Should sodium be the real target of fluid restriction?

Manoj K Saxena

The pathophysiology of the host response to stress includes activation of the neurohumoral system that is targeted at conserving both sodium and water through the renin–angiotensin–aldosterone axis, natriuretic peptides, the sympathetic nervous system and antidiuretic hormone. The amount and type of fluid administered by clinicians to critically ill patients affects this acute adaptive response and, through this, may affect subsequent survival and recovery.

Data from high-quality randomised controlled trials (RCTs) suggest that the type of resuscitation fluid has an impact on patient-centred outcomes.[1-3] As part of the process of understanding the safety and efficacy of fluid therapy, attention is drawn to the dose of fluid administered. There are data from an observational study,[4] post-hoc analyses of randomised trials,[5] and two RCTs[6,7] suggesting that a conservative approach to the use of intravenous fluid may be associated with improved patient outcomes. In this issue of the Journal, Bihari and colleagues question fluid accumulation as the perpetrator of adverse effects, and suggest that sodium accumulation may be the salient issue.

In their linked article, the authors report on the observational relationship between sodium and fluid balance and oedema scores, oxygenation indices, biochemical parameters of hydration and bioelectrical impedance spectroscopy (as a surrogate for body water estimation). The single-centre patient cohort were medical intensive care patients, who were early in their intensive care admission. A modest accumulation of sodium (average 50 mmol/day) was associated with a significant reduction in the lowest Pa_{O_2}/F_{IO_2} ratio and increased radiological evidence of oedema (as judged by the relationship between sodium accumulation and the chest radiograph oedema score). There was an overall decrease in negative fluid balance of about 1 L after 5 days, but this was not associated with changes in any of the measured parameters. These preliminary data could be interpreted as suggesting that a modest sodium accumulation rather than fluid accumulation may contribute to morbidity.

The data are consistent with other observations related to sodium and chloride balance having effects on morbidity.[8] However, the generalisability of these data from a single centre is limited. Inferences of causation between sodium accumulation and surrogate outcomes of morbidity cannot reliably be drawn from these observational data. Further information is required for specific patient populations (such as postoperative patients and those with sepsis or trauma), in which sodium accumulation may be implicated in the development of morbidity. Identification of sources of sodium input that may be amenable to modification are also required if this hypothesis is to be tested in an interventional clinical trial.

The highest-quality data that we have to date on the subject of the amount (or dose) of fluid administered, and its relationship to patient outcomes, come from two randomised studies. First, a multicentre RCT from the United States (the comparison of two fluid-management strategies in acute lung injury [FACTT] study[7]) in which, in a mixed cohort of patients with acute lung injury, the mean cumulative fluid balance during the first 7 days was examined. The mean cumulative fluid balance was – 136 mL ± 491 mL in the conservative-strategy group and 6992 mL ± 502 mL in the liberal-strategy group. The study was designed to detect an implausibly large reduction in mortality,[9] and there was no associated difference in the primary end point of landmark mortality between the two groups. However, there was an improvement in two surrogate indices for respiratory morbidity (a reduction in the duration of mechanical ventilation and an improvement in indices of oxygenation) with no associated change in the important surrogate for tissue perfusion of renal morbidity.

Second, the results of the fluid expansion as supportive therapy (FEAST) trial[6] suggest that fluid accumulation may be associated with increased mortality. The study, conducted in a paediatric population with compensated shock under extreme conditions of deprivation, found that bolus fluid resuscitation with albumin or saline was associated with a significant increase in mortality at 48 hours compared with no boluses of fluid. The control group (no fluid boluses) received significantly less fluid input (median, 40 mL/kg; interquartile range [IQR], 0–60 mL/kg) compared with the intervention groups receiving albumin (median, 76.2 mL/kg; IQR, 40–96.5 mL/kg) or saline (median, 78.1 mL/kg; IQR, 40–96.6 mL/kg).

In the context of the hypothesis-generating observations made by Bihari and colleagues, sodium balance may be an unreported confounder in the FACTT and FEAST studies. However, it would be premature to conclude that sodium should be the real target for fluid restriction strategies. At present, limited evidence

appears to favour fluid accumulation as the primary culprit associated with morbidity. Fluid and sodium accumulation are probably both important issues for critically ill patients and these issues need to be tested, ideally in high-quality RCTs.

Competing interests

None declared.

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References

1 SAFE Study Investigators, Australian and New Zealand Intensive Care Society Clinical Trials Group, Australian Red Cross Blood Service, et al. Saline or albumin for fluid resuscitation in patients with traumatic brain injury. *N Engl J Med* 2007; 357: 874-84.

2 Perner A, Haase N, Guttormsen AB, et al. Hydroxyethyl starch 130/0.42 versus Ringer's acetate in severe sepsis. *N Engl J Med* 2012; 367: 124-34.

3 Myburgh JA, Finfer S, Bellomo R, et al. Hydroxyethyl starch or saline for fluid resuscitation in intensive care. *N Engl J Med* 2012; 367: 1901-11.

4 Smith SH, Perner A. Higher vs. lower fluid volume for septic shock: clinical characteristics and outcome in unselected patients in a prospective, multicenter cohort. *Crit Care* 2012; 16: R76.

5 Boyd JH, Forbes J, Nakada TA, et al. Fluid resuscitation in septic shock: a positive fluid balance and elevated central venous pressure are associated with increased mortality. *Crit Care Med* 2011; 39: 259-65.

6 Maitland K, Kiguli S, Opoka RO, et al. Mortality after fluid bolus in African children with severe infection. *N Engl J Med* 2011; 364: 2483-95.

7 National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome Clinical Trials Network, Wiedemann HP, Wheeler AP, et al. Comparison of two fluid-management strategies in acute lung injury. *N Engl J Med* 2006; 354: 2564-75.

8 Yunos NM, Bellomo R, Hegarty C, et al. Association between a chloride-liberal vs chloride-restrictive intravenous fluid administration strategy and kidney injury in critically ill adults. *JAMA* 2012; 308: 1566-72.

9 Aberegg SK, Richards DR, O'Brien JM. Delta inflation: a bias in the design of randomized controlled trials in critical care medicine. *Crit Care* 2010; 14: R77. ❑

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