A randomized, controlled trial of furosemide with or without albumin in hypoproteinemic patients with acute lung injury*

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Objective: **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.**

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.**

Patients: **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.**

Interventions: **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.**

Measurements and Main Results: **The primary outcome was change in oxygenation from baseline to day 1, with secondary physiologic and clinical outcomes. 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 $Pa_{O_2}/F_{I_{O_2}}$: +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.**

Conclusions: **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. (Crit Care Med 2005; 33:1681–1687)**

KEY WORDS: acute respiratory distress syndrome; albumin; blood proteins; hydrostatic pressure; hypoproteinemia; lung diseases; osmotic pressure; respiratory distress syndrome (adult)

Acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) are among the most common conditions encountered in the intensive care unit (ICU) (1). ALI/ARDS may affect as many as 150,000 people per year in the United States, with mortality exceeding 40% in most published series (2). Patients with ALI/ARDS often require weeks of intensive hospital care and account for an estimated $5 billion per year in direct healthcare expenditures (3). Thus, any therapy that shortens the duration of illness may have great clinical importance, even without affecting mortality.

Hypoproteinemia is one of the strongest independent predictors of the development of ALI/ARDS and subsequent clinical outcomes among patients with sepsis (4). Hypoproteinemic patients are twice as likely to develop ALI/ARDS and three times more likely to die after its onset. Both physiologic and clinical data support fluid restriction to reduce edema formation in ALI/ARDS (5–7). Negative fluid balance is associated with improved outcomes in critically ill patients, (8) and implementation of a fluid-restrictive strategy reduces the duration of mechanical ventilation and may affect survival of patients with pulmonary edema (9). Physiology also supports restoration of the colloid osmotic pressure (COP) gradient to prevent edema formation, at least when permitted by capillary permeability (5). Administration of colloids to patients with ALI/ARDS does not worsen pulmonary edema when hydrostatic pressures remain unchanged (10).

Expanding evidence associates elevated hydrostatic pressures, fluid retention, and weight gain with mortality in ALI/ARDS, yet there has never been a prospective, randomized trial of diuretic therapy in this patient population (11, 12). Data from our previous clinical trial found significant benefits in oxygenation and systemic hemodynamics for patients with ALI/ARDS treated with the combination of albumin and furosemide, in com-

* See also p. 1857

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parison with placebo (13). We conducted a randomized, controlled trial involving hypoproteinemic patients with ALI/ARDS to further our understanding of the implications for active reductions in hydrostatic pressure, with particular focus on the role of colloid supplementation beyond diuretic monotherapy.

MATERIALS AND METHODS

This investigation was approved by the Institutional Review Boards of Emory University and Vanderbilt University and the Research Oversight Committees of Crawford Long and Grady Memorial Hospitals. Surrogate informed consent was obtained in each case from the next of kin, because no patient at the time of study enrollment was capable of providing informed consent.

Study Design. The primary outcome variable for which this study was powered was change in oxygenation over a 24-hr period. This trial was designed with 80% power, with use of a two-tailed α of .05 to detect a minimum 20% change in oxygenation (Pao_2/Fio_2 ratio), and had at least 80% power to detect comparable changes in net fluid balance (intake and output), body weight (kg), serum total protein, serum albumin, and serum creatinine, as estimated on the basis of data from our previous clinical trials (4, 13).

No interim analyses were planned. Adverse events were monitored by a data safety monitoring board, consisting of an independent critical care physician, a biostatistician, and a second independent physician, as needed.

Patient Selection. We identified patients from February 1999 through December 2002 by prospectively screening all adult ICUs within Grady Memorial Hospital (a 900-bed urban level I trauma center), Emory University Hospital (a 600-bed tertiary referral academic hospital), Crawford Long Hospital (a 583-bed academic community hospital), and Vanderbilt University Hospital (a 553-bed academic level I trauma center)—including approximately 190 ICU beds. Eligible subjects met each of the following criteria at study enrollment: (1) the American-European Consensus Conference definition for ALI (bilateral infiltrates evident on frontal chest radiograph, Pao_2/Fio_2 ratio $\leq$300 mm Hg, and no evidence of left atrial hypertension or a pulmonary artery occlusion pressure $\leq$18 mm Hg, if available); (2) serum total protein level $<$6.0 g/dL; (3) ongoing nutritional support; and (4) mechanical ventilation for $\geq$24 hrs. Patients were excluded for hemodynamic instability (defined by administration of $>$2 L of intravenous fluid boluses or transfusion of $>$4 units of packed red blood cells within 24 hrs before eligibility or by vasopressor requirements [dopamine at a dosage $>$5 μg/kg per min; any dosage of epinephrine, phenylephrine, norepinephrine, or vasopressin; or $>$1 vasoactive drug infusion]); renal disease (serum creatinine level $\geq$3.0 mg/dL or urine output $<$500 mL/24 hrs); clinically documented cirrhosis; allergy to albumin or furosemide; age $<$18 yrs; pregnancy; or serum sodium level $>$155 mEq/L or potassium level $<$2.5 mEq/L. The existence of an exclusion criterion did not preclude subsequent enrollment once the criterion was resolved.

Treatment Protocol. Participants were assigned to one of two interventions by random allocation with a computer-generated four-subject-block randomization list held by the investigational pharmacy at each hospital, which was also responsible for study drug preparation, camouflage, blinding, and dispensation. Patients hereafter referred to as treated received 25 g of 25% human serum albumin (Plasbumin, Bayer Healthcare, Research Triangle Park, NC) intravenously infused over 30 mins and immediately followed by a loading dose of intravenous furosemide (20 mg) and a continuous infusion of furosemide (1 mg/mL) for 3 days. Subsequent albumin doses were administered every 8 hours for 3 days. Control patients received identical intravenous-bolus and continuous-infusion furosemide, with an equivalent volume of placebo (0.9% sodium chloride solution) substituted for albumin. Albumin study drug was concealed within a sterile plastic container and infused in opaque intravenous tubing to obscure visual detail. The protocol called for the investigational pharmacy to substitute placebo for albumin whenever daily serum total protein levels exceeded 8.0 g/dL (assay upper limit of normal), although this did not occur. The furosemide infusion drip rate was started at 4 mg/hr except for patients $<$50 yrs of age with serum creatinine concentration $<$1.5 mg/dL (started at 3 mg/hr) and patients $>$50 yrs of age with serum creatinine concentration $\geq$1.5 mg/dL (started at 5 mg/hr), and then the rate was titrated every 4 hrs to achieve a net negative fluid balance and daily weight loss of $\geq$1 kg. The maximum dose of furosemide allowed was 10 mg/hr, and the infusion was suspended for hypotension requiring vasopressors or persisting $>$30 mins (systolic blood pressure $<$90 mm Hg), serum sodium level $\geq$155 meq/L, or serum potassium level $\leq$2.5 meq/L. If hypotension occurred, furosemide administration was discontinued and treatment (intravenous fluid or vasopressors, as needed) was administered according to the orders of the clinical treating physician. No additional diuretic or colloid therapy was permitted during the study. Blood products could be administered only when clinically necessary, exclusive of emergency resuscitation purposes. Other management and treatment modalities were at the discretion of the clinical treating physician, including ventilator management and weaning.

Data Collection. At study enrollment, demographic information, prior medical conditions, etiology of lung injury, severity of illness (APACHE [Acute Physiology and Chronic Health Evaluation] II data), Sequential Organ Failure Assessment (SOFA) scores, and lung injury scores were recorded (14–16). Study data (vital signs, fluid balance, hemodynamics, serum chemistries, ventilator parameters, and oxygenation via arterial blood gas sampling) were collected at the same time each day during the treatment period. Data were subsequently collected for 30 days after enrollment for outcome measures, including the need for mechanical ventilation, shock, documented nosocomial infections, and death. Patient weight was measured daily by means of integrated bed scales, with identical items in contact with the bed at each evaluation. Systemic hemodynamics (cardiac output, stroke volume, end-diastolic volume) were measured by electrical bioimpedance technology (BioZ System, Cardiodynamics, San Diego, CA) (17). Oxygenation index was calculated as mean airway pressure $\times$ Fio_2 $\times$ 100/Pao_2. COP was calculated from the Landis-Pappenheimer equation, where $COP = 2.1(STP) + 0.16(STP)^2 + 0.009(STP)^3$, where STP = serum total protein (18). Single missing SOFA values were calculated as the mean of the sum of the preceding and following values (15). Ventilator-free survival days and intensive-care-free survival days were calculated during the 30-day follow-up period; organ-failure-free days and shock-free days were calculated during the first 14 days of follow-up. These variables are previously defined combined end points for group comparison of specific modalities (e.g., mechanical ventilation) with respect to mortality, representing the number of days in the defined period following study enrollment that the patient is both alive and not meeting the specified criteria. Patients were defined as shock-free if systolic blood pressure was $>$90 mm Hg without vasopressor requirements, as defined above in the exclusion criteria. For purposes of analysis, patients were considered extubated if they remained free from mechanical ventilation for $\geq$48 hrs. All patients were observed until hospital discharge or death.

Statistical Analysis. Descriptive statistics are presented as mean $\pm$ SD as determined with statistical software (NCSS 2001, NCSS Statistical Software, Kaysville, UT); subsequent statistical analyses were performed with SAS 8.2 (SAS Institute, Cary, NC). We analyzed data on an intent-to-treat basis, comparing the treatment and control groups, and calculated temporal changes during the treatment period (day 3—day 0). *A priori* analyses were planned to stratify the patient groups by clinical site, hospital service (medical vs. surgical), cause of ALI (direct vs. indirect, sepsis vs. others), and duration of ALI before enrollment. Comparisons between two groups (either by time or treatment assignment) were made by unpaired Student's *t*-test or Mann-Whitney U test for normally or nonnormally distributed data, respectively. Multiple between-group comparisons of continuous variables were analyzed by repeated-measures

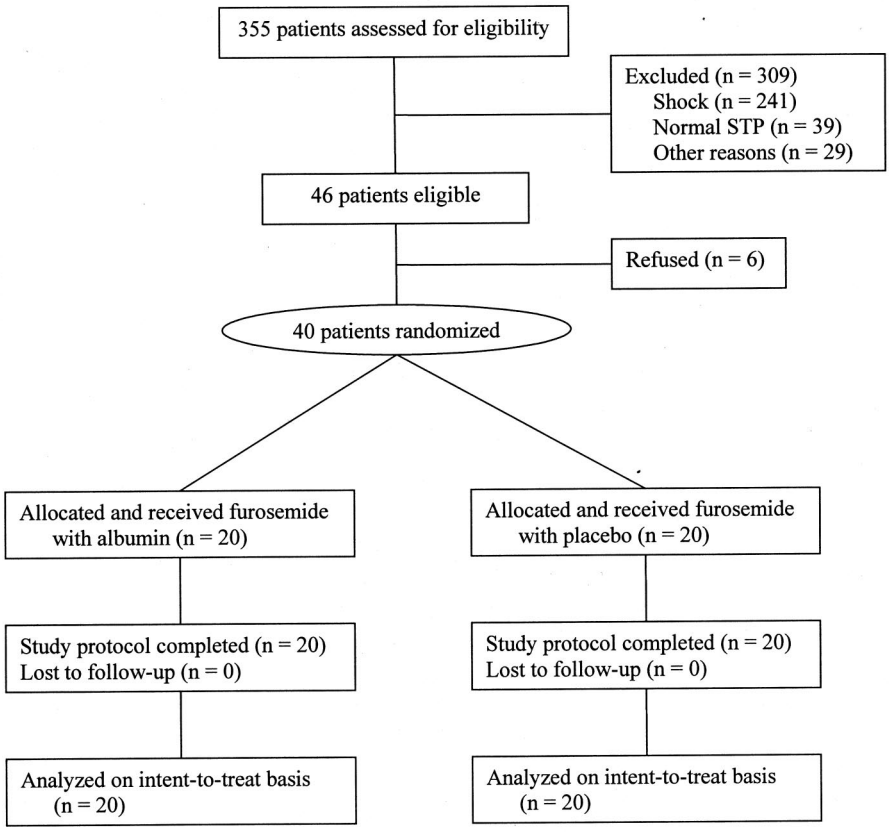

Figure 1. CONSORT-style flow diagram of patient screening, eligibility, and enrollment in the trial. *STP*, serum total protein.

analysis of variance with application of Tukey's procedure for multiple comparisons. The chi-square statistic was chosen for dichotomous variables and analysis of proportions. Univariate linear regression was employed for correlation of continuous variables, including predictors for changes in the primary outcome variable. Multivariable regression and logistic modeling were used to examine independent predictors of clinical outcome variables (death or extubation). All p values are two-sided, with a threshold α of .05 used to assign significance.

RESULTS

Characteristics of Enrolled Patients

Forty patients were enrolled and all completed the study protocol (Fig. 1). Eligible patients who were not enrolled were similar in demographic characteristics, cause of ALI, and survival. Fifty-seven percent of patients were enrolled from Emory University and 43% from Vanderbilt University. Randomization groups did not differ with respect to age, sex, race, APACHE II score, lung injury score, or SOFA score or according to clinical site (Table 1). Sixty-five percent of patients were enrolled from a medical ICU, and sepsis was the most common cause of ALI (Table 1). Patients developed ALI a median of 3 days (interquartile range [IQR] = 1.0–5.0 days) before study enrollment, and there was no difference between groups. Compliance with the study protocol was achieved in 98.9% of study drug administrations. The mean starting furosemide dosage of 3.7 mg/hr did not differ between groups, although by day 3 for control patients the dosage had been titrated higher than for patients in the treatment group (7.0 vs. 5.2 mg/hr; $p = .06$). Furosemide was transiently withdrawn from 12 patients because of hypotension (3 treatment and 9 control; $p = .04$) and from 1 patient for hypokalemia during the protocol treatment period.

Physiologic Treatment Effects

The combined patient groups had a mean serum total protein concentration of 4.5 g/dL and serum albumin concentration of 1.7 g/dL at enrollment (Table 1). Patients in the treatment group had a mean 1.5-g/dL increase in serum total protein concentration during the 3-day treatment protocol, whereas that of control patients increased by only 0.5 g/dL (Fig. 2), accompanied by similar rises in serum albumin (1.3 g/dL vs. 0.3 g/dL; $p < .001$ for both variables between groups). Similar temporal changes occurred in calculated COP, with significantly greater increases in the treatment group at all time points (increasing by 6.7 vs. 2.1 mm Hg by day 3; $p < .01$). At 24 hrs, changes in serum albumin accounted for nearly all of the changes in serum total protein (coefficient of determination, 0.76; $p < .01$). Changes in serum total protein concentration from baseline were no longer different by day 7 (1.1 vs. 0.9 g/dL; n = 31; $p = .54$). Serum total protein levels did not exceed 8.0 g/dL at any time in either group, obviating substitution of placebo for albumin in the treatment group.

Treated patients had modest but insignificantly greater urine output and weight loss on each day. All patients experienced cumulative fluid loss during the study period that was greater in the treatment group (net intake/output at day 3 was −5480 mL vs. −1490 mL; $p < .01$), in part because of greater fluid-bolus administration in the control group (1050 mL vs. 275 mL; $p = .06$) (Fig. 3). A net negative fluid balance was not achieved during the study period for seven patients in the control group and for one patient in the treatment group ($p = .02$). No significant change was observed in electrolytes (serum sodium, potassium, and bicarbonate) or biochemical measures of organ dysfunction (blood urea nitrogen, serum creatinine, platelets, and hepatic transaminases) in either group (Table 2).

Respiratory mechanics were similar between groups at all time points, including minute ventilation, inspiratory pressures, and dynamic respiratory system compliance (Table 2). Oxygenation, as measured by the Pao_2/Fio_2 ratio, increased significantly in the albumin-treated group within 24 hrs (43 vs. −24 mm Hg; $p < .01$) and remained higher than in the control group throughout the duration of the study (Fig. 4). Levels of PEEP did not change significantly over time; thus, similar improvements were evident in the oxygenation index (−2.2

Table 1. Demographic and physiologic characteristics of enrolled patients at baseline

Characteristic	Control Patients n = 20		Treatment Patients n = 20	
Demographic				
Mean age, yrs (SD)	46.4	(18.0)	48.9	(21.6)
Sex, male, %	50		45	
Race, no. (%)				
White	14	(70)	15	(75)
African-American	6	(30)	5	(25)
Hospital service, no. (%)				
Medical	14	(70)	12	(60)
Surgical	6	(30)	8	(40)
Acute lung injury etiology, no. (%)				
Sepsis	8	(40)	7	(35)
Trauma	4	(20)	6	(30)
Pneumonia	5	(25)	3	(15)
Aspiration	1	(5)	1	(5)
Other	2	(10)	3	(15)
Physiologic, mean ± SD				
Lung Injury Score	2.8	(0.5)	2.8	(0.5)
APACHE II score	14.0	(7.5)	13.4	(5.5)
SOFA score	5.6	(2.6)	4.9	(2.0)
Serum total protein (g/dL)	4.5	(0.7)	4.5	(0.6)
Serum albumin, g/dL	1.6	(0.4)	1.7	(0.4)
Serum creatinine, g/dL	1.0	(0.7)	0.9	(0.5)
COP, mm Hg	13.8	(3.1)	13.6	(2.5)
Minute ventilation, L/min	12.5	(5.4)	12.3	(3.1)
F_{IO_2}	0.51	(0.13)	0.51	(0.20)
Pa_{O_2}/F_{IO_2} ratio, mm Hg	182	(53)	162	(54)
PEEP, cm H_2O	9.9	(3.3)	8.8	(2.5)
$P_{\overline{AW}}$, cm H_2O	17.8	(3.8)	17.0	(3.1)
Oxygenation index, cm H_2O/mm Hg	10.8	(4.6)	11.5	(4.6)
P_{PEAK}, cm H_2O	33.6	(7.6)	33.1	(7.6)
C_{DYN}, mL/cm H_2O	17.1	(4.8)	19.3	(7.4)
Mean tidal volume, mL	552	(155)	578	(137)
Tidal volume/PBW, mL/kg	8.8	(2.1)	9.1	(2.0)
Cardiac index, L/min/m^2	3.0	(0.9)	3.0	(1.0)
Stroke volume index, mL/m^2	30	(9.2)	30	(9.6)
End-diastolic volume index, mL/m^2	69	(16)	71	(16)

APACHE, Acute Physiology and Chronic Health Evaluation; SOFA, sequential organ failure assessment; COP, colloid osmotic pressure; PEEP, positive end-expiratory pressure; $P_{\overline{AW}}$, mean airway pressure; P_{PEAK}, peak airway pressure; C_{DYN}, dynamic respiratory system compliance; PBW, predicted body weight.

vs. +1.8 cm H_2O/mm Hg at 24 hrs; $p < .01$). Treated patients were more likely to have improved oxygenation at 24 hrs (17 of 20 treatment vs. 6 of 20 controls; $p < .001$) and to reverse the oxygenation criteria for ALI by the end of the study period (5 of 20 vs. 1 of 20; $p = .08$).

Changes in cardiac index at 24 hrs were significantly greater in the treated patients (+0.4 vs. −0.3 L/min per m^2; $p = .008$) and were not significantly different either within or between groups at other time points (Table 2). There were no differences in end-diastolic volume, blood pressure, or heart rate between groups, although control patients were more likely to require discontinuation of the furosemide infusion and received more intravenous fluid boluses (data provided above). From baseline to day 7, control patients received 35 fluid boluses in 13 episodes, compared with 11 fluid boluses in 7 episodes for treated patients.

Stratified Analyses

Changes in the primary outcome variable were not different among the four *a priori* strata: clinical site, cause of ALI (direct vs. indirect or sepsis vs. others), hospital service, and time to enrollment after onset of ALI. Although not significantly different from other subgroups, sepsis-induced ALI patients had the greatest improvement in oxygenation at 24 hrs (mean Pa_{O_2}/F_{IO_2}, +64 vs. −21 mm Hg for treatment vs. control; $p < .001$). The duration of ALI preceding study enrollment was not a significant predictor of changes in oxygenation when analyzed either as a continuous predictor variable or as a discrete predictor variable dichotomized at the median.

Regression Models

Oxygenation changes in treated patients were best predicted by changes in COP and fluid balance, accounting for 26% of such changes (model coefficient of determination, 0.26; $p < .001$). Twenty-three patients' oxygenation improved by 24 hrs, and treatment allocation to receive albumin with furosemide was associated with improved oxygenation in a univariate analysis (odds ratio, 13.2; 95% confidence interval [95% CI], 2.2–62.6). The effect of treatment allocation on oxygenation remained significant in a multivariable logistic regression model (odds ratio, 19.3; 95% CI, 2.9–127.3) adjusting for age, race, severity of illness (APACHE II), clinical site, hospital service, and cause of ALI. Cox proportional hazards regression revealed no significant affect of group assignment on time to successful extubation, after adjustment for age, APACHE II score, duration of ALI before enrollment, and clinical site (treatment group hazard ratio = 1.12; 95% CI, 0.48–2.64).

Clinical Outcomes

Other than more frequent hypotension in the control group, there were no adverse events (bleeding diatheses, transfusion requirements, or infectious complications) during the study. Mean SOFA scores at the end of the treatment period decreased for treated patients by 0.6 and increased for control patients by 1.1 ($p = .01$ between groups). There were seven deaths in the treatment group and nine in the control group (35% vs. 45% mortality rate; $p = .52$). The median number of shock-free days was greater in the treatment group: 14.0 days vs. 7.0 days (difference, 7.0 days; 95% CI, 3.9–10.1). Treated patients accrued a median of 5.5 ventilator-free days during 30-day follow-up, compared with 1.0 days in the control group (difference, 4.5 days; 95% CI, −2.5 to 11.5 days).

DISCUSSION

In this study, we showed that hypoproteinemic ALI patients treated with the combination of albumin and furosemide have significantly greater improvements in oxygenation than do patients receiving only furosemide. These differences are not fully explained by differences in fluid balance, COP, or cardiovascular function, according to statistical regression findings. Furthermore, the addition of albu-

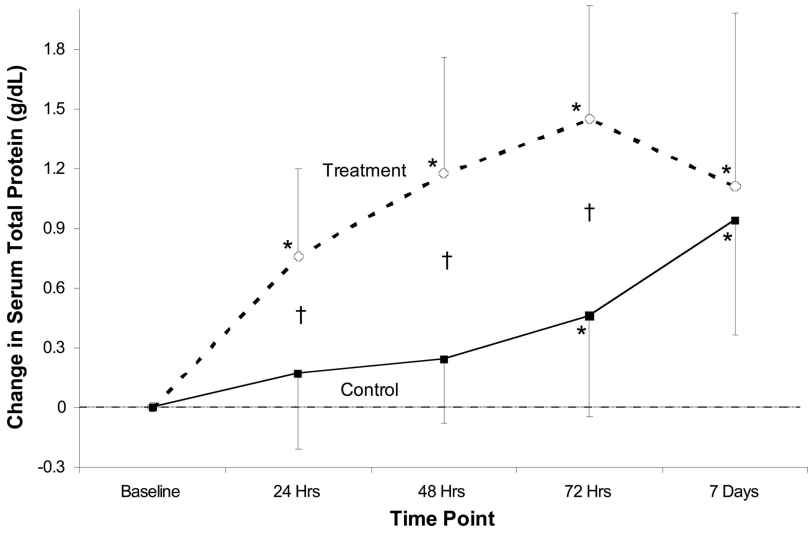

Figure 2. Changes from baseline in serum total protein between hypoproteinemic acute lung injury patients treated with furosemide and albumin (treatment, *dashed line*) or furosemide and placebo (control, *solid line*). *Points* are mean values with error bars depicting standard error of the mean (mean ± SD) at each time point. *Significant differences from baseline; †significant between-group differences at $p < .05$.

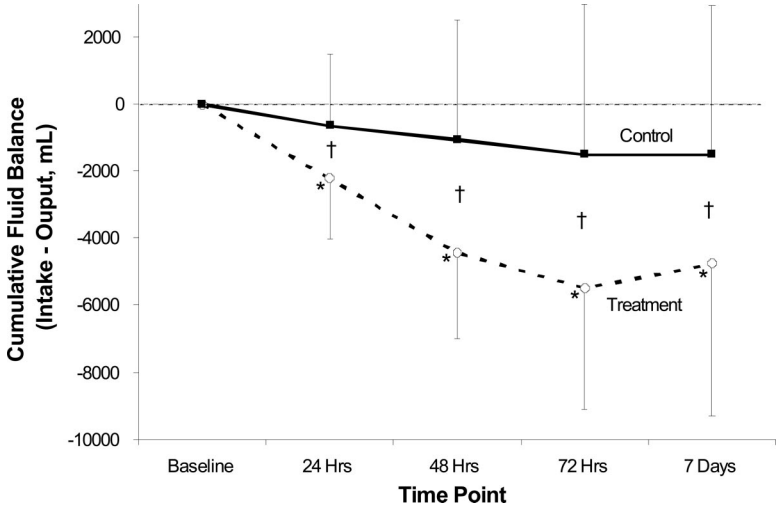

Figure 3. Cumulative fluid balance during the study period, comparing patients treated with furosemide and albumin (treatment, *dashed line*) or furosemide and placebo (control, *solid line*). *Points* are mean values with error bars depicting standard error of the mean (mean ± SD) at each time point. *Significant differences from baseline; †significant between-group differences at $p < .05$.

Combination therapy with albumin and furosemide for hypoproteinemic patients with acute lung injury improves oxygenation through mechanisms that require further examination.

min to furosemide therapy promoted diuresis while reducing hypotension and shock from furosemide monotherapy.

Changes in oxygenation were related to the administration of albumin and were only minimally modulated by diuretic-induced changes in fluid balance. The mechanism of these changes is likely multifactorial. Treated patients had greater improvements in cardiac output than did control patients and may have had improvement in oxygen delivery, thus increasing systemic arterial oxygenation. Colloid- and diuretic-induced changes in pulmonary edema may have reduced extravascular lung water while maintaining cardiovascular function, resulting in better ventilation-perfusion matching (19, 20). Specific biochemical attributes of albumin may have further contributed to the improvements in oxygenation, either through modulation of oxidant stress or the inflammatory milieu, as we and others have shown that exogenous albumin administration favorably alters systemic redox balance in this patient population (21–26). The role of albumin in improving longer-term clinical outcomes is uncertain, given group convergence of protein levels by day 7, but could involve prolonged redox cycling after initial albumin administration (21).

Our previous controlled trial involving hypoproteinemic ALI patients showed important physiologic benefits from the combination of colloid and diuretic therapy (13). The current data suggest that albumin is a critical component of this regimen, both for maintenance of hemodynamic stability and for improved oxygenation. Diuresis and restoration of COP were similar to that in our previous trial, as was the magnitude of change in oxygenation, whereas control groups in each study achieved similar fluid balance, and neither had improvements in oxygenation. Although a fluid-restrictive treatment regimen has been shown to reduce the duration of mechanical ventilation and ICU stay for patients with pulmonary edema, (9) similar management strategies for critically ill patients have been complicated by hypotension and tissue hypoperfusion (27). The addition of albumin to a diuretic strategy stabilizes hemodynamics, presumably through maintenance of effective circulating blood volume, while promoting egress of pulmonary edema fluid from the alveolar space. Although albumin and other colloids have not been shown to improve outcomes in large groups of critically ill patients, (28) the use of albumin in well-defined "niche" populations has proven effective (29–33).

The results of this trial are limited primarily by the number of enrolled patients, making conclusions about clinical outcomes unfeasible. The strength of this study lies in the strictly defined study population and use of multiple ICUs in two different institutions. Although the

Table 2. Treatment-related changes from baseline in primary outcome variables

Outcome Variable	Change in Value (% Change)			
	Control Patients n = 20		Treatment Patients n = 20	
	Day 1	Day 3	Day 1	Day 3
Pao_2/Fio_2 ratio, mm Hg	−24 (34)	−13 (76)	43[a] (46)	49[a] (86)
Minute ventilation, L/min	−0.5 (2.5)	−0.5 (4.6)	0.5 (4.0)	−1.5 (3.9)
C_{DYN}, mL/cm H_2O	−0.8 (3.7)	1.3 (4.6)	1.4 (3.0)	2.8 (4.4)
PEEP, cm H_2O	10.1 (3.9)	8.8 (8.4)	8.7 (3.1)	8.0 (3.3)
Serum albumin, g/dL	0.2 (0.3)	0.3 (0.6)	0.6[a] (0.4)	1.3[a] (0.5)
Weight, kg	−2.2 (3.4)	−5.4 (6.8)	−2.2 (3.8)	−7.4 (4.3)
Cardiac index, L/min per m^2	−0.3 (0.8)	−0.1 (0.8)	0.4[a] (0.7)	0.2 (0.6)
Mean arterial pressure, mm Hg	−1.9 (16.9)	−1.5 (16.4)	0.1 (14.4)	0.6 (13.7)
Heart rate, beats/min	3 (12)	5 (17)	−8 (14)	−2 (18)
Blood urea nitrogen, mg/dL	2.4 (4.3)	8.2 (15.2)	0.9 (5.4)	6.1 (12.9)
Serum creatinine, mg/dL	0.09 (0.16)	−0.01 (0.44)	0.04 (0.14)	0.08 (0.27)
Serum potassium, meq/L	−0.4 (0.7)	−0.2 (1.0)	−0.3 (0.5)	−0.2 (0.7)
Hemoglobin, g/dL	0.1 (0.7)	−0.5 (1.0)	−0.4 (1.1)	−0.3 (1.5)

C_{DYN}, dynamic respiratory system compliance; PEEP, positive end-expiratory pressure.
[a]Significant difference from baseline value at $p < .05$.

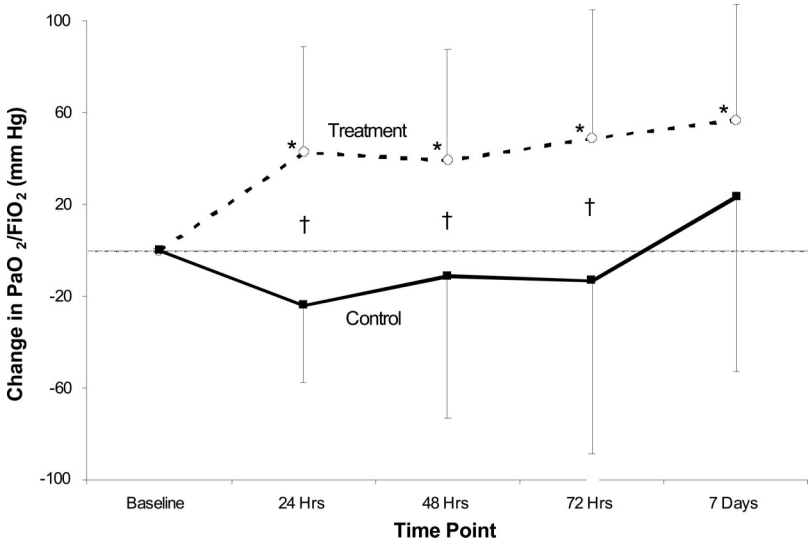

Figure 4. Changes in oxygenation from baseline in hypoproteinemic patients with acute lung injury treated with furosemide and albumin (treatment, *dashed line*) or furosemide and placebo (control, *solid line*). *Points* are mean values with error bars depicting standard error of the mean (mean ± SD) at each time point. *Significant differences from baseline; †significant between-group differences at $p < .05$.

specific population was important for testing the stated hypothesis, it limits the external validity of the results. Generalizability may also be affected by the inherent heterogeneity of ALI, although stratified analyses did not detect differences based upon demographics or clinical condition (such as surgical vs. medical patients). The literature contains conflicting conclusions about the influence of colloid or diuretic therapy on hemodynamics and extravascular lung water, and many of the previous studies were uncontrolled or utilized noncontemporaneous fluid administration protocols (34–37). The monitoring techniques we utilized contributed valuable insights into physiologic changes and potential mechanisms by permitting rapid, noninvasive continuous measurement of cardiopulmonary function, yet they have not been as fully validated in ALI patients, in whom pulmonary edema may reduce accuracy (17, 38, 39). Finally, the consistent improvements in oxygenation observed in our clinical trials are of uncertain clinical relevance, given that some previous therapies that improved oxygenation did not yield clinical benefits (40), whereas therapies that de-emphasized oxygenation led to important improvements (41). However, persistent defects in oxygenation have been reported to both predict outcomes (42–45) and influence long-term quality of life for ALI patients (46).

CONCLUSIONS

In summary, the combination of albumin and furosemide in therapy for hypoproteinemic ALI patients improves oxygenation through mechanisms that require further examination. Consistent trends toward improved duration of mechanical ventilation are apparent from this and previous studies; thus, a large-scale randomized trial is warranted to determine whether such a clinical benefit may be achieved. Such a trial should consider the role of synthetic colloids and should include an integrated pharmacoeconomic analysis to determine whether the cost of albumin may be offset by overall reductions in ICU utilization and healthcare resource consumption.

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