RESEARCH PAPER

Early Goal-Directed Therapy With and Without Intermittent Superior Vena Cava Oxygen Saturation Monitoring in Pediatric Septic Shock: *A Randomized Controlled Trial*

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Objective: To compare early goal-directed therapy (EGDT) 'with' and 'without' intermittent superior vena cava oxygen saturation ($ScvO_2$) monitoring in pediatric septic shock.

Design: Open label randomized controlled trial.

Setting: Pediatric intensive care unit in a tertiary care center.

Participants: Children aged 1 month to 12 year with septic shock.

Intervention: Patients not responding to fluid resuscitation (up to 40 mL/kg) were randomized to EGDT 'with' (*n*=59) and 'without' (*n*=61) $ScvO_2$ groups. Resuscitation was guided by $ScvO_2$ monitoring at 1-hour, 3-hour, and later on six-hourly in the 'with' $ScvO_2$ group, and by clinical variables in the 'without' $ScvO_2$ group.

Outcome: Primary outcome was all-cause 28-day mortality. Secondary outcomes were time to and proportion of patients achieving therapeutic endpoints (at 6 hours and PICU stay), need for organ supports, new organ dysfunction (at 24 hours and PICU stay), and length of PICU and hospital stay.

Results: The study was stopped after interim analysis due to lower mortality in the intervention group. There was significantly lower all-cause 28-day mortality in EGDT with $ScvO_2$ than without $ScvO_2$ group [37.3% vs. 57.5%, adjusted hazard ratio 0.57, 95%CI 0.33 to 0.97, *P*=0.04]. Therapeutic endpoints were achieved early in 'with' $ScvO_2$ group [mean (SD) 3.6 (1.6) vs. 4.2 (1.6) h, *P*=0.03]. Organ dysfunction by sequential organ assessment score during PICU stay was lower in 'with' $ScvO_2$ group [median (IQR) 5 (2,11) vs. 8 (3,13); *P*=0.03]. There was no significant difference in other secondary outcomes.

Conclusion: EGDT with intermittent $ScvO_2$ monitoring was associated with reduced mortality and improved organ dysfunction in pediatric septic shock.

Keywords: *Mortality, Organ dysfunction, Septic shock.*

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Worldwide, sepsis in children is a significant cause of mortality [1,2]. Despite the understanding of septic shock and novel therapeutic strategies, the mortality rate is reported up to 20% in high-income and 57% in low-middle income countries (LMICs) [3-5]. The pediatric septic shock guideline has been extrapolated from adult studies, but significant pathophysiological differences exist bet-ween adults and children [6]. Early goal-directed therapy (EGDT) has been reported to be associated with reduced mortality in adult septic shock [7]. EGDT approach involves adjustments in cardiac preload, after-load, and contractility to balance oxygen supply with oxygen demand [6,7]. Hemodynamic assessment based on clinical findings, central venous pressure (CVP), and urine output may fail to detect persistent global tissue hypoxia [7].

Superior vena cava oxygen saturation ($ScvO_2$) is a surrogate marker of cardiac index, and it is one of the targets to be achieved during hemodynamic stabilization [7]. Few studies examined the role of $ScvO_2$ monitoring in pediatric septic shock [4,5]. However, there are constraints in adopting EGDT in LMICs, despite the recommendation of surviving sepsis campaign [4]. There are significant differences in the organizational structure of critical care and demographic characteristics between high and LMIC.

Editorial Commentary: Pages1117-18

Limited studies in pediatric septic shock reported a favorable outcome in EGDT [5,8]. The crucial need to reduce septic shock mortality, and the paucity of high-quality controlled studies in children warrants examining the role of EGDT in LMICs [9]. Hence, this study was conducted to compare EGDT with and without intermittent $ScvO_2$ monitoring in pediatric septic shock and its effect on all-cause 28-day mortality.

METHODS

This open-label randomized controlled trial was conducted

in the pediatric intensive care unit (PICU) of a tertiary care center from September, 2015 to June, 2019. The study was approved by the institutional ethics committee and written informed consent was obtained from parents/caregivers. Children aged 1 month to 12 years diagnosed with septic shock and who continued to have impaired perfusion despite fluid bolus (up to 40 mL/kg) within the first hour of resuscitation were included in the study. Septic shock, sepsis, and organ dysfunction were defined as per the international pediatric sepsis consensus conference [10]. Fluid bolus was discontinued, if clinical signs of fluid overload (hepatomegaly, basal lung crepitation) developed. Children with contraindication to insertion of a central venous catheter (CVC), cardiac disease, severe malnutrition, and referred with a CVC in-situ and/or already received more than 6 hours of care were excluded.

Computer-generated block randomization with a variable size of blocks was generated by a person not directly involved in the study. Individual assignments were kept in serially numbered, opaque sealed envelopes (SNOSE). The investigator opened the envelopes, and eligible patients were enrolled sequentially. The study intervention was not blinded because of the nature of the interventions. However, the person handling the data and the statistician were blinded for treatment assignment during the analysis. The assignment was disclosed after finalizing the first draft of the results.

Before starting the trial, we conducted multiple discussion sessions among investigators, resident doctors, and nursing staff about the nature of the trial, its components, and how EGDT had to be delivered. The basic concept of EGDT was adopted from Rivers, et al. [7], and the concept of without $ScvO_2$ monitoring was adopted from Sankar, et al. [5]. Supplemental oxygen and mechanical ventilation were administered based on clinical need. CVC was inserted in all patients in the internal jugular vein by study investigators. A 5Fr CVC was used for infants and younger children and 7Fr for older children. The CVC tip position was confirmed at the junction of the superior vena cava and right atrium by ultrasound and *X*-ray. $ScvO_2$ values were analyzed using a blood gas analyzer with a co-oximetry module (Cobas b221 blood gas system, Roche Diagnostics). Values of $ScvO_2$ were recorded in both groups, but they were not used to guide treatment in EGDT the without $ScvO_2$ group.

In EGDT with $ScvO_2$ group, resuscitation was carried out as per the protocol (**Web Fig. 1a**). After achieving target CVP and mean arterial blood pressure (MABP) by fluid and vasoactive drugs, the $ScvO_2$ ≥70% was targeted and estimated at enrollment, 1, 3, and every 6-hourly. Epinephrine was the initial choice for cold shock and nor-epinephrine for a warm shock. Packed red blood cells (PRBC) was transfused when ScvO2 was <70%, and hematocrit was ≤30% during the first hour of resuscitation. If $ScvO_2$ remained <70% even after PRBC transfusion, dobutamine was started and titrated according to hemodynamic parameters. In EGDT without $ScvO_2$ group, resuscitation was carried out as per the protocol (**Web Fig. 1b***)*. After achieving target CVP and MABP by fluids and vasoactive drugs, the arterial lactate level was targeted to <1.6 mmol/L. If the arterial lactate was ≥1.6 mmol/L, PRBCs and inotropic support were provided. Lactate values were obtained at enrollment, 1 hour, 3-hour, and then every 6-hourly. In both groups, the additional choice of vasopressor, inotropic agents, and fluid bolus was decided according to the hemodynamic parameters, CVP, $ScvO_2$/lactate values, and type of shock. The therapeutic endpoints of septic shock were defined as capillary refill of ≤2 second, normal blood pressure for age, normal pulses with no differential between peripheral and central pulses, warm extremities, urine output ≥1 mL/kg/hour, normal mental status (without sedation), arterial lactate <1.6 mmol/L or decreasing trend and $ScvO_2$ saturation ≥70% [5,11]. The only difference between the two groups was that the $ScvO_2$ ≥70% was the final therapeutic endpoint in EGDT with $ScvO_2$ group, whereas $ScvO_2$ was not used as a therapeutic endpoint in the without $ScvO_2$ group. The standby extracorporeal membrane oxygenation (ECMO) service was not available in our unit. After achieving the therapeutic endpoints, patients were monitored and if any worsening occurred, the protocol was repeated as per the assigned group. Details of hourly hemodynamic parameters, investigations and interventions were noted in a predesigned proforma.

Our primary outcome was all-cause 28-day mortality. Secondary outcomes were time to and proportion of patients who achieved therapeutic endpoints (at 6-hour and PICU stay), need for organ supports (mechanical ventilation, vasoactive support, and renal replacement therapy-RRT), new organ dysfunctions (at 24-hour and PICU stay by sequential organ failure assessment score-SOFA, Pediatric Logistic Organ Dysfunction-(PeLOD) score, and length of PICU and hospital stay.

Unpublished data from our center from January – December 2014 and Sankar, et al. [5] reported a 55% mortality rate in the EGDT without $ScvO_2$ group and 30% mortality 'with' $ScvO_2$ group [5]. With the assumption of 25% absolute risk reduction in the intervention group and 95% power, alpha error of 5%, we calculated the sample size of 110 in each group (total of 220), including a 10% attrition rate (nQuery Advisor+nTerim 3.0). These results assumed that two sequential tests at equally spaced intervals were made. The study progression was monitored by the

independent data monitoring and ethics committee. An independent statistician who was also a physician analyzed the data in a blinded manner. The trial had to be stopped after an interim analysis of 120 patients contended lower mortality in the intervention group. The power of the study decreased from 95% to 80% with a two-sided alpha error of 5% after the planned interim analysis.

Statistical analysis: Data was analyzed according to the assigned group (intention to treat analysis). Kolmogorov-Smirnov *Z*-test was used to check the distribution of data. Normally distributed continuous data were compared by Student *t*-test and by Mann-Whitney U test if skewed data. Chi-square test or Fisher exact test were used for analyzing qualitative data. Kaplan-Meier survival estimates with log-rank test was used for time to event analysis. Cox proportional hazard analysis was done to adjust the predefined variables (age, sex, shock type-compensated/ hypotensive). Relative risk and hazard ratio with 95%CI were calculated as necessary. The general linear model-repeated measures analysis of variance (RM-ANOVA) was performed to compare the trends of the first 72-hour of hemodynamic and laboratory variables in the study groups. The missing values in the data (amounting to 9.8%) during the RM-ANOVA analysis were handled using the last observation carried forward (LOCF) method. All the tests were two-tailed, and a *P* value <0.05 was considered statistically significant. IBM SPSS version 20.0 (SPSS Inc.) and Epi Info 7 (7.0.9.7, CDC) were used for data analysis.

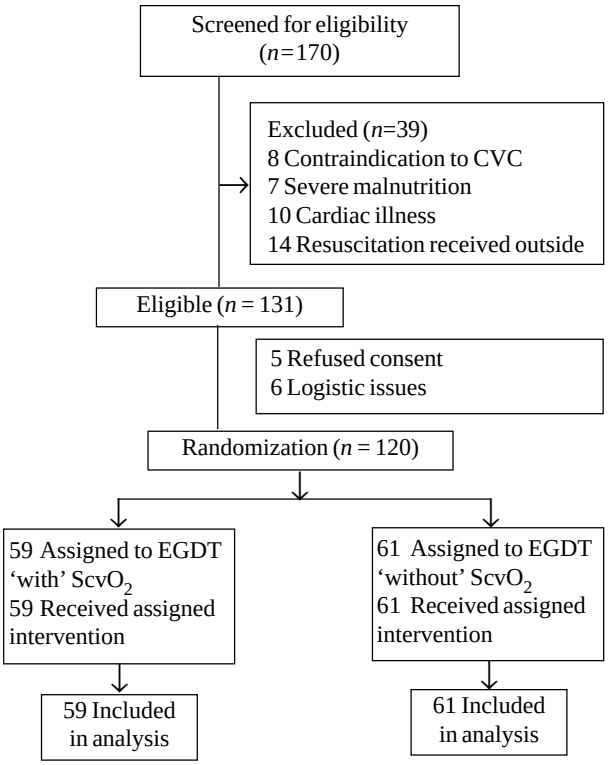
RESULTS

Of the 131 eligible children screened, 120 were randomized and analyzed (59 in 'with' $ScvO_2$ group and 61 in 'without' $ScvO_2$) (**Fig. 1)**. No protocol violation was noted. Baseline characteristics of both the groups are shown in **Table I**. The most common focus of infection was pulmonary (*n*=67, 55.8%), followed by bloodstream infections (*n*=20, 16.7%). Culture were positive in 34 (28.3%) patients, and the most common gram-negative and gram-positive organisms isolated were *Pseudomonas aeruginosa* (31.4%) and *Staphylococcus aureus* (14.3%), respectively. A significantly higher number of children received dobutamine in the EGDT with $ScvO_2$ group (61% vs. 33%, *P*=0.002); no significant difference was seen in the need for other interventions (**Table II**).

The overall all-cause 28-day mortality rate was 47.5% (*n*=57). EGDT with $ScvO_2$ group had 20.1% absolute reduction in all-cause 28-day mortality which was significant than EGDT without $ScvO_2$ group [37.3%, *n*=22 vs. 57.4%, *n*=35; RR (95%CI) 0.66 (0.45-0.97); *P*=0.028] and adjusted hazard ratio 0.57 (0.33-0.97), *P*=0.038] (**Table III** and **Fig. 2**). The number needed to treat was 5 (2.7-38.6). In EGDT with $ScvO_2$ group, the mean time to achieve all therapeutic endpoints at 6-hour (*P*=0.035) and the SOFA score calculated daily (24 hrs) (*P*=0.039) was significantly lower than the without $ScvO_2$ group. No significant difference was noted in other secondary outcomes (**Table III**). Seven patients had minor bleeding at the site of CVC placement (3 with $ScVO_2$ and 4 without $ScvO_2$ groups). No serious complications occurred like significant bleeding, air leak, or other CVC-related complications.

DISCUSSION

In our study, EGDT with intermittent $ScvO_2$ guided management in pediatric septic shock was associated with 20.1% absolute reduction of all-cause 28-day mortality than without $ScvO_2$ monitoring. Both the mean time to achieve all therapeutic endpoints at 6 hours, and the SOFA score were significantly lower in EGDT with $ScvO_2$ group. $ScvO_2$ is a surrogate marker of oxygen utilization at the tissue level. Hence, targeting $ScvO_2$ ≥70% ensures adequate microcirculation and organ perfusion [5-8]. American College of Critical Medicine (ACCM) guidelines emphasized using $ScvO_2$ ≥70% as a therapeutic endpoint in pediatric and neonatal septic shock [6].



CVC-central venous catheter, EGDT-early goal directed therapy, $ScvO_2$-superior vena cava oxygen saturation.

Fig. 1 Study flow chart.

Table I Baseline Characteristics of the Study Participants

Characteristics	*EGDT (with ScvO2) group (n=59)*	*EGDT (without ScvO2) group (n=61)*
Age, mo[a]	12 (7-39)	12 (4-54)
Males	31 (52.5)	29 (47.5)
PRISM III[a]	17 (13 - 21)	16 (13 - 23)
PeLOD[a]	12 (8 - 24)	16 (11 - 23)
SOFA[a]	8 (5 - 13)	9 (6 - 13)
Transferred from		
Pediatric emergency	42 (71)	43 (71)
Pediatric ward	10 (17)	13 (21.3)
Others	7 (12)	5 (8.2)
Prior antibiotic therapy	27 (46)	33 (54)
Focus of infection		
Lung (pneumonia)	34 (57.6)	33 (54.1)
Bloodstream infection	8 (13.6)	12 (19.7)
Abdominal infection	6 (10.2)	6 (9.8)
Skin and musculoskeletal infection	6 (10.2)	5 (8.2)
Central nervous system infection	2 (3.4)	1 (1.6)
Renal system infection	1 (1.7)	1 (1.6)
Without focus	2 (3.4)	3 (4.9)
Cold shock	54 (91.5)	53 (87)
Warm shock	5 (8.5)	8 (13)
Hypotensive shock	38 (64.4)	41 (67.2)
Compensated shock	21 (35.6)	20 (32.8)
Clinical and laboratory parameters		
Mean arterial blood pressure, mmHg[b]	52 (13)	49 (13)
Central venous pressure, cmH2O[b]	8.3 (2)	8.3 (1.9)
Hemoglobin, gm/dL[b]	8.7 (2.1)	9 (2.1)
Hematocrit, %[b]	26.2 (6.4)	26.8 (6.5)
Lactate, mmol/L[b]	4.6 (3.1)	4.6 (2.9)
ScvO2, %[b]	66.3 (10.4)	64.7 (10.8)
ScvO2 <70%	43 (73)	46 (75.4)
ScvO2 among patient with <70%[b]	61.4 (6.5)	60.2 (7.4)
Culture positive	18 (31)	16 (26.2)

Values presented as no. (%) except [a]median (IQR) or [b]mean (SD). EGDT-early goal-directed therapy, $ScvO_2$-superior vena cava oxygen saturation, PRISM-pediatric risk of mortality, PeLOD-pediatric logistic organ dysfunction, SOFA-sequential organ failure assessment.

Table II Treatment and Hemodynamic Variables in the Two Study Groups During the First 72 Hours

Parameter	*EGDT (with ScvO2) group (n=59)*	*EGDT (without ScvO2) group (n=61)*
Time to first antimicrobial dose, min[a]	24 (12)	22 (11)
Bolus received, mL/kg[b]	64.8 (27.1)	65.4 (29.9)
Need for colloids	5 (8.3)	9 (14.8)
Need for any vasopressor	55 (93.2)	57 (93.4)
Need for dobutamine[c]	36 (61)	20 (33)
Need for milrinone	10 (17)	5 (8.2)
Inotropic score[b]	23.3 (1.8)	22.7 (1.8)
Vasoactive-Inotropic score[b]	35.6 (3.7)	37.4 (3.6)
Need for PRBC	33 (56)	24 (39.3)
PRBC transfused, mL/kg[a]	19.2 (7.7)	18.4 (10.7)
Need for FFP	7 (11.9)	9 (14.8)
Need for platelet concentration	10 (17)	11 (18)
Received steroid	26 (44.1)	29 (47.5)
Fluid balance (%FO)[a]	0.70 (0.50)	0.74 (0.39)
Mean arterial blood pressure[a]	57.3 (1.6)	57.3 (1.6)
Central venous pressure, cmH_2O[b]	8.7 (0.2)	8.9 (0.2)
$ScvO_2$ (%)[b]	70.4 (1.5)	65.1 (1.5)
Lactate, mmol/L[b]	4.1 (0.6)	4.6 (0.6)
Delta-lactate at 6h,[a,e] mmol/L	- 0.43 (1.24)	0.65 (2.72)

Data presented as no. (%) except [a]mean (SD) or [b]mean (SE). EGDT- early goal-directed therapy, $ScvO_2$-superior vena cava oxygen saturation, PRBC-packed red blood cell, FFP-fresh frozen plasma, %FO-percentage fluid overload. [c]P=0.002, [d]P=0.012, [e]P=0.007.

Previous reports [5,8] also reported mortality reduction similar to ours in the $ScvO_2$ group. However, the patient population in our study was sicker than those in the previous study [8]. The timely administration of bundled care is the cornerstone for improved outcomes in septic shock. In EGDT with $ScvO_2$ group, the mean time taken to achieve therapeutic endpoints at the first 6-hour was significantly lower, and the $ScvO_2$ values (0 to 6-hour and 0 to 72-hour) were significantly higher. Thus, our study showed that $ScvO_2$ monitoring helps early recognition of septic shock and guides interventions to correct this pathophysiology, thereby improving outcomes, similar to previous work [5,8]. The mortality rate in our study was almost the same as previously reported [7]. However, in three major controlled trials in adults [12-14] conducted in high-income countries, no difference in mortality was found by the EGDT compared with usual care and protocol-based standard therapy, respectively. Their low baseline mortality could be one of the reasons for this difference.

Timely administration of resuscitation bundle and targeting tissue perfusion variable, namely $ScvO_2$, in septic shock has been associated with improved organ

Table III Outcome Comparison of Primary and Secondary Between the Two Study Groups

Outcome	*EGDT (with ScvO2) group (n=59)*	*EGDT (without ScvO2) group (n=61)*	*Relative risk (95% CI)*	*P value*
Primary outcome				
All cause 28-d mortality	22 (37.3)	35 (57.4)	0.66 (0.45-0.97)	0.028
Secondary outcomes				
Achieved therapeutic endpoint at 6h	37 (62.7)	33 (54.1)	1.16 (0.86-1.57)	0.34
Time to achieve therapeutic endpoints during 6h, h[a]	3.6 (1.6)	4.2 (1.6)	–	0.03
Achieved therapeutic endpoints during PICU stay	45 (76.3)	38 (62.3)	1.22 (0.96-1.56)	0.097
Time to achieve therapeutic endpoints during PICU stay, h[a]	6.3 (8.1)	7 (11.1)	–	0.77
Organ support				
Need for invasive ventilation	45 (76.3)	45 (73.8)	1.03 (0.84-1.27)	0.75
Duration of ventilation, d[b]	4 (3-7)	4 (2-7)	–	0.72
Average Vasoactive-inotropic score (first 7d)[a]	30 (25.6)	31.5 (22.9)	–	0.73
Need for renal replacement therapy	11 (18.6)	10 (16.4)	1.14 (0.52-2.48)	0.75
New organ dysfunction				
Patients with new-onset organ dysfunction	25 (42.4)	30 (49.2)	0.86 (0.58-1.28)	0.45
No. of new organ dysfunction[b]	2 (1-3)	2 (1-2)	–	0.68
PeLOD score				
At 24h[b]	12 (8-24)	16 (11-23)	–	0.21
During PICU stay[b]	8 (3-18)	13 (4-20)	–	0.17
SOFA Score				
At 24h	8 (5-13)	10 (6-14)	–	0.08
During PICU stay[b]	5 (2-11)	8 (3-13)	–	0.04
Duration				
PICU stay, d[b]	5 (3-9)	5 (2-10)	–	0.72
Hospital stay, d[b]	8 (6-13)	7 (4-13)	–	0.40

All data presented as no. (%) except [a]mean (SD) or [b]median (IQR). EGDT-early Goal-Directed Therapy, $ScvO_2$ - superior vena cava oxygen saturation, CI-confidence Interval, PeLOD-pediatric Logistic Organ Dysfunction score, SOFA-sequential Organ Failure Assessment, PICU -pediatric intensive care unit.

dysfunction and reduced mortality [5,15]. Otherwise, inadequate resuscitation leads to progressive organ dysfunction and death [16]. We found that new-onset organ dysfunction was similar in study groups; however, during PICU stay, the SOFA score was significantly lower in EGDT with $ScvO_2$ group. This contrasts to previous pediatric studies that have reported a lower new-onset organ dysfunction in EGDT with $ScvO_2$ group [5,8].

In our study, the need for vasoactive therapy and blood transfusion were similar in both groups; however, the need for dobutamine was higher in EGDT with $ScvO_2$ group. Previous adult and pediatric studies reported a higher proportion of patients receiving both inotropic and blood transfusion in the $ScvO_2$ targeted group [7,8]. This could be due to sepsis-associated myocardial dysfunction in septic shock [5-8]. We used the same blood transfusion threshold (10 g/dL) in both study groups. A similar observation was reported by Sankar, et al. [5]. The need for other interventions was similar in both groups including fluid bolus, ventilation, and additional vasoactive therapy.

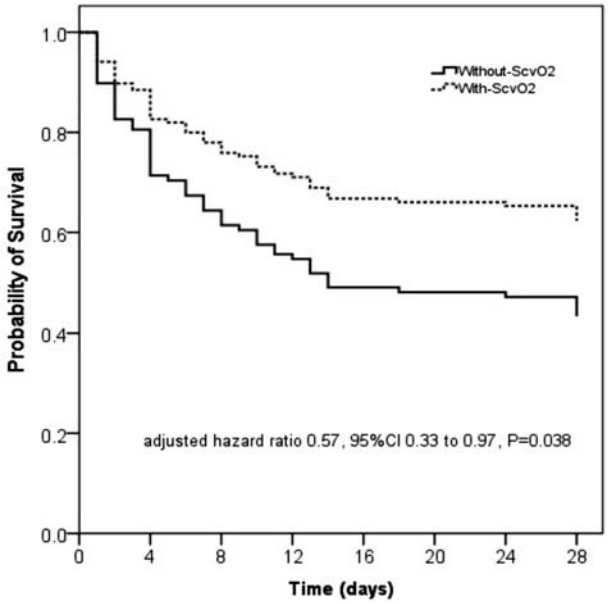


Fig. 2 Kaplan-Meier survival curve showing mortality up to 28-day in the study groups.

WHAT IS ALREADY KNOWN?

- Limited studies on early goal-directed therapy in pediatric septic shock reported reduced mortality and improved organ dysfunction.

WHAT THIS STUDY ADDS?

- Early goal-directed therapy with intermittent superior vena cava oxygen saturation monitoring reduces mortality and improves organ dysfunction in pediatric septic shock.

In our study, the baseline lactate was higher and the declining trend was significantly more in EGDT with $ScvO_2$ group, which contrasts with previous studies [5,8]. Hence, targeting the $ScvO_2$ with an inotropic agent and bundle care might improve the myocardial contraction and optimize tissue perfusion.

The limitations of the study were that $ScvO_2$ was not monitored continuously. However, recent studies have showed non-inferiority of intermittent $ScvO_2$ monitoring in pediatric septic shock [17]. It is a single center, and our baseline mortality was high, which limits the generali-zation of our results to other settings. The strengths of our study are that it enrolled children with various types of infections presenting as septic shock, measurement of $ScvO_2$ was done using blood gas analyzer with a co-oximetry module, which contrasts with the previous study [5]. Future studies in different settings are required to validate the generalizability of our results.

Our study concludes that EGDT with intermittent $ScvO_2$ monitoring (and targeting ScvO2 ≥70%) was associated with reduced mortality and improved organ dysfunction in pediatric septic shock.

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Ethical clearance: Institutional Ethics committee, JIPMER; No.JIP/IEC/2015/16/598, dated June 25, 2015.
Contributors: RR: had full access to all the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis; RR, SM: study concept and design; PJ, PS: acquisition, analysis, or interpretation of data; PJ: drafting of the first manuscript; RR: critical revision of the manuscript for important intellectual content; RR, SM: study supervision. All authors approved the final version of the manuscript.
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Conflict of interests: None stated.
Note: Additional material related to this study is available with the online version at *www.indianpediatrics.net*

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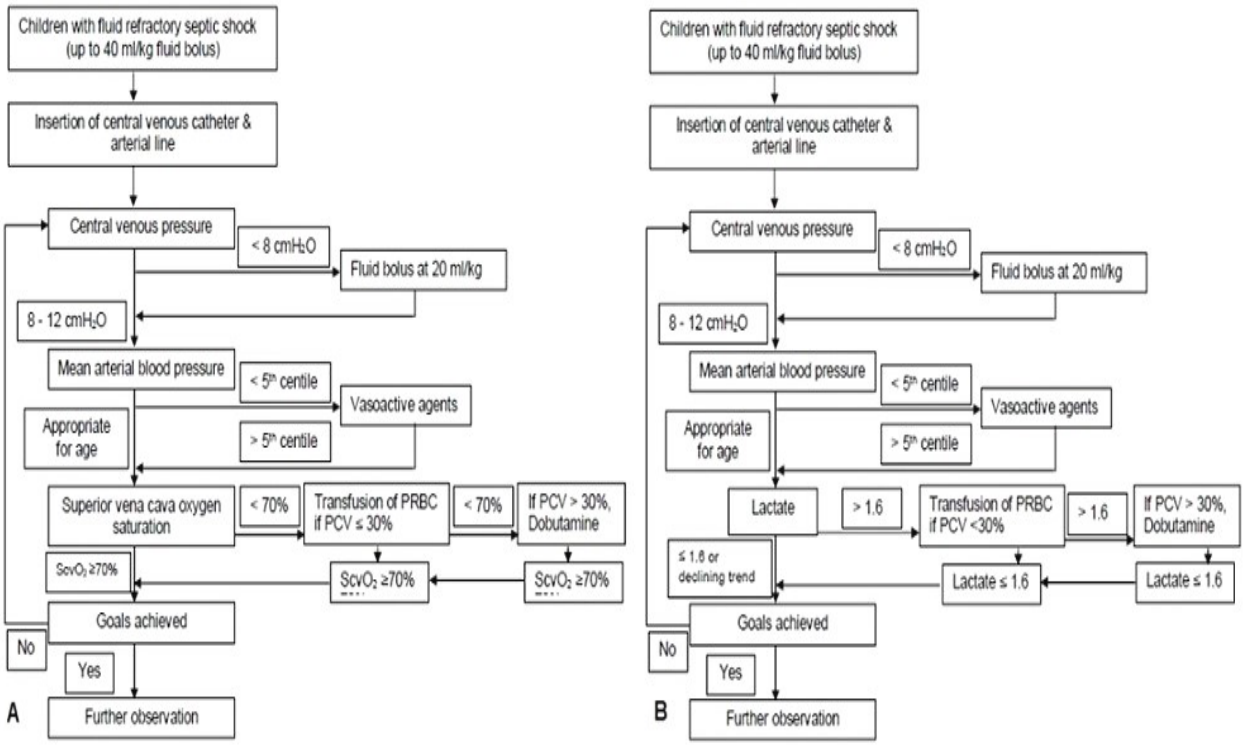

Web Fig. 1 (a) Early goal-directed therapy with superior vena cava oxygen saturation protocol; **(b)** Early goal-directed therapy without superior vena cava oxygen saturation protocol.