Early Goal-Directed Therapy in Pediatric Septic Shock: Comparison of Outcomes "With" and "Without" Intermittent Superior Venacaval Oxygen Saturation Monitoring: A Prospective Cohort Study

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Objective: To evaluate the effect of intermittent central venous oxygen saturation monitoring ($Scvo_2$) on critical outcomes in children with septic shock, as continuous monitoring may not be feasible in most resource-restricted settings.

Design: Prospective cohort study.

Setting: PICU of a tertiary care teaching hospital.

Patients: Consecutive children younger than 17 years with fluid refractory septic shock admitted to our ICU from November 2010 to October 2012 were included.

Interventions: Enrolled children were subjected to subclavian/internal jugular catheter insertion. Those in whom it was successful formed the "exposed" group ($Scvo_2$ group), whereas the rest constituted the control group (no $Scvo_2$ group). In the former group, intermittent $Scvo_2$ monitoring at 1, 3, and 6 hours was used to guide resuscitation, whereas in the latter, only clinical variables were used.

Measurements and Main Results: The major outcomes were in-hospital mortality and achievement of therapeutic goals within first 6 hours. One hundred twenty children were enrolled in the study–63 in the $Scvo_2$ group and 57 in the no $Scvo_2$ group. Baseline characteristics including the organ dysfunction and mortality risk scores were comparable between the groups. Children in the $Scvo_2$ group had significantly lower in-hospital mortality (33.3% vs 54%; relative risk, 0.61; 95% CI, 0.4, 0.93; number needed to treat, 5; 95% CI, 3, 27). A greater proportion of children in exposed group achieved therapeutic endpoints in first 6 hours (43% vs 23%, $p = 0.02$) and during entire ICU stay (71% vs 51%, $p = 0.02$). The mean number of dysfunctional organs was also significantly lesser in $Scvo_2$ group in comparison with no $Scvo_2$ group (2 vs 3, $p < 0.001$).

Conclusion: Early goal-directed therapy using intermittent $Scvo_2$ monitoring seemed to reduce the mortality rates and improved organ dysfunction in children with septic shock as compared with those without such monitoring. (*Pediatr Crit Care Med* 2014; XX:00–00)

Key Words: early goal-directed therapy; Pediatric Logistic Organ Dysfunction Scores; $Scvo_2$; septic shock; therapeutic goals

Despite advances in understanding of the pathophysiology of septic shock in the last two decades, mortality due to severe sepsis in children is reported to be 10–13% in the developed countries (1, 2). The corresponding figures are higher in units from resource-restricted countries where it may vary anywhere from 18% to 24% in most units (3, 4), but it may even reach proportions as high as 34–58% in few others (5, 6). Although factors such as delayed recognition and treatment and suboptimal transport system may be partly responsible for the increased illness severity and poor outcomes (7, 8), inadequate/inappropriate fluid and vasoactive therapy and delay in instituting supportive care even after admission may further worsen the outcomes. Instituting a comprehensive bundle of care at admission that ensures optimal fluid and vasoactive support therefore becomes equally important. One such strategy that has shown to improve outcomes in adults with septic shock is the "early goal-directed therapy" or EGDT as it is popularly known as (9–13). From the time of publication of the first study on EGDT by Rivers et al (9) in 2001, 19 before-and-after adult studies have reexamined and validated one or more components of EGDT and

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showed outcome benefit of almost 20% in terms of mortality and cost worldwide (14). EGDT when implemented saved one additional out of every six patients treated.

EGDT strategy has been extrapolated to management of pediatric septic shock as well (15–18). However, few clinical studies exist to prove or disprove its efficacy in children (19–22). There is only one randomized controlled trial on EGDT till date in children with septic shock (19). The authors of this study found reduction in in-hospital mortality rates by almost 70% in those undergoing continuous "superior venacaval oxygen saturation" ($Scvo_2$) monitoring as compared with those without $Scvo_2$ (no $Scvo_2$) monitoring. Other observational studies have evaluated one or more components of the EGDT approach in a prospective or retrospective manner and have found encouraging results too. Although one study (20) showed fluid volumes in excess of 40 mL/kg in first hour to be associated with improved outcomes, in another study (21), the authors observed that early reversal of septic shock by community physicians improved the mortality rates of children presenting to the emergency department of their tertiary care hospital. The third study (22) was on the physiology of fluid refractory septic shock in children, and this formed the basis of the current inotrope and vasoactive therapy recommendations in warm and cold shock in children.

The EGDT protocol advocates continuous monitoring of $Scvo_2$ as an additional resuscitation target apart from other hemodynamic variables in patients with septic shock. However, continuous or even intermittent monitoring of $Scvo_2$ may not be feasible in most units from resource-restricted countries. Also, there are no studies in children till date evaluating effect of intermittent $Scvo_2$ monitoring on mortality in children with septic shock. Therefore, we decided to evaluate if a simplified protocol using intermittent monitoring of $Scvo_2$ in the golden hours would have the same impact on critical outcomes in children with septic shock in these settings.

With the recent reports of unequivocal advantage of continuous monitoring of $Scvo_2$ in adults and children with septic shock as compared with no monitoring, we decided against conducting a randomized controlled trial as it was unethical to deprive children of this important monitoring tool. Instead, we chose to conduct a cohort study in which children would be "naturally selected" into one of the groups based on whether superior vena cava catheter insertion was successful in them or not.

MATERIALS AND METHODS

Design and Setting

This was a prospective cohort study conducted over a period of 2 years (November 2010–October 2012) in children younger than 17 years with fluid refractory septic shock in a tertiary care unit of a developing country. Our ICU is a well-equipped 10-bedded ICU with facilities for continuous hemodynamic monitoring, mechanical ventilation, total parenteral nutrition, and an in-house arterial blood gas machine. We also have bedside echocardiography and ultrasound facilities available.

Participants

All children with features of septic shock as per definitions given by the international consensus conference on pediatric sepsis were screened for eligibility (**Appendix 1**, Supplemental Digital Content 1, http://links.lww.com/PCC/A89) (23–28). Of these, children who did not respond to initial fluid resuscitation of up to 60 mL/kg of isotonic crystalloid/colloid bolus administered in the first hour of resuscitation were eligible for enrollment. We excluded those with contraindication to central venous catheter (CVC) insertion, primary cardiac illness, severe malnutrition (Appendix 1, Supplemental Digital Content 1, http://links.lww.com/PCC/A89), and failure to comply with the protocol in the first hour of resuscitation of septic shock. The eligible children were enrolled after obtaining informed consent from one of the parents. The enrolled children were subjected to subclavian/internal jugular catheter insertion. Those children in whom it was successful formed the exposed or $Scvo_2$ group. The remaining formed the unexposed or no $Scvo_2$ group; a femoral catheter was inserted in all such cases. The study was approved by the institutional ethics committee.

Objectives and Outcome Measures

Our primary objective was to examine if using intermittent $Scvo_2$-guided therapy in comparison with no $Scvo_2$–guided therapy results in 1) reduction of in-hospital mortality in children with fluid refractory septic shock and 2) higher proportion of patients achieving the predetermined therapeutic endpoints. The therapeutic goals included achieving a normal heart rate; appropriate-for-age mean arterial pressure (MAP) measured noninvasively (18); normal pulses with no difference between peripheral and central pulses; warm extremities; capillary refill time less than 2 seconds; normal mental status; urine output more than or equal to 1 mL/kg/hr; a decreasing trend in serum lactate from the time of admission (hyperlactatemia was defined as arterial lactate value of ≥ 1.6 mmol/L, based on our laboratory cutoff of 0.5–1.6 mmol/L); and a central venous pressure (CVP) of 8–12 mm Hg (16, 17). CVP was measured intermittently using indwelling CVC and a pressure manometer manually (Romsons International, Noida, India). The size used for subclavian/internal jugular vein catheterization was 5F for infants and children and 7F for adolescents. For femoral venous catheterization, Cavafix MT (B Braun, Mumbai, India) 18 gauge/32 cm length was used for infants and children and 14 gauge/32 cm length catheter was used for adolescents. Attaining a $Scvo_2$ of more than or equal to 70% was an additional target in the $Scvo_2$ group. Our secondary objectives were to evaluate if such therapy affected the time to achievement of resuscitation endpoints, Pediatric Logistic Organ Dysfunction (PELOD) score, number of dysfunctional organs, inotrope score (Appendix 1, Supplemental Digital Content 1, http://links.lww.com/PCC/A89), need for fluid boluses during first 6 hours, need for mechanical ventilation, need for blood products, duration of mechanical ventilation, and duration of ICU stay.

Methods

Before the start of the study (mid-2010), the EGDT protocol was introduced in the unit and the residents were trained to

insert subclavian/internal jugular catheters and follow a protocolized approach to the management of septic shock in children. Once the protocol was put into place and compliance with the protocol improved to above 90%, the study was started.

During the study period, children in both groups were managed as per the study protocols (adapted from study by Rivers et al [9]) during the first 6 hours of admission with the only difference being intermittent $Scvo_2$ monitoring at 1, 3, and 6 hours after initiation of therapy in $Scvo_2$ group patients (**Fig. 1**). All children received three boluses of normal saline at admission with careful monitoring for features of fluid overload such as liver size and basal crackles. After the initial fluid resuscitation, if the children continued to show evidence of hypoperfusion or were hypotensive, a central catheter was inserted into the subclavian/jugular vein ($Scvo_2$ group) or femoral vein (no $Scvo_2$ group). In the $Scvo_2$ group, we first titrated fluids and vasoactive agents to achieve the target CVP and MAP. Once this was achieved, we estimated the $Scvo_2$ at 1, 3, and 6 hours. If the first hour $Scvo_2$ was less than or equal to 70%, we looked at the hematocrit. If it was less than or equal to 30%, we transfused packed RBCs. If the $Scvo_2$ or the lactate values were abnormal (≤ 70% and > 1.6 mmol/L, respectively) and the packed cell volume (PCV) was more than 30%, we gave an additional fluid bolus of 20 mL/kg depending on CVP and started dobutamine provided the patient was normotensive. If the patient was hypotensive and had abnormal $Scvo_2$ or lactate, after the fluid bolus, we started low-dose epinephrine at 0.05 µg/kg/min and increased it till we achieved the target MAP. Once the target MAP was achieved, we once again assessed the $Scvo_2$ and lactate at 3 hours. If the $Scvo_2$ or the lactate continued to be abnormal, we gave another fluid bolus of 20 mL/kg depending on the CVP and added dobutamine to the regime and increased it depending on the clinical response and the $Scvo_2$/lactate values. The choice of inotropes/vasopressors in this group was dependent on both the $Scvo_2$ and/or lactate values and the clinical type of shock. Blood transfusion was dependent solely on PCV values; transfusion was given if the PCV was less than or equal to 30% whether the $Scvo_2$ was low or not.

In the other group (no $Scvo_2$ group) also, we first titrated fluids and vasoactive agents to achieve the target CVP and MAP. Once this was achieved, we estimated the lactate levels and PCV. If the first hour lactate was elevated, we looked at the hematocrit. If it was less than or equal to 30%, we transfused packed RBCs. If not, we gave an additional fluid bolus of 20 mL/kg of normal saline depending on the CVP and started dobutamine provided the patient was normotensive. If the patient was hypotensive and had abnormal lactate, after the fluid bolus, we started low-dose epinephrine at 0.05 µg/kg/min and increased it till we achieved the target MAP. After the first hour, however, we followed the trend in lactate levels in each patient to decide further escalation of doses or addition of other agents. If there was no improvement or there was worsening, we escalated the doses of the vasopressors/inotropes or gave additional fluid bolus of 20 mL/kg depending on the CVP. If there was

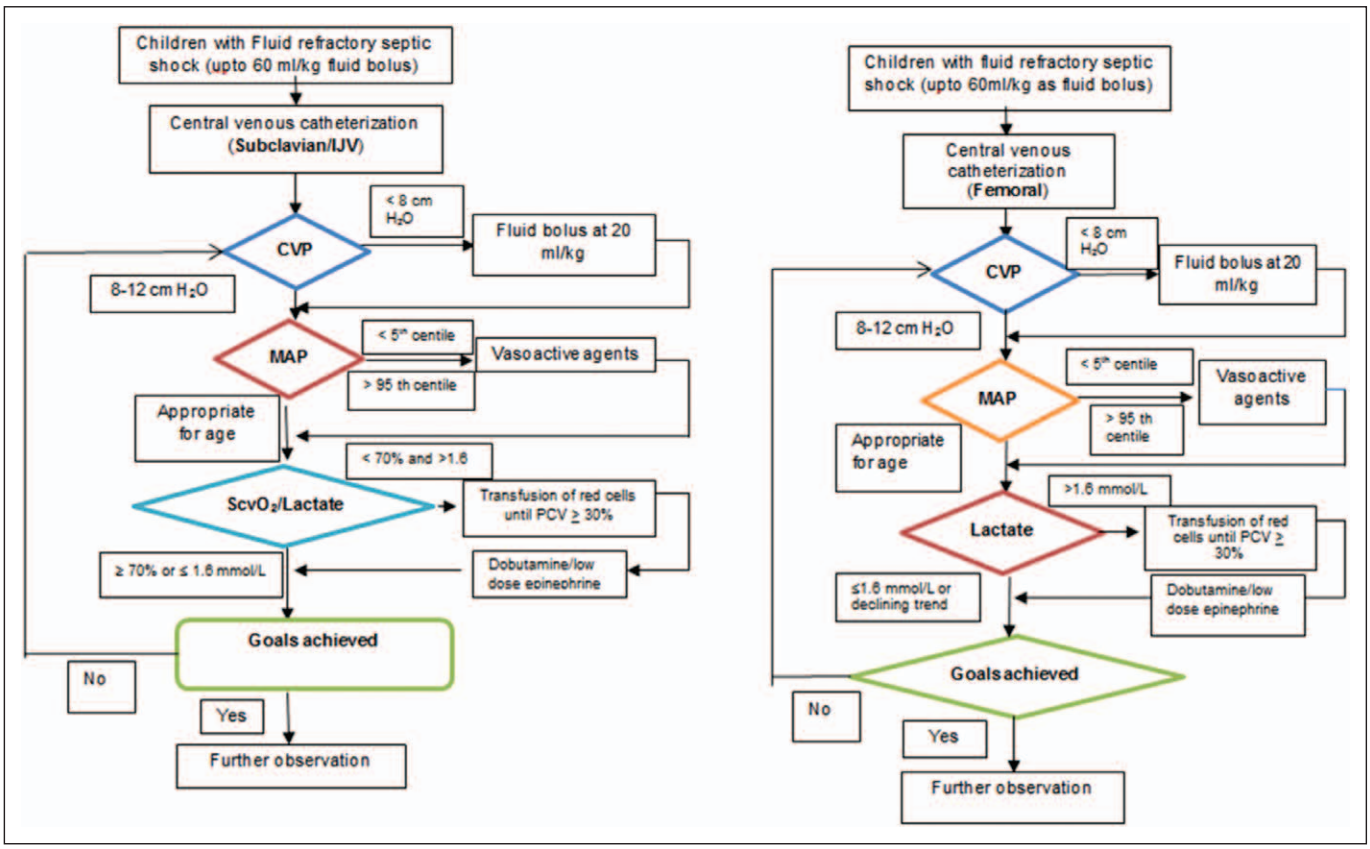

Figure 1. Study protocol in superior vena cava oxygen saturation ($Scvo_2$) group and no $Scvo_2$ group. CVP = central venous pressure, MAP = Mean arterial pressure, PCV = packed cell volume. *Therapeutic goals, goals; lactate values are provided in units of mmol/L.

improvement but the levels were elevated, we based our decisions on more than one clinical variable to administer further fluid boluses or inotropes/vasopressors. In this group also, the decision to transfuse red cells was based on the PCV values. In both the groups, the choice of inotropes/vasopressors for warm shock was dopamine and norepinephrine, and for cold shock, it was dobutamine, epinephrine, and/or vasopressin depending on the MAP of the patient.

The choice of fluid for administering further boluses (after the initial hour) was normal saline in those without evidence of ongoing fluid loss (diarrhea and vomiting). In those with ongoing losses, we used degraded gelatin polymers (Haemaccel) as 20 mL/kg boluses, instead of normal saline. In addition, children in both groups were started on appropriate antibiotics based on the patient's age, focus of infection, and likely organisms and their known susceptibility pattern (after taking cultures) during the first hour, and any electrolyte or blood glucose disturbances were corrected.

Subsequently, the vasoactive agents, inotropes, and RBC transfusion were titrated to attain or maintain the "therapeutic goals" in both groups till the shock improved or the patient died. All the patients were monitored continuously for the above therapeutic goals and for all other clinically important variables till discharge or death.

Data Collection

Data regarding the demographic characteristics, clinical features, clinical course, and investigations were recorded on a daily basis by the principal investigator in a predesigned proforma designed for the purpose of the study. Admission Pediatric Index of Mortality (PIM) (Appendix 1, Supplemental Digital Content 1, http://links.lww.com/PCC/A89), PELOD score, and number of dysfunctional organs were noted for all children at admission. The $Scvo_2$ values were obtained by analyzing venous blood samples drawn from the subclavian catheter (position of which was confirmed by chest radiograph within 30 min of insertion; in 57 of the 63 cases, the catheter tip was in the right atrium initially which was then corrected by withdrawing the appropriate length of the catheter out) using basic blood gas analyzer ABL 800 (Radiometer, Copenhagen, Germany). Arterial lactate and central venous oxygen saturation values were obtained at inclusion and then every 3 hours thereafter till 6 hours and then 6 hourly in both groups. Blood culture and other relevant microbiology investigations were obtained in all patients.

Sample Size Estimation

The mortality rate in children with fluid refractory septic shock in our unit over 1 year before the start of the study was 65%. Assuming a two-sided type I error rate of 5% and a power of 80%, a sample size of 57 in each group was required to detect a 40% relative reduction (i.e., to a mortality rate of 40%) of in-hospital mortality in the study group.

Statistical Analysis

Data were entered into Microsoft Excel 2007 and analyzed using Stata 11 (Stata Corp, College Station, TX). Categorical data are presented as number (%), whereas continuous variables are presented as mean (SD), if normally distributed and median (interquartile range), if skewed. Statistical analysis was performed using Student *t* test/Wilcoxon rank-sum test and chi-square test for continuous and categorical variables, respectively. We calculated the relative risk (RR)/mean difference with 95% CI for all the outcomes. In addition, we performed time-to-event analysis using Kaplan-Meier survival estimates followed by Cox proportional hazard model, with dependent variable being in-hospital mortality and the independent variable being the group, to estimate the hazard ratio (HR) for the primary outcome. *p* value of less than 0.05 was considered significant.

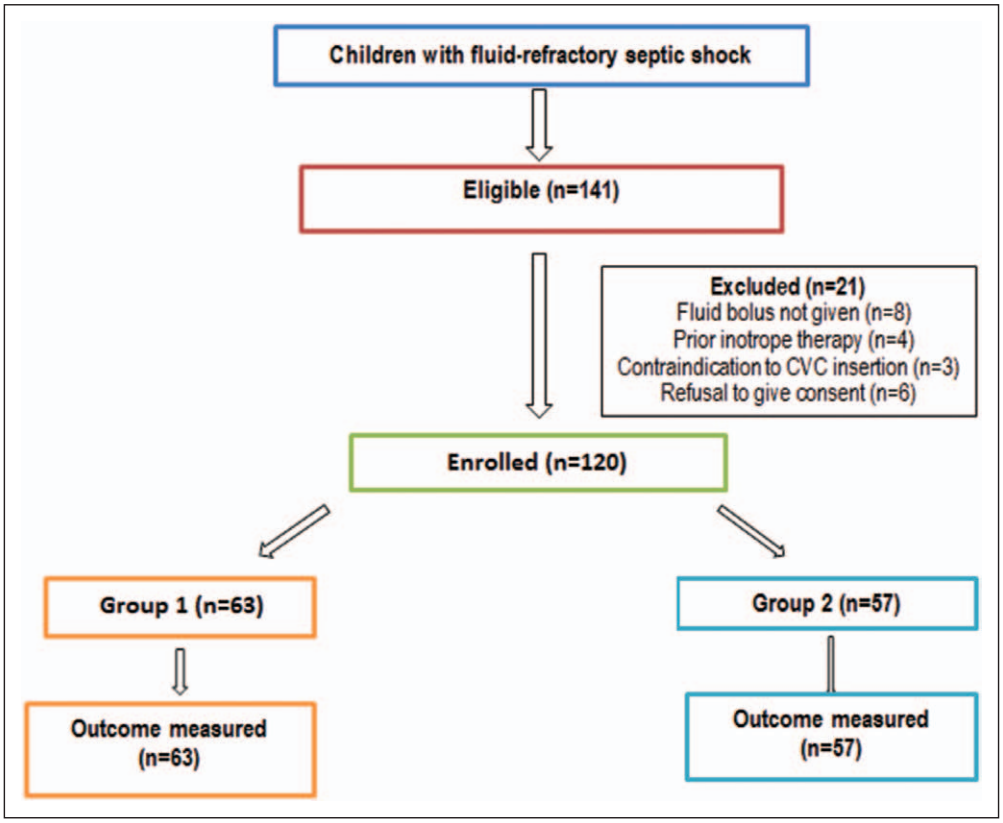

Figure 2. Study flow chart. CVC = central venous catheterization.

RESULTS

Of a total of 591 admissions during the study period, 141 children (24%) had fluid

TABLE 1. Baseline Characteristics of the Two Study Groups

Variable	$Scvo_2$ Group ($n = 63$)	No $Scvo_2$ Group ($n = 57$)	p
Age	6 (1.2, 12)	5 (1, 10)	0.22
Male gender	32 (51)	31 (54)	0.71
Pediatric Index of Mortality score (predicted probability of death %)	77 (51, 89)	75 (43, 91)	0.24
Pediatric Logistic Organ Dysfunction score at admission	11 (11, 21)	12 (11, 21)	0.51
No. of dysfunctional organs at admission (multiple organ dysfunction syndrome)	2 (2, 3)	2 (2, 3)	0.92
Patient transferred from			0.47
Emergency department	51 (81)	43 (75)	
Ward	12 (19)	14 (25)	
Prior antibiotic therapy	40 (63.5)	35 (61)	0.81
Days of antibiotic therapy	3.8 (1.9)	3.4 (1.8)	0.19
Source of infection			0.12
Pneumonia	20 (32)	16 (28)	
Meningitis	18 (29)	21 (37)	
Abdominal infection	10 (16)	8 (14)	
Skin and soft-tissue infection	2 (3)	0	
Tuberculosis	4 (6)	4 (7)	
Malaria	2 (3)	5 (9)	
Septicaemia without focus	7 (12)	3 (5)	
Clinical and laboratory findings			
Heart rate (beats/min)[a]	137 (27)	137 (26)	0.9
Respiratory rate[a]	36 (15)	36.7 (15)	0.8
Mean arterial pressure (mm Hg)[a]	61 (14)	58 (15)	0.24
Central venous pressure (cm H_2O)[b]	9.5 (6, 13)	10 (8, 15)	0.16
Capillary refill time (s)[a]	3.4 (1)	3 (3, 4)	0.8
Glasgow Coma Scale[a]	10.8 (3.6)	10.2 (3.6)	0.3
Lactate in mmol/L[b,c]	1.6 (0.9, 5.2)	3.2 (1.3, 4.5)	0.45
pH[a]	7.34 (0.14)	7.22 (0.9)	0.28
HCO_3 in mmol/L[a]	18.1 (5)	17.5 (5.5)	0.5
Superior vena cava saturation (%)[a]	67.5 (13)	–	–
Proportion with $Scvo_2 \leq 70\%$[a]	43 (68)	–	–
Spo_2 (%)[a]	96 (4)	95 (10)	0.8
Hemoglobin (gm/dL)[a]	9 (2.5)	9.1 (2.2)	0.7
Total leukocyte count (per mm^3)[b]	11,700 (8,000, 18,000)	11,000 (8,000, 18,200)	0.8
C-reactive protein (semiquantitative, positive 6 mg/L)	46 (73)	40 (70)	0.73
Blood-culture positive	23 (37)	19 (33)	0.72
Organisms isolated	23 (37)	19 (33)	0.72
Escherichia coli	3 (4.7)	4 (7)	

(*Continued*)

TABLE 1. (*Continued*). Baseline Characteristics of the Two Study Groups

Variable	$Scvo_2$ Group ($n = 63$)	No $Scvo_2$ Group ($n = 57$)	p
Klebsiella pneumoniae	4 (6.3)	4 (7)	
Pseudomonas aeruginosa	0	1 (1.7)	
Haemophilus influenzae	4 (6.3)	2 (3.5)	
Acinetobacter baumannii	2 (3)	1 (1.7)	
Enterococcus viridans	1 (1.6)	1 (1.7)	
Streptococcus pneumoniae	5 (8)	3 (5)	
Staphylococcus aureus	4 (6.3)	3 (5)	
Type of shock			0.7
Cold shock	54 (86)	50 (87.7)	
Warm shock	9 (14)	7 (12.3)	

$Scvo_2$ = superior vena cava oxygen saturation.

Dashes indicate values are available for the $Scvo_2$ group only.

[a]Mean (SD).

[b]Median (interquartile range).

[c]Lactate could be estimated in 41 and 48 cases only in the $Scvo_2$ and no $Scvo_2$ groups, respectively.

Data are presented as number (proportion). Pediatric Logistic Organ Dysfunction score includes a total of 12 variables for six key organ dysfunctions (cardiovascular, respiratory, hematologic, neurologic, renal, and hepatic HCO_3). Multiple organ dysfunction syndrome (MODS) is defined as simultaneous occurrence of two or more organ dysfunctions. Organ systems typically included in the diagnostic criteria of pediatric MODS are cardiovascular, pulmonary, neurologic, hematologic, renal, hepatic, and gastrointestinal.

refractory septic shock. Of these, 21 were excluded as per prespecified exclusion criteria (**Fig. 2**). Of the 120 enrolled children, 63 were in $Scvo_2$ group and 57 in no $Scvo_2$ group. The reasons for failure of subclavian/IJV catheter insertion in the no $Scvo_2$ group patients were primarily failure to insert the catheter in 54 patients and parental refusal for subclavian/IJV catheter insertion in nine patients. There were no complications related to placement of central catheter such as hemo/pneumothorax in either group.

The baseline characteristics including median age, gender, primary diagnosis, PIM, PELOD scores, and number of dysfunctional organs at admission were comparable between the groups (**Table 1**). The most common focus of infection in the overall study population was the lung (36, 30%) followed by brain (39, 32.5%) and abdomen (18, 15%). Majority of the children were transferred from the emergency department (94, 78%). About one third of the patients (35%) had culture-positive sepsis in both the groups. The most common Gram-negative organisms isolated were *Escherichia coli*, Klebsiella, Pseudomonas, *Haemophilus influenzae*, whereas the common Gram-positive organisms were *Streptococcus pneumoniae* and *Staphylococcus aureus* (Table 1).

Primary Outcomes

The overall in-hospital mortality rate of the study population was 43% (52). The mortality was significantly different between the two groups—children in the $Scvo_2$ group had 39% lower risk of mortality than those in the no $Scvo_2$ group (33.3% vs 54%; RR = 0.61; 95% CI, 0.4, 0.93). The number needed to treat was 5 (95% CI, 3, 27).

The proportion of children attaining therapeutic endpoints during either the first 6 hours of admission or during PICU stay was also significantly greater in the $Scvo_2$ group (43% vs 23% and 71% vs 51%) (**Table 2**). On Cox proportional hazard analysis, the instantaneous risk of mortality was found to be significantly lower in the exposed group (HR = 0.48; 95% CI, 0.27, 0.8; $p = 0.01$) (**Fig. 3**).

Secondary Outcomes

The time to achieve therapeutic endpoints was not significantly different between the two groups in the children who attained the endpoints during ICU stay. The mean inotrope score and the need for ventilation, dialysis, or RBCs were also not different between the groups. The PELOD score and the median number of dysfunctional organs at 24 hours were, however, significantly lower in the $Scvo_2$ group (**Table 2**).

Hemodynamic Variables and Administered Treatments

There was no difference in the physiological variables like heart rate, MAP, and CVP between the two groups at any time point in the first 6 hours (**Table 3**). The mean $Scvo_2$ increased from 68% to 72% by 3 hours and to 74% by 6 hours in the $Scvo_2$ group. The median lactate values improved from 1.6 to 1.2 mmol/L and from 3.2 to 2.1 mmol/L in the $Scvo_2$ and no $Scvo_2$ groups, respectively ($p \geq 0.05$ between the two groups at all three time points).

On comparing the treatment administered between the two groups, we found that the proportion of children who received dobutamine in the first 6 hours was significantly greater in the $Scvo_2$ group (85% vs 70%; $p = 0.04$) (**Table 3**). The proportion

TABLE 2. Primary and Secondary Outcomes of the Study Population

Variable	Study Group ($n = 63$)	Comparison Group ($n = 57$)	Relative Risk/Mean Difference (95% CI)	p
Primary outcomes				
1.Mortality	21 (33.3)	31 (54)	**0.61 (0.4, 0.93)**	**0.02**
2.Proportion of children attaining all therapeutic endpoints in first 6 hr	27 (43)	13 (23)	**1.88 (1.08, 3.28)**	**0.02**
3.Proportion of children attaining all therapeutic endpoints during ICU stay	45 (71)	29 (51)	**1.4 (1.04, 1.89)**	**0.021**
4.Proportion of children attaining normal $Scvo_2$ values by 6 hr	27(43)	–		
5.Proportion of children showing declining trend in lactate levels by the end of first 6 hr (data available for 43 and 48 patients, respectively)	29 (67)	16 (33)	**2 (1.3, 3.1)**	**0.001**
Secondary outcomes				
1.Time to achievement of therapeutic endpoints[a,b]	6 (5, 48)	24 (6, 72)	–	0.39
2.Inotrope score[c]	390 (176)	408 (187)	−18 (−84, 48)	0.59
3.Need for mechanical ventilation	39 (62)	38 (67)	0.93 (0.71, 1.21)	0.59
4.Need for dialysis	8 (13)	3 (5)	2.4 (0.67, 8.7)	0.16
5.Need for packed RBCs	25 (40)	28 (49)	0.81 (0.54, 1.21)	0.30
6.Pediatric Logistic Organ Dysfunction score at 24 hr[b]	11 (1, 21)	20 (11, 22)	–	**0.02**
7.No. of dysfunctional organs at 24 hr[b]	2 (2, 3)	3 (2, 3)	–	**< 0.001**

$Scvo_2$ = superior venacaval oxygen saturation.
Dashes indicate values are available for the $Scvo_2$ group only. Values in boldface font indicate that the p values were significant for these outcomes.
[a]Data available for 45 and 29 children, respectively, in the two groups.
[b]Data are presented as median (interquartile range).
[c]Data are presented as mean (SD).
Data are presented as number (proportion).

who received dopamine was slightly lower in this group. Even though the lactate values were used to guide therapy in the no $Scvo_2$ group, the proportion of children requiring dobutamine was not as high as in the $Scvo_2$ group. After 6 hours, fewer children in the $Scvo_2$ group required addition of one or more inotropes to the existing inotrope regime as compared with the no $Scvo_2$ group (37% vs 60%; $p = 0.01$) (Table 3). There were no significant differences between the two groups in terms of need for additional fluids in mL/kg, in the number of colloid boluses (other than blood), in the time of administration of first dose of antibiotics, in the number of units of RBCs transfused, in the duration of administration of initial fluid boluses, mechanical ventilation, inotrope therapy, or PICU stay (Table 3). The median duration of hospitalization was, however, lower in the $Scvo_2$ group (6 vs 10 d; $p = 0.05$).

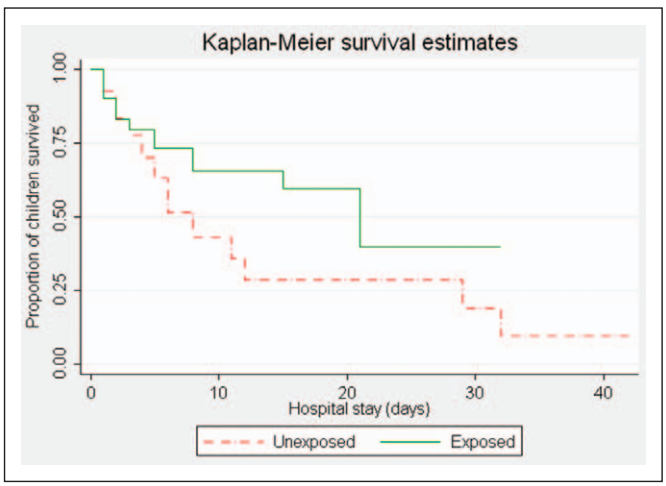

Figure 3. Kaplan-Meier survival estimates of patients undergoing 'intermittent $Scvo_2$ monitoring' versus 'no $Scvo_2$' monitoring.

The predominant causes of death in the study population were refractory shock, raised intracranial pressure, refractory hypoxemia, and tachyarrhythmia (**Table 3**). Twenty children (32%) in the $Scvo_2$ group and 21 (37%) in the no $Scvo_2$ group received steroids, whereas only one child in the $Scvo_2$ group was given IV immunoglobulin. Steroids were administered in cases refractory to maximal recommended doses of second-line agents, such as epinephrine, norepinephrine, and vasopressin. None of the children were on steroids at the time of admission.

TABLE 3. Comparison of the Hemodynamic Variables and Treatment Details of the Two Study Groups

Variable	$Scvo_2$ Group ($n = 63$)	No $Scvo_2$ Group ($n = 57$)	p
Clinical course			
Heart rate[a]			
1 hr	139 (27)	136 (26)	0.5
3 hr	136 (25)	132 (32)	0.31
6 hr	133 (27)	131 (29)	0.5
Mean arterial pressure[a]			
1 hr	62 (13)	59 (12)	0.20
3 hr	66.5 (13.6)	65.1 (12)	0.55
6 hr	67.1 (15)	69.6 (15.7)	0.39
Central venous pressure[b]			
1 hr	9.5 (6, 13)	10 (8, 15)	0.13
3 hr	10 (8.5, 12)	10 (9, 13)	0.62
6 hr	10 (9, 12)	11 (9, 12)	0.31
$Scvo_2$[a]			
1 hr	67.5 (13)	–	–
3 hr	72 (10)	–	
6 hr	74 (8)	–	
Lactate[b]			
1 hr	1.6 (0.9, 5.2)	3.2 (1.3, 4.5)	0.45
3 hr	1.4 (0.9, 3.8)	2.7 (1.2, 3.8)	0.27
6 hr	1.2 (0.9, 3.3)	2.1 (1.1, 3.1)	0.18
Base deficit[b]			
1 hr	6.8 (3.1, 9.8)	7.1 (3.5, 11)	0.5
3 hr	5.8 (3.2, 8.5)	6 (3.2, 9.6)	0.73
6 hr	5.4 (2.5, 8.4)	5 (2.9, 9.6)	0.85
Treatment details			
Need for boluses in first 6 hr	15 (24)	11 (19)	0.44
Total fluids received in first 6 hr in mL/kg[a]	78 (15)	77 (16)	0.95
No. of colloid boluses (other than blood products) in first 6 hr (median, range)	0 (0–2)	0 (0–1)	0.37
No. of units of RBCs transfused	0 (0, 1)	0 (0, 1)	0.3
Cumulative fluid balance after dialysis[d] (mL/kg)	22 (–22, 42)	35 (30, 40)	0.45
Need for dopamine in first 6 hr	53 (84)	54 (95)	0.06
Need for dobutamine in first 6 hr	54 (85)	40 (70)	**0.04**
Need for epinephrine in first 6 hr	10 (16)	10 (18)	0.8
Need for additional inotropes after 6 hr	23 (37)	34 (60)	**0.01**
Time of administration of first dose of antimicrobials (min)[a]	25 (12)	22 (11)	0.16
Duration of administration of three boluses (min)[a]	37.4 (13)	37 (16)	0.9

(*Continued*)

TABLE 3. (*Continued*). Comparison of the Hemodynamic Variables and Treatment Details of the Two Study Groups

Variable	$Scvo_2$ Group ($n = 63$)	No $Scvo_2$ Group ($n = 57$)	p
Duration of mechanical ventilation[e,b]	72 (24, 120)	72 (48, 120)	0.59
Duration of inotrope therapy[b]	72 (48, 144)	85 (43, 120)	0.73
Duration of PICU stay[b]	5 (3, 7)	7.5 (3, 12)	0.1
Duration of hospitalization[b]	6 (4, 12)	10 (5, 14)	0.05
Cause of death			
Refractory shock	11 (52)	16 (52)	0.17
Raised increased intracranial pressure	4 (19)	8 (26)	0.18
Refractory hypoxemia	4 (19)	6 (19)	0.43
Tachyarrhythmia	2 (10)	1 (3.2)	0.67

$Scvo_2$ = superior venacaval oxygen saturation.

Values in boldface font indicate that the p values were significant for these outcomes.

[a]Data are presented as mean (SD).

[b]Data are presented as median (interquartile range).

[d]Negative sign indicates fluid removed; otherwise it indicates fluid retained by the patient.

[e]Number ventilated were 39 and 38 in $Scvo_2$ and no $Scvo_2$ groups, respectively.

Data are represented as number (proportion) unless otherwise indicated. Total fluids include normal saline/Haemaccel boluses and blood products received in first 6 hr after admission.

DISCUSSION

We found that EGDT with intermittent $Scvo_2$ monitoring resulted in relative reduction in mortality by 39% when compared with that with no $Scvo_2$ monitoring. The proportion of patients achieving therapeutic goals in first 6 hours was also higher in the $Scvo_2$ group (44% vs 23%) (**Table 2**). The results are in accordance with that of the previous two studies—Rivers et al (9) reported 40% reduction in risk of mortality (56.8% vs 42.3%; odds ratio, 0.60; 95% CI, 0.36, 0.98) in adults, whereas de Oliveira et al (19) reported 70% reduction (11.8% vs 39.2%) in children with septic shock. This was despite the fact that $Scvo_2$ monitoring was only "intermittent" in our study compared with the above two studies in which it was "continuous."

The benefits of $Scvo_2$ monitoring continued to extend beyond the first 6 hours with almost 70% of $Scvo_2$ group patients attaining therapeutic endpoints during their hospital course as compared with only 50% in the other group. The possible reason for improved outcomes could be the early identification of "cryptic shock" using "$Scvo_2$ values" and instituting measures to correct this (29). This may have led to restoration of microcirculation and organ tissue perfusion, which are the two major goals of resuscitation of patients with septic shock (9, 14, 16, 17).

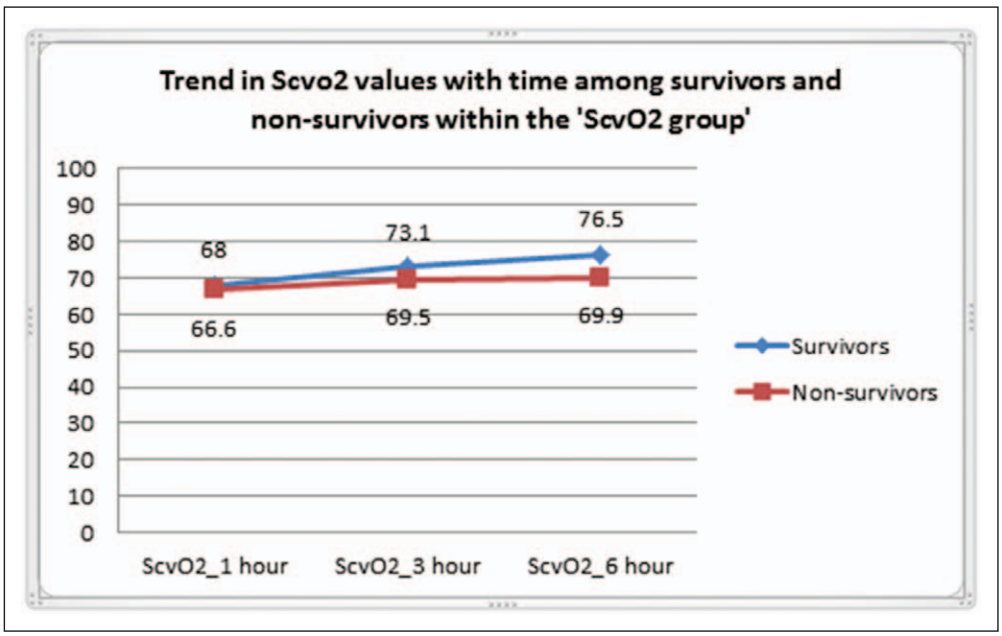

Figure 4. Trend in $Scvo_2$ values with time among survivors and non-survivors within the $Scvo_2$ group.

Can we ascribe the mortality benefit observed in our study to use of $Scvo_2$ alone? There is an ongoing debate among researchers as to which of the component(s) is most important in the EGDT bundle and several researchers are of the opinion that the success of EGDT is due to early recognition and timely care (9–11, 16–19, 22, 30, 31). Although we agree that the timing and bundling of care is central to improving outcomes, the mortality benefit observed in the "$Scvo_2$ group" underscores the importance of $Scvo_2$ monitoring to guide the ongoing treatment

in children with septic shock. The fact that among the 47% children who presented with low $Scvo_2$ at admission, only those in whom the $Scvo_2$ normalized in the first 6 hours survived clearly emphasizes the role of $Scvo_2$ monitoring (**Fig. 4**). The findings in our study are somewhat supported by similar studies in adults in which the authors observed that of all sepsis treatment elements, failure to reach a $Scvo_2$ more than or equal to 70% within first 6 hours had the only significant impact on survival (10). At the cellular level, it has been observed that tissue hypoxia (low $Scvo_2$) significantly correlated with activity of inflammatory mediators (32). Thus, $Scvo_2$ adds to the clinicians' judgment regarding circulatory adequacy as it integrates both global oxygen supply and demand.

Optimizing $Scvo_2$ requires optimization of all the three, that is, preload, afterload, and contractility, which are essentially the resuscitation targets in any patient with shock. Several studies and a meta-analysis have demonstrated that lack of rapid restoration of adequate microcirculation triggers a cascade of inflammation and disseminated microthrombosis for which no effective treatment is available at present (16, 33). Inadequate early resuscitation results in multiple organ system failure and in death days to weeks after the initial presentation. On the other hand, aggressive resuscitation efforts that begin early and are guided by an objective variable of tissue perfusion, such as $Scvo_2$, may probably help avoid triggering the inflammation cascade and thereby the progression of organ failure (16, 30–33). We observed that the PELOD score and the number of dysfunctional organs improved in the $Scvo_2$ group with time as compared with the other group, where it continued to be same or worse.

Effect of Intermittent $Scvo_2$ Monitoring on Administered Treatments

Similar to observations made in previous studies on EGDT, we observed that inotrope requirement especially that of dobutamine was higher in the $Scvo_2$ group in first 6 hours (9, 19). On the other hand, the need for additional inotropes increased in the no $Scvo_2$ group after the first 6 hours with the cumulative inotrope score being higher in this group as compared with the $Scvo_2$ group during the entire hospital course. Inotropes were started earlier in EGDT group even when clinical variables were apparently normal. In contrast, reliance on only clinical variables and failure to detect metabolic derangements in the no $Scvo_2$ group probably led to delayed starting of inotropes and subsequent greater requirement of inotropes after the first 6 hours. In both the study by Rivers et al (9) and de Oliveira et al (19), the transfusion requirement of patients in the $Scvo_2$ group was higher than that in the control group. Although we used similar thresholds for transfusion in our study, we did not find any difference in transfusion requirements between the two groups. This could be because proportion of children with low PCV was almost similar in both groups at admission and need for transfusion was therefore similar.

Strengths and Limitations

Ours is the first study in children to validate "intermittent monitoring" of $Scvo_2$ in patients with septic shock and we used non-co-oximetric blood gas estimation method for $Scvo_2$ estimation. Only one previous study in adult patients had compared intermittent versus continuous monitoring in adults with septic shock, and the authors found continuous monitoring to be better (published only as conference proceeding) (34). Given that most units from developing countries are not likely to have co-oximeters, our study findings would be more generalizable to these units.

The major limitation of our study is that it was a cohort study in which the selection bias cannot be entirely ruled out. Although the baseline characteristics of the study children were not significantly different between the two groups, the imbalance between the groups cannot be completely ruled out.

CONCLUSION

To conclude, EGDT using intermittent $Scvo_2$ monitoring seemed to reduce the mortality rates and improved organ dysfunction in children with septic shock.

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