

Original Article

Effects of the Preoperative Administration of a Fibrinogen Concentrate on Bleeding and Transfusion Requirements in Cardiac Surgery

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ABSTRACT

Background: Contact of blood with the cardiopulmonary bypass (CPB) circuit during cardiac surgery induces acquired multifactorial coagulopathy, which results in an increased risk of bleeding and transfusion requirements. In this study, we investigated the effects of the preoperative administration of fibrinogen concentrates on bleeding and transfusion requirements in cardiac surgery.

Methods: Seventy-eight patients scheduled for elective coronary artery bypass graft (CABG) or valvular surgery were included in this clinical trial between March 2017 and November 2017. The patients were randomly assigned to fibrinogen and control groups. In the fibrinogen group, the patients received 2 g of fibrinogen dissolved in 100 mL of normal saline over a 15-minute period 30 minutes after the induction of anesthesia. In the control group, the patients received the same volume of normal saline during the same period of time. The evaluation of the coagulation system was performed via thromboelastometry (Rotem device). Postoperative bleeding was recorded as the overall mediastinal drainage or the other drainage at the surgical site during a 24-hour period after surgery. The volumes of transfused packed red blood cells, fresh frozen plasma (FFP), and platelet concentrates were recorded.

Results: The value of Fibtem-MCF did not show any significant difference between the groups (12.4 ± 4 vs 11.7 ± 4 ; $P=0.46$). The mean volume of bleeding was significantly lower in the fibrinogen group than in the control group (168 ± 12 vs 344 ± 37 ; $P=0.001$). The mean volume of the platelet concentrate used was significantly lower in the fibrinogen group than in the control group ($P<0.05$). However, there was no significant difference in terms of RBCs and FFP consumption between the groups.

Conclusions: It appears that although preoperative supplementation with fibrinogen has no effect on transfusion with RBCs and FFP, it results in a reduction in postoperative blood loss and platelet concentrate requirement during cardiac surgery. (*Iranian Heart Journal 2019; 20(1):39-44*)

KEYWORDS: Fibrinogen, Cardiac surgery, Transfusion

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Excessive perioperative bleeding during cardiac surgery with cardiopulmonary bypass (CPB) is a serious condition which is accompanied by an increased risk of transfusion, morbidity, and mortality. The management of perioperative bleeding can efficiently decrease the amount of the transfusion of blood products and transfusion-related complications.¹⁻⁴

The cause of bleeding is often multifactorial and includes numerous variables such as platelet dysfunction, factor consumption, and increased fibrinolysis. Fibrinogen is a critical coagulation factor which is converted into fibrin by thrombin and forms a clot at the site of tissue damage. Several studies have shown that the concentration of fibrinogen decreases during CPB in cardiac surgery.^{1, 5-8} Low preoperative concentrations of plasma fibrinogen may be directly associated with the amount of postoperative bleeding.⁹ Recently, fibrinogen concentrates have been considered an alternative to blood product transfusion in hemostatic management because of their rapid reconstitution and easy administration.¹⁰⁻¹² However, there are contradictory reports about the impact of preoperative supplemental fibrinogen on outcomes in patients without hypofibrinogenemia. The aim of the present study was to investigate the effects of the preoperative administration of a fibrinogen concentrate on bleeding and transfusion requirements in cardiac surgery.

METHODS

This randomized controlled trial was conducted in Rajaie, Cardiovascular, Medical, and Research Center (RCMRC), a tertiary care center for cardiovascular patients in Tehran, Iran, from March to November 2017. The study protocol was approved by the Ethics Committee of RCMRC. A total of 78 patients scheduled for first-time elective coronary artery bypass grafting (CABG) or valvular surgery were included. Patients with known defects of the

hemostatic system or liver diseases, known hypofibrinogenemia, preoperative hemoglobin values of less than 12 g/dL, preoperative platelet counts of less than 100 000/mm³, left ventricular ejection fractions of less than 35%, and serum fibrinogen levels of less than 3.5 g/L were not included. All the patients were fully informed before they signed a written consent form before registration.

Randomization and intervention

The study population was randomized to 2 groups of fibrinogen and control using a computer-generated randomization list. The method of randomization was permuted balanced block (block of 4). In the fibrinogen group, the patients received 2 g of fibrinogen dissolved in 50 mL of normal saline over a 15-minute period 30 minutes before the induction of anesthesia. In the control group, the patients received the same volume of normal saline during the same period of time.

Anesthetic protocol

A balanced type of anesthesia which was comprised of 1 mg of intravenous (IV) midazolam, 8 g/kg of IV fentanyl, 3 mg/kg of IV sodium thiopental, and 0.1 mg/kg of IV pancuronium bromide, followed by a continuous infusion of remifentanyl and isoflurane, as well as boluses of fentanyl or sufentanyl, was administered to maintain an end-tidal concentration of 1% to 2% until the initiation of CPB. Before cannulation for CPB, an IV bolus of 300 U/kg of heparin was administered to all the patients to achieve a target activated clotting time (ACT) of greater than 430 to 480 seconds. An additional dose of heparin was administered if the ACT value was less than the expected value.

Point-of-care coagulation testing

During CPB rewarming, blood samples were taken for thromboelastometry. The FIBTEM and HEPTM tests including the coagulation time (CT) and maximal clot firmness (MCF)

parameters were performed using the ROTEM system (ROTEM Delta, GmbH, Munich, Germany). In the HEPTEM test, heparinase was added to detect the anticoagulant effects of any residual heparin. In the FIBTEM test, the extrinsic pathway of the coagulation system was activated by tissue factor, and also cytochalasin as a potent platelet inhibitor was added. MCF in the FIBTEM test reflects the strength of the clot due to fibrinogen levels and fibrin polymerization.

Study end points

The end points of the study were postoperative bleeding and transfusion requirements. Postoperative bleeding was defined as the overall mediastinal drainage or other drainages at the surgical site during the first 24 hours after surgery. Furthermore, the amounts of transfused packed red blood cells (RBCs), fresh frozen plasma (FFP), and platelets during the first postoperative day were also documented.

Statistical Analysis

The data were described as means \pm standard deviations for the scale data and counts (percentages) for the nominal variables. The one-sample Kolmogorov–Smirnov test was applied to investigate the fitness of the interval data to a normal distribution. Comparisons of the continuous variables between the 2 study groups were made using the independent samples *t* (or the Mann–Whitney *U*) test for the scale and the Pearson χ^2 (or the Fisher exact) test for the nominal variables. The significance level was considered to be a *P* value equal to or less than 0.05. All the study data were analyzed using SPSS 15.0 for Windows (SPSS Inc, Chicago, IL, USA).

RESULTS

The study population was comprised of 78 patients, who were randomized to the fibrinogen group (*n*=38) and the control group (*n*=40). There were no significant differences

between the groups regarding the basic patient characteristics and intraoperative data (*P*>0.05) (Table 1). Table 2 shows the comparisons of various thromboelastometry parameters between the groups. Among the thromboelastometry parameters, CT in HEPTEM and FIBTEM was longer in the fibrinogen group than in the control group (*P*=0.04). There were no differences in the MCF of the HEPTEM and FIBTEM tests between the study groups (*P*=0.4).

We also compared the postoperative laboratory testing results between groups. As Table 3 shows, hemoglobin was significantly higher in the fibrinogen group than in the control group (9.9 ± 1.0 vs 8.9 ± 1 ; *P*=0.008). Furthermore, mediastinal drainage (*P*=0.01) and total bleeding (*P*=0.001) were significantly lower in the fibrinogen group than in the control group. The other variables were similar in both groups (*P*>0.05). The consumption of perioperative transfused blood product units is compared between the 2 groups in Table 4. The volume of the consumed platelets was lower in the fibrinogen group than in the control group (*P*=0.03). However, the consumption of RBCs and FFP revealed no significant difference between the groups (*P*>0.05).

DISCUSSION

The main finding in this study was that preoperative supplementation with fibrinogen resulted in a reduction in postoperative blood loss and transfusion requirements in cardiac surgery. CPB induces multifactorial coagulopathy in patients undergoing cardiac surgery, which results in bleeding and increased transfusion requirements. The contact of blood with the CPB circuit strongly activates both primary and secondary hemostases during surgery, resulting in an extensive consumption of coagulation factors, especially fibrinogen.^{6,7,13,14} We hypothesized that preoperative supplemental fibrinogen might compensate for the reduction in fibrinogen during CPB. Within

thromboelastometry tests, the MCF parameter in FIBTEM is used for clot formation and stability evaluation. Accordingly, we assayed MCF-FIBTEM as a parameter which reflects fibrinogen levels and fibrin polymerization. Surprisingly, there was no significant difference in the mean of MCF-FIBTEM between the intervention and control groups. This finding is consistent with the results of a study by Karlsson et al,¹⁵ who reported that the infusion of a prophylactic fibrinogen concentrate had no effect on thromboelastometry parameters. These results could be explained by the effects of CPB on the other coagulation factors including the von Willebrand factor and factor XIII as critical factors for clot formation and stability, which are not detectable by the FIBTEM test.

Various studies have shown weak-to-moderate correlations between fibrinogen levels and blood loss in cardiac surgery.¹⁶ Bosch et al¹⁷ surveyed the correlation between thromboelastometry parameters and blood loss after cardiac surgery. Their results indicated the most significant association between blood loss and MCF-FIBTEM parameters. In our study, the patients who received supplemental fibrinogen had significantly less bleeding than did the control group. Furthermore, the mean of postoperative hemoglobin was significantly higher in these patients. Prophylactic supplemental fibrinogen in patients undergoing cardiac surgery without documented hypofibrinogenemia has so far been surveyed in only a few studies. Other investigations have yielded conflicting results in relation to the prophylactic administration of fibrinogen in cardiac surgery. Karlsson et al¹⁵ and Sadeghi et al¹⁸ reported similar results to our study, whereas Jeppsson¹² did not find any significant influence on postoperative bleeding. These findings could be explained by the difference in the sample size or the type of surgery between the studies. The sample size in our study was greater than that in the previous

studies. Moreover, patients with CABG or valve surgery were included in our study.

Several studies have reported high consumption rates of blood and blood products in cardiac surgery.^{19,20} Blood transfusion is introduced as a supportive care; however, in some cases, it is associated with adverse events such as infection and transfusion-associated circulatory overload. Patient blood management is an evidence-based approach aimed at reducing the need for a blood transfusion and improving the patient outcome. In this study, the use of supplemental fibrinogen resulted in a reduction in platelet consumption.

CONCLUSIONS

There have been a variety of studies on the use of fibrinogen in the management of bleeding and transfusion. Nonetheless, there is a dearth of evidence regarding the usefulness of supplemental fibrinogen in cardiac surgery. According to the results of our study, supplemental fibrinogen in patients without hypofibrinogenemia undergoing cardiac surgery resulted in a reduction in postoperative blood loss and transfusion requirements.

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