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Low dose tranexamic acid effect on post-coronary artery bypass grafting bleeding

Bakhtiari Rostam Esfandiari[1], Mohammad Moazeni Bistgani[2] and Majid Kabiri[3]

Abstract

Objective: This study investigated the effects of low-dose tranexamic acid on post-coronary artery bypass surgery bleeding.

Background: Diffuse microvascular bleeding is still a common problem after cardiac procedures. This study was designed to evaluate the hemostatic effects of low-dose tranexamic acid in on-pump coronary artery bypass graft surgery.

Methods: In this prospective randomized placebo-controlled study, 150 patients who were candidates for coronary artery bypass were enrolled and randomly assigned to 1 of 2 groups (tranexamic acid or placebo). Total drainage volume and the need for transfusion as well as surgical complications were recorded and compared in the 2 groups.

Results: There was significantly less mediastinal chest tube drainage up to 48 h in the tranexamic acid group (432 ± 210 mL) compared to the placebo group (649 ± 235 mL, $p = 0.006$). In the placebo group, 43 (58%) patients were given allogeneic blood during hospital stay compared to 22 (25%) in the tranexamic acid group ($p < 0.001$). No significant difference in postoperative complications was seen.

Conclusion: The use of low-dose tranexamic acid can significantly reduce blood loss and need for transfusion, with no increase in complications.

Keywords

Antifibrinolytic agents, blood transfusion, coronary artery bypass, postoperative hemorrhage, tranexamic acid

Introduction

Diffuse microvascular bleeding is still a common problem after cardiac procedures which account for more than 700,000 surgeries per year.[1] Of these, 50%–80% were found to be of the medical rather than the surgical kind.[2] Fibrinolysis was shown to be responsible for 25%–45% of significant post-bypass bleeding.[3] Approximately 70% of these cases require antifibrinolytic therapy.[1] Systemic use of antifibrinolytics reduces postoperative blood loss. The 2 main classes of antifibrinolytics used in coronary artery bypass grafting (CABG) procedures are synthetic lysine analogues such as epsilon-aminocaproic acid (EACA) and tranexamic acid (TA), and serine-protease inhibitors (aprotinin); both classes have been widely used for this purpose and shown to decrease the incidence of blood transfusions. However, consistent data or guidelines on the type of antifibrinolytic drugs that should be used and their appropriate dose and indications are still unsatisfactory. Although antifibrinolytics reduce transfusion requirements, complication such as

[1]Department of Cardiothoracic Surgery, Faculty of Medicine, Shahr-e-kord University of Medical Sciences, Shahr-e-kord, Iran
[2]Department of Cardiothoracic Surgery, Faculty of Medicine, Shahr-e-kord University of Medical Sciences, Shahr-e-kord, Iran
[3]Department of Anesthesiology, Faculty of Medicine, Shahr-e-kord University of Medical Sciences, Shahr-e-kord, Iran

Corresponding author:
Mohammad Moazeni Bistgani, Section of Cardiothoracic Surgery, Department of Surgery, Faculty of Medicine, Shahrekord University of Medical Sciences, Shahrekord, Iran.
Email: dr_m_moazeni@yahoo.com

thromboembolism have been reported.[4–6] Thus the benefit of antifibrinolytic agents must be always measured in view of a possible increase in the risk of thromboembolic complications that could result in early graft closure. Moreover, these patients are at increased risk of cerebral, pulmonary, mesenteric and retinal artery, and venous thrombosis. Among antihemorrhagic drugs employed to prevent hemostatic derangement in cardiac surgery performed with the aid of cardiopulmonary bypass (CPB), ε-aminocaproic acid and TA, two synthetic low-cost antifibrinolytic drugs, have recently been investigated as alternatives to the more expensive drug, aprotinin. Both ε-aminocaproic acid and TA act by forming a reversible complex with plasminogen and plasmin through the lysine-binding sites, thereby preventing interaction with the specific lysine residues of fibrin. TA is approximately 10-times more potent than ε-aminocaproic acid.[7] Decline in commercial approval for aprotinin forced more clinicians to administer TA to patients at higher risk of bleeding and adverse outcomes. Intravenously administered TA (most commonly, $10\,mg{\cdot}kg^{-1}$ followed by infusion of $1\,mg{\cdot}kg^{-1}{\cdot}h^{-1}$) brought about a reduction of 29%–54% in postoperative blood loss compared to placebo, in patients undergoing cardiac surgery with CPB, with a significant reduction in transfusion requirement in some studies.[5] Among some retrospective analyses of observational data, the latest suggest an increase in mortality, in contrast to the data pertinent to the aprotinin era, among patients undergoing surgery with opening of a cardiac chamber. In addition, an increase in cerebral excitatory phenomena (seizure activity) with TA has a known mechanism and questions whether such patients should be treated with this drug.[8] This study aimed to examine potential complications and the effectiveness of systemic use of low-dose TA to reduce blood loss after CABG.

Patients and methods

After obtaining institutional ethics committee approval, all patients planned for primary isolated elective CABG at Kashani Hospital, Shahrekord, Iran, from March 2009 to November 2011, were scrutinized for this prospective randomized placebo-controlled study. Patients who had emergency surgery, rheumatic fever, bleeding diathesis (hemophilia or platelet count $<100\times10^{9}{\cdot}L^{-1}$), renal failure (creatinine $>160\,mg{\cdot}dL^{-1}$), known allergy or contraindication to TA (acquired visual defect, subarachnoid hemorrhage, gall bladder disease, emboli, venous thrombosis), recent (<7 days before surgery) intake of Plavix or heparin, or streptokinase administration within 48 h of operation, were excluded from the study. There were 150 patients (60 men and 15 women) who satisfied the inclusion criteria. They were informed about the use of TA during surgery and its side effects, and their informed consent was obtained. The patients were randomly divided into 2 groups. The TA group included 75 patients who received $10\,mg{\cdot}kg^{-1}$ of TA added to the priming solution and a bolus dose of $1\,mg{\cdot}kg^{-1}$ after weaning from CPB and infusion of protamine sulphate. Retrograde priming was not undertaken in all patients. The placebo group included 75 patients who received 100 mL of normal saline per procedure, as described for the TA group. Randomization was carried out by a staff nurse who prepared the 2 solutions in identical bottles and delivered them to the operating room. Neither surgeon, assistant, anesthetist, scrub nurse nor the perfusionist knew the composition of the administered solutions. Only one cardiac surgeon was responsible for the surgical homeostasis.

The anesthetic management and CPB conduct were standardized. All patients received heparin $300\,unit{\cdot}kg^{-1}$ before CPB to achieve a target activated clotting time $\geqslant 480$ s. During CPB, extra heparin was given if necessary to maintain the target activated clotting time. After weaning from CPB, heparin was reversed using protamine sulphate in a dose of 1 mg per 100 units of heparin, to achieve activated clotting time of 80–120 s in all patients. After transfer to the intensive care unit, continuous low-grade suction (10–15 cm H_2O) and periodic milking of the drains were applied. Hemoglobin level, hematocrit, platelet count, international normalized ratio, partial thromboplastin time, and fibrinogen level were measured prior to the operation and on arrival in the intensive care unit. The drainage of the chest tubes was measured hourly, and they were removed when the total drainage was less than 100 mL over the previous 12 h and the secretions were clear. All patients underwent a uniform transfusion protocol. If hematocrit levels were <24% or the hemoglobin levels $\leqslant 8.0\,mg\ mg{\cdot}dL^{-1}$ in the postoperative period, a blood transfusion was carried out. Postoperative complications including reoperation, myocardial infarction (new Q wave >40 ms duration on an electrocardiogram obtained on the morning of the 2nd postoperative day, increase in creatine kinase-MB 5-times the upper limit of normal, and echo findings), pericardial effusion, neurologic complications, and renal injury were recorded. Surgical reexploration was considered when coagulation variables were normal and bleeding was greater than 500 mL during the first 1 h, or >1000 mL for 4 h consecutively.

Demographic data were analyzed using descriptive tests and presented as mean ± standard deviation. Data analysis of transfusion requirements and mediastinal chest tube drainage (MCTD) was performed using Fisher's exact test, the chi-square test, and Student's

t test. To remove bias and time effects, MCTD data were analyzed using repeated measures analysis of variance. A *p* value less than 0.05 was considered statistically significant.

Results

Mean age was 54.6 ± 10.4 years in the placebo group and 54.2 ± 9.7 years in the TA group, and there was no significant difference in terms of age or sex based on the *t* test ($p = 0.94$) and Fisher's exact test ($p = 0.94$). The 48-h postoperative MCTD in the TA group was 432 ± 210 mL compared to 649 ± 235 mL in the placebo group, with a significant difference between groups ($p = 0.006$; Figure 1). In the placebo group, 43 (58%) patients were given allogeneic blood during hospital stay compared to 22 (25%) in the TA group. In this regard, there was a significant difference between groups ($p < 0.001$; Figure 2). There was no significant difference in morbidity or mortality between the 2 groups (Table 1).

Discussion

TA is used during cardiac surgery primarily to prevent fibrinolysis, but optimal doses, timing, and methods of administration of TA are still debated. In our study, 75 patients received a placebo whereas the other 75 received 10 $mg \cdot kg^{-1}$ of TA added to the priming solution and 1 $mg \cdot kg^{-1}$ after weaning from CPB and injection of protamine sulphate, which is less than the dose commonly used in cardiac surgery. We also discontinued the treatment in the postoperative period. Nevertheless, there was a significant difference between the 2 treatment groups with respect to MCTD up to 48 h and blood transfusions postoperatively. In some studies with different protocols, limited TA use during surgical procedures has been proposed;[9–12] while in other studies originating from the report of Horrow and colleagues,[13] administration of TA infusion during the first hours of the postoperative period has been supported.[14–16] The plasma concentration required to suppress fibrinolysis in vitro is 10 $mg \cdot kg^{-1}$, and to suppress plasmin-induced platelet activation, it is 16 $mg \cdot mL^{-1}$.[18–19] A study on the dose-response

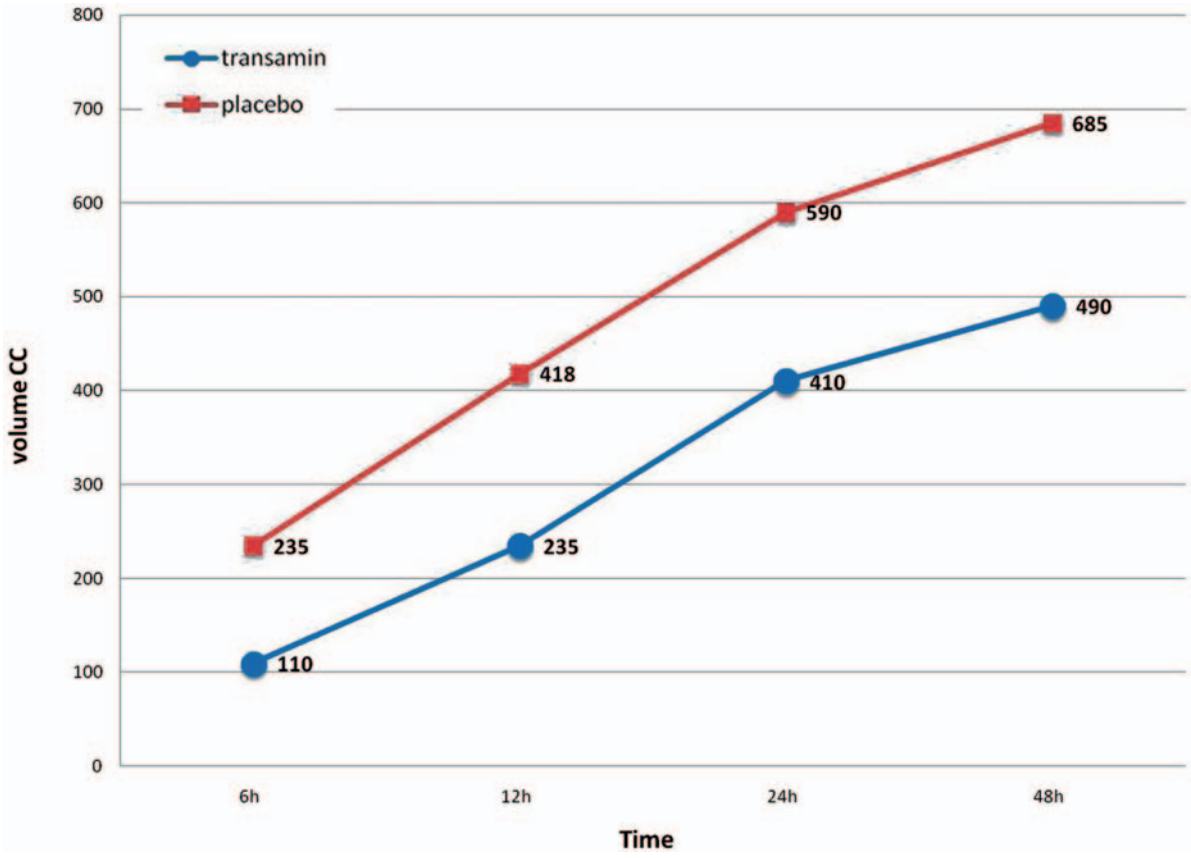

Figure 1. Postoperative mediastinal chest tube drainage.
tran: tranexamic acid; plac: placebo.

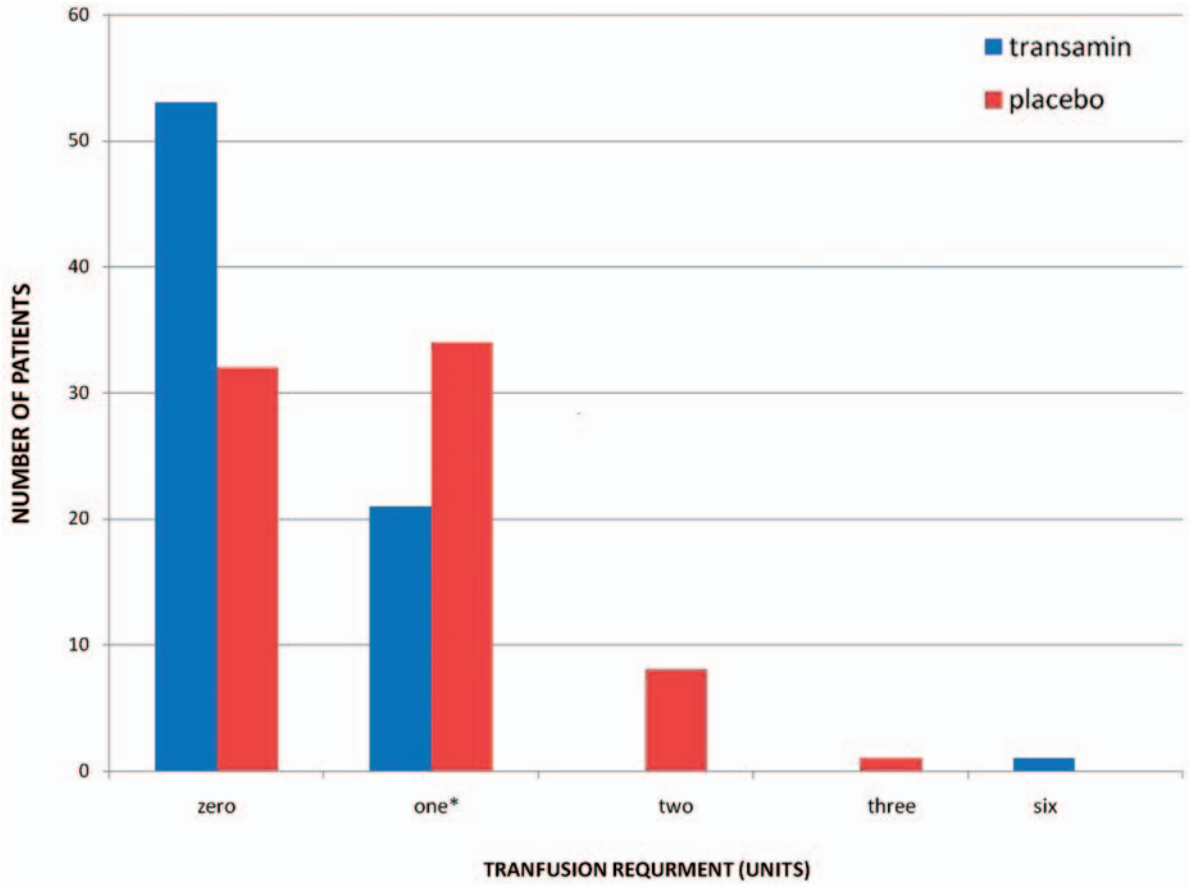

Figure 2. Postoperative blood transfusion.

Table 1. Frequency of complications in 150 patients undergoing coronary artery bypass.

Complication	Tranexamic acid	Placebo	*p* value
Reoperation	1	1	0.752
Myocardial infarction	4	1	0.341
Pericardial effusion	5	3	0.359
Cerebrovascular accident	3	5	0.359
Acute tubular necrosis	2	1	0.5
Mortality	2	2	0.69

association showed a plateau effect on drainage losses with a total dose of 3 g of TA, while no effect on transfusions was seen.[20] Intravenous TA in cardiac surgery with CPB has been administered most commonly at a dose of $10\,mg{\cdot}kg^{-1}$ followed by infusion of $1\,mg{\cdot}kg^{-1}{\cdot}h^{-1}$. TA at this dose caused reductions compared to placebo of 29%–54% in postoperative blood loss in patients undergoing cardiac surgery with CPB, and significant reductions in transfusion requirements were obtained in some studies.[5] In our study, TA treatment during the surgical procedure caused a 33% reduction in the need for allogeneic transfusions, compared to placebo, which is similar to the findings when TA was used at a higher dose.

According to our findings, consistent with the study of Casati and colleagues,[7] prolongation of treatment with TA after cardiac surgery yields no advantage over intraoperative administration alone in reducing bleeding and the number of allogeneic transfusions. A study by Pleym and colleagues[21] showed that a single dose of tranexamic acid before CPB significantly reduced postoperative bleeding in CABG patients treated with aspirin until the day before surgery. Lambert and colleagues[12] demonstrated the equivalence of the 3 doses of TA in primary cardiac surgical procedures. Our study showed that the low dose ($20\,mg{\cdot}kg^{-1}$) of TA resulted in comparable outcomes, without additional complications. In a study by Armellin and colleagues[22] in 250 patients planned for elective primary coronary revascularization, one group received TA $30\,mg{\cdot}kg^{-1}$ soon after the induction of anesthesia and the same dose was added to the CPB prime solution,

whereas the other group received TA 15 mg·kg^{-1} after systemic heparinization followed by an infusion of 1 mg·kg^{-1}·h^{-1} until the end of the operation. Transfusion of blood products, bleeding in the postoperative period, and coagulation profiles were no different between the 2 groups. The study also demonstrated that the different start times of the first infusion and dosages of TA were equally effective. It appears to be safer, in theory, to administer TA when patients are protected from thrombus formation by full heparinization.

Because the TA half-life is approximately 80 min, approximately 30%, 45%, and 90% of the dose administered is recovered in urine after 1, 3, and 24 h, respectively.[23] Probably, the doses administered after weaning from CPB are sufficient to last for the immediate postoperative period without additional doses. The heterogeneity of the fibrinolytic response to CPB was described by Chandler and colleagues[24] who also demonstrated that fibrinolysis is restricted in the postoperative period by high levels of plasminogen activator inhibitor type 1, produced as part of the systemic acute-phase response to surgical trauma. Although MCTD is a variable routinely included in studies evaluating blood conservation measures, it is only a surrogate marker of allogeneic transfusions. In our study, in the first 24 h postoperatively when hematocrit is not a suitable factor for deciding transfusion, MCTD was a helpful. In our study, 1.33% of TA patients needed reexploration for control of postoperative bleeding. However, no significant difference was observed between the 2 groups. Reexploration for bleeding following cardiac surgery with CPB is reported to be 2%–7%.[25]

Adverse effects such as nausea and diarrhea were uncommon in our patients, and TA was well tolerated, similar to the report of Dunn and colleagues.[5] Three patients in the TA group and 5 in the placebo group had a cerebrovascular accident. There was no significant difference in the frequency of cerebrovascular accident between the 2 groups. Also, we did not observe seizure activity in our patients. Neurological outcomes have long been a safety concern because administration of TA has an association with clinically significant cerebral vasospasm with acute cerebral hemorrhage.[6] Several studies have independently detected increased seizure activity.[26,27] Based on our finding, the patients in placebo group had surprisingly less postoperative myocardial infarction compared to patients in TA group, although this difference was not statistically significant. Future studies on the use of TA in cardiac surgery should systematically record postoperative myocardial ischemia and infarction. The possibility of thromboembolic complications, in particular, graft occlusion with myocardial ischemia and infarction caused by TA, must be considered when giving this drug to cardiac patients. Several publications have highlighted this issue.[28–31] There is no available evidence that prophylactic use of TA causes graft occlusion or other thromboembolic complications. However, it should be born in mind that controlled clinical studies are not suitable for detecting infrequent adverse drug reactions.[32] In our study, postoperative pericardial effusion and mortality showed no significant difference between the 2 groups.

Limitations of the study include the fact that the number of the patients was relatively small. Larger multicenter prospective controlled trials using a low dose of TA are suggested to investigate its effect in procedures with a higher risk of bleeding, such as repeat sternotomy, multiple valve, combined procedures, or aortic arch operations. We concluded that use of low-dose TA in primary isolated elective CABG operations can significantly reduce blood loss and need for transfusion, without an increase in complications.

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Conflicts of interest statement

None declared.

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