Effect of Exogenous Albumin on the Incidence of Postoperative Acute Kidney Injury in Patients Undergoing Off-pump Coronary Artery Bypass Surgery with a Preoperative Albumin Level of Less Than 4.0 g/dl

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ABSTRACT

Background: Hypoalbuminemia may increase the risk of acute kidney injury (AKI). The authors investigated whether the immediate preoperative administration of 20% albumin solution affects the incidence of AKI after off-pump coronary artery bypass surgery.

Methods: In this prospective, single-center, randomized, parallel-arm double-blind trial, 220 patients with preoperative serum albumin levels less than 4.0 g/dl were administered 100, 200, or 300 ml of 20% human albumin according to the preoperative serum albumin level (3.5 to 3.9, 3.0 to 3.4, or less than 3.0 g/dl, respectively) or with an equal volume of saline before surgery. The primary outcome measure was AKI incidence after surgery. Postoperative AKI was defined by maximal AKI Network criteria based on creatinine changes.

Results: Patient characteristics and perioperative data except urine output during surgery were similar between the two groups studied, the albumin group and the control group. Urine output (median [interquartile range]) during surgery was higher in the albumin group (550 ml [315 to 980]) than in the control group (370 ml [230 to 670]; $P = 0.006$). The incidence of postoperative AKI in the albumin group was lower than that in the control group (14 [13.7%] *vs.* 26 [25.7%]; $P = 0.048$). There were no significant between-group differences in severe AKI, including renal replacement therapy, 30-day mortality, and other clinical outcomes. There were no significant adverse events.

Conclusion: Administration of 20% exogenous albumin immediately before surgery increases urine output during surgery and reduces the risk of AKI after off-pump coronary artery bypass surgery in patients with a preoperative serum albumin level of less than 4.0 g/dl. **(Anesthesiology 2016; 124:1001-11)**

ACUTE kidney injury (AKI) after coronary bypass surgery is not an uncommon clinical problem, and even transient and less severe AKI is associated with an increased risk of morbidity and mortality after surgery.[1–3] Although off-pump coronary artery bypass surgery (OPCAB) has been reported to reduce the risk of postoperative AKI by avoiding cardiopulmonary bypass (CPB), many other factors, including inflammatory response, oxidative stress, transient circulatory failure, and global hypoperfusion resulting from displacement of the heart to expose the grafting site, can cause renal injury in these patients.[4–6] In the absence of proven effective treatments for AKI, the development of renal protective strategies

What We Already Know about This Topic

- Hypoalbuminemia may increase the risk of acute kidney injury
- The current study was a prospective, single-center, randomized, parallel-arm double-blind trial that investigated whether preoperative administration of 20% albumin solution affects the incidence of acute kidney injury after off-pump coronary artery bypass surgery

What This Article Tells Us That Is New

- Administration of 20% exogenous albumin immediately before surgery increased urine output during surgery and reduced the risk of acute kidney injury after off-pump coronary artery bypass surgery in patients with a preoperative serum albumin level of less than 4.0 g/dl

This article is featured in "This Month in Anesthesiology," page 1A. Corresponding article on page 983. Supplemental Digital Content is available for this article. Direct URL citations appear in the printed text and are available in both the HTML and PDF versions of this article. Links to the digital files are provided in the HTML text of this article on the Journal's Web site (www.anesthesiology.org). Dr. E.-H. Lee participated in study design, execution, data analysis, statistical analysis, and manuscript drafting; Dr. W.-J. Kim participated in study execution, data analysis, and manuscript drafting; Dr. J.-Y. Kim participated in study execution and data analysis; Drs. Chin and D.-K. Choi participated in study execution, statistical analysis, and manuscript drafting; Drs. Sim and Choo participated in study design, execution, and revision of manuscript; Drs. Chung and J.-W. Lee participated in study design and revision of manuscript; and Dr. I.-C. Choi participated in study design, data analysis, and the revision of manuscript. All authors read and approved the final version of the manuscript.

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would be beneficial, especially in patients with known modifiable risk factors.[7]

Albumin is the main protein responsible for plasma oncotic pressure. Besides its maintenance effect on plasma oncotic pressure and its volume expansion effect, albumin has some protective properties, for example: binding to various toxic endogenous and exogenous compounds, scavenging free radicals, exerting antithrombotic effects, acting as a reservoir for nitric oxide, and maintaining capillary membrane permeability.[8] Moreover, hypoalbuminemia may be concentration-dependently linked to increased risk of morbidity, mortality, AKI, and other clinical outcomes in both hospitalized and surgical patients.[2,9–13] In our previous study, we found that a preoperative serum albumin level of less than 4.0 g/dl was also independently associated with postoperative AKI in patients undergoing OPCAB.[2] Thus, correction of perioperative hypoalbuminemia may be a reasonable preventive strategy. However, although human albumin (HA) replacement therapy for correcting perioperative hypoalbuminemia has been widely used in clinical medicine, its usefulness is still a matter of debate because the effect of exogenous albumin supplementation on morbidity and mortality has not been proven in controlled clinical trials and the critical threshold value of serum albumin at which exogenous albumin can be considered to be beneficial remains to be established.[11,14–16] Furthermore, no study has evaluated the impact of preoperative exogenous albumin administration to correct hypoalbuminemia on postoperative renal outcomes.

We, therefore, conducted our current randomized, controlled, double-blind trial to evaluate whether the preemptive administration of exogenous albumin for correcting hypoalbuminemia reduces the incidence of AKI after OPCAB in patients with a preoperative serum albumin level of less than 4.0 g/dl. We hypothesized that preemptive exogenous albumin administration could improve renal outcome after OPCAB.

Materials and Methods

Study Population

This single-center, prospective, randomized, double-blind, parallel-arm superiority study was conducted at a tertiary academic hospital in Seoul, Republic of Korea. The study protocol was approved by the Institutional Review Board at the Asan Medical Center (Seoul, Republic of Korea, 2011-0549), and the study was registered with the Clinical Research Information Service (https://cris.nih.go.kr, August 26, 2011 [KCT0000210]; In-Cheol Choi, M.D.). Patients scheduled for elective OPCAB were recruited for possible enrollment in the study during preoperative surgical and anesthetic assessment by study staff, and those older than 20 yr and of either sex who were undergoing elective OPCAB and had a serum albumin level of less than 4.0 g/dl the day before surgery were enrolled. Written informed consent was obtained from all participating subjects. The threshold value of preoperative serum albumin was chosen according to the results of our previous report, which found that preoperative serum albumin levels less than 4.0 g/dl were an independent risk factor for AKI after OPCAB.[2] We excluded patients with preoperative renal dysfunction (serum creatinine concentration of 1.5 mg/dl or greater before surgery); a history of allergic reactions to HA; left ventricular ejection fraction of 40% or less; preoperative inotrope, intraaortic balloon pump, or ventricular assist device support; or patients who required preoperative dialysis due to preexistent renal failure or who were undergoing repeat operations or concomitant valvular or aortic surgery. Because 20% albumin solutions were routinely used as the priming solution for CPB in our institution, we decided *a priori* to discontinue the study in patients who required conversion to CPB and exclude them from the data analysis. Data and safety monitoring of this trial was overseen by an independent data and safety monitoring board to ensure the safety of participants, the validity of data, and the credibility of study findings.

Protocol

Patients were prospectively randomized into two groups in a 1:1 ratio using a computer-generated list that was stored in sealed envelopes until allocation. The group assignment was performed on the morning of the surgery in a blind manner (*i.e.*, for all patients, medical personnel, and investigators involved in patient management). On the morning of surgery and before induction of anesthesia, the allocation envelope was opened by a nurse or anesthesiologist with no involvement in patient management, who then prepared either 20% albumin or 0.9% NaCl in coded and concealed 100-ml bottles. At induction of anesthesia, patients in the albumin group were administered 100, 200, or 300 ml of 20% HA (Green Cross Co., Korea) at a rate of 5 ml/min according to the preoperative serum albumin level (3.5 to 3.9, 3.0 to 3.4, or less than 3.0 g/dl, respectively), and the infusions were completed before skin incision; patients in the control group were administered with 0.9% NaCl at the same volume and rate. This amount and rate of albumin to increase the serum albumin level to greater than 4 g/dl was chosen by referring to the results and recommendations of previous studies.[17,18]

Perioperative Management

Cardiovascular surgery and perioperative management were performed according to our institutional standards.[19,20] Briefly, general anesthesia was maintained with a continuous infusion of remifentanil and propofol using a target-controlled infusion pump. During study periods, the goals of anesthetic management during OPCAB were to maintain hemodynamic stability (heart rate greater than 60 beats/min, mean arterial pressure greater than 65 mmHg, central venous pressure of 8 to 12 mmHg, pulmonary capillary wedge pressure of 12 to 15 mmHg, urine output greater than

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0.5 ml/kg/h, cardiac index greater than 2.0 $l \cdot min^{-1} \cdot m^{-2}$, and mixed venous oxygen saturation greater than 70%). Standard hemodynamic management for OPCAB included mainly fluid administration to achieve normovolemia and preset hemodynamic goal in addition to vasopressors or inotropes to prevent excessive fluid administration. Intraoperative fluid management consisted of continuous infusion (4 ml/kg/h) of 0.9% NaCl as maintenance fluid, and additional 6% hydroxyethyl starch 130/0.4 (Voluven®; Fresenius Kabi, Germany) was administered for optimization of circulating blood volume. When mean arterial pressure or cardiac index decreased below target values despite optimization of circulating blood volume, agents such as phenylephrine, dopamine, or norepinephrine were given. The choice of the agent was determined by hemodynamic parameters such as heart rate, stroke volume, and systemic vascular resistance. Patients with hemoglobin less than 8 g/dl received packed erythrocytes. Blood salvaged using a cell salvage device (autoLog; Medtronic Inc., USA) was reinfused before the end of surgery.

All surgical procedures were performed by three cardiac surgeons who were highly experienced in OPCAB and who were blind to the treatment allocations. After surgery, patients were transferred to the intensive care unit (ICU). Patients were extubated when they breathed spontaneously, achieved adequate blood gases, and had stable hemodynamics. Fluid management was performed with infusion of 5% dextrose with additional 0.9% NaCl, 6% hydroxyethyl starch 130/0.4, or blood to correct hypovolemia (the presence of at least two of the following criteria: (1) a decrease in pulmonary capillary wedge pressure to 10 mmHg or less, (2) a decrease in central venous pressure of 2 mmHg or greater, and (3) a decrease in systemic mean arterial pressure of 20 mmHg or greater), hemoglobin less than 9 g/dl, or coagulation abnormalities. Although the patients did not receive additional albumin during surgery, patients with a serum albumin level of less than 3.0 g/dl were administered 100 ml of 20% albumin regardless of their volume status in the ICU by an independent ICU physician who was not aware of each patient's group assignment. Patients were transferred from the ICU to the general ward when their clinical status was stabilized and further ICU monitoring and care was not needed.

Study Outcomes and Measurements

The primary outcome was the development of AKI after OPCAB. AKI was defined by the AKI Network criteria by the change in serum creatinine within 48 h of surgery compared with the preoperative serum creatinine level. Patients who met the AKI Network criteria were classified as "AKI," whereas those who did not were classified as "no AKI." Patients with AKI were stratified according to the maximum AKI Network criteria. Stage I was defined as an increase in serum creatinine level of 0.3 mg/dl or greater or 150 to 200% or greater; stage II as an increase in serum creatinine level greater than 200 to 300%; and stage III as an increase in serum creatinine level greater than 300%, or 4.0 mg/dl or greater with an acute increase of at least 0.5 mg/dl, or the need for renal replacement therapy (RRT).[21] RRT was defined as any use of intermittent hemodialysis or continuous venovenous hemodiafiltration. Serum creatinine levels were measured 1 day before surgery; on arrival at the ICU; 6 h after surgery; 1, 2, and 3 days after surgery; at discharge; and additionally as needed according to the clinical situation. The highest concentration that was measured in the first 48 h after surgery was used for the primary endpoint evaluation. We also assessed urine output and the use of diuretics intraoperatively and up to 48 h after surgery, but we did not use the data on urine output for diagnosis of AKI due to the effects of the administered diuretics. We also evaluated AKI defined and staged using the Kidney Disease Improving Global Outcomes (KDIGO) classification (increase in serum creatinine by 0.3 mg/dl or greater within 48 h of surgery or increase in serum creatinine to 1.5 times or greater baseline within 7 days of surgery).[22]

Secondary outcomes were the incidence of severe AKI (AKI Network or KDIGO stage 2 or greater), requirement for RRT, renal outcome at the time of discharge, time to extubation after surgery, length of ICU and hospital stay after surgery, and death from any cause within 30 days after surgery. Renal outcome at the time of discharge was assessed by comparing the discharge serum creatinine level to the baseline serum creatinine. Renal recovery existed if the patient met the criteria for postoperative AKI, but then the serum creatinine returned to a level less than 50% above baseline serum creatinine, whereas no renal recovery existed if there was a serum creatinine greater than 50% above baseline serum creatinine or the need for RRT at the time of hospital discharge.[1]

Serum concentrations of albumin were measured preoperatively, 10 min after the end of the infusion of the study solution, at the end of surgery, and on postoperative day 1 using a Synchron LX20 analyzer® (Beckman Coulter, USA), based on the bromocresol green dye-binding method. Heart rate, mean arterial pressure, central venous pressure, pulmonary artery pressure, cardiac index, mixed venous oxygen saturation, right ventricular end-diastolic volume index, and regional cerebral oxygen saturation were measured 10 min after the end of the infusion of the study solution, 15 min after beginning graft anastomosis, 15 min after completion of anastomoses, and at the end of surgery. Heart rate and mean arterial pressure were also measured before anesthetic induction. The cumulative doses of propofol and remifentanil during anesthesia were calculated. The total amount of phenylephrine administered, the number of patients requiring inotropes such as dopamine or norepinephrine, and the amount of salvaged blood infused during surgery were recorded. We also recorded the amount of crystalloids, synthetic colloids, exogenous albumin, and blood products infused as well as urine output both during surgery and until

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24 h postoperatively. The clinical personnel recording these data were not aware of each patient's group assignment. The sponsor of the study had no role in the design of the protocol, trial conduct, collection or analysis of data, or writing of the report.

Statistical Analysis

Continuous variables are expressed as mean ± SD or medians with interquartile range and categorical variables as numbers and percentages. A sample size of at least 220 patients was estimated based on the results of a previous study, in which the incidences of postoperative AKI in patients with a serum albumin concentration of less than 4.0 g/dl and 4.0 g/dl or greater were 35 and 17%, respectively.[2] We hypothesized that albumin treatment would decrease this incidence by 35 to 17% and that a sample size of 103 patients per group would be required to obtain a power of 80% at a significance level of 0.05 (two-tailed) to detect this difference. To allow for a 10% dropout rate during the study period, we intended to recruit a total of 220 patients. Between-group differences were evaluated using the independent *t* test or Mann–Whitney rank sum test for continuous variables and the chi-square test or Fisher exact test for categorical variables, as appropriate. Normal distribution and equality of variances were tested. We calculated standardized differences for continuous $\left(\frac{\left(\overline{x_a}-\overline{x_b}\right)}{\sqrt{\frac{s_a^2+s_b^2}{2}}}\right.$, where $\overline{x_a}$ and $\overline{x_b}$ denote the sample mean, and s_a^2 and s_b^2 denote the sample variances of baseline variable in each group, respectively), and categorical $\left(\frac{\left(\widehat{P}_a-\widehat{P}_b\right)}{\sqrt{\frac{\left[\widehat{P}_a\left(1-\widehat{P}_a\right)+\widehat{P}_b\left(1-\widehat{P}_b\right)\right]}{2}}}\right.$, where $\widehat{P}_a$ and $\widehat{P}_b$ denote the proportion of a binary variable in each group) variables to assess the comparability of the two groups on baseline characteristics.

Changes in hemodynamic and laboratory data were analyzed by two-way ANOVA with repeated measurements and the Holm–Sidak method for multiple comparisons. Additionally, we conducted several *post hoc* sensitivity analyses. The effect of albumin treatment on AKI after surgery was tested using multivariable logistic regression analysis by accounting for age, diabetes mellitus, preoperative hematocrit, and the amount of fluid. Because of the number of outcomes, not all potential predictors could be tested together in the logistic regression model; the variables were selected based on their importance in the univariate logistic regression analysis and the previous study.[2] We tested for the presence of any interaction between the effect of albumin treatment and age or history of diabetes. We also conducted additional analyses, including 15 subjects who discontinued and were excluded from the study due to conversion to CPB. Although there was no statistical significance, more patients received diuretic therapy preoperatively in the control group, which could be a confounding factor because diuretics can cause intravascular volume depletion. Therefore, we also performed additional *post hoc* adjustment for diuretic use using logistic regression. Additionally, we also examined the effect of albumin treatment on the postoperative AKI in subgroup without preoperative use of diuretics and angiotensin-converting enzyme inhibitor or angiotensin receptor blocker. All reported *P* values are two sided, and values of *P* less than 0.05 were considered statistically significant. All data manipulations and statistical analyses were performed using SPSS Version 21.0 (IBM, USA) and SAS Version 9.1 (SAS Institute Inc., USA) software.

Results

Of 538 patients screened between September 2011 and August 2014, 220 were randomized to albumin (n = 110) or control (n = 110) groups. Two of these patients were excluded after enrollment because the surgery was cancelled. Of the remaining 218 patients, 15 who received the intervention discontinued the study due to conversion to CPB. Thus, 203 patients were included in the final analysis (fig. 1).

The demographic and preoperative characteristics of patients did not differ between groups (table 1). The intraoperative characteristics, including durations of operation and anastomosis, total amounts of anesthetics and infused fluid, and lowest hematocrit during surgery, were similar between groups, with the exception of a higher urine output during the operation in the albumin group (*P* = 0.006; table 2). Intraoperative hemodynamic variables were comparable between the groups (table 3), as were the incidence of arrhythmias requiring treatment, the requirement for vasopressors, and the amount of phenylephrine used. Postoperative data were similar between groups. The median infused volume of study solution (0.9% NaCl or 20% albumin) after randomization was 100 ml (100 to 100) in the control group and 100 ml (100 to 150) in the albumin group, respectively (*P* = 0.677).

Figure 2 shows the changes in serum albumin concentration during the operation in the albumin (n = 102) and control (n = 101) groups. The two groups had similar preoperative serum albumin concentrations (*P* = 0.560). However, the median serum albumin concentration was higher in the albumin group than in the control group at 10 min after the intervention (4.0 [3.9 to 4.2] *vs.* 3.4 [3.1 to 3.6] g/dl; *P* < 0.001) and at the end of surgery (2.7 [2.4 to 2.9] *vs.* 2.2 [2.0 to 2.4] g/dl; *P* < 0.001). Serum albumin concentrations on postoperative day 1 were similar between the albumin and control groups (3.0 [2.7 to 3.3] *vs.* 2.9 [2.8 to 3.2] g/dl, respectively; *P* = 0.156). At 10 min after the intervention in the albumin group, 64 patients (62.7%) had a serum albumin concentration of 4.0 g/dl or greater, and 38 patients (37.3%) had a serum albumin concentration of 3.5 to 3.9 g/dl. At 10 min after the intervention in the control group,

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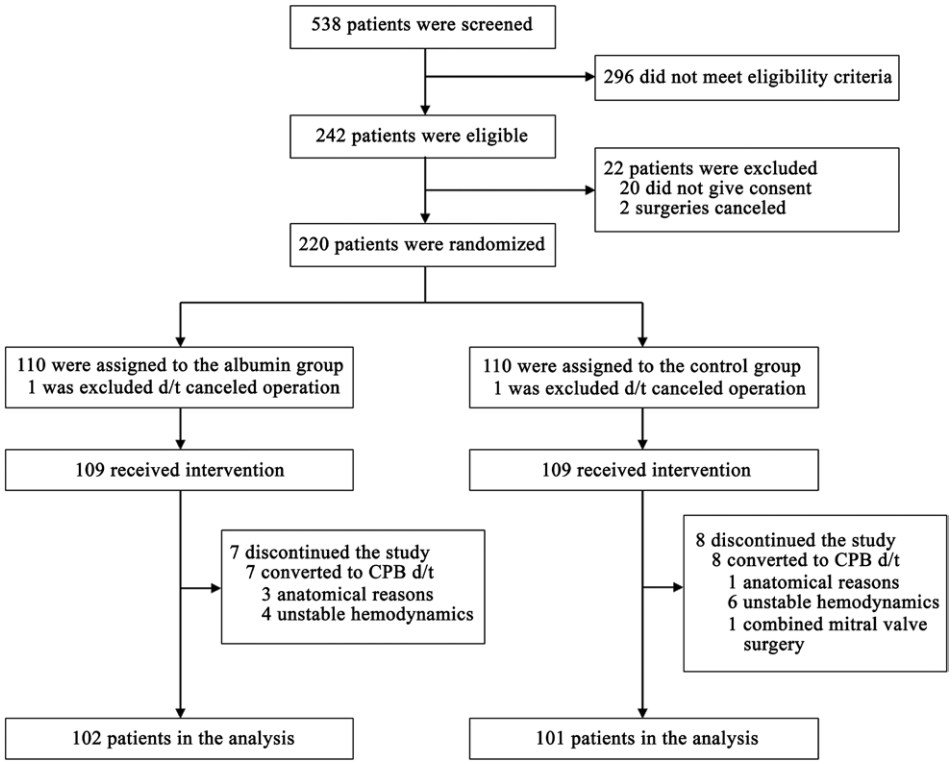

Fig. 1. Trial flow chart. CPB = cardiopulmonary bypass; d/t = due to.

44 patients (43.6%) had a serum albumin of 3.5 to 3.9 g/dl, 45 patients (44.6%) had a serum albumin of 3.0 to 3.4 g/dl, and 12 patients (11.9%) had a serum albumin of less than 3.0 g/dl.

Postoperative outcome data are shown in table 4. The incidence of postoperative AKI was lower in the albumin group than in the control group (AKI Network criteria: 14 [13.7%] *vs.* 26 [25.7%], $P = 0.048$; KDIGO criteria: 18 [17.6%] *vs.* 32 [31.7%], $P = 0.031$). Multivariable logistic analysis also showed a protective effect of albumin treatment (AKI Network criteria: odds ratio, 0.43; 95% CI, 0.21 to 0.89, $P = 0.024$; KDIGO criteria: odds ratio, 0.42; 95% CI, 0.21 to 0.83, $P = 0.012$). After additional adjustment for preoperative use of diuretics using logistic regression, similar results were found (odds ratio, 0.41; 95% CI, 0.20 to 0.86, $P = 0.019$). Additionally, in the subgroup without preoperative use of diuretics and angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, the incidence of postoperative AKI was lower in the albumin group than in the control group (9 [13.04%] *vs.* 18 [31.58%], $P = 0.021$). The protective renal effect of albumin treatment did not depend on age (interaction $P = 0.471$) or history of diabetes (interaction $P = 0.250$). The effect of the intervention on postoperative AKI stratified by preoperative serum albumin levels is shown in Supplemental Digital Content 1 (see table 1, http://links.lww.com/ALN/B257, which demonstrates the incidence of postoperative AKI according to preoperative serum albumin levels). When patients (n = 15) who discontinued the study due to conversion to CPB were included, AKI remained nonsignificantly lower in the albumin group (AKI Network criteria: 17 [15.6%] *vs.* 27 [24.8%], $P = 0.129$; KDIGO criteria: 21 [19.3%] *vs.* 34 [31.2%], $P = 0.061$). However, multivariable logistic analysis showed a marginally protective effect of albumin treatment (AKI Network criteria: odds ratio, 0.49; 95% CI, 0.25 to 0.99, $P = 0.049$; KDIGO criteria: odds ratio, 0.45; 95% CI, 0.23 to 0.88, $P = 0.019$).

In the albumin group, the incidence of AKI did not differ between patients with a postintervention serum albumin of 3.5 to 3.9 g/dl and patients with a postintervention serum albumin of 4.0 g/dl or greater (AKI Network criteria: 6 [15.8%] *vs.* 8 [12.5%], $P = 0.866$; KDIGO criteria: 7 [18.4%] *vs.* 11 [17.2%], $P = 0.912$). In the saline group, postoperative AKI was experienced by 12 (27.3%) AKIN-criteria patients and 13 (29.5%) KDIGO-criteria patients with a postintervention serum albumin of 3.5 to 3.9 g/dl, in 10 (22.2%) and 14 (31.1%) KDIGO-criteria patients with a postintervention serum albumin of 3.0 to 3.4 g/dl, and 4 (33.3%) and 5 (41.7%) KDIGO-criteria patients with a postintervention serum albumin of less than 3.0 g/dl. The incidences of severe AKI, need for RRT, and no renal recovery at the time of discharge were similar between the two groups. There were no significant between-group differences in extubation time, ICU stay, hospital stay, and 30-day mortality. No patients experienced adverse events related to albumin infusion during surgery, such as anaphylactoid reactions or clinical evidence of pulmonary edema (*i.e.*, pink frothy pulmonary secretions, progressive oxygen saturation decrease, and rales or crackles on chest auscultation).

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Table 1. Demographic Characteristics of the Study Patients

Characteristics	Control (n = 101)	Albumin (n = 102)	STD (%)	*P* Value
Age (yr)	65.8 ± 8.3	66.3 ± 8.9	5.6	0.580
Female sex	21 (20.8)	19 (18.6)	5.4	0.833
Body mass index	24.4 ± 3.0	24.6 ± 3.1	9.0	0.416
ASA class	3 (2–3)	3 (2–3)	4.8	0.462
NYHA class	1 (1–2)	1 (1–2)	8.4	0.519
Logistic EuroSCORE	2.9 ± 2.3	3.5 ± 2.9	22.5	0.111
Hematocrit (%)	38.1 ± 4.4	38.2 ± 4.6	0.0	0.871
Creatinine (mg/dl)	0.9 ± 0.2	0.9 ± 0.2	8.7	0.465
Albumin (g/dl)	3.6 ± 0.3	3.6 ± 0.3	10.5	0.560
3.5–3.9	76 (75.2)	75 (73.5)	3.9	0.842
3.0–3.4	21 (20.8)	24 (23.5)	6.6	
< 3.0	4 (4.0)	3 (2.9)	5.6	
Ejection fraction (%)	58.8 ± 6.9	59.9 ± 6.3	16.6	0.393
Diabetes mellitus	42 (41.6)	45 (44.1)	10.5	0.824
Hypertension	68 (67.3)	62 (60.8)	13.7	0.409
Cerebrovascular disease	15 (14.9)	17 (16.7)	5.0	0.871
Peripheral vascular disease	10 (9.9)	10 (9.8)	3.7	0.832
Previous MI	10 (9.9)	19 (18.6)	22.6	0.115
CAG ≤ 7 days	62 (61.4)	61 (59.8)	3.2	0.931
Medication				
ACEI or ARB	37 (36.6)	29 (28.4)	17.6	0.272
β-Blocker	71 (70.3)	69 (67.6)	5.7	0.798
Calcium channel blocker	76 (75.2)	73 (71.6)	12.6	0.664
Diuretics	13 (12.9)	6 (5.9)	24.1	0.142
Aspirin	81 (80.2)	75 (73.5)	15.9	0.337
Clopidogrel	62 (61.4)	61 (59.8)	3.2	0.931
Statins	87 (86.1)	89 (87.3)	11.5	0.978

Data are expressed as number of patients (%), mean ± SD, or median (first–third quartiles).

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; ASA = American Society of Anesthesiologists; CAG = coronary angiography; EuroSCORE = European System for Cardiac Operative Risk Evaluation; MI = myocardial infarction; NYHA = New York Heart Association; STD = standardized difference.

Discussion

Our current prospective, randomized study assessed the effect of the administration of 20% albumin immediately before OPCAB on postoperative AKI in patients with a preoperative serum albumin level of less than 4.0 g/dl. We found that preemptive albumin treatment increased urine output during surgery and reduced the risk of AKI by 47% although no changes were seen in either the need for RRT or mortality.

Several previous studies have suggested that a preoperatively reduced serum albumin level may contribute to an increased risk of postoperative AKI.[2,11,23] Thus, correcting hypoalbuminemia through nutritional support or exogenous albumin supplementation may be a reasonable preventive strategy. However, the potential effect of exogenous albumin is still controversial.[16,24–26] Dubois *et al.*[24] have suggested that the administration of 20% albumin to correct hypoalbuminemia (3.0 g/dl or less) might have beneficial effects on organ function and fluid balance in critically ill patients. However, other studies reported that 20% albumin administration to correct hypoalbuminemia after surgery did not have additional benefits on clinical outcomes.[25,26] A recent large, randomized trial showed that the addition of 20% albumin to crystalloids to correct hypoalbuminemia during ICU stay in patients with severe sepsis conferred a significant hemodynamic advantage, but did not provide a survival benefit.[16]

Contrary to previous studies, our results show that the preemptive administration of albumin has beneficial effects on renal function. The differences might be partly explained by the timing of albumin administration. In this study, albumin was administered before surgery, that is, the main insult. Indeed, surgery and the systemic inflammatory response significantly increase capillary permeability and cause massive fluid shifts that can significantly alter serum albumin levels.[8] Therefore, the administration of albumin after a major insult (such as during or after surgery) will have a lesser effect on serum values for a shorter period, and the changes will tend not to be sustained.[17] Our study also showed that, despite more exogenous albumin given within the first 24 h after OPCAB in the control group, the incidence of AKI in the control group was still higher than that in the albumin group. To the best of our knowledge, our study is the first to investigate the impact of preemptive albumin administration on

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Table 2. Perioperative Data

	Control (n = 101)	Albumin (n = 102)	*P* Value
Pretreatment hemodynamics			
Heart rate (beats/min)	67 (60–76)	66 (60–73)	0.575
Mean arterial pressure (mmHg)	95.2 ± 14.2	95.5 ± 15.5	0.879
Anesthetic agent			
Propofol (mg)	930 (791–1,164)	986 (814–1,197)	0.172
Remifentanil (μg)	7,000 (5,875–8,948)	7,461 (6,001–9,758)	0.493
Anesthetic time (min)	285 (270–315)	285 (259–340)	0.906
Operation time (min)	220 (200–245)	225 (191–261)	0.627
Anastomosis time (min)	70 (55–86)	70 (53–86)	0.975
Lowest hematocrit during surgery	25 (22–27)	25 (22–28)	0.795
Intraoperative fluid balance			
0.9% NaCl (ml)*	2,000 (1,500–2,500)	1,800 (1,300–2,425)	0.268
6% hydroxyethyl starch (ml)	1,000 (1,000–1,000)	1,000 (600–1,125)	0.398
Crystalloid-to-colloid volume ratio	1.8 (1.3–2.5)	1.8 (1.3–2.8)	0.998
p-RBC (unit)	0 (0–2)	1 (0–2)	0.657
Cell saver blood (ml)	0 (0–230)	90 (0–250)	0.223
Urine output (ml)	370 (230–670)	550 (315–980)	0.006
Intraoperative dopamine use	11 (10.9)	17 (16.7)	0.322
Intraoperative norepinephrine use	7 (6.9)	8 (7.8)	0.984
Intraoperative arrhythmia	10 (9.9)	19 (18.6)	0.115
Intraoperative phenylephrine (μg)	600 (125–1,250)	425 (100–1,000)	0.285
Postoperative data in intensive care unit			
Maximal SOFAc score†	2 (0–3)	3 (0–3)	0.838
Crystalloid (ml)†‡	1,050 (900–1,500)	1,240 (973–1,850)	0.080
6% hydroxyethyl starch (ml)†	500 (0–1,000)	725 (450–1,000)	0.104
Urine output (ml)†	2,835 (2,279–3,665)	2,875 (2,304–3,581)	0.896
Blood loss (ml)†	600 (415–745)	610 (430–785)	0.429
Use of diuretics†	5 (4.95%)	2 (1.96%)	0.434
20% Albumin supplement (ml)†	170 (85–180)	85 (34–180)	< 0.001
p-RBC (unit)	1 (0–1)	0 (0–1)	0.946
Postoperative weight gain (%)	2.6 ± 2.1	2.3 ± 2.4	0.289
Reoperation for bleeding	3 (2.94%)	1 (0.99%)	0.621

Data are expressed as number of patients (%), mean ± SD, or median (first–third quartiles).
*Except study fluid. †For 24 h after surgery. ‡0.5% dextrose and 0.9% NaCl.
p-RBC = packed erythrocyte; SOFAc = cardiovascular sequential organ failure assessment.

renal function in patients undergoing cardiac surgery and to show the importance of the timing of albumin replacement.

Although we did not investigate the underlying mechanism of the renal effect of albumin administration in current analysis, several earlier studies have suggested mechanisms by which serum albumin could protect kidney function. Albumin can increase effective circulating volume by promoting effective reabsorption of fluid accumulation from the interstitial space, increasing renal flow and urine output.[8] Additionally, albumin has antioxidant properties, such as scavenging and limiting the production of reactive oxygen species and delivering protective lysophosphatidic acid.[8,27] The specific ligand-binding capacity of albumin could mitigate the effect of nephrotoxic medications,[28] and albumin could maintain renal perfusion and glomerular filtration by renal vasodilation through the reaction of albumin with oxides of nitrogen to form S-nitroso-albumin.[11,29] Albumin administration can also improve microcirculatory blood flow and reduce the inflammatory response.[24,30] These functions of albumin may be crucial to the pathophysiological mechanisms responsible for AKI after OPCAB, including oxidative stress, the inflammatory response, direct nephrotoxicity, and reduced renal perfusion pressure due to hemodynamic instability.[4–6] Thus, the preemptive administration of exogenous albumin could allow these beneficial effects on renal function to reduce the risk of AKI after OPCAB.

On the other hand, beneficial renal effects of exogenous albumin may be due to augmentation of intravascular volume rather than correction of hypoalbuminemia. Indeed, previous studies have reported that administration of 20% albumin results in about a two-fold volume expansion by drawing fluid from the interstitial space into the circulation by osmotic forces.[17,31] Furthermore, a previous study has suggested that enhanced urine output after infusion of albumin might be associated with increased fluid intake and not with the serum levels of albumin.[32] In our analyses, similar hemodynamics during surgery and perioperative infused volume were seen in the two groups. However, hemodynamic

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Table 3. Intraoperative Hemodynamic Data

	T1	T2	T3	T4	*P* Value for Group	*P* Value for Interaction
Heart rate (beats/min)						
Control	60 ± 10	66 ± 12	70 ± 12	73 ± 13	0.786	0.852
Albumin	59 ± 10	65 ± 11	69 ± 11	74 ± 13		
MAP (mmHg)						
Control	71 ± 10	72 ± 8	75 ± 10	77 ± 12	0.546	0.310
Albumin	73 ± 13	74 ± 10	74 ± 9	78 ± 11		
CVP (mmHg)						
Control	6 ± 3	10 ± 3	7 ± 3	7 ± 3	0.673	0.871
Albumin	6 ± 3	10 ± 4	7 ± 3	7 ± 3		
mPAP (mmHg)						
Control	14 ± 3	18 ± 5	17 ± 5	17 ± 4	0.711	0.916
Albumin	14 ± 3	19 ± 5	17 ± 4	17 ± 4		
CI ($l \cdot min \cdot m^{-2}$)						
Control	2.4 ± 0.6	2.6 ± 0.6	2.8 ± 0.8	2.8 ± 0.7	0.532	0.110
Albumin	2.5 ± 0.7	2.5 ± 0.5	2.6 ± 0.6	2.6 ± 0.5		
Svo_2 (%)						
Control	73 ± 8	73 ± 9	75 ± 8	74 ± 8	0.388	0.834
Albumin	75 ± 8	74 ± 9	76 ± 7	75 ± 8		
RVEDVI (ml/m^2)						
Control	138 ± 46	136 ± 38	140 ± 34	136 ± 36	0.926	0.693
Albumin	143 ± 39	137 ± 26	139 ± 31	133 ± 27		
Mean $rSco_2$ (%)						
Control	62 ± 8	61 ± 8	60 ± 8	60 ± 7	0.112	0.903
Albumin	61 ± 8	60 ± 9	58 ± 8	58 ± 7		

Data are expressed as mean ± SD.

CI = cardiac index; CVP = central venous pressure; MAP = mean arterial pressure; mPAP = mean pulmonary artery pressure; $rSco_2$ = regional cerebral oxygen saturation; RVEDVI = right ventricular end-diastolic volume index; Svo_2 = mixed venous oxygen saturation; T1 = 10 min after infusion of saline or 20% albumin solution; T2 = 15 min after beginning of graft anastomosis; T3 = 15 min after completion of anastomoses; T4 = at the end of surgery.

variables such as filling pressures and static volume parameters are weak surrogates for evaluating the volume status.[33] Thus, we cannot completely exclude the possibility that differences in the patient volume status could have influenced our results, and that volume expansion with a control fluid might have produced the same results. Further studies are warranted to evaluate whether the beneficial renal effect of 20% albumin is due to the correction of hypoalbuminemia or the optimization of intravascular volume.

In the current study, the threshold value (less than 4.0 g/dl) of preoperative serum albumin below which administration of exogenous albumin is beneficial was chosen according to the results of our previous report.[2] However, although the level of serum albumin in 37% of patients did not exceed 4.0 g/dl after albumin administration, the incidence of AKI did not differ between serum albumin levels of less than 4.0 g/dl and 4.0 g/dl or greater. Thus, the threshold value that can be considered to be tolerable is likely to be lower than that found in the current study. Further studies aimed at identifying a critical threshold value below which administration of exogenous albumin is beneficial or essential are needed.

We found a lack of benefit from exogenous albumin treatment when patients who required conversion to CPB were included in the analysis. The cause of AKI after coronary artery bypass surgery is complex and multifactorial. Use of CPB itself contributes to the pathogenesis of AKI *via* hemodilution, generation of microemboli, formation of oxygen free radicals, and induction of a massive systemic proinflammatory response, imposing additional burdens on renal function.[6] Indeed, patients undergoing coronary artery bypass surgery with CPB are more vulnerable to AKI than those undergoing OPCAB.[4] Thus, the isolated modification of a single risk factor to mitigate the risk of AKI may not be enough to inhibit the multiple molecular pathways leading to AKI in these high-risk patients. Additionally, this observation may be due to an insufficient sample size to detect group differences in high-risk patients. Further studies are needed to determine the effects of exogenous albumin treatment in patients who are undergoing cardiac surgery with CPB.

We did not find any significant differences in the incidence of severe AKI and no renal recovery between the two groups. This may be due to our relatively small sample size that resulted in a reduced statistical power. Additionally, it is possible that the renal protective effects of preemptive albumin treatment may be limited to mild renal injury after surgery. In other words, the dose and treatment regimen used in our study may not have been sufficient to have any protective effects against severe AKI or to maintain the beneficial effects on renal recovery at discharge. Thus, the protective effects of

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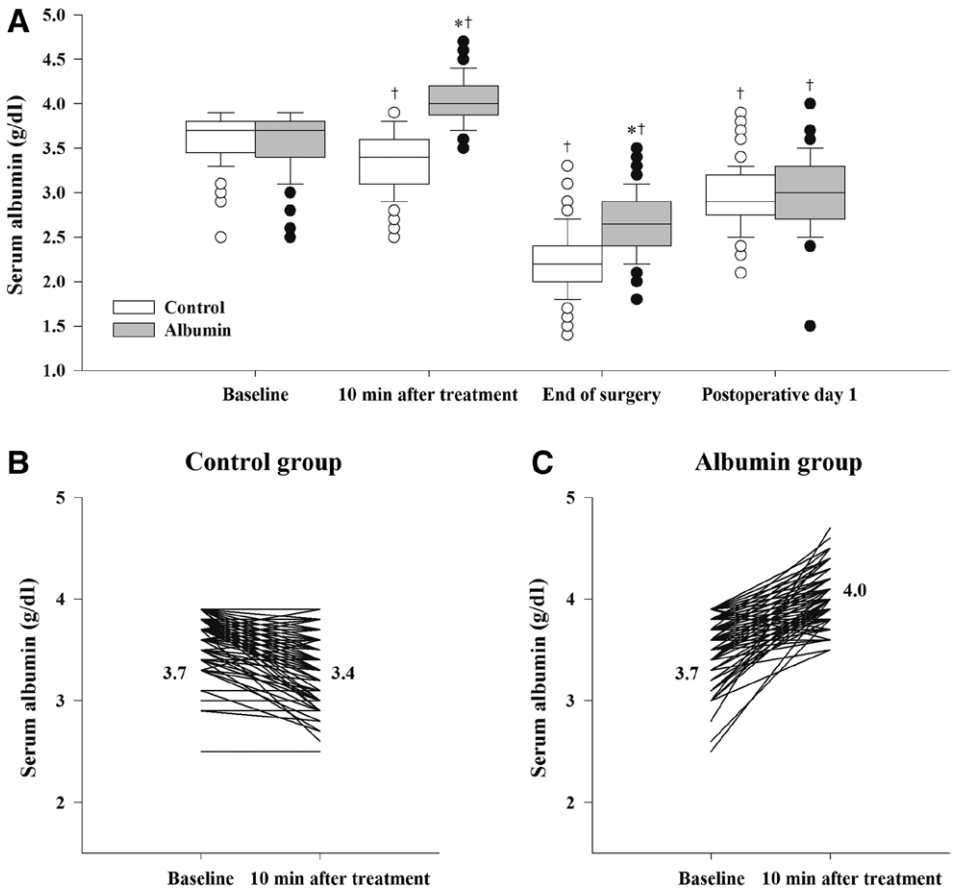

Fig. 2. (*A*) Serum albumin concentrations and (*B* and *C*) individual serum albumin concentration values before and after the intervention in both groups. Data are expressed as median (interquartile range). *Horizontal lines*, *boxes*, and *error bars* represent the median, interquartile range, and outliers, respectively (*A*). The respective median serum albumin concentrations are given at the side of the line graphs (*B* and *C*). *$P < 0.001$ *versus* control group. †$P < 0.001$ *versus* baseline.

Table 4. Clinical Outcomes

	Albumin	Control	RR (95% CI)	*P* Value
N	102	101	—	
Primary endpoint				
AKI by AKIN	14 (13.7%)	26 (25.7%)	0.533 (0.296–0.961)	0.048
AKI by KDIGO	18 (17.6%)	32 (31.7%)	0.557 (0.335–0.925)	0.031
Secondary endpoints				
≥ AKIN stage 2	3 (2.94%)	2 (1.98%)	1.485 (0.254–8.702)	0.991
≥ KDIGO stage 2	4 (3.92%)	6 (5.94%)	0.660 (0.192–2.269)	0.734
RRT	2 (1.96%)	0 (0%)	—	0.482
No recovery	6 (5.88%)	8 (7.92%)	0.750 (0.309–1.821)	0.767
Extubation time (h)	8 (6–14)	8 (6–14)	—	0.716
ICU stay (h)	47 (42–49)	47 (43–50)	—	0.559
Hospital stay (days)	8 (7–9)	8 (7–10)	—	0.715
30-day mortality	1 (0.98%)	0 (0%)	—	0.996

Data are expressed as number of patients (%) or median (first–third quartiles).

AKI = acute kidney injury; AKIN = Acute Kidney Injury Network; ICU = intensive care unit; KDIGO = Kidney Disease Improving Global Outcomes; RR = relative risk; RRT = renal replacement therapy.

albumin may be associated with timing, the dosage level, and the severity of AKI. Larger scale studies are therefore again necessary to establish the optimal dosing and treatment regimen and to confirm the clinical implications of our findings.

Because we wanted to determine the efficacy of preemptive administration of 20% albumin before the main insult (*i.e.*, surgery) on reducing the risk of AKI within the time frames routinely used in our hospital for elective OPCAB,

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we administered 20% albumin relatively rapidly immediately before surgery. Rapid infusion (20 to 50 ml/min) of concentrated solutions of albumin can induce manifest congestive heart failure, particularly in patients with compromised cardiac function.[18] Our study was conducted in patients with preserved cardiac function, so this regimen should be used with caution in patients with cardiac dysfunction.

This study has several limitations. First, the incidence of AKI was lower than that expected from our previous study, from which the sample size of current study was calculated, thereby increasing the likelihood that present analysis was underpowered. Furthermore, the observed difference in current study was only marginally significant ($P = 0.048$). Thus, further large-scale studies are required to confirm our results. Second, because our study was conducted on patients with preoperatively normal renal function, the results should not be extrapolated to patients with renal dysfunction. However, a previous study in liver cirrhotic patients with renal dysfunction has suggested that albumin infusion could improve renal function by impacting renal blood flow autoregulation.[34] Third, we used 0.9% NaCl as a control fluid. Given the adverse renal effects of chloride reported in recent studies,[35,36] although we used small volumes of 100 to 300 ml, a supraphysiologic concentration of chloride in 0.9% NaCl could have influenced our results. Thus, we cannot exclude the possibility that our current findings may have been due to the negative renal effects of chloride rather than the beneficial effects of albumin. Accordingly, our results should be interpreted with caution, and further studies are needed to assess these issues.

Conclusions

The preemptive administration of 20% exogenous albumin immediately before surgery is associated with a reduction in the risk of AKI after OPCAB in patients with a preoperative serum albumin level of less than 4.0 g/dl. This finding needs to be confirmed by further large clinical investigations in other institutional settings.

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Competing Interests

The authors declare no competing interests.

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Full protocol available from Eun-Ho Lee (leho@naver.com) or In-Cheol Choi (icchoi@amc.seoul.kr). Raw data available from Eun-Ho Lee (leho@naver.com) or In-Cheol Choi (icchoi@amc.seoul.kr).

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