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Original Article

A Pre-Post analysis of Albumin Exposure with Ideal Body Weight Dosing Compared to Fixed-Dosing of Albumin in Cirrhosis

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Abstract

Background: The American Association for the Study of Liver Diseases (AASLD) guidelines recommend intravenous (IV) albumin for patients with hypovolemia-induced acute kidney injury (AKI) at a dose of 1 g/kg body weight daily for 2 days, without specifying whether actual body weight (ABW) or ideal body weight (IBW) should be used.

Objective: To compare cumulative albumin exposure and clinical outcomes following an institutional transition from a fixed-dose order set approximating ABW to an IBW-based dosing protocol in patients with cirrhosis and AKI.

Methods: This single-center, retrospective cohort study evaluated adult patients with cirrhosis and AKI who received IV albumin during the 6 months before and 6 months after an institutional dosing protocol change. The primary outcome was cumulative albumin dose at 48 hours (day 2) and day 7. Secondary outcomes included AKI response rates, changes in serum creatinine (SCr), and in-hospital mortality. Unadjusted and adjusted multivariable logistic regression evaluated the association between dosing strategy and response.

Results: Sixty patients met inclusion criteria: 27 in the pre-intervention fixed-dose group and 33 in the post-intervention IBW-dosing group. No significant difference was observed in cumulative albumin exposure at day 2 (median 150 g vs. 150 g; p= 0.476) or day 7 (median 175 g vs. 187.5 g; p = 0.403). Albumin response rates by day 7 or discharge were comparable between the pre- and post-intervention cohorts (70.4% vs. 69.7%; adjusted OR 1.03, 95% CI 0.30–3.46; p = 0.966). No significant differences were observed in complete response rates (48.2% vs. 66.7%; p = 0.192) or in-hospital mortality. Partial response was observed more frequently in the pre-intervention group (22.2% vs. 3.0%; p = 0.039).

Conclusion: Transitioning from a fixed-dose order set approximating ABW to an IBW-based dosing protocol did not significantly alter cumulative albumin exposure or AKI response rates. IBW-based dosing represents a safe and feasible institutional strategy that avoids unintended exposure reductions or adverse clinical outcomes.

Keywords: Liver Cirrhosis, Albumin, Acute Kidney Injury, Ideal Body Weight

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Introduction

Acute kidney injury (AKI) is prevalent in hospitalized patients with decompensated cirrhosis and associated with increased morbidity and mortality.[1,2] The mechanism by which patients with cirrhosis develop AKI includes systemic vasodilation, compensatory mechanisms including renin-angiotensin-aldosterone system activation, and intravascular fluid loss leading to hypovolemia and decreased renal perfusion. [1,3] Hypovolemia accounts for about 50% of AKI cases in patients with cirrhosis and may be driven by compensatory processes and concurrent diuretic use.[4]

Volume resuscitation with albumin is recommended to improve renal perfusion in the treatment of AKI in cirrhosis and prevent hepatorenal syndrome (HRS).[2,5] The American Association for the Study of Liver Diseases (AASLD) recommends intravenous (IV) albumin for volume resuscitation in patients with hypovolemia-induced AKI, dosed at 1 gram (g)/kilogram (kg) body weight daily for 2 days.[2] No delineation is made, however, between actual body weight (ABW) or ideal body weight (IBW).[2] IBW dosing may better represent the plasma volume retention of albumin by reducing the effect of adipose tissue included in ABW. This distinction is important as the choice of weight used may result in a wide variance in albumin received, ABW can fluctuate significantly due to fluid displacement to extravascular spaces, and overexposure may cause pulmonary edema and volume overload.[6] The optimal dosing strategy of albumin to reverse AKI associated with cirrhosis remains undefined.

Our institution changed the albumin dosing for patients with cirrhosis and AKI from a fixed-dosing strategy approximating ABW to an IBW-based dosing strategy to more closely reflect guideline recommendations for weight-based dosing strategies. The purpose of this evaluation was to compare the change in albumin exposure in patients with cirrhosis and AKI receiving albumin between a fixed-dosing and an IBW-dosing strategy.

Methods

Study Design

This was a single-center, retrospective evaluation of an institutional albumin dosing protocol change reviewing patients admitted between November 9, 2022, and November 9, 2023. Patients included were at least 18 years of age, diagnosed with cirrhosis and AKI, and received IV albumin via an institutional albumin order-set.[5] Exclusion criteria included septic shock or receipt of IV vasopressors, albumin use outside of the AKI dosing order-set, weight other than IBW used for albumin weight-based dosing, large-volume paracentesis, diagnosis or treatment for HRS, transition to renal replacement therapy (RRT), or receipt of nephrotoxic medications during the initial 48-hour albumin resuscitation period.

Prior to May 9, 2023, the albumin dosing order-set for AKI with cirrhosis at our institution was a fixed regimen approximating ABW of 25g IV every 6 hours for 24 hours. This dosing strategy was implemented via the use of pre-built order-sets for patients with cirrhosis and AKI. Our institution altered this order-set with a change on May 9, 2023 to 0.5g/kg IV albumin every 12 hours using IBW dosing for 2 days. Both orders were followed by 12.5g albumin every 8 hours until AKI resolution or order discontinuation.

Patients were divided into two groups. The pre-intervention group contained all patients meeting inclusion criteria from November 9, 2022 to May 8, 2023 and used the fixed-dosing strategy of 25g IV every 6 hours for 24 hours followed by 12.5g every 8 hours until AKI resolution or order discontinuation. The post-intervention group contained all patients meeting inclusion criteria from May 9, 2023 to November 9, 2023 and the IBW-based albumin dosing strategy of 0.5 g/kg IV every 12 hours for 2 days followed by 12.5g every 8 hours until AKI resolution or order discontinuation. No run-in time was provided as the change did not require new education and was immediately available to order on the electronic health record. Of note, our institution rounds albumin to the nearest 12.5 g vial size.

Study data were collected and stored using the secure web-based electronic tool Research Electronic Data Capture (REDCap), with grant

support from the National Center for Advancing Translational Sciences (Grant-UL1TR001070).[7,8] Data were retrospectively collected from the electronic medical record and included baseline demographic variables; etiology of cirrhosis; Model for End-Stage Liver Disease 3.0 (MELD 3.0) at initiation of albumin infusion; mean arterial pressure (MAP) at time of initial albumin infusion; serum creatinine (SCr) at baseline, day 2, and day 7 or discharge during albumin administration; serum albumin at baseline, day 2, and day 7 or discharge during albumin administration; and administered crystalloid volume during the initial 2 day resuscitative period. Prior to the initiation of this evaluation, the protocol was reviewed by The Ohio State University Office of Research Institutional Review Board (IRB) and was approved with approval number 2023H0408. All research was conducted in accordance with both the Declaration of Helsinki and Declaration of Istanbul. The research received a waiver of informed consent by The Ohio State University Office of Research Institutional Review Board (IRB).

Definitions

AKI was defined per Kidney Disease Improving Global Outcomes (KDIGO) and AASLD guidance as an increase in SCr ≥0.3 mg/dL within 2 days or a ≥50% increase in serum creatinine within the preceding 7 days.[5] AKI stage was defined as the following: Stage 1, SCr increase ≥0.3 mg/dL in 2 days or 1.5-1.9 times the baseline SCr within 7 days; Stage 2, SCr increase 2-2.9 times baseline SCr within 7 days; Stage 3, SCr increase ≥3 times the baseline SCr or an increase to ≥4 mg/dL within 7 days, or transition to RRT. Baseline SCr was defined as the lowest SCr within 3 months of index admission, closest to the date of admission.[5] If no SCr value within 3 months, the lowest SCr value between month 4 and 12 prior to admission was deemed the baseline; if no SCr was available >1 year prior to hospitalization, the first SCr value at admission was deemed the baseline.[5] In patients who did not have a SCr available >1 year prior to hospitalization, AKI was defined as a clinical diagnosis of AKI on presentation with an initial response to volume resuscitation with albumin.

Albumin response was defined as patients who had a decrease of ≥1 AKI stage or a return of SCr to within 0.3 mg/dL of baseline by day of discharge or hospital day 7 after albumin initiation. Complete responders were subsequently defined as a return to within 0.3 mg/dL of baseline SCr by day of discharge or hospital day 7. Partial responders were subsequently defined as a decrease in AKI stage by ≥1, by day of discharge or hospital day 7. Non-responders were defined as a decrease in SCr without regression of AKI stage, an increase in SCr, diagnosis of HRS, or RRT following initial 48-hour albumin resuscitation.

Nephrotoxic medications were defined as receipt of the following: non-steroidal anti-inflammatory medications (NSAIDs), aminoglycosides, amphotericin, angiotensin-converting enzyme (ACE)-inhibitors, angiotensin receptor blockers (ARBs), calcineurin inhibitors, contrast dye (iodixanol, iohexol, barium), diuretics (loop, thiazide, acetazolamide), IV acyclovir, or lithium. Vasopressors were defined as angiotensin II, dopamine, epinephrine, norepinephrine, phenylephrine, terlipressin, or vasopressin.

Outcomes

The primary outcome was the cumulative albumin dose received in grams and g/kg in the first 2 days and 7 days of albumin infusion. Secondary outcomes included: proportion of patients with a partial or complete response by day of discharge or hospital day 7; comparison of SCr change in response to albumin resuscitation; proportion of patients who had a complete response to albumin resuscitation; proportion of patients who had a partial response to albumin within the same time frame; and, in-hospital all-cause mortality.

Statistical Analysis

Descriptive statistics were used to describe variables of interest, including counts and proportions for categorical variables and mean (standard deviation) and/or median (interquartile range) for continuous variables as appropriate. T-tests or Fisher's exact tests were used to compare outcomes between treatment groups for unadjusted continuous and categorical outcomes, respectively. Unadjusted and adjusted logistic regression models were used to

Table 1: Baseline Characteristics

Characteristic	Pre-intervention, n = 27	Post-intervention, n = 33
Age, years, median [IQR]	55 [45 – 63]	57 [47 –63]
Male, n (%)	14 (51.9)	17 (41.5)
Race, n (%)		
White	25 (92.6)	26 (78.8)
African-American	1 (3.7)	4 (12.1)
Other	1 (3.7)	3 (9.1)
Actual Body Weight, kg, median [IQR]	92.9 [65.7 – 117.9]	87.6 [74.2 – 95.9]
Ideal Body Weight, kg, median [IQR]	63.9 [57.0 – 77.7]	63.9 [57.0 – 70.8]
Body Mass Index, kg/m2, median [IQR]	31.6 [23.4 – 36.2]	28.6 [25.7 – 31.1]
MELD 3.0, median [IQR]	26 [22 – 31]	28 [21 – 32]
SCr, mg/dL, median [IQR]		
Baseline SCr prior to albumin	1.01 [0.72 – 1.33]	0.92 [0.80 – 1.16]
Time of first albumin dose	1.71 [1.38 – 2.46]	1.58 [1.38 – 1.93]
Day 2	1.55 [1.17 – 1.97]	1.25 [1.10 – 1.62]
Day 7 or discharge	1.42 [0.93 – 2.55]	1.22 [1.08 – 1.52]
Serum albumin, g/dL, median [IQR]		
Time of first albumin dose	2.8 [2.7 – 3.3]	2.8 [2.5 – 3.1]
Day 2	3.5 [3.0 – 3.7]	3.5 [3.2 – 3.8]
Day 7 or discharge	3.2 [3.0 – 3.5]	3.3 [3.0 – 3.9]
MAP, mmHg, median [IQR]	74 [78 – 82]	81 [75 – 94]
Duration of albumin use, days, median [IQR]	4 [3 – 5]	5 [3 – 7]
Crystalloid volume administered in first 48 hours of resuscitation, mL, median [IQR]	232 [41 – 288]	189 [250 – 1000]
Etiology of cirrhosis, n (%)		
Alcohol	14 (51.9)	20 (60.6)
MASH	10 (37.0)	10 (30.3)
AIH	0 (0.0)	2 (6.1)
PBC	0 (0.0)	1 (3.0)
PSC	0 (0.0)	3 (9.1)
Hep B virus	2 (7.4)	1 (3.0)
Hep C virus	0 (0.0)	4 (9.8)
Other	3 (11.1)	2 (6.1)

compare responder proportions between the pre- and post-intervention groups, with adjusted models accounting for prespecified covariates. Unadjusted and adjusted linear regression models were used to estimate the difference in percent change of SCr from baseline to day 7 or discharge between the two groups. Covariates for inclusion in adjusted models were determined a priori based on expert knowledge and a review of the literature. All analyses were conducted in SAS Statistical Software version 9.4 (Copyright © 2024, SAS Institute Inc., Cary, NC).

Results

A total of 595 patients were screened for inclusion between November 9, 2022 and

November 9, 2023. Sixty patients met inclusion criteria with 27 patients in the pre-intervention group and 33 patients in the post-intervention group. The most common reason for exclusion was albumin administration duration of <48 hours (n=239), nephrotoxic medication administration (n=167), and albumin administration outside of the order panel (n=141). Patients may have met more than one exclusion criterion. Baseline characteristics are displayed in Table 1. Alcohol was the most common etiology of cirrhosis at 51.9% and 60.6% for the pre- and post-intervention groups, respectively. Serum creatinine and albumin were similar between the fixed-dosing and IBW-dosing groups at time of albumin infusion, day 2, and day 7 or discharge.

Primary and secondary outcome data are displayed in Table 2. No significant difference was found in either the cumulative or weight-based albumin dose by day 2 (150 g vs 150 g, p=0.476) or day 7 (175 g vs 187.5 g, p=0.403). There was no difference observed in g/kg ABW or g/kg IBW at either time point.

No significant difference was found in the proportion of patients classified as albumin responders between pre-intervention fixed-dosing and post-intervention IBW-dosing strategies. The proportion of albumin responders by day 7 or day of discharge in the pre- and post-intervention group was 70.4% and 69.7%, respectively. This finding remained unchanged after adjustment for age, sex, and receipt of crystalloid fluids (OR 1.03, 95% CI 0.30 to 3.46; p=0.966). Among albumin responders, we did not observe a difference in the percent change in SCr from initiation of albumin infusion to day 7 or discharge between treatment groups (difference in change for post-intervention group=-0.18 [SE=0.28]; p=0.517, compared to the pre-intervention group). Complete response rates were higher in the post-intervention group but did not reach statistical significance (48.2% vs 66.7%; p=0.192). Partial response was observed more frequently in the pre-intervention group (22.2% vs 3.0%; p=0.039).

Discussion

When compared to fixed-dosing of albumin, an institutional change from a fixed-dose approximating ABW to an IBW-dosing strategy was not associated with a meaningful change in cumulative albumin exposure or a change in serum creatinine response to albumin. These findings provide support for the feasibility of implementing IBW-based albumin dosing protocols, which to date has not been described in comparison to other dosing strategies in the literature.

A concern with any weight-based dosing institutional change is the potential for unintended drug exposure changes. In this cohort, the median ABW of 92.9 kg in the pre-intervention and 87.6 kg in the post-intervention group substantially exceeded the median IBW of 63.9 kg in both groups, raising the hypothesis that IBW-based dosing would result in meaningfully lower albumin administration. This was not observed: both groups received a median of 150 g of albumin in the first 48 hours. This equivalence likely reflects the conservative structure of the fixed-dose regimen – standard 100 g over 24 hours - combined with institutional rounding conventions. While these overlapping exposures represent the practical reality of real-world protocol implementation, they provide reassurance that the IBW-based strategy does not inadvertently reduce albumin exposure to potentially sub-therapeutic amounts.

The rationale for changing to IBW-dosing was due to the pharmacokinetic characteristics of albumin. Albumin may reduce antinatriuretic systems for a short period of time, but this effect is neither consistent nor prolonged.[9] Albumin dosing based on IBW may therefore better reflect the relevant compartment for dosing in patients with elevated ABW. Additionally, ABW in patients with cirrhosis is subject to fluctuation due to ascites and peripheral edema, reducing its reliability as a dosing weight. The transition to IBW-based dosing aligns with guideline intent and may reduce pharmacokinetic variability without compromising clinical outcomes.

There is no literature comparing weight-based dosing of albumin and limited literature on clinical outcomes of weight-based albumin infusions on SCr, though our findings may complement prior work by China et al, who demonstrated no difference in renal, infectious,

or mortality outcomes with higher albumin exposure when targeting a serum albumin level of ≥3.5 g/dL.[6] The median albumin exposure in our evaluation of 150 g over 48 hours fell within the interquartile range of the albumin-targeted group in China et al [IQR 140-280 g] supporting the safety profile of the doses delivered in both dosing arms.[6] China and colleagues did suggest an increase, however, in pulmonary edema and fluid overload.[6] Our evaluation adds to the literature by characterizing the exposure of albumin with a dosing change but highlights the potential need for optimized dosing strategies to limit albumin exposure.

Our evaluation has several limitations. The retrospective single-center nature coupled with the small sample size precludes drawing causative conclusions. Retrospective single-center evaluations are also susceptible to documentation variability. The use of admission SCr as the baseline for patients who had no SCr available >1 year prior to hospitalization may have overrepresented the number of responders, as a reduction in SCr within the stated definitions would have resulted in a responder classification. An additional limitation was the lack of urine output. Given the retrospective nature of this evaluation, the decision was made to rely on SCr as a marker of renal function, which alone is not a comprehensive representation of renal function. Pulmonary edema and volume overload were not systematically captured as safety endpoints. Future prospective studies should formally evaluate safety outcomes, including fluid overload and pulmonary edema, when comparing albumin dosing strategies.

Conclusion

An institutional transition from a fixed-dose to an IBW-based dosing strategy for albumin infusion in the treatment of AKI in hospitalized patients with cirrhosis was not associated with a significant change in cumulative albumin exposure or AKI response when compared to fixed dose albumin. These findings support the safety and feasibility of IBW-based albumin dosing as a reasonable institutional protocol. Larger prospective studies are warranted to evaluate safety outcomes, including pulmonary edema and volume overload, and to define optimal weight-based albumin dosing strategies in this population

List of abbreviations:
AKI: Acute Kidney Injury
HRS: Hepatorenal syndrome
AASLD: American Association for the Study of Liver Disease
IBW: Ideal Body Weight
IV: Intravenous
MELD 3.0: Model for End-Stage Liver Disease 3.0
SCr: Serum Creatinine
KDIGO: Kidney Disease Improving Global Outcomes
NSAIDs: Non-steroidal anti-inflammatory medications
ACE: Angiotensin-converting enzyme
ARB: Angiotensin receptor blocker
MAP: Mean Arterial Pressure
IQR: Interquartile range
AIH: Autoimmune Induced Hepatitis
MASH: Metabolic Dysfunction-Associated Steatohepatitis
PBC: Primary Biliary Cholangitis
PSC: Primary Sclerosing Cholangitis

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