EDITORIAL

Fluids – A Double-edged Sword?

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"All things are poison, and nothing is without poison, the dosage alone makes it so a thing is not a poison" – Paracelsus (1538)'.

Restoration of intravascular volume remains the cornerstone of therapy in children with septic shock. Protocolized goal-directed approach, to achieve macro- and micro-circulatory targets during resuscitation, engenders administration of crystalloids and colloids, often veering on overuse. The deleterious consequences of aggressive fluid resuscitation surface in the post-resuscitation phase as fluid overload and organ dysfunction, which become a nightmare for intensivists.

An increasing number of studies in adults and children have shown an association between fluid overload and adverse outcomes. Although majority have been retrospective, a correlation between cumulative fluid balance, and increased length of mechanical ventilation, pediatric intensive care unit (PICU) stay and incidence of acute lung- and kidney-injury have been universal findings.

The current study [1] conducted in a tertiary-care PICU in Northern India mirrors the same trend. The study included 118 mechanically ventilated children, 49% of whom had septic shock. The median (IQR) peak fluid overload at 48 hours, in non-survivors was significantly higher than that in survivors [9% (6.1%, 12.7%) *vs.* 6.6% (3.1%, 10.3%); *P*=0.039]. The cumulative maximum fluid overload >15% on multivariate analysis was associated with higher PELOD (Pediatric logistic organ dysfunction) scores, longer median duration of mechanical ventilation and PICU stay.

Unlike morbidity outcomes, mortality outcomes have been inconsistent. Two pediatric studies [1,2], which included mechanically ventilated children failed to demonstrate increased mortality with fluid overload. On the other hand, a few studies have reported findings to the contrary. Sutawan, *et al*. [3], in a case-control study including 60 cases (non-survivors) and 60 controls (survivors), found an association between fluid overload and mortality. Similar findings were replicated by Chen, *et al*. [4] in children with severe sepsis, where both early and cumulative fluid overload increased risk of death. A systematic review and meta-analysis by Alobaidi, *et al*. [5] included 44 studies on fluid overload in critically ill children, and revealed a 6% increase in odds for mortality with every 1% increase in fluid overload.

So, what is the explanation for fluid therapy turning out to be a double-edged sword? The answer lies in endotheliopathy. Widespread inflammation, releasing cytokines and free radicals, causes endothelial injury and disrupts tight junctions, leading to altered vascular reactivity and leaky blood vessels. The resultant ebb phase causes a state of intra-vascular hypovolemia (without actual fluid loss), vasodilatation and trans-capillary leakage of plasma proteins. This is the stage at which the child is fluid-responsive. It is, however, pertinent to understand that about 1.5-4 hours after bolus administration, less than 5-15% is retained within the intravascular space. The brunt of this interstitial seepage of fluid is borne by the lungs and kidneys [6]. Rightly so, the association between Acute respiratory distress syndrome (ARDS) and fluid overload has been the subject of many studies, and practice over time has evolved to consciously keep fluid balance as negative as possible in patients with ARDS [7,8]. On the other hand, fluid overload leading to acute kidney injury is much akin to a chicken and egg situation as kidney injury by itself might contribute to fluid overload [9]. Furthermore, proving a causal link between fluid overload and renal damage may not be straightforward, given the multifactorial nature of renal insults in a child with septic shock.

Once shock has stabilized and inflammation is controlled, there is advent of flow phase in which myocardial and renal function improve, resulting in fluid removal through a process of spontaneous diuresis. When this fails to happen, the excess fluid has to be removed by diuretics, with or without albumin, or renal replacement

therapy. This process, known as de-resuscitation, is crucial to prevent organ dysfunction secondary to fluid overload. Kwiatkowski, *et al*. [10] showed that peritoneal dialysis (PD) for early fluid removal resulted in lower mechanical ventilation days, less fluid overload and lower inotrope use than furosemide in post-cardiac surgery children. At present, however, there is lack of consensus on the timing, modality and end points for de-resuscitation.

Given the above context, the findings from the present study are relevant to critical care in resource-limited settings. With wide disparity between demand and supply, reduction in mechanical ventilation days and ICU stay will go a long way in decreasing expenditure and allocating resources judiciously. Inclusion of children with kidney injury, however, could have thrown light on this important subset of adverse outcome of fluid overload. Further studies are required to establish causal link between fluid overload and kidney injury, and to determine timing and ideal mode of de-resuscitation.

Funding: None; *Competing interests*: None stated.

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