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Research Article

Prophylactic Use of Fibrinogen Concentrate on Postoperative Blood Fibrinogen Levels, Amount of Bleeding, and the Need for Blood Transfusion in Normofibrinogenemic Patients Undergoing Coronary Artery Bypass Graft Surgery

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ABSTRACT

Background: Different studies investigated strategies to prevent perioperative bleeding in cardiac surgeries. The use of fibrinogen concentrate is one of these efforts. In this study, we will investigate the efficacy and proper dosage of fibrinogen concentrate as a prophylactic adjuvant for reducing postoperative bleeding in patients with normal blood fibrinogen under coronary artery bypass grafting (CABG) surgery.
Methods: Patients with preoperative normal plasma fibrinogen levels were randomly divided into two groups (15 patients in each). At the final stage of cardiac surgery and after reversal of heparin, the first group received 2gr of fibrinogen IV concentrate in 15 minutes, while the other group received the same volume of placebo. In each patient, postoperative haematocrit percentage, intraoperative and postoperative administered blood products, and postoperative drainage amount were collected.
Results: Although in the study group, the postoperative amount of plasma fibrinogen increased compared to preoperative and decreased in the control group, but this change was not statistically significant. Also there wasn't any significant difference in terms of blood drainage and blood product consumption.
Conclusion: We did not find evidence of a significant difference in the change of fibrinogen blood level before and after the operation, the amount of drainage, and the consumption of blood products in the fibrinogen and placebo groups.

Introduction

Although advances in surgical techniques and technology have improved patient outcomes over recent years, severe perioperative bleeding remains a notable complication of cardiac operations, particularly when cardiopulmonary bypass is used [1]. Severe bleeding occurs in almost 10% of patients [2], and obviously, this complication will lead to blood product requirements and their side effects [3], longer hospitalization, postoperative complications [4], and increased medical system costs [5-7]. Different studies investigated strategies to prevent perioperative bleeding in cardiac surgeries. Fibrinogen concentrate has been evaluated in a variety of scenarios [8-9]. Fibrinogen is a glycoprotein with a half-life of 3 to 5 days that is produced in the liver [10]. During substantial

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hemorrhage, endogenous plasma fibrinogen is among the first coagulation components to fall below critical thresholds [11-12]. Some of the indications for fibrinogen concentrate treatment are multiple traumas, disseminated intravascular coagulation, hepatic failure, postpartum hemorrhage, and cardiac surgeries [13].

Several studies have linked lower perioperative endogenous fibrinogen concentrations with an increased likelihood of postoperative blood loss [14-16]. The European Society of Anesthesiology therefore advises the use of fibrinogen concentrate in bleeding patients who are hypofibrinogenemic [17].

The present study aims to evaluate whether prophylactic administration of fibrinogen concentrate — and the appropriate dosing for such prophylaxis — can reduce postoperative bleeding in patients who have normal preoperative plasma fibrinogen levels and are undergoing coronary artery bypass grafting (CABG).

Methods

A total of 30 patients with normal preoperative plasma fibrinogen levels (200–400 mg/dL) who were scheduled for CABG surgery in a tertiary cardiac surgery center were prospectively evaluated in a randomized case–control clinical trial. The study protocol was reviewed and approved by the Ethics Committee of Shahid Beheshti University of Medical Sciences, Tehran, Iran under number IR.SBMU.RETECH.REC.1403.349. This clinical trial has also been registered on the Iranian Registry of Clinical Trials under number 69205. Patients who were candidates for CABG were included, whereas those with a history of liver dysfunction, renal failure, or any coagulation disorder were excluded.

Participants with normal preoperative fibrinogen concentrations were randomly allocated into two equal groups (15 patients in each). At the final stage of cardiac surgery and after reversal of heparin by protamine, the first group (F group) received 2gr of fibrinogen IV concentrate in 15 minutes, while the other group (P group) received the same volume of placebo (100 ml of 0.9% normal saline) in the same duration.

In each patient, postoperative hematocrit levels, intraoperative and postoperative administration of blood products, and the total amount of postoperative drainage were recorded and analyzed.

Data analysis was carried out using SPSS software version 26. Continuous variables were expressed as mean standard deviation or as median (interquartile range). The differences between continuous variables were assessed using the independent t-test or Mann–Whitney U test. Categorical variables were compared with the Chi-square or Fisher's exact test. A P-value of less than 0.05 (two-tailed) was considered statistically significant.

Results

After meeting inclusion criteria, 30 patients enrolled in the trial. All patients were scheduled for CABG, and all patients provided written consent. 15 patients enrolled in the F group, and others participated in taking a placebo.

Among them, four patients in the P group (25%) and five patients in the F group (31.3%) were females. Statistical analysis showed no significant difference in gender distribution between the two groups (P = 0. 5). Table 1 shows information about the patient's age, height, and weight. After analyzing collected data, there wasn't any significant difference in terms of these features. Almost all of the participants were classified as ASA class III — fifteen in the placebo group and fourteen in the fibrinogen group — with no statistically significant difference between the two groups (P = 0. 5).

Cardiac preoperative ejection fraction (EF) in both groups was measured using echocardiography. The mean EF in the P group was 49.06±5.543, and in the F group it was 47.19±8.938 (P value=0.482). Three patients in the placebo group required re-exploration surgery due to excessive mediastinal bleeding, whereas no patient in the F group experienced this complication (P = 0.226). Operation information in both groups is described in Table 2. We measured fibrinogen plasma level before and after surgery (Table 3). The difference between preoperative and postoperative fibrinogen levels between groups wasn't statistically significant. In the fibrinogen group, postoperative fibrinogen levels tended to increase compared with preoperative values, while in the placebo group, a slight decrease was observed; however, these variations were not statistically significant.

Table 4 describes the amount of intraoperative and postoperative blood products consumed in each group. There wasn't any significant difference in terms of any blood product consumption. Blood drainage was measured in the operating room and after surgery. (Table 5) describes the amount of drainage in both groups.

Table 1- Demographic data

	F group	P group	P value
Age(y)	62.06±7.325	64.81±8.232	0.218
Height(cm)	164.13±7.571	167.75±9.726	0.249
Weight(kg)	73.88±10.112	77.13±12.981	0.436

Table 2- Operation information

	F group	P group	P value
Pump time (min)	118.63±19.609	122.06±25.536	0.672

Clamp time (min)	72.44±14.533	73.44±18.144	0.865
Number of grafts	3.63±0.719	3.63±0.619	1.000
Filtered volume during CPB (ml)	2643.75±929.494	2400.00±834.266	0.441

Table 3- Fibrinogen level

	F group	P group	P value
Preoperative(mg/dl)	299.06±78.736	298.61±63.473	1.000
Postoperative(mg/dl)	305.31±86.097	296.88±104.796	0.805
Amount of change (mg/dl)	6.25±122.733	-1.73±98.224	0.831

Table 4- consumed blood products

	F group	P group	P value
PC in OR (unit)	1.19±1.047	1.19±1.047	1.000
PC in ICU (unit)	1.44±0.892	1.19±0.981	0.457
FFP in OR (unit)	1.50±0.894	1.56±0.814	0.838
FFP in ICU (unit)	3.00±1.673	3.25±1.390	0.649
Plt in OR (unit)	0	0	-
Plt in ICU (unit)	0.75±1.342	2.13±3.948	0.203

Table 5- Blood drainage

	F group	P group	P value
In OR (ml)	278.12±60.467	228.12±91.230	0.079
In ICU (ml)	643.75±323.973	803.13±557.814	0.333

Discussion

Fibrinogen is in fact a key factor in the process of hemostasis, mediating platelet aggregation through its interaction with the platelet glycoprotein IIb/IIIa receptor [18]. As an acute-phase reactant, its hepatic synthesis rises after surgical trauma and the inflammatory response that is induced by cardiopulmonary bypass. Even in the absence of overt bleeding, fibrinogen contributes to several essential processes such as wound healing, tissue repair, angiogenesis, modulation of inflammation, and host defense against infection [19]. During CABG, a combination of hemodilution, consumption, and activation of coagulation pathways often results in decreased levels of some coagulation factors, like fibrinogen [20-23]. Hypofibrinogenemia can develop in nearly half of patients undergoing complex cardiac operations, impairing clot formation, as well as increasing the risk of bleeding [24-25].

Cardiac surgeries increase the risk of bleeding and blood transfusion [26]. Estimates suggest that 30% to 60% of patients require allogeneic blood products [27-29], Severe postoperative bleeding [30], blood transfusion [30-31], and surgical re-exploration [32] are all associated with increased morbidity and mortality. In order to improve patient outcomes and reduce mortality and morbidity rates, several efforts will be performed. Maintaining plasma fibrinogen within the normal or high-normal range during surgery is a strategy which may effectively reduce the need for transfusions.

This review aims to evaluate the efficiency of intraoperative fibrinogen administration in patients with normal fibrinogen levels to reduce intra- and postoperative bleeding and decrease the amount of blood products consumption. In the initial design of this study, there were 4 groups: two normofibrinogenemic groups and two hypofibrinogenemic groups. In the design, since the effectiveness of fibrinogen concentrate has been confirmed in hypofibrinogenemic patients, we considered two different doses of fibrinogen concentrate for two groups.

Significantly, the number of samples that were hypofibrinogenemic was very small, so that until the completion of the samples of the normofibrinogenemic group, only two cases of hypofibrinogenemia were included in the study. For this reason, while removing these two cases, a modification was made in the study design, and only normofibrinogenemic samples were included in the study. According to Nishi et al.'s study, the incidence of hypofibrinogenemia is 26.5% in the population of patients undergoing CABG [33], but in our study, this incidence was much lower, although it was not fully analyzed statistically.

Karlsson et al. (2008) investigated the relationship between fibrinogen plasma level and postoperative bleeding or blood transfusion after on-pump CABG [34]. Their findings demonstrated that lower preoperative fibrinogen levels were independently associated with greater postoperative blood loss. Similarly, Erodes et al. In 2018 [21] reported that administration of fibrinogen concentrate could in fact normalize clot firmness and fibrinogen activity in cases of diffuse microvascular bleeding following a cardiopulmonary bypass. However, current evidence does not support maintaining

supraphysiologic fibrinogen levels. In our study, prophylactic fibrinogen infusion in normofibrinogenemic patients did not elevate postoperative fibrinogen levels beyond physiological limits.

A meta-analysis conducted by Li and colleagues in 2018 [9], pooling data from eight randomized controlled trials, found that fibrinogen concentrate administration did not significantly affect mortality but did in fact result in a meaningful reduction in the need for allogeneic red blood cell transfusions. In contrast, our results did not show a significant decrease in transfusion requirements following intraoperative fibrinogen administration. Another investigation by Jahangirfard et al. (2018) [35] on prophylactic fibrinogen use during heart transplantation reported reduced postoperative bleeding, shorter hospital stays, and fewer transfused blood units within the first 24 hours. However, they also noted an increased incidence of acute kidney injury in the fibrinogen-treated group.

Conclusion

Several studies have been performed on the efficacy of fibrinogen's prophylactic administration on the improvement of postoperative hemostasis in hypofibrinogenemic patients under CABG surgery. However, the lack of enough studies for investigating intraoperative fibrinogen concentrate in normofibrinogenemic patients was our motivation to conduct this study. We did not find evidence of a significant difference in the change of fibrinogen blood level before and after the operation, the amount of drainage, and the consumption of blood products in the fibrinogen and placebo groups. However, the small sample size in our study creates a very significant limitation in the final conclusion. We suggest performing more studies in this area of cardiac anesthesia.

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