Fluid balance and colloid osmotic pressure in acute respiratory failure: emerging clinical evidence

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Abstract

Available evidence suggests that both hydrostatic and osmotic forces are important in the development of acute respiratory distress syndrome (ARDS) or, more broadly, acute lung injury (ALI). More than 80% of ARDS patients in a large-scale randomized controlled trial (RCT) exhibited, at least intermittently, pulmonary artery wedge pressures (PAWP) above 18 mmHg. Retrospective analyses have shown that PAWP elevation is associated with increased mortality. Reduction in serum total protein (STP) has been shown, in a recent retrospective analysis of data from a sepsis patient population with a high frequency of ARDS, to be highly predictive of positive fluid balance, weight gain, development of ARDS, prolonged mechanical ventilation, and mortality. These findings suggest that therapy with diuretics and colloids might be of benefit in the prevention or treatment of ALI. A prospective RCT was designed and conducted to evaluate combination therapy with furosemide and albumin over a 5-day period in 37 ALI patients. Both mean serum albumin and mean STP increased promptly and substantially in furosemide + albumin recipients. The furosemide + albumin group also achieved a mean weight loss of 10 kg by the end of the treatment phase, and their weight loss exceeded that of placebo patients throughout. Hemodynamics improved in the treatment group during the 5-day protocol. Oxygenation, as assessed by the ratio between the fraction of inspired oxygen and the partial pressure of oxygen in arterial blood (PaO_2/FiO_2), was significantly higher within 24 h after commencement of treatment in the furosemide + albumin than the placebo group. No clinically important adverse effects of furosemide + albumin therapy were encountered. These results provide evidence that combined therapy with furosemide and albumin is effective in augmenting serum albumin and STP levels, promoting weight loss, and improving oxygenation and longer-term hemodynamic stability. Although mortality did not differ between groups, the RCT showed a trend toward reduced duration of mechanical ventilation and length of stay in the intensive care unit in patients receiving furosemide + albumin. The findings of the RCT further highlight the importance of both hydrostatic and osmotic forces in hypoxemic respiratory failure, a subject that requires further investigation.

Keywords: furosemide, hydrostatic pressure, osmotic pressure, respiratory distress syndrome (adult), serum albumin

ALI = acute lung injury; ARDS = acute respiratory distress syndrome; ICU = intensive care unit; PaO_2/FiO_2 = ratio between the fraction of inspired oxygen and the partial pressure of oxygen in arterial blood; PAWP = pulmonary artery wedge pressures; PEEP = positive end-expiratory pressure; RCT = randomized controlled trial; STP = serum total protein.

Introduction

Both hydrostatic and osmotic forces are at play in the development of ARDS or, more broadly, ALI. There could consequently be a potential clinical role for diuretic and colloid therapy in patients at risk for ALI. This potential role has been investigated in a recent randomized controlled clinical trial.

Hydrostatic forces in ALI

Hydrostatic pressure is a key contributor to the formation of edema regardless of the integrity of the capillary barrier, although it exerts an exaggerated effect in states of increased capillary permeability, which is a pathognomonic hallmark of ARDS or ALI. One exclusionary component of the consensus conference definition for ALI and ARDS is PAWP >18 mmHg [1]. PAWP, nevertheless, at least intermittently exceeded 18 mmHg in more than 80% of patients enrolled in a large-scale RCT of patients with ARDS [2]. Furthermore, mortality risk is known to be increased in ARDS patients with elevated PAWP [3,4]. The mortality rate was thus greater than 50% in patients with PAWP consistently above 18 mmHg, compared with approximately 30–35% in patients without such persistent PAWP elevation.

Retrospective observations have similarly revealed an association between PAWP reduction and improved survival in ARDS patients [5]. The survival rate was nearly three-fold higher among patients experiencing a >25% decline in PAWP compared with patients who did not. In a randomized prospective trial of patients with pulmonary edema, a fluid restrictive strategy was effective in reducing extravascular lung water, days of mechanical ventilator support and length of intensive care unit (ICU) stay, while resulting in an encouraging trend towards reduced mortality [6].

Loop diuretics such as furosemide serve as first-line therapy for renal insufficiency, nephrotic syndrome and congestive heart failure, and second-line treatment in cirrhosis [7]. The role of loop diuretics in patients with ALI remains to be defined. Most ARDS patients in one small-scale prospective study reported over 20 years ago responded favorably to diuretic therapy in conjunction with positive end-expiratory pressure (PEEP) ≤ 20 cmH_2O [8]. Improvements were observed in static compliance of the respiratory system, arterial oxygen tension and urine output. There is hence suggestive, although limited, evidence that interventions to reduce hydrostatic pressure in the lung might lead to improved patient outcomes.

Osmotic forces in ALI

Based upon Starling's equation, a reduced colloid osmotic pressure gradient between the intravascular space and interstitium can promote edema formation. Re-establishment of this gradient through colloid administration might serve to diminish edema; however, there is a potential concern for exacerbating edema in states of increased capillary permeability such as ALI. This concern does not appear to be warranted in the absence of elevated hydrostatic pressure, in that albumin infusion in ARDS patients was found not to augment pulmonary transmicrovascular flux of low or high molecular weight solutes when colloid-related increases in pulmonary hydrostatic pressure were minimized [9].

Hypoproteinemia as risk factor for ARDS

Further insights into the role of plasma oncotic forces in ALI have been provided by a retrospective analysis of data from a large-scale multicenter RCT of ibuprofen treatment in patients with sepsis [10]. This RCT, conducted from 1989 to 1995, involved 455 patients. Development of ARDS occurred in 39% of these patients, and hypoproteinemia was documented in 92% of patients in this group.

Reduction in STP (ie in the primary determinant of serum colloid osmotic pressure) was found, based upon regression analysis of the study database, to be highly predictive of positive fluid balance, weight gain, development and maintenance of ARDS, prolonged mechanical ventilation, and mortality [11]. The incidence of ARDS was 22% among normoproteinemic patients (STP ≥ 6 g/dl) compared with 41 and 45% in patients with borderline (5 g/dl $<$STP$<$ 6 g/dl) or severe (STP≤ 5 g/dl) hypoproteinemia, respectively ($P=0.0006$). Whereas normoproteinemic patients lost 3.6 kg body weight on average during the trial, their counterparts with borderline or severe hypoproteinemia gained 3.9 and 4.9 kg, respectively ($P=0.004$). Furthermore, the mortality rate of patients with borderline (48%) or severe (45%) hypoproteinemia exceeded that of normoproteinemic patients (14%) more than three-fold ($P=0.04$). The clear association between hypoproteinemia and unfavorable clinical outcomes revealed by the retrospective analysis suggests the possibility that patients may derive benefit from interventions to increase serum protein levels and, by inference, colloid osmotic pressure.

Furosemide and albumin in ALI: design of a RCT

The evidence already reviewed supports the concept that reduction in hydrostatic forces and maintenance of normal colloid osmotic pressure might improve clinical outcomes in ALI patients. This evidence equally suggests that combined diuretic and colloid therapy may benefit ALI patients. Approximately 99% of furosemide in the circulation is bound to albumin, and this binding facilitates delivery of furosemide into the tubular lumen. Combined treatment with furosemide and albumin was, in a recent RCT, significantly more effective than either agent alone in promoting volume excretion in patients with the nephrotic syndrome [12]. In another recent RCT, a significantly higher proportion of patients with cirrhosis and ascites responded to co-administered furosemide and albumin with body weight loss ≥ 2.5 kg and/or resolution of ascites, as compared

with patients receiving furosemide but not albumin [13]. Combination therapy with furosemide and albumin in a rabbit model of experimentally induced lung injury reduced lung water accumulation and alveolar–arterial oxygen pressure difference, whereas monotherapy with either agent alone was ineffective [14]. The potential utility of diuretic and colloid therapy in patients with lung injury has not, however, been the subject of clinical investigations to date.

A RCT of ALI patients was designed and conducted to test the hypotheses that albumin will enhance the diuretic response to furosemide while avoiding potential adverse effects of diuretic monotherapy, and that combined albumin and furosemide therapy will improve respiratory physiology [15]. Furosemide plus albumin was compared with dual placebo under a randomized, double-blind protocol with the therapeutic goals of attaining net negative fluid balance, weight loss, and an increase in serum proteins over a period of 5 days. Outcome measures consisted of vital signs and hemodynamics, respiratory mechanics and oxygenation, blood chemistries, duration of mechanical ventilation, and mortality.

Eligibility for study entry required a diagnosis of ALI or ARDS by the American–European Consensus Conference definition, with the additional requirements for mechanical ventilation and hypoproteinemia. Patients were excluded primarily for hemodynamic instability, renal or chronic hepatic failure, or marked electrolyte abnormalities.

Patients randomized to the furosemide + albumin group received furosemide by continuous intravenous infusion, as titrated to achieve negative fluid balance, and 25 g albumin intravenously every 8 h. Furosemide administration was suspended in cases of hypotension or severe electrolyte disturbances, and placebo was substituted for albumin when STP exceeded the lower limit of normal.

Results of furosemide and albumin therapy in ALI/ARDS

Patients were enrolled in the RCT over an 18-month period, and the mean age of the 37 study patients was 42 years. The etiology of ALI was predominantly trauma related, with common critical illnesses predisposing to lung injury accounting for the remainder. No significant differences existed between the 19 furosemide + albumin treated patients and the 18 placebo patients in age, race, gender, apportionment across etiologic categories or baseline APACHE III score.

Both mean serum albumin and STP in the furosemide + albumin group increased to a significantly greater extent than that in placebo patients. The observed increase in mean serum albumin among furosemide + albumin patients was more than 1.5 g/dl. Mean STP rose continuously in the furosemide + albumin group to a plateau approaching the lower limit of normal.

The furosemide + albumin group experienced a marked decline in body weight over the follow-up period, and this decline was significantly greater than that of the placebo patients after day 1. Mean weight loss totaled 10 kg by day 5 in furosemide + albumin treated patients.

The pronounced changes in serum albumin, STP and body weight associated with the furosemide + albumin regimen were not accompanied by evidence of renal dysfunction, as judged by the lack of significant between-group difference in blood urea nitrogen or creatinine. These patients did, however, exhibit electrolyte effects typical of diuretic treatment.

Mean arterial pressure in the furosemide + albumin group had increased significantly by the conclusion of the 5-day treatment period, while heart rate declined during the same period. Placebo group hemodynamic status did not depart appreciably from baseline.

No between-group or within-group differences were noted in variables designed to detect alterations in respiratory physiology. The baseline ratio between the fraction of inspired oxygen and the partial pressure of oxygen in arterial blood (PaO_2/FiO_2 ratio) in all patients was approximately 180 mmHg, in conformity with the definition for ARDS. Oxygenation, however, as assessed by PaO_2/FiO_2 ratio, was significantly increased by 40% in the furosemide + albumin treated patients at 1–2 days, but not in the placebo group.

Recipients of furosemide + albumin had shorter median duration of mechanical ventilation and length of stay in the ICU. In this comparatively small population, however, these differences were not statistically significant. Three patients died in each study group, and the mortality rate of the furosemide + albumin group (16%) was similar to that of the placebo group (17%).

Conclusion

Critically ill patients have difficulty maintaining fluid balance, an effect exacerbated by reductions in the colloid osmotic pressure gradient. Hypoproteinemia, as a surrogate for colloid osmotic pressure, is associated with the development and maintenance of ARDS, prolonged duration of mechanical ventilation, and mortality in patients with sepsis. A RCT of 37 patients with ALI or ARDS has provided evidence that combined therapy with furosemide and albumin is effective in augmenting serum albumin and STP levels, promoting weight loss, acutely increasing oxygenation and, despite substantial diuresis and weight loss, improving longer-term hemodynamic stability. Clinically important treatment-associated adverse effects were not

encountered aside from expected electrolyte changes. These results support the concept that both hydrostatic and osmotic forces play pivotal roles in hypoxemic respiratory failure. Further studies will be needed to confirm these findings and evaluate the observed trend toward reduced duration of mechanical ventilation and length of ICU stay in patients receiving furosemide and albumin.

Commentary

AB Johan Groeneveld, MD: PaO_2/FiO_2 ratios are difficult to interpret outside the context of PEEP levels associated with mechanical ventilation. Were there any differences in PEEP between the groups, or in radiographic appearances?

Greg Martin, MD: PEEP is clearly an important factor in considering oxygen requirements. No between-group differences were observed with respect to PEEP at any time, including the first 2 days of treatment–the period when oxygenation changed most dramatically. Mean airway pressure, which correlates moderately with oxygenation, declined slowly from baseline in both groups without difference. Daily radiographs did not appear to change significantly in the first 2 days, although standard radiographs are poor indicators of changes in oxygenation and extravascular lung water, since such changes may not be immediately observable. Further evaluation of these findings is underway.

William J Sibbald MD: The results of this RCT, particularly in terms of weight loss and acute increase in PaO_2/FiO_2 ratio, appear to be conveying a strong biological signal. Adoption of this treatment approach in the ICU would optimally need to be based upon a demonstration of reduced need for other healthcare resources such as mechanical ventilation. It is difficult to see how this might be accomplished other than by conducting a larger-scale RCT.

The significant decline in heart rate among diuretic and albumin recipients was of particular interest. A recent meta-analysis underscored the difficulties in making a clinical diagnosis of hypovolemia [16]. However, a postural pulse increment $\geq$30 beats/min was a reasonably good marker for severe but not moderate hypovolemia. Was PAWP measured in the RCT?

Greg Martin, MD: Yes, but pulmonary artery catheters were present in approximately one-third of the study patients. In these patients, no significant differences were noted with respect to PAWP. The question of healthcare resources is certainly salient. Detecting a difference in mechanical ventilation requirements of this magnitude might require a RCT enrolling more than 200 patients.

Jean-Louis Vincent, MD, PhD: The study population evidently may have included cases of hemodynamic pulmonary edema as well as of ARDS. Patients with fluid overload could clearly have benefited from negative fluid balance. Since PAWP was monitored in $<$40% of the study patients, might fluid overload following resuscitation from trauma have contributed to the observed treatment effects?

Greg Martin, MD: That possibility cannot be excluded, although in the monitored patients baseline PAWP was in the 12–14 mmHg range, thus providing some assurance that gross fluid overload was unlikely. As previously described, PAWP at least intermittently exceeding 18 mmHg has been demonstrated in more than 80% of ARDS patients. Thus, uncertainties regarding fluid overload will be inherent in any trial of patients with ARDS.

AB Johan Groeneveld, MD: Under conditions of low colloid osmotic pressure, threshold hydrostatic pressure is decreased, so the lungs may be readily susceptible to fluid overload even with PAWP $\leq$16 mmHg. This means, in effect, that there may be pressure-dependent pulmonary edema at low wedge pressures.

Andrew R Webb, MD: Lymphatic drainage also need to be taken into account. At lower filling pressures, lymphatic drainage is greater. Therefore, while the lungs may be producing more edema, they are clearing it more quickly as well.

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