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Research Article

Time to Vasoactive Agents Initiation, Restricted Volume Resuscitation Effect on Fluid Balance and Clinical Outcomes in Children with Septic Shock

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ABSTRACT

Background: Several studies have shown that positive fluid balance is associated with worse outcomes in pediatric severe sepsis and septic shock patients. Early vasopressor administration in children with septic shock after ≤ 40 cc/kg of fluid bolus may be beneficial.

Methods: This is a retrospective analytic study in children with septic shock (aged between one month and 18 years from 2012-2020.) They were recruited at a referral tertiary university hospital in Bangkok, Thailand and were treated with either restricted volume resuscitation (≤ 40 cc/kg of fluid bolus) combined with vasopressors or standard volume resuscitation. The clinical effect on fluid balance and other outcomes were measured.

Results: One hundred and forty three patients were diagnosed with septic shock. Ninety three patients started vasoactive agents at ≤ 40 mL/kg (study group) compared to 50 patients who started the vasopressor drugs after 40 mL/kg of fluid bolus (control group). Volume administered at 6 hours, 24 hours and 48 hours in study group was significantly less than control group ($p<0.001$). There was a trend of higher %Fluid Overload (%FO) at 24 hours to 72 hours in control group but it was not statistically significant. %FO at 24 hours was significantly correlated with time initiation of vasoactive agent ($R^2=0.17$, $p=0.03$) and length of PICU stay ($R^2=0.2$, $p=0.02$). In addition, the multivariate analysis showed that initial serum level of albumin was less than 3 g/dL and positive %FO of more than 10% at 24 hours significantly increased mortality by 6.3 (95% CI, 1.25 to 32.12; $p=0.03$) and 6.1 folds (95% CI, 1.47 to 25.46; $p=0.01$), respectively.

Conclusion: There was a trend of decreasing %FO overtime in study group compared to the control group. Time initiation of vasoactive agent and %FO significantly correlated with prolonged PICU stay.

Keywords: Pediatrics; Septic shock; Percentage of fluid overload; Vasoactive agents; Resuscitation; Mortality

INTRODUCTION

Sepsis is a life threatening condition and is one of the leading causes of children mortality. The prevalence of severe sepsis and septic shock among hospitalized children is 1%-26%. The most common causes of death include refractory shock, followed by secondary organ dysfunction. The mortality rate is at 5% in developed countries and up to 35% in developing countries [1]. The hemodynamic resuscitation practice is consistent with the American college of critical care medicine clinical practice parameters for pediatric and neonatal septic shock (ACCM-PALS) guidelines. It demonstrated lower mortality at 8% *vs.* 38% [2]. Initiating early gold directed therapy (control) in the emergency department for treating patients with severe sepsis and septic shock is associated with a significant reduction in hospital mortality and length of stay in the ICU [3,4].

Administering oxygen and fluid bolus at 20 mL/kg to 60 mL/kg is recommended in initial fluid resuscitation. If there is a refractory shock after fluid bolus then inotropic/vasoactive drugs will be initiated. The dose of inotrope/vasoactive drugs would be adjusted according to the vital signs or perfusion pressure as recommended in the recent hemodynamic resuscitation guideline [5]. Septic shock patients have decreased

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the vasomotor tone together with intravascular volume depletion from the loss of fluid into the extravascular space *via* the capillary endothelial dysfunction. Fluid boluses transiently increase the intravascular volume. Subsequently, the volume bolus can lead to extravascular leakage, which interferes with cellular function including kidneys, liver, heart, and lungs. A recent study demonstrated that fluid bolus is associated with increased mortality in African children with severe infection [6]. In addition, the harm of Fluid Overload (FO) was noted in critically ill children, especially in children with septic shock. Additionally, the use of vasoactive could increase venous return and cardiac output without excess extravascular fluid [7].

Multiple studies both in adults and pediatrics showed that more of %FO increased mortality, in contrast, early use of vasoactive agents can decrease the mortality rate. However, the evidence in critically ill children is limited [8-12]. Therefore, this study aimed to investigate whether early use of vasoactive agents (defined as 40 ml/kg fluid resuscitation) as compared to the standard control strategy during pediatric septic shock is associated with reduced cumulative fluid balance and time initiation of vasoactive correrate with clinical outcomes [13,14].

MATERIALS AND METHODS

Study design and setting

This study is a retrospective review of medical records of all septic shock children admitted to the PICU and general ward at King Chulalongkorn Memorial Hospital (KCMH), Bangkok, Thailand from January 2012 to April 2020. This 10 bed PICU was a mixed medical surgical unit in a university affiliated hospital providing medical care at tertiary level. The criteria for PICU admission were endotracheal intubation, need for renal replacement therapy, or need for invasive hemodynamic monitoring. If not compatible with inclusion criteria, patients were admitted to pediatric ordinary wards. This study was registered as clinical trial.

Study population

All pediatric patients aged between one month to 18 years admitted to the PICU with septic shock who received at least one vasoactive agent were enrolled. Those with congenital heart disease with congestive heart failure, chronic kidney disease, and/or signs of volume overload, palliative treatment, and missing data collection were excluded.

Data collection

This study was approved by our ethical committee of King Chulalongkorn Memorial Hospital (KCMH), faculty of medicine, Chulalongkorn university (IRB no. 297/63) and access to medical records was approved by KCMH. Data collected included baseline clinical characteristics, septic shock management, and clinical outcomes. The study population was divided into two groups; the first group was defined as patients receiving vasoactive agents before being administered 40 mL/kg of fluid resuscitation (study group). Another group received vasoactive agents after 40 mL/kg of fluid bolus (control group). The severity scores which comprised Pediatric Risk of Mortality score III (PRISM III) and Pediatric Logistic Organ Dysfunction-2 (PELOD-2) score were collected on the first day of shock. The Vasoactive Inotropic Score (VIS) was collected on the first and second day of treatment. %FO=(total daily input total daily output (L)/admission body weight (kg) × 100 was the calculated data in the outcome [15-17].

The definition of pediatric septic shock was made according to the ACCM-PALS: Suspected infection manifested by hypothermia or hyperthermia, and clinical signs of inadequate tissue perfusion including any of the following:

- Decreased or altered mental status, prolonged capillary refill greater than two seconds, diminished pulses, mottled cool extremities, flash capillary refill, bounding peripheral pulses and wide pulse pressure, and decreased urine output less than 1 mL/kg per hour, or hypotension.
- The vasoactive agents were epinephrine, norepinephrine, dopamine, dobutamine, and milrinone

Statistical analysis

The continuous variables were expressed as the median (Inter Quartile Range: IQR) and percentage for the categorical variables. The differences in the continuous and categorical variables between the two groups were assessed using a Wilcoxon rank sum test and *chi-square* test, or fisher's exact test, respectively. ANOVA multiple comparison test was used to compare continuous variables where appropriate. The Pearson correlation coefficient was used to measure the strength of a linear association between two variables. The cumulative survival rate was calculated by the Kaplan Meier estimator and the log rank test for the comparison between the groups. Cox regression was used to determine the factors associated with death. Multivariate models were developed by adjusting the covariates with $p<0.1$ in the univariate models. Stepwise backward LR was selected for the final model. All reported P values were two sided. The statistical significance was defined as $p<0.05$. Stata version 15.1 (Stata corp., college station, Texas), was used for the analysis.

RESULTS

A total of 144 medical records were reviewed. Ninety three patients received vasoactive agents before completing the initial fluid resuscitation (≤ 40 mL/kg), and 50 patients received vasoactive drugs after 40 mL/kg of fluids bolus. Most patients had a hematologic malignancy as an underlying disease, and the most common source of infection was pneumonia. The patient's baseline clinical characteristics, including age, underlying conditions, disease severity, and treatment are shown in Tables 1 and 2.

Table 1: Baseline clinical characteristics of the patients.

Characteristics	Study group (n=93)	Control group (n=50)	p
Age (years), median (IQR)	5 (1.2-11.7)	1.8 (0.7-6.3)	0.006
Male, n (%)	50 (53.8)	31 (62)	0.34
Underlying disease, n (%)	25 (26.9)	16 (32)	
Hematologic malignancy			0.52
Biliary cirrhosis	9 (9.7)	2 (4)	0.22
Chronic lung disease	17 (18.3)	3 (6)	0.04
Neurological disease	22 (23.7)	9 (18)	0.43
Others[a]	35 (37.6)	19 (38)	0.97
Source of infection, n (%)			0.76
Pneumonia	9 (9.7)	7 (14)	
Blood	13 (14)	6 (12)	
Intra-abdominal	10 (10.8)	9 (18)	
Cather	10 (10.8)	3 (6)	
Urinary tract	9 (9.7)	7 (14)	
Febrile neutropenia	9 (9.7)	7 (14)	
Skin	5 (5.4)	2 (4)	
Others[b]	9 (9.7)	5 (10)	
The identified pathogen, n (%)			0.22
Gram-positive bacteria	7 (7.5)	2 (4)	
Gram negative bacteria	40 (43)	16 (32)	
Fungus	3 (3.2)	1 (2)	
Virus	3 (3.2)	0 (0)	
Unable to identify	40 (43)	31 (62)	
Severity score	5 (2-9)	5 (2-9)	
PRISM III*score, median (IQR)			0.84
PELOD-2 score, median (IQR)	4 (3-6)	4 (2-5)	0.39
Initial laboratory values	9.4 (7.9-11.8)	9.3 (8.1-11.2)	
Hemoglobin (g/dL), median (IQR)			0.62
White blood cell count (103/ul), median (IQR)	9.3 (2.3-18.2)	8.4 (1.2-14.0)	0.44

Platelet count (103/ul), median (IQR)	168 (51-342)	216 (37.7-394)	0.48
Lactate (mmol/L, n=114), median (IQR)	1.7 (1.2-2.8)	1.5 (1-2)	0.2
Albumin (g/dL, n=127), median (IQR)	3.3 (2.9-3.8)	3.5 (3.2-3.9)	0.23

Note: IQR: Interquartile Range; PRISM III: Pediatric Risk of Mortality III; PELOD-2: Pediatric Logistic Organ Dysfunction-2. Others[a] included syndromic, solid organ tumor, thalassemia, hypertension, short bowel syndrome, etc; Others[b] included meningitis or without any source; *: PRISM III score ranged from 0-49, and a higher score indicated a more severe disease.

Table 2: Comparison of treatment administered between the study and control group.

Treatment	Study group (n=93)	Control group (n=50)	p
Time to antibiotic (minutes), median (IQR)	60 (20-105)	45 (30-90)	0.76
Time to vasoactive (hours), median (IQR)	1.5 (1.2-2.8)	3 (1.9-4.7)	<0.001*
Fluid resuscitation	80 (86)	49 (98)	
Normal saline, n (%)			0.02*
Acetar solution, n (%)	7 (7.5)	6 (12)	0.38
Ringer lactate solution, n (%)	7 (7.5)	1 (2)	0.26
5% albumin, n (%)	15 (16.1)	14 (28)	0.09
Packed red cell, n (%)	3 (3.2)	1 (2)	0.67
Platelet concentrate, n (%)	2 (2.2)	3 (6)	0.23
Freeze frozen plasma, n (%)	3 (3.2)	1 (2)	0.68
Fluid administered (mL/kg), median (IQR)	57.8 (47.3-66.7)	77 (70-88.6)	
6 hours			<0.001*
24 hours	136.4 (119-163)	172.3 (150.7-218.1)	<0.001*
48 hours	237.5 (199.2-281.5)	300.8 (256.9-371.3)	<0.001*
Initial vasoactive agent			
Epinephrine, n (%)	21 (22.6)	13 (26)	0.54
Norepinephrine, n (%)	26 (28)	15 (30)	0.7
Dopamine, n (%)	46 (49.5)	22 (44)	0.53
Maximum dose of vasoactive agents	29 (31.2)	17 (34)	
Epinephrine, n (%)			0.43

Dose (mcg/kg/min), median (IQR)	0.1 (0.1-0.3)	0.1 (0.1-0.5)	0.81
Norepinephrine, n (%)	62 (66.7)	33 (66)	0.63
Dose (mcg/kg/min), median (IQR)	0.2 (0.1-0.3)	0.2 (0.1-0.5)	0.46
Dopamine, n (%)	48 (51.1)	22 (44)	0.38
Dose (mcg/kg/min), mean (SD)	12.8 (3.5)	12.4 (3.8)	0.64
Dobutamine, n (%)	12 (12.9)	5 (10)	0.57
Dose (mcg/kg/min), median (IQR)	10 (5-12.5)	10 (10-10)	0.42
Milrinone, n (%)	9 (9.7)	4 (8)	0.59
Dose (mcg/kg/min), median (IQR)	0.3 (0.3-0.5)	0.5 (0.4-0.6)	0.24
VIS score maximum in 24 hours, median (IQR)	15 (10-30)	10 (10-20)	0.53
VIS score at 48 hours (n=101), median (IQR)	10 (8-22)	10 (5-36)	0.83
Hydrocortisone, n (%)	22 (23.7)	10 (20)	0.62
Furosemide used, n (%)	65 (69.9)	29 (58)	0.15

Note: IQR: Interquartile Range; VIS:Vasoactive Inotropic Score; *: $p<0.05$

There was a trend of increased %FO at 24 hours to 72 hours in control group compared to the study group but not statistically significant. In addition, there was a significant correlation of %FO at 24 hrs and time initiation of vasoactive agent (R^2=0.17, p=0.03) and length of PICU stay (R^2=0.2, p=0.02). The other secondary outcomes, e.g., PICU length of stay, ventilator days, 28 days PICU mortality and complications were not different between the two groups. The leading cause of death was multiple organ failure and refractory septic shock (Table 3).

Table 3: Comparison of the clinical outcomes between the study group and control group.

Treatment	Study group (n=93)	Control group (n=50)	p
%FO, mean (SE)			
24 hours (n=142)	4.5 (0.3)	4.7 (0.7)	0.15
48 hours (n=141)	6.3 (0.6)	6.5 (1.1)	0.11
72 hours (n=140)	7.4 (0.7)	8.5 (0.6)	0.09
Admission, n (%)			0.74
ICU	82 (88.2)	45 (90)	
Ward	11 (11.8)	5 (10)	
ICU length of stay (days), median (IQR)	5 (2-10)	4.5 (2-7)	0.2
Ventilator (days), median (IQR)	6.5 (3-14.5)	6 (3-9)	0.32
CRRT, n (%)	5 (5.4)	1 (2)	0.67

CRRT (days), median (IQR)	7 (6-8)	1	NA
ECMO, n (%)	2 (2.2)	0 (0)	0.54
ECMO (day), median (IQR)	8,18	NA	NA
Complication	20 (21.5)	8 (16)	
Pulmonary edema, n (%)			0.43
ARDS, n (%)	8 (8.6)	5 (10)	0.78
Hospital acquired infection, n (%)	36 (38.7)	16 (32)	0.43
Others[a], n (%)	24 (25.8)	9 (18)	0.29
28 days PICU mortality, n (%)	8 (8.6)	2 (4)	0.49
Multiple organ failure, n (%)	6 (6.5)	1 (2)	0.42
Refractory septic shock, n (%)	3 (3.2)	0 (0)	0.55
Others[b], n (%)	3 (3.2)	2 (4)	0.81

Note: IQR: Interquartile Range; ICU: Intensive Care unit; %FO: Fluid Overload; CRRT: Continuous Renal Replacement Therapy; ECMO: Extracorporeal Membrane Oxygenation; ARDS: Acute Respiratory Distress Syndrome; Others[a]: Including pneumothorax, pulmonary hemorrhage, upper GI bleeding, seizure, drug withdrawal, etc; Others[b]: Including massive GI bleeding, heart arrhythmia

Twenty eight day PICU mortality in this study was at 7% (10/144). The PELOD-2 score (≥ 5), maximum VIS score (>15), CRRT, and ECMO requirement significantly increased the rate of mortality. In addition, the multivariate analysis showed that two factors increased mortality: An initial albumin level less than 3 mg/dl (HR, 6.36; 95% CI, 1.25-32.12; p=0.03) and had more than 10% of %FO at 24 hours (HR, 6.1; 95% CI, 1.47-25.46; p=0.01), respectively.

DISCUSSION

Principle findings

This study addressed the important concept of the early use of vasoactive agents with limited amount of fluid resuscitation and fluid balance in children with septic shock. The volume of fluid administration at 6 hours, 24 hours, and 48 hours and time of starting the vasoactive agents was significantly less in the study group. There was no significant difference in fluid balance at 24 hours, 48 hours, and 72 hours after hemodynamic resuscitation between the two groups. However, there was a trend of increasing %FO from 24 hours to 72 hours compared to control group (p=0.09). The increased in %FO had significant correlation with sepsis morbidity. The vasoactive agents were started at the median time of 1.5 (1.2-2.8) hours after the diagnosis of septic shock in the study group compared to 3 (1.9-4.7) in control group. This is quite a delay compared to current SSC recommendation. We also found significant correlation between time initiation of vasoactive agent and %FO at 24 hours and length of PICU stay. This demonstrates the importance of appropriate volume requirement and timely initiation of vasoactive agent during sepsis resuscitation.

The %FO was one of the key factors related to the sepsis outcomes, following hemodynamic resuscitation as shown in this study. Positive %FO by more than 10% at 24 hours was statistically associated with mortality. Furthermore, the early use of 5% of albumin as the third choice of fluid resuscitation was observed more in control group compared with the study group (14/50 (28%), 15/93 (16%), p=0.09). The early use of albumin solution may result in better control of fluid balance. Several studies previously demonstrated the beneficial effect of albumin administration in sepsis resuscitation. The use of albumin could maintain the intravascular fluid for a longer period than using crystalloid. Furthermore, it will assist in the early achievement of the negative fluid balance, potentially reserving renal function in critical patients and can reduce sepsis mortality [18-20]. We found that the %FO was not statistically different between the two groups although there was a higher trend in the control group. This may explain why we did not find the significant difference in %FO and other clinical outcomes between the two groups.

The high %FO in the sepsis patients was shown to have worse outcomes in multiple studies. Recent studies including our previous study demonstrated that a cumulative %FO was associated with increased mortality and decreased inotropic free day [21,22]. Another study in sepsis children found that a %FO greater than 20% had higher mortality [23]. A recent systematic review and meta-analysis of severe sepsis in adult septic shock showed that a high %FO had a 70% increased risk of mortality [24]. In addition, we found that initial serum albumin level<3

mg/dL and higher initial PELOD-2 score were related to mortality. Initial serum albumin is a nutritional biomarker often found to be low in the acute phase of sepsis and can represent the severity of fluid leakage [25]. A previous study also showed that hypoalbuminemia (<3.5 g/dL) in sepsis, severe sepsis, and the septic shock groups had a significantly higher rate of mortality [26].

The SSC recommends applying vasoactive agent within the first hour when fluid administration is not sufficient to achieve the hemodynamic resuscitation goals. However, recent evidence showed the benefit of starting vasoactive agents early before the full completion of fluid resuscitation in adult septic shock [27]. Our study demonstrated a significant correlation in time initiation of vasoactive agent and %FO at 24 hours and prolonged PICU stay. A previous study of early norepinephrine showed a decreased positive fluid balance at 24 hours and ventilator days with no significant change in shock resolution or mortality [28]. Because multiple vasoactive/inotropic agents are currently used in the hemodynamic treatment of pediatric septic shock, the difference in utilization could affect the outcomes. Early administration of peripheral or intraosseous epinephrine was associated with increased survival in contrast with dopamine that was associated with an increased risk of death and healthcare-associated infection [29]. A resolution of shock was achieved in groups receiving epinephrine within the first hour which was faster than dopamine in fluid refractory septic shock [30]. A large randomized controlled trial of adult sepsis (CENSER) demonstrated that the early use of norepinephrine can increase shock control by six hours [31]. We found that using initial epinephrine or norepinephrine significantly reduced the time to shock reversal by 32.7 h (95% CI, -58.28 to -7.21; p=0.01) and 5/10 (50%) of our mortality case prescribed dopamine as initial vasoactive agent. It was our common practice to use dopamine as the first line drug before we recently changed to the use of either epinephrine or norepinephrine. Therefore, the type of vasoactive drugs used may affect the overall outcomes. Nevertheless, this study did not decide to compare the differences in clinical outcomes of using different types of vasoactive agents.

There are a few studies that previously explored the clinical impact of hemodynamic resuscitation in children with sepsis. This is the first study to investigate the possible clinical effect of limited fluid resuscitation combined with early use of vasoactive drugs. However, this study was a retrospective single center with limited enrolled subjects. Thus, further large prospective and well controlled studies will give a better insight into pediatric septic shock resuscitation.

CONCLUSION

Strength and limitations

The early use of vasoactive agents and limited fluid resuscitation showed a trend of improving %FO compared to control. Shorter time of vasoactive initiation is significantly correlated with less %FO at 24 hours and PICU stay. The high %FO in children with sepsis at first 24 hours was related with mortality. Controlling fluid balanced post resuscitation is an important factor associated with improving the outcomes.

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