Postoperative Course of Serum Albumin Levels and Organ Dysfunction After Liver Transplantation

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ABSTRACT

Background and aims. Postoperative hypoalbuminemia, especially following liver transplantation, can lead to adverse multisystem effects and even death. We investigated the relationship between postoperative albumin levels and organ failure (assessed using Sequential Organ Failure Assessment [SOFA] scores).

Methods. Sixty liver transplant recipients admitted to the intensive care unit (ICU) from 2012 to 2015 were retrospectively divided into 2 groups: lower albumin (LA) (n=28) and higher albumin (HA) (n=32), using whether serum albumin level fell below 3.0 g/dL during the first postoperative week as the stratifying factor. The SOFA scores (primary endpoint) and associated complications (ascites amount, rejection, re-intubation, abdominal re-operation, thrombosis), additional treatment (dialysis, pleural effusion drainage), and duration of ICU stay (secondary endpoints) of the 2 groups were compared.

Results. Average serum albumin levels were significantly different between HA and LA groups (3.6 [3.4–3.8] vs 3.1 [2.9–3.3], respectively, $P < .05$), although the amounts of albumin infused in the 2 groups during the first postoperative week were not different (HA vs LA: 42 [30–71] vs 40 [30–58], respectively, $P = .37$). Mean daily SOFA scores were not significantly different between the HA and LA groups (8.3 [6.6–9.0] vs 7.2 [6.3–8.6], $P = .73$), although the HA group had lower mean cardiovascular SOFA sub-scores than the LA group (0.1 [0–0.4] vs 0.4 [0–1.3], $P = .032$). There were no significant differences between the groups with regard to complication rates and duration of ICU and hospital stays.

Conclusions. Serum albumin level might not influence cumulative organ function, but it decreases the amount of hemodynamic support required in liver transplant recipients.

ALBUMIN is a product of hepatic protein synthesis and plays an essential role in the generation of colloid-osmotic pressure. Hypoalbuminemia, which is frequently observed in hospitalized patients, can be associated with several different diseases, including cirrhosis, malnutrition, nephrotic syndrome, and sepsis. Regardless of its cause, hypoalbuminemia has strong predictive value in terms of mortality and morbidity. The traditional use of albumin for volume expansion, the potential therapeutic role of albumin in liver disease, and the role of albumin therapy in nutrition have been the focus of studies all over the world [1,2].

Postoperative hypoalbuminemia is common in liver transplant recipients and is used as an indicator of post-operative outcome. The negative effects of postoperative hypoalbuminemia have been long known and several papers

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have addressed this subject [2,3]. Retrospective analyses showed that postoperative hypoalbuminemia is associated with postoperative mortality and acute kidney injury [3,4]. However, whether or not this hypoalbuminemia should be corrected is controversial [5–7], and correct timing and volume for albumin supplementation during the perioperative period is not yet known. Additionally, little is known about prolonged elevation in serum albumin concentrations' effect on organ function.

We aimed to evaluate the impact of postoperative human albumin levels on organ function during the first postoperative week in recipients of orthotopic and living donor liver transplantations.

MATERIALS AND METHODS

This retrospective study involved 60 patients who underwent liver transplantation for hepatic failure between May 2012 and December 2015 at Okayama University Hospital. Patients who had multiple organ transplantations and those younger than 16 years of age were excluded. The study was approved by the institutional review board of our hospital and informed consent was obtained from patients or their guardians. The study was performed in accordance with the ethical standards of the Declaration of Helsinki.

We included only consecutive patients. We noted the patients' preoperative data (age, sex, height, weight, body mass index), underlying disease (etiology: liver cirrhosis from viral infection or non-viral, fulminant hepatitis), Model for End-stage Liver Disease scores, Child-Pugh scores, serum albumin level, and type of liver transplantation from their charts as the clinical variables. Intraoperative data (surgical time, cold and warm ischemia time, anhepatic time, estimated blood loss, transfusions, and graft weight/recipient weight ratio), and postoperative data (serum albumin level, amount of albumin infused, and transfusion volume) during the first postoperative week were also noted using the patients' hospital medical records. Intraoperative blood loss was estimated using the gauze count and suction volume from the surgical field. The primary endpoint evaluated was the relationship between postoperative Sequential Organ Failure Assessment (SOFA) scores and serum albumin levels. In this score, lower scores indicate better organ function during the first postoperative week. Secondary endpoints were perioperative complications (rejection, re-intubation, abdominal re-operation, thrombosis, ascites, re-transplantation), additional treatment required (dialysis, pleural effusion drainage), and duration of intensive care unit (ICU) and hospital stay. Although we do not have a definite protocol for serum albumin supplementation at our institute, we try to maintain albumin levels above 3.0 g/dL if possible. Hence, we divided the patients into 2 groups. Patients whose serum albumin levels were above 3.0 g/dL during the first week after surgery were included in the higher albumin (HA) group, while the lower albumin (LA) group included patients whose serum albumin levels fell below 3.0 g/dL at least once. We routinely gave all the patients a 5% albumin and crystalloid infusion for at least 5 or 7 days post-operation according to the amount of ascitic fluid issuing from the drainage tube, to maintain serum albumin levels at a higher level (>3.0 g/dL) and maintain intravascular volume. Our transfusion protocol also included administration of fresh frozen plasma to maintain prothrombin activity at $>40\%$. If possible, we tried to provide all patients with nutritional support via a nasal tube as soon as possible after surgery [8]. The assessed parameters were compared between the 2 groups.

Data are presented as percentages (n) or as median (25% quartile, 75% quartile) for continuous variables. Categorical data are presented as proportions. Differences between groups were assessed using the Mann-Whitney U test for continuous variables, and Fisher exact test or χ^2 test for categorical variables. We considered a value of $P<.05$ to indicate a significant difference. JMP version 11 software (SAS Institute, Cary, NC, United States) was used for statistical analyses.

RESULTS

There were no significant differences between the groups with regard to preoperative, intraoperative, or postoperative variables (Table 1). As was to be expected, average serum albumin levels during the postoperative period were significantly higher in the HA group compared to the LA group, except at the time of ICU admission. An average of 30 to 50 g of albumin was infused daily in both groups during the first week after surgery, except at the time of ICU admission. The amount of albumin infused during the first postoperative week in the HA group was not statistically significantly greater than in the LA group (304 [212–509] vs. 283 [210–406] g, respectively, $P=.44$). There were no significant differences in mean daily SOFA scores between the HA and LA groups (8.3 [6.6–9.0] vs 7.2 [6.3–8.6], $P=.73$). Daily SOFA scores gradually decreased during the postoperative period in both groups (Fig 1). There was no significant relationship between serum albumin levels and SOFA scores, although the HA group had a lower mean cardiovascular SOFA sub-score than the LA group (0.1 [0–0.4] vs 0.4 [0–1.3], $P=.032$). There were no significant differences between the 2 groups in terms of neurologic (0.8 [0.5–1.5] vs 0.6 [0.4–1.0], $P=.19$), hepatic (2.3 [2–2.7] vs 1.9 [1.5–2.5], $P=.10$), respiratory (1.5 [1.2–1.8] vs 2.0 [0.8–2.3], $P=.20$), coagulation (2.3 [1.9–2.5] vs 2.3 [1.9–2.5], $P=.76$), or renal SOFA scores (0.0 [0.0–0.8] vs. 0.0 [0.0–0.4], $P=.17$) (Fig 2), nor were there any significant differences between the groups in the rate of occurrence of complications (rejection, re-intubation, abdominal re-operation, thrombosis, re-transplantation), need for additional treatment (dialysis, pleural effusion drainage), or duration of ICU and hospital stay (Table 1).

DISCUSSION

In this study, we found that maintenance of serum albumin levels at >3.0 g/dL during the first postoperative week in liver transplant recipients does not protect against organ injury as assessed using daily SOFA scores. A higher albumin level did, however, decrease the need for postoperative catecholamine support.

Definitive guidelines regarding the appropriate level that serum albumin should be maintained at post-operation have not been established, although it is believed that maintaining higher albumin levels reduces the amount of abdominal or thoracic fluid collection in transplant recipients. Traditionally, in our hospital, the amount of serum albumin and

crystalloids administered depends on the abdominal drainage volume, the aim being to maintain intravascular volume post-operation. Per Ito et al [9], low postoperative albumin levels, which reflect a decreased functional reserve of the liver, are likely to cause ascites and prolong hospital stays following liver resections for hepatocellular carcinomas. However, there is controversy regarding postoperative albumin infusion. Mukhtar et al [5] found no difference in hemodynamic variables or postoperative complications following infusion of human albumin or placebo in living donor liver transplant recipients. Yet, Ertmer et al [6] reported that continuous infusion of albumin might preserve cumulative organ function (as measured by SOFA scores), especially cardiovascular function, in patients undergoing orthotopic liver transplantation. Their study differs from ours in that albumin was not administered to their study's control group, although the higher albumin level did not affect postoperative complications and mortality, as with our results. While the exact amount of serum albumin infused in their study was not mentioned, their maintenance serum albumin level of > 2.8 g/dL reportedly reduced acute kidney injury until postoperative day 3. Although hypoalbuminemia is known to reflect delayed graft function, albumin levels were not associated with graft function or other complications in our study.

The mechanisms and clinical implications of the postoperative decrease in serum albumin levels following hepatic transplantation remain unclear. Surgical stress and delayed graft function are likely associated with the decrease in serum albumin levels in liver transplant recipients. Labgaa et al [10] reported in a prospective cohort study from Europe that a postoperative decrease in serum albumin (especially by ≥ 1.0 g/dL on postoperative day 1) is a predictor of early complications following major abdominal surgery. Hübner et al [11] also showed that a decrease in postoperative albumin levels is a marker of surgical stress and a predictor of clinical outcome. Replenishing this deficit by infusing albumin might prevent serious postoperative complications.

Our target albumin level of > 3.0 g/dL was high compared to other reports and the study period (1 week after surgery) was

Table 1. Baseline Characteristics of the Study Participants

	LA Group (n = 28)	HA Group (n = 32)	*P*
Preoperative Data			
Age (y)	54 (51–61)	55 (46–62)	.50
Male sex	14 (50.0)	16 (50.0)	1
BMI (kg/m^2)	23.8 (20.6–26.1)	22.8 (20.6–25.4)	.40
Child-Pugh score	11 (10–12)	11 (10–12)	.63
MELD score	17 (13–21)	19 (15–22)	.18
Viral liver cirrhosis	11 (39.3)	12 (37.5)	.89
Non-viral liver cirrhosis	17 (60.7)	17 (53.1)	.29
Fulminant hepatitis	0 (0.0)	3 (9.4)	.08
LDLT	23 (82.1)	29 (90.6)	.35
Intraoperative data			
Duration of anesthesia (min)	664 (595–728)	645 (561–737)	.88
Duration of surgery (min)	546 (494–593)	526 (459–632)	.83
Cold ischemia time	76 (37–137)	48 (37–95)	.22
Warm ischemia time	43 (35–47)	44 (33–54)	.49
Anhepatic time	152 (114–193)	168 (137–201)	.50
GW/RBW (%)	1.09 (0.92–1.59)	1.04 (0.75–1.29)	.15
Blood loss (mL)	4517 (3184–8218)	4033 (2680–7688)	.44
Urine output (mL)	1024 (660–1488)	905 (625–1138)	.34
Infusion volumes			
Crystalloids (mL)	2674 (2126–3540)	2335 (1517–5001)	.98
HES (mL)	800 (0–1500)	750 (0–1500)	.88
5% Albumin (mL)	2625 (1738–3313)	2250 (1500–3313)	.68
RBCs (mL)	1960 (1400–2800)	1960 (1120–3080)	.91
FFP (mL)	2520 (1680–3360)	2640 (1680–3180)	.86
Platelets (mL)	400 (200–400)	200 (200–450)	.75
Ascites (mL)	500 (0–2600)	125 (0–1538)	.41
Postoperative data			
RBCs (mL)	280 (0–560)	280 (0–350)	.40
FFP (mL)	1200 (480–1740)	1560 (660–2220)	.13
Platelets (mL)	200 (150–600)	400 (200–600)	.24
Ascites (mL)	9830 (7465–14506)	10719 (5948–19374)	.34

Data are presented as n (%) or as median (25% quartile, 75% quartile). Postoperative data is total volume over 7 days.

Abbreviations: BMI, body mass index; FFP, fresh frozen plasma; GW/RBW, graft weight/recipient weight ratio; HES, hydroxyethyl starch; HA, higher albumin; LA, lower albumin; LDLT, living donor liver transplantation; MELD, Model for End-stage Liver Disease; RBCs, red blood cells.

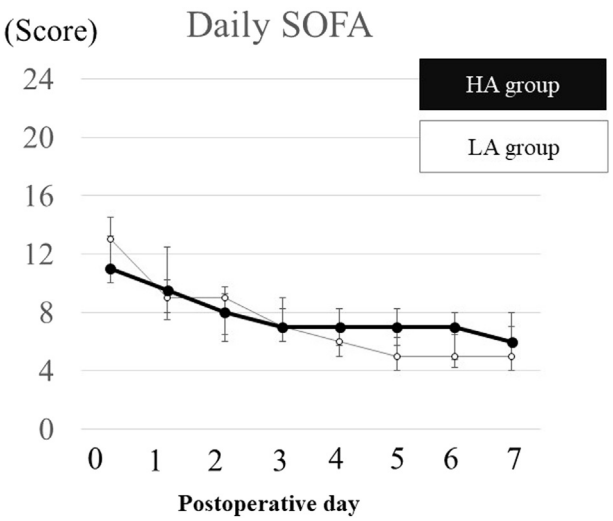

Fig 1. Mean daily SOFA scores in the 2 groups in the first week after transplantation. There were no significant differences in mean daily SOFA scores between the HA and LA groups (8.3 [6.6–9.0] vs 7.2 [6.3–8.6], $P = .73$). Abbreviations: HA, higher albumin level; LA, lower albumin level; SOFA, Sequential Organ Failure Assessment.

long, suggesting that we need to change our postoperative albumin infusion protocol and maintain higher albumin levels for 3 days rather than 7 days after transplantation.

We used SOFA scores to assess organ function in our study. Other scores besides the SOFA score can also be used for assessment of organ injury, such as the Simplified Acute Physiology Score or Acute Physiologic Assessment and Chronic Health Evaluation score [12,13]. Daily assessment of SOFA scores is now common in the ICU setting, especially in transplant recipients, since their pathophysiology might change significantly from infection or acute cellular rejection. Hence, we chose daily SOFA scores to assess organ injury, like Ertmer's study [6].

Our study indicated improvement in cardiovascular performance (as judged by reduced vasopressor requirements and improved cardiovascular SOFA sub-scores) in the HA group compared to the LA group. We believe that this may have resulted from several mechanisms, including mobilization of extravascular fluid into the intravascular compartment. Since we did not measure any oncotic pressure parameters, we cannot definitively state the mechanism of the improved cardiovascular performance with higher albumin levels. Albumin offers several benefits: it scavenges radical oxygen species, has anticoagulant properties, limits tubular cell apoptosis, is intimately related to fluid movement across the endothelial barrier, and is central to maintaining adequate microvascular blood flow [14], all of which are crucial in the perioperative period.

Our study has certain limitations. This study was a small retrospective analysis conducted at a single center. We did not follow any definite criteria regarding albumin infusion. Our control group (the LA group) received the same amount of albumin infusion during the first postoperative week as the HA group. Therefore, it might be difficult to strictly confirm the significance of albumin infusion based

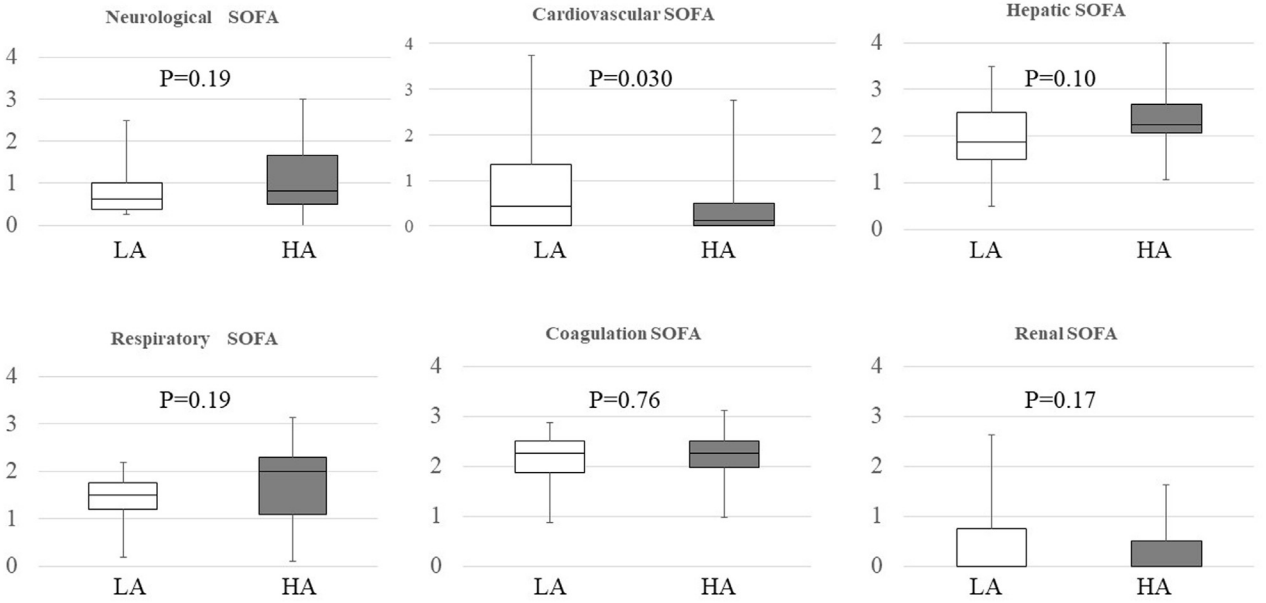

Fig 2. Cardiovascular SOFA sub-scores in the 2 groups. The HA group had lower mean cardiovascular SOFA sub-scores than the LA group (0.1 [0–0.4] vs 0.4 [0–1.3], $P = .03$). There were no significant differences between the 2 groups in terms of neurologic (0.8 [0.5–1.5] vs 0.6 [0.4–1.0], $P = .19$), hepatic (2.3 [2.0–2.7] vs 1.9 [1.5–2.5], $P = .10$), respiratory (1.5 [1.2–1.8] vs 2.0 [0.8–2.3], $P = .20$), coagulation (2.3 [1.9–2.5] vs 2.3 [1.9–2.5], $P = .76$), and renal SOFA scores (0.0 [0.0–0.8] vs 0.0 [0.0–0.4], $P = .17$). Abbreviations: HA, higher albumin level; LA, lower albumin level; SOFA, Sequential Organ Failure Assessment.

on our results. Furthermore, we could not examine the mechanism of the lower cardiovascular SOFA scores in the HA group because we did not measure osmotic pressure.

CONCLUSION

Our results suggest that while serum albumin levels might not influence cumulative organ function (as measured by the SOFA score), maintaining serum albumin levels above 3.0 g/dL may reduce the amount of hemodynamic support required in liver transplant recipients.

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