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Journal club critique

Albumin and furosemide for acute lung injury

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Expanded Abstract

Citation

Martin GS, Moss M, Wheeler AP, Mealer M, Morris JA, Bernard GR: A randomized, controlled trial of furosemide with or without albumin in hypoproteinemic patients with acute lung injury. Crit Care Med 2005, 33:1681-1687 [1].

Background

Hypoproteinemia is a common condition in critically ill patients, associated with the development of acute lung injury and acute respiratory distress syndrome and subsequent worse clinical outcomes. Albumin with furosemide benefits lung physiology in hypoproteinemic patients with acute lung injury/acute respiratory distress syndrome, but the independent pharmacologic effects of these drugs are unknown.

Methods

Objective: To determine the independent pharmacologic effects of albumin and furosemide in hypoproteinemic patients with acute lung injury/acute respiratory distress syndrome.

Design: Randomized, double-blinded, placebo-controlled multicentered trial.

Setting: Eleven medical, surgical, and trauma intensive care units including 190 beds within two university hospital systems.

Subjects: Forty mechanically ventilated patients with acute lung injury/acute respiratory distress syndrome, whose serum total protein concentrations were <6.0 g/dL were included. Patients were excluded for hemodynamic instability or significant renal or hepatic failure.

Intervention: Subjects were equally randomly allocated to receive furosemide with albumin or furosemide with placebo for 72 hrs, titrated to fluid loss and normalization of serum total protein concentration.

Outcomes: The primary outcome was change in oxygenation from baseline to day 1, with secondary physiologic and clinical outcomes.

Results: There were no differences in baseline characteristics of the subjects in relation to group assignment. Albumin-treated patients had greater increases in oxygenation (mean change in Pao2/Fio2: +43 vs. -24 mm Hg at 24 hrs and +49 vs. -13 mm Hg at day 3), serum total protein (1.5 vs. 0.5 g/dL at day 3), and net fluid loss (-5480 vs. -1490 mL at day 3) throughout the study period (all $p < .05$). Fluid bolus administration to control patients reduced net negative fluid balance; control patients more frequently developed hypotension and had fewer shock-free days, which translated to differences in organ failure at study end. Apart from more frequent hypotension in the control group, there were no adverse events. There were seven deaths in the treatment group and nine in the control group (35% vs. 45% mortality rate; $p = .52$).

Conclusion

The addition of albumin to furosemide therapy in hypoproteinemic patients with acute lung injury/acute respiratory distress syndrome significantly improves oxygenation, with greater net negative fluid balance and better maintenance of hemodynamic stability. Additional randomized clinical trials are necessary to examine mechanisms and determine the effect on important clinical outcomes, such as the duration of mechanical ventilation.

Commentary

Acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) are common, deadly, and costly [2]. The appropriate management of fluids and the use of colloid therapy in these patients have been debated for decades

and remain controversial. Hypoproteinemia, as previously shown by Martin and colleagues, is a strong independent predictor of development of ARDS and mortality in patients with sepsis [3]. In a small (n=37) randomized pilot study in hypoproteinemic ALI patients, those who received albumin plus furosemide had improved oxygenation, greater weight loss, and shorter duration of mechanical ventilation and ICU length of stay compared to those who received placebo [4]. Because both agents were given together in the intervention arm, it was not possible to distinguish which therapy, albumin, furosemide, or the combination, was responsible for the observed benefit.

The current study by Martin and colleagues was conducted to evaluate the independent effect of these therapeutic agents in hypoproteinemic ALI patients [1]. Subjects (n=40) were randomized to receive furosemide with or without albumin (25g of 25% human serum albumin every 8 hours) for 72 hrs, titrated to fluid loss and normalization of serum total protein concentration. Hypoproteinemia was defined as serum total protein <6.0 g/dL. Subjects with hemodynamic instability or requiring vasopressors were excluded, as were those with significant renal or hepatic disease. Enrollment occurred a median of 3 days after subjects met international consensus conference criteria for ALI. The authors found that the addition of albumin to furosemide significantly improved oxygenation, with greater net negative fluid balance and better maintenance of hemodynamic stability. Hospital mortality was lower in the albumin/furosemide group, but this difference was not statistically significant (35% vs. 45%, p=0.52). The authors concluded that additional (i.e., larger) randomized trials would be necessary to determine if this treatment strategy improves clinical outcomes, such as duration of mechanical ventilation or mortality.

This was a well-conducted study with a number of strengths. Despite the study's small size, randomization succeeding in balancing key baseline characteristics across treatment groups. Investigators went to great lengths to ensure blinding. Albumin was camouflaged in sterile plastic containers and infused in opaque tubing to prevent it being distinguished from the placebo (0.9 % sodium chloride solution). No patients were lost to follow-up and compliance with the study protocol was achieved in 99% of study drug administrations.

Because of its size, this study was not powered on clinical endpoints, such as duration of mechanical ventilation or mortality, and instead focused on surrogate endpoints, such as improvement in oxygenation. Though improvement in oxygenation is certainly desirable, we know from other studies that this may not translate into improved clinical outcomes, as was the case with inhaled nitric oxide in ALI. In fact, as pointed out by in the accompanying editorial, the only therapy that has been shown improve survival in ALI (low tidal volume ventilation) actually led to an initial reduction in oxygenation [6].

Though published in late 2005, the findings of this study are particularly noteworthy in light of the ARDS Network FACTT trial, in which two ALI fluid-management strategies, fluid liberal versus fluid conservative, were compared [7] starting an average of 24 hours after subjects met ALI criteria. In FACTT, subjects in the fluid conservative group had greater net fluid loss. As in the albumin/furosemide trial, this greater net fluid loss translated into improved lung function. In the FACTT trial, this also led to shortened duration of mechanical ventilation and ICU stay without increasing nonpulmonary-organ failures. Like the albumin/furosemide trial, the improvement in lung function in the FACTT trial was not accompanied by a statistically significant mortality reduction, though 60-day mortality was slightly less in the fluid conservative group (25.5% vs. 28.4%, p=0.30).

Based on the results of these two studies, it would seem that ALI patients should be "run a bit on the dry side," which on the surface might be seen to contradict the findings of Rivers and colleagues [8]. However, it is important to remember that in the Rivers study, early goal-directed resuscitation of septic shock (with or without ALI/ARDS) occurred in the first six hours after presentation to the emergency department, well before the FACTT trial and albumin/furosemide trial interventions were initiated (1 day and 3 days after meeting ALI criteria, respectively). While differences in patient populations (severe sepsis vs. ALI/ARDS) and interventions preclude drawing firm conclusions from the combined findings of these three trials, it seems reasonable to conclude that the exact approach to fluid management in ALI depends on timing. Early on in the acute resuscitative phase, additional fluid may be beneficial. Yet, once the patient is fluid resuscitated, a more conservative approach to fluid management may be in order. This "ebb and flow" hypothesis, which is well-described in the editorial accompanying the FACTT trial report [9], has face-validity but remains untested.

Recommendation

Because of the limited size of the Martin study and its use of surrogate endpoints, we cannot currently recommend routine use of albumin and furosemide in patients with ALI. We do, however, anxiously await the testing of this strategy in a much larger randomized controlled trial.

Competing interests

The authors declare no competing interests.

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