Effect of 5% albumin on endothelial glycocalyx degradation during off-pump coronary artery bypass

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ABSTRACT

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Purpose: The integrity of the endothelial glycocalyx (EG), a critical player in vascular ho meostasis, reportedly influences the outcomes of critically ill patients. We investigated the effect of 5% albumin, which preserved EG integrity in preclinical studies, vs balanced crys talloid solution on EG degradation in patients undergoing off- pump coronary surgery.

Methods: Patients were randomized to receive either 5% albumin (N = 51) or balanced cr ystalloid solution (Plasma-Lyte [Baxter Incorporated, Seoul, Republic of Korea]; N = 53) f or intravenous volume replacement during surgery (double-blinded). The primary outcome was plasma syndecan-1 concentration, a marker of EG degradation, measured after anesthet ic induction (baseline), completion of grafting, and sternal closure. Secondary outcomes we re atrial natriuretic peptide (ANP), tumour necrosis factor (TNF)-a, soluble thrombomodulin, and perioperativefluid balance.

Results: The mean (standard deviation) fluid requirements were 833 (270) mL and 1,323 (492) mL in the albumin and Plasma-Lyte group, respectively (mean difference, -489 mL; 95% confidence interval [CI], -643 to-335; P <0.001). Plasma syndecan-1concentration incre ased after completion of grafting (median difference, 116 $ng \cdot mL^{-1}$; 95% CI,67 to 184; P < 0.001) and sternal closure (median difference, 57 $ng \cdot mL^{-1}$; 95% CI, 36 to 80; P <0.001) compared with those at baseline, without any intergroupdifferences. Atrial natriuretic peptid e, TNF-a, and soluble thrombomodulin concentrations were similar between the two groups. The amount of chest tube drainage was greater in the albumin group than that in the Pla sma-Lyte group (median difference, 190 mL; 95% CI, 18 to 276; P = 0.03).

Conclusion: Off-pump coronary surgery was associated with significant EG degradation. Ye t, intraoperative fluid therapy with 5% albumin could not ameliorate EG degradation when compared with balanced crystalloid solution.

Key words :albumin,cardiac surgery,fluid resuscitation,glycocalyx,syndecan-1,vascular homeo stasis

1. Introduction

Endothelial glycocalyx (EG), a gel-like structure consisting of proteoglycans and glycoproteins, forms the matrix covering the luminal surface of the vascular endothelium.[1] Endothelial glycocalyx is involved in avariety of physiologic functions, including vascular permeability, mechanotransduction of shear stress by blood flow, and interaction between the endothelium and its surroundings.[2]

Endothelial glycocalyx is liable to damage due to the accompanying oxidative stress and systemic inflammatory response.[3] Clinically, damage to the EG is observed in sepsis, severe trauma, and major surgeries, including cardiac surgeries with or without cardiopulmonary bypass (CPB).[4-6] The degradation of EG may result in increased vascular permeability, interstitial edema, amplification of the inflammatory response, and a prothrombotic environment, potentially leading to adverse outcomes.[7] Indeed, an increase in the serum levels of EG constituents, such as syndecan-1, has been documented in the aforementioned clinical settings of critical illness and surgery, and severity of degradation was associated with worse outcomes.[8-12]

Albumin, which normally accounts for 50–70% of the plasma protein, is intercalated within the EG layer, contributing to its integrity.[1] Albumin also has antioxidant and immunomodulatory effects and carries sphingosine-1-phosphate to the endothelium, which suppresses degradation of the EG layer by metalloproteinase.[13-15] Several preclinical studies have shown that supplementation with albumin could protect the integrity of EG and improve endothelial function,[16-20]suggesting that the choice of intraoperative resuscitation fluid can affect the degree of EG degradation. Nevertheless, the efficacy of albumin in preventing EG degradation when used as an intraoperative fluid has not been evaluated in clinical trials. Thus, we investigated the effect of intraoperative volume replacement with 5% albumin vs balanced crystalloid solution on EG degradation in patients undergoing off-pump coronary artery bypass graft (OPCAB).

2. MATERIALS AND METHODS

1.Participants

This prospective, randomized, double-blinded single-centre trial was conducted at SeveranceCardiovascular Hospital, Seoul, Republic of Korea, from November 2018 to October2020. It was approved on 28 August 2018 by the institutional review board of the Yonsei Unive

rsity Health System, Seoul, Republic of Korea, and registered at ClinicalTrials.gov (NCT03 699462, registered 9 October2018). Written informed consent was obtained from all partici pants. This research was conducted in accordance with the declaration of Helsinki.

Adult patients (aged 20 yr or greater) undergoing elective OPCAB were eligible for enr olment. The exclusion criteria were minimally invasive coronary artery bypass surgery, chro nic kidney disease stage 4 (estimated glomerular filtration rate < 30 mL · min^{-1} · 1.73 m^{-2}), dialysis, preoperative acute kidney injury, infectious diseases, malignant tumours, and know n allergy to albumin preparations.

2.Study design, randomization and masking

Patients were randomly allocated to receive either 5% albumin (N = 53) or balanced cr ystalloid solution (Plasma-Lyte [Baxter Incorporated, Seoul, Republic of Korea];N = 53) for intravascular volume replacement during surgery. The 5% albumin solution(GC Biopharma Corp. ,Yongin, South Korea) was manufactured by dissolving human plasma, cold ethanol fractionation, stabilization with sodium caprylate and N-acetyltryptophan, ultrafiltration/diafilt ration, and pasteurization at 60 °C for 10–11hr.The final product contained 5g albumin, 33 0mg sodium, 0.06648 g sodium caprylate, and 0.0985 g N-acetyltryptophan per 100 mL. R andom allocation was performed with a computer-generated random number sequence in bl ocks of four withoutstratification. The allocation was concealed from all study participants, investigators, and medical care-providers, except one investigator who was not involved in the perioperative patient management; this investigator was dedicated to randomization, pr eparation, and administration of the study fluids. The study fluids were covered with a bla ck plastic bag, placed behind the anesthesia machine, and administered upon request from the attending anesthesiologists.

Perioperative care, including anesthetic management, was conducted according to the inst itutional standard protocol. Briefly, anesthesia was induced with 0.05–0.07mg·kg^{-1} of intrave nous midazolam and 1.5–2 lg·kg^{-1} of sufentanil and maintained with inhaled sevoflurane an d continuous infusion of sufentanil. Continuous arterial pressure monitoring, a pulmonary a rtery catheter (PAC, Swan-Ganz CCombo CCO/SvO_2, Edwards Lifesciences LLC, Irvine, C A, USA), and transesophageal echocardiography (TEE) were used in all patients.

In both groups, Plasma-Lyte was administered as the maintenance fluid at a rateof 2 mL ·kg^{-1}·hr^{-1}. For intravascular volume replacement, the investigator behind theanesthesia machi ne administered the study fluids according to the requested doseand infusion speed, which were decided by the attending anesthesiologist using information from the hemodynamic m onitors and TEE. The attending anesthesiologist was not aware of the choice of fluid. In c ase of severe acute hypovolemia and hemodynamic instability, unblinded Plasma-Lyte was

allowed to be administered as a rescue fluid at the discretion of the attending anesthesiologists. Beside Plasma-Lyte and 5% albumin, no other fluids were administered intraoperatively.

Hematocrit was maintained above 24% by transfusion of packed red blood cells or salvaged blood. Norepinephrine and vasopressin were used as the first-line andadditional vasopressor, respectively. Severe ventricular dysfunction was managed with intravenous milrinone. During the grafting of coronary arteries, activated clottingtime was maintained above 250 sec with intermittent boluses of intravenous heparin. Heparinization was reversed with protamine sulphate after the completion of coronary artery grafting.

3.Outcome measures

The primary endpoint was the plasma syndecan-1 concentration, measured uponinduction of anesthesia (baseline), after the return of the heart to the normal position, and after sternal closure. Secondary endpoints were atrial natriuretic peptide (ANP), tumour necrosis factor(TNF)-a, and soluble thrombomodulin (sTM)concentrations, which were measured at the same time points as that of syndecan-1.Fluid, transfusion, vasopressor and inotrope requirements; cardiac index; serum creatinine; hematologic variables including hematocrit, white blood cell, and platelet count; cardiactroponin-T and creatine kinase-MB; andPaO_2/FiO_2ratio were assessed until 48 hr postoperatively. Postoperative outcomes included acute kidney injury according to the definition of the Kidney Disease: Improving Global Outcomes guidelines,[21] renal replacement therapy, mechanical ventilation for more than 24 hr, hemostatic reoperation, sternal wound infection, newly developed atrial fibrillation, stroke, postoperative mechanical circulatory support, mortality during hospitalization or within 30 postoperative days, and duration of intensive care unit (ICU) stay and hospitalization.

An enzyme-linked immunosorbent assay was used to measure the plasma concentration of plasma syndecan-1 (Abcam PLC, Cambridge, MA, USA, Cat. No. ab46506), ANP (Cloud-Clone Corp., Katy, TX, USA, CEA225Hu), TNF-a (R&D Systems Inc., Minneapolis, MN, USA, HSTA00E), and sTM (DiacloneSAS, Besanc¸on, France,850.720.096).

4.Statistics analysis

In a previous study, the mean (standard deviation [SD]) syndecan-1 concentration measured at 30 min after the completion of coronary grafting in patients undergoing OPCAB was 188.6 (66.4) ngÁmL-1. We assumed that administration of 5% albumin would decrease syndecan-1 concentration by 20%. Fifty patients per group were required to detect the assumeddifference at an a of 0.05 and 80% power. After considering dropout, we planned to enro

l53 patients per group.

The analysis plan was approved before the analyses began. Continuous variables are expressed as means (SD) or medians [interquartile range (IQR)], and were analyzed using the independent t test or Mann–Whitney *U* test according to the normality of distribution, assessed using the Shapiro–Wilk test. Serially measured variables were analyzed with repeated-measures analysis of variance or Friedman's test, according to the normality of distribution. Variables with nonnormal distribution between time-points were compared by the paired samples Wilcoxon signed rank test. Between-group comparisons of variables with non-normaldistribution were performed using the Mann–Whitney U test. The 95% confidence intervals (CIs) for difference in medians were constructed by Hodges–Lehmann estimator. Bonferroni's method was used to adjust the P values of post hoc analysis. Categorical variables were analyzed using the Chi square test or Fisher's exact test. All statistical tests were two-tailed, and P values less than 0.05 were considered significant. Statistical analyses were performed with NCSS 12 (NCSS, LLC, Kaysville, UT, USA).

3. RESULTS

Two patients in the albumin group were excluded because of conversion to CPB(Fig.1).Patient characteristics are shown in Table1.The mean (SD) a mount of 5% albumin administered to the patients in the albumin group was 833 (270)mL,whereas mean(SD) amount of Plasma-Lyte for intravenous volume replacement in the Plasma-Lyte group was 1,323 (492) mL (mean difference,-489;95% CI,-643 to -335;P <0.001).The mean(SD) postoperative serum albumin concentration was higher in the albumin group than that in the Plasma-Lyte group [3.6(0.3) $g \cdot dL^{-1}$vs 3.0 (0.3) $g \cdot dL^{-1}$; mean difference, 0.6; 95% CI,0.5to0.8;P < 0.001].

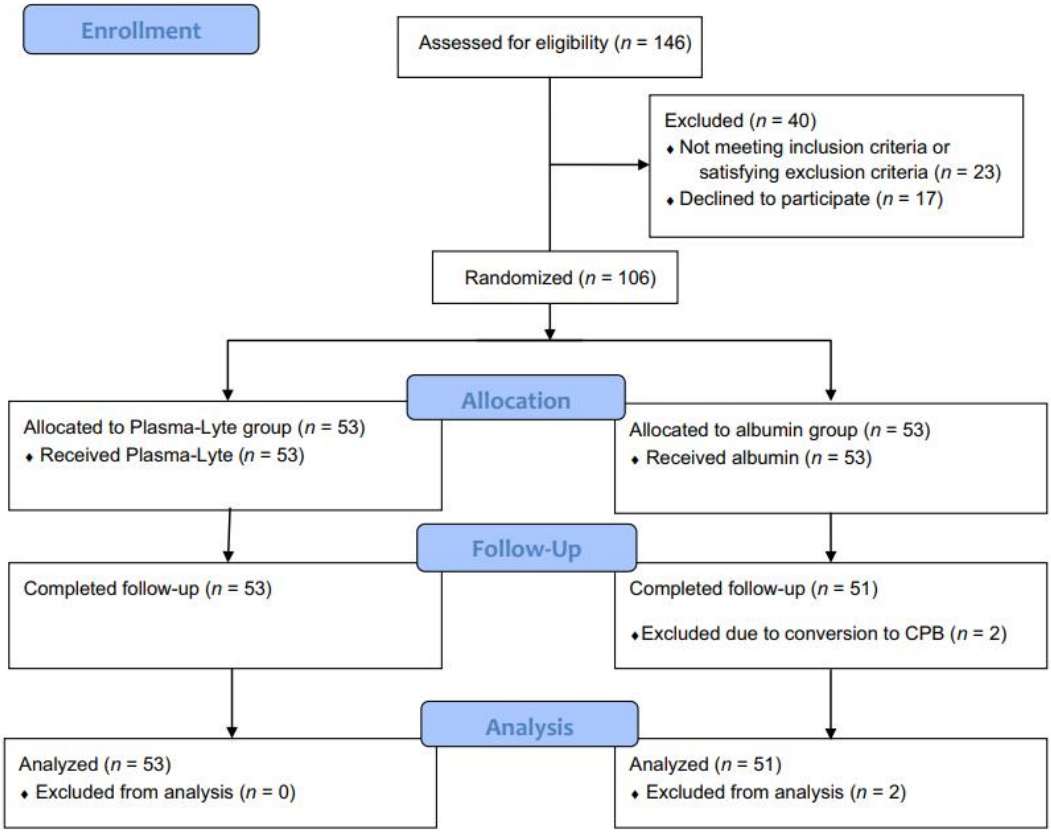

Fig. 1 Trial profile flow diagram
CPB = cardiopulmonary bypass

Table 1 Patient characteristics

	Plasma-Lyte N =53	Albumin N =51
Age (yr), mean (SD)	69(8)	65 (9)
Female, n/total *N* (%)	10/53 (19%)	9/51 (18%)
Body surface area (m^2), mean (SD)	1.76 (0.16)	1.77 (0.16)
Hypertension, n/total N (%)	48/53 (91%)	40/51 (78%)
Diabetes, *n*/total *N* (%)	34/53 (64%)	29/51 (57%)

Cerebrovascular accident, *n*/total *N* (%)	13/53 (25%)	5/51 (10%)
COPD, *n*/total *N* (%)	2/53(4%)	2/51 (4%)
PAOD, *n*/total *N* (%)	2/53(4%)	4/51 (8%)
3-vessel disease, n/total N (%)	50/53 (94%)	45/51 (88%)
Left main disease, n/total N (%)	10/53 (19%)	14/51 (28%)
Congestive heart failure, n/total N (%)	9/53 (17%)	5/51 (10%)
Myocardial infarction within 1 week, n/total N (%)	5/53 (9%)	2/51 (4%)
Unstable angina, n/total N (%)	20/53 (38%)	19/51 (37%)
Ejection fraction (%), mean (SD)	58(11)	60(11)
C-reactive protein (mg-L^{-1}), median [IQR]	1.4 [0.6-3.1]	1.0 [0.3-4.9]
Albumin (g-L^{-1}), mean (SD)	4.3 (0.4)	4.2 (0.4)
EuroSCORE2 (%), median [IQR]	1.11 [0.85-1.70]	1.03 [0.73-1.39]
Medications		
Nitrate, n/total N (%)	23/53 (43%)	26/51 (51%)
Calcium channel blocker, n/total N	24/53 (45%)	19/51 (37%)
Beta blocker, n/total N (%)	24/53 (45%)	29/51 (57%)
ACEi or ARB, n/total N (%)	31/53 (59%)	32/51 (63%)
Diuretic, n/total N (%)	6/53 (11%)	8/51 (16%)
Statin, n/total N (%)	45/53 (85%)	41/51 (80%)
Heparin, n/total N (%)	33/53 (62%)	22/51 (43%)
Acetylsalicylic acid, n/total N (%)	43/53 (81%)	45/51 (88%)
Clopidogrel, n/total N (%)	27/53 (51%)	24/51 (47%)
Duration of surgery (min), median [IQR]	231 [215-261]	243 [224-257]
Number of coronary grafts, median [IQR]	3 [3-4]	4 [3-4]
Duration of coronary grafting (min), median [IQR]	37[31^4]	40 [34-45]

ACEi = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; COPD = chronic obstructive pulmonary disease; IQR = interquartile range; SD = standard deviation; PAOD = peripheral artery occlusive disease

Beside the study fluids, the amount of other crystalloid solutions administered, the urine o

utput, and the transfusion, inotrope, and vasopressor requirements during the surgery were similar between the two groups (Table 2).

Table 2 Fluid balance, transfusion, and vasoactive drug requirements

	Plasma-Lyte N =53	Albumin N =51	Difference (95% CI)	*P* value
Intraoperative				
Intervention fluid (mL), mean (SD)	1,323 (492)	833 (270)	—489 (—643 to —335)	<0.001[a]
Crystalloid (mL), median [IQR]	1,050 [900-1,300]	1,100 [800-1,300]	50 (—100 to 150)	0.87[b]
Urine output (mL), median [IQR]	250 [150-350]	260 [150^03]	10 (—50 to 80)	0.65[b]
Salvaged blood (mL), median [IQR]	225 [220-240]	230 [220-240]	5 (—6 to 10)	0.60[b]
Erythrocyte transfusion, n/total N (%)	5/53 (9%)	2/51 (4%)	—6 (—17 to 6)	0.54[d]
Norepinephrine (ig), median [IQR]	1,120 [611-1,798]	1,168 [560-1,912]	48 (312 to 346)	0.98[b]
Vasopressin (U), median [IQR]	0.4 [0.1-3.6]	0.3 [0-2.5]	—0.1 (—0.3 to 0.1)	0.27[b]
Inotropic agents, n/total N (%)	4/53 (8%)	7/51 (14%)	6 (—8 to 20)	0.31[d]
Postoperative 48 hr				
Weight gain (kg), mean (SD)	1.8 (3.1)	1.7 (2.6)	—0.1 (—1.3 to 1.2)	0.90[a]
Crystalloid (mL), median [IQR]	4,849 [4,439-5,497]	5,230 [4,613-5,615]	381 (—215 to 455)	0.38[b]
Colloid (mL), median [IQR]	580 [100-710]	230 [0-530]	—350 (—280 to 0)	0.01[b]
Urine output (mL), median [IQR]	4,967 (1,157)	4,927 (1,404)	—41 (—540 to 459)	0.87[a]
Chest tube drainage (mL), median [IQR]	960 [843-1,237]	1,150 [947-1,352]	190 (18 to 276)	0.03[b]
Erythrocyte transfusion, n/total N (%)	13/53 (25%)	17/51 (33%)	9 (—11 to 28)	0.09[c]

Allogeneic plasma product transfusion, n/total N (%)	14/53 (26%)	18/51 (35%)	9 (—11 to 29)	0.42[c]
Norepinephrine (ig), median [IQR]	1,920 [640-5,280]	1,600 [320-4,400]	—320 (—1,280 to 320)	0.38[b]
Vasopressin, n/total N (%)	7/53 (13%)	2/51 (4%)	—9 (—22 to 3)	0.09[d]
Inotropic agents, n/total N (%)	5/53 (9%)	7/51 (14%)	4 (—10 to 19)	0.49[c]

Differences are (albumin group — Plasma-Lyte group)

Independent t test

[b]Mann-Whitney *U* test

[c]Chi square test

[d]Fisher's exact test

IQR = interquartile range; SD = standard deviation

The plasma concentrations of syndecan-1 increased after the return of heart positioning (median difference, 116 ng·mL^{-1};95% CI, 67 to 184; P < 0.001) and sternal closure (median difference, 57 ng·mL^{-1};95% CI, 36 to 80; P < 0.001) compared with the corresponding baseline values. Nevertheless, the changes in syndecan-1 concentration were not different between the two groups. Atrial natriuretic peptide concentrations were higher after the return of heart positioning (median difference, 37 pg·mL^{-1};95% CI, 12 to 57; P = 0.01) and sternal closure (median difference, 85 pg·mL^{-1}; 95% CI, 43 to 113; P< 0.001) than their corresponding baseline values, without any between-group differences. Similarly, TNF-a increased after the return of heart positioning (median difference, 0.30 pg·mL^{-1};95% CI, 0.24 to 0.40; P < 0.001) and sternal closure (median difference, 0.36 pg·mL^{-1};95% CI, 0.24 to 0.50; P < 0.001) when compared with the corresponding baseline values, without any between-group differences. Soluble thrombomodulin concentrations were similar throughout the study period in both groups (Fig. 2, Electronic Supplementary Material [ESM] eTable 1).

There were no significant differences in the cardiac index; serum creatinine; hematologic variables including hematocrit, white blood cells, and platelet count; cardiac troponin-T and creatine kinase-MB; and PaO_2/FiO_2 ratio between the two groups throughout the study period (ESM eTable 2)

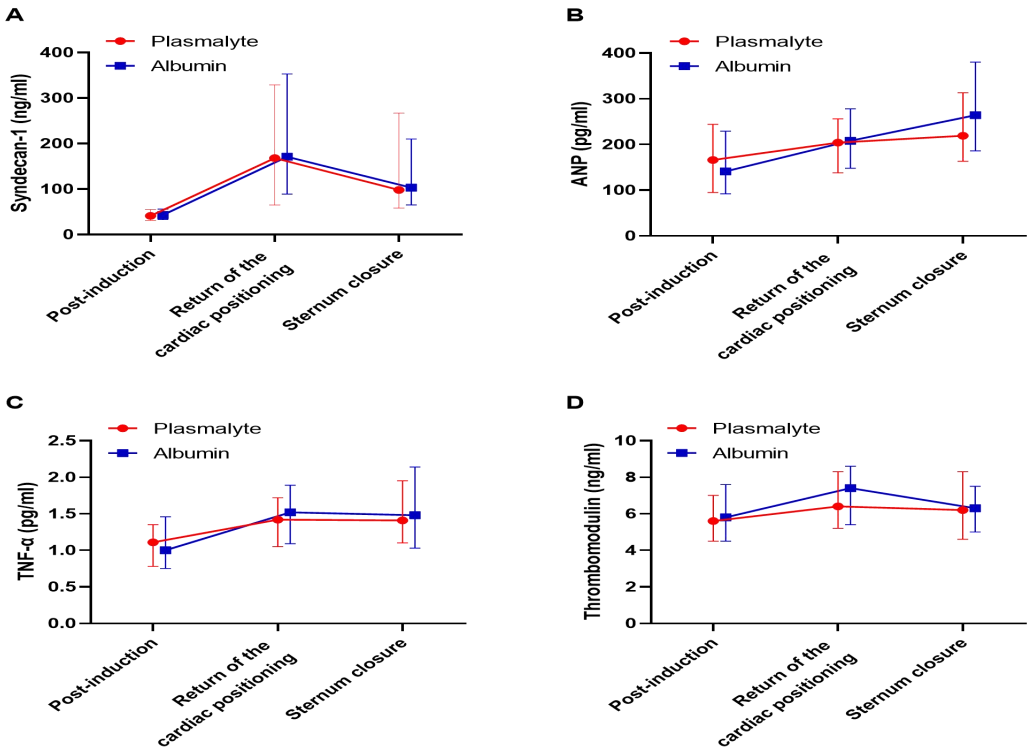

Fig. 2 Plasma syndecan-1, atrial natriuretic peptide (ANP), tumour necrosis factor (TNF) -a,and soluble thrombomodulin concentrations.

Plasma syndecan-1 (a), ANP (b), TNF-a(c), and soluble thrombomodulin (d) were measu red after the induction of anesthesia, at the return of cardiac positioning, and after sternal closure. Values are expressed as medians and interquartile range.

*P\ 0.05 vs postinduction (paired samples Wilcoxon signed rank test). Figures were creat ed using Prism 9(GraphPad Software LLC, San

Diego, CA, USA).

The mean (SD)weight gain at 48 hr postoperatively was similar between the two groups (1.7 [2.6] kg vs 1.8 [3.1] kg, albumin vs Plasma-Lyte, respectively; mean difference, -0.1; 95% CI, -1.3 to 1.2; P = 0.90). During the first postoperative 48 hr, the median [IQR]a mount of chest tube drainage was greater in the albumin group than that in the Plasma-Ly tegroup (1,150 [947–1,352] mL vs 960 [843–1,237] mL; median difference, 190; 95% CI, 18 to 276; P = 0.03). The amounts of crystalloid solution, urine output, and transfusion, i

notrope, and vasopressor requirements were similar between the two groups, except the median [IQR] amount of synthetic colloid solution (balanced 6% hydroxyethyl starch 130/0.4), which was greater in the Plasma-Lyte group (580 [100–710] mL) than in the albumin group(230 [0–530] mL) (median difference,-350; 95% CI, -280 to 0; P=0.01, Table 2).Postoperative outcomes, including 30-day or in-hospital morbidity and mortality and the duration of ICU stay and hospitalization were also similar betweenthe two groups (Table 3).

Table 3 Postoperative outcomes

	Plasma-Lyte (N =53)	Albumin *(N* = 51)	Difference (95% CI)	*P* value
Acute kidney injury, n/total *N* (%)	6/53 (11%)	6/51 (12%)	0 (—14 to 15)	0.94[b]
Renal replacement therapy, n/total *N* (%)	1/53 (2%)	2/51 (4%)	2 (—6 to 10)	0.54[c]
Newly developed atrial fibrillation, n/total *N* (%)	10/53 (19%)	9/51 (18%)	—1 (—18 to 16)	0.87[b]
Mechanical ventilation > 24 hr (%), n/total *N* (%)	2/53 (4%)	1/51 (2%)	—2 (—10 to 7)	0.58[c]
Stroke, n/total *N* (%)	1/53 (2%)	2/51 (4%)	2 (—6 to 10)	0.54[c]
Reoperation, n/total *N* (%)	0/53 (0%)	0/51 (0%)		N/A
Sternal wound infection, n/total *N* (%)	0/53 (0%)	1/51 (2%)	2 (—7 to 12)	0.31[c]
Mechanical circulatory support, n/total *N* (%)	0/53 (0%)	1/51 (2%)	2 (—7 to 12)	0.31[c]
Mortality, n/total *N* (%)	0/53 (0%)	1/51 (2%)	2 (—7 to 12)	0.31[c]
Duration of ICU stay (days), median [IQR]	2 [2, 3]	2 [2, 3]	0 (0 to 0)	0.71[a]
Duration of hospitalization (days), median [IQR]	9 [8-12]	8 [8-11]	—1 (—1 to 0)	0.61[a]

Differences are (albumin group — Plasma-Lyte group) [a]Mann-Whitney *U* test [b]Chi square test [c]Fisher's exact test

ICU = intensive care unit; IQR = interquartile range

4. DISCUSSION

In this randomized, double-blinded trial, intraoperative fluid resuscitation with 5% albumin or balanced crystalloid solution resulted in a similar degree of EG degradation in patients undergoing OPCAB. The amount of 5% albumin administered during surgery was significantly less than that of balanced crystalloid solution (volume expansion efficacy of approximately 1:1.6), while the transfusion requirements, cardiac index, and perioperative weight gain were comparable between the two groups.

Despite the theoretical and experimental advantages of using albumin to protect EG degradation and improve endothelial function, the efficacy of albumin in preventing EG degradation when used as an intraoperative fluid has not been evaluated in clinical trials.[22] In the current pragmatic clinical trial, albumin solution was used for the purpose of intraoperative plasma volume replacement. Because the volume effect of 5% albumin and balance crystalloid solution is not equal, the attending anesthesiologists, who were blinded to the type and amount of resuscitation fluid, managed the administration of the intervention fluids according to the information obtained from the hemodynamic monitors, TEE, and direct visual observation of the heart. The mode of intervention fluid administration in our study was designed to pursue euvolemia in both groups because hypervolemia is known to induce the degradation of EG.[23] As a result, the ratio of the amount of 5% albumin and balanced crystalloid solution for volume resuscitation was 1:1.6,while the cardiac output throughout the study period was similar between the two groups, indicating that the intraoperative volume status was maintained similarly in both groups. Of note, the volume expansion efficacy of albumin may have lasted longerin the postoperative period than that of the crystalloid as less synthetic colloid was administered in the postoperative period despite the larger amount of blood loss observed in the albumin group. Nevertheless, it might be a false-positive finding considering the comparable postoperative weight gain in the two groups.

In this study, the plasma concentration of syndecan-1 was found to be elevated after the return of cardiac positioning and sternal closure compared with the baseline concentration in both groups. Nevertheless ,there were no differences between the groups. Plasma sTM concentration, a marker of endothelial injury, was also similar between the groups. In addition, ANP and TNF-a were increased during the surgery in both groups without intergroup differences. Atrial natriuretic peptide is released upon atrial stretch due to hypervolemiaor displacement of the heart during OPCAB and may contribute to the degradation of EG.[24] Tumour necrosis factor-a induces EG degradation under inflammatory conditions.[25] These findings indicate that EG was degraded to a similar degree during surgery in both groups and albumin was not able to ameliorate the degradation. Unlike experimental models, albumin appears to be ineffective in terms of EG protection in an actual clinical setting.

The lack of effectiveness of albumin in this trial may be related to the uncertainty and variability of dosing. Owing to its multifaceted biological actions, the in vivo dose– response relationship of the protective effect of albumin on EG has not been established yet. Thus, it cannot be excluded that the amount of albumin administered in this trial was below the therapeutic range.

Because albumin was used for intraoperative volume resuscitation, the actual amount of albumin was quite variable in this study. Nonetheless, the higher postoperative serum albumin concentration in the albumin group suggests that fluid resuscitation with 5% albumin was able to prevent postoperative hypoalbuminemia. Of note, most patients in this study were not hypoalbuminemic preoperatively, although patients with hypoalbuminemia would likely benefit more from albumin supplementation.

The differences between endogenous and exogenous albumin may influence the clinical impact of albumin administration on EG. Various commercially available albumin preparations have been reported to be significantly different in terms of oxidation, charge, and metal ion content,[26] which may potentially alter the clinical effect due to variable binding capacity and antioxidant property.[27] Nevertheless, the clinical impact of the variations in albumin preparation has not been determined yet and requires further investigation.

During the first 48 hr after surgery, the amount of drainage via the chest tube was greater in patients who received albumin. Albumin has been thought to exert minimal effect on coagulation when compared with synthetic colloids.[28] Nevertheless, a study that assessed the coagulation profile in whole-blood samples prepared with low, physiologic, and high albumin levels showed the anticoagulant property of albumin.[29] A retrospective analysis of 2,594 patients who underwent cardiac surgery showed that albumin administration was associated with an increased incidence of hemostatic reoperation and transfusion.[30] The results of our study are also in accordance with those of the Albumin in Cardiac Surgery (ALBICS) trial,[31] which compared the effectiveness and safety of albumin as the priming solution and intravascular volume resuscitation fluid in patients undergoing cardiac surgery with CPB. In the ALBICS trial, the primary composite outcome of major adverse events was similar between the patients who received 4% albumin and those who received Ringer's acetate solution; however, the incidence of major bleeding and reoperation was higher in the albumin group. Taken together, albumin might induce hemostatic impairment in patients undergoing cardiac surgery, and further studies are needed to clarify its clinical relevance and underlying mechanisms.

One of the limitations of this study is that the magnitude of EG degradation was solely assessed by plasma concentrations of the released EG constituent,syndecan-1. Syndecan-1 is not endothelial cell-specific. Furthermore, its serum concentration is not a direct measure of EG dimension or functional integrity.Nevertheless, direct visualization, for example using intravital microscopy, is not feasible in the clinical setting. Moreover, syndecan-1 was shown to be well correlated with EG thickness in a controlled experimental model.[18]

5. CONCLUSION

In conclusion, OPCAB was associated with significant EG degradation as evidenced by increased breakdown of its constituents represented by syndecan-1. Nevertheless, intraoperative fluid resuscitation with 5% albumin could not reduce the degradation of EG when compared with

balanced crystalloid solution in patients undergoing OPCAB and yielded a volume expansion efficacy of approximately 1:1.6.

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Abstract in Korean

무체외순환 관상동맥우회술을 시행 받는 환자에서 수술 중 수액 요법으로 5% 알부민 또는 균형정질액 사용에 따른 혈관내피 당질층 보호 효과 비교

배경: 혈관내피 당질층(endothelial glycocayx)은 혈관 항상성에 중요한 역할을 한다. 심장 수술, 패혈증 및 중증 외상에서 EG 의 손상이 관찰되며 나쁜 예후와 관련이 있다. 알부민은 전임상 연구에서 EG 에 대한 보호 작용을 하는 것으로 나타났으며, 이는 수술 중 수액의 선택이 EG 손상 정도에 영향을 미칠 수 있음을 시사한다. 따라서 이 연구는 무체외순환 관상동맥우회술을 받는 환자의 EG 손상에 대한 5% 알부민과 균형정질액의 효과를 비교하였다.

방법: 이중 맹검, 무작위 배정 임상시험으로 대조군(N=53)은 혈장량 보충을 위한 수액 요법으로 균형정질액(Plasmalyte)을 투여받았고 실험군(N=51)은 5% 알부민을 투여받았다. 수액 부하 여부 및 필요량은 군 배정을 알지 못하는 마취 담당의가 경식도 심초음파 소견, 혼합 정맥혈 산소포화도, 심박출지수, 활력 징후 등의 지표를 통해 임상적으로 판단하여 결정하였다. plasma syndecan-1, 심방 나트륨 이뇨 펩티드(ANP), 종양 괴사 인자(TNF)-α, soluble thrombomodulin 은 마취유도 시, 관상동맥 문합 완료 후 및 흉골 봉합 후 측정하였다 수술 중, 수술 후 48 시간까지 수액 투여량, 소변량, 출혈량 및 수혈량을 기록하였다.

결과: 알부민 군과 균형정질액군은 각각 833 ± 270 ml 의 5% 알부민과 1323 ± 492 ml 의 plasmalyte 을 투여받았다(평균차이 −489 ml, 95% 신뢰구간 −643 ~ −335, P<0.001). EG 분해의 지표인 syndecan-1 의 혈장 농도는 관상동맥 문합 완료 후(알부민: 171 [89-353] ng/ml, 균형정질액: 168 [65-329] ng/ml) 및 흉골 봉합 후(알부민: 103 [65-210] ng/ml, 균형정질액: 98 [58-267] ng/ml) 마취유도 시(알

부민: 43 [33-56] ng/ml, 균형정질액: 41[31-55] ng/ml)보다 증가하였으나 (P<0.001) 두 군 간 차이는 없었다(P=0.651). ANP, TNF-α 및 soluble thrombomodulin 농도는 두 군 간 차이가 없었다. 수술 후 48시간 동안 배액관을 통한 출혈량은 알부민군에서 더 많았다 (중위값차 190 ml, 95% 신뢰구간 18 ~ 276, P=0.03).

결론: 무체외순환 관상동맥우회술 중 EG 손상이 관찰되었다. 수액요법으로 5% 알부민을 사용했을 때 균형정질액에 비해 비슷한 정도의 EG 손상을 보였다.

핵심되는 말 : 내피 글리코칼릭스,알부민,수액소생술,심장수술