Section: Pediatrics

Original Research Article

THE EFFICACY OF DOPAMINE VS ADRENALINE IN PEDIATRIC FLUID REFRACTORY COLD SEPTIC SHOCK IN A TERTIARY CARE HOSPITAL

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Received : 03/12/2023
Received in revised form : 21/01/2024
Accepted : 06/02/2024

Keywords:
Inotrope, Resuscitation, Vasoactive drug, Rapid cardiopulmonary assessment.

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DOI: 10.47009/jamp.2024.6.1.346

Source of Support: Nil,
Conflict of Interest: None declared

Int J Acad Med Pharm
2024; 6 (1); 1752-1757

Abstract

Background: The aim is to compare the efficacy of dopamine (10microgram/kg/min) vs adrenaline (0.2 microgram/kg/min) in fluid refractory cold septic shock. **Materials and Methods:** A double blinded randomized control trial was conducted in the Pediatric Intensive Care Unit (PICU) of MGMGH, over a period of one year (July 2019 to July 2020) The study included 100 children, aged between 1 month to 12 years admitted in PICU who met the criteria for fluid refractory cold septic shock. After randomization, one group received dopamine while the other received adrenaline. After the administration of drug, the children were reassessed at 20 minutes and then at 40 minutes by rapid cardiopulmonary assessment, to assess the response to the inotrope. The collected data were analyzed with chi-Square test. **Result:** Out of all children admitted to the PICU, shock was found to be significantly higher in infants compared to older children. Both genders were found to be nearly equally affected. Among all children who presented with shock, the most frequent system involved was respiratory, followed by central nervous system and abdomen. Of the total study population, 15(30.6%) children in dopamine group and 36(70.6%) in the adrenaline group responded within 20 minutes of drug infusion with a significant P value ($p<0.001$). Of the initial non-responders, 9 responded at 40 min. It was significantly more (60%) in the adrenaline group compared to the dopamine group (0%) with a P value <0.001. **Conclusion:** As the use of adrenaline is associated with earlier resolution of shock along with a dose dependent response compared to dopamine, we recommend the use of adrenaline as the first line inotrope in the management of fluid refractory cold septic shock in children.

INTRODUCTION

Sepsis is recognized to be a significant health care problem worldwide.[1] In India, the leading causes for visit to paediatric outpatient department are infections and fever, while the most common cause for mortality is sepsis. It accounts for nearly 6 million neonatal and childhood deaths a year, amounting to 60-80% of childhood mortality annually.[1] Most of these deaths occur in the early hours of hospitalization.[2]

The definition of sepsis is according to the guidelines recommended by the international sepsis definitions conference.[3] The body's immune response to microbial invasion by the release and activation of inflammatory mediators like cytokines is called Systemic Inflammatory Response Syndrome (SIRS). When SIRS occurs in association with suspected or obvious infection it is called as sepsis. Features of sepsis include fever (>38.5°C) or hypothermia (<36.5°C), tachypnea (Respiratory Rate >2SD above normal), tachycardia (Heart Rate >2SD above normal), leukocytosis (white blood cell count >12000/mm3 or leucopenia (white blood cell count <4000/mm3). Severe sepsis is diagnosed when sepsis is associated with dysfunction of organs distant from the infection site.[3] The cases are managed as per the standard recommendations of paediatric advanced life support / American college of critical care medicine (ACCM).[4,5]

Shock is a syndrome of cardiovascular dysfunction characterized by inability of the circulating system to provide nutrition and oxygen which is required to meet the metabolic demands of the various organs, recognized clinically by inadequate perfusion. Septic shock clinically manifests with signs of organ

hypoperfusion like abnormal heart rate for age, altered capillary refill time(CRT), abrupt change in mental status, diminished or bounding peripheral pulse, mottled cool peripheries, systolic blood pressure < 5th centile for age and urine output of < 1 ml/kg/hr. In cold septic shock, hypoperfusion is manifested as altered mental status, prolonged CRT, mottled cool extremities, diminished peripheral or central pulses and decreased urine output. In warm septic shock, hypoperfusion is manifested as altered mental status, flash CRT, warm extremities, bounding peripheral pulse, decreased urine output with metabolic acidosis or increased lactate. When there is persistence of clinical signs of hypoperfusion despite fluid bolus of 60ml/kg, it is considered as fluid refractory shock. The presence of shock at PICU admission is associated with an increased risk of death.[6]

There are studies that have identified that delayed recognition of septic shock has been associated with adverse clinical outcome.[7-10] As sepsis leads to myocardial dysfunction, children with fluid refractory septic shock are benefited more with an early and aggressive supportive therapy as the use of a potent inotrope.[11-13]

The choice of vasoactive drug used in the initial few minutes of resuscitation of fluid refractory cold septic shock is pivotal to the outcome of the patient. The Surviving Sepsis Campaign 2012 guidelines have recommended dopamine as the first-line vasoactive agent in fluid-refractory septic shock.[14] Treatment for pediatric septic shock in compliance with the Surviving Sepsis Campaign recommendations was not associated with better outcomes compared with children whose initial therapies in the emergency department were administered more slowly. However, all patients were treated rapidly and low morbidity and mortality reported. This underscores the importance of rapid recognition and treatment of septic shock.[15]

Dopamine, dobutamine or epinephrine can be used as first line inotropic support.[4] It is necessary to consider the various available vasoactive drugs, their pharmacological profile, specific advantages, absolute as well as relative contra indications and all known side effects with their use, for arriving at a decision.[14] As of date there are no standard recommendations regarding the initial vasoactive agent to be used for children with fluid refractory septic shock.[16] The choice of the initial vasoactive drug in these cases have till now remained the individual institution's choice. This is due to the fact that there are very few studies conducted worldwide to compare the efficacy of inotropes in such a clinical scenario.[17-19] More studies across the globe are needed to help arrive at a consensus for the same. Hence we decided upon this study as an initial effort to address the unmet need in this regard.

The aim of this study is to compare the efficacy of dopamine vs adrenaline in resolving fluid refractory cold septic shock.

MATERIALS AND METHODS

This double blinded randomized control trial was conducted in the PICU of a tertiary care referral hospital in Tamilnadu, India over a period of one year, from July 2019 to July 2020. Ethical clearance for the study was obtained from the institutional ethical committee [IEC No.44/2019]. Informed written consent was obtained from the parent of the children included in the present trial. Inclusion criteria: The study included children aged 1 month to 12 years admitted in PICU who met the criteria for fluid refractory cold septic shock. The criteria included children who had abnormal heart rate for age, altered mental status, prolonged CRT, mottled cool extremities, diminished peripheral or central pulses, decreased urine output of <1ml/kg/hr and systolic blood pressure <5th centile for the child's age, gender and height even after initial fluid resuscitation with up to 60ml/kg/hr.[4,19,20] The hemodynamic parameters of the study population, suggesting fluid refractory cold septic shock at the time of admission were taken as the baseline parameters. Further clinical improvement following interventions were assessed for these children during the course of the study.

Exclusion Criteria

Children with known cardiac disease and those who had received vasoactive drugs prior to PICU admission were excluded from the study.

Sample Size: During the study period, out of 720 children admitted in the PICU, rapid cardiopulmonary assessment identified 260 children to be in shock. After exclusion, 100 children who met the criteria were included in the study by convenient sampling.

Data Collection: Randomization of the cases was done by computer generated assignment sequence and monitored by a person who was not involved in the trial. Patient case number, hospital record number, patient's age and weight were all entered in the computer. The allocation of the patient to group A (dopamine) or group B(adrenaline)was done using random number generator open available in the link: https://www.gigacalculator.com/calculators/random-number-generator.php.

As per allocation sequence, they were packed in sealed opaque envelopes and serial numbers assigned. Nurse in the PICU was in-charge of all sealed envelopes. Treating paediatrician and the parents did not know about the drug administered in this double blinded trial.

As shown in the CONSORT flow diagram [Figure 1], following randomization one group received dopamine at 10mcg/kg/min while the other received adrenaline at 0.2mcg/kg/min.[17,18] After the administration of drug, the children were reassessed at 20 minutes. All those children whose heart rate became normal for age, mental status normalized, had capillary refill time <2 sec, palpable peripheral pulse, warm extremities, urine output >1ml/kg/hr and

ISSN (O): 2687-5365; ISSN (P): 2753-6556

systolic blood pressure >5th centile were considered to be responders. Others who did not show any significant improvement in the hemodynamic parameters were considered to be non-responders. If there was response to the drug, the same inotrope was continued.[5] If no response noted by rapid cardiopulmonary assessment, the dose of the drug was increased. Dopamine was titrated to 15mcg/kg/min while adrenaline was titrated to 0.3mcg/kg/min and again the children were reassessed 20 minutes after titration to determine the response to the inotrope. The infusion rate of the inotropes were set in such a way that titration of the dose was achieved with increase in the flow rate by 1ml/hr for both the drugs. The criteria for responders and non-responders at 40 minutes reassessment remained the same as for the assessment at 20 minutes. If no response noted at 40 minutes from initiation of the drug, an open label inotrope was added. The choice of the open label inotrope was made based on the blood pressure of the child. Systolic blood pressure <5th centile for the child's age, gender and height was considered as the cut off value for hypotension.[5] Adrenaline was added in cold septic shock while noradrenaline was added in those cases where there was persistent hypotension with wide pulse pressure despite adequate fluid resuscitation and initial inotrope administration, to increase the systemic vascular resistance. The occurrence of shock in the various age groups, its distribution among both the genders, the frequency of different organ systems involved in the study population, response of the study population to the inotropes at the initial dosage (at 20 minutes) and again with increasing dosages (at 40 minutes) were all assessed.

Statistical Analysis: The collected data were analysed with SPSS software 16.0 version. To find the significance of the data, chi-Square test was used. The probability value of <0.05 was considered to be statistically significant.

RESULTS

The distribution of the study population based on age and sex were analysed. It was found that shock was more common in infants, amounting to 41% of the total study population. In the age group of 1 to 5 years, 38(38%) children and in the age group above 5 years, 21(21%) children presented with shock. The occurance of shock in the various age groups was found to be statistically significant (p= 0.034) [Table 1].

On analysing the incidence of shock with regard to the gender, it was found that both genders were nearly equally involved. Statistical significance with regard to sex distribution was not established (P=0.997 [Table 2].

When the frequency of system involved in the children who were suffering from shock was analysed, it revealed that the most common system involved was respiratory 39(39%)followed by CNS 29(29%) and abdomen 21(21%). The occurrence of shock pertaining to the particular organ system did not show any statistical significance [Table 3].

The frequency of symptoms in the study population that included fever 96(96%), breathlessness 41(41%) and seizure 29(29%) were also analysed [Table 4].

After randomization of the study population, it was seen that 51 children received adrenaline while 49 received dopamine.

Of the total study population, 51 showed response to the inotrope within first 20 minutes of administration. On analyzing the initial 51 responders, it was found that 15 of them were from dopamine group while the remaining 36 were from adrenaline group. Thus 30.6% children in dopamine group and 70.6% in the adrenaline group responded within 20 minutes of drug infusion and the P value was found to be significant [Table 5].

Of the initial 49 non responders, 9 showed response at 40 minutes of drug administration while the remaining 40 did not. All the 9 children who responded at 40 minutes of drug administration belonged to the adrenaline group. Thus 0% of the children in dopamine group and 60% in the adrenaline group responded at 40 minutes of drug infusion and the P value was found to be statistically significant [Table 6].

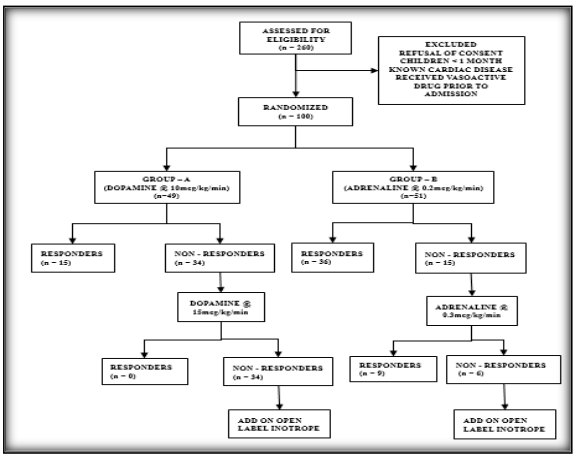

Figure 1: Consort flow diagram

Table 1: Shock occurrence among different age groups

			Group		Total	P-value
			Dopamine	Adrenaline		
Age	1month to 12 months	Count (% within age)	23 (56.1%)	18(43.9%)	41 (100.0%)	0.034
	1-5yr	Count (% within age)	21(55.3%)	17(44.7%)	38 (100.0%)	
	>5yr	Count (% within age)	5(23.8%)	16(76.2%)	21 (100.0%)	
Total		Count (% within age)	49(49.0%)	51(51.0%)	100 (100.0%)	

Chi-Square test was used to find the P value

ISSN (O): 2687-5365; ISSN (P): 2753-6556

Table 2: Shock distribution according to gender

			Group		Total	P value
			Dopamine	Adrenaline		
Sex	F	Count (% within sex)	24(49.0%)	25(51.0%)	49 (100.0%)	0.997
	M	Count (% within sex)	25(49.0%)	26(51.0%)	51 (100.0%)	
Total		Count (% within sex)	49(49.0%)	51(51.0%)	100 (100.0%)	

F-Female
M-Male
Chi-Square test was used to find the P value

Table 3: Shock occurrence pertaining to particular organ system.

			Group		Total	P value
			Dopamine	Adrenaline		
System involved	Abdomen	Count (% within system involved)	12(57.1%)	9(42.9%)	21 (100.0%)	0.029
	CNS	Count (% within system Involved)	9(31.0%)	20(69.0%)	29 (100.0%)	
	RS	Count (% within system involved)	24(61.5%)	15(38.5%)	39 (100.0%)	
	Skin & soft tissue	Count (% within system Involved)	4(57.1%)	3(42.9%)	7 (100.0%)	
	Deep seated infection	Count (% within system involved)	0(0.0%)	4(100.0%)	4 (100.0%)	
Total		Count (% within system involved)	49(49.0%)	51(51.0%)	100 (100.0%)	

CNS-Central nervous system
RS-Respiratory system
Chi-Square test was used to find the P value

Table 4: Frequency of symptoms in the study groups

			Group		Total
			Dopamine	Adrenaline	
Symptom	Fever	Count (% within system involved)	49(51.0%)	47(49.0%)	96 (100.0%)
	Breathlessness	Count (% within system Involved)	26(63.4%)	15(36.6%)	41 (100.0%)
	Seizures	Count (% within system involved)	13(44.8%)	16(55.2%)	29 (100.0%)

Table 5: Group wise response to inotrope within first 20 minutes of administration.

			20MIN		Total	P value
			NR	R		
Group	Dopamine	Count (% within Group)	34 (69.4%)	15 (30.6%)	49 (100.0%)	<0.001
	Adrenaline	Count (% within Group)	15 (29.4%)	36 (70.6%)	51 (100.0%)	
Total		Count (% within Group)	49 (49.0%)	51 (51.0%)	100 (100.0%)	

NR-Non responders
R-Responders
Chi-Square test was used to find the P value

Table 6: Group wise response to inotrope at 40 minutes of administration.

			40MIN		Total	P value
			NR	R		
Group	Dopamine	Count (% within Group)	34 (100.0%)	0 (0.0%)	34 (100.0%)	<0.001
	Adrenaline	Count (% within Group)	6 (40.0%)	9 (60.0%)	15 (100.0%)	
Total		Count (% within Group)	40 (82.0%)	9 (18.0%)	49 (100.0%)	

NR-Non responders
R-Responders
Chi-Square test was used to find the P value

DISCUSSION

WHO in the "Global report on the epidemiology and burden of sepsis. Current evidence, identifying gaps and future directions" has stated that, in the year 2017, almost half (20 million) of all estimated sepsis cases worldwide occurred in children under 5 years of age.[21] The GBD (Global burden of disease, injuries and risk factors) sepsis study has estimated that 41.5% (20.3 million) of incident sepsis cases and 26.4% (2.9 million) deaths related to sepsis worldwide were among children younger than five years and sepsis incidence and mortality in children under one year of age was exceptionally high.[21-23] From our study also we have seen that the incidence of shock is highest among infants amounting to 41% (41/100) of the total study population. One of the largest reported pediatric severe sepsis cohort study conducted by Ruth et al has identified age, cardiovascular comorbidity and organ dysfunction as

ISSN (O): 2687-5365; ISSN (P): 2753-6556

significant individual prognostic factors, where age less than 1 year conferred higher odds of mortality.[24] This is very similar to another recent study conducted by Cruz et al, which states that the majority of pediatric sepsis deaths occur within 48 hours of presentation and specific risk factors for mortality have been identified, where age less than 1 year has higher odds of mortality.[23]

From the current study it is seen that the most frequent primary system involved in the study population is respiratory (39%), which is very similar to a study conducted by Weiss et al, where the incidence of respiratory infection was about 40%.[25]

A meta analysis of randomized controlled studies conducted by Wen et al has found that dopamine and epinephrine show comparable efficacy for the treatment of pediatric or neonatal septic shock.[26] Hence the current trial was conducted in children admitted in our institution to study if adrenaline as a first choice of inotrope was superior to dopamine in significantly improving the outcome of the patient.

From the present study it is seen that a significant proportion of the initial responders to inotrope belonged to the adrenaline group. This is comparable to a study conducted by Ventura et al, where the results showed that dopamine was associated with an increased risk of death (odds ratio 6.5) and healthcare-associated infection (odds ratio 67.7) while early administration of peripheral or intra osseous epinephrine was associated with increased survival in the study population, with a survival odds ratio of 6.49.[17]

While our present study shows that resolution of shock is earlier in the group treated with adrenaline when compared to those treated with dopamine ($p<0.001$), it also shows a dose dependent response to adrenaline unlike dopamine that is statistically significant ($p<0.001$). This is comparable to a double blinded randomized control study conducted by Ramaswamy et al that has also found that epinephrine is more effective than dopamine in achieving resolution of fluid-refractory hypotensive cold shock within the first hour of resuscitation and improving organ functions. Though the number of children in the study who had resolution of shock within 6 hours was more with epinephrine group (48.3%) than dopamine group (29%) it was not statistically significant ($p=0.184$). Also, the study could not establish any statistical significance between the two groups in terms of mortality ($p= 0.605$) or adverse effect ($p=0.80$). There was also no significant difference in the survival analysis of the two groups ($p=0.27$).[18]

In a double blind randomized controlled trial conducted by Baske et al, epinephrine and dopamine were found to have comparable efficacy and safety as a first-line vasoactive drug in management of neonatal septic shock. But on stratified analysis in a limited sample, epinephrine was associated with better outcomes in neonates $\leq$ 306/7 weeks.[27] According to a recent article on "updates of pediatric sepsis" by Cruz et al, adrenaline or noradrenaline are recomnmended as first line vasopressors over dopamine for fluid refractory sepsis.[23] There is also an ongoing pilot multicentre randomized controlled trial that compares the efficacy of early adrenaline administration(after 20ml/kg of fluid resuscitation) over the standard administration of adrenaline(after 40-60ml/kg of fluid resuscitation), advocating the need for further studies in this regard.[28]

Also the use of dopamine as a first line vasoactive drug in the management of septic shock is associated with certain adverse effects as seen from previous studies. An observational study conducted by Sakr et al suggests that dopamine administration may be associated with increased mortality rates in shock.[29] A study by Backer et al showed that the use of dopamine was associated with a greater number of adverse events.[30] Dopamine in a few earlier trials was also shown to be associated with certain endocrine disturbances.[31,32]

Hence it is only prudent to conduct more clinical trials to address the different aspects of the current management protocols to arrive at better treatment strategies with lower adverse effects. The new major recommendation in the 2014 ACCM update is that hemodynamic support of septic shock now be addressed at the institutional level and that each institution implement their own adopted home grown bundles.[4] These clinical trial based knowledge will help us in making the right choice of first line vasoactive drug in our PICU to successfully treat more children in future.

Limitation

Biochemical parameters were not included and organ severity dysfunction scores not assessed. The secondary outcomes like length of PICU stay, morbidities including adverse drug effects and mortality were also not assessed and the children in the study were not followed up beyond the period of the study. As our study was primarily conducted as an institutional initiative to establish a first-line drug protocol for our institution and the drugs used in the study were based on established standard protocols and guidelines, we did not register it in CTRI. The research was conducted under the oversight of the institutional ethical committee to ensure that ethical and methodological standards were met.

CONCLUSION

From the current study it is evident that the use of adrenaline in children with fluid refractory cold septic shock is associated with earlier resolution of shock when compared to dopamine. It is also found that shock is not resolved with higher dose of dopamine whereas with adrenaline there is a dose dependant response. Hence we recommend the use of adrenaline as the first line inotrope in the management of fluid refractory cold septic shock in children. Further studies done on a wider basis with a larger population and longer duration of follow up,

ISSN (O): 2687-5365; ISSN (P): 2753-6556

overcoming the limitations of the current study are needed to establish standard recommendations.

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ISSN (O): 2687-5365; ISSN (P): 2753-6556