

Effect of Local Fibrinogen Administration on Postoperative Bleeding in Coronary Artery Bypass Graft Patients

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Abstract

Background: There are always concerns regarding postoperative bleeding in coronary artery bypass graft (CABG) patients; several different strategies have been used to compensate for it and to reduce the amount of blood transfusion. We designed this study to investigate local fibrinogen conditions in postoperative bleeding in adult patients undergoing CABG.

Materials and Methods: In a double-blind clinical trial, after matching the inclusion and exclusion criteria, 50 patients entered the study. Pre- and postoperative data, including clinical and laboratory variables were assessed. Among them, preoperative and postoperative fibrinogen levels were measured. One group received 1g fibrinogen as a 50mL solution flushed over the epicardium before sternal closure; the other received 50mL normal saline as a placebo in the same method.

Results: No difference between the two groups regarding preoperative and postoperative fibrinogen levels. Also, the two groups were the same regarding PT, PTT, INR, and platelet. However, bleeding was less and hematocrit level was higher in the local fibrinogen group.

Conclusion: Local fibrinogen could decrease postoperative bleeding in CABG patients leading to decreased need for blood transfusion.

Keywords: fibrinogen, coronary artery bypass graft, postoperative bleeding

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Introduction

Cardiovascular diseases are among the main topics imposing a great burden of disease; ischemic heart diseases being one of the leading topics. Each year, many patients with ischemic heart disease undergo coronary artery bypass graft (CABG) surgery to treat their ischemic heart disease. However, there are some postoperative complications in CABG patients, postoperative bleeding is one of them. In the current era, to avoid the administration of blood products, several different agents have been used, both topically and intravenously (1-3).

Fibrinogen is a multifunctional plasma protein that is a key protein in the coagulation cascade. Before being activated, fibrinogen is soluble; while it is changed to fibrin, it becomes insoluble and with help of platelets, forms a fibrin clot. As a matter of fact, in the pre-final step, change from fibrinogen to fibrin needs to yield the final product (4).

Often, fibrinogen as a single product is used in patients with selective fibrinogen deficiency; however, usually, there are different degrees of impaired coagulation disorders in patients after cardiac surgery, during the post bypass period. Fibrinogen is among the first factors which would be

compromised (5-8).

This study assessed the effect of local fibrinogen on the amount of postoperative bleeding, the need for blood transfusion, and lab tests of coagulation in adult patients undergoing CABG to compare the results with local placebo.

Methods

The study was approved by institutional review board (IRB) committees, Shahid Beheshti University of Medical Sciences, Tehran, Iran, regarding ethical and research considerations. Also, the study was registered and approved in the IRCT.ir with this code: IRCT201510222804N9. In a double-blind randomized clinical trial, all the patients admitted in the cardiac surgery operation room of a tertiary university hospital undergoing the first-time CABG entered the study.

By using a randomization table, the patients were randomized into the two groups of study. Just a constant surgeon was considered as the study surgeon to assimilate the patients as much as possible between the two groups.

The patients entered the study after matching the inclusion and exclusion criteria:

Inclusion criteria were:

- Age 40-75
- Elective CABG with cardiopulmonary bypass (CPB)

- Constant surgeon
- Informed written consent

The following conditions were considered as exclusion criteria:

- Emergent or urgent surgery
- Diabetes mellitus (or any of its complications like diabetic ketoacidosis or non-ketonic hyperosmolar diabetic coma)
- Any previous history of stroke or underlying cerebral vascular disease
- History of deep vein thrombosis
- History of underlying hematologic disorders
- Any carotid plaque creating significant stenosis (stenosis > 75%)
- Underlying pulmonary disorders affecting the spirometry indices significantly (>50% decrease)

- Acute renal failure
- Chronic kidney disease leading to serum Cr>2mg/dL
- Hepatic failure causing liver function test failure (>3 times than normal)
- Off-pump CABG
- Any unwanted complication in the operation period
- Re-starting CPB after weaning from bypass
- Pulmonary artery pressure >30 before the operation
- Ejection fraction<30%
- Congestive heart failure

The patients were operated on with CPB and then, after weaning from bypass and administration of protamine, one of the two following approaches was used and after that, the sternum was closed and wired with steel wires:

In the fibrinogen group, a solution including 1g of fibrinogen in 50mL volume was flushed over the epicardium just before sternal closure, and in the placebo group, 50 mL of normal saline solution is flushed to the same place.

Then, the patients were transferred to the cardiac intensive care unit to pass their normal course of postoperative care.

- The patients were controlled regarding the following variable demographic data
- Preoperative and postoperative fibrinogen levels in fibrinogen group
- Chest tube drainage at 3, 12, and 24 hours after the operation
- Need for transfusion of blood products
- preoperative and postoperative assessment of hemoglobin and platelet count
- Coagulation lab tests, both preoperative and postoperative, including PT, PTT, and INR.

Results

The results of this study demonstrated that the two groups were similar regarding age (59.5 ± 9.2 in fibrinogen group vs. 63.3 ± 8.4 in the control group; p value=0.17) and also, regarding weight (73.1 ± 11.8 in fibrinogen group vs. 73 ± 7.8 in the control group; p value=0.99). The majority of patients were male;

however, there was no difference between the two groups regarding gender (Table 1). The amount of chest tube blood drainage was significantly lower in

Table 1: Gender distribution between the two groups

	Fibrinogen group	Control group	p value
Male	10	15	0.10
Female	12	13	

the fibrinogen group in 3, 12, and 24 hours after the operation (Table 2).

On the other hand, the results of 5 other hematologic variables (PT, PTT, INR, hematocrit, and platelet) were measured (Table 3). Each of these variables was compared between the two groups before and after surgery.

The final results demonstrated no difference between the two groups regarding all these variables except for one occasion: only hematocrit level after surgery was higher significantly in the fibrinogen group which could be due to less bleeding in this group and could be in concordance with the results of chest tube blood drainage.

Discussion

The results of this study demonstrated that local fibrinogen could decrease the amount of postoperative bleeding after CABG in adult patients. Also, topical fibrinogen could improve some of the parameters in the coagulation lab tests in these patients. It seems that topical fibrinogen has been able to activate local mechanisms of coagulation; possibly without activating systemic coagulation cascade, based on the

results of fibrinogen levels in the two study groups postoperatively. In other words, local fibrinogen could improve postoperative bleeding in these patients and decrease the amount of bleeding when added as a topical flush; possibly because it improves local clot or local coagulation process.

Postoperative bleeding is a major concern after cardiac surgery; many factors predispose these patients to bleed including high heparin dose administration throughout the cardiopulmonary bypass and also, the inflammatory process imposed by the bypass circuit; also, major shifts in blood components are among the other inevitable factors predisposing these patients to bleed. Some different preventive and therapeutic strategies have been proposed to resolve this problem; for example administration of anti-fibrinolytic agents like tranexamic acid and ϵ -Aminocaproic acid or selective coagulation factor administration though none have been fully effective (9). Another study also demonstrated that plasma fibrinogen level drops after cardiac surgery (10). Systemic administration of fibrinogen in some patients has been tried with its potential side effects. However, topical fibrinogen alone has not been used yet; while the combination of topical fibrinogen–thrombin patch (TachoSil®) has been tried with relatively satisfactory results in some surgeries (11-13). In a systematic review, the effects of TachoSil were assessed based on previous studies and it was demonstrated to be effective in thoracic, urology, and liver surgeries; however, this study did not include cardiac surgeries (9). In another study, TachoSil did not demonstrate any benefit compared to conventional therapies in cardiac surgeries regarding bleeding and blood requirements (11). On the other hand, human Fibrin Glue which is composed of fibrinogen, factor XIII, fibronectin, and thrombin has been demonstrated to be effective in controlling

Table 2: Chest tube drainage in the two groups in mL

	Fibrinogen group (Mean±SD)	Control group (Mean±SD)	p value
3 hours after operation	42.5±104	135±112.5	0.009
12 hours after operation	105±114.6	317±136	0.0001
24 hours after operation	200±176.2	482.5±113.9	0.0001

Table 3: PT, PTT, INR, Hematocrit and Platelet in the two groups in before and after the operation.

Variable	Fibrinogen group (Mean±SD)	Control group (Mean±SD)	p value
PT (before surgery)	13.4±4	12.6±0.7	0.41
PT (after surgery)	15.1±5.3	13.3±1.5	0.15
PTT (before surgery)	33.4±7.1	36.8±16	0.39
PTT (after surgery)	40.1±16.6	38±7.2	0.61
INR (before surgery)	1.2±0.22	1.1±0.15	0.37
INR (after surgery)	1.3±0.28	1.2±0.14	0.25
Hematocrit (before surgery)	43.3±3.4	44.2±2.2	0.32
Hematocrit (after surgery)	37.1±6	32.5±3.3	0.004
Platelet ($\times 10^3$) (before surgery)	254.2±69.4	237.5±47	0.11
Platelet ($\times 10^3$) (after surgery)	205±50.3	192.6±50.4	0.44

bleeding in inguinal hernia repair, in a study that used Human Fibrin Glue in patients with underlying coagulation abnormalities; the results of the latter study using Human Fibrin Glue are somewhat similar to the results of our study (12).

In two other studies, prophylactic fibrinogen was used in CABG. In one study, which was a prospective randomized pilot study, the main research outcome was to assess the effect of prophylactic fibrinogen infusion on bleeding after CABG and demonstrated that preoperative fibrinogen concentrate infusion could decrease the amount of postoperative bleeding in CABG patients and increase postoperative hematocrit level; while there was no evidence of postoperative hypercoagulability or any significant effect on postoperative coagulation profile which was assessed by thromboelastography (14). Our study is different from this research because we have used local fibrinogen and also, the results of our study did not demonstrate an increased level of plasma fibrinogen in the postoperative period.

In the other study, the main study outcome was to assess the effects of fibrinogen on biomarkers of coagulation, fibrinolysis, and platelet function, this

study demonstrated that administration of systemic fibrinogen as a prophylactic agent in patients undergoing CABG has “no or minimal changes in biomarkers reflecting coagulation and platelet function” (15). Again, our study is different from the latter study because of using local fibrinogen and improved blood needs in the postoperative period; however, our results were similar since the results of our study did not demonstrate an improved coagulation profile in the lab tests during the postoperative period.

Our study had several limitations:

- We did not use thromboelastography while it could help us assess the coagulation profile better than our tests
- We did not assess other coagulation factors while they could be affected or could be different in the two groups;
- We did not assess platelet function in the postoperative period while it could be different in the two groups.
- However, we did not assay the above variables and these could be drawbacks in the study.

Conclusion

Our study demonstrated that adding local fibrinogen could decrease postoperative bleeding and decrease the need for blood products, while postoperative hematocrit level was higher in the local fibrinogen group. Meanwhile, there was no increase in the postoperative level of plasma fibrinogen; suggesting a possible effect of local fibrinogen in improving local clotting mechanisms without a significant rise in plasma fibrinogen. The latter is important because in coronary patients we are worried about increased coagulation status especially in the new coronary grafts in the postoperative period.

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Conflicts of Interest

The authors declare that there are no conflicts of interest.

References

- Colombo GL, Bettoni D, Di Matteo S, Grumi C, Molon C, Spinelli D, et al. Economic and outcomes consequences of TachoSil®: a systematic review. *Vasc Health Risk Manag.* 2014;10:569-75.
- Rousou JA. Use of fibrin sealants in cardiovascular surgery: a systematic review. *J Card Surg.* 2013;28(3):238-47.
- Payani N, Foroughi M, Dabbagh A. The Effect of Intravenous Administration of Active Recombinant Factor VII on Postoperative Bleeding in Cardiac Valve Reoperations; A Randomized Clinical Trial. *Anesth Pain Med.* 2015;5(1):e22846.
- Martinez M, Weisel JW, Ischiropoulos H. Functional impact of oxidative posttranslational modifications on fibrinogen and fibrin clots. *Free Radic Biol Med.* 2013;65:411-8.
- Ranucci M, Baryshnikova E, Colella D. Monitoring prohemostatic treatment in bleeding patients. *Semin Thromb Hemost.* 2012;38(3):282-91.
- Dell'Amore A, Caroli G, Nizar A, Cassanelli N, Luciano G, Greco D, et al. Can topical application of tranexamic acid reduce blood loss in thoracic surgery? A prospective randomised double blind investigation. *Heart Lung Circ.* 2012;21(11):706-10.
- Levy JH, Sniecinski RM. Prohemostatic treatment in cardiac surgery. *Semin Thromb Hemost.* 2012;38(3):237-43.
- Levy JH, Tanaka KA. Prohemostatic agents to prevent perioperative blood loss. *Semin Thromb Hemost.* 2008;34(5):439-44.
- Rickenbacher A, Breitenstein S, Lesurtel M, Frilling A. Efficacy of TachoSil a fibrin-based haemostat in different fields of surgery--a systematic review. *Expert Opin Biol Ther.* 2009;9(7):897-907.
- Momeni M, Carlier C, Baele P, Watremez C, Van Dyck M, Matta A, et al. Fibrinogen concentration significantly decreases after on-pump versus off-pump coronary artery bypass surgery: a systematic point-of-care ROTEM analysis. *J Cardiothorac Vasc Anesth.* 2013;27(1):5-11.
- Alizadeh Ghavidel A, Mirmesdagh Y, Samiei N, Gholampour Dehaki M. Haemostatic Role of TachoSil Surgical Patch in Cardiac Surgery. *J Cardiovasc Thorac Res.* 2014;6(2):91-5.
- Canonica S. The use of human fibrin glue in the surgical operations. *Acta Biomed.* 2003;74 Suppl 2:21-5.
- Filosso PL, Ruffini E, Sandri A, Lausi PO, Giobbe R, Oliaro A. Efficacy and safety of human fibrinogen-thrombin patch (TachoSil®) in the treatment of postoperative air leakage in patients submitted to redo surgery for lung malignancies: a randomized trial. *Interact Cardiovasc Thorac Surg.* 2013;16(5):661-6.
- Karlsson M, Ternström L, Hyllner M, Baghaei F, Flinck A, Skrtic S, et al. Prophylactic fibrinogen infusion reduces bleeding after coronary artery bypass surgery. A prospective randomised pilot study. *Thromb Haemost.* 2009;102(1):137-44.
- Karlsson M, Ternström L, Hyllner M, Baghaei F, Skrtic S, Jeppsson A. Prophylactic fibrinogen infusion in cardiac surgery patients: effects on biomarkers of coagulation, fibrinolysis, and platelet function. *Clin Appl Thromb Hemost.* 2011;17(4):396-404.