'Intermittent' versus 'continuous' $ScvO_2$ monitoring in children with septic shock: a randomised, non-inferiority trial

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'Intermittent' versus 'continuous' $ScvO_2$ monitoring in children with septic shock: a randomised, non-inferiority trial

Jhuma Sankar*, Man Singh, Kiran Kumar, M. Jeeva Sankar, Sushil Kumar Kabra and Rakesh Lodha

Abstract

Purpose: To compare the effect of 'intermittent' central venous oxygen saturation ($ScvO_2$) monitoring with 'continuous' $ScvO_2$ monitoring on shock resolution and mortality in children with septic shock.

Methods: Primary outcome was the achievement of therapeutic goals or shock resolution in the first 6 h. We randomly assigned children < 17 years' age with septic shock to 'intermittent $ScvO_2$' or 'continuous $ScvO_2$' groups. All children were subjected to subclavian/internal jugular line insertion and managed as per Surviving Sepsis Campaign Guidelines. To guide resuscitation, we used $ScvO_2$ estimated at other clinical and laboratory parameters were monitored similarly in both groups.

Results: We enrolled 75 and 77 children [median (IQR) age: 6 (1.5–10) years] in the 'intermittent' and 'continuous' groups, respectively. Baseline characteristics were comparable between the groups. When compared to the 'continuous' group, fewer children in the 'intermittent' group achieved shock resolution within first 6 h [19% vs. 36%; relative risk (RR) 0.51; 95% CI 0.29–0.89; risk difference − 18.0%; 95% CI − 32.0 to − 4.0]. The lower bound of confidence interval, however, crossed the pre-specified non-inferiority margin. There was no difference in the proportion of children attaining shock resolution within 24 h (63% vs. 69%; RR 0.86; 95% CI 0.68–1.08) or risk of mortality between the groups (47% vs. 43%; RR 1.06; 95% CI 0.74–1.51).

Conclusions: Given that a greater proportion of children attained therapeutic end points in the first 6 h, continuous monitoring of $ScvO_2$ should preferably be used to titrate therapy in the first few hours in children with septic shock. In the absence of such facility, intermittent monitoring of $ScvO_2$ can be used to titrate therapy in these children, given the lack of difference in the proportion of patients achieving shock resolution at 24 h or in risk of mortality between the intermittent and continuous groups.

Keywords: EGDT, $ScvO_2$, Intermittent $ScvO_2$ monitoring, Continuous $ScvO_2$ monitoring

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Introduction

Despite advances in understanding of the pathophysiology of septic shock in the last two decades, morbidity and mortality due to severe sepsis and septic shock continue to be high [1–6]. Early goal-directed therapy (EGDT) is a bundle of care that has shown to improve outcomes in patients with septic shock in the first landmark study by Rivers et al. [7]. Monitoring central venous oxygen saturation ($ScvO_2$) and lactate along with clinical parameters and instituting therapy to attain resuscitation targets was an essential component of this strategy [7]. Several studies from the time of first publication of the Rivers' study on EGDT or the protocolised approach have shown a beneficial effect on mortality in adult patients with septic shock [7–10]. However, recent data from three large multicentre studies after a decade of the original Rivers' study from high income countries (HIC) have raised questions on using this protocolised approach [11–13].

Unlike adults, data in paediatric septic shock on the use of EGDT using this protocolised approach is limited [14, 15]. The available data suggest EGDT using $ScvO_2$ as an additional therapeutic target or end point along with other clinical parameters favourably affects shock resolution and mortality in children with septic shock [14, 15]. Children have lower thresholds for decompensation as compared to adults and, therefore, recognising and treating them in early stages of shock ('potential golden hours') might have been beneficial as compared to adults. The absolute mortality benefit varied from 21 to 30% in these studies using either 'intermittent' or 'continuous' forms of monitoring as compared to 'no monitoring' in the first 6 h. Shock resolution was earlier in these groups and in greater proportion of patients in first 6 h considered as the 'golden hours' of resuscitation in children presenting with shock [14–17].

The recommended method of monitoring $ScvO_2$ is continuous like any other clinical parameter and therapy is directed to attain normal values (> 70%) as early as possible. However, continuous $ScvO_2$ monitoring requires expensive catheters and equipment and may not be feasible or sustainable in most units from LMIC (Low Middle Income) countries. Most adult and paediatric studies have compared the effect of 'continuous' $ScvO_2$ monitoring versus 'no monitoring' on important clinical outcomes [6, 8–11]. Only two studies in adult patients with sepsis have reported outcomes comparing the two methods of $ScvO_2$ estimation [18, 19]. Both studies have shown conflicting results with one favouring 'intermittent' [18] and the other favouring 'continuous monitoring' [19]. There are no published studies comparing the two methods in children till date. If proven to be non-inferior, intermittent monitoring which is feasible, less expensive and sustainable could be used in LMIC settings. The objective of this study was to evaluate whether 'intermittent $ScvO_2$' monitoring is not inferior to 'continuous $ScvO_2$' monitoring in children with septic shock.

Take-home message

Continuous $ScvO_2$ monitoring resulted in greater proportion of children attaining therapeutic end points in the first 6 h. However, there was no difference in the proportion of patients who attained therapeutic goals at 24 h or in the mortality risk between the 'intermittent' and 'continuous' $ScvO_2$ monitoring groups. If available and feasible, one should preferably use continuous monitoring of $ScvO_2$, at least in the first 6 h. In the absence of such facility, intermittent monitoring of $ScvO_2$ can be used to titrate therapy in children with septic shock, especially in those having low $ScvO_2$ at the time of initial evaluation—in children with septic shock.

Methods

Design and setting

This was a randomised, unblinded non-inferior clinical trial conducted between September 2015 and March 2018 in the paediatric intensive care unit (PICU) of a tertiary care centre. The PICU is a fully equipped eight-bedded unit well equipped with facilities for advanced haemodynamic monitoring including continuous $ScvO_2$ monitoring, bedside echocardiography, ultrasonography and other facilities. The trial was designed and overseen by the investigators and was supported by the Institute Research Grant. The funders had no influence on the design or conduct of the trial and were not involved in data collection or analysis, in the writing of the manuscript, or in submission of the manuscript for publication. The trial protocol, available at Clinical Trials Registry of India (CTRI number: CTRI/2015/10/006264), was approved by the Institute Ethics Committee of the All India Institute of Medical Sciences, Delhi. The trial was performed in accordance with the principles of the Declaration of Helsinki. The authors assume responsibility for the accuracy and completeness of the data and analyses, as well as for the fidelity of the trial and this report.

Participants

All children < 17 years with features of fluid-refractory septic shock (who did not respond to initial fluid resuscitation of up to 40–60 mL/kg of isotonic crystalloid/colloid bolus) were included. Children with severe acute malnutrition, primary cardiac condition, chronic kidney disease and those with contraindication to superior vena caval central venous catheter insertion were excluded from study. Septic shock was defined as per definitions given by the International Consensus Conference on Paediatric Sepsis (Electronic Supplement 1) [20].

Outcomes

The primary outcome was the proportion of children attaining all of the therapeutic end points (TEP) (composite outcome) described below or shock resolution in the first 6 h from the time of resuscitation in both groups. The therapeutic end points targeted included achieving a normal heart rate [20]; appropriate-for-age mean arterial pressure (MAP) [21]; normal pulses with no difference between peripheral and central pulses; warm extremities; capillary refill time less than 2 s; improving mental status; urine output more than or equal to 1 mL/kg/h; and attaining a $ScvO_2$ of more > 70% [22–24]. Shock resolution was defined as attaining all of the therapeutic end points that could be measured at any time point (ES1).

The important secondary outcomes were (a) proportion of patients attaining therapeutic end points at 24 h and any time during the episode of shock; (b) time to attain therapeutic end points; and (c) mortality. Other outcomes were time to achievement of individual TEP in hours, requirement of additional fluid boluses in 1–6 h, vasoactive inotrope score in first 24 h, Pediatric Logistic Organ Dysfunction (PELOD-2) scores at 24 and 48 h, Sequential Organ Failure Assessment (SOFA) scores at 24 and 48 h, requirement of mechanical ventilation during ICU stay, dialysis in the first 7 days, requirement of blood products and duration of PICU and hospital stay. We also wanted to compare the proportion of patients developing central line-associated infections in both groups.

Measurement of end points of shock resolution

Two physicians (MS and KK) assessed the end points of shock throughout the study period. Both were trained by the principal investigator (PI; JS) for a period of 2 months in assessment of clinical end points before study initiation. Each patient admitted during this period ($n = 50$) was evaluated by both of them as well as by the PI. The inter-rater agreement between both the physicians and PI was excellent (kappa 0.88). Discrepancies, if any, in recording the data were discussed and resolved during this period. To ensure ongoing quality control after the study began, the PI checked the data, discussed new issues and queries with the scientists regarding assessment of signs, and re-emphasised the method of evaluation after enrollment of every ten patients.

Methodology

The eligible children were enrolled after obtaining informed consent from one of the parents. Those children in whom subclavian/internal jugular line insertion was successful were enrolled into the study. They were randomised to either 'intermittent monitoring group' or 'continuous monitoring group' (Fig. 1). Randomisation was done as per study protocol (Electronic Supplement 2) (also available at CTRI).

Intervention

1. Experimental arm— 'intermittent $ScvO_2$' monitoring group: a central venous catheter (CVC) was inserted for monitoring the central venous pressure (CVP) and samples were drawn at 1, 3 and 6 h of initial resuscitation from the distal lumen of the catheter for estimation of central venous oxygen saturation ($ScvO_2$). The blood gas sample was processed by using basic blood gas analyser ABL 800 (Radiometer, Copen- Hagen, Germany). The study team used this information to give fluid, blood, and heart medications as described in Electronic supplement 3.
2. Comparison arm— 'continuous $ScvO_2$' monitoring group: central venous oximetry catheter (PediaSat Oximetry Catheter, Edwards Lifesciences, Irvine, California, USA) was inserted into the internal jugular vein/subclavian vein. Details on the catheter used and the technology are described in ES 3. $ScvO_2$ was measured continuously in this group and the study team used an average of 15 min readings to give fluid, blood, and heart medications as described in ES 3 and under "Management of enrolled patients" (see below).

Management of enrolled patients

During the study period, children in both groups were monitored and managed as per study protocol (ES 3) during the first 6 h of admission, with the only difference being $ScvO_2$ monitored intermittently at 1, 3 and 6 h after initiation of therapy in the 'intermittent group' and $ScvO_2$ measured continuously in the 'continuous group'. Monitoring of all other parameters was continuous and same in both the groups. $ScvO_2$ monitoring along with other clinical and laboratory parameters was continued till shock resolution in both groups. Data collection included demographic details, clinical course, investigations, and organ dysfunction scores. Enrolled children were followed up till recovery/death for recording all the relevant outcomes.

Sample size estimation

The proportion of children attaining therapeutic end points including $ScvO_2$ at 6 h was 40% (unit data for 1 year preceding study). Assuming 'intermittent monitoring' will not be inferior to 'continuous monitoring' in terms of shock resolution at 6 h (and same proportion will attain shock resolution at 6 h), an alpha error (one sided) of 5%, power of 80%, and a non-inferiority margin of 20%, we had to enrol 75 children in each group. The

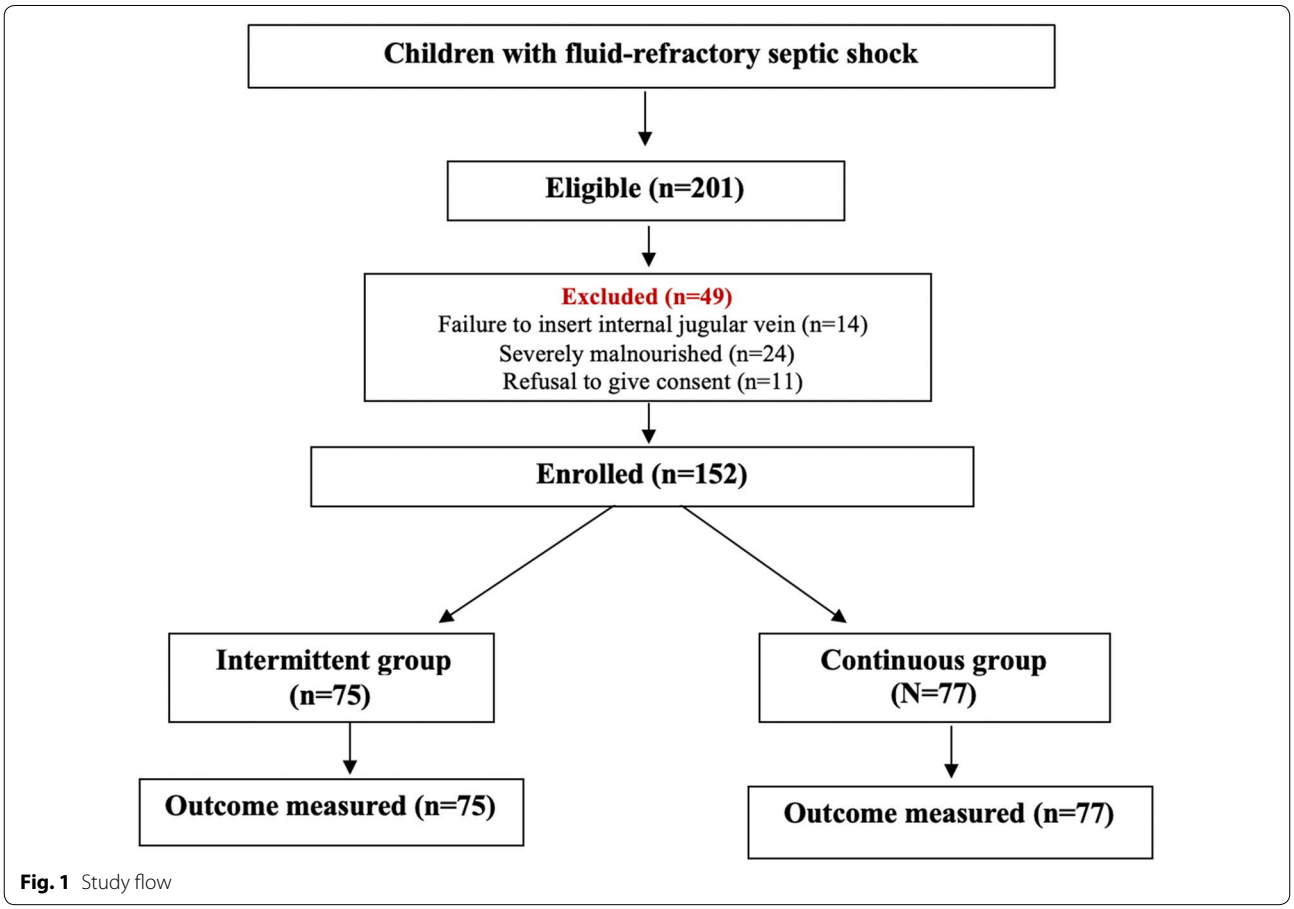

Fig. 1 Study flow

non-inferiority margin was kept at 20% based on our previous study data in which we had observed a difference of 21% in the proportion of patients attaining shock resolution between 'intermittent $ScVO_2$ monitoring' and 'no $ScvO_2$ monitoring' groups [15]. We assumed that a difference of this magnitude between intermittent and continuous $ScvO_2$ monitoring would be clinically relevant and therefore chose that as the non-inferiority margin.

Statistical analysis

Data were entered into Microsoft Excel 2007 and analysed using *Stata* 15.1 (Stata Corp, College Station, TX). Categorical data are presented as number (%) while continuous variables are presented as mean (SD), if normally distributed and as median (interquartile range), if skewed. Statistical analysis was performed using Student's *t* test/Wilcoxon rank sum test and Chi square test for continuous and categorical variables, respectively. Relative risk (RR) or difference in means with 95% CI was calculated for all the outcomes. *P* value of < 0.05 was considered significant. All analyses were performed with intention-to-treat principle. There were no protocol violations in either of the groups as care was taken that catheters remained in place till shock resolution or death.

Results

Baseline characteristics

Of 201 children with fluid-refractory septic shock during the study period, 49 were excluded. The remaining 152 children were enrolled—75 in 'intermittent $ScvO_2$' group and 77 in 'continuous $ScvO_2$' group (Fig. 1). Key baseline characteristics including age, gender, and PIM-3 score at admission were comparable between the groups (Table 1). Clinical and laboratory parameters including heart rate, mean arterial pressure, central venous pressure, and lactate as well as the proportion with low $ScvO_2$ were also comparable. The most common focus of infection in both groups was the lung (43%). The common organisms isolated in both groups were *E coli*, *Klebsiella pneumoniae*, and *Acinetobacter baumannii* (Table 1).

Outcomes

The proportion of children attaining all therapeutic end points (composite outcome) at 6 h was lower in the 'intermittent $ScvO_2$' group than the 'continuous $ScvO_2$' group

Table 1 Baseline characteristics of the enrolled patients

Variable	Intermittent $ScvO_2$ group ($n=75$)	Continuous $ScvO_2$ group ($n=77$)	*P* value
Age (months)	60 (14, 128)	72 (39, 108)	0.13
Male gender	50 (67)	45 (58)	0.30
PIM—2 probability	35 (19, 53)	44 (25, 62)	0.70
No of dysfunctional organs at admission (MODS)	2 (1, 3)	2 (1, 3)	0.97
Patient transferred from			
Emergency	48 (64)	56 (73)	0.24
Ward	27 (36)	21 (27)	0.24
Nosocomial infections	20 (30)	18 (26)	0.55
Any underlying medical condition	36 (48)	29 (38)	0.20
Source of infection			
Pneumonia	32 (43)	34 (44)	0.04
Meningitis	13 (17)	18 (23)	0.04
Abdominal infections	13 (17)	6 (8)	0.04
Skin and soft tissue infection	3 (4)	10 (13)	0.04
Urinary tract infections	2 (2.67)	2 (2.6)	0.04
Tuberculosis	1 (1.33)	0 (0)	0.04
Malaria	2 (3)	3 (4)	0.04
Hepatitis	2 (3)	0 (0)	0.04
Septicaemia without focus	7 (9)	4 (5)	0.04
Clinical and laboratory findings			
Heart rate (bpm)[a] at admission	148 (31)	153 (33)	0.59
Respiratory rate[a] at admission	46 (18)	48 (16)	0.30
Mean arterial pressure (mmHg)[a]	64 (21)	66 (19)	0.38
Proportion with low systolic BP as per IPSCC	40 (53)	35 (46)	0.33
Central venous pressure (cmH_2O)[b]	10 (5.4, 12)	6 (3, 8)	0.24
Capillary refill time (s)[a]	2.8 (0.82)	2.8 (0.86)	0.68
Glasgow Coma Scale[a]	10.4 (3.7)	10.3 (4)	0.50
Superior vena cava saturation (%)[a]	74.5 (14)	74 (13)	0.52
Proportion with $ScvO_2 < 70\%$[a]	25 (33)	30 (39)	0.31
SpO_2 (%)[a]	94 (9)	93 (8)	0.30
Lactate at 1 h	2.1 (1.2, 4.1)	2 (1.1, 3.7)	0.51
Other laboratory tests			
pH[a] at admission	7.26 (0.18)	7.25 (0.14)	0.58
HCO_3 in mmol/L[a] at admission	17.5 (5.5)	19.4 (6.2)	0.09
Haemoglobin (gm/dL)[a] at admission	9.4 (3)	10 (2.1)	0.08
Total leucocyte count (mm^3) at admission	13,800 (8600, 21200)	13,400 (9800, 22000)	0.71
Neutrophils	62 (25)	72 (16)	0.005
Platelet count at admission	2 (0.73, 2.62)	1.9 (0.71, 3.3)	0.78
CRP (semi-quantitative, mg/L)	27 (26, 75)	145 (30, 176)	0.05
PCT at 24 h	25.7 (14.6, 157)	18 (0.93, 30)	0.01
PCT positive	23 (92)	31(86)	0.68
Urea at 24 h	47 (24, 106)	32 (21.5, 46)	0.002
Creatinine at 24 h	0.4 (0.3, 0.9)	0.4 (0.2, 0.6)	0.56
SGOT at 24 h	57 (27, 355)	40 (23, 76)	0.02
SGPT at 24 h	44 (16, 177)	26 (12, 49)	0.006
Culture positive sepsis	18 (23)	16 (28)	0.94
Organisms isolated			
Escherichia coli	3	6	-
Klebsiella pneumoniae	4	4	-

Table 1 (continued)

Variable	Intermittent $ScvO_2$ group ($n=75$)	Continuous $ScvO_2$ group ($n=77$)	*P* value
Staphylococcus aureus	3	0	-
Acinetobacter baumannii	4	3	-
Enterobacter	1	0	-
Citrobacter	0	1	-
Pseudomonas aeruginosa	3	1	-
Proteus mirabilis	0	1	-

$ScvO_2$ superior vena cava oxygen saturation, *PIM* paediatric index of mortality, *MODS* multi organ dysfunction syndrome, *IPSCC* International Pediatric Sepsis Consensus Conference

Data presented as number (proportion), [a]mean(SD), or [b]median (IQR)

(19% vs. 36%; RR: 0.51; 95% CI 0.29–0.89). The lower bound of 95% CI of the risk difference (RD), however, crossed the pre-specified non-inferiority margin (RD −0.18; 95% CI −0.32 to −0.04). Therefore, the non-inferiority of intermittent monitoring could not be proven.

There was no difference in mortality between the two groups (47% vs. 43%; RR 1.06; 95% CI 0.74–1.51). The proportion of children attaining therapeutic end points any time during the ICU stay was also similar in both groups (Table 2). In the intermittent group, the median (IQR) time to attain therapeutic end points was 12 h (8, 30) and in the continuous group it was 11 h (5, 21); the difference was statistically significant ($P=0.03$).

Organ dysfunction and organ support

The median PELOD and SOFA scores at 24 and 48 h were higher in the 'intermittent group', and the urine output was lower and blood urea higher at 24 h in the 'intermittent group' (Tables 1, 3). A greater proportion of children received renal replacement therapy in the 'intermittent group' (Table 2). However, none of these differences were statistically significant.

Trend in individual therapeutic end points and fluid and inotrope requirement

The heart rate, respiratory rate, SpO_2, capillary refill time, peripheral pulses and urine output individually showed steady improvement in both groups over the first 6 h (Table 3). The proportion of patients attaining individual therapeutic goals at different time points (1 h, 6 h, 24 h and at any time during ICU stay) is depicted in Fig. 2 and Table 4. The mean arterial pressure was significantly lower in the 'intermittent group' at 6 h as compared to the 'continuous group' (71 mmHg vs. 76 mmHg; $P=0.02$). The difference was no longer significant at 24 h (Table 3). The mean arterial pressure, capillary refill time, peripheral pulses, and lactate improved in more than 75% of patients in both groups at the end of first 6 h of resuscitation. The proportion of children with low $ScvO_2$ decreased from 33 to 28% in the 'intermittent group' compared to a decline from 39 to 22% at 6 h in the 'continuous group' (Fig. 2). The mean $ScvO_2$ at 6 h was also lower in the 'intermittent group' as compared to the 'continuous group'($P=0.001$). In a few children (four in intermittent and two in continuous groups), the $ScvO_2$ decreased after reaching target values of > 70% by 6 h. Analysis of data excluding $ScvO_2$ as a therapeutic end point showed an absolute difference of 11% in proportion attaining shock resolution between the groups at 6 h (35% vs. 46%, in the 'intermittent' and 'continuous groups', respectively). The lactate showed steady improvement in both groups and was normal in more than 80% patients by the end of 24 h (Fig. 2). The greatest separation between the groups in therapeutic end points at 6 h was in heart rate: tachycardia decreased in 55% and 69% in the 'intermittent' and 'continuous' groups, respectively ($P=0.037$). On analysis of data excluding heart rate, the proportion attaining all other therapeutic end points was 15% lower in the intermittent group (44% vs. 59%) in the 'intermittent' and 'continuous' groups, respectively. The heart rate was also the last to normalise in both the groups—it continued to be abnormal in about 1/5th of patients throughout the ICU stay.

The proportion of patients receiving milrinone and dobutamine was lower in the 'intermittent group' (52% vs. 65%, $P=0.09$), but the difference was not significant. There was no difference in terms of proportion of children receiving dopamine or epinephrine in the first 6 h in both groups (Table 3). A greater proportion of children received additional boluses in 1–6 h (median of two boluses vs. one bolus) and packed red blood cells in the first 6 h in the 'continuous group'; the differences were, however, not statistically significant (Table 3). The median vasoactive inotrope score in the first 24 h was 30 and 33 in the 'intermittent' and 'continuous' groups, respectively ($P=0.30$).

Discussion

Fewer children in the 'intermittent $ScvO_2$' group achieved shock resolution (the primary outcome or composite

Table 2 Primary and secondary outcomes of the study population

Variable	Intermittent $ScvO_2$ group ($n=75$)	Continuous $ScvO_2$ group ($n=77$)	Relative risk/mean difference (95% CI)	*P* value
Primary outcomes				
Proportion of children attaining therapeutic end points (TEP) in the first 6 h	14 (19)	28 (36)	0.51 (0.29–0.89)	0.015
Secondary outcomes				
Proportion attaining therapeutic end points in the first 24 h	47 (63)	53 (69)	0.86 (0.68, 1.08)	0.43
Proportion attaining TEP during ICU stay	58 (77)	59 (78)	1.0 (0.84, 1.2)	0.91
Time to achievement of therapeutic end points (h)[a]	12 (8, 30)	11 (5, 21)	–	0.03
Received mechanical ventilation during ICU stay	64 (85)	66 (86)	0.99 (0.87, 1.13)	0.94
Receieved dialysis in the first 7 days	19 (38)	14 (26)	1.32 (0.71, 2.43)	0.29
Received packed RBCs during ICU stay	38 (51)	42 (55)	0.90 (0.67, 1.23)	0.52
Platelet transfusion during ICU stay	27 (36)	18 (23)	1.54 (0.92, 2.55)	0.09
Mortality	35 (47)	33 (43)	1.06 (0.74, 1.51)	0.74
Organ dysfunction and support				
Duration of mechanical ventilation[a,b]	7 (4, 15)	6.5 (5, 17)	–	0.73
Duration of inotrope therapy[b]	48 (24, 72)	39 (19, 80)	–	0.87
Duration of PICU stay[b]	9 (3, 16.5)	8 (4, 21)	–	0.82
Duration of hospitalisation[b]	16.5 (9, 30)	18 (8, 29)	–	0.59
PELOD score at 24 h	3 (2, 11)	3 (1, 13)	–	0.89
PELOD score at 48 h	3 (2, 11)	3 (1, 11)	–	0.34
SOFA score at 24 h	9 (6, 10)	7 (5, 10)	–	0.22
SOFA score at 48 h	7 (4, 11)	6 (2, 9)	–	0.14
Central line-associated blood stream infection	5 (7)	3 (4)	1.71 (0.42, 6.91)	0.47

PELOD paediatric logistic organ dysfunction, *RBCs* red blood cells, *ICU* intensive care unit, *IVIG* intravenous immune globulin, @ data available for 55 and 62 patients, respectively, in intermittent and continuous groups, *SOFA* sequential organ failure assessment, *PARDS* paediatric acute respiratory distress syndrome, *TEP* therapeutic end points

[a] Mean values were 22 and 13 h in the 'intermittent' and continuous groups, respectively

Data presented as number (proportion) or median (IQR)[b]

outcome of all therapeutic end points (TEP)) at 6 h as compared to the 'continuous $ScvO_2$' group. But the non-inferiority of intermittent monitoring vis-à-vis continuous monitoring for the primary outcome of proportion attaining shock resolution or therapeutic end points at 6 h could not be proven conclusively, because the 95% confidence interval of the risk difference crossed the predecided non-inferiority margin.

Intermittent monitoring of $ScvO_2$ can be done without the requirement of costly equipment and specialised central venous catheters. With this modality, $ScvO_2$ can be measured at regular intervals from the catheters routinely used in the patient care. Theoretically, it has the disadvantage of time lag in detection of changes and in initiation of necessary interventions, when compared to continuous monitoring. This may have been one of the reasons for the lower proportion of children achieving shock resolution in the first 6 h in the intermittent group. The time to achieve TEP was earlier in the 'continuous' group, probably due to the continuous monitoring. Continuous monitoring prompted administration of more fluids, inotropes and blood products than the 'intermittent group' where there was limited window of opportunity for interventions in the first 6 h (even though the difference was not significant). Proportion receiving vasoactive agents was comparable between the two groups at 24 h, except for use of milrinone which was higher in the continuous group in the first 6 h. Incidentally, the proportion of children with myocardial dysfunction detected in the first 3 h was higher in the 'continuous group' (36% vs. 29%) as compared to the 'intermittent group' (cardiac dysfunction was examined in those with low $ScvO_2$ and not routinely as part of protocol). Use of cardiac imaging as part of standard pediatric septic shock care needs to be encouraged. After the target levels of $ScvO_2$ were reached in both groups (by 24 h in most cases), the shock resolution did not differ between the groups. Overall, this additional monitoring and additional treatment led to more patients in the continuous group reaching targets within 6 h. Whether this is clinically beneficial or not needs to be tested in a larger study.

Table 3 Comparison of haemodynamic variables and fluid and inotrope requirement in both groups

Variable	Intermittent $ScvO_2$ group ($n=75$)	Continuous $ScvO_2$ group ($n=77$)	*P* value
Clinical course			
Heart rate[a] (mean, SD)			
1 h	145 (30)	150 (30)	0.21
6 h	148 (36)	147 (33)	0.92
24 h	145 (32)	145 (26)	0.91
Mean arterial pressure[a] (mean, SD)			
1 h	67 (17)	69 (16)	0.45
6 h	70.6 (14)	76 (13)	0.02
24 h	71 (16)	74 (12)	0.33
CRT (mean, SD)			
1 h	2.7 (0.8)	2.7 (0.75)	0.43
6 h	2.5 (0.73)	2.4 (0.63)	0.15
24 h	2.2 (0.5)	2.3 (0.67)	0.42
CVP[b] (median, IQR)			
1 h	8.1 (4, 11)	5.5 (3, 8.2)	0.31
6 h	6.8 (4, 10)	4 (4, 10)	0.27
24 h	10 (7, 12)	7 (6, 11)	0.07
$ScvO_2$[a]			
6 h	72 (11)	78 (12)	0.001
24 h	73 (11)	76 (9)	0.14
Lactate[b] (median, IQR)			
6 h	1.4 (1, 3.3)	1.75 (1.05, 3.3)	0.43
24 h	1.1 (1, 2.5)	1.3 (1, 2.9)	0.24
Base deficit[b]			
1 h	−3.1 (−10.4, 2.25)	−5 (−9, −1.7)	0.27
6 h	−3.35 (−9, 0.8)	0.15 (−8, 3)	0.15
24 h	−1.75 (−5.3, 2)	−3.05 (−7.55, 2.1)	0.25
PCO_2[b] (mean, SD)			
1 h	45 (14)	45 (19)	0.82
6 h	44 (13)	45 (20)	0.72
24 h	42 (10)	42 (19)	0.91
Urine output[b] (median, IQR)			
6 h	1.9 (0.51, 3)	1.8 (0.8, 3)	0.36
24 h	1.5 (0.95, 2.18)	2 (1, 2.72)	0.02
Fluids and inotrope requirement			
Received additional boluses in 1–6 h	1 (0, 2)	2 (0, 2)	0.06
VIS at 24 h (median, IQR)	30 (15, 45)	33 (19, 53)	0.30
Dopamine or epinephrine in first 6 h	47 (62)	52 (67)	0.31
Dobutamine or milrinone in first 6 h	39 (52)	50 (65)	0.09
Number of units of packed red blood cells in first 6 h	0 (0, 1)	1 (0, 1)	0.05

CVP central venous pressure, *CRT* capillary refill time, *$ScvO_2$* superior vena caval oxygen saturation, *PICU* paediatric intensive care unit, *ICP* increased intracranial pressure, *VIS* vasoactive inotrope score

Data presented as number (proportion), mean (SD)[a] or median (IQR)[b]

The two previous studies that have compared 'continuous' and 'intermittent' $ScvO_2$ monitoring in adults with septic shock showed conflicting results [18, 19]. Our findings are similar to that of Ising et al. who reported higher proportion of patients attaining therapeutic end points in the 'continuous' group (75.7% vs. 60.3%; $P=0.007$) [19]. In contrast, Huh JW et al. reported similar proportion of patients attaining therapeutic end points at 6 h in both groups (41.5% vs. 35.8%; $P=0.55$) in 106 adults with septic shock [18]. In our study, the proportion attaining

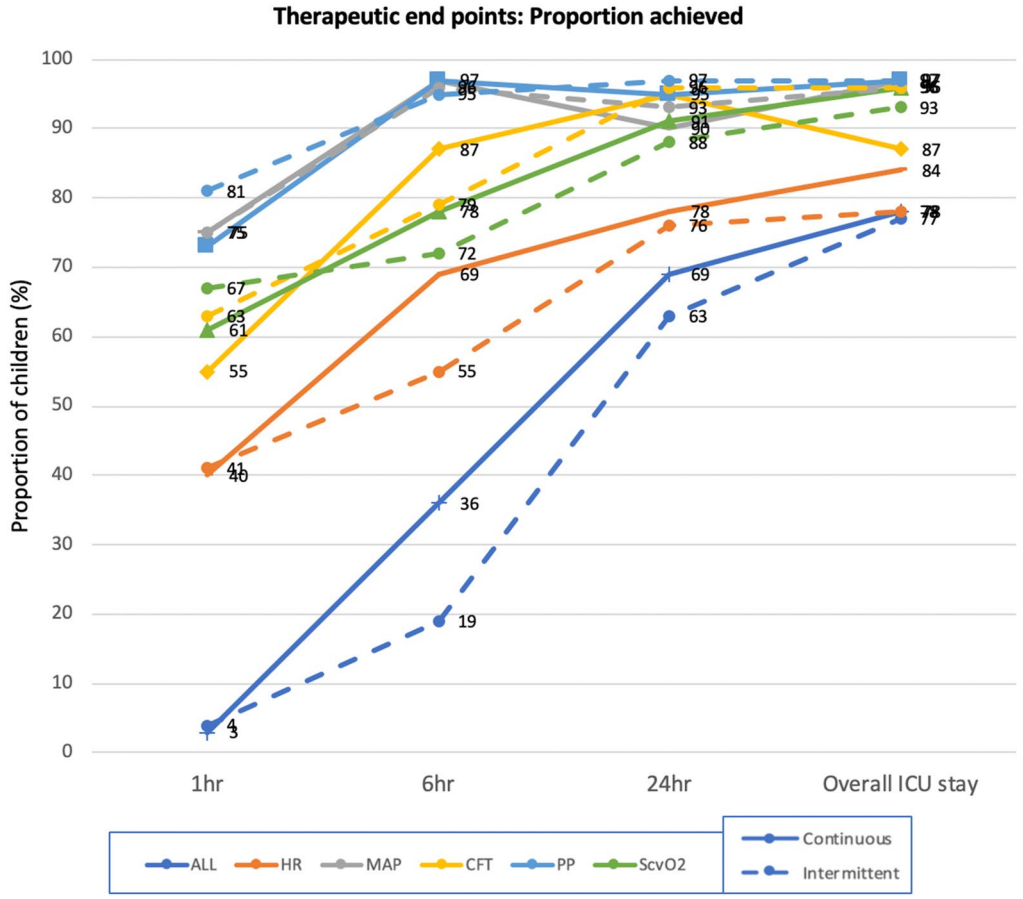

Fig. 2 Proportion attaining various therapeutic end points in the 'intermittent' and 'continuous groups' at different time points during ICU stay

Table 4 Proportion attaining individual therapeutic end points in the 'intermittent' and 'continuous groups' at different time points during the ICU stay

Time points	Intermittent group ($N=75$)				Continuous group ($N=77$)			
	1 h	6 h	24 h	Entire ICU stay (%)	1 h	6 h	24 h	Entire ICU stay (%)
Attaining all end points	4%	19%	63%	77	3%	36%	69%	78
Tachycardia resolved (%; mean (SD)	41%; 145 (30)	55%; 148 (36)	76%; 145 (32)	78	40%; 150 (30)	69%; 147 (33)	78%; 145 (26)	84
Mean arterial pressure (%; mean (SD)	75%; 67 (17)	96%; 70.6 (14)	93%; 71 (16)	96	75%; 69 (16)	97%; 76 (13)	90%; 74 (12)	97
Capillary refill time (%, mean (SD))	63%; 2.7 (0.8)	79%; 2.5 (0.73)	96%; 2.2 (0.5)	96	55%; 2.7 (0.75)	87%; 2.7 (0.75)	95%; 2.3 (0.67)	87
Peripheral pulses normal (%)	81%	95%	97%	97	73%	97%	95%	97
$ScvO_2$	67%; 74.5 (14)	72%; 72 (11)	88%; 73 (11)	93	61%; 74 (13)	78%; 78 (12)	91%; 76 (9)	96
Lactate (%; median, IQR)	73%; 2.1 (1.2, 4.1)	79%; 1.4 (1, 3.3)	89%; 1.1 (1, 2.5)	93	68%; 2 (1.1, 3.7)	77%; 1.75 (1.05, 3.3)	82%; 1.3 (1, 2.9)	92

$ScvO_2$ superior vena caval oxygen saturation, *SD* standard deviation, *IQR* interquartile range

composite outcome was higher in the 'continuous group' at 6 h. On analysis of the proportion attaining individual end points, the greatest separation appears to be for heart rate between the two groups. However, this alone is unlikely to explain the real magnitude of difference observed in the incidence of composite outcome between the groups. For example, the proportion of children who attained all therapeutic end points except the heart rate was still different between the two groups (44% vs. 59%). The relative risk and 95% CI were 0.75 and 0.55–1.03, respectively. It is unlikely that removing heart rate from the composite outcome would completely change the direction of the effect—the relative risk, though more towards the null value now, still shows a clinically relevant difference between the two groups. These findings suggest that the composite outcome might not have been unduly influenced by heat rate alone.

The mean $ScvO_2$ at baseline was higher in our study patients (75% in both groups) compared to the study by Huh JW (63% and 64.4% in the 'intermittent' and 'continuous' groups, respectively). Huh et al. reported increase in mean $ScvO_2$ from 63 to 72.5% by 24 h in the 'intermittent group' as compared to an increase from 64.4 to 69.3% in the 'continuous group'. The higher $ScvO_2$ values at admission in our study could mean the children were sicker and oxygen extraction had reached its nadir due to ongoing cell death and therefore $ScvO_2$ levels were more than 70% so early in the course [25, 26].

Targeted interventions to improve $ScvO_2$ might have contributed to lower mortality in the EGDT group in Rivers' study [6]. The same may not be effective if the $ScvO_2$ levels are already at an expected level of > 70%. This could explain the lack of significant difference in mortality between the two groups. In terms of organ dysfunction, we observed greater proportion with acute kidney injury receiving renal replacement therapy in the first 7 days in the 'intermittent group'. Likewise, the pSOFA and PELOD scores were higher at 48 h in the 'intermittent group'. None of these differences were, however, significant. Overall, it appears that there is some benefit of continuous monitoring and resuscitation in the first 6 h, but it would require a large sample size to prove this benefit on acute kidney injury or other organ dysfunction.

The benefit of EGDT in a small subset of patients with low $ScvO_2$ may hold promise and needs to be explored further. A recent meta-analysis by Xian-Fei Ding et al. of 16 studies also seems to support this notion [27]. The authors reported that EGDT was associated with lower mortality compared to usual care, with the results being more pronounced in the subgroup of usual care patients with mortality > 30% [27]. Improvement at 6 h, increased use of milrinone and cardiac monitoring, changes in organ dysfunction and renal replacement could suggest EGDT has not been fully explored in High Income Countries with proxy outcomes in pediatrics and may still have some utility.

The real life scenario, however, would be less rigorous intermittent monitoring and this may result in less frequent goal-directed treatment. On the other hand, continuous monitoring may result in greater awareness of tissue oxygenation and interventions would follow suit. However, we need to consider the cost and feasibility of using continuous monitoring in resource-limited settings. Given the facts, it appears reasonable to use continuous monitoring, if available, particularly during the initial 6 h. If that is not feasible, using intermittent monitoring especially in the subset of patients with low initial $ScvO_2$ values may be beneficial in terms of not losing the opportunity to intervene during the potential 'golden hours'.

Ours is the first study to compare 'continuous' versus 'intermittent' $ScvO_2$ monitoring in children with septic shock. As most units from developing countries may not have continuous $ScvO_2$ monitoring device, intermittent $ScvO_2$ monitoring would help in the management of shock. Strict adherence to the study algorithm was ensured throughout.

Our study has several limitations. The major limitation of our study is the non-inferiority margin of 20% we used as per our previous study data [15] to calculate the sample size. We had observed a difference of 21% in a proportion of patients attaining shock resolution between 'intermittent $ScVO_2$ monitoring' and 'no $ScvO_2$ monitoring' groups in that study [15]. We assumed that a difference of this magnitude between 'intermittent' and 'continuous' $ScvO_2$ monitoring would be clinically relevant and therefore chose 20% as the non-inferiority margin. A non-inferiority margin of 10% or even lower would probably have been more appropriate. But this would have required a sample size of 297 in each group (594 total), which was not feasible with the limited manpower and resources we had. Other limitations include single centre study and lack of blinding. Mortality in our cohort of patients is high, though consistent with those of other developing countries. Our results may not be generalisable to developed nations where the patient profile and mortality rates are different.

Conclusions

Given that a greater proportion of children attained therapeutic end points in the first 6 h, continuous monitoring of $ScvO_2$ should preferably be used to titrate therapy in the first few hours in children with septic shock. In the absence of such facility, intermittent monitoring of $ScvO_2$ can be used to titrate therapy, given the lack of difference in the proportion achieving shock resolution at 24 h or in

risk of mortality between the intermittent and continuous groups.

Electronic supplementary material
The online version of this article (https://doi.org/10.1007/s00134-019-05858-w) contains supplementary material, which is available to authorized users.

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Compliance with ethical standards

Conflicts of interest
On behalf of all authors, the corresponding author states that there is no conflict of interest.

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