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The effect of vitamin C supplementation additive to the priming solution on postoperative bleeding in coronary artery bypass grafting: A randomized controlled trial

Alireza Hosseini[1], Mehran Shahzamani[1], Asieh Maghami-Mehr[2,3], Mahsa Moshgelgosha[4*]

1- Department of Cardiovascular Surgery, Isfahan University of Medical Sciences, Isfahan, Iran
2- Department of Statistics, Yazd University, Yazd, Iran
3- Cardiac Rehabilitation Research Center, Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran
4- Department of Circulation Technology, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran

Correspondence:

Mahsa Moshgelgosha;
Department of Circulation Technology, School of Medicine, Isfahan University of Medical Sciences, Hezar Jerib Avenue, Azadi Square, Isfahan, Iran;
Email: mahsamg94@gmail.com

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Abstract

BACKGROUND: Patients undergoing cardiac surgery often experience bleeding during and after the procedure. Antioxidants such as Vitamin C (VC) are used to manage postoperative bleeding and inflammation after cardiac surgery.

METHODS: A total of 110 patients undergoing elective coronary artery bypass grafting (CABG) with cardiopulmonary bypass (CPB) were enrolled. Patients were randomly assigned into two groups of 55 participants each. In the intervention group, 25 mg/kg of VC was added to the CPB priming solution. In the control group, 25 mg/kg of normal saline was added instead. Nurse recorded the amount of chest tube drainage on intensive care unit (ICU) entry, and 2, 4, 6, 12, and 24 hours. They also documented the amount of blood product transfusion required during surgery and in the ICU.

RESULTS: The amount of chest tube drainage in the control group was higher than the intervention group, but this difference was not statistically significant between the two groups ($P > 0.05$). The amount transfused blood in the operating room and in the ICU in the intervention group was 1.64±0.79 and 2.14±1.17 ml, respectively, and in the control group it was 1.69±0.84 and 2.52±1.68 ml, which was not statistically significant between the two groups ($P > 0.05$). There was no significant difference in duration of ICU and hospital stay between the two groups ($P > 0.05$).

CONCLUSION: Adding VC to the CPB prime showed a non-significant trend toward reduced postoperative bleeding after CABG. Current evidence from this study is insufficient to recommend routine use; further larger trials are needed.

Keywords: Vitamin C; Coronary Artery Bypass Grafting; Prime Solution; Bleeding; Cardiopulmonary Bypass

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Introduction

Patients undergoing cardiac surgery often experience bleeding during and after the procedure[1,2]. Reports indicate that postoperative bleeding occurs in about 25% to 50% of cases after coronary artery bypass grafting (CABG) with cardiopulmonary bypass (CPB)[1]. As a result, patients undergoing cardiac surgery usually require more allogeneic blood transfusions than other surgical procedures[3]. However, the use of blood products is associated with several adverse outcomes, including the risk of infectious and viral diseases, immunosuppression, increased mortality, and prolonged hospitalization[1,3].

One of the primary causes of bleeding during cardiac surgery is the use of CPB. The priming volume of the bypass circuit leads to hemodilution, and the contact of blood with the internal surfaces of the CPB machine induces mechanical damage to blood cells, disrupts platelet function, and disrupts coagulation mechanisms[1]. These effects contribute to reduced hemoglobin levels, impaired thrombin generation, converted fibrin formation, quantitative or qualitative platelet defects, and hyperfibrinolysis[2,3].

In addition, postoperative bleeding may also be due to coagulation factor and platelet deficiency, incomplete reversal of heparinization, and increased fibrinolytic activity[1]. Despite these concerns, there is currently no universally accepted definition of intraoperative bleeding in cardiac surgery[2]. Nevertheless, the range of bleeding can be assessed by the requirement of the amount of chest tube drainage and the transaction of blood products[4].

Previous studies have demonstrated that the use of CPB during cardiac surgery reduces plasma vitamin C (VC) during and after surgery[1,5], decreasing by approximately 70% by 24 hours after surgery and may remain low for up to 2 weeks[6]. VC is a water-soluble vitamin that is not stored in the body and hence it should be replenished regularly through dietary intake[7].

Antioxidants such as VC are used to manage postoperative bleeding and inflammation after cardiac surgery. VC plays an important role in strengthening immune function, collagen synthesis, iron absorption, anemia management and capillary walls[1]. It also contributes to hemostasis to promote platelet aggregation and prevent platelet disintegration, which reduces bleeding. Additionally, the first dose of VC can facilitate effective collagen cross-linking and capillary stability, potentially preventing bleeding within 24 hours[8].

VC deficiency (below 0.2 mg/dL) has also been implicated in patients with heart disease in the pathogenesis of atherosclerosis and vascular stiffness[1]. Severe deficiency can lead to scurvy, which is a state of impaired collagen production and vascular delicate condition. The scurvy is associated with prolonged clotting time and delayed platelet aggregation, which highlights the important role of VC in the coagulation process[9].

Given the inherent nature of cardiac surgery, the need for blood and blood product transfusions is often unavoidable. However, due to the limited availability of blood reserves, the high costs associated with transfusion, the reluctance of some patients to receive blood products, and the potential for transfusion-related complications[1], efforts to reduce intraoperative and postoperative bleeding and thereby reduce transfusion requirements are of critical clinical importance.

Only a limited number of studies have examined the effects of VC on bleeding and blood product transfusion during cardiac surgery[1,10,11]. In these investigations, VC has been administered by various routes, including intravenous[1,10], oral[10], and cardioplegic solution delivery[11]. However, to date, no studies have specifically evaluated the effects of VC when included in the prime solution used during CPB.

Accordingly, the present study was conducted to investigate the effect of adding VC to the CPB prime solution on postoperative bleeding and the requirement for blood product transfusions in patients CABG.

Materials and Methods

The study was designed as a random, triple-blind, single-center, controlled clinical trial held

between 2024 and 2025. This trial was conducted in accordance with the Declaration of Helsinki and was approved by the Research Ethics Committee of Isfahan University of Medical Sciences (Code: IR.MUI.MED.REC.1403.193) and registered with the Iranian Registry of Clinical Trials (Trial Code: IRCT20200825048515N75).

With a 95% confidence level and 80% power, considering the standard deviation of drainage volume 2 hours after surgery in the tranexamic acid and tranexamic acid + Vitamin C groups in previous studies[1] equal to 20 and 15, respectively and the error level obtained from the mean of two groups equal to 0.8, the sample size of 55 patients was considered for each group. A total of 110 patients undergoing elective CABG with CPB were enrolled. Inclusion criteria included age over 35 years and EF over 30%. Exclusion criteria included undergoing concurrent cardiac surgeries along with CABG, history of VC use in the last three months, history of corticosteroid use before hospitalization, redo surgery, drug reaction and any problems during surgery and anesthesia, use of intra-aortic balloon pump or extracorporeal membrane oxygenation (ECMO), and history of celiac disease (due to its effect on VC levels) or malabsorption problems.

Prior to enrollment, all patients were provided with detailed information about the study protocol, and written informed consent was obtained. Participants who withdrew consent at any point were excluded from the study.

Then using random allocation software, these patients were divided into two groups of 55 (Fig. 1). In the intervention group, 25 mg/kg of VC was added to the CPB priming solution. In the control group, 25 mg/kg of normal saline was added instead[12]. The standard priming solution consisted of 1000 cc of Ringer's lactate, 500 cc of Voluven, and 10,000 units of heparin.

In order to achieve a triple-blind study, both

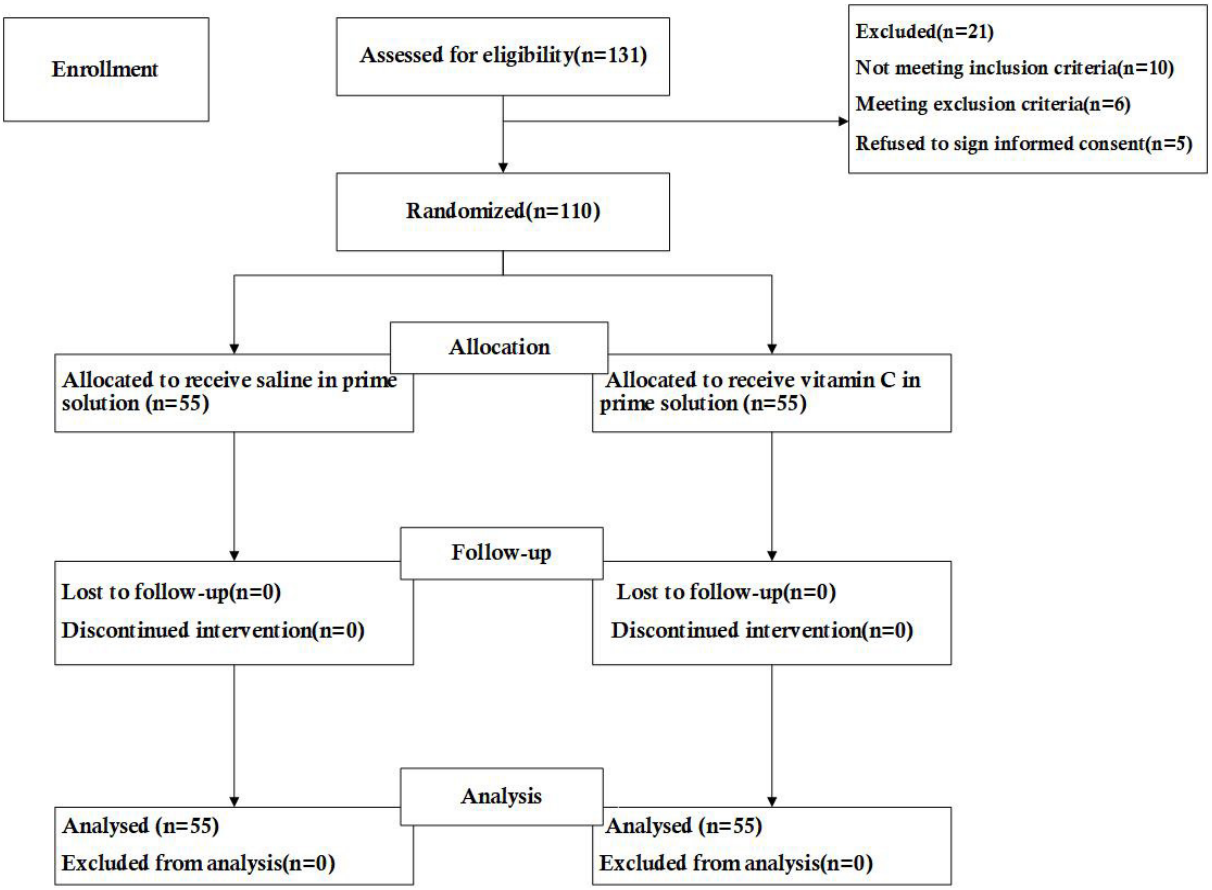


Figure 1. CONSORT flowchart showing the number of patients at each phase of the study

VC and placebo solutions were pre-prepared and labeled as "A" and "B" by the principal investigator. The perfusionist, blinded to the group allocation, added the assigned solution to the priming fluid and collected the necessary intraoperative data. intensive care unit (ICU) nurses, patients, and the data analyst were all blinded to group assignments.

Demographic information was collected preoperatively. All patients underwent standard ASA monitoring, and arterial and central venous lines (CVC) were placed. General anesthesia was induced according to the hospital's standard protocol, followed by CABG with CPB. Intraoperatively, all administered blood products were recorded.

After surgery, patients were transferred to ICU. ICU nurses recorded the amount of chest tube drainage on ICU entry, and 2, 4, 6, 12, and 24 hours[1]. They also documented the amount of blood product transfusion required during the ICU stay.

Statistical Analysis

Finally, the collected data was entered into SPSS (version 27; SPSS Inc., Chicago, Ill., USA) and was represented by frequency (percent), Mean ± SD or Median [IQR]. To compare the mean or frequency distribution of the patients' baseline characteristics between the two groups, independent sample t-test and Chi-square were used, respectively. Also, according to the result of the Kolmogorov-Smirnov test indicating the abnormality of data distribution, the Mann-Whitney test was used to compare quantitative variables (chest tube drainage or amount of blood product transfusion) between the two groups, and the Friedman test was used to compare the trend of mean changes over time. Also, the frequency percentage of blood product needs was compared between the two groups with Fisher's exact test. In all analyses, a significance level of less than 0.05 was considered.

Results

In the present study, the intervention group included 15 (27.3%) female and 40 (72.7%) male with a mean age of 62.44±7.04 years, and the control group included 15 (27.3%) women and 40 (72.7%) men with a mean age of 60.44±7.81 years. The two groups were similar in terms of basic and clinical characteristics (P > 0.05) (Table 1).

The amount of chest tube drainage in the control group was higher than that in the intervention group at all follow-up times after

Table 1. Comparison of the patients' basic and clinical characteristics between two groups

Characteristics		Intervention Group (n = 55)	Control Group (n = 55)	P-value
Gender	Female	15(27.3%)	15(27.3%)	>0.99*
	Male	40(72.7%)	40(72.7%)	
Age (years)		62.44±7.04	60.44±7.81	0.161**
Weight (kg)		73.20±10.28	74.24±14.89	0.672**
Comorbidities	Diabetes	23(41.8%)	18(32.7%)	0.430*
	Hypertension	22(40.0%)	27(49.1%)	0.443*
	Hyperlipidemia	30(54.5%)	28(50.9%)	0.849*
	Other	1(1.8%)	1(1.8%)	1.00*
Number of Grafts	2 grafts	7(12.7%)	6(10.9%)	0.949*
	3 grafts	30(54.5%)	30(54.5%)	
	4 grafts	18(32.7%)	19(34.5%)	
Aortic Clamp Time (min)		57.43±16.07	57.01±15.43	0.890**
Total Cardiac Arrest Time (min)		59.32±16.47	59.78±16.43	0.885**

*: The significance level obtained from the independent t-test to compare the means of quantitative variables between the two study groups.
**: The significance level obtained from the chi-square test to compare the frequency distribution of qualitative variables between the two study groups.

surgery, although this difference was not statistically significant (P > 0.05). In contrast, in each of the two groups, the amount of chest tube drainage increased significantly during the first 24 hours after surgery (P < 0.001) (Table 2).

The results of comparing amount transfused blood and blood product transfusion in the operating room and in the ICU between the two groups showed that the frequency of blood and platelet transfusion in the operating room was higher than in the ICU, and the lowest percentage of fresh frozen plasma (FFP) transfusion was reported. The amount transfused blood in the operating room and in the ICU in the intervention group was 1.64±0.79 and 2.14±1.17 ml, respectively, and in the control group it was 1.69±0.84 and 2.52±1.68 ml, which was not statistically significant between the two groups (P > 0.05). Also, the mean amount of platelets and FFP in the operating room and in the ICU were not significantly different between the two groups (P > 0.05) (Table 3).

Finally, according to Table 4, no postoperative complications (including atrial fibrillation (AF), stroke, and sternal wound infection) were reported, and only one patient (1.8%) died in

Table 2. Comparison of the mean amount of chest tube drainage between two groups

Amount of Chest tube drainage (ml)	Intervention Group (n = 55)	Control Group (n = 55)	P value[1]
After admission to the ICU	19.09±49.52 0[0-100]	28.18±62.92 0[0-100]	0.679
2 hours after surgery	86.36±109.05 50[0-100]	108.18±114.56 100[0-150]	0.177
4 hours after surgery	59.09±133.71 0[0-100]	70.90±121.97 0[0-100]	0.525
6 hours after surgery	85.45±137.99 50[0-100]	95.45±106.40 50[0-150]	0.326
12 hours after surgery	105.45±139.00 100[0-150]	110.90±122.73 100[0-150]	0.609
24 hours after surgery	95.45±95.39 100[0-150]	130.90±136.24 100[0-150]	0.206
P value[2]	<0.001	<0.001	

Data presented as mean ± standard deviation(SD) and median [IQR]. 1-The significance level obtained from the Mann-Whitney test comparing the variable mean rank between two groups at each time 2- The significance level obtained from the Friedman test for comparing the variable mean rank over time in each of the two groups

Table 3. Comparison of the amount transfused blood and blood product transfusions between two groups

Variables		Intervention Group (n = 55)	Control Group (n = 55)	P value[1]
Blood Transfusion				
In operating room	Transfusion	42(76.4%)	45(81.8%)	0.794
	Amount transfused	1.64±0.79 1.00[1.00-2.00]	1.69±0.84 1.00[1.00-2.00]	
In ICU	Transfusion	44(80.0%)	47(85.5%)	0.176
	Amount transfused	2.14±1.17 2.00[1.00-2.00]	2.52±1.68 2.00[1.00-3.00]	
Platelet Transfusion				
In operating room	Transfusion	35(63.6%)	45(72.7%)	0.496
	Amount transfused	4.20±1.78 5.00[1.00-5.00]	3.92±1.70 5.00[1.00-5.00]	
In ICU	Transfusion	13(23.6%)	13(23.6%)	0.296
	Amount transfused	4.69±1.11 5.00[1.00-5.00]	4.08±1.75 5.00[1.00-5.00]	
FFP Transfusion				
In operating room	Transfusion	2(3.6%)	2 (3.6%)	0.875
	Amount transfused	3.50±1.00 3.00[1.00-2.00]	5.00±1.00 5.50[1.00-2.00]	
In ICU	Transfusion	6(10.9%)	12(21.8%)	0.749
	Amount transfused	4.50±2.34 5.00[1.00-5.00]	4.25±0.96 4.00[1.00-5.00]	

Data presented as mean ± standard deviation (SD) and median [IQR]. 1- The significance level obtained from the Mann-Whitney test comparing the variable mean between two groups at each time

Table 4. Comparison of postoperative complications and outcomes between two groups

Outcomes	Intervention Group (n = 55)	Control Group (n = 55)	P value
Length of ICU stay (days)	2.75±0.72	2.65±0.61	0.480*
Length of hospital stay (days)	4.09±1.25	4.22±1.44	0.623*
Need for defibrillation after aortic unclamping	2(3.6%)	4(7.3%)	0.679**
Postoperative Complications			
AF	0(0.0%)	0(0.0%)	-
Stroke	0(0.0%)	0(0.0%)	-
Sternal wound infection	0(0.0%)	0(0.0%)	-
Final Outcome			
Alive	54(98.2%)	55(100.0%)	>0.99**
Deceased	1(1.8%)	0(0.0%)	

Data presented as frequency (percentage) or mean ± standard deviation(SD). *: The significance level obtained from the independent sample t-test comparing the variable mean between two groups **: The significance level obtained from the Fisher exact test comparing the frequency percentage of variable between two groups

the intervention group. There was no significant difference in the duration of ICU and hospital stay, and need for defibrillation after aortic unclamping between the two groups (P > 0.05).

Despite substantial advances in cardiac surgery, the management of perioperative bleeding remains a major clinical challenge. Cardiac surgery remains a high risk of bleeding, and intraoperative blood loss is often managed using allogeneic blood products, making it one of the surgical procedures with the highest transfusion rates[2]. This randomized clinical trial aimed to evaluate the effect of adding VC to the CPB prime solution on postoperative bleeding and transfusion requirements in patients undergoing CABG.

The results demonstrated that chest tube drainage in both groups was minimal upon admission to the ICU, increased between 2 and 12 hours postoperatively, and subsequently decreased within 24 hours after surgery. Although the mean drainage volume was consistently lower in the VC group compared with the control group, the difference did not reach statistical significance. Nonetheless, this finding suggests a potential hemostatic benefit from the addition of VC to the prime solution.

Blood transfusions occurred more frequently in the ICU than in the operating room for both groups. Platelet transfusions occurred predominantly intraoperatively, while FFP administration was relatively low overall. The mean volume of blood and blood product transfusion was lower in the VC group, especially in the ICU, although this reduction was not statistically significant. From a clinical perspective, even small reduction in transfused blood units can have a positive impact on patient outcomes and reduce healthcare costs.

To date, few studies have explored the effects of VC on postoperative bleeding in cardiac surgery, and most have not determined the exact amount of postoperative blood loss. Ghorbaninezhad et al.[1] compared tranexamic acid alone with tranexamic acid combined with VC in CABG patients and found that the combination reduced bleeding without affecting the incidence of AF. Similarly, Sadeghpour et al.[10] administered intravenous VC before surgery followed by oral supplementation for four days postoperatively, reporting reductions in ICU mortality, hospital length of stay, postoperative drainage, and intubation time. Jalili Shahandashti et al.[11] added VC to the cardioplegic solution during CABG and a lower rate of FFP transfusion was observed in the ICU; however, no significant differences were found in blood or platelet transfusion frequencies between the groups.

Other researchers have investigated the hemostatic effects of VC in non-cardiac surgeries, with variable results. Significant reductions in blood loss were reported during large

colorectal polypectomy[7] and total abdominal hysterectomy[8], whereas no association was observed in laparoscopic myomectomy[13], a finding likely due to the less bleeding of minimally invasive surgery. In a systematic review and meta-analysis, Abu-Zaid et al.[9] reported no significant difference in intraoperative blood loss between groups, but there was less need for blood product transfusions among patients receiving VC.

Although the physiological mechanisms of VC are similar in all surgical contexts, the pathophysiological conditions differ markedly between cardiac and non-cardiac surgery. Cardiac procedures associated with CPB expose blood to non-endothelial surfaces, triggering a strong systemic inflammatory response, hemodilution, hypothermia, and both quantitative and qualitative platelet dysfunction. Additional factors, including heparin administration and its reversal with protamine, CPB duration, and aortic cross-clamp time, further influence the risk of bleeding[3]. Therefore, findings from non-cardiac surgeries cannot be directly extrapolated to cardiac operations.

VC is a reversible reducing agent and an essential electron donor in many biochemical and enzymatic reactions. It plays an important roles in collagen synthesis, neurotransmitter production, nitric oxide synthesis, and fatty acid metabolism[14]. VC exerts both enzymatic and non-enzymatic effects: enzymatically, it facilitates collagen cross-linking, enhancing capillary integrity and tissue repair; non-enzymatically, it acts as a potent intra- and extracellular antioxidant. During hemostasis, platelet aggregation and activation form the primary hemostatic plug, a process that depletes platelet VC levels. In the subsequent fibrin-clot phase, reactive oxygen species are generated, contributing to platelet damage. As a result, VC administration may reduce secondary or functional thrombocytopenia and increase platelet-fibrin clot stability, thereby reducing primary bleeding. Furthermore, VC acts as an important cofactor for lysyl and prolyl hydroxylase, two enzymes essential for collagen biosynthesis. VC deficiency results in unstable, poorly cross-linked collagen with low tensile strength and high susceptibility to enzymatic degradation. VC supplementation promotes effective collagen cross-linking within 24 hours, improves vascular integrity, and promotes hemostasis[7]. These biochemical mechanisms may underlie the reduction in surgical bleeding observed in previous studies.

In our study, no statistically significant differences were observed between the two groups regarding postoperative complications. Neither group experienced AF, stroke, or sternal wound infection, and only one patient died in the intervention group. Considering that chest tube drainage, as well as blood and blood product transfusions, were not increased in the intervention group, the administration of VC in the CPB prime solution appears safe, without adverse effects, and can be used reliably.

This study was conducted at a single center by the same surgeon and surgical team. Therefore, all surgery-related confounding factors, including CPB duration, aortic cross-clamp time, type of procedure, surgical technique and surgeon experience, body temperature during CPB, use of hemostatic medications, and the number and type of surgical drains, were consistent between groups. This uniformity represents a major strength of the study. However, due to some limitations, baseline VC levels were not measured in patients before the intervention. Furthermore, VC was administered only intraoperatively via the prime solution and was not continued postoperatively. Although the use of a single intraoperative dose may not maintain high plasma levels throughout the postoperative period, the focus of this study was to target the critical step of endothelial injury, oxidative stress during CPB.

The absence of meta-analyses evaluating the effect of VC on bleeding and transfusion requirements in cardiac surgery suggests that robust evidence for its efficacy remains limited. As a result, we recommend that future trials, in the form of multicenter studies with larger sample sizes investigate the role of VC in reducing bleeding and transfusion needs in cardiac

surgery. Future studies should also evaluate combined intraoperative and postoperative regimens to determine the optimal dosing strategy.

Conclusion

According the results of this study, the administration of VC in the prime solution demonstrated a trend toward reduced bleeding after CABG; however, this effect was not significant. Thus, this purpose cannot be recommended based on the present findings. Also, no differences in postoperative complications were observed between the intervention and control groups. To strengthen the evidence regarding the role of VC in reducing bleeding and related complications during CABG surgery, further research is needed. In particular, larger-scale, randomized controlled trials are needed to provide more robust and generalizable findings.

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Conflict of interests

The authors declare no conflict of interest.

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Author's Contributions

Study Conception or Design: AH; MS; MM
Data Acquisition: AH; MM
Data Analysis or Interpretation: AMM
Manuscript Drafting: MS; MM
Critical Manuscript Revision: AH; AMM

All authors have approved the final manuscript and are responsible for all aspects of the work.

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