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SCIENTIFIC ARTICLE

A randomized, double blind trial of prophylactic fibrinogen to reduce bleeding in cardiac surgery

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KEYWORDS
Blood transfusion;
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Abstract
Background and objectives: Postoperative bleeding has a great clinical importance and can contribute to increased mortality and morbidity in patients undergoing coronary artery bypass graft surgery. In this prospective, randomized, double-blind study, we evaluated the effect of prophylactic administration of fibrinogen concentrate on post-coronary artery bypass graft surgery bleeding.
Methods: A total of 60 patients undergoing coronary artery bypass surgery were randomly divided into two groups. Patients in the fibrinogen group received 1 g of fibrinogen concentrate 30 min prior to the operation, while patients in the control group received placebo. Postoperative bleeding volumes, prothrombin time, partial thromboplastin time, INR, hemoglobin and transfused blood products in both groups were recorded. A strict red blood cell transfusion protocol was used in all patients.
Results: There were no significant differences between intra-operative packed red blood cells infusion in the studied groups (1.0 ± 1.4 in fibrinogen group, and 1.3 ± 1.1 in control group). Less postoperative bleeding was observed in the fibrinogen group (477 ± 143 versus 703 ± 179, $p = 0.0001$). Fifteen patients in the fibrinogen group and 21 in the control group required post-op packed red blood cells infusion ($p = 0.094$). No thrombotic event was observed through 72 h after surgery.
Conclusion: Prophylactic fibrinogen reduces post-operative bleeding in patients undergoing coronary artery bypass graft.

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PALAVRAS-CHAVE
Transfusão de sangue;
Sangramento;
Cirurgia cardíaca;
Circulação extracorpórea;
Hemostasia

Estudo randômico e duplo-cego de profilaxia com fibrinogênio para reduzir o sangramento em cirurgia cardíaca

Resumo
Justificativa e objetivo: A hemorragia no período pós-operatório é de grande importância clínica e pode contribuir para o aumento da morbidade e mortalidade em pacientes submetidos à cirurgia de revascularização coronária. Nesse estudo prospectivo, randômico e duplo-cego, avaliamos o efeito da administração profilática de concentrado de fibrinogênio sobre o sangramento após cirurgia de revascularização coronária.
Métodos: No total, 60 pacientes submetidos à cirurgia de revascularização coronária foram randomicamente divididos em dois grupos. Os pacientes do grupo fibrinogênio receberam 1 g de concentrado de fibrinogênio 30 minutos antes da operação, enquanto os doentes do grupo controle receberam placebo. Os volumes de sangramento no pós-operatório, tempo de protrombina, tempo de tromboplastina parcial, INR, hemoglobina e hemoderivados transfundidos em ambos os grupos foram registrados. Um protocolo de conduta rigoroso para transfusão de hemácias foi usado em todos os pacientes.
Resultados: Não houve diferenças significantes entre as infusões de concentrados de hemácias nos grupos estudados ($1{,}0 \pm 1{,}4$ no grupo fibrinogênio e $1{,}3 \pm 1{,}1$ no grupo controle). O grupo fibrinogênio apresentou menos sangramento no pós-operatório (477 ± 143 versus 703 ± 179, $p = 0{,}0001$). Quinze pacientes do grupo fibrinogênio e 21 do grupo controle precisaram de infusão de concentrado de hemácias no pós-operatório ($p = 0{,}094$). Evento trombótico não foi observado durante 72 h após a cirurgia.
Conclusão: Profilaxia com fibrinogênio reduz o sangramento no período pós-operatório de pacientes submetidos à revascularização coronária.

Introduction

Optimal prevention and management of intra- and post-operative bleeding has a great clinical importance in various types of surgeries, including coronary artery bypass graft surgery (CABG). Such management can efficiently decrease the amount of blood products transfusion and as a result, may lead to less transfusion related complications.

Two to 6 percent of CABG surgery patients would be re-explored due to intraorpost-operative hemorrhage, which can lead to high morbidity and mortality rates. Furthermore, complications such as sternal wound infections are more frequent along with post-operative transfusion.[1–2] Consequently, the importance of any approach or intervention to decrease intra- or post-operative hemorrhage is obvious.[2] Coagulopathy is one possible reason of excessive bleeding during and following surgery. Multiple factors including platelet dysfunction, fibrinolysis and coagulation factor deficiencies may affect post-operative bleeding following cardiac surgery.[3]

During CABG surgery, low fibrinogen plasma concentration may directly be associated with blood loss.[4] This association is likely since fibrinogen is essential in the cross-linking of platelets during primary hemostasis and plays a central role in the coagulation cascade,[5] and it had been shown that following hemorrhage, fibrinogen concentration decreases more than other coagulationfactors.[6–9]

The purpose of present study was to investigate the effect of pre-operative infusion of fibrinogen concentrate on post-operative bleeding volume in CABG surgery patients. The percentage and amount of transfused blood products were considered as secondary outcome parameters.

Methods

Following the approval of the study protocol by the Institutional Ethics Committee, this trial was registered by the Iranian Registry of Clinical Trial. All participants provided a written form of consent after they were fully informed of nature and design of the study.

Sixty patients, scheduled for first time elective CABG, were enrolled in this double-blinded randomized placebo-controlled clinical trial. The patients with the following criteria were not considered eligible to take part in this study: previously diagnosed hematologic or liver diseases, uncontrolled or insulin dependent diabetes, pregnancy, unstable angina, serum creatinine more than 130 μmol/L, left ventricular ejection fraction less than 35%, serum fibrinogen levels more than 3.5 g/L. The patients also needed to be mentally capable of giving a written informed consent.

Using a computer generated randomization list, patients were assigned to fibrinogen and control groups. All the required study drugs were prepared by an anesthetist who was not involved in the surveillance of the patients. Furthermore, all the fluid plastic containers were covered by textile, so content of plastic containers was invisible.

Anticoagulant therapy with aspirin, warfarin and clopidogrel was discontinued 48 h prior to surgery. On arrival to the operating room, all the patients received oxygen via a facemask at a rate of 4 L/min, and an 18-gauge intravenous catheter was placed in a peripheral vein to allow for hydration of the patients using lactated ringer's solution (7 mL/kg) and administration of medications. Standard monitoring which consisted of invasive and non-invasive arterial blood pressure, heart rate, electrocardiogram, pulse oximetry,

and capnometery was initiated and continued throughout anesthesia.

Anesthesia was induced by 1 mg of IV midazolam, 8 μg/kg of IV fentanyl and 3 mg/kg of IV sodium thiopental, and 0.1 mg/kg of IV pancuronium bromide. Prior to the start of surgery a percutaneous central venous line was placed. Isoflurane was used for maintaining general anesthesia. Before beginning of cardiopulmonary bypass, a baseline activated clotting time (ACT) was measured and an IV bolus dose of heparin (400 U/kg) was administered to all patients. Next heparin dosing was targeted to maintain ACT values more than 480 seconds. Myocardial protection techniques were identical in both groups, and priming of the blood cardioplegialine was performed on CPB with autologous blood. Identical fluid therapy was used in both groups.

In the fibrinogen group the patients received 1 gram of fibrinogen dissolved in 50 mL of normal saline over a 15 min period 30 min before induction of anesthesia. In the control group the patients were administered the same volume of normal saline during the same period of time as a placebo. All the drugs were prepared and administered by an anesthetist who was not anyhow involved in the study.

Hemoglobin concentration, platelet count, partial thromboplastin time (PTT), prothrombin time (PT) and plasma fibrinogen concentrations were measured before induction of general anesthesia and were repeated again 24 h following surgery. Plasma concentrations of fibrinogen were adjusted to a standard hematocrit of 40% according to the formula: corrected concentration = measured concentration × (standard hematocrit/measured hematocrit). Hematocrit levels were measured every 30 min until termination of bypass. Red blood cells were transfused if the intraoperative hematocrit was less than 20%. In the intensive care unit, hematocrit values less than 25% were considered as transfusion trigger. Plasma was administered in patients with ongoing bleeding and abnormal PT or PTT. Platelets were transfused with ongoing bleeding and platelets count less than 7×10^9 per liter.

Post-operative bleeding was described as the overall chest tube drainage during the first 12 post-operative hours and was recorded by a trained intensive care nurse. The amount of transfused packed red blood cells, fresh frozen plasma, and platelets during the first 24 h post-surgery were also documented. For a period of 72 h following surgery clinical signs and symptoms of thrombotic adverse effects were followed and recorded. If any of these events occurred, the patient was considered a candidate for further evaluation such as Doppler ultrasound.

Statistics

It was determined that a sample size of 18 patients in each group would be sufficient to detect a minimum of 200 mL bleeding differences in 12 h following surgery with a standard deviation of 150 mL, power of 90% and a significant level of 0.01.

Statistical analysis of the data was performed using SPSS for windows version 17 (SPSS, Chicago, IL). The distribution of data was checked by Kolmogorov–Simonov test, which consisted of a normal distribution. Group comparisons were performed with two-sample *t*-tests for continuous data. Sex was compared by χ^2 test. Statistical significance was defined as a p-value < 0.05.

Results

A total of 60 patients (70% male, 30% female) were enrolled in this study. There was no protocol violation and all of the participants were included in the analysis. Basic characteristics of the participants such as age, weight, height, aortic clamp time and number of anastomoses were similar between both groups (Table 1). Baseline and post-operative laboratory variables including PTT, PT, hemoglobin concentration and platelet count in both fibrinogen and control groups were similar (Table 2).

Post-operatively, a lower blood loss was observed in the fibrinogen group (477 ± 143) in comparison with the control group (703 ± 179) ($p < 0.0001$) (Fig. 1). Fifteen (50%) patients in the fibrinogen group and 21 (70%) patients in the control group received packed red blood cells post-operatively, and there were no significant differences in groups ($p = 0.094$). Yet, total amount of packed red blood cells infusion in groups did not differ significantly ($p = 0.096$).

Table 1 Basic characteristics of the patients and baseline coagulation values.

	Fibrinogen group	Control group
Female/male	10/20	8/22
Age (years)	59 ± 9	58 ± 9
Weight (kg)	73 ± 14	71 ± 11
Height (cm)	164 ± 8.9	164.6 ± 6.9
Base line fibrinogen ($g\,L^{-1}$)	2.7 ± 0.3	2.7 ± 0.3
Aortic clamp time (min)	52.2 ± 12.1	56.8 ± 8.0
Anastomoses (numbers)	2.8 ± 0.4	2.6 ± 0.4
Post-op packed red blood cell transfusion (*n*)	1.5 ± 1.8	2.0 ± 1.5
Heparin (units administered)	34,000 ± 9500	36,000 ± 11,000
Baseline hemoglobin ($g\,L^{-1}$)	13.8 ± 1.5	13.6 ± 1.6
PTT (s)	29.9 ± 6.4	28.8 ± 6.6
PT (s)	12.4 ± 0.9	12.4 ± 0.7
Platelets (μL^{-1})	2,570,000 ± 99,223	255,733 ± 56,774

[a] Data were presented mean ± SD.
[b] There is no significant difference between groups.

Table 2 Coagulation at postoperative day 1.

Post-operative value	Fibrinogen group	Control group
Hemoglobin ($g\,dL^{-1}$)	9.7 ± 1.39	8 ± 1.2
PTT (s)	40.5 ± 25.2	44.7 ± 18.1
PT (s)	15.6 ± 8.5	14.6 ± 2.1
Platelets (μL^{-1})	1,670,000 ± 55,000	1,680,000 ± 54,000
Fibrinogen ($g\,dL^{-1}$)	2.9 ± 0.4	2.9 ± 0.4

[a] Data were presented as mean ± SD.
[b] There is no significant difference in groups.

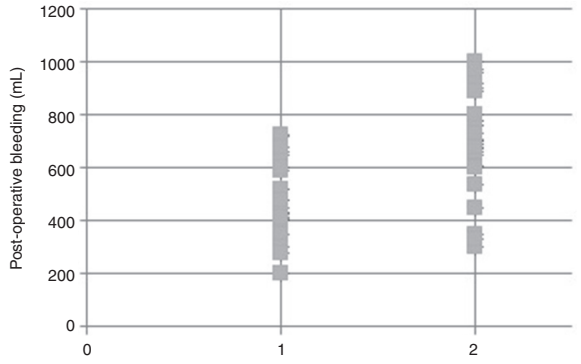

Figure 1 Post-operative bleeding (the overall chest tube drainage during the first 12 post-operative hours) in the fibrinogen group (1) compared to the control group (2).

There were no significantly differences in the number of packed red blood cells infusion in groups (1.5 ± 1.8 in the fibrinogen group, and 2.0 ± 1.5 in the control group). Four patients in the fibrinogen group received fresh frozen plasma to in comparison to 2 in the control group (ns). Only one of patients in the fibrinogen group received a platelet transfusion.

In neither of groups any clinically apparent thrombotic events were found.

Discussion

This study showed that the immediate preoperative administration of fibrinogen concentrates to CABG surgery patients can decrease post-operative hemorrhage.

Surgical bleeding is a major concern in cardiac surgery.[10] Preventing blood product transfusion and decreasing hemorrhage dependent re-exploration rates improve patients' outcomes and could lower the overall burden on health care costs.[11]

Relatively low fibrinogen concentrations may play an important role in bleeding following cardiac surgery.[12,13] Low preoperative fibrinogen level has been found to be an independent predictor of post-operative bleeding and transfusion,[13] low fibrinogen levels during and after CABG surgery were found to be associated with bleeding[14,15] and fibrinogen administration after cardiopulmonary bypass reduced the bleeding significantly.[16] And last but not least, in the so far only small prospective randomized study, Karlsson et al. showed in 20 patients that the preoperative administration of 2 g of fibrinogen decreased postoperative blood loss and minimized the decrease of the hemoglobin concentration postoperatively.[13] Our study confirms these results and expands the knowledge in a larger group of 60 patients in that already the administration of 1 g of fibrinogen is capable of reducing postoperative bleeding in patients undergoing first time CABG surgery.

Karlsson et al. also looked at thrombotic complications and concluded that the administration of 2 g of fibrinogen was safe in this regard.[12] We confirm this conclusion in a larger group of patients although we only assessed clinical thrombotic events. We thus concluded that prophylactic fibrinogen infusion significantly reduces post-operative bleeding without clinical adverse events. Yet, the investigation of Karlson et al. was a pilot study and only 10 patients participated in it. So, the power of study is not sufficient to make a strong conclusion. In our study, prophylactic administration of the lower amount of fibrinogen (1 g) could reduce the post-operative blood loss by 32%; however, the decrease in a blood transfusion was not significant but there was a trend.

In our study, the packed red blood cells infusion was not different statistically in groups; however, based on calculated p value ($p = 0.096$), it is possible that the power of the study was not sufficient to show such a difference. As the present sample size was estimated considering post-operative hemorrhage as a primary outcome, a higher powered study is necessary to assess the effect of fibrinogen concentrate administration on post-CABG packed red blood cells infusion.

There are limitations of this study such as the lack of any form of thromboelastometric monitoring (TEG or ROTEM) perioperatively and the fixed dose (1 g) of fibrinogen. Future studies with individualized and more precise coagulation monitoring are needed to define the optimal dose of fibrinogen. The rationale for choosing the present dosage was based on a previous study conducted by Karlsson et al.[13] and due to the fact that the plasma fibrinogen level was not evaluated frequently in our study aiming at decreasing the postoperative blood loss along with minimal thrombotic adverse effects.

In conclusion, administration of 1 g of intravenous fibrinogen concentrate before induction of general anesthesia in CABG surgery can reduce post-operative bleeding.

Conflicts of interest

The authors declare no conflicts of interest.

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