A Study to Compare Ultrasound-guided and Clinically Guided Fluid Management in Children with Septic Shock

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Abstract

Background: To evaluate the role of ultrasound during initial fluid resuscitation along with clinical guidance in reducing the incidence of fluid overload on day 3 in children with septic shock.

Materials and methods: It was a prospective, parallel limb open-labeled randomized controlled superiority trial done in the PICU of a government-aided tertiary care hospital in Eastern India. Patient enrolment took place between June 2021 and March 2022. Fifty-six children aged between 1 month and 12 years, with proven or suspected septic shock, were randomized to receive either ultrasound-guided or clinically guided fluid boluses (1:1 ratio) and subsequently followed up for various outcomes. The primary outcome was frequency of fluid overload on day 3 of admission. The treatment group received ultrasound-guided fluid boluses along with the clinical guidance and the control group received the same but without ultrasound guidance upto 60 mL/kg of fluid boluses.

Results: The frequency of fluid overload on day 3 of admission was significantly lower in the ultrasound group (25% vs 62%, $p = 0.012$) as was the median (IQR) cumulative fluid balance percentage on day 3 [6.5 (3.3–10.3) vs 11.3 (5.4–17.5), $p = 0.02$]. The amount of fluid bolus administered was also significantly lower by ultrasound [median 40 (30–50) vs 50 (40–80) mL/kg, $p = 0.003$]. Resuscitation time was shorter in the ultrasound group (13.4 ± 5.6 vs 20.5 ± 8 h, $p = 0.002$).

Conclusion: Ultrasound-guided fluid boluses were found to be significantly better than clinically guided therapy, in preventing fluid overload and its associated complications in children with septic shock. These factors make ultrasound a potentially useful tool for resuscitation of children with septic shock in the PICU.

Keywords: Cumulative fluid balance, Fluid resuscitation, Pediatric, Septic shock, Ultrasound.

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Highlights

This pilot randomized controlled trial demonstrates that ultrasound-guided fluid therapy is significantly better than clinically guided therapy, in preventing fluid overload and its associated complication during resuscitation of children with septic shock admitted to a tertiary care hospital.

Background

Septic shock is defined as severe infection leading to cardiovascular dysfunction, including hypotension, need for treatment with a vasoactive medication, or impaired perfusion.[1] It causes 6 million pediatric deaths worldwide with at least 25–40% in-hospital mortality, irrespective of geographic region.[2,3] With the evolution of knowledge on the dynamic pathophysiology of septic shock, there has been a paradigm shift from the early goal-directed therapy to a more individualized approach.[4] The dangers of overzealous fluid boluses were first demonstrated by the FEAST trial, performed on African children with septic shock.[5]

Adult studies demonstrated increased risk of fluid-related adverse events like acute kidney injury, acute respiratory distress syndrome, prolonged mechanical ventilation, mortality, and intra-abdominal hypertension.[6–10] Thus, there is growing emphasis on dynamic markers of fluid responsiveness, and ultrasound is one such user-friendly technology available to Pediatric Intensive Care Unit (PICU) physicians. A retrospective Indian study on echo-guided management in children with fluid and inotrope-resistant shock showed that out of 22 patients, 12 had uncorrected hypovolemia and 10 had impaired ventricular function.[11] The single pediatric randomized controlled trial (RCT) showed improved shock reversal by echocardiography.[12] Reduced variations in inferior vena cava (IVC) diameter with ventilation, B lines on lung ultrasound to detect pulmonary edema, and a low ejection fraction (EF) would make the physician exercise restraint with fluid boluses and thus reduce the incidence of fluid overload and other associated complications. In this study, we combined

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Table 1: Outcome measurements, definition and cut-off points of various USG parameters

Method	*Procedure*	*Aim*	*Cut-off for giving fluid bolus*
IVC collapsibility = (maximum IVC diameter - minimum IVC diameter)/ maximum IVC diameter	mC 3–11 probe (3–11 mHz) placed in sub-xiphoid area and M-mode pointer 2 cm distal to hepatic vein confluence	Assess fluid responsiveness	>50%
IVC distensibility = (maximum IVC diameter - minimum IVC diameter)/ minimum IVC diameter	Same as above	Same as above	>12%
Ejection fraction	6S-RS (6 mHz) probe placed in parasternal long axis view	Assess cardiac contractility	>50%
Lung ultrasound	L 3–11 (3–11 mHz) probe placed in intercostals space to count B lines	Assess extra-vascular lung water	≤3 B lines/view

these three modalities in early fluid resuscitation of pediatric septic shock. Hence, our study is expected to add much needed insight on this topic.

Objectives

Primary objective: To determine the superiority of USG-guided fluid bolus along with clinical guidance versus clinical-guided fluid bolus alone in terms of the number (%) of patients with cumulative fluid balance (CFB) of more than 10% at the end of day 3 of PICU stay.[13,14]

Secondary objectives: To determine the efficacy of ultrasound on resuscitation and shock reversal time, ventilator use/duration, inotrope use, mortality, and length of PICU/hospital stay.

Materials and Methods

This prospective parallel limb randomized controlled open-labeled superiority design single-center study was based at the PICU of a government-aided tertiary care hospital in Eastern India. Patient enrolment was done between June 2021 and March 2022. Informed consent was taken from parents/caregivers of all children after initial stabilization. Prior ethical approval was obtained from the Institutional Ethics Committee (Ref. no. MC/KOL/IEC/NON-SPON/30/01-2019).

Inclusion Criteria

Children aged between 1 month and 12 years, who met the American Academy of Pediatrics trigger tool for early septic shock recognition criteria, were initially included in the study.[15]

Exclusion Criteria

Preexisting congenital or acquired heart disease, cardiac tamponade, pneumothorax, massive pleural effusion, ascites leading to intra-abdominal hypertension, dengue shock syndrome, preexisting adrenal insufficiency, known cases of interstitial lung disease or chronic kidney disease, and children who received any bolus or inotropes in the last 24 hours before admission were excluded.

Late exclusions included children who succumbed to septic shock within 24 hours of admission, those with poor echo windows, and late diagnosis of dengue shock syndrome.

An updated exclusion criterion was children having multisystem inflammatory syndrome of childhood (MIS-C).

Variables and Outcomes

We recorded demographics, history, lab investigations, pediatric index of mortality edition 2 scores at admission (PIM2), preexisting comorbidities, and multi-organ dysfunction syndrome (≥2 organs injury).[16] Vaso-active inotrope score (VIS) at 6 hours of admission and maximum value during hospitalization were recorded.[17]

Primary Outcome

The frequency of fluid overload on day 3 of admission, which was defined as CFB of >10% of admission weight.[13,14]

Secondary Outcomes

Total fluid bolus, resuscitation time (time from detection of shock to stabilization of MAP >5th centile for 2 hours even with inotrope/s), shock reversal time (time from detection of shock to stabilization of MAP >5th centile for 24 hours without inotrope), maximum VIS at 6 hours; CFB on day 1 and day 3; fluid overload on day 1, requirements of furosemide, incidence of AKI, duration of invasive ventilation, length of PICU stay and hospital stay, and overall mortality and mortality due to unresolved shock were also assessed.[12,18]

Measurement of Ultrasound Parameters

We measured IVC collapsibility (in spontaneously breathing patient) or distensibility (in mechanically ventilated patient) using convex 3–11-MHz probe, lung ultrasound using linear 3–11-MHz probe of a Esaote MyLab™X7 ultrasound machine (Esaote, Italy), and echocardiography by 6S probe on a GE Vivid S6 ultrasound machine to assess ejection fraction as per POCUS protocol.[19] Ultrasound and functional echocardiography (Table 1) were done by on-duty-trained PICU consultants on rotational duty.

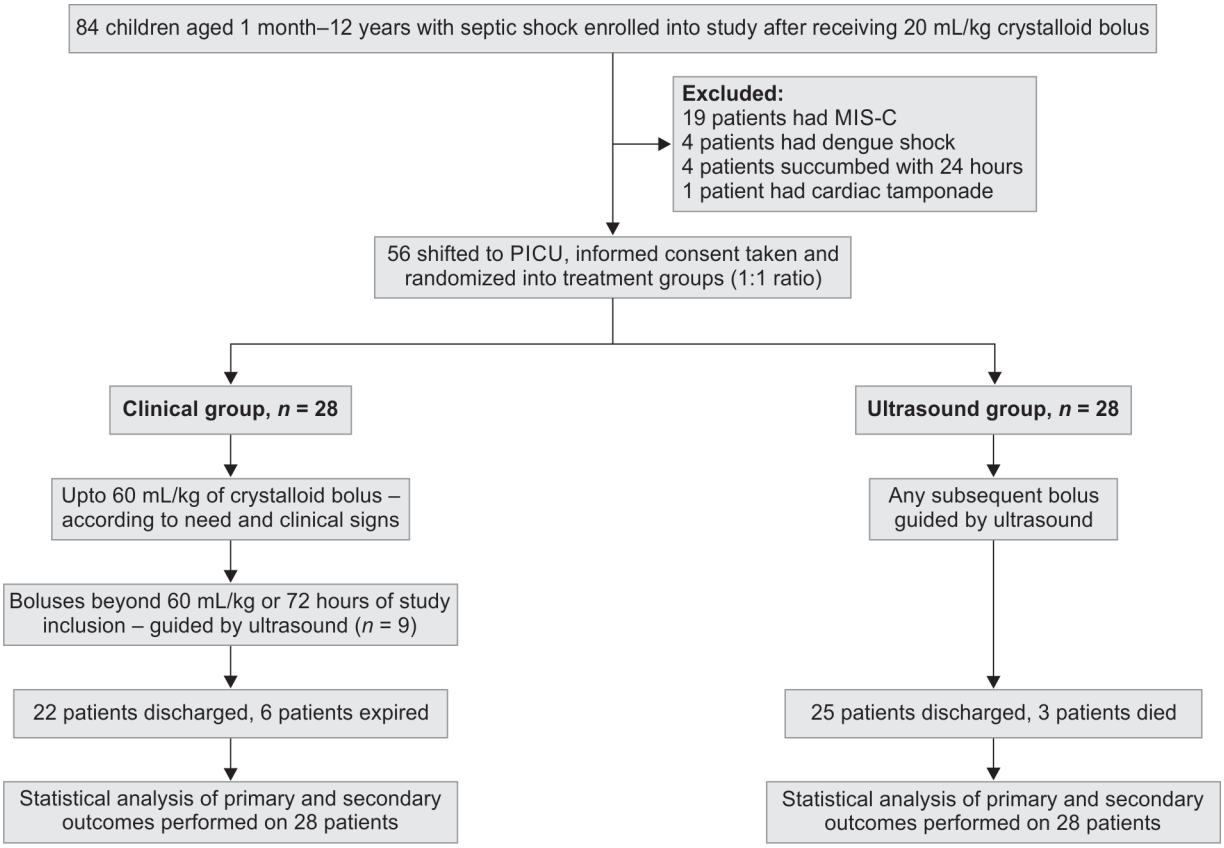
Training for Uniform Outcome Assessment

Ten PICU residents were trained in performing point-of-care ultrasound and functional echocardiography (ejection fraction, IVC indices, and ultrasound lung) and interpretation under direct observation as well as feedback on 25 patients of different ages over a month period prior to start of the study. Next, they performed on 25 different patients independently, wherein their measurements were compared to that of the expert pediatric intensivists. Interrater reliability was calculated as intraclass coefficient on SPSS. Eventually, six residents were selected to take part in the study as their intraclass coefficient was greater than 0.8. During the study, each patient's USG/IVC indices/EF status was discussed over video consultation with an on-call duty consultant in real time.

Study Protocol

Selected patients with septic shock were initially stabilized for airway and breathing and were administered 20 mL/kg of fluid boluses over 15 minutes without any ultrasound assessment. Following enrolment, patients were randomized after obtaining

Flowchart 1: Flowchart of study protocol ($n = 56$)



consent in two study arms by nursing staff unrelated to the study. Assessment of heart rate, respiratory rate, new-onset basal crepitations, urine output, mentation, and hepatomegaly was done prior to and after each bolus in both the groups and also every hour till shock reversal. In the ultrasound group, decision on further fluid bolus (10 mL/kg over 15 minutes) was taken on the basis of point-of-care ultrasound for fluid resuscitation guide (POCUS protocol) along with clinical judgment. In the clinical group, fluid resuscitation was performed only on clinical judgment as per Surviving Sepsis Campaign guideline, and ultrasound examination was done only after the patient had received (i) 60 mL/kg bolus and/or (ii) bolus requirement beyond 72 hours of inclusion in the study (Flowchart 1).[1] The initial inotrope of choice was adrenaline or noradrenaline, as per clinical assessment of narrow or wide pulse pressure. Dobutamine was used for cardiac inotropy, followed by milrinone and levosimendan. Appropriate antibiotics were given within 1 hour of presentation, to all patients, after drawing blood for culture. If ultrasound lung was required for any other indications in clinical arm, the patient was still analyzed as part of their original group, as per "Intention to Treat" method.

Sample-size Calculation

The previous pediatric RCT showed 33% reduction in fluid overload in children managed with echo-guided fluid resuscitation compared with standard therapy (11% vs 44%).[12] Considering a significance level α of 0.05 and power (β) of 80% the sample size for this study was 50. Considering the 10% attrition rate/late exclusion, we had planned to enroll 56 patients (28 patients in each group).

Randomization was done by computerized generation of a random number table, followed by 1:1 allocation in both groups through an opaque sealed envelope. The experimental group was labeled "Ultrasound group" and controlled group was labeled as "Clinical group". The sequence generation and preparation of envelopes were done by persons not related to this study.

Statistical Analysis

The above data were fed into IBM SPSS Statistical Software v25. Categorical variables were represented as percentage and compared using the Chi-square test or Fisher's exact tests as appropriate. Normally distributed numerical data were represented as mean ± SD and compared using unpaired Student's *t*-test. Skewed numerical data were represented as median and interquartile range (IQR) and compared using Mann–Whitney *U* test. A *p*-value of <0.05 was the cut-off to reject the null hypothesis. Multivariate regression was conducted on all significant outcomes to rule out the effect of other patient parameters.

Results

In total, 97 patients were screened and 84 were eligible for enrolment. Out of 84 patients, 28 patients were excluded at different stages, and eventually, 56 patients were eligible for final analysis (Fig. 1). About 9 patients in the clinical group received ultrasound-guided fluid as they required more than 60 mL/kg of boluses within 72 hours of admission.

Baseline Characteristics

There were no differences between the ultrasound and clinical groups on the basis of age, sex, weight, presence of co-morbidities, multi-organ dysfunction syndrome (MODS), myocardial dysfunction,

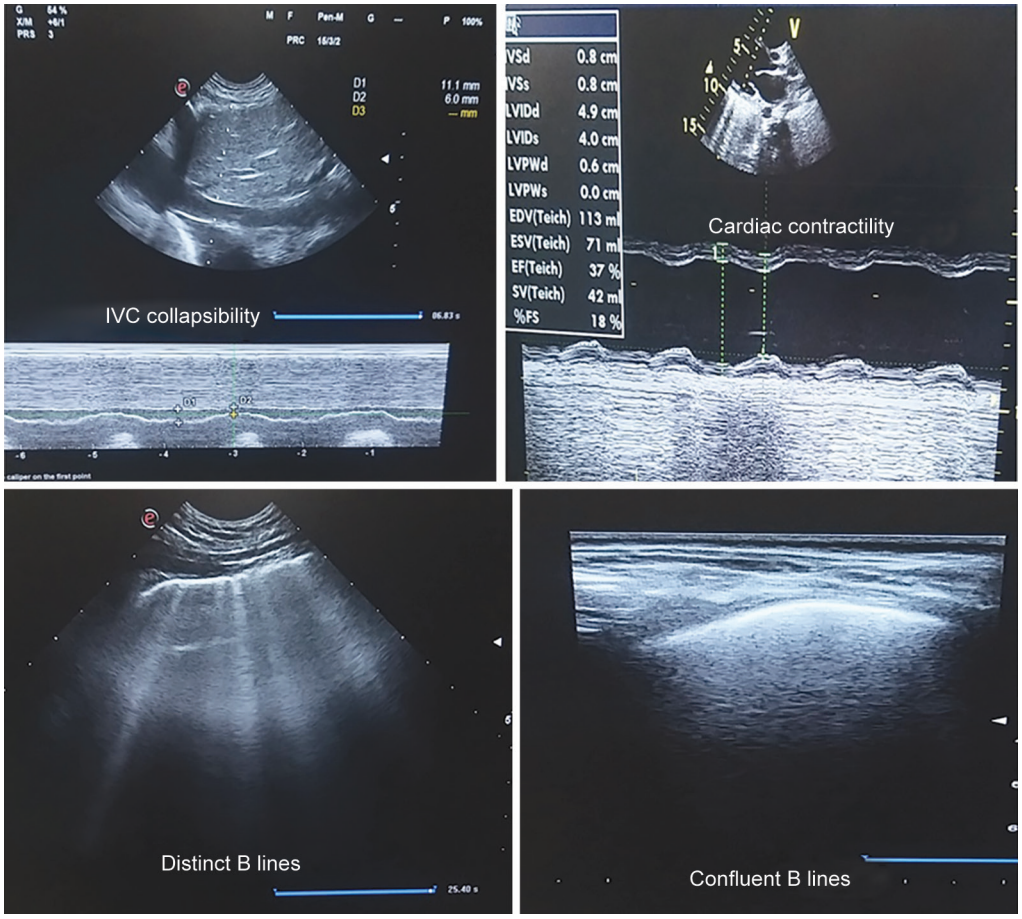


Fig 1: Ultrasound parameters used in the study to decide fluid bolus (Top left – IVC in the subcostal view with M-mode tracing, Top right – Ejection fraction measurement in parasternal left axis view, Bottom left – Distinct B lines on lung ultrasound, and Bottom right – Confluent B lines on lung ultrasound)

PIM2 score, source of infection, and laboratory parameters (Table 2). Although there were a larger proportion of infants and undernourished children in the clinical group, this was not statistically significant. The most common primary infection in both groups was pneumonia, followed by blood stream infection. None of the patients received colloids.

Primary Outcome

Significantly fewer number of patients in the ultrasound group developed fluid overload, i.e., CFB >10% on day 3 of admission [25% vs 62%, $p = 0.012$, RR = 2.5 (1.1–5.3)]. Percentage of CFB on day 3 was also significantly lower in the ultrasound group [6.5 (3.3–10.3) vs 11.3 (5.4–17.5), $p = 0.02$] (Table 3).

Secondary Outcomes

Significantly lesser fluid bolus was administered to the ultrasound group [40 (30–50) vs 50 (40–80) mL/kg, $p = 0.003$]. Though the incidence of fluid overload after 24 hours of admission was lower in the ultrasound group, this was not statistically significant (7% vs 25%, $p = 0.143$) (Table 3).

Resuscitation time was significantly shorter for patients in the ultrasound group (13.4 ± 5.6 vs 20.5 ± 8 hours, $p = 0.003$). Shock reversal time was shorter in ultrasound group [48 (34–85) vs 67 (44–84) hours, $p = 0.356$], but did not reach statistical significance. There was no significant difference in terms of inotrope/vasopressor usage as per the VIS at initial 6 hours (33 ± 13 vs 34 ± 12, $p = 0.93$) and maximum VIS throughout hospitalization (55 ± 35 vs 57 ± 30 hours, $p = 0.72$).

Significantly lesser number of patients in the ultrasound group required Furosemide to alleviate fluid overload (39.3% vs 71.4%, $p = 0.016$). AKI though less frequent in the ultrasound group, it was not a significant reduction (3.5% vs 21.4%, $p = 0.1$). Eventually, 1 patient in the clinical group and 2 patients in the ultrasound group required peritoneal dialysis.

There was no significant difference in ventilator requirement or duration of invasive ventilation and length of PICU/hospital stay between both groups. The overall mortality though lesser in ultrasound group, this was not significant. There were no deaths due to unresolved shock in the ultrasound group.

Regression Models

We ran multivariate linear regression on all the significant quantitative outcomes to evaluate the effect of other variables. Ultrasound independently reduced the CFB% on day 3 by 6.8% and reduced the total fluid bolus administered by 15.3 mL/kg. Similarly, the time to initial hemodynamic stabilization, i.e., resuscitation time, was reduced by 6.2 hours by virtue of being in the ultrasound group. We also ran binomial logistic regression on the occurrence of fluid overload on day 3. Ultrasound independently reduced the odds

Table 2: Demographics, clinical and laboratory characteristics between groups (*N* = 56)

Variables	*Ultrasound (N = 28)*	*Clinical (N = 28)*	*p-value*
Age in years	4 (1.4–8.5)	1.4 (0.5–7.5)	
Infants	6 (21.4)	11 (39.3)	0.32
Male sex	20 (71)	15 (53.5)	0.168
Weight (kg)	16.5 (8.5–23.8)	9.5 (5–20)	0.09
Number of undernourished children	7 (25)	13 (46.5)	1.00
Chronic comorbidities	6 (21)	8 (29)	0.54
Myocardial dysfunction	16 (57)	16 (57)	1.0
MODS at admission	20 (71)	21 (75)	0.76
PIM2 score (mean ± SD)	32.3 ± 4.6	31 ± 3.9	0.92
Source of infection			
Pneumonia	9 (32)	9 (32)	0.69
Blood stream	10 (36.5)	9 (32)	
Osteomyelitis	1 (3.5)	0	
Meningitis	6 (21)	6 (21.5)	
Abdominal infection	1 (3.5)	3 (10.5)	
Urosepsis	1 (3.5)	0	
Pericardial effusion	0	2 (7)	
Hemoglobin (gm%)	9.5 (8.5–10.5)	9.7 (8.8–12.2)	0.16
Total leukocyte count (/mm^3) (mean ± SD)	17,794 ± 10,828	20,480 ± 9,220	0.32
Total platelet count (/mm^3)	2,77,500 (1,09,000–3,60,000)	2,58,000 (1,48,000–3,95,000)	0.82
Serum CRP (mg/dL) (mean ± SD)	6.4 ± 3.2	5.2 ± 3.1	0.156
Serum creatinine (mg/dL) (mean ± SD)	0.6 ± 0.3	0.8 ± 0.6	0.14
Serum albumin (gm/dL) (mean ± SD)	3.1 ± 0.4	3 ± 0.3	0.17
SGOT (U/L)	63 (45–91)	78 (47.5–138.5)	0.5
Serum lactate (mmol/L) (mean ± SD)	3.2 ± 1.2	3.1 ± 1.3	0.8
Inotropes received			
Adrenaline	5 (18)	2 (7)	0.4
Noradrenaline	6 (21)	9 (32)	
Combination	17 (61)	17 (61)	
Need of steroid			
Hydrocortisone	6 (21.4)	8 (28.5)	

All quantitative variables are presented as median (IQR), unless otherwise mentioned in the Table. All categorical variable are presented as *n* (%)

of fluid overload on day 3 by nearly 11 times with a 95% interval of 1.6–71.1 (Table 4).

Effect of Fluid Overload on Mortality

Fluid overload on day 3 significantly increased the mortality rate by around five times (36.8% vs 7.6%, $p = 0.03$), though it had no significant effect on AKI (Table 5).

Discussion

Prompt and adequate fluid resuscitation is a fundamental but challenging procedure in children with septic shock. Both deficient and excessive fluid resuscitation are associated with a poor prognosis. Our study set out to demonstrate the usefulness of ultrasound in reducing adverse effects of aggressive fluid resuscitation in children with septic shock, with the primary outcome being frequency of fluid overload on day 3.

The frequency of fluid overload on day 3 was significantly lower by 37%, with ultrasound usage. Binomial logistic regression demonstrated a nearly 11-fold reduction in odds ratio for developing fluid overload on day 3. Though there were a few RCTs done on the adult population,[20–23] there was only one such study done in the pediatric age group, conducted in Egypt by El-Nawawy et al. This particular study serially measured echocardiographic parameters and showed significantly reduced incidence of fluid overload on day 3 of admission (11% vs 44%, $p < 0.05$), similar to our study.[12] Kelm et al. revealed that clinical evidence of fluid overload could reach up to 67% in adults with septic shock treated with early goal-directed therapy.[6] In a study by Ranjit et al., on multimodal monitoring in fluid-resistant septic shock in children, the incidence of fluid overload was 44%.[24]

We found a statistically significant reduction in total fluid bolus at 72 hours of admission and cumulative fluid balance on day 3 in the ultrasound group. The adult study by Musikatavorn et al. also found lesser fluid bolus requirement in the USG-guided arm [79 (51–102) vs 88 (67–123) mL/kg, $p = 0.005$] at 24 hours.[20] El-Nawawy et al. revealed that by the end of the 24 hours, children in the echocardiography group received significantly lower fluid

Table 3: Comparison of primary and secondary outcomes between two study groups ($n = 56$)

Outcome parameters	*Ultrasound (N = 28)*	*Clinical (N = 28)*	*p-value*	*Relative risk (95% CI)*
Amount of fluid bolus (mL/kg)	40 (30–50)	50 (40–80)	0.003	
Cumulative fluid balance on day 1 (%, IQR)	3.9 (2.5–8.4)	6.5 (3.8–9.9)	0.13	
Fluid overload (CFB >10%) on day 1, *N* (%)	2 (7%)	7 (25%)	0.143	3.6 (0.8–15.4)
Cumulative fluid balance % on day 3, Median (IQR)	6.5 (3.3–10.3)	11.3 (5.4–17.5)	0.02	
Fluid overload (CFB >10%) on day 3, *N* (%)	6 (25%)	13 (62%)	0.012	2.5 (1.1–5.3)
Change in cumulative fluid balance% (IQR) from day 1 to day 3	0.7 (–1.5 to 5.8)	0.8 (–1.5 to 8.9)	0.37	
Resuscitation time (hours) (mean ± SD)	13.4 ± 5.6	20.5 ± 8	0.003	
Shock reversal time (hours) Median (IQR)	48 (34–85)	67 (44–84)	0.356	
Vaso-active inotrope score in first 6 hours, Median (IQR)	35 (20–45)	40 (20–40)	0.93	
Maximum VIS score, Median (IQR)	50 (20–74)	51 (37–80)	0.72	
Number of patients needing Furosemide, *N* (%)	11 (39.3%)	20 (71.4%)	0.016	1.8 (1.1–3.0)
Occurrence of AKI, *N* (%)	1 (3.5%)	6 (21.4%)	0.1	6 (0.8–47.6)
Duration of invasive ventilation (days), Median (IQR)	2 (1–3.5)	2.5 (1.5–4.5)	0.34	
Ventilator requirement (%)	19 (67%)	23 (82%)	0.217	1.2 (0.5–6.5)
Length of PICU stay (days), Median (IQR)	6 (3.5–11)	7 (4–13)	0.67	
Length of hospital stay (days), Median (IQR)	14 (10–25)	15 (10.5–25)	0.85	
Mortality, *N* (%)	3 (10.7%)	6 (21.4%)	0.131	2 (0.7–3.4)
Death due to unresolved shock, *N* (%)	0	5 (50%)		

Table 4: Regression analysis for each significant outcome from univariate analysis ($n = 56$)

Significant quantitative outcomes	*Coefficient of regression*	*p-value*	*95% CI (for coefficient of regression)*
Cumulative fluid balance (%)	6.8	0.039	0.12–14.2
Amount of fluid bolus (mL/kg)	15.3	0.046	0.08–31.48
Resuscitation time (hours)	6.2	0.014	1.14–11.35
Significant categorical outcome	*Odds ratio*	*p-value*	*95% CI (for odds ratio)*
Frequency of fluid overload on day 3	10.8	0.013	1.6–71.1

Table 5: Association of fluid overload on day 1 and day 3 with mortality and AKI ($n = 56$)

Variables	*Fluid overload present on day 1 (n = 9)*	*Fluid overload absent on day 1 (n = 47)*	*p-value*	*Relative risk (95% CI)*
Mortality	3 (33.3%)	6 (12.7%)	0.13	2.6 (0.8–8.2)
AKI	3 (33%)	4 (8.5%)	0.074	3.9 (1.1–6.6)
	Fluid overload present on day 3 (n = 19)	*Fluid overload absent on day 3 (n = 26)*	*p-value*	*Relative risk*
Mortality	7 (36.8%)	2 (7.6%)	0.03	4.8 (1.1–20.5)
AKI	3 (15.8%)	2 (7.7%)	0.636	2.1 (0.4–11.1)

(86 vs 98 mL/kg, $p = 0.027$), probably due to early and successful titration of fluid volume.[12] The additional help of lung ultrasound may have resulted in an overall lesser fluid bolus in our treatment arm, and a larger proportion of malnourished children in our control arm (though nonsignificant) had led to overall lesser amount of fluid bolus.

There was a significant reduction in resuscitation time, hence, ultrasound usage led to earlier hemodynamic stabilization by 6.2 hours in our study arm, though shock reversal time was similar in both the groups. Resuscitation time was similarly lesser in the echocardiography arm of a pediatric study.[12] But contrary to our observation, they showed a markedly shorter shock reversal time [3.3 (1,8) vs 4.5 (1.3,10) days, $p = 0.01$]. Repeated echocardiography assessment at various time points during the initial phase of stabilization may have had led to improve shock reversal time in that study. Ranjit et al. demonstrated a shock reversal time of 19.4 ± 9.4 hours in 48 PICU children where echo was performed after 6 hours of PICU admission, but in that study, LV/RV dysfunction was less prevalent [19 out of 48 (39%)] in comparison to 57% in our cohort.[24]

We did not find any difference between both groups on the basis of inotrope and ventilator requirement and VIS. El-Nawawy et al. showed earlier inotrope usage and overall lesser VIS in their study arm.[12] Repeated measurements to diagnose systolic and diastolic dysfunction early might have helped in early optimization of vasopressors/inotropes and allowed tailor-made prescription of each patient. Regular assessment of diastolic dysfunction was not in our study protocol. These limitations of our study possibly did not allow earlier optimization of inotrope doses. Comparable to our study cohort, Musikatavorn et al. found no difference in ventilator usage at 72 hours in an adult cohort through ultrasound-guided resuscitation (23% vs 30%, $p = 0.26$).[20] Diuretics usage and AKI were slightly lesser in the USG arm of this study, though it was

not statistically significant. Lower cumulative fluid balance in the treatment arm may have been the reason.

Duration of PICU and hospital stay was similar in both the groups of our study. PICU stay among survivors of the study group in Egyptians was significantly shorter (8 ± 3 vs 14 ± 10 days, $p = 0.005$).[12] In comparison to the same study cohort, the overall PICU stay in the control group was shorter in our study. Lower PIM2 score in our cohort (31 vs 51 in Egyptian cohort) may have caused this difference. Comparable to our observation, lengths of ICU and hospital stay were similar in both groups of the adult studies.[20,22,23]

Although the mortality was lower in our ultrasound group, it was not statistically significant. Similar observation was noted by both pediatric and adult studies from different corners of the globe.[12,22,23] A larger study might find a mortality benefit of ultrasound guidance. However, on subgroup analysis, the Egyptian study has albeit found significant benefit in mortality due to unresolved shock in study group [38% (5/13) vs 88% (15/17)].[12] Though there were no deaths due to unresolved shock in the ultrasound group of our study, but it was not significant, probably due to less event rate in both the arms.

The adult RCT from China, much like our study, assessed lung ultrasound, ejection fraction, IVC variations, and additionally RV dilatation but only at a single time point.[22] Cumulative fluid balance at 72 hours, vasoactive drug usage, lactate clearance, duration of ventilation, and ICU stay were similar in both groups. The author stated that lesser number of patients (22.4%) than expected had abnormal ultrasound findings, which weakened its clinical effect. Hence, a larger study might be needed. Higher incidence of myocardial dysfunction in our study (57% in our study vs 18–20% in the Chinese study) along with the basic difference in age group might have shown improvement in CFB% in the ultrasound group. Similarly, the multicenter adult RCT by Atkinson et al. found no difference in 30-day survival, ventilator and inotrope usage, and lengths of ICU/hospital stay between two groups.[23]

Subgroup Analysis

The incidence of fluid overload on day 3 (CFB%>10) was significantly increased mortality by 29%, irrespective of treatment group ($p = 0.03$). This was an indication of the fact that fluid overload may indirectly contribute toward mortality in these children. These findings were mirrored by an American retrospective cohort study by Neyra et al., where higher CFB% at 72 hours was independently associated with higher rates of AKI and mortality.[25] A Chinese observational study found a much lower occurrence (4.5%) of children with CFB% >10 when children with septic shock were treated with standard fluid boluses, but this was significantly associated with mortality.[26]

Strengths of this Study

Unlike most other RCTs, three different ultrasound parameters – ejection fraction, IVC status, and lung ultrasound – were assessed, thus lending a comprehensive state of the patients' overall hemodynamic and pulmonary fluid status. Inadequacy of similar pediatric RCTs makes the findings of this study important.

Limitations of this Study

This is a single-center study. Larger multicenter randomized controlled trials are a must to provide uniformity. Due to the nature of the intervention, blinding was not possible. The inability to assess diastolic dysfunction was an important limitation, as up to 41% of children with septic shock may have diastolic dysfunction and with a high mortality.[27] Serial USG might have improved inotrope dose adjustments. However, parameters to measure stroke volume [velocity time integra (IVTi)] and left ventricular volume [end point septal separation (EPSS)] as suggested in new POCUS guidelines[28] were not assessed in our study.

Conclusion

Early commencement of ultrasound-guided fluid boluses was found to be significantly better than clinically guided therapy in preventing fluid overload and its associated complications in children with septic shock. Ultrasound-guided resuscitation aids in significantly quicker hemodynamic stabilization. These factors make point-of-care ultrasound a potentially useful tool for resuscitation of children with septic shock in resource-restricted setting, where there is dearth of invasive hemodynamic monitoring. Larger multicenter trials are required to prove its benefits on mortality.

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