Details of the research work

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PEDIATRIC ORIGINAL

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

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Title of the research work: 'Intermittent' versus 'continuous' ScvO2 monitoring in children with septic shock: a randomised, non-inferiority trial

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Findings in brief

We compared the effect of 'intermittent' superior vena caval oxygen saturation ($ScvO_2$) monitoring with 'continuous' $ScvO_2$ monitoring on shock resolution and mortality in 152 children with septic shock in this non-inferiority trial conducted at a tertiary care institute of India.

Our study demonstrated that greater proportion of children attained therapeutic end points with 'continuous' monitoring of $ScvO_2$ as compared to 'intermittent' monitoring of $ScvO_2$ as part of the resuscitation bundle in the first 6 hours of identification of 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 continuous and intermittent groups.

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Highlights: This study is a clinical practice informing study supporting the role of continuous $ScvO_2$ monitoring as part of resuscitation bundle in the first 6 hours of identification of septic shock. As there was no difference in mortality between the groups, in the absence of availability of continuous monitoring of $ScvO_2$, intermittent monitoring of $ScvO_2$ can be used to titrate fluid and inotrope therapy in these children.

The current Surviving Sepsis Campaign guidelines for the management of septic shock in children (2020) has recommended using advanced hemodynamic variables such as $ScvO_2$ and/or lactate, when available, in addition to bedside clinical variables to guide the resuscitation of children with septic shock or sepsis-associated organ dysfunction.

Scientific summary of the research work

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

Background and novelty: Current guidelines for septic shock in children advocate advanced hemodynamic monitoring using $ScVO_2$ and/or lactate where feasible in children with septic shock during the first 6 hours. However, what should be the method of monitoring or how frequently it should be monitored was not supported by high quality evidence. 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 Low Middle Income (LMIC) countries. Most adult and pediatric studies have compared the effect of 'continuous' $ScvO_2$ monitoring versus 'no monitoring' on important clinical outcomes. Only two studies in adult patients with sepsis have reported outcomes comparing the two methods of $ScvO_2$ estimation. Both studies have shown conflicting results with one favoring 'intermittent' and the other favoring

'continuous monitoring'. We therefore conducted this non-inferiority clinical trial in children with septic shock with an aim to answer this important research question.

The novelty of our study is, it is the first and only study to compare the 'continuous' versus 'intermittent' monitoring of $ScvO_2$ as part of the resuscitation bundle in the first 6 hours in children with septic shock. Our study provides high quality data to support the recent SSCG 2020 recommendations of using advanced hemodynamic variables in addition to clinical variables to guide the resuscitation of children with septic shock or sepsis associated organ dysfunction.

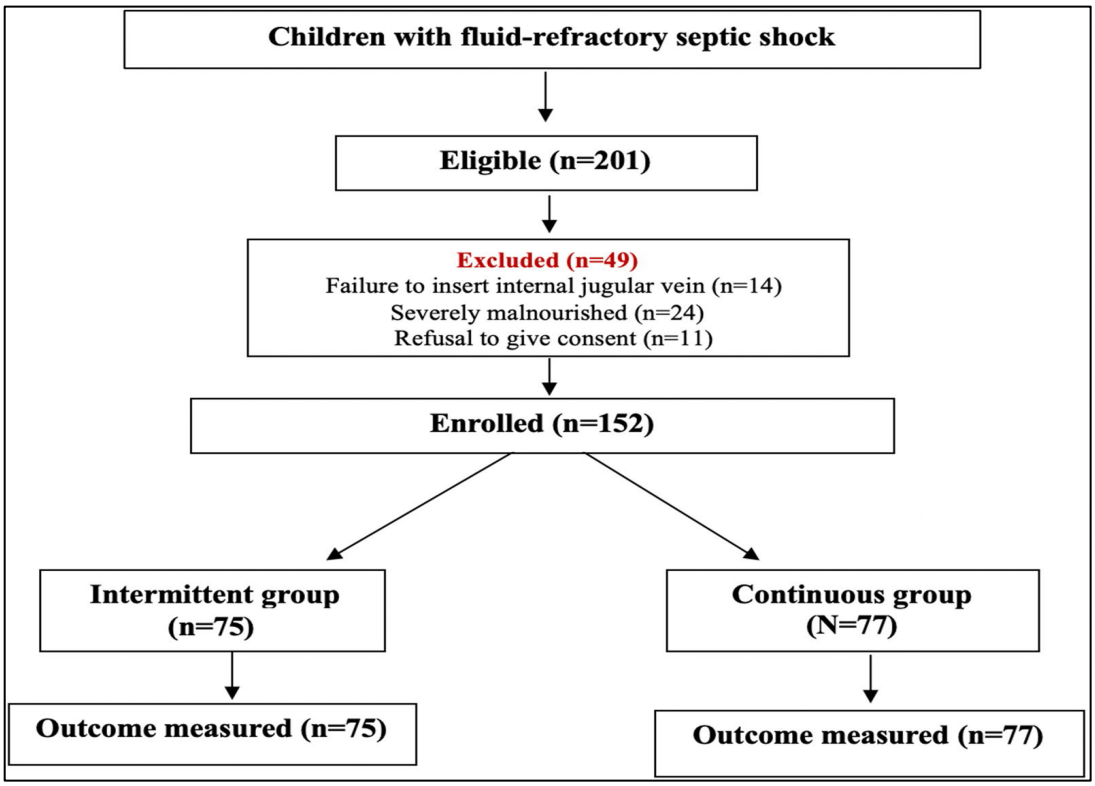
Outcome: The primary outcome was the proportion of children attaining shock resolution in the first 6 h from the time of resuscitation in both the groups. Shock resolution was defined as attaining all the therapeutic end points that could be measured at any time point. The important secondary outcomes were the proportion of patients attaining shock resolution at 24 h and mortality.

Methods: 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. During the study period, children in both groups were monitored and managed as per the study protocol 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 in both the groups.

Assuming 'intermittent monitoring' was not inferior to 'continuous monitoring' in terms of 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 enroll 75 children in each group. Data were analyzed using Stata 11.5. All analyses were performed with intention-to-treat principle.

Results: We enrolled 75 and 77 children [median (IQR) age: 6 (1.5–10) years] in the 'intermittent' and 'continuous' groups, respectively. The study flow is provided in **Figure 1**.

Figure 1. Study flow



The baseline characteristics were comparable between the groups and are provided in **Table 1.**

Primary and secondary outcomes: We observed that - when compared to the 'continuous' group, fewer children in the 'intermittent' group achieved shock resolution within the first 6 hours [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 between the groups (47% vs. 43%; RR 1.06; 95% CI 0.74–1.51). The primary and secondary outcomes of the study are provided in **Table 2.**

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 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]

Strengths and limitations: 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. The major limitation of our study is the non-inferiority margin of 20% we used as per our previous study data 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 the previous study. 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. Other limitations were single centre study and lack of blinding.

Conclusion: 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.

Implications of the study: Our study provides high quality data to support the recent surviving sepsis campaign 2020 recommendations of using advanced hemodynamic monitoring variables such as $ScvO_2$ in addition to clinical parameters to guide the resuscitation of children with septic shock or sepsis associated organ dysfunction in the first 6 hours. Our study also provides evidence to support the method of monitoring – i.e. 'continuous' $ScvO_2$ monitoring is preferred to titrate fluid and inotrope therapy; in the absence of such facility intermittent $ScvO_2$ monitoring at 1, 3 and 6 hours of resuscitation may provide additional hemodynamic data to titrate/optimize ongoing fluid and vasoactive therapy in children with septic shock.

Challenges encountered: It was a challenging study in terms of arranging logistics in carrying out the trial. Central line insertion (Internal jugular vein or subclavian vein) is a highly skilled procedure with scope for 'zero error' and therefore required the PI (myself) or a highly skilled DM resident to be present every time a child was eligible. The cost of the continuous co-oximetry catheters was very high (14000 INR per catheter and we could procure them only through the Institute Research Grant). Parents were not keen on inserting central lines in some of the children keeping in view the risks involved with the procedure and 11 children had to be excluded. This prolonged the study. The oximetry catheters (Edwards life sciences) had to be imported as they were not locally manufactured and required planning and procuring the catheters in advance so that the study was not interrupted.

Citations of the published work under consideration

Publication: Sankar J, Singh M, Kumar K, Sankar MJ, Kabra SK, Lodha R. 'Intermittent' versus 'continuous' $ScvO_2$ monitoring in children with septic shock: a randomised, non-inferiority trial. Intensive Care Med. 2020 Jan;46(1):82-92.

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