Best evidence in critical care medicine

Fluid management in acute lung injury: friend or foe?

Article appraised

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

Structured abstract

Design: Prospective, randomized, clinical trial comparing "liberal" *vs* "conservative" fluid management strategies in patients with acute lung injury (ALI). Patients were simultaneously randomized to management of ALI with either a central venous catheter or pulmonary artery catheter (PAC).[1] Results of this second randomization were reported separately.

Patients: 11,512 patients screened; 1,001 enrolled. Inclusion required intensive care unit (ICU) admission; age > 13; intubation and positive-pressure-ventilation; and fulfillment of the American/European Diagnostic criteria for ALI (a partial pressure of oxygen to fractional inspired oxygen (PaO_2/F_I0_2) ratio ≤ 300; bilateral chest radiograph infiltrates; and no evidence of cardiogenic pulmonary edema). Patients were excluded if they: were > 48 hr from ALI onset; had suffered an acute myocardial infarction within 30 days; had severe chronic lung disease; required dialysis prior to enrolment; had liver or neuromuscular disease; had a high risk of death within six months from other causes; or already had a PAC.

Groups were equivalent with respect to age, sex, race, inciting event (70% had pneumonia or sepsis), comorbidity, APACHE III score and renal, respiratory and hemodynamic indices. Sixty-six percent of patients from each group were in medical ICUs.

Intervention: 1,001 patients randomized to either a "liberal" (n = 497) or "conservative" (n = 503) fluid management strategy. Complex protocols provided group-specific instructions for fluids, diuretics and inotropes based on central-venous or pulmonary-artery occlusion pressure, mean arterial pressure, urine output and effectiveness of circulation. The protocol was applied to each patient at least every four hours.

Target central venous pressure (CVP) was 10–14 mmHg in the liberal group and < 4 mmHg in the conservative group. Target pulmonary artery occlusion pressure (PAOP) was 14–18 mmHg in the liberal group and < 8 mmHg in the conservative group. Protocols outlined volume resuscitation and/or inotropic support in cases of hypotension, decreased urine output or ineffective circulation. Protocols outlined diuresis in cases of volume overload.

Endpoints: Primary endpoint was 60-day mortality with a statistical power of 90% to detect a 10% reduction in mortality (from 31 to 21%). Secondary endpoints were ventilator free days (to 28 days after enrolment), ICU free days (between days seven and 28), organ failure free days (between days seven and 28) and requirement for dialysis (up to day 60).

Results: The mean seven-day cumulative fluid balance was -136 ± 491 mL for the conservative group and +6992 ± 502 mL for the liberal group (P < 0.001). Diuretic-use was significantly higher in the conservative group (41% compared to 10% in the liberal group (P < 0.001). Dobutamine utilization was similar in both groups (4% *vs* 6%).

There was no significant difference in primary outcome: 60-day mortality was 25.5% in the conservative group *vs* 28.4% in the liberal group (P = 0.3). However, patients in the conservative group had more ventilator-free days (14.6 *vs* 12.1, P < 0.001), more ICU-free days (13.4 *vs* 11.2, P < 0.001) and fewer days with central nervous system (CNS) failure (17.2 *vs* 18.8, P = 0.03) over 28 days. The liberal group had more days free of cardiovascular failure (4.2 *vs* 3.9, P = 0.04). There was no difference in dialysis requirement. The conservative group had lower mean arterial pressure, stroke volume and cardiac index. However, there was no difference in heart rate, venous oxygen saturation or percentage of patients receiving vasopressors. While there was an increase in metabolic alkalosis and hypokalemia for the conservative group (42 *vs* 19 events), there was no increase in dysrhythmias. The results were also independent of allocation to CVP *vs* PAOP monitoring in the concurrent trial.[1]

Conclusion: While fluid management did not influence 60-day mortality rates, a "conservative" fluid management protocol which allowed lower CVP or pulmonary artery occlusion pressure targets resulted in shortened ICU lengths of stay and earlier weaning from mechanical ventilation, without increasing the rates of non-pulmonary organ failure.

Commentary

This is a well-designed prospective, randomized clinical trial with an appropriate intention-to-treat analysis. A large number of patients were enrolled, and the study protocol incorporated a myriad of the therapeutic advances in critical care medicine of the last 20 years, therefore being reflective of contemporary ICU practice. While the authors are to be applauded for the specificity of the protocols and strict enrolment criteria, the complexity of their protocols and the exclusion of 90% of those screened may limit clinical applicability. The average patient age of only 50 yr and the exclusion of overt heart failure and renal failure also makes generalization challenging. However, pertinent prescriptive goals such as a target CVP of 10–14 mmHg in the liberal group and < 4 in the conservative group are easy to remember and apply in the critical care setting.

Although a conservative fluid strategy was not associated with improved 60-day survival, it was associated with lower morbidity: the acute respiratory distress syndrome (ARDS) Clinical Trials Network found improved lung function, improved CNS functioning, less need for sedation, shorter mechanical ventilation and shorter ICU stay. While comparable mortality could be used to justify either a "conservative" or "liberal" fluid strategy, improved secondary outcomes and the absence of an obvious downside may encourage clinicians to default to limiting fluids. Regardless, this study needs to be understood in context.

Two decades ago, two studies comparing fluid management in ARDS showed correlation between lower fluid balance and both earlier weaning from mechanical ventilation and ICU-discharge.[2,3] Unfortunately, both were retrospective designs, meaning that there may have been either an association between outcome and management strategy, or simply, that less sick patients required less fluid. Therefore, in 1992, Mitchell *et al.* completed a randomized-controlled trial contrasting a "liberal" and "conservative" approach using PAOP as a guide and aimed to lessen net-fluid-balance and extravascular lung water.[4] Again, lower fluid balance was associated with earlier weaning and less time in the ICU. This time, the small study size, and a protocol that required routine measurement of extravascular lung water minimized clinical applicability. As such, this work by the ARDS Clinical Trials Network is welcome.

A simple fluid strategy that lowers mortality in all-comers has not still been found. However, once again "conservative" fluid administration is associated with earlier weaning from mechanical ventilation and shorter ICU stay. Importantly, these benefits were accomplished without alternate morbidity such as hypotension or increased need for dialysis. Rather than conclude that we have no clinical direction, ample evidence supports a more "conservative" approach. However, the absence of a mortality benefit emphasizes that fluid management is likely more complex than an "either/or" option.

Critical-illness is heterogeneous and as such treatment is typically individualized, not dogmatic. ALI and ARDS for example, can result from a direct insult (so called "pulmonary ALI" and secondary to causes such as bacterial or aspiration pneumonia) or indirectly (so called "extra-pulmonary ALI" from pancreatitis, trauma, non-pulmonary sepsis). Pelosi *et al.* have shown physiologic, radiologic, and histologic differences between these entities, and have suggested that these variances might explain differing therapeutic responses (for example, following physiologic alveolar-recruitment maneuvers or pharmacologic surfactant).[5] Fluid therapy may be equally complex. For example, proponents of the crystalloid-colloid debate argue that all fluids are not equal, while proponents of the strong-ion difference argue that many of our basic assumptions are naïve.[6,7] The criteria for ARDS/ALI are also non-specific. While designed primarily to aid research enrolment, criteria such as "bilateral radiographic infiltrates" do not distinguish between varied pathologies. A $Pa0_2/F_I0_2$ ratio simply provides an assessment of hypoxemia at a single moment. The arbitrary distinction between ALI and ARDS ($Pa0_2/F_I0_2$ < 300 and < 200 respectively) tell us nothing about etiology, nor does it separate therapies. Perhaps most provocatively, our definitions fail to acknowledge the importance of timing.

The "early goal directed therapy" (EGDT) work of Rivers *et al.* implies that "timing really is everything".[8] During the early hours of resuscitation, fluid can mitigate supply-demand imbalance. If not treated, this imbalance can spiral into microcirculatory failure, then organ failure, and ultimately death. There is no adequate treatment except prevention and support. As such, acutely, it would seem potentially more harmful to under-resuscitate than to over-resuscitate. Later in the disease process, cellular mechanisms are comparatively quiescent, and the balance between pro-

and anti-inflammatory mediators has altered. Sodium and water avidity therefore decreases, and there is less need for fluid resuscitation. Failure to decrease fluid administration will increase lung water through a combination of increased capillary hydrostatic pressure, increased alveolar-capillary permeability and decreased oncotic pressure. Therefore, at this time fluids should be minimized and diuretics are indicated to facilitate mobilization of interstitial water. Less fluid should aid weaning from mechanical ventilation, but should no longer result in cellular imbalance, organ dysfunction, or resultant mortality. These stages of illness have been coined the "ebb and flow".[9] Unfortunately, the transition from one phase to the next is indistinct, and not identified by any single clinical or laboratory finding.

When Rivers studied EGDT, he used a six-hour period which began at the time of emergency room presentation.[8] His approach to early resuscitation algorithms significantly decreased mortality, and also decreased patient morbidity, as reflected in shorter durations of mechanical ventilation and ICU stay. In contrast, the average time between ICU admission and initiation of the ARDS Clinical Trials Network fluid protocol was 43 hr. This suggests that protocol implementation *followed* acute resuscitation. As such, the ARDS Clinical Trials Network results do not really reflect the early inflammatory phase. This means "conservative" therapy later in the course of treatment is not at odds with "liberal" therapy early on. Equally, "liberal" therapy during established lung injury would be as inappropriate as "conservative" therapy during shock. Of note, River's EGDT work showed a comparable cumulative fluid volume over 72 hr between his control and experimental groups. River's fluid resuscitation has been inaccurately categorized as "aggressive". In fact, the EGDT group simply received fluids earlier in the course of treatment, where this strategy had the highest likelihood of success and the least detriment. In short, these trials are complementary, rather than being at odds. As Rivers stated: "in contrast to politics…in fluid management…it is okay to be both liberal and conservative". Regardless, both remain an "art".

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J. Damian Paton-Gay MD
Peter G. Brindley MD FRCPC
Robert C. McDermid MD FRCPC
University of Alberta, Edmonton, Canada

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