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Fluid balance and outcome in acute kidney injury: is fluid really the best medicine?

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Fluid resuscitation, to expand intravascular volume and maintain organ perfusion is a core concept in the management of critical illness. Indeed the notion of “golden hours” or “minutes” of shock is highly engrained in critical care medicine. However, one important consequence of fluid administration is the risk of developing fluid overload. Susceptibility to fluid overload increases in patients with, or who are at risk for acute kidney injury (AKI), resulting in tissue and organ edema, which has been associated with increased morbidity, and mortality in a number of observational studies.[1-4]

In this issue of Critical Care Medicine, Bellomo and colleagues examine the association between daily fluid balance and outcomes in critically ill patients receiving renal replacement therapy (RRT). The authors found that nearly one-half of patients developed a mean daily negative fluid balance. Patients with negative fluid balance, as one might expect, had lower severity of illness, and were less likely to be hypotensive as evidenced by a lower APACHE and cardiovascular SOFA scores. However, when adjusted for these differences, the authors found that if a patient achieved a negative fluid balance they had an markedly reduced risk of death at 90 days (adjusted odds ratio [OR]=0.31, 95% CI, 0.24-0.43, P <0.0001). Patients with negative fluid balance also had a significantly more days alive and free of RRT and mechanical ventilation and out of the ICU and hospital compared to patients with a positive fluid balance. These findings were robust across propensity score and Cox survival analyses.

Although Bellomo and colleagues need to be commended for doing such an extensive analysis to show that the association between negative fluid balance and lower risk of death, several important limitations of the study are noteworthy. First, the author’s finding raises questions about the biologic plausibility of the association between negative fluid balance and lower mortality. For instance, the authors found that survivors had a mean fluid balance of only −234 mls per day compared to non-survivors who had a mean fluid balance of 560

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mls per day. When adjusted for differences in body weight, the authors found that the survivors had a mean fluid balance of −2.7 ml/kg compared with 7.2 ml/kg in non-survivors.

How can such small change in fluid balance translate into such a huge (i.e., 70%) reduction in the risk of death? Although observational studies are likely to provide inflated estimates of treatment effect size, the observed association raises question about whether such association is truly due to fluid balance. Most single interventions in the critically ill are only able to achieve modest effect sizes. This is because, critically ill patients have complex and varying pathophysiology and the incremental effects of individual processes are relatively small.

Similarly, as is true with all observational studies, and as acknowledged by the authors, an association does not prove causality and that the association between negative fluid balance and lower mortality is hypotheses generating at best. The reason why positive fluid balance is associated with a higher risk of death could be due to a potential source of confounding by indication for fluid administration. For instance, as one might expect, there was a higher severity of illness and hypotension among those who received a more fluids, which are well known clinical risk factors for AKI and mortality, which are also indications for fluid use. Although the authors adjust for severity of illness at randomization and using cardiovascular SOFA scores for hypotension, residual confounding due to indication for fluid use (*i.e.*, the underlying condition that prompted fluid administration by clinicians) and other unmeasured risk factors (that are surrogate for fluid use) might have contributed to the increased risk of death and potential spurious observed association between positive balance and mortality. Indeed the association may simply be with patients who “can” obtain a negative fluid balance and thus failure to achieve negative fluid balance may be a biomarker of critical illness indicating ongoing hemodynamic instability. This instability, rather than the fluid balance per se, may be what is driving adverse outcomes.

So what can we learn from this important study? Does this study suggest that we should restrict fluid administration in critically ill patients with AKI? Or does it mean that we should adopt a highly proactive strategy to attain a negative balance on a daily basis in our critically ill patients with shock at the potential expense of compromising organ perfusion? These are important questions that can only be answered in a future randomized trial. Nevertheless, current evidence suggests that there are two factors that are likely to influence the association between fluid administration and outcome – timing and the volume of administered fluid. In a landmark trial, Rivers *et al.*, demonstrated that early goal-directed resuscitation in the first 6 hours of admission to the emergency department with septic shock was associated with lower hospital-, and 28-day mortality compared to usual care.[5] This study suggests that early resuscitation attenuates or prevents organ dysfunction and subsequent downstream consequences even though a similar positive fluid balance at 72 hours was found in the both the study arms. Thus, one might hypothesize that a strategy that maximizes early resuscitation but avoids fluid overload later might enjoy the benefits of both strategies. Ongoing multi-center trials of early goal directed therapy may help answer this question.

Meanwhile, a number of previous studies that have examined the association between volume of fluid and outcomes in patients with AKI are in agreement with the findings by Bellomo and colleagues. In a *post-hoc* analysis of the Program to Improve Care in Acute Renal Disease (PICARD) study, Bouchard *et. al.*,[1] found that fluid overload at cessation of RRT and adjusted for severity of illness and modality of dialysis was associated with increased risk death at 60 days (OR=2.52, 95% CI 1.55-4.08). Payen *et al.* using the Sepsis Occurrence in Acutely ill Patients (SOAP) study reported a 54% adjusted risk of death at 60 days in patients with AKI and a mean positive fluid balance (Hazard Ratio = 1.21, 95%CI

1.13-1.28).[2] Using data from the Fluid and Catheter Treatment Trial (FACTT), Grams *et. al.* found that after adjusting for severity of illness, demographics, fluid-strategy, mean daily central venous pressure and shock, a positive fluid balance remained significantly associated with 60-day mortality (adjusted OR =1.61 per L/d, 95% CI: 1.29 to 2.00).[4]

Thus, there is a growing and consistent body of literature that suggests that patients receiving "excessive" fluid especially at a time when organ ischemia is not present or late in the illness after onset of organ dysfunction are also likely to develop complications related to fluid overload and organ edema (Figure 1). What point in time does fluid become harmful? How much fluid is required at a given point in time? These questions need further research.

Furthermore, the exact mechanism of deleterious effect of fluid overload on organ function is unknown. Although it is not difficult to conceptualize that organ edema could cause organ dysfunction, what is not known is whether this is mediated through impaired tissue oxygenation, function of key enzyme and cellular systems, metabolite clearance or other mechanisms.[6] Future controlled studies examining the relationship between fluid balance and outcomes need to take into account the indications for fluid use, volume, timing and the mechanisms by which conservative fluid balance mediates its salutary effects.

Until such studies are completed however, clinicians would do well to reassess the risk benefit equation for fluid administration in the ICU. For too long we have assumed that a liter of saline is a benign intervention. As we've been arguing repeatedly in the pages of this journal, the evidence should be making us question this assumption.[7;8]

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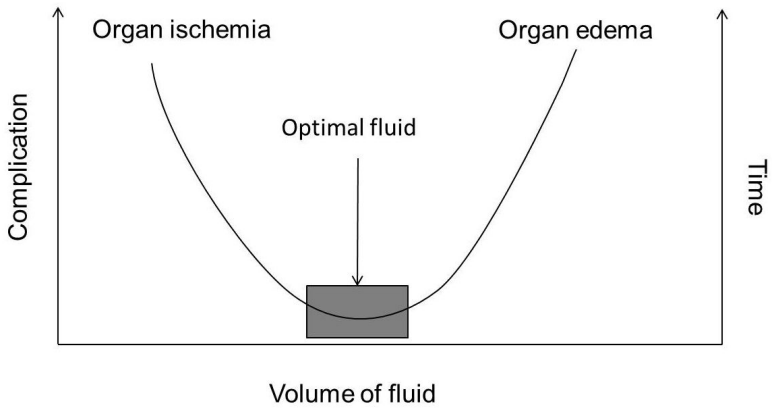

Figure 1. Conceptual model illustrating relationship between time, volume of fluid, and potential complications

The model depicts a curvilinear association between time, volume of fluid, and morbidity. Insufficient volume of fluid early during illness is likely to lead to complications due to organ ischemia. In contrast, late administration of excess fluid after onset of organ dysfunction could potentiate organ edema. Optimal volume of fluid at any given time is likely to preserve organ viability without increasing morbidity.