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Decreasing blood loss and the need for transfusion after CABG surgery: a double-blind randomized clinical trial of topical tranexamic acid

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Aim: Reopening sternotomy to control bleeding after coronary artery bypass grafting surgery (CABG) has been reported in 2%–7% of cases. Platelet dysfunction and activation of fibrinolytic cascade are the common causes of bleeding after on-pump CABG. Different antifibrinolytic drugs have been used to reduce bleeding. In this study, we aimed to investigate the efficacy of topical tranexamic acid in reducing postoperative mediastinal bleeding after CABG.

Materials and methods: This was a double-blind placebo-controlled randomized clinical trial on 40 patients as the control and another 40 patients as the study group. On completion of CABG before sternotomy wound closure, tranexamic acid (2 g/20 mL) or placebo (20 mL of saline) was diluted in 500 mL of warm saline (37 °C), poured into the pericardial cavity, and left for 5 min.

Results: There was no significant difference in baseline demographic data and laboratory results between the 2 groups ($P > 0.05$). Mediastinal bleeding and packed red cell transfusion requirements were significantly lower in the study group ($P \leq 0.01$). There were no complications related to topical tranexamic such as mortality, myocardial infarction, cerebrovascular accident, seizure, or renal failure.

Conclusion: Topical tranexamic acid can reduce mediastinal bleeding and packed red cell transfusion requirements after CABG.

Key words: Bypass surgery, coronary artery, tranexamic acid, postoperative hemorrhage

1. Introduction

Today, coronary artery diseases (CADs) are the most common causes of morbidity and mortality (1) and coronary artery bypass graft (CABG) surgery is a common intervention annually performed in more than 800,000 cases worldwide (2). Bleeding is a common complication after CABG. Excessive bleeding and blood transfusion play an important role in post-CABG mortality and morbidity (3–5). Patients undergoing cardiac surgery still receive more blood transfusions than in other surgical procedures, consuming 20% of blood bank reserves (6).

Reopening sternotomy to control bleeding has been reported in 2%–7% of cases (7). Blood transfusion can cause infection and immunological reactions and increase hospital length stay and cost, which justifies all efforts to reduce bleeding after CABG (4).

Activation of fibrinolytic cascade and platelet dysfunction have proven to have a major role in on-pump CABG mediastinal bleeding (3). Fibrinolysis plays a major role in 25% to 45% of cases (7).

Tranexamic acid is an antifibrinolytic agent that is substituted for more expensive drugs like aprotinin in recent years (3,4). It can be used both systemically and topically (5). Tranexamic acid binds to lysine binding sites of plasmin and plasminogen. Saturation of these sites displaces plasminogen from the fibrin surface, thus inhibiting fibrinolysis (7).

Intravenous tranexamic acid can increase risk of thromboembolism and early graft occlusion (7). This drug has been used topically in patients with a bleeding tendency and in patients taking anticoagulation medication to reduce bleeding after surgery. Tranexamic acid also has been used topically in bladder, gynecology, and ear, nose, and throat operations successfully (7). Systemic complications and the higher expense of its intravenous use prompted us to investigate the efficacy of topical tranexamic acid to reduce blood loss after CABG surgery.

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2. Materials and methods

This was a double-blind placebo-controlled clinical trial on 80 patients undergoing CABG at the Mazandaran Heart Center, Sari, Iran. The study was approved by the ethics committee of the Mazandaran University of Medical Sciences (approval number: 8411) and registered in the Iranian Registry of Clinical Trials Database (IRCT138901243646N2). After giving informed consent, patients were randomly assigned to 2 equal groups of study and control by a third party.

Patient inclusion criteria were first time on-pump elective CABG surgery with left ventricular ejection fraction of more than 35% and use of the left internal mammary artery with or without venous graft. Exclusion criteria include age of more than 75 years; advanced liver, kidney, lung, or severe peripheral vascular disease; internal carotid artery narrowing of >50%; recent myocardial infarction, New York Heart Association class 3 and 4; CABG with valve operation; insulin-dependent diabetes mellitus; reexploration; history of seizure disorder; hemoglobin (Hb) levels of <10 g/dL or hematocrit (Hct) levels of <30%; and anticoagulation usage 5 days before surgery.

Anesthetic protocol, surgical procedures, and cardiopulmonary bypass management were similar in both groups. Patients were premedicated with promethazine (25 mg) and morphine (5 mg) intramuscular injections 1 h before entering the operating room. Anesthesia in all patients was based on moderate doses of fentanyl (20 to 30 µg/kg) and midazolam (0.05 to 0.15 mg/kg), supplemented with isoflurane (<1%) or propofol (hourly rate of 2.5 to 4.0 mg/kg) during cardiopulmonary bypass (CPB). Muscle relaxation was maintained with cisatracurium. Median sternotomy was performed in all patients, and CPB was instituted through cannulation of the ascending aorta and the right atrium. Aortic palpation was used to detect atherosclerosis and, if it was present, to select an appropriate site for cannulation and clamping.

Heparin was given at an initial dose of 300 IU/kg to achieve an activated clotting time (ACT) of >480 s, and at the end of CPB it was reversed with a full dose of protamine chloride to achieve an ACT of <120 s. In all patients, blood-based St. Thomas' Hospital cardioplegic (BSTH1) solutions at 12 °C were used for myocardial protection. Distal coronary anastomoses were completed with the proximal aorta cross-clamped and the heart arrested. For proximal aortic anastomoses, the aorta was partially clamped and the heart was beating.

The CPB circuit lines were not heparin-coated and included a roller pump (Stöckert Instrumente, Munich, Germany), a hollow-fiber membrane oxygenator (Medtronic Inc., Minneapolis, USA), and a 34-µm screen arterial filter (Medtronic Inc.). Colloid (Voluven) without any blood product was used as the priming solution. During CPB, the minimum and maximum allowed Hct levels were 20% and 24%, respectively. Moderate hypothermia (32 °C) was used during CPB. During rewarming, the maximum allowed blood temperature at heat exchanger was 37.5 °C, and the maximum allowed nasopharyngeal temperature was 37 °C. The warming rate was approximately 1 °C and core temperature increased per 3–5 min during the bypass time. Perfusion was nonpulsatile, with indexed flows set at 2.4 L m^{-2} min^{-1} during cooling and rewarming and at 2.0 L m^{-2} min^{-1} during stable CPB. Mean arterial blood pressure was maintained between 60 and 80 mmHg. α-Stat acid–base management was used for all patients.

On completion of CABG before sternotomy wound closure, tranexamic acid (2 g/20 mL) or placebo (20 mL of saline) was diluted in 500 mL of saline 37 °C and poured into the pericardial cavity. Five minutes later it was cleared out and the sternotomy was then closed.

Packed red blood cells were administered when Hb decreased to <8 g/dL and/or Hct decreased to <24% during the procedures, and when Hb decreased to <10 g/dL and/or Hct decreased to <30% during intensive care. When chest drainage blood increased to >150 mL/h or to >100 mL/h for 2 consecutive hours and the international normalized ratio (INR) was >1.5, fresh frozen plasma (FFP) was administered, and when the platelet count was $<100 \times 10^9$/L, platelet concentrate was administered. Postoperatively, reexploration was performed when chest drainage was >300 mL/h for 2 consecutive hours or >200 mL/h for 3 h, or when echocardiography confirmed the presence of tamponade.

Preoperative and postoperative laboratory tests including Hb, Hct, platelet count, and coagulation tests were performed. Postoperative data, including units of transfused packed red cells, FFP, and platelet concentrate, were documented and the volume of mediastinal drainage was also measured 6, 12, and 18 h after surgery. Volume of mediastinal bleeding was the primary outcome and units of transfused packed red cells, FFP, and platelet concentrate were the secondary investigated outcome in this study.

This was a double-blind study, and with the exception of one nurse who prepared the solution, none of the patients, doctors, nurses, or laboratory staff were aware of the type of therapy. Statistical analysis was performed with SPSS 17 software using chi-square tests, Student tests, and paired t-tests.

3. Results

A total of 80 patients entered the study; 40 patients were assigned to the control and 40 to the study (tranexamic) group. During the study, no patients were excluded and data from all patients were analyzed.

The mean age of the control and case group was 59.64 ± 10.03 and 60 ± 9.64 years, respectively ($P > 0.05$). Mean

left ventricular ejection fraction was 48.96 ± 9.48% in the study group and 50.44 ± 7.3% in the control group, and the difference was not statistically significant (P > 0.05).

There were no significant differences between the 2 groups regarding smoking, opium addiction, hypertension, non-insulin-dependent diabetes mellitus, body mass index (BMI), hyperlipidemia, creatinine, bypass time, cross-clamp time, and number of grafts (Table 1).

Table 2 shows a significant difference in mediastinal drainage and mean packed red cell transfusion between the 2 groups after surgery (P < 0.01). There was no statistically significant difference for FFP and platelet transfusion between the 2 groups (P > 0.05).

Preoperative ACT was about the same in the 2 groups, but it was significantly reduced in the study group postoperatively (Table 3). Laboratory tests results (platelet count, Hb, Hct, blood sugar, blood urea nitrogen, creatinine, direct and total bilirubin, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, and white blood cell count) and body temperature were about the same pre- and postoperatively (P > 0.05). There were no complications related to topical tranexamic acid such as mortality, myocardial infarction (MI), cerebrovascular accident (CVA), seizure, reexploration, and renal failure in the postoperative period.

4. Discussion

Advances in surgical techniques and pharmacological methods did not reduce blood transfusion requirements in cardiac surgery (8). Due to hemodilution, residual effects of heparin, platelet dysfunction, and consumption of coagulation factors in the extracorporeal circuit, patients undergoing cardiac surgery can develop severe bleeding (6). Ünlü et al. suggested that ongoing subclinical hemostatic activation associated with CABG is due to decreased protein c, protein s, and fibrinogen and increased t-PA levels during CPB (9). Postoperative bleeding increases morbidity and mortality in cardiac surgery (10). There is considerable evidence to suggest that blood transfusion increases the risk of postoperative infection and mortality following cardiac surgery (11). The results of our study demonstrated that topical application of tranexamic acid can significantly reduce blood loss and the need for red blood cell transfusion in patients undergoing CABG. In a study by Jimenez Rivera et al., excessive blood loss (>1 L/24 h) was observed in 50% of the patients after elective cardiac surgery under CPB. These patients did not receive antifibrinolytic prophylaxis (12).

Jakobsen et al. showed that low-risk patients undergoing simple cardiac surgery have a more than 10% higher mortality rate if they receive perioperative red blood cell transfusion. Even a transfusion of 1–2 units seems to carry a risk (13). Paone et al. proved that red blood cell transfusion is an independent risk factor for mortality after CABG (14).

In another study in Germany, Christensen et al. showed that the average hospital costs related to excessive postoperative hemorrhage in cardiac surgery are substantial and it is associated with a significant risk of postoperative complications and death (15).

To reduce bleeding after cardiac surgery, different techniques such as autotransfusion, hemodilution, and antifibrinolytic agents such as aprotinin, desmopressin, tranexamic acid, and e-aminocaproic acid have been used (16). Topical application of tranexamic acid to decrease postsurgical bleeding after major surgical procedures is a promising strategy, but further data are needed regarding the safety of this hemostatic approach (17).

Table 1. Basic and clinical characteristics in both groups.

Variable	Control group	Study group	P-value
Sex (male)	25 (62.5%)	29 (72.5%)	>0.05
Smoking	11 (27.5%)	7 (17.5%)	>0.05
Addiction	6 (15%)	9 (22.5%)	>0.05
Hyperlipidemia	26 (65%)	25 (62.5%)	>0.05
Diabetes	15 (37.5%)	13 (32.5%)	>0.05
Hypertension	22 (55%)	24 (60%)	>0.05
BMI	27.1	26.6	>0.05
Creatinine	0.86	0.93	>0.05
Bypass time (min)	86	92	>0.05
Cross-clamp time (min)	51.8	52.2	>0.05
Number of grafts	3.1	2.9	>0.05

Table 2. Bleeding and units of blood and blood products transfusion until 18 h after operation in 2 groups.

Variable	Control group	Study group	P-value
Bleeding volume (cc)	454 ± 268	313 ± 173	<0.01
Packed red cells (U)	2.12 ± 0.9	1.45 ± 0.7	<0.01
Fresh frozen plasma (U)	2.19 ± 0.7	2.27 ± 0.8	>0.05
Platelet concentrate (U)	1.82 ± 0.5	1.94 ± 0.6	>0.05

Antifibrinolytic drugs such as tranexamic acid can reduce bleeding after orthopedic surgeries (18,19). There are also some controversies about efficacy of tranexamic acid in reducing bleeding (20,21). Used topically, tranexamic acid did not increase mortality or even morbidity and complications such as CVA, MI, and renal failure (16). Although Abrishami et al. demonstrated advantages of topical use of antifibrinolytic drugs after open heart surgery in reducing postoperative bleeding and transfusion requirements, they recommended further clinical trials (22).

In a study by Mehr-Aein et al., which was conducted on patients undergoing off-pump coronary artery bypass surgery, tranexamic acid effectively reduced postoperative blood loss and the need for allogeneic blood products after surgery. Patients in the study group (tranexamic acid) had lower postoperative D-dimer plasma levels compared with the control group (23). A systematic review and metaanalysis by Adler Ma et al. also demonstrated that tranexamic acid reduces blood transfusion after off-pump CABG surgery without adverse events (24).

Dryden et al. showed that using tranexamic acid in redo heart valve operations can reduce bleeding after surgery. Like our study, ACT was equal in both groups before surgery but reduced after topical tranexamic acid, which shows some coagulation improvement (25).

Fawzy et al. showed that topical application of tranexamic acid in patients undergoing primary CABG led to a significant reduction in postoperative blood loss without adding extra risk to the patient (7), which is in line with our findings.

In our study, the use of packed red cells in the study group was significantly lower than in the control group. In a study by De Bonis et al., the use of blood product was not statistically significant between the study (topical tranexamic acid) and control groups (26). In another study by Abdul-Azm and Abdullah, the use of topical tranexamic acid significantly reduced the use of packed red cell (27), which is compatible with our findings. In a study on patients undergoing on-pump CABG, Ghaffari Nejad et al. showed that low-dose tranexamic acid can significantly reduce blood loss and transfusion requirements without increasing mortality and morbidity (28). Fawzy et al. reported a significant reduction in platelet transfusion after local application of tranexamic acid after CABG (7), but in our study, transfusion of FFP and platelets between 2 groups was not significantly different. A recent study conducted on patients undergoing heart valve surgery demonstrated that combined use of topical and systemic tranexamic acid had no statistically significant effect on amount of postoperative hemorrhaging between study and placebo groups. However, postoperative transfusion of FFP was significantly lower in these patients (29).

Table 3. Coagulation test results in the 2 groups.

Variable		Control group	Study group	P-value
ACT (min)	Before	5.15 ± 1.9	5.26 ± 1.45	>0.05
	After	4.93 ± 1.7	2.58 ± 1.05	<0.01
INR	Before	1.05 ± 0.2	1.01 ± 0.04	>0.05
	After	1.34 ± 0.5	1.17 ± 0.3	>0.05
PT (s)	Before	12.76 ± 0.8	12.5 ± 0.5	>0.05
	After	14.67 ± 0.8	13.5 ± 1.9	>0.05
PTT (s)	Before	30.85 ± 6.8	31.23 ± 7.6	>0.05
	After	38.46 ± 2.39	40.27 ± 3.02	>0.05

Different results may be due to different protocols for dose and volume of topical tranexamic acid in the literature (7,26,29,30). In the majority of studies regarding topical tranexamic acid application, saline containing tranexamic acid was poured while tubes were clamped before closure of sternotomy and clamps were removed after closure. In contrast to these studies, the time interval was not accurate and possibly very different in each case. In our study, the time period was standardized (5 min).

One of the potential complications of tranexamic acid usage after cardiac surgery is postoperative seizure (31). Its intravenous high-dose (≥100 mg/kg) administration is associated with clinical seizures in susceptible cardiac surgery patients (32). Considering that most studies used the intravenous route for administration of this drug (32,33), no occurrence of seizure in our trial can be explained by the use of topical tranexamic acid, which certainly can result in lower systemic absorption and side effects, although no tests for systemic tranexamic acid monitoring were conducted in this study. A recent study stated that the dose of tranexamic acid may be a readily modifiable risk factor for postoperative seizures in patients after cardiac surgery (34).

In conclusion, the use of topical tranexamic acid in CABG surgery can reduce bleeding and red packed cell transfusion requirements. Consequently, tranexamic acid could be advocated for routine use topically in patients undergoing CABG.

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