Adverse Outcomes due to Aggressive Fluid Resuscitation in Children: A Prospective Observational Study

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Abstract

Fluid management has a major impact on the duration, severity, and outcome of critically ill children. The aim of this study was to examine the relationship between cumulative fluid overload (CFO) with mortality and morbidity in critically ill children. This was a prospective observational study wherein children (1 month–16 years) who were critically ill (with shock requiring inotropes and/or mechanically ventilated) were enrolled. CFO was defined as the sum of daily fluid balances. Daily fluid balance was calculated as a difference between fluid intake (oral and intravenous) and output (urine output, discharge from nasogastric tube) in 24 hours. Percentage of fluid overload (FO) (PFO) was calculated as the ratio of CFO with weight at admission in kilogram. The CFO and PFO at 24, 48, 72 hours and at 7 days or end of PICU stay were calculated. A total of 291 children (244 survivors and 47 non-survivors; 47% males) were included in the final analysis. A higher mortality was observed in children with higher PFO (>20% FO: 45.8% mortality vs. 14.5% < 10% FO, $p < 0.01$) and CFO (10.97 ± 6.4 mL/kg in survivors vs. 13.95 ± 9.6 mL/kg in non-survivors; $p = 0.022$) at 72 hours. A 1% increase in fluid overload was associated with 6% and 4% increase in mortality at 72 hours and 7 days, respectively. Similarly, the impact of every 1% increase in fluid overload on both ventilation (yes/no) and acute kidney injury (AKI; yes/no) were found to be significant for both parameters at 72 hours, but only AKI had significant correlation on seventh day. In the multivariate stepwise Cox's proportional hazard model for PICU stay and hospital stay, 3% ($p < 0.05$) and 2% ($p > 0.05$) increase were found for every 1% increase in fluid overload, respectively. Oxygenation index is also associated with fluid overload with the adjusted model estimated 0.27 units (95% confidence interval: 0.18–0.36) increase per 1% increase in fluid overload. FO was associated with increased mortality and morbidity in critically ill children.

Keywords

- ▶ critically ill
- ▶ intensive care units
- ▶ pediatric
- ▶ critical care
- ▶ fluid
- ▶ therapy

Introduction

Fluid management plays a major role in resuscitation of critically ill. Aggressive volume expansion to support tissue oxygen delivery as part of early management of septic shock has

been associated with dramatic improvements in outcome. Recent data suggest that the cost–benefit of aggressive fluid resuscitation is more complex than previously thought and may depend on clinical scenario and the availability of intensive

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care.¹ After the resuscitation phase, critically ill children tend to retain free water while having reduced insensible losses. A dose-response relationship between cardiopulmonary complications and increasing degrees of fluid overload (FO) has been demonstrated in adult critical care patients; those with less fluid gain and lower lung water had more ventilator free days and shorter intensive care unit and hospital length of stays which indicates lesser morbidity.^{1,2} Retrospective studies have looked at positive fluid balance and morbidity in pediatric population.³ However, only few studies have evaluated the degree of daily positive fluid balance and its relation to morbidity and mortality prospectively.⁴

The aim of this study was to examine the association of degree of cumulative FO (CFO) with the morbidity and mortality in critically ill children.

Materials and Methods

Setting and Participants

This prospective observational single-center study was conducted in the pediatric intensive care unit (PICU) of a tertiary care hospital. Children were enrolled between October 2016 and September 2017. Children aged between 1 month and 16 years who were critically ill (with shock requiring inotropes and/or mechanically ventilated) were included. Children with chronic kidney disease, nephrotic syndrome, congestive cardiac failure, and those with PICU stay less than 24 hours were excluded. The study was approved by the Institutional Ethics and Research Board Committee. Informed written consent was obtained from the parent (s)/guardian(s) of each patient before enrollment.

Objectives and Outcome Measures

The objective was to determine the association between positive fluid balance with clinically important outcome measures, such as duration of ventilation, oxygenation index (OI), incidence and severity of acute kidney injury (AKI), PICU and hospital length of stay (LOS) and death.

Methodology

Data recorded prospectively at admission included age, gender, severity of illness (Pediatric Risk of Mortality [PRISM] III score) and the diagnosis. The PRISM III score is based on clinical and laboratory parameters assessed during the first 12 hours. Additional information recorded during the PICU stay included duration of inotropes and mechanical ventilation, OI, presence or absence of AKI, need for renal replacement therapy, and duration of stay in the PICU and the hospital. Routine and specific investigations including cultures done in all cases were also recorded. The children were treated as per standard protocol guidelines.

Estimating Cumulative and Percent Fluid Overload

Fluid balance was calculated based on total fluid intake and urine output every day for the first 7 days of PICU stay. The patients were followed up until death, hospital discharge, or for 28 days. Daily fluid balance was calculated as a difference between fluid intake (oral and intravenous) and output (diur-

esis, discharge from nasogastric tube). CFO was defined as the sum of daily fluid balances until the given day and calculated at 24, 48, 72 hours, and at 7 days or end of PICU stay. The percentage of FO (PFO) is calculated as the ratio of CFO with weight at admission in kilogram ($\text{CFO} \div \text{weight at admission [kg]} \times 100$) at the given day.⁵ Based on previous studies, < 10% is considered as mild FO, 10 to 20% as moderate, and above 20% as severe FO. OI was calculated according to standard formula ($\text{mean airway pressure} \times \text{FiO}_2 \times 100 / \text{PaO}_2$) and the worst recorded OI was used for analysis.⁶ AKI was defined according to KDIGO criteria.⁷

Sample Size Calculation

Assuming 5% level of significance and 80% power, our required sample size was a minimum of 42 each of survivors and non-survivors. This calculation was done using “*n.for.2p* ()” of “epi Display” package of R.

Statistical Analysis

Data were entered into Microsoft Excel 2013. All quantitative variables are summarized by mean and standard deviation classified by group indicator. Independent *t* test or Mann-Whitney's test⁸ was applied for statistical significance depending on shape of the data. The qualitative variables are summarized in terms of count and percentage stratified by group indicator. Chi-square test of independence was applied for statistical significance. The FOs at different days stratified by survivor and non-survivor were compared by box-whisker plot. A stepwise multivariate logistic regression⁹ for all dichotomous outcome on exposure adjusted for potential risk factors and a stepwise multivariate linear regression model for continuous outcome on exposure adjusted for potential risk factor were applied to estimate the impact of FO on different outcomes. For PICU and hospital stay, a stepwise Cox's proportional hazard model was applied. Finally, impact of FO on all outcomes with their 95% confidence intervals (CIs) is presented in terms percentage increase or unit increase per unit increase of FO by an error bar plot. The data have been analyzed by statistical Software R version 3.4.3.

Results

A total of 291 cases were enrolled during the study period (—Fig. 1). Among them were 244 survivors and 47 non-survivors. Median age of the study children was 47 months (interquartile range [IQR]: 6, 171) and 47% were males. Median PRISM III score at admission was 9 (IQR: 0, 28). Median duration of PICU stay was 6 days (IQR: 2, 24) and hospital stay was 10 days (IQR: 3, 28); 15.1% of study population required mechanical ventilation with a median duration of 96 hours (IQR: 24, 483). Most common diagnosis at admission was related to respiratory system (66%). AKI was seen in 17.2% of the study population and 74.9% had one or more organ dysfunction detected as per standard guidelines, while 17% had anemia. One in five children required inotropes. Coagulopathy was found in 20%. Overall mortality rate was 16% among those recruited for the study. Other key

Fig. 1 Study design.

baseline characteristics of the study population are described in **Table 1**. PFO of 24, 48, 72 hours and 7 days among survivors and non-survivors were assessed (**Fig. 2**). Further analysis was done on CFO and PFO at 72 hours and 7 days. Based on the above analyses, mortality was increased significantly among children with higher PFO (>20% FO: 45.8% mortality vs. 14.5% <10% FO, $p < 0.01$) and CFO (10.97 ± 6.4 mL/kg in survivors

vs. 13.95 ± 9.6 mL/kg in non-survivors; $p = 0.022$) at 72 hours. Similar observations were seen for data at 7 days; PFO (>20% FO: 7% in survivor group vs. 22% in non-survivor group; $p < 0.01$) and CFO (122.9 ± 88.6 mL/kg in survivors vs. 172.6 ± 112.6 mL/kg in non-survivors; $p = 0.024$). Higher PFO was associated with increased PICU LOS in 10 to 20% FO group compared with <10% FO group (10.1 ± 6.3 vs. 5.7 ± 2.7 days; $p = 0.001$). Likewise, higher degree of PFO was

Table 1 Baseline characteristics of the study population

Parameter	Overall (n = 291)	Survivor (n = 244)	Non-survivor (n = 47)	p-Value
Age (mo)	48 (3,172)	48 (3,154)	46 (5,172)	0.9
Weight (kg)	13.9 (3.1,48.4)	14.24 (3.2,36.8)	13.42(3.1,48.4)	0.8
Gender (males %)	47.1	43.4	56.6	0.4
Number of children receiving fluid bolus	273	229	44	0.6
Number of children ventilated	116	69	47	0.04**
PaO ₂ /FiO ₂	181.5 (48,361)	182.6 (72,361)	142.2 (48,278)	0.814
Number of children requiring RRT (%)	14.43	7.6	24.16	0.001**
Labs at admission				
Hemoglobin (g/dL)	10 ± 2.5	10.2 ± 1.9	9.7 ± 2.3	0.09
Lactate (mmol/L)	2.5 (0.8, 6.8)	2.26 (0.4, 5.1)	3.7 (0.8, 6.8)	0.07
Creatinine (mg/dL)	0.42 (IQR 0.25, 0.68)	0.2 (IQR 0.1, 0.6)	0.3 (IQR 0.2, 0.8)	0.069
Admission diagnosis—organ system primarily involved				
Respiratory	192 (66%)	161	31	
Cardiac	6 (2%)	5	1	
Neurology	23 (8%)	20	3	
Hematology	9 (3%)	7	2	
Trauma	20 (7%)	17	3	
GI	12 (3.6%)	9	3	
Others	29 (10.7%)	25	4	

Abbreviations: GI, gastrointestinal system; RRT, renal replacement therapy.

**p-Value < 0.05.

also associated with increased hospital LOS among the same groups (10.8 ± 8.3 vs. 15.8 ± 9.4 days; $p = 0.04$).

Fluid overload at 72 hours was analyzed to look for possible association with duration of ventilation and OI. There was significant difference observed in duration of ventilation across the levels of PFO at 72 hours. The mean ventilation duration in the 10 to 20% FO group was found to be 83.6 ± 52.3 hours compared with 162.7 ± 122.4 hours for <10% FO group ($p = 0.001$). A significant difference in OI was

found between the two groups for the levels of PFO at 72 hours, described above. The OI in >20% FO group was 8.1 ± 3.4 as compared with 12.8 ± 8.1 in <10% FO group ($p = 0.018$).

A higher incidence of AKI was also seen when the 10 to 20% FO group was compared with the <10% FO group (21.8 vs. 5.5%; $p = 0.018$). Also, the PFO was greater in AKI children versus those children who did not have AKI (9.0 ± 7.1 vs. 11.9 ± 9.2 , $p = 0.009$).

A multivariate stepwise logistic regression (→Fig. 3) of mortality at 72 hours and 7 days was performed. CFO was adjusted for PRISM III score, organ dysfunction, infection, and comorbidities (→Table 2) (best subset selected by Akaike Information Criterion). The model showed odds ratios (ORs) of 1.06 (95% CI: 1.01–1.11) and 1.04 (95% CI: 1.01–1.08), which implies 6 and 4% increase in mortality for every 1% ($p < 0.05$) increase in FO at 72 hours and 7 days, respectively. Similarly, the impact of every 1% increase in 72 hours FO on both ventilation (yes/no) and AKI (yes/no) were found to be significant but only for AKI for FO at seventh day. The ORs with their 95% CIs were estimated as 1.07 (95% CI: 1.01–1.13) and 1.09 (95% CI: 1.03–1.14) for 72 hours and 7 days FO, respectively, after adjusting for sex, age, PRISM III score, infection, comorbidity, organ dysfunction, and the need for inotrope(s).

A multivariate stepwise Cox's proportional hazard model (→Fig. 3) of PICU stay and hospital stay considering mortality as the censoring, estimated hazard ratio as 0.97 (95% CI: 0.95–0.99) and 0.98 (95% CI: 0.96–1.001) due to 72 hours FO,

Fig. 2 Comparison of daily fluid balance between the two study groups.

Fig. 3 Increase in outcome per 1% increase in fluid overload (multivariate analysis).

respectively. This latter finding implies a 3% ($p < 0.05$) and 2% ($p > 0.05$) increase in PICU stay and hospital stay, respectively, for every 1% increase in 72 hours FO. Similarly, the 7 days FO also estimated a significant increase in both PICU (2.9%) and hospital stay (3.7%). Similarly, the adjusted model for OI estimated that for a 0.27 unit (95% CI: 0.18–0.36) increase in OI per 1% increase in 72 hours FO.

Discussion

This was a prospective observational study to assess the effects of FO on mortality and morbidity in critically ill children. FO at 72 hours and 7 days was used for analysis, and it was found that in multivariate analysis with age, sex, PRISM III score, organ dysfunction, and comorbid conditions being controlled, FO independently increased the morbidity and mortality.

We also evaluated the degree of FO and risk of morbidity and mortality. It was observed that children with higher degree of FO had higher risk of mortality, longer PICU and hospital LOS, higher incidence of mechanical ventilation, longer duration of ventilation, and higher OI. This once again shows that not just the presence but also degree of FO affects the eventual outcome of these patients. A percentage FO of more than 20% was found

to be associated with significantly increased mortality and morbidity. Children with $>20\%$ FO had higher risk of mortality in the initial 72 hours of admission as compared with children with $<20\%$ FO. However, on comparing the length of PICU and hospital stay between survivors and non-survivors, a significant correlation to FO was found only among $<10\%$ versus 10 to 20% PFO groups. This latter result could be because children with higher FO did not survive long enough to reveal a significant correlation. The same bias can be considered to be present for the $>20\%$ group for the duration of mechanical ventilation. Comparable to previous studies,¹⁰ this study also reports that positive fluid balance increased the duration of mechanical ventilation, PICU, and hospital stay.

In pediatric patients with acute lung injury, OI at admission predicted death and length of mechanical ventilation, with high specificity and sensitivity^{11–13} as well as predicting the development of chronic lung disease in neonates.¹⁴ Our study showed statistically significant correlation between positive fluid balance and OI, both at the end of 72 hours and 7 days, thereby again showing the increased respiratory morbidity associated with FO.

This study also investigated the association between FO and AKI. It has been previously reported that children with a higher degree of FO were found to have higher rate of AKI, as

Table 2 Univariate analysis by outcome among survivors and nonsurvivors at 72 hours

Factor	Subgroup	Survivors (%)	Non-survivor (%)	Odds ratio, <i>p</i> -Value
Fluid overload group	<10%	106 (85.5%)	18 (14.5%)	0.368 (95% CI = 0.14–0.91) <i>p</i> < 0.001**
	10–20%	112 (94.1%)	7 (5.9%)	
	>20%	26 (54.2)	22 (45.8)	
Age	<1	110 (86.6)	17 (13.4)	1.50 (95% CI = 0.68–3.31) <i>p</i> = 0.522
	1–5	56 (81.2)	13 (18.8)	
	6–16	78 (82.1)	17 (17.9)	
PRISM III	0–10	142 (91)	14 (9)	3.54 (95% CI = 1.70–737) <i>p</i> < 0.001**
	11–16	63 (74.1)	22 (25.9)	
	16–21	30 (85.7)	5 (14.3)	
	>21	9 (60)	6 (40)	
Organ dysfunction	No	68 (93.2)	5 (6.8)	3.24 (95% CI = 1.23–8.54) <i>p</i> = 0.021**
	Yes	176 (80.7)	42 (19.3)	
Infection	No	31 (81.6)	7 (18.4)	0.83 (95% CI = 0.34–2.01) <i>p</i> = 0.864
	Yes	213 (84.2)	40 (15.8)	
Comorbidities	No	234 (86.3)	37 (13.7)	6.23 (95% CI = 2.46–16.23) <i>p</i> < 0.001**
	Yes	10 (50)	10 (50)	
Anemia	No	201 (83.4)	40 (16.6)	0.81 (95% CI = 0.34–1.94) <i>p</i> = 0.808
	Yes	43 (86)	7 (14)	
Coagulopathy	No	204 (87.6)	29 (12.4)	2.99 (95% CI = 1.50–5.98) <i>p</i> = 0.003**
	Yes	40 (70.2)	17 (29.8)	
Inotrope requirement	No	200 (84.7)	36(15.3)	1.38 (95% CI = 0.65–2.94) <i>p</i> = 0.511
	Yes	44 (80)	11 (20)	

Abbreviations: CI, confidence interval; PRISM, Pediatric Risk of Mortality.

***p*-Value < 0.05.

compared with children with lesser FO.¹⁵ A similar finding of increased frequency and higher grade of AKI was seen in this study (*p* = 0.04). However, whether FO causes increased risk of AKI or FO was caused by the renal injury could not be ascertained.

Our study has several limitations. The sample size used in this particular study is small and a larger study involving multiple centers is required to confirm our findings in this study. Fluid status prior to admission was not accounted for in this study, which may have underestimated FO. Also, fluid balance was calculated based on the daily intake and output which can be an inaccurate method of assessing FO. Children with AKI and other organ dysfunction were included in the study which could have independently affected the outcome. Whether FO was the cause or the result of the same could not be ascertained and will require a stratified data analysis for clarification. Finally, the duration of hospital stay can be an inaccurate method of assessing morbidity, as several factors such as the type of illness and chronicity of illness can alter the duration of stay, perhaps explaining the lack of correlation between FO and duration of hospital stay.

Conflict of Interest

None declared.

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References

- Brandstrup B, Tønnesen H, Beier-Holgersen R, et al; Danish Study Group on Perioperative Fluid Therapy. Effects of intravenous fluid restriction on postoperative complications: comparison of two perioperative fluid regimens: a randomized assessor-blinded multicenter trial. *Ann Surg* 2003;238(05):641–648
- Schuller D, Mitchell JP, Calandrino FS, Schuster DP. Fluid balance during pulmonary edema. Is fluid gain a marker or a cause of poor outcome? *Chest* 1991;100(04):1068–1075
- Foland JA, Fortenberry JD, Warshaw BL, et al. Fluid overload before continuous hemofiltration and survival in critically ill children: a retrospective analysis. *Crit Care Med* 2004;32(08):1771–1776
- Sakr Y, Vincent JL, Reinhart K, et al; Sepsis Occurrence in Acutely Ill Patients Investigators. High tidal volume and positive fluid balance are associated with worse outcome in acute lung injury. *Chest* 2005;128(05):3098–3108

- 5 Goldstein SL, Somers MJ, Baum MA, et al. Pediatric patients with multi-organ dysfunction syndrome receiving continuous renal replacement therapy. *Kidney Int* 2005;67(02):653–658
- 6 Pediatric Acute Lung Injury Consensus Conference Group. Pediatric acute respiratory distress syndrome: consensus recommendations from the Pediatric Acute Lung Injury Consensus Conference. *Pediatr Crit Care Med* 2015;16(05):428–439
- 7 Kidney Disease. Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO Clinical Practice Guideline for Acute Kidney Injury. *Kidney Int Suppl* 2012;2:8–9
- 8 Zhang Z. Univariate description and bivariate statistical inference: the first step delving into data. *Ann Transl Med* 2016;4(05):91
- 9 Zhang Z. Model building strategy for logistic regression: purposeful selection. *Ann Transl Med* 2016;4(06):111
- 10 Arikan AA, Zappitelli M, Goldstein SL, Naipaul A, Jefferson LS, Loftis LL. Fluid overload is associated with impaired oxygenation and morbidity in critically ill children. *Pediatr Crit Care Med* 2012;13(03):253–258
- 11 Murphy CV, Schramm GE, Doherty JA, et al. The importance of fluid management in acute lung injury secondary to septic shock. *Chest* 2009;136(01):102–109
- 12 Trachsel D, McCrindle BW, Nakagawa S, Bohn D. Oxygenation index predicts outcome in children with acute hypoxemic respiratory failure. *Am J Respir Crit Care Med* 2005;172(02):206–211
- 13 Erickson S, Schibler A, Numa A, et al; Paediatric Study Group; Australian and New Zealand Intensive Care Society. Acute lung injury in pediatric intensive care in Australia and New Zealand: a prospective, multicenter, observational study. *Pediatr Crit Care Med* 2007;8(04):317–323
- 14 Subhedar NV, Tan AT, Sweeney EM, Shaw NJ. A comparison of indices of respiratory failure in ventilated preterm infants. *Arch Dis Child Fetal Neonatal Ed* 2000;83(02):F97–F100
- 15 Payen D, de Pont AC, Sakr Y, Spies C, Reinhart K, Vincent JL; Sepsis Occurrence in Acutely Ill Patients (SOAP) Investigators. A positive fluid balance is associated with a worse outcome in patients with acute renal failure. *Crit Care* 2008;12(03):R74