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ORIGINAL ARTICLE

Restricted versus Usual/Liberal Maintenance Fluid Strategy in Mechanically Ventilated Children: An Open-Label Randomized Trial (ReLiSCh Trial)

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Abstract

Objectives To assess the impact of restricted vs. usual/liberal maintenance fluid strategy on fluid overload (FO) among mechanically ventilated children.

Methods This open-label randomized controlled trial was conducted over a period of 1 y (October 2020-September 2021) in a Pediatric intensive care unit (PICU) in North India. Hemodynamically stable mechanically ventilated children were randomized to 40% (restricted group, n = 50) and 70-80% (usual/liberal group, n = 50) of maintenance fluids. The primary outcome was cumulative fluid overload percentage (FO%) on day 7. Secondary outcomes were FO% >10%; vasoactive inotropic score, sequential organ failure assessment score, pediatric logistic organ dysfunction score and oxygenation index from day 1-7; ventilation free days (VFDs) and PICU free days (PFDs) through day 28; and mortality.

Results The restricted group had statistically non-significant trend towards lower cumulative FO% at day 7 [7.6 vs. 9.5, $p = 0.40$]; and proportion of children with FO% >10% (12% vs. 26%, $p = 0.21$) as compared to usual/liberal group. The increase in FO% from day 1-7 was significant in usual/liberal group as compared to restricted group ($p < 0.001$ and $p = 0.134$, respectively). Restricted group received significantly lower amount of fluid in the first 5 d; had significantly higher VFDs (23 vs. 17 d, $p = 0.008$) and PFDs (19 vs. 15 d, $p = 0.007$); and trend towards lower mortality (8% vs. 16%, $p = 0.21$).

Conclusions Restricted as compared to usual/liberal maintenance fluid strategy among mechanically ventilated children was associated with a trend towards lower rate and severity of FO and mortality; and significantly lower fluid volume received, and higher VFDs and PFDs.

Keywords Fluid creep · Fluid overload · Maintenance fluids · Mechanical ventilation · Critically ill children

Introduction

In critically ill children, both resuscitation fluid during acute phase and maintenance fluids are important for restoration of intravascular volume to maintain organ perfusion, fluid and electrolyte homeostasis, and to replace insensible and ongoing losses [1, 2]. While early fluid administration is life-saving, excess administration can be detrimental. Critically ill children are predisposed to develop positive fluid balance or fluid overload (FO) due to overzealous fluid resuscitation during acute phase, administration of more fluid than required during the maintenance phase, administration of large amount of obligatory fluid (drugs, infusions, blood products etc.), capillary leakage, proinflammatory state, compromised cardiopulmonary function, and mechanical ventilation (humidified gases, controlled temperature, and syndrome of inappropriate secretion of anti-diuretic hormone) [3, 4]. It has been noted that among critically ill children, FO is associated with increased need and duration of mechanical ventilation, higher oxygenation index (OI), longer duration of PICU and hospital stay, and higher mortality [5–8].

Maintenance fluids contribute significantly to FO among critically ill children. Therefore, administration of just

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enough maintenance fluid (restricted) to replace insensible and overt losses, to maintain adequate hemodynamics and tissue perfusion, and adequate blood glucose under strict monitoring could be a useful strategy to prevent FO and its adverse consequences [9, 10].

Among critically ill adults, conservative fluid strategy in post-resuscitation phase has shown to decrease the duration of mechanical ventilation and ICU/hospital stay [9, 11, 12]. However, such information is limited among critically ill children. Therefore, authors conducted this randomized controlled trial (RCT) with hypothesis that restricted maintenance fluid strategy (40% of maintenance fluid) as compared to usual/liberal maintenance fluids strategy (70-80% of maintenance fluids) will lead to decrease in rate and severity FO among mechanically ventilated children.

Material and Methods

This was an open-label RCT conducted in Pediatric intensive care unit (PICU) of a tertiary care hospital in North India over a period of 1 y (October 2020-September 2021). The study protocol was approved by the Institute Ethics Committee (INT/IEC/2020/SPL-763 dated 24/6/2020) and registered with Clinical Trial Registry of India (CTRI/2020/09/028102 dated 28/09/2020). Informed consent was obtained from the parent/guardian before enrolment.

Children (3 mo to 12 y) who were mechanically ventilated and hemodynamically stable (no requirement of fluid boluses or increase in vasoactive drugs in last 6 h) were enrolled. Children with hemodynamic instability (those who required continuous fluid resuscitation and hiking in vasoactive drugs); anticipated mechanical ventilation for <48 h; diabetic ketoacidosis; diarrhea with dehydration; congenital heart disease; acute kidney injury (AKI); post-operative children; need of renal replacement therapy (RRT) at the time of enrolment; chronic disorders (liver disease, kidney disease, or lung disorders); known diabetes insipidus, syndrome of inappropriate antidiuretic hormone secretion (SIADH) and cerebral salt wasting; raised intracranial pressure; hypoglycemia; inborn error of metabolism; and severe acute malnutrition were excluded.

Eligible children were randomized into 2 groups using computer generated block randomization. A person not involved in the study performed the random number allocation and prepared the serially numbered opaque sealed envelopes containing the allocation number and treatment group. These envelops were kept inside the PICU at the designated place. The treating team, study investigators, study patients/guardians, and person doing data entry and analysis were aware of the group allocation.

Group A received restricted maintenance fluid (40% of the normal maintenance fluid). Whereas, Group B received usual/liberal maintenance fluid (70-80% of the normal maintenance fluid), as per the unit policy (standard practice). The normal daily maintenance fluid requirement was calculated based on the Holliday-Segar formula [13]. The maintenance fluid included intravenous fluids, infusions, drugs, and enteral feeds.

Enrolled children were managed by the treating team as per the unit's protocols for care of mechanically ventilated children (intubation, mode and setting of ventilation, sedation-analgesia, weaning, extubation, hemodynamic support and monitoring, nutrition, organ supportive therapies, and nursing care). Enteral feeding was started as soon as possible (within 24-48 h).

Admission weight was taken for calculation of fluid overload percentage (FO%). Fluid intake included all boluses, maintenance fluids, blood and blood components, drugs, infusions, and feeds; and output included urine output, gastrointestinal aspirates, and surgical drains. If child was not catheterized, diaper weighing was used for the documentation of urine output. FO% was calculated as [Fluid intake (L)-Fluid output (L)]/Admission weight X 100 (%)]. FO will be defined as FO% >10% [14, 15].

The blood pressure >5th centile for age, adequate perfusion, no dehydration, urine output >1 ml/kg/h, serum sodium 135-145 meq/L, and blood glucose 80-150 mg/dl were considered appropriate. Based on these parameters, treating team was free to increase or decrease the maintenance fluid by 10% at a time; administer fluid boluses; start, taper or stop vasoactive drugs; start diuretics or RRT; or transfuse blood products, as per the clinical need.

The study protocol was discussed on multiple sessions with the treating team working in PICU by the principal investigator (SC) throughout the study duration and it was displayed as a poster at prominent places in the PICU. Implementation and adherence to the study protocol was checked daily by the principal investigator and weekly by a senior investigator (SKA).

The study endpoint was day 7 of enrolment or extubation, whichever is earlier, after which the amount of maintenance fluid was decided by the treating team. The daily/net and cumulative FO% was recorded till day 7. Follow-up was done till discharge from PICU or death. All enrolled children were included in final analysis.

The primary outcome was cumulative FO% on day 7 of enrolment. Secondary outcomes included FO% >10%; vasoactive inotropic score (VIS) [16, 17], sequential organ failure assessment (SOFA) score [18], pediatric logistic organ dysfunction (PeLOD) score [19], and oxygenation index (OI) [20] on day 1-7; need of RRT; ventilator free days (VFD) and PICU free days (PFD) at day 28; and mortality. Data regarding amount of maintenance fluid received (%age and ml/kg/day) till day 7 and increase in cumulative FO% from day 1-7 were also recorded.

Sample size was calculated based on the assumption that liberal/usual maintenance fluid group had cumulative FO% of at least 15% on day 7 (a rough estimate based on available literature) [5, 7, 21]. As a superiority trial, considering the effect size of 0.6, β-error 20%, α-error 5%, and drop out 10%, the sample size came out as 50 children in each group.

The data was collected on a pre-designed study proforma and entered on the Microsoft Excel 2010 (Microsoft, Redmond, WA). Data analysis was done by using SPSS software version 20 (SPSS, Inc, Chicago, IL). Descriptive statistics [median (IQR) and number (percentages)] were used for baseline variables. Dichotomous outcomes were compared by chi-square test or Fisher's exact test as applicable. Continuous variables were compared by Mann-Whitney U test. All tests were two-tailed and p value <0.05 was considered significant.

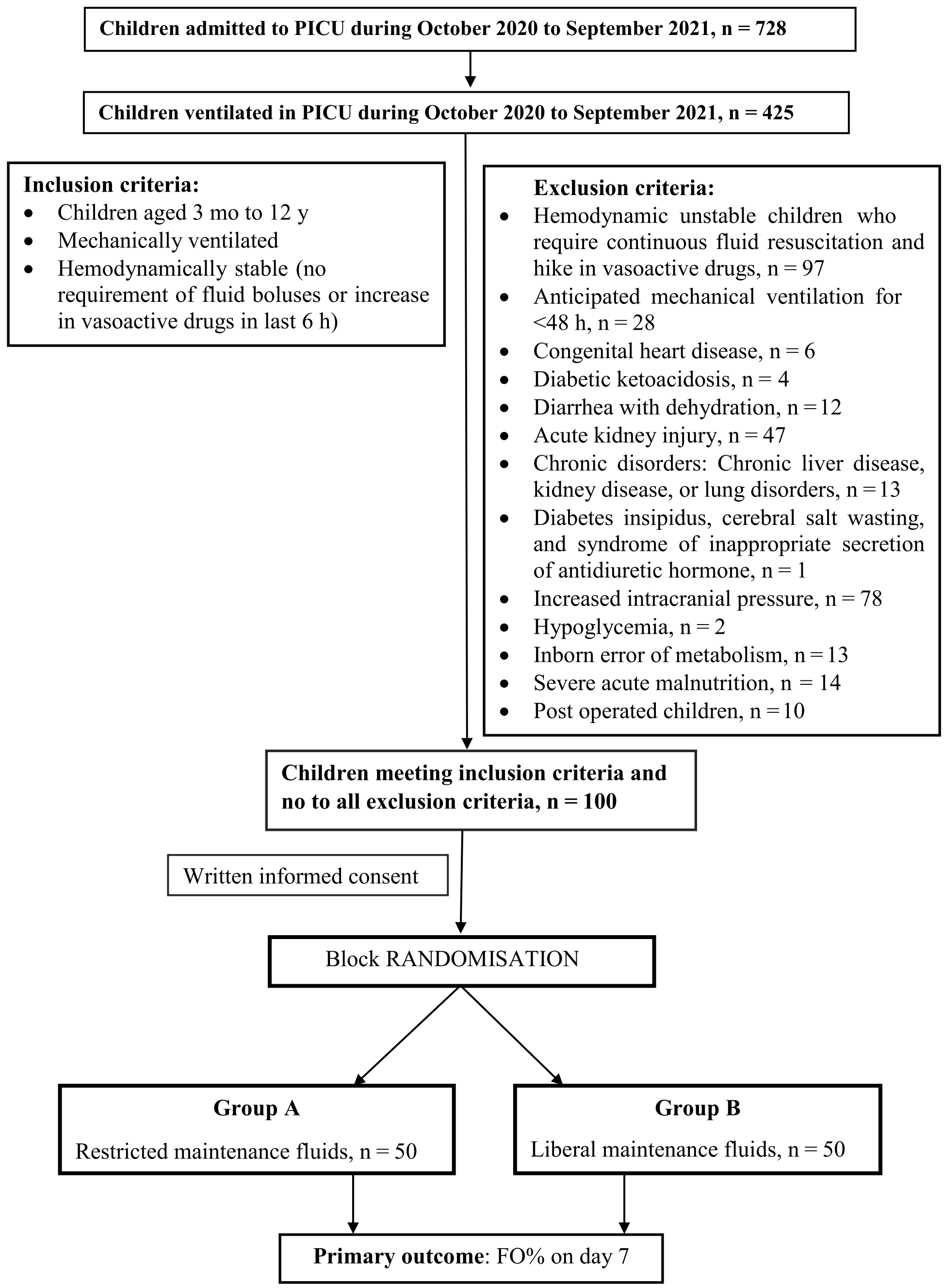

Fig. 1 Study flow diagram. *FO%* Fluid overload percentage, *PICU* Pediatric intensive care unit

Table 1 Baseline characteristics among children in restricted and liberal fluid groups

Characteristics	Restricted group (n = 50)	Liberal group (n = 50)	*p*
Age in years, median (IQR)	4 (0.96-8)	3.0 (0.75-7)	0.77
Male, n (%)	23 (46)	34 (68)	0.034
Duration of illness (days), median (IQR)	5 (2.5-8)	5 (2-7)	0.36
Interval between emergency admission to PICU admission (in hours), median (IQR)	20 (11.5-42)	24 (14.5-48)	0.26
Interval between PICU admission to enrolment (in hours), median (IQR)	13 (12-18)	14 (12-18)	0.76
PRISM III, median (IQR)	17 (14.5-21)	16 (13-18)	0.27
GCS at admission, median (IQR)	9 (6.5-11)	10 (7.77-11)	0.73
Indication of PICU admission			0.16
Mechanical ventilation	50 (100)	50 (100)	
Hemodynamic support	20 (40)	11 (22)	
Neurological monitoring	13 (26)	16 (32)	
Indication of mechanical ventilation			0.10
Respiratory, n (%)	27 (54)	30 (60)	
Neurological, n (%)	14 (28)	16 (32)	
Shock, n (%)	9 (18)	4 (8)	
Diagnosis			0.61
Pneumonia, n (%)	12 (24)	15 (30)	
Scrub typhus, n (%)	8 (16)	6 (12)	
Dengue, n (%)	5 (10)	3 (6)	
Central nervous system infections, n (%)	5 (10)	6 (12)	
Staphylococcal sepsis, n (%)	2 (4)	4 (8)	
LGBS, n (%)	5 (10)	4 (8)	
MIS-C, n (%)	2 (4)	3 (6)	
Gastrointestinal sepsis, n (%)	3 (6)	2 (4)	
Miscellaneous, n (%)	8 (16)	7 (14)	

GCS Glasgow coma scale, *IQR* Interquartile range, *LGBS* Laundry Guillain Barre syndrome, *MIS-C* Multisystemic inflammatory syndrome in children, *PICU* Pediatric intensive care unit, *PRISM III* Pediatric risk of mortality

Results

A total of 100 children were enrolled (Fig. 1). The common indications for mechanical ventilation were respiratory, neurological, and shock; and common diagnosis were pneumonia, dengue, scrub typhus, staphylococcal sepsis, and Landry-Guillain-Barre syndrome (Table 1).

There was statistically non-significant trend towards lower median cumulative FO% at day 7 in restricted as compared to usual/liberal groups [7.6 (-1.3-14.4)% vs. 9.5 (0.3-14.4)%, respectively, $p = 0.40$]; and lower proportion of children with FO% >10% (12% vs. 26%, respectively, $p = 0.20$). The FO% after 24 h of enrolment (day 1) was significantly low in restricted group as compared to usual/liberal group [0.6 (-0.2-1.5) vs. 1.8 (0.2-3.1), $p = 0.005$] (Table 2). The increase in cumulative FO% from day 1-7 was significantly higher in usual/liberal group as compared to restricted group ($p < 0.001$ and $p = 0.134$, respectively, Friedman test).

The VIS, SOFA, and PeLOD scores were similar in 2 groups from day 1-7 (Table 2). On day 4, OI was lower in restricted group ($p = 0.013$), however, it was similar in 2 groups on rest of the days (Table 2). The restricted group and significantly higher VFD [23 (17.5-24) vs. 17 (5.7-23.2), $p = 0.008$] and PFD [19 (11.5-21) vs. 15 (2.2-20), $p = 0.007$]. The need for RRT was similar in 2 groups (4% vs. 6%, $p = 0.54$). There was trend towards lower mortality in restricted group than usual/liberal group (8% vs. 16%, $p = 0.21$) (Table 2).

The restricted group received significantly lower amount of maintenance fluids on first 5 d; and had a trend towards lower net and cumulative fluid balance on first 7 d, however, the difference was not statistically significant (except on day 1) (Supplementary Table S1). Significantly higher proportion of children in restricted group underwent changes in

Table 2 Primary and secondary outcomes among children in restricted and liberal fluid groups

Characteristics	Restricted group (n = 50)	Liberal group (n = 50)	*p*
FO%, median (IQR)			
Day 1	0.6 (-0.2-1.5)	1.8 (0.2-3.1)	0.005
Day 2	1.5 (-2.8-3.1)	2.5 (0.2-5.8)	0.17
Day 3	1.3 (-1.4-4.8)	3.1 (1.1-7.1)	0.29
Day 4	2 (-1.2-7.1)	5.5 (1.1-8.1)	1
Day 5	4.4 (0.6-10.1)	8.3 (1.5-12.6)	0.33
Day 6	6.5 (-1.9-13.3)	9.2 (0.8-13.6)	1
Day 7	***7.6 (-1.3-14.4)***	***9.5 (3.2-14.4)***	***0.40***
FO >10%, n (%)	6 (12)	13 (26)	0.20
VIS score, median (IQR)			
Day 1	10 (6-20)	20 (15-30)	0.16
Day 2	8 (3-22)	18.7 (10-21.5)	0.27
Day 3	4 (3-14)	10 (1.5-17)	0.44
Day 4	4 (3-9)	10 (4.7-18.7)	0.10
Day 5	3 (2-3)	7 (4-20)	0.16
Day 6	-	4 (3-20)	-
Day 7	-	-	-
SOFA score, median (IQR)			
Day 1	5 (3-10)	5.5 (3-8.25)	0.75
Day 2	5 (3-7)	4 (3-8)	0.55
Day 3	5 (3-7)	4 (2.7-7.5)	0.51
Day 4	4 (3-6)	4 (3-6.5)	0.96
Day 5	4 (3-5.5)	4 (2-6)	0.91
Day 6	4 (3-5)	3 (2-5.7)	0.78
Day 7	4 (3-5)	3 (2-5.7)	0.93
PeLOD score, median (IQR)			
Day 1	2 (2-3.5)	2 (2-11)	0.71
Day 2	2 (2-2)	2 (2-3)	0.94
Day 3	2 (2-2)	2 (2-2)	0.86
Day 4	2 (2-2)	2 (2-2)	0.61
Day 5	2 (2-2)	2 (2-2)	0.92
Day 6	2 (2-2)	2 (2-2)	0.86
Day 7	2 (2-2)	2 (2-2)	0.73
OI, median (IQR)			
Day 1	2.9 (2.1-3.8)	2.8 (1.9-5.6)	0.92
Day 2	2.8 (2.2-4.3)	3 (2.1-4.4)	0.67
Day 3	2.6 (2.1-3.7)	3 (2.2-4.8)	0.73
Day 4	2.3 (1.8-3)	3.4 (2.1-4.1)	0.013
Day 5	2.8 (2.1-3.8)	2.9 (1.9-4.8)	0.57
Day 6	2.5 (2.1-3.3)	3.4 (2.1-4.2)	0.34
Day 7	2.7 (2.1-3.2)	2.9 (2.1-4.3)	0.34
RRT, n (%)	2 (4)	3 (6)	0.54
VFD at day 28, median (IQR)	23 (17.5-24)	17 (5.7-23.2)	0.008
PFD at day 28, median (IQR)	19 (11.5-21)	15 (2.2-20)	0.007
Mortality, n (%)	4 (8)	8 (16)	0.21

FO Fluid overload, *IQR* Interquartile range, *OI* Oxygenation index, *PeLOD* Pediatric logistic organ dysfunction, *PFD* Pediatric intensive care unit free days, *RRT* Renal replacement therapy, *SOFA* Sequential organ failure assessment, *VFD* Ventilator free days, *VIS* Vasoactive inotropic score

Table 3 Data regarding organ failure, biochemical parameters, and healthcare associated infection among children in restricted and liberal fluid groups

Characteristics	Restricted group (n = 50)	Liberal group (n = 50)	*p*
AKI, n (%)	5 (10)	4 (8)	0.56
ARDS, n (%)	16 (32)	25 (50)	0.13
Shock, n (%)	18 (36)	19 (38)	0.59
Fluid bolus requirement after enrolment, n (%)	3 (6)	4 (8)	0.565
Vasoactive hike/addition after enrolment, n (%)	6 (12)	7 (14)	0.584
Dehydration, n (%)	1 (2)	0 (0)	0.36
Hyponatremia, n (%)	17 (34)	21 (42)	0.45
Hypernatremia, n (%)	10 (20)	17 (34)	0.19
Hypokalemia, n (%)	15 (30)	22 (44)	0.23
Hyperkalemia, n (%)	1 (2)	2 (4)	0.31
Hyperchloremia, n (%)	15 (30)	16 (32)	0.35
Hypoglycemia, n (%)	0 (0)	2 (4)	0.22
HCAI, n (%)	6 (12)	7 (14)	0.58

AKI Acute kidney injury, *ARDS* Acute respiratory distress syndrome, *HCAI* Healthcare associated infection

maintenance fluid as compared to usual/liberal group (42% vs. 20%, $p = 0.015$) and common reasons included decreased urine output, AKI, and calorie requirement (Supplementary Table S1).

The rates of AKI, acute respiratory distress syndrome (ARDS), shock, requirement of fluid boluses, hike/addition of vasoactive drugs after enrolment, dyselectrolytemias and dysglycemia, and healthcare associated infections were similar in 2 groups (Table 3).

Discussion

In this open-label RCT involving mechanically ventilated children, restricted maintenance fluid strategy was associated with a statistically non-significant trend towards lower cumulative FO% on day 7, lower rate of FO% >10%, and lower mortality; and significantly higher VFD and PFD at day 28 as compared to usual/liberal maintenance fluid. In restrictive group, the increase in FO% from day 1-7 was not significant as compared to usual/liberal group. Also, restricted group received significantly lower volume of maintenance fluids during first 3-5 d. However, higher proportion of children in restricted groups underwent changes in maintenance fluid.

In critically ill children, fluid administration (resuscitation and maintenance fluids) is the cornerstone of management. However, excess fluid administration can lead to FO which can have adverse clinical outcomes including increased morbidity and mortality [5–8, 22]. In order to avoid FO, strategies are suggested during each stage of fluid administration [i.e. resuscitation, optimization, stabilization, and evacuation (ROSE)] [23]. During resuscitation phase, excessive fluid administration should be minimised. During optimization phase, response to fluid therapy should be assessed and fluid should be administered in responders and avoided in non-responders. During stabilization phase, fluid should be restricted in hemodynamically stable children. During evacuation phase, fluid removal strategies (diuretics, renal replacement therapies) should be adopted [23].

Whereas resuscitation fluids account for FO during initial few hours of PICU admission, maintenance fluids are major contributor to FO beyond resuscitation phase. However, the maintenance fluid (amount and type) has not received much attention and is often overlooked. Moreover, despite several limitations, the Holliday-Segar formula [13] is still widely used to calculate maintenance fluid among critically ill children. It has been suggested to use 60-80% of the normal maintenance fluid among critically ill children and isotonic fluids have given preference [24–26]. The data on feasibility of further restriction of maintenance fluids among mechanically ventilated children as a strategy to limit FO and its impact on other clinically important outcome is limited.

In 2006, ARDS clinical trial network compared conservative fluid-management protocol [with a lower central venous pressure (CVP) or pulmonary-artery occlusion pressure (POAP) target] with liberal fluid-management in a RCT involving adults with acute lung injury receiving invasive mechanical ventilation for first 7 d [11]. The interventions included fluid boluses, intravenous fluids to keep veins open, vasoactive drugs, and diuretics based on central venous pressure, pulmonary artery occlusion pressure, urine output, and effective or ineffective circulation. It was demonstrated that conservative group had significantly lower cumulative fluid balance during first 7 d, improved OI and lung injury scores, and higher number of VFDs and ICU free days ($P < 0.001$) during first 28 d. The mortality, rate of shock, and need of RRT during first 60 d were similar [11]. Other studies involving adults also demonstrated that restricted fluids after initial resuscitation resulted in lower cumulative fluid balance, higher VFDs, shorter ICU stay, and no difference in mortality [9, 12, 27].

Ingelse et al. randomized 23 children undergoing mechanical ventilation for respiratory tract illness without hemodynamic support to a conservative or standard maintenance fluid therapy (<70% vs. >85% of normal maintenance, respectively) [28]. Authors demonstrated that conservative fluid strategy was feasible without any limitation of metabolic needs, with no hemodynamics and electrolyte imbalance, associated with lower cumulative fluid intake, and no difference in cumulative fluid balance. Diaz et al. conducted a quality improvement study involving children with ARDS and sepsis on mechanical ventilation [29]. Authors demonstrated that implementation of pre-emptive fluid strategy bundle (n = 37) (maintenance intravenous fluids at 50% of requirements, drug volume reduction, dynamic monitoring of preload markers to determine the need for fluid boluses, early use of diuretics, and early initiation of enteral feeds) resulted in significantly lesser peak FO, decrease in duration of mechanical ventilation and PICU stay as compared to the historic cohort with standard fluid strategy (n = 39). In a meta-analysis involving 11 RCTs (n = 2051 patients), it has been demonstrated that among adults and children with ARDS, sepsis or Systemic inflammatory response syndrome (SIRS), a conservative or deresuscitative fluid strategy after hemodynamic stabilization (resuscitation phase) resulted in increased number of VFDs, shorter ICU stay, and no difference in mortality as compared to liberal strategy or standard care [9].

As indicated in literature [9, 11, 27–29], authors also demonstrated that restricted maintenance fluid strategy led to higher VFDs and PFDs with a trend towards lower mortality (8% vs. 16%). The possible reasons for these effects include higher FO% resulting in more interstitial edema in lungs, decrease in lung compliance, higher positive end-expiratory pressure (PEEP) requirement, and increase in duration of mechanical ventilation [30]. The findings of similar rates of shock and requirement of fluid bolus and/or vasoactive drugs after enrolment, AKI, ARDS, electrolyte and glucose disturbances, and need of dialysis confirm the safety of the restricted fluid strategy [11, 28].

The possible reason for no statistically significant difference in cumulative FO% on day 7 and rate of FO% >10% in two groups include more frequent changes (increase) done in maintenance fluid in restricted group. This had led to increase in maintenance fluid in the restricted group from day 1-7 whereas it remained static in usual/liberal group, which in turn had led to similar cumulative FO% at day 7.

The strengths of this trial include enrolment of heterogenous population (varied diagnosis) of mechanically ventilated children. The sample size was adequate for the primary outcome. All the children were followed-up till 7 d for primary outcome and till discharge or death for final outcomes. The limitations include single-centre study. The daily weight-based assessment of positive fluid balance was not done. The authors could not assess the contribution to FO individually by fluid boluses and maintenance fluid. The effect of diuretics was not considered. There was lack of long-term follow-up.

Large multicentric randomized trials are needed to evaluate restricted maintenance fluid strategy, optimal volume, and its impact on FO and important clinical outcomes among critically ill mechanically ventilated children.

Conclusions

In this open-label RCT, authors demonstrated that restricted maintenance fluid strategy among mechanically ventilated children was associated with a non-significant trend towards lower cumulative FO% at day 7, rates of FO% >10%, and mortality; significantly higher VFDs and PFDs; and lower volume of maintenance fluids received in first 3-5 d.

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Authors' Contributions SC: Designed the study protocol, data collection, data analysis, literature review, preparation of initial draft of the manuscript, and approved the final manuscript; SKA: Conceptualized the study, data analysis, literature review, revision of the manuscript, and approved the final manuscript; KN: Data analysis, reviewed the manuscript critically, and approved the final manuscript; and MJ: Helped in designing the study, provided critical revision to the manuscript, and approved the final manuscript. SKA will act as the guarantor for this manuscript.

Declarations

Conflict of Interest None.

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