Hospital Pharmacy
2020, Vol. 55(2) 130–134

DOI: 10.1177/0018578719828331
journals.sagepub.com/home/hpx
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Hyperoncotic Albumin Reduces Net Fluid Loss Associated With Hemodialysis

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Abstract

Purpose: The purpose of this study was to compare the volume of fluid removal associated with and without 25% albumin administration in conjunction with hemodialysis. **Methods:** This retrospective, cohort study was conducted at a large academic medical center over a 6-month period to compare the net fluid amount removed (mL) during hemodialysis between patients administered 25% albumin and those without albumin. **Results:** A total of 238 patients consisting of 973 unique hemodialysis sessions were evaluated. The mean overall net fluid removed by hemodialysis in the 25% albumin and no albumin groups were 1242 mL and 1899 mL, $P < .001$, respectively. No albumin group had significantly higher mean fluid losses compared with 25% albumin for a total dose of either 25 g ($P = .001$) or 50 g ($P = .001$). There were no significant differences in mean fluid loss between the no albumin group and patients receiving 75 g or 100 g of albumin. Post hoc analysis failed to demonstrate a dose-dependent response in those patients receiving 25% albumin and no albumin. **Conclusion:** Hyperoncotic albumin administered during hemodialysis sessions reduced net fluid loss associated with hemodialysis. The findings of this study do not support the routine use of 25% albumin to improve fluid removal during dialysis.

Keywords

human serum albumin, colloid, fluid, hemodialysis

Background

A multicenter survey of albumin use in the United States conducted approximately 2 decades ago found that albumin was utilized for a variety conditions, including intradialytic hypotension, despite a lack of high-level evidence for most indications.[1] No multicenter evaluations of albumin use in the United States have been conducted since that survey, although so-called appropriate use criteria listed in published studies suggest that albumin continues to be used in association with dialysis.[2,3] Albumin has a variety of pleiotropic effects, but the purported justification for albumin administration during hemodialysis is to prevent or treat intradialytic hypotension through its plasma expanding actions. A systematic review investigating the possible benefits of albumin for the treatment of intradialytic hypotension concluded that normal saline (0.9% sodium chloride) should be the first-line therapy based on similar efficacy and decreased cost compared with albumin.[4] The conclusion of the systematic review was based on one double-blind, randomized crossover study involving 72 patients in which 5% albumin was found to no have no significant advantages over normal saline for target ultrafiltration goals (primary endpoint), blood pressure restoration and maintenance goals, or the prevention of episodes of recurrent intradialytic hypotension.[5] Two other small (n = 10 and n = 9), non-blinded, randomized crossover studies comparing 20% albumin to either a normal saline or a 3% sodium chloride solution found no significant differences in blood pressure restoration or symptom alleviation between the colloid and crystalloid solutions when the solutions were administered based on decreased blood volume or lowered systolic blood pressure recordings.[6,7]

Internal audits of albumin usage at one of our hospitals found substantial use of 25% (hyperoncotic) albumin in association with hemodialysis. Subsequent discussions with dialysis personnel revealed that the hyperoncotic albumin was being used in hemodialysis sessions in an attempt to pull fluid from the interstitial to intravascular space to enhance fluid removal. This perceived mechanism of benefit has not been formally evaluated based on published literature to date. Therefore, the purpose of our evaluation was to

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Table 1. Baseline Comparisons Albumin and No Albumin Groups.

Variable	Albumin (n = 56)	No albumin (n = 167)	*P* value
Age, mean (SD), years	62 (12.2)	58 (15.9)	.002
Sex (male), %	60.6	56.5	.359
Admission weight, mean (SD), kg	82.0 (18.1)	83.1 (24.5)	.559
Height, mean (SD), cm	169.9 (12.57)	167.2 (12.96)	.022
Medical history			
Diabetes, %	67.8	68.2	.929
Heart failure, %	35.0	33.5	.727
End-stage renal disease, %	54.4	81.3	<.001

compare the volume of fluid removal associated with and without 25% albumin administration in conjunction with hemodialysis.

Methods

Study Population

This retrospective, cohort study was conducted at a 700-bed major university medical center (Phoenix, Arizona) over a 6-month period (January 1, 2016-June 30, 2016). Patients were categorized into 2 groups depending on whether they received 25% albumin or no albumin during hemodialysis.

After institutional review board approval, patients were identified through the hospital electronic medical record database. Inclusion criteria consisted of the following: (1) ≥18 years of age; (2) intermittent hemodialysis administered as an inpatient; and (3) patients either received 25% albumin 100 mL administered during hemodialysis or no albumin. Patients were excluded if iso-oncotic (5%) albumin was utilized, indication for albumin was other than for improving ultrafiltration, sustained low-efficiency daily dialysis was employed, or pregnancy. Pertinent demographic data were collected including age, gender, race, height, weight, and comorbidities (diabetes mellitus, heart failure, end-stage renal disease). Clinical data collected also included total albumin (grams) administered per hemodialysis session, net fluid loss or gain (mL) at the end of treatment, and lowest blood pressure recorded during hemodialysis sessions.

Definitions

Net fluid loss was defined as the total volume of fluid (mL) that was either removed from the patient at the end of the hemodialysis session minus the total amount of fluids administered during each dialysis session including rinseback. Rinseback is the process of administering 0.9% sodium chloride to return any blood in the hemodialysis circuit following the completion of treatment. Net fluid gain was defined as the total volume (mL) the patient was positive at the end of the hemodialysis session also accounting for the amount of rinseback.

Statistical Analysis

The primary endpoint was to compare the total net amount of fluid removed between patients receiving 25% albumin during hemodialysis and those without albumin. Dialysis was performed with the Dialog+ Hemodialysis System (B. Braun Avitum AG, Melsungen, Germany) using polysulfone membranes (Diacap Polysulfone HI PS 15; B. Braun Avitum AG). Secondary analyses included any net fluid loss or gain associated with the total grams of albumin administered and the incidence of hypotension. Intradialytic hypotension was defined as systolic blood pressure <90 mm Hg at any time during hemodialysis.

For the demographic information, categorical values of sex and past medical history were compared using Fisher exact test, and continuous variables for age, height, weight, and albumin vs no albumin were compared using the 2-sample Student *t* test. Analysis of variance with Sidak post hoc testing was used to investigate potential differences in net fluid loss by albumin dose (ie, 0, 25, 50, 75, and 100 g). Multivariate regression analysis was performed to evaluate the effects of other independent variables on the primary outcome variable of net fluid loss during dialysis. Significance for all testing was defined as an alpha of 0.05. All analyses were conducted using STATA 13 (College Station, Texas).

Results

A total of 238 patients consisting of 973 unique hemodialysis sessions (180 and 793 sessions in the 25% albumin and no albumin groups, respectively) were evaluated. Baseline characteristics of the patients in the albumin and no albumin groups are listed in Table 1. Significantly more patients in the no albumin compared with the albumin group had end-stage renal disease (81.3% vs 54.4%, $P < .001$, respectively). The mean overall net fluid removed by hemodialysis in the 25% albumin and no albumin groups were 1242 mL and 1899 mL, $P < .001$, respectively. About 70% of patients receiving intradialytic albumin were administered a total of 25 g as a "one-time" dose (25% albumin 100mL), while the remaining patients received between 50 and 100 g total during each hemodialysis session. The net fluid loss associated

Table 2. Net Fluid Loss by Dose of Albumin Administered.

Total number of patients (n)[a]	Total number of dialysis sessions (n)	Dose of albumin given during dialysis	Mean	SD	*P* value
179	793	0 g	−1899	1112	reference
48	128	25 g	−1261	1227	<.001
23	42	50 g	−1086	1184	<.001
5	6	75 g	−1933	1353	1
3	4	100 g	−1150	850	.874

[a]Total number of patients administered each dose of albumin exceeds total number of included patients in study because some patients may have received different doses for each dialysis session.

Table 3. Multivariate Analysis of Fluid Loss.

Variable	Coefficient	95% CI	*P* value
Age	4.32	−2.29 to 10.93	.20
Sex	16.19	−210.54 to 242.92	.889
Admission weight	−8.54	−12.86 to −4.23	<.001
Height	4.45	−4.82 to 13.73	.346
History of diabetes	−151.07	−368.32 to 66.18	.173
History of end-stage renal disease	−188.08	−417.29 to 41.12	.108
History of heart failure	−99.19	−315.81 to −117.43	.369

Note. CI = confidence interval.

with hemodialysis was significantly different depending on the dose (0, 25, 50, 75, and 100 g) of albumin administered (Table 2). The no albumin group was found to have significantly higher mean fluid loss compared with patients receiving 25% albumin for a total dose of either 25 g ($P = .001$) or 50 g ($P = .001$). There were no significant differences in mean fluid loss between the no albumin group and patients receiving 75 or 100 g of albumin, but there were only 10 patients (6 or 4, respectively) in the latter groups. Only one statistically significant relationship with net fluid loss was found using multivariable regression analysis (Table 3). An inverse relationship was observed between weight and net fluid loss with increasing weight associated with a decreased net fluid loss during hemodialysis ($P < .001$). No patients experienced intradialytic hypotension.

Discussion

A hyperoncotic 25% albumin solution was found to decrease not increase fluid removal during hemodialysis, despite the perceived benefits by dialysis personnel who thought that albumin would shift fluid to the intravascular compartment making it more available for removal by ultrafiltration. The only previous study designed to look at ultrafiltration goals used a more iso-oncotic 5% albumin solution and found a similar lack of benefit.[5] Two small crossover studies using 25% albumin in association with hemodialysis found no advantages of albumin over normal saline using endpoints of blood pressure stabilization or symptom alleviation.[6,7]

Our retrospective evaluation differs from the 3 previously published crossover studies evaluating albumin for hemodialysis both in terms of design and proposed mechanism of action of albumin's effects. The previously published crossover investigations focused on the plasma expanding actions of iso-oncotic albumin for achieving ultrafiltration goals or hyperoncotic albumin for treating intradialytic hypotension, while our retrospective evaluation involving much larger number of patients focused on the fluid removal actions of hyperoncotic albumin.[6,7] In the United States, albumin is available as 5% and 25% formulations. A 5% albumin formulation is often referred to as iso-oncotic meaning that in theory it expands blood volume approximately equal to the volume infused, whereas 25% albumin formulations are considered to be hyperoncotic suggesting that blood volume expansion is much greater than the volume infused. For the latter formulation, the blood volume expansion beyond the volume of the product infused is due to shifting of fluid from the interstitial to the intravascular compartment, which in theory could result in more effective fluid removal by ultrafiltration. However, studies have shown that the actual blood volume expansion associated with albumin products is time and disease dependent and often substantially less than what would be predicted based on theoretical distribution models.[8] For example, in one study 200 mL of a 20% albumin bolus given over 2 minutes yielded a maximum plasma expansion of 500 mL in control subjects and 430 mL in subjects with septic shock.[9] The lack of benefit in hemodialysis-associated fluid removal with hyperoncotic albumin in our evaluation

suggests that either a substantial increase in blood volume expansion did not occur, or if it did occur it did not lead to increased fluid removal.

Efficacy is not the only appropriate consideration when making a choice between two therapeutic options. Safety and cost are 2 additional factors that should be considered in the decision-making process. None of the studies involving albumin and saline solutions for hemodialysis have suggested clinically important safety differences between the products. In contrast to crystalloid solutions like normal saline, albumin is a blood-derived protein so there is the possibility, albeit unlikely, of hypersensitivity reactions. In addition, there is the theoretical risk of bloodborne pathogen contamination leading to viral or prion disease.

A recently published cohort study from the University HealthSystem Consortium database observed a significant increase in albumin utilization among academic medical centers in the United States over a 5-year period.[10] The total estimated albumin cost significantly increased from $325 million in 2009 to $468 million in 2013 ($P < .0001$). Although the investigators report rates of albumin use determined as appropriate, occasionally appropriate, or inappropriate, the definitions of appropriateness based on indication for use remains debatable. Unfortunately, this report did not disclose the proportion of use among dialysis patients and may not be reflective of annualized costs for this specific indication. An evaluation of albumin use in British Columbia found that almost 20% of the use of albumin was for intradialytic hypotension.[11] This has substantial cost implications given that an equivalent amount of albumin can be 100-fold more expensive than normal saline. This increased cost to the institution is difficult to justify when there are no established effectiveness or safety benefits attributable to albumin over saline in association with hemodialysis.

In our multivariate regression analysis that looked at variables other than albumin dose as possible predictors of net fluid loss, increasing weight was associated with decreasing net fluid loss ($P < .001$). The explanation for this relationship is unknown, but we could speculate that an accurate estimation of dry weight in more obese patients might be more difficult particularly when relatively rapid changes in weight are occurring over relatively short periods of time.

The primary limitation of this study is its retrospective nature with the potential for missing or inaccurate data, although no data points were missing for the primary outcome assessment (dose of albumin and net fluid loss). Another limitation is that this is a single center study with the prescription for fluid removal targeted to the prescribing physician's patient-specific goals rather than an overarching measure of adequacy of fluid removal.[12] The small number of patients receiving more than 50 g of albumin in a dialysis session precludes firm conclusions about fluid removal compared to no albumin in this subset of patients.

Conclusion

Hyperoncotic albumin compared with no albumin administered during hemodialysis sessions reduced overall net fluid loss associated with hemodialysis. A dose-dependent relationship in the net amount of fluid removed in patients administered 25% albumin and no albumin was not observed. The findings of this study do not support the routine use of 25% albumin to improve fluid removal during dialysis.

Authors' Note

This original research was presented as a poster presentation at the 2017 American College of Clinical Pharmacy Annual Meeting in October 2017.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

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