Original Article

The Effects of Albumin 20% and Hydroxyethyl Starch 6% on Bleeding and Interleukin-6 Levels as Priming Solutions for Cardiopulmonary Bypass: A Randomized Controlled Trial

Alireza Hosseini, MD[1*], Mehran Shahzamani, MD[1], Atefe Hashemabadi, MS[2], Alireza Andalib, PhD[3]

[1]*Department of Surgery, Chamran Hospital, Isfahan University of Medical Sciences, Isfahan, Iran.*
[2]*Department of Blood Circulation Technology, Isfahan University of Medical Sciences, Isfahan, Iran.*
[3]*Department of Immunology, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran.*

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Abstract

Background: *Cardiopulmonary bypass (CPB) can adversely affect coagulation and systemic inflammatory response. Given that the optimal strategy for priming CPB in cardiac surgery remains a matter of debate, this study aimed to investigate the effects of albumin 20% and hydroxyethyl starch 6% as priming solutions on bleeding and interleukin-6 (IL-6) levels during CPB.*

Methods: *This randomized clinical trial involved 40 patients undergoing coronary artery bypass surgery at Shahid Chamran Hospital between July 2021 and July 2022. Participants were assigned to 2 groups: the first group received 50 mL of albumin 20% as the priming solution for the CPB circuit, while the second group received 500 mL of hydroxyethyl starch 6%. Bleeding and IL-6 levels were assessed before and after the intervention.*

Results: *The albumin group comprised 80.0% men and 20.0% women, with a mean age of 66.45±5.84 years. The hydroxyethyl starch 6% group consisted of 85.0% men and 15.0% women, with a mean age of 63.05±5.92 years (P>0.05). The findings revealed that 12 hours after CPB, the IL-6 level in the hydroxyethyl starch 6% group (mean: 171.6±77.71 pg/mL) was significantly higher than that in the albumin group (mean: 105.8±36.45 pg/mL; P=0.002). At 48 hours after CPB, the mean bleeding was not significantly different between the groups (P=0.950).*

Conclusion: *Albumin 20% was more effective than hydroxyethyl starch 6% concerning IL-6 levels. However, no significant differences in bleeding were observed between the groups at 48 hours post-CPB.*

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[*]**Corresponding Author:** ***Alireza Hosseini,*** *Assistant Professor of Cardiovascular Surgery, Department of Surgery, Chamran Hospital, Moshtagh Street, Isfahan, Iran. 8166173414. Tel: +98 31 32600961. E-mail: drhosseiny@yahoo.com, & hosseiny@med.mui.ac.ir.*

Introduction

Coronary artery bypass graft (CABG) surgery involves the removal of healthy blood vessels from another part of the body and their subsequent grafting onto blocked blood vessels of the heart to restore blood flow to the affected area. The cardiopulmonary bypass (CPB) machine plays a critical role in this procedure, as it oxygenates the blood, maintains an appropriate cardiac index, and facilitates surgery on the non-beating heart.[1] CPB machines must be filled with priming solutions that prepare the extracorporeal circulation circuit during CPB.[2]

Colloidal solutions, compared with crystalloid solutions, require a smaller volume for distribution. Consequently, a lower volume of fluid and less time are needed to restore intravascular volume when using colloidal solutions.[3] Colloids are more effective than crystalloids in stabilizing volume and maintaining colloid osmotic pressure, thereby preventing interstitial fluid accumulation.[4]

The priming solution can impact the physicochemical balance of blood and modulate the body's metabolic and inflammatory responses to the stress of heart surgery and the CPB machine. Furthermore, the choice of priming solution can affect acid management during the procedure.[5] As a result, extensive efforts have been made over several decades to identify an ideal priming solution that can minimize complications, such as pulmonary issues, prolonged intubation, the need for blood transfusions, and coagulation disorders. Despite these efforts, a consensus on the optimal priming solution remains elusive.[4] Today, the detrimental effects of fluid accumulation in the interstitial space are well-recognized, and evidence supporting the preference for colloid solutions over crystalloids continues to mount. One such colloid that has become a routine component of the priming solution in many clinical centers is albumin. The inclusion of albumin in the priming solution can help mitigate the decrease in colloid-oncotic pressure that typically occurs during CPB.[6] Albumin is crucial to the integrity of blood vessels that supply the lungs and other organs and, thus, prevents excessive fluid buildup in these organs. Additionally, albumin can contribute to platelet activation and the release of inflammatory factors, further highlighting its importance in the overall physiological response during cardiovascular procedures.[7]

Reports have indicated that the administration of large amounts of hydroxyethyl starch (HES) 6% during the perioperative period may have inhibitory effects on hemostasis.[8] The HES-induced impairment of hemostasis is particularly notable with highly substituted and large HES molecules, such as hetastarch. This molecule has a substitution degree of 0.7 (HES 450/0.7) and an average molecular weight of 450,000 Da. Furthermore, the impairment can be significant following long-term application of medium molecular weight starches with a high substitution degree (200,000 Da; 0.62–0.66).[9]

The pharmacokinetic profile of HES 130/0.4 (Voluven) was developed as a novel specification, focusing on modifying the molecular structure of HES to improve both safety and efficacy. To achieve this, the substitution degree was reduced to 0.4, and the average molecular weight was lowered to 130,000 Da. This modified molecule is distinct from the European standard HES 200/0.5 (pentastarch). The pharmacological concept underpinning this development aimed to enhance renal elimination and metabolism of the substance, improving its safety profile. Additionally, it sought to maintain effectiveness by providing more osmotically effective small molecules.[10]

Waitzinger et al[11] reported that HES 130/0.4 6% exhibited a volume effect of approximately 100% of the infused volume, with a duration of 4 to 6 hours. Notably, this study found no evidence of HES 130/0.4 accumulation in plasma following repeated doses, which differs from observations made with other HES specifications.

This synthetic solution triggers a minimal inflammatory response, causes only a slight rise in blood urea nitrogen and creatinine levels, and is not linked to major complications or kidney failure.[12]

In contrast, a different investigation found that HES was associated with improved kidney function and a reduced inflammatory response when compared with albumin.[13] Furthermore, the use of HES has been linked to a lower incidence of anaphylactic reactions than other artificial colloids, such as gelatin dextran and albumin.[14]

It is essential to recognize that priming solutions, both crystalloid and colloid, could impact the normal blood coagulation system and homeostasis. The risk of these effects increases when large volumes of priming solutions are used. Due to the reduction in the concentration of coagulation factors resulting from hemodilution, some degree of coagulation disorder and hemostasis disruption may be anticipated.[14] Therefore, postoperative blood loss is a common occurrence in patients who have undergone open-heart surgery. The severity of blood loss can vary greatly among patients, ranging from minor and inconsequential to severe and life-threatening. In more serious cases, increased transfusion-related morbidity and mortality may occur, along with decreased perfusion and potential damage to vital organs.

Given the importance of managing postoperative blood loss effectively, several studies have investigated the potential benefits of specific interventions such as the use of albumin or HES. These interventions aim to improve clinical outcomes by addressing coagulation and hemostasis issues that may arise during open-heart surgery and contribute to postoperative blood loss.[13-18]

Considering the diverse types of priming solutions employed in cardiac surgery centers and the conflicting findings regarding their impact on inflammatory responses

and post-surgery blood loss, there is a clear need for further research to identify the optimal solution with the fewest associated complications. With this goal in mind, the present study was designed to compare the effects of HES 6% and albumin 20% as CPB colloid priming solutions on blood loss volume and interleukin-6 (IL-6) levels following CABG.

Methods

This randomized controlled trial was conducted at the Shahid Chamran Cardiovascular Training Center in Isfahan, Iran, from July 2021 through July 2022. The study population comprised patients who were candidates for CABG during this period.

A sample size of 40 patients (20 in each group) was determined based on a confidence level of 95%, a test power of 80%, and previously reported mean blood loss values of 1121.00±584.58 mL for the HES 6% group and 799.84±382.75 mL for the albumin group.[15]

The inclusion criteria for this study encompassed adult patients aged 40 to 75 years who were scheduled for non-emergency open-heart surgery involving a CPB machine during CABG. Eligible patients were required to have an ejection fraction of greater than 35% and to discontinue the use of acetylsalicylic acid and clopidogrel at least 48 hours before surgery.

Patients were excluded from the study if they were scheduled for cardiovascular surgery without the use of a CPB machine or if they had any of the following underlying conditions: end-stage renal disease, liver or kidney failure (serum creatinine level >1.4 mg/dL), pre-surgical infections such as infective endocarditis, inflammation symptoms, preoperative coagulation disorders, a recent myocardial infarction, a history of previous cardiac surgery, or a preoperative hemoglobin level of less than 10 mg/dL.

The study received ethical approval (code: IR.MUI.MED.REC.1401.010) from the Ethics Committee of Isfahan University of Medical Sciences and was registered (code: IRCT20220410054470N1) in the Iranian Registry of Clinical Trials. Written informed consent was obtained from eligible patients. A total of 40 patients were randomly selected to participate in this study.

Baseline and clinical characteristics, such as age, sex, body mass index, and ejection fraction, were recorded for each participant. Afterward, the patients were randomized with random allocation software into 2 groups of 20 patients each (Figure 1). The first group received 50 mL of albumin 20% as the priming solution for the CPB circuit, while the second group received 500 mL of HES 130/0.4 6% (manufactured

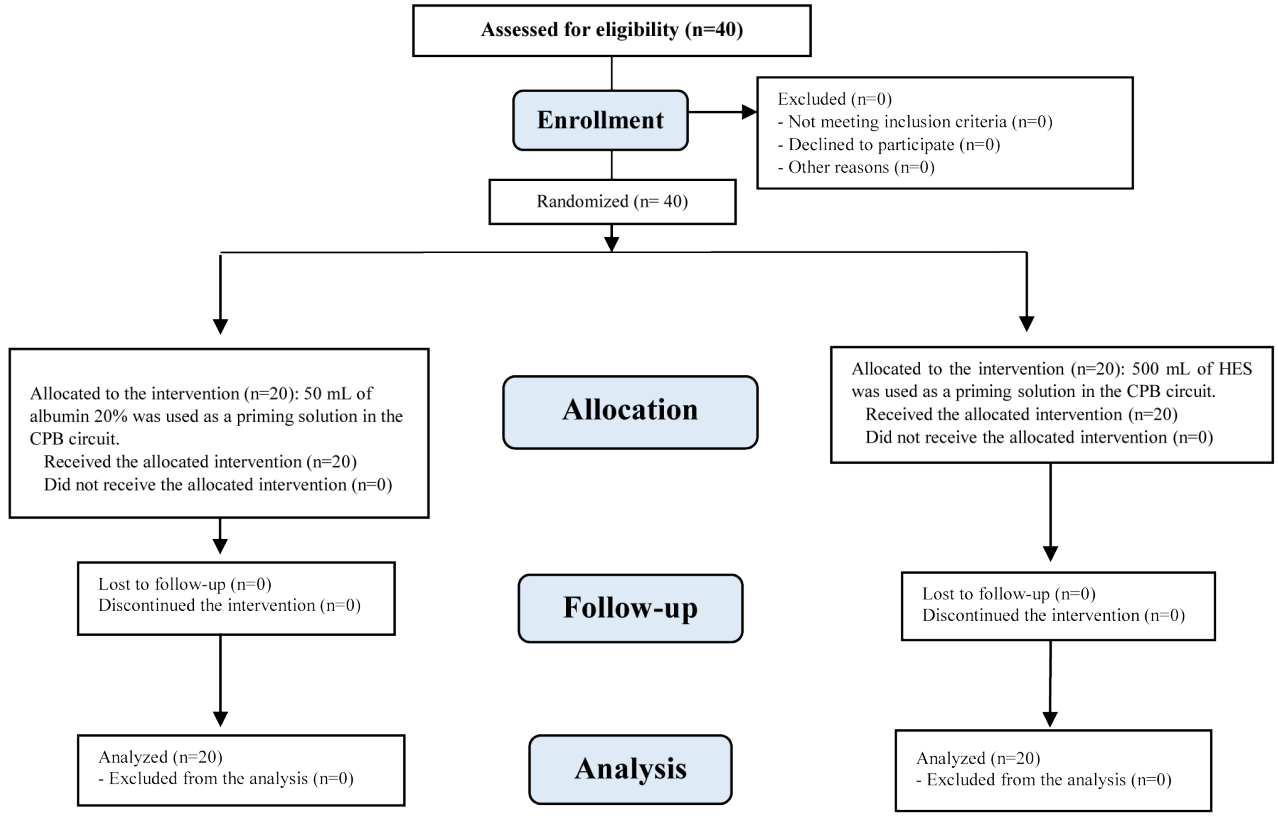

Figure 1. The image presents the CONSORT flowchart of the studied patients.
HES, Hydroxyethyl starch; CPB, Cardiopulmonary bypass

by Shahid Ghazi Company, Iran) for the CPB circuit priming solution.

Before CPB commencement, an initial bolus of heparin (3 mg/kg) was administered using a Sorin 8f oxygen generator and heat pump. The circuit volume was maintained by adding acetate Ringer's solution as needed. Packed red blood cells were only administered if the patient's hematocrit level dropped below 20%. Moderate hypothermia (32–34 °C) and cold blood cardioplegia were utilized in all cases.

The anesthesia and surgical procedures were standardized for all patients. Anesthesia induction was achieved using sodium thiopental, pancuronium bromide, and fentanyl, while anesthesia maintenance was accomplished with either propofol or isoflurane gas. A consistent cardioplegia solution was employed to protect the myocardium and induce cardiac arrest in the study population. Additionally, 10,000 units of heparin were used for priming in every case.

The α-stat acid-base gas management strategy was employed, with a target range of PaO_2 set at 200–300 mm Hg. Throughout the CPB process, arterial pressure was maintained between 60 mm Hg and 80 mm Hg using norepinephrine or nitroglycerin. Once CPB was completed, protamine sulfate (1 mg per mg of heparin) was administered to reverse the effects of heparin. All patients were warmed to a temperature of 36 °C before weaning from CPB. The surgical technique was consistent across all patients.

To maintain the double-blind nature of the study, the priming solutions were prepared in advance by a perfusionist who did not participate in the research. This approach ensured that the surgeon was unaware of the type of intervention received by each group. Moreover, both the patients and the statistical analyst were kept uninformed of the intervention type in each group until the completion of the study. To further preserve the blinding conditions, the postoperative management of all patients was overseen by physicians who were not involved in the study and were unaware of its specific objectives.

Following the surgical procedure, all patients were transferred to the ICU, where they received controlled mechanical ventilation until their hemodynamics stabilized, allowing for spontaneous breathing and the attainment of appropriate blood gas levels. Consistency was maintained by utilizing the same type of heart-lung machine, oxygenator, and arterial filter for each patient. Cooling to a temperature of 32 °C was achieved using a heat exchanger, and the average arterial blood pressure was kept at around 60 mm Hg.

Postoperatively, fluid therapy was administered to maintain pulmonary artery occlusion pressure between 10 mm Hg and 14 mm Hg, a cardiac index above 2 lit/min/m^2, and a urine output of more than 0.5 mL kg/h.

During the procedure, the CPB time and aortic cross-clamp time were documented for each patient. Additionally, 5 mL blood samples were collected 12 hours post-CABG from the central venous catheter to assess IL-6 levels.

The integrity of the samples was ensured by placing them on ice and centrifuging them immediately. The serum was then separated and stored in a freezer at −70 °C. Subsequently, the inflammatory marker IL-6 was measured in the laboratory using the stored serum samples. In addition to measuring IL-6 levels, various coagulation parameters were also assessed 12 hours after CPB. These parameters included platelet count and hematocrit. Furthermore, the total volume of blood loss was measured via drainage up to 48 hours following CPB.

The transfusion volumes of blood and its products, which included packed red blood cells, fresh frozen plasma (FFP), and platelets, were also recorded for each patient. Additionally, the CPB time and aortic cross-clamp time were documented.

The collected data were subsequently entered into the SPSS software (version 26) for analysis. Qualitative variables were expressed as numbers and percentages (n, %), while quantitative variables were presented as mean±standard deviation (SD).

The Kolmogorov-Smirnov test was employed to assess the normality of data distribution. Based on the normal distribution, the independent samples T and χ^2 tests were utilized to compare the mean of quantitative variables and the distribution of qualitative variables between the 2 groups, respectively.

In all statistical analyses, a significance level of less than 0.05 was considered to indicate statistical significance.

Results

In this study, the albumin group was composed of 16 (80.0%) male and 4 (20.0%) female patients, with a mean age of 66.45±5.84 years. On the other hand, the HES group consisted of 17 (85.0%) male and 3 (15.0%) female patients, with a mean age of 63.05±5.92 years. The statistical analysis indicated no significant difference concerning age and sex distribution between the groups (P>0.05) (Table 1). Prior to surgery, there was no significant difference in the mean IL-6 level between the albumin and HES groups (P=0.324). However, 12 hours after CPB, a significant increase in IL-6 levels was observed in both groups.

Notably, the mean IL-6 level was significantly lower in the albumin group than in the HES group (105.8±36.45 pg/mL vs 171.6±77.71 pg/mL; P=0.002) at the 12-hour post-CPB mark.

Contrary to the observed difference in IL-6 levels, the total volume of blood loss 48 hours after CPB was not significantly different between the albumin and HES groups (HES group: 625.00±278.86 vs albumin group: 620.00±215.45; P=0.950).

Nevertheless, a significant difference was noted in the transfusion of blood and blood products between the groups (P=0.034). In the albumin group, 65.0% of patients received blood transfusions and 25.0% received platelet transfusions,

Table 1. Baseline and clinical characteristics of the 2 study groups

Variables	Albumin Group (n=20)	HES Group (n=20)	P
Sex			
male	16 (80.0%)	17 (85.0%)	0.677
female	4 (20.0%)	3 (15.0%)	
Age, y	66.45±5.84	63.05±5.92	0.075
BMI, kg/m^2	22.61±2.34	23.21±3.01	0.486
EF, %	45.40±7.11	48.6±6.50	0.146
Serum Cr, mg/dL	0.90±0.12	0.86±0.20	0.447
Hemoglobin, mmol/L	7.48±0.80	7.82±0.37	0.093
CPB time, min	94.36±29.16	89.28±32.06	0.559
ACC, time	66.32±21.36	65.01±19.87	0.842

Cr, Creatinine; EF, Ejection fraction; BMI, Body mass index; CPB, Cardiopulmonary bypass; ACC, Aortic cross-clamp

Table 2. Comparisons of coagulation parameters, IL-6, total blood loss, and blood product transfusion after CPB between the 2 groups*

Variables	Albumin Group (n=20)	HES Group (n=20)	P
Hematocrit, %	28.74±4.36	27.11±4.36	0.244
Platelet count, 10^3/μL	108.16±36.21	123.56±31.69	0.160
IL-6, pg/mL			
Before surgery	1.32±0.24	1.11±0.91	0.324
After surgery	105.83±36.46	171.65±77.71	0.002
PT, s			
Before surgery	13.30±1.00	13.00±0.81	0.304
After surgery	15.01±2.61	14.55±2.73	0.557
PTT, s			
Before surgery	30.50±5.70	30.60±5.67	0.955
After surgery	37.50±23.00	38.00±19.32	0.941
Total blood loss, mL	620.00±215.45	625.00±278.86	0.950
Blood Products			
PRBC	13 (65.0%)	11 (55.0%)	0.034
Platelets	5 (25.0%)	3 (15.0%)	
FFP	0 (0.0%)	2 (10.0%)	

*Data are shown as mean±SD and median (interquartile range) or n (%).
IL-6, Interleukin-6; PRBC, Packed red blood cell, FFP, Fresh frozen plasma
IL-6 and coagulation parameters were measured 12 hours after CPB, and total blood loss was measured based on chest drain at 48 hours after CPB.

with no FFP transfusions required. On the other hand, in the HES group, 55.0% of patients received blood transfusions, 15.0% received platelet transfusions, and 10.0% received FFP transfusions (Table 2).

Discussion

Our results demonstrated that the plasma level of IL-6 was significantly lower in the albumin group than in the HES group 12 hours after CPB.9 Nonetheless, no significant differences were observed in coagulation parameters between the groups at the same time point.

The potential mechanism behind the lower IL-6 levels in the albumin group may be attributed to albumin's ability to cover the surface of the CPB system, thereby reducing the contact between blood and the non-physiological circuit. This interaction between blood proteins and the circuit can result in the activation of platelets, the release of inflammatory factors, and the initiation of the complement cascade.[19]

The use of albumin in the priming solution is also effective in preventing thrombosis of the oxygenator, which can lead to emergency membrane replacement.[19] The activation of platelets during surgery can indeed lead to thrombosis in the oxygenator. Albumin's ability to reduce platelet activation may help minimize this risk, contributing to a smoother surgical procedure and better patient outcomes.

Conversely, HES has been shown to possess beneficial properties in managing inflammation and tissue edema. Studies have indicated that HES can improve endothelial

function, maintain endothelial integrity, and preserve Starling's forces, particularly oncotic pressure.[20] These effects contribute to reduced capillary edema, which can be especially helpful in cases of increased capillary permeability.

Moreover, research has demonstrated that HES solutions with lower molecular weight are effective in mitigating capillary edema resulting from various clinical conditions and laboratory-induced increases in capillary permeability.[21]

Additionally, one notable advantage of employing HES as the primary CPB solution is its potential to significantly improve microcirculation and enhance oxygen delivery to tissues.[22] This aspect of HES contributes to better perfusion and oxygenation, which can be crucial for ensuring optimal surgical outcomes and reducing complications.

Another potential mechanism of action of HES may involve its direct effect on inflammation. Studies have reported that HES 6% (Voluven) can modify the inflammatory response by reducing the levels of pro-inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α) and IL-1β.[23]

In contrast to the findings of the current study, Choi et al[12] observed a significant rise in the serum concentrations of IL-6, IL-8, and TNF-α 12 hours post-surgery compared with pre-surgery levels. Still, their study did not find significant differences between the 2 groups in terms of coagulation parameters and serum concentrations of these inflammatory markers. This discrepancy in findings could be attributed to differences in study design, patient populations, or other factors that may influence the inflammatory response and coagulation parameters following CABG.

The complex interplay between coagulation and inflammation in patients undergoing CABG is influenced by several factors, including hemodilution, the activation of the coagulation and fibrinolysis systems, and the choice of priming solution for the CPB circuit. These aspects contribute to variations in inflammatory response and coagulation parameters among patients.

To minimize fluid overload after CPB, colloid solutions, such as albumin and HES, are commonly employed as priming solutions. The choice of priming solution can significantly impact the patient's inflammation and coagulation systems. Albumin, for instance, is believed to form a nearly non-thrombogenic layer on the surfaces of the CPB circuit, reducing platelet adhesion and activation.

The potential benefits of endothelium-mimicking coatings may be particularly relevant when non-biocompatible circuits are employed. Over time, a range of biocompatible CPB circuits have been developed, offering potential advantages in mitigating inflammation and coagulation-related complications. Nonetheless, the clinical superiority of biocompatible circuits remains inconclusive. Consequently, non-biocompatible circuits continue to be commonly utilized in clinical settings due to their cost-effectiveness. To reduce health care costs, HES, a non-protein colloid, is often used in place of albumin.[24] However, this substitution has raised concerns regarding the potential risks associated with using allogeneic blood-derived products. While the safety and efficacy of HES as an intravascular volume expander have been well-documented in clinical studies, its impact on the coagulation system remains a significant concern. The use of HES in the priming solution of the CPB circuit may lead to adverse circulatory effects and compromise active hemostasis outside the body.[23]

In the present study, the number of platelets following the use of human albumin was marginally higher than that following the use of HES, although this difference was not statistically significant. These findings are in agreement with the results of a study conducted by Tiryakioğlu et al,[25] which demonstrated that the use of HES did not adversely impact the international normalized ratio, platelet count, or postoperative blood loss volume.

A meta-analysis study by Wei et al,[16] which examined 10 studies comparing the effects of HES and albumin on surgical outcomes, found that the total infusion volume and blood loss volume were not significantly different between the 2 groups. On the other hand, Hosseinzadeh Maleki et al[15] reported contrasting results, showing that the administration of albumin, compared with HES, in patients undergoing CABG resulted in a decreased platelet count and lower blood loss volume. In contrast to the aforementioned result, our findings demonstrated that the volume of blood loss was lower in the albumin group than in the HES group 48 hours after CPB, although this difference did not reach statistical significance. Additionally, the albumin group exhibited a significantly reduced need for blood products compared with the HES group. Notably, FFP was not required in the albumin group, whereas it was used in 10.0% of patients in the HES group. Contrary to the results of the current study, Jacob et al[18] observed that the use of HES was associated with lower blood loss volume and reduced need for blood transfusion when compared with albumin. Nevertheless, it is important to note that other studies have reported no significant differences in blood transfusion requirements after CABG when HES was used as a priming solution instead of Ringer's lactate.[27,28] In another study, the use of HES in the priming solution did not result in significant changes in blood loss volume or kidney function within the first 24 hours post-surgery. However, the volume of blood received was lower in the HES group than in the Ringer's group during the CPB procedure.[5] In our study, despite the similarity in crystalloid solutions between the 2 groups, no significant differences in blood loss volume were observed. Nevertheless, the albumin group demonstrated a markedly reduced need for blood product transfusions when compared with the HES group.

Several limitations of this study must be acknowledged. One such limitation is the lack of evaluation of kidney function, which may not provide a comprehensive understanding of the effects of priming solutions on renal

health. Other limitations include the small sample size, the absence of a comparison between different doses of albumin or HES, and the lack of a comparison with crystalloid priming solutions such as Ringer's lactate. Additionally, coagulation parameters were not assessed in this study, which could have provided further insight into the impact of these priming solutions on hemostasis.

Despite these limitations, the study possesses a notable strength in its examination of inflammatory parameters, such as IL-6. This aspect is particularly important because few studies have investigated the influence of priming solutions on inflammatory responses following CPB.

Considering the significance of inflammatory responses in the context of CPB and the potential impact of priming solutions on these responses, it is recommended that future studies place greater emphasis on the role of solutions like albumin and HES in influencing inflammatory parameters, such as IL-6, IL-8, and TNF-α.

Conclusion

The findings of this study suggest that although there were no significant differences in coagulation parameters and blood loss volume between the 2 groups, the use of albumin 20% as a priming solution for CPB was associated with significantly lower IL-6 plasma levels and reduced need for blood product transfusions post-surgery compared with HES 6%.

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