RESEARCH ARTICLE

Autologous platelet-rich plasma fibrin-glue reduces bleeding after coronary artery bypass grafting, a randomized clinical study

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Abstract

Background: Excessive bleeding is common and can be life-threatening in patients undergoing coronary artery bypass grafting (CABG) surgery. Existing conventional methods for preventing bleeding are ineffective or impractical; thus, additional strategies are required. This study used the autologous platelet-rich plasma fibrin-glue (PRP-FG) as a topical hemostatic and tissue regenerative agent to evaluate its preventive effect in postoperative bleeding in off-pump CABG surgery anastomosis.

Methods: Patients undergoing elective off-pump CABG were randomly allocated into control (16 males and ten females) and case (19 males and seven females) groups. In the control group, hemostasis was accomplished exclusively using electrocautery and overcharging. In contrast, in the case group, PRP-FG was applied in the place of distal and proximal coronary graft anastomosis and sternotomy at the end of the operation and after surgical homeostasis. Patients were closely monitored for 48 hours in the intensive care unit (ICU), and the drainage volume was estimated based on blood accumulation in the chest tube bottle. Mean hemoglobin, platelet count, international normalized ratio (INR), time of surgery, bleeding volume in the operating room, and bleeding (drainage) volume in ICU after 48 hours were documented for both case and control groups.

Results: There were no meaningful differences between the two groups regarding sex, age, mean hemoglobin, platelet count, INR, time of surgery, and bleeding volume in the operating room. A significant decrease in the postoperative bleeding volume was observed in ICU after 48 hours for the case group compared to the control group.

Conclusion: Topical application of autologous PRP-FG significantly reduces postoperative bleeding volume after CABG surgery without adding extra risks to the patient. HIPPOKRATIA 2022, 26 (4):143-146.

Keywords: Coronary artery bypass grafting, platelet-rich plasma, fibrin-glue, bleeding

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Introduction

Coronary artery disease (CAD) is one of the leading causes of death worldwide[1]. Approximately 15 % of patients presenting with CADs will require coronary artery bypass grafting (CABG) surgery. CABG is a safe method to restore the normal blood flow to an obstructed coronary artery performed worldwide with low mortality and morbidity rates. Although CABG is an excellent option for treating obstructive CAD, bleeding and red blood cell transfusions are associated with unfavorable outcomes in these patients[2,3]. Profuse postoperative bleeding increases the transfusion requirements associated with postoperative infections, ischemic incidence, and increased mortality[4,5]. It has been estimated that 10-15 % of the blood supply in the United States is used for cardiac surgery patients[6]. Patients who suffer severe bleeding stay more extended periods in the intensive care unit (ICU) and have more postoperative complications and higher hospital costs than patients who do not experience major bleeding[7,8].

All in all, transfusion leads to detrimental impacts on the human body based on the amount transfused and boosts the burden of health care resources[8]. Several strategies have been explored in clinical practice for bleeding control, including cauterization, suture ligation, and manual compression. These prophylactic and therapeutic methods decrease the need for postoperative blood transfusion[9]. Additional strategies, such as platelet-rich plasma (PRP) and fibrin clot use[8,10], are proposed when these conventional approaches are ineffective or impractical. PRP is a concentrated plasma fraction consisting of platelets in higher numbers, some growth factors, and cytokines, which are essential for tissue regeneration[10].

Fibrin clot as a topical hemostatic agent was initially

developed in 1970. It is formed from the polymerization of fibrinogen under the effect of thrombin, fibrin stabilizing factor, and calcium[11]. This agent is usually used in the liquid formulation [fibrin-glue (FG)] and is particularly beneficial for achieving hemostasis in patients with coagulation disorders. The hemostatic efficacy of FG has been ascertained in more than 20 multicenter clinical trials, showing benefits in total hip or knee arthroplasty, peripheral vascular, liver resection, donor harvest site in skin grafts, and abdominal, cardiac, pediatric extracorporeal oxygenation cannulation. FG can be applied after surgery to control residual oozing, particularly at vascular anastomoses[12,13].

In this study, in addition to the suture used for connecting two blood vessels in an anastomotic location, we applied topically autologous platelet-rich plasma FG (PRP-FG) around the anastomotic site and evaluated its preventive effect in postoperative bleeding.

Methods

The study was approved by the Ethics Committee of Mashhad University of Medical Sciences, Iran (decision No 921735/2018) and performed in 2020. Patients undergoing elective off-pump CABG were randomly allocated into control (16 males and ten females) and case (19 males and seven females) groups. This is the first reported study on using autologous PRP-FG to reduce bleeding after CABG, and as such is considered a pilot study. Therefore, after statistical consultation, we decided to randomize 52 patients in total into both groups. We used the sealed envelope method as a means of randomization and allocation concealment. Informed consent was obtained from all patients. In both groups, hemostasis was performed using bone waxing and electrocautery on the sternotomy region. In the case group, after the operation's end, four ml of PRP-FG was applied in the distal and proximal coronary graft anastomosis and sternotomy after assuring surgical homeostasis and controlling suturing efficacy. Patients were closely monitored for 48 hours in the ICU. The patients' drainage volume was estimated based on blood accumulation in the chest tube bottle. Mean hemoglobin, platelet count, international normalized ratio (INR), time of surgery, bleeding volume in the operating room, and bleeding (drainage) volume in ICU after 48 hours were documented for both case and control groups.

Preparation of autologous PRP-FG

Three days before the operation, 100 mL of blood was withdrawn from the brachial vein and poured into two 50 ml sterile, non-pyrogenic, non-cytotoxic, DNA-free conical centrifuge tubes (SPL Life Sciences Co. Ltd., Naecho Pochon, Korea), which contain six ml sterile citrate-phosphate-dextrose solution (pH 7.4). We utilized these sterile conical centrifuge tubes in all processes performed in a clean room regularly checked regarding particles, anaerobic and aerobic microbial contamination. We prepared platelets and FG according to standard procedures. The platelet growth factor was prepared by centrifugation at 800 ×g for eight min (to separate red blood cells). Subsequently, PRP centrifugation at 2000 ×g for 15 min was performed (for deposition of platelets). We utilized platelet plasma to prepare the FG. The obtained plasma, initially frozen at -70 °C, was thawed at 4 °C and centrifuged at 2300 ×g for five min, separating seven mL of fibrinogen and mixing with the platelets. The final volume was about eight mL of RPR-FG[14]. Although the preparation time in this study was designed to be 72 hours, it could be reduced to 30 hours by using a -80 °C freezer to freeze the plasma sooner. One should bear in mind that despite the reduction in the preparation time mentioned above, this product cannot be used in urgent cases.

Data analysis

All statistical analyses were conducted using the Statistical Package for the Social Sciences (SPSS) for Windows, Version 16.0 (SPSS Inc., Chicago, IL, USA). Continuous variables are presented as means with standard deviation, while categorical variables are presented as absolute values. The appropriate method for the comparison of variables was the t-test. Frequency variables were tested with a chi-squared test. We considered a p-value <0.05 to be statistically significant.

Results

The two groups had no significant differences regarding sex, age, mean hemoglobin, platelet count, INR, time of surgery, and bleeding volume in the operating room (Table 1). Also, comorbidities and numbers of grafts per patient are displayed in Table 1. A significant difference in the postoperative bleeding (drainage) volume in ICU after 48 hours was observed between the case and the control groups (329.6 ± 208.9 vs 602.8 ± 310.2, respectively; p =0.001) (Table 2).

In the control group, 14 patients (54 %) were transfused with packed cells, four patients (15 %) received fresh frozen plasma (FFP), and one patient (4 %) received platelets. In contrast, in the case group, only seven patients (27 %) were transfused with packed cells, two (8 %) received FFP, and none received platelets. The difference between patients transfused with packed cells in both groups was statistically significant (p =0.048).

In this study, no patients required re-exploratory surgery due to the low amount of postoperative bleeding in both cases and controls. No postoperative morbidities were recorded, such as tamponade, early graft failure, and acute renal failure.

Discussion

The most important finding of this study is that the topical application of autologous PRP-FG in patients undergoing off-pump CABG was safe and effective in reducing postoperative blood loss without submitting patients to additional risks[3].

Excessive bleeding after CABG surgery requires

Table 1: Comparison of sex, age, mean hemoglobin, platelet count, international normalized ratio, and time of surgery between the case and control groups, which included randomly allocated patients undergoing coronary artery bypass grafting surgery.

	Controls	Cases	p-value
Sex	M: 19, F: 7	M: 16, F: 10	0.204
Age (years)	59.8 ± 10.3	55.9 ± 9.6	0.167
Hemoglobin (mg/dL)	13.7 ± 1.9	13.2 ± 2.0	0.339
Platelets (×100,000)	238 ± 48	245 ± 54	0.558
INR	1.0 ± 0.09	1.0 ± 0.15	0.359
Time of surgery	4.5 ± 1.2	5.1 ± 1.2	0.09
Comorbidities			
Hyperlipidemia	16	10	
Hypertension	12	11	
Diabetes	19	10	
Myocardial Infarction	6	0	
Renal Disease	1	0	
Number of patients per graft number			
5 grafts	1 (3.8 %)	2 (7.7 %)	
4 grafts	8 (31.8 %)	10 (38.5 %)	
3 grafts	12 (46.2 %)	10 (38.5 %)	
2 grafts	5 (19.2 %)	3 (11.5 %)	
1 graft	0	1 (3.8 %)	

Values are presented as means ± standard deviation, or absolute values with percentage in brackets. A p-value <0.05 is considered statistically significant. M: male, F: female, INR: international normalized ratio.

Table 2: Comparison of bleeding in the operating room and bleeding (drainage) in the intensive care unit between the case and control groups, which included randomly allocated patients undergoing coronary artery bypass grafting surgery.

	Controls	Case	p-value
Bleeding volume in the operating room (ml)	1176.9 ± 434.7	1072.6 ± 337.4	0.33
Bleeding (drainage) volume in ICU (ml)	602.8 ± 310.2	329.6 ± 208.9	**0.001**

Values are presented as means ± standard deviation. A p-value <0.05 is considered statistically significant. ICU: intensive care unit.

blood transfusion and reoperation for control of the bleeding site in case it is life-threatening bleeding[3]. This is related to increased morbidity and mortality[3,6].

Commercial FG has been used as a topical hemostatic agent in various surgical procedures to facilitate bleeding control, potentially reducing bleeding-related complications and the demand for transfusions with red blood cells[9]. There is a debate about the effects of FG on postoperative bleeding after CABG surgery. Tavilla et al reported that using FG did not result in 48-hour blood loss. This study did not support routine FG application implementation in elective-isolated CABG[15]. However, other studies demonstrated that FG could decrease bleeding complications of coronary anastomosis[6].

Wan et al compared two commercially available FGs, EVICEL (Ethicon Inc., Somerville, NJ, USA) and TISSEEL (Baxter Healthcare Corp., Westlake Village, CA, USA), and showed fewer bleeding complications and lower cost in individuals who underwent CABG surgery and received EVICEL® compared to TISSEEL®[16].

Hirayama et al used autologous fibrin glue in CABG, and bleeding did not occur in 97.8 % of anastomoses[17]. Shiono et al concluded that autologous fibrin sealant (AFS) prepared from a patient's own FFP had a potent homeostatic effect compared to commercial FG and was a valuable homeostatic agent during cardiac surgery. The amount of postoperative bleeding was slightly lower in AFG compared to the commercial FG group, but this was not significantly different[18].

Lamm et al reported a considerable risk of myocardial damage or even death in CABG individuals when commercial Tissucol® fibrin sealant (Immuno, Austria) was applied intraoperatively, related to the high amount of thrombin and its release from the clot[19].

Our innovation in the current study was adding PRP in autologous FG to increase the regenerative effect on anastomosis in CABG surgery. PRP includes a cocktail of tissue regenerative growth factors, which play a significant and essential role in tissue repair[14]. Commercial FG contains no growth factors due to the harsh procedures in its preparation to eliminate any blood-borne diseases; therefore, in this study, autologous PRP-FG was applicated instead of allogenic FG. Autologous PRP-FG decreases the costs and prevents blood-borne diseases that can be transmitted via commercially available FG. Since autologous thrombin was used, therefore there are no immunological risks. It should be noted that commercial FG is expensive, whereas the preparation of autologous PRP-FG costs almost one-fifth of commercial products[20].

Dyke et al introduced a universal definition for peri-

operative bleeding (UDPB) consisting of a simple 5-class system[21]. They mentioned that excessive bleeding after cardiac surgery remained a complex clinical problem despite significant advances in surgical techniques. They reported a general agreement that the less the bleeding, the better it is, and avoiding transfusion is a laudatory goal. In the present study, bleeding was reduced from approximately 600 ml to 330 at 48 hours, which was statistically significant. However, it was completely insignificant in clinical terms as it is classified as Class 0 bleeding according to Dyke's classification. The critical point of this study is that the topical application of autologous PRP-FG in patients undergoing off-pump CABG caused a significant reduction in postoperative blood loss, which may be very important in clinical terms in other classes, in which patients need a blood transfusion[21].

The limitations of this study are i) the limited number of patients and ii) the performance of this clinical study just in a single academic institution. Therefore, there is a need to do a subsequent multi-institutional study with a larger sample size selected, which would determine the accuracy of the study's reported results.

In conclusion, autologous PRP-FG could remarkably decrease postoperative bleeding after CABG surgery which is cost-effective and without adding extra risk to the patient.

Conflict of interest

All authors report no conflicts of interest relevant to this article.

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