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ORIGINAL ARTICLE

Comparison of efficacy of dopamine versus epinephrine infusion in fluid refractory septic shock in a tertiary care pediatric ICU.

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ABSTRACT… Objective: To compare the effectiveness of dopamine versus epinephrine as 1st line vasoactive therapy among children aged 6 months to 12 years and presenting with fluid-refractory septic shock in pediatric intensive care unit (PICU). **Study Design:** Randomized Controlled Trial. **Setting:** Department of Medicine, The Children's Hospital, Multan, Pakistan. **Period:** August 2022 to January 2023. **Material & Methods:** A total of 156 children aged between 6 months to 12 year presenting to PICU with fluid refractory shock. Children were randomized to either Group-A (epinephrine) or Group-B (dopamine) till end points of resolution of shock was achieved. When the maximum recommended dose of the study drugs was reached, open-label vasoactive was initiated. Frequency of resolution of shock within 1st hour of resuscitation was noted. **Results:** In a total of 156 children, there were 85 (54.5%) children between 7 to 12 years of age. There were 90 (57.7%) males and 66 (42.3%) females. The efficacy was observed in 41 (52.6%) children in Group-A (epinephrine) versus 18 (23.1%) in Group-B (dopamine), p=0.0001. **Conclusion:** The epinephrine was more effective than dopamine as first-line vasoactive therapy in fluid-refractory septic shock in children aged 6 months to 12 years presenting in PICU.

Key words: Dopamine, Efficacy, Epinephrine, Septic Shock, Vasoactive.

INTRODUCTION

In developed countries, 2-3% of admissions in pediatric intensive care units (PICUs) are due to septic shock, whereas among the Asian population, its estimation is around 40-67%.[1] Severe pediatric sepsis cases have risen due to an increase in the survival of patients at high risk which include children with complicated medical disorders, small for gestational age neonates and preterm newborns.[2] Global statistics describe that diarrheal disease is the most frequently mentioned cause of sepsis while lower respiratory infections are found to be the commonest cause behind mortality in sepsis.[3] In recent years, critically ill children have gone through invasive procedures and vascular access exposing them to higher rates of infection rates causing sepsis and septic shock.[4]

Septic shock is described as substantial organ dysfunction and increased mortality caused by cellular, metabolic, and circulatory anomalies.[5] Septic shock is associated with excessive nitric oxide (NO) production, which is a factor of great importance in causing vasopressor-resistant hypotension. Mitochondrial dysfunction results in compromised utilization of oxygen at the cellular level and malfunctioning of tissues and organs during sepsis.[6] A study analyzing 60 children having fluid-refractory hypotensive shock revealed that the adrenaline group had a higher shock resolution as compared todopamine group when assessed at 1 hour (41% vervus 13%) and at 6 hours (48.3% versus 29%) after resuscitation.[7]

In several recent studies, varying results for dopamine and epinephrine have been described in investigating their efficacy in pediatric septic shock. This study was aimed to compare the effectiveness of dopamine versus epinephrine as

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1st line vasoactive therapy among children aged 6 months to 12 years and presenting with fluid-refractory septic shock in PICU.

MATERIAL & METHODS

This was a randomized controlled trial carried out at the PICU of Children's Hospital Multan, Pakistan from August 2022 to January 2023. A sample size of 156 (78 in each group) was calculated taking efficacy in the epinephrine group (P1) = 48.3%,[9] ii) efficacy in the dopamine group (P2) = 29.0%,[9] iii) power of study = 80%, and iv) significance level = 5%.

Inclusion criteria were children of either gender, between 6 months and 12 years of age, and presenting to the ICU with fluid-refractory shock. Exclusion criteria were the patients who had cardiopulmonary bypass during the past 5 days and those who already had treatment at the periphery for hypovolemia without any record of medication or sequential organ failure at presentation. Children with chronic diseases like chronic kidney disease, cerebral palsy, congenital heart disease on history and medical examination, and children with neuromuscular disorders and metabolic disorders on history or medical record were also excluded. Sepsis was labeled on clinical and laboratory parameters, which included: i) temperature instability (>100.5 ^{0}F or <96.0 ^{0}F) and any three or more clinical features of refusal to feed, lethargy, capillary refill time >3 seconds, hypotonia, tachypnea (respiratory rate >60/minute in 1–2 month age, >50 /min in >2–11month age, and > 40/min in ≥12 month age), apnea and gasping respiration and heart rate ≥±2SD the age and sex-specific limits, ii) presence of 2 or more of the laboratory parameters, including total leukocyte count <4000/mm^3 or >11000/mm^3, absolute neutrophil count <1800/mm^3, C-reactive protein >6mg/dL. Septic shock was termed as "systolic blood pressure (60 mmHg for term infants <1 month, 70 mmHg for 1–12 months, 70 + (2 × age in years) mmHg for children aged between 1 and 10 years, 90 mmHg for children older than 10 years) and serum lactate level >2 mmol/L or 18 mg/dL".[8] Fluid-refractory shock was defined as "persistence of hypotension, signs of poor perfusion (decreased pulse volume, tachycardia, abnormal capillary refill time (CFT), temperature abnormality, altered mental status, decreased urine output), or signs of fluid overload (rales, hepatomegaly, worsening respiratory distress) after administration of a maximum of 60 ml/kg of fluid bolus within 60 min of presentation".[8] "Sequential organ failure assessment (SOFA)" score was also noted. Informed and written consent from the children's parents/guardians was obtained. Permission from the "Institutional Ethical Committee" was also obtained (1310/Admin.CK& ICH, Multan).

Age, gender and weight were noted at enrollment time. The lottery method was employed to randomly distribute the total number of patients into two groups. In Group-A (n=78), patients received epinephrine (0.1-0.3 µg/k/minute) while in Group-B (n=78), they were given dopamine (in incremental doses, 10-20 µg/kg/minute) till the end points of resolution of shock were achieved. Once test drugs reached to the maximum doses, the launch of open-label vasoactive medication took place as per guidelines or departmental protocols. Labeling of the primary outcome was done on the basis of the achievement of a resolution of shock within the initial hour of resuscitation. The SOFA score was recorded at baseline and then at 6 hours. We also analyzed heart rate, mean arterial pressure, and systolic blood pressure.

Statistical analysis was done using "Statistical Package for Social Sciences (SPSS)", version 26.0. Quantitative variables were expressed in the form of mean and standard deviation (SD) while qualitative data were shown as percentages and frequencies. Chi-square test was used to compare the efficacy between the two groups. The drug was considered effective if it caused reversal of septic shock characterized by improvement in heart rate from baseline, 75th centile of systolic blood pressure as per age, capillary refill time <3sec in one hour, or improvement of 4 points from baseline in SOFA score at 6 hours. The data was stratified for age, gender, and weight to determine the effect on efficacy between the two groups. Post stratification chi-square test

was applied. P-value<0.05 was considered as significant.

RESULTS

In a total of 156 children, the mean age was 6.88±2.28 year ranging between 6 months to 12 years while 85 (54.5%) children were aged between 7 to 12 years. There were 90 (57.7%) male and 66 (42.3%) female patients. The mean SOFA score on ICU admission was 14.22±3.41. Table-I is representing baseline demographic characteristics.

Efficacy was seen in 41 (52.6%) in Group-A (epinephrine) versus 18 (23.1%) in Group-B (dopamine), p=0.0001 as shown in Table-II. The overall mean SOFA score after 6 hours of PICU admission was 7.89±3.12. Stratification of efficacy with respect to age, gender and weight in both study groups is shown in Table-III.

Characteristics		Total	Group-A	Group-B	P-Value
Gender	Male	90 (57.6%)	43 (55.1%)	47 (60.2%)	0.5168
	Female	66 (42.4%)	35 (44.9%)	31 (39.8%)	
Age	0.5-6	71 (45.5%)	31 (39.7%)	40 (51.2%)	0.1479
	7-12	85 (54.5%)	47 (60.3%)	38 (48.8%)	
Weight	≤15	78 (50.0%)	34 (43.5%)	44 (56.4%)	0.1093
	>15	78 (50.0%)	44 (56.5%)	34 (43.6%)	

Table-I. Comparison of gender, age and weight in both groups

Group-A received epinephrine; Group-B received dopamine

Efficacy	Groups		P-Value
	A (n=78)	B (n=78)	
Yes	41 (52.5%)	18 (23.0%)	0.0001
No	37 (47.5%)	60 (77.0%)	

Table-II. Comparison of efficacy

Group-A received epinephrine; Group-B received dopamine

Study Variables		Efficacy				P-Value
		Group A (n=78)		Group B (n=78)		
		Yes(41)	No(37)	Yes(18)	No(60)	
Age (years)	0.5-6	14 (45.16%)	17 (54.84%)	11 (27.50%)	29 (72.50%)	0.122
	7-12	27 (57.45%)	20 (42.55%)	07 (18.42%)	31 (81.58%)	0.0003
Gender	Male	26 (60.47%)	17 (29.53%)	12 (25.53%)	35 (74.47%)	0.0008
	Female	15 (42.86%)	20 (57.14%)	06 (19.35%)	25 (80.65%)	0.041
Weight (kg)	≤15	22 (64.71%)	12 (35.29%)	09 (20.45%)	35 (79.55%)	0.0001
	>15	19 (43.18%)	25 (56.82%)	09 (26.47%)	25 (73.53%)	0.127

Table-III. Gender, age, and weight stratification with respect to efficacy (N=156)

Group-A received epinephrine; Group-B received dopamine

DISCUSSION

Dopamine and epinephrine, both are capable of providing vasopressor and inotropic effects.[9] Vasopressors are the vasoactive drugs utilized as the 1st line treatment in septic shock among neonates caused by a reduction in the systemic vascular resistance (SVR).[10,11] It has been recommended in the "Surviving Sepsis Campaign" guidelines 2012 that in fluid-refractory septic shock, the first-line vasoactive agent is dopamine. It acts on dopaminergic and adrenergic receptors as a dose-dependent agonist.[12] Epinephrine is capable of increasing the mean arterial pressure and cardiac output, but in septic shock, an increase in serum lactate and impaired gut perfusion might also be acheived.[13]

Our study showed that efficacy was seen in 52.6% with epinephrine and 23.1% with dopamine (p=0.0001) groups. Ramaswamy KN et al[14] conducted a study and assessed resolution of shock to find that the children who received epinephrine, showed a higher a proportion (41%) against dopamine (13%) within the first hour after

resuscitation (p=0.019), and a similar trend (48.3% versus 29%; p = 0.184) was noted at 6 hours too. The SOFA score on day-3 (8 versus 12; p=0.05) was lower for epinephrine group. Children in both study groups were found to have relatively higher rates of adverse effects ((16% versus 14%; p=0.80) and death rates (58% versus 48%; p=0.605).[14] Ventura et al included 118 patients in their randomized control trial (RCT) to distribute them as 58.5% in the dopamine group and 41.5% in the epinephrine group. Among patients receiving epinephrine, 11 days was the median hospital stay, and it was 13 days for dopamine-receiving patients (p = 0.554), whereas both groups gave an assessment of 4 days (0-81 days) as the median stay in ICU (p=0.748). Mortality rates were 5% and 9% for the epinephrine and dopamine groups, respectively.[15] Our findings confirm that epinephrine should be used as first-line vasoactive therapy in fluid-refractory septic shock in children presenting in PICU in order to decrease the morbidity and mortality. Some researchers have pointed out that the use of dopamine in septic shock is strongly evident in increasing the mortality and adverse events.[16,17] In comparison to epinephrine, a research found that children who got dopamine for paediatric septic shock had a considerably higher fatality rate.[1]

CONCLUSION

This study showed that epinephrine is more effective than dopamine as first-line vasoactive therapy in fluid-refractory septic shock in children aged 6 months to 12 years presenting in PICU.

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2	Asim Khurshid	Study concept, Proof reading.	
3	Imran Maqsood	Drafting, Critical Revisions.	
4	Muhammad Sohail Arshad	Drafting, Literature review.	