responded positively to the treatment. The remaining 48.6% of patients did not respond to the treatment, showing that while epinephrine is a viable option for many, there are still a significant number of cases where it may not be fully effective.

Table 2: Distribution of Patients by Gender, Socioeconomic Status, and Efficacy

Category	**Frequency**	**Percentage (%)**
Gender		
Male	86	58.9
Female	60	41.1
Family Socioeconomic Status		
Poor	33	22.6
Middle	99	67.8
Rich	14	9.6
Efficacy		
Yes	75	51.4
No	71	48.6

Table 3 revealed that there was no statistically significant difference in the efficacy of epinephrine in younger children aged 1–6 years (55.6% efficacy) and older children aged 7–12 years (49.5% efficacy) with a p-value of 0.499. This suggests that the age of the child does not significantly affect how well they respond to epinephrine.

The efficacy of epinephrine was slightly higher in males (52.3%) than in females (50.0%), but the difference is not statistically significant (p-value = 0.782). This indicates that gender does not play a significant role in the response to treatment.

There wasa statistically significant difference in efficacy based on socioeconomic status (p-value = 0.000). Notably, all patients from the rich category (100%) responded positively to epinephrine, while only 24.2% of patients from the poor category showed a positive response. This suggests that socioeconomic factors may influence outcomes, possibly due to differences in access to healthcare or underlying health conditions.

No significant difference in efficacy based on the duration of complaints, with patients who had symptoms for 1–7 days showing 50.9% efficacy compared to 51.6% for those with symptoms for more than 7 days (p-value = 0.938). This suggests that the length of time a child had symptoms before treatment did not significantly impact the effectiveness of epinephrine.

Table 3: Stratification of Efficacy by Age, Gender, Socioeconomic Status, and Duration of Complaints.

Variable	Efficacy Yes (%)	Efficacy No (%)	p-value
Age (years)			
1–6	55.6	44.4	0.499
7–12	49.5	50.5	
Gender			
Male	52.3	47.7	0.782
Female	50.0	50.0	
Family Socioeconomic Status			
Poor	24.2	75.8	0.000
Middle	53.5	46.5	
Rich	100.0	0.0	
Duration of Complaints (days)			
1–7	50.9	49.1	0.938
>7	51.6	48.4	

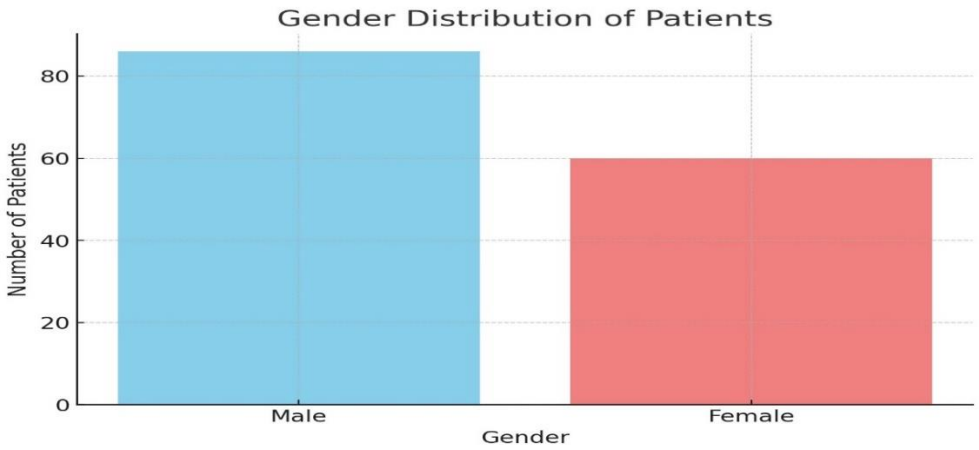

Figure 1: Gender Distribution of Patients: The bar chart shows that there are more male patients (86) compared to female patients (60).

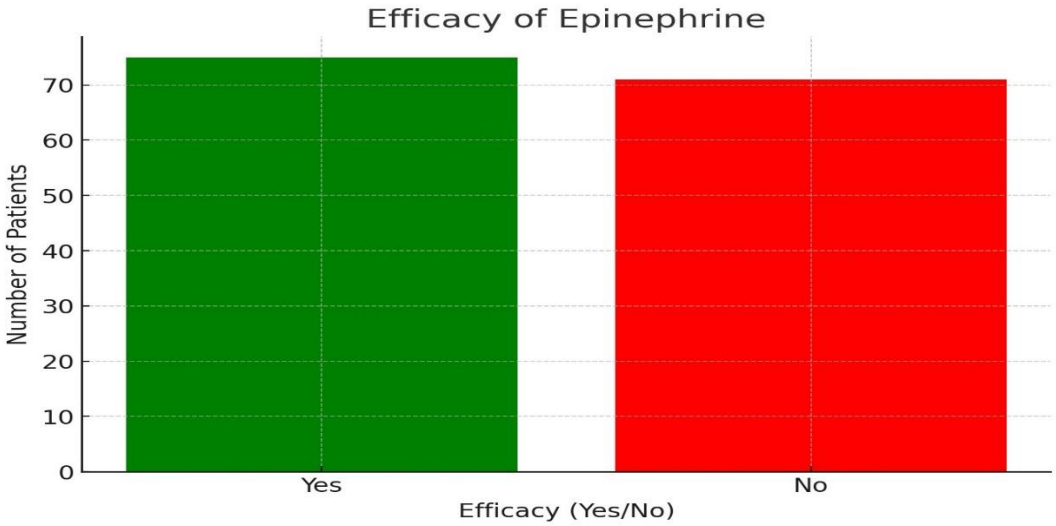

Figure 2: Efficacy of Epinephrine: This shows that epinephrine was effective in 51.4% of the patients, while it was not effective in 48.6%.

Discussion

Our research revealed that epinephrine was considerably more successful than dopamine in resolving shock within the initial hour of resuscitation. This pattern continued through the six-hour mark. 'Early shock resolution with epinephrine' was linked to better organ function, as reflected by reduced 'SOFA scores' and a greater number of 'organ failure-free days'. Furthermore, epinephrine enhanced capillary refill time, indicating improved microcirculation, and contributed to a slight decrease 'in systemic vascular resistance'.

These findings were consistent with previous studies in adults, where epinephrine showed better outcomes in septic patients compared to dopamine (11, 12). Epinephrine increased cardiac index and arterial pressure, with fewer adverse events and a slight reduction in systemic vascular resistance (13). Evidence from the literature suggests that dopamine use in septic shock, especially in patients with myocardial dysfunction, is associated with increased mortality (14).

While epinephrine proved effective in our study, 'concerns' about it potentially causing 'lactic acidosis' were not supported. This outcome is likely due to the enhanced 'cardiac output and improved microcirculation' observed with epinephrine at doses ranging from' 0.1 to 0.3 µg/kg/min'.

Despite adherence to ACCM guidelines, mortality in the study cohort remained high, possibly due to the severity of illness, greater organ dysfunction, and the failure to achieve shock resolution within six hours in non-survivors (15).

Our study found that shock resolution within six hours was only achieved in 48.3% of children in the epinephrine group. This result mirrors those of previous studies, such as the findings by Sankar et al., who reported a 42% mortality rate in fluid-refractory septic shock despite high adherence to guidelines (16). These findings emphasize the difficulty of managing cold hypotensive septic shock and achieving therapeutic endpoints within six hours.

One of the primary limitations of our study was the 'small sample size', which may have hindered our ability to identify 'significant differences in long-term outcomes', such as '28-day mortality'. Furthermore, 'the majority of the children in the study had community-acquired sepsis, limiting the generalizability of our findings to cases of hospital-acquired sepsis'. 'Hospital-acquired septic shock is typically identified earlier during the warm shock phase, whereas community-acquired septic shock often presents later in the cold shock phase, necessitating more aggressive treatment'.

In conclusion, our study supports the use of epinephrine as a first-line vasoactive agent in children with fluid-refractory cold hypotensive septic shock. It effectively achieves early shock resolution and appears to be safe in this population. However, larger, multicenter studies are needed to further evaluate the long-term benefits and mortality outcomes associated with the use of epinephrine in pediatric septic shock.

Conclusion

In this study, epinephrine was shown to be an effective and safe 'first-line vasoactive agent for the management of fluid-refractory cold hypotensive septic shock in children'. It significantly improved early shock resolution, organ function, and capillary refill time without inducing lactic acidosis. However, despite these benefits, overall mortality remained high, likely due to the severity of illness and failure to achieve shock resolution within six hours in a portion of the patients. The findings suggest that epinephrine offers clear advantages over dopamine, but further large-scale, multicenter studies are needed to fully assess its impact on long-term outcomes, including mortality, in pediatric septic shock.

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