

The effect of tranexamic acid in reducing postoperative hemorrhage in patients undergoing coronary artery bypass graft

ABSTRACT

Introduction: Nowadays, cardiovascular diseases such as coronary heart disease are one of the most important causes of human mortality worldwide. Coronary artery bypass graft (CABG) surgery is a standard therapy approach for those suffering from coronary artery disease. Tranexamic acid (TXA), an antifibrinolytic drug, which, in turn, inhibits fibrinolysis, leading to the prevention of bleeding, thus, the present study aimed to evaluate the effect of topical TXA on bleeding reduction after coronary artery CABG.

Materials and Methods: In this study 62 patients were randomly divided into two groups of TXA and control. After surgery and removal from the cardiopulmonary pump, TXA (2 g) was injected locally into the mediastinum by the surgeon. In the second group (control) the same amount of normal saline (100 cc) was given. Data were analyzed by SPSS 19 software via the *t*-test and Fisher's test.

Results: A significant difference was found between the 2 groups in terms of postoperative hemorrhage, packed cell volume, platelet transfusion, duration of surgery, and received FFP ($P = 0.0001$; $P = 0.01$; $P = 0.0001$; $P = 0.0001$; $P = 0.0001$), where were found to be lower in the TXA group than in the placebo group. There was no significant difference in age, sex, return to the operating room, and discharge.

Conclusion: The use of topical TXA in GABC significantly reduced postoperative hemorrhage, packed cell volume, platelet transfusion, and FFP after surgery. Besides, it had no significant effect on the return to the operating room and mortality.


Key word: Anti-fiberinolytic; local tranexamic acid; prophylaxis

Introduction

At present, cardiovascular disease, and among them, coronary heart disease, is a leading cause of mortality worldwide.^[1] In the eastern Mediterranean and the Middle East, including Iran, cardiovascular diseases are major health and social problems that are increasing rapidly. In a sporadic study in

Iran, 25 to 45% of deaths are estimated to be associated with cardiovascular disease.^[2]

Coronary heart disease is one of the most common cardiovascular diseases that cause various complications such as angina, myocardial infarction, and heart failure, each

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of which is health problems.^[3] Coronary artery bypass graft (CABG) surgery is a standard treatment for those patients suffering from coronary artery disease,^[4] by which a bypass is made between the anterior segment of the narrowed or blocked artery and next segment through saphenous vein grafts (SVGs), thereby increasing coronary blood flow and/or reperfusion in the coronary artery is attempted through a link between the internal mammary artery and the coronary artery.^[5] Severe hemorrhage as a major cause of morbidity and mortality plays a key role in CABG.^[6] Postoperative excessive bleeding has been attributed to acquired platelet dysfunction, coagulation disorder, and increased fibrinolysis.^[7] Cardiac surgery on the pump is more associated with coagulation disorder than other types of surgery. This indicates that cardiac surgery (especially on-pump CABG) is associated with a high risk of bleeding, requiring blood transfusion in 30–70% of cases. Postoperative blood transfusion in patients with CABG has been associated with numerous side effects, including the transmission of infectious agents (e.g., hepatitis, the transmission of human immunodeficiency virus, cytomegalovirus, and other infectious agents),^[8] To this end, a variety of antifibrinolytic drugs have been introduced to decrease postoperative bleeding in CABG, including TXA.^[9]

TXA is a synthetic antifibrinolytic that is used both intravenously and topically. TXA is a lysine analog that links to lysine receptor sites in plasminogen and plasmin. Conversion of plasminogen to plasmin and displacing plasminogen from the fibrin surface could be reduced through the saturation of these sites by TXA, thereby fibrinolysis is inhibited.^[10]

Intravenous injection of TXA increases the risk of thromboembolic complications and early graft closure in CABG compared to topical use. TXA can be effectively used to control bleeding in hemorrhagic patients and those who are under treatment with preoperative anticoagulants. Also, it has been reported that topical use of TXA led to successes in the control of bleeding in the context of the bladder and oral disease, as well as laryngeal surgery.^[11] The present study aimed to assess the efficacy of topical TXA on postoperative bleeding in patients undergoing CABG.

Materials and Methods

This randomized double-blind clinical trial study was performed on patients undergoing coronary artery bypass grafting referred to Amir al Momenin Hospital in Arak, Iran. These patients were enrolled in the study after obtaining written consent and having inclusion criteria.

Inclusion criteria included: 1 - Patients candidate for elective CABG, 2- ASA Class 2 and 3, 3 - lack of sensitivity to TXA, 4 - Surgery performed by a surgeon, and 5 - Duration of surgery for 4–6 h.

Exclusion criteria included: 1 - patients with a history of cardiopulmonary bypass (CPB) 2 times during operation, 2 - All patients who die during surgery for any reason other than bleeding 3 - All patients requiring pump balloons after removal from the cardiopulmonary pump.

In this study, 62 CABG candidates were divided into two equal groups of TXA and control groups using block randomization. All of the patients received the necessary information about the study and lack of complications and then were randomly entered into the study after obtaining consent. All patients were candidates for CABG with ASA grade 2 and 3. All of the patients were elective (nonemergency) and only CABG was performed for them. Patients received pre-medication oxazepam 5 mg the night before surgery, 3 to 5 mg IV morphine and 15 to 25 mg promethazine in the morning and then went into the operating room.

After entering the operating room, 3 to 5 cc of CVC was given per kg of weight. Patients were assigned to complete monitoring including ECG, RR, SPO₂, and NIBP after being placed on a bed in the operating room. Each patient received 1 to 2 cc fentanyl to insert an arterial line for IBP monitoring. The arterial line was inserted from the radial artery by a 20 or 20 G arterial needle and transferred to the monitoring. After arterial line insertion and complete monitoring, patients were anesthetized. All patients were then given 5 to 10 µg/kg body weight of sufentanil, 0.1 mg midazolam, and 10 to 12 mg Pavulon (pancuronium). Intubation was performed and the patient was placed under anesthesia after fixation of the endotracheal tube.

Patients were then prepared to receive a CV line from the internal jugular vein. Anesthetic preservatives, including relaxants, opiates, benzodiazepines, and propofol were administered to patients with total IV anesthesia. Eventually, after the sternum incision, surgery began and the patients underwent a heart pump to perform coronary surgery. Before separation from the cardiopulmonary pump, 2 g of TXA at 100 cc was topically injected into the patient's mediastinum (intervention group) by the surgeon.

In the second group, the same amount of normal saline (100 cc) was given by the surgeon. Both the surgeon and the scrub nurse were unaware of the type of therapy and were blinded to both groups. In both groups, the solutions of the

study were prepared by the anesthesiologist. If hemodynamic conditions were stable, patients were excluded from the cardiopulmonary pump and entered the cardiac ICU with intubation.

In case of bleeding and need to re-enter the operating room, the bleeding rate was recorded in the questionnaires for all the patients after ICU admission; in addition to the number of readmissions to the operating room, the amount of bleeding was recorded after surgery based on the CC.

Other demographic data of patients including age, sex, number of grafts, and length of stay in ICU were recorded by the intern in the questionnaire. Patients were monitored in the open heart ICU during 72 h postoperatively, a maximum duration of stay in the open heart ICU, and bleeding and reoperation were recorded in the questionnaires.

The sample size was calculated based on the following formula:

$$N = \frac{(Z_{1-\frac{\alpha}{2}} + Z_{1-\beta})^2 (\delta_1 + \delta_2)^2}{(\mu_1 - \mu_2)^2} = 22$$

$$N = 22 * (\text{loss flow up patient}) = 22 * 30\% = 31$$

Data analysis

After data collection and entering into SPSS19, data were analyzed using the *t*-test and Fisher's test and the results were then reported in tables and statistical charts.

Ethical considerations

The details of the patients were kept confidential and no cost was imposed on the patient's family. Completion of the questionnaire was done with patient consent and written consent was obtained from patients. Researchers committed to ethics in research approved by the Ministry of Health and the Helsinki Declaration during the research stages, including proposal writing, sample collection, and data analysis. This research project has been approved by the Ethics Committee of the Research Council of Arak University of Medical Sciences with the code of ethics IR.ARAKMU.REC.1396.152 and IRCT: IRCT 20141209020258N62.

Results

A total of 62 patients were enrolled in the study and were divided into two equal groups of TXA and control. Data on the age of patients in the placebo and TXA groups showed that the mean and standard deviation in the TXA group were 61.94 and 9.62%, respectively, and 59.45 and 12.20% in the placebo group, respectively. There was no statistically

significant difference between the two groups in terms of age ($P = 0.377$). The number and percentage of men and women in the TXA group were 9 (29%) and 22 (71%), respectively, and in the placebo group were 7 (22.6%) and 24 (77.4%), respectively. No statistically significant difference was found between the two groups in terms of gender ($P = 0.772$).

Table 1 shows the information on the graft variable in the TXA and placebo groups. Statistically, no significant difference was found between the 2 groups in terms of the graft ($P = 0.678$).

In Table 2, information on the post-CABG hemorrhage variable in both groups was reviewed. The results showed a statistically significant difference in the post-CABG hemorrhage variable between the 2 groups ($P = 0.0001$).

The results of the packed cells received in both groups showed that the mean and standard deviations were 1.42 and 0.92%, 3 and 1.13% in the placebo group, respectively. These results show a statistically significant difference in the packed cells of patients between the two groups ($P = 0.0001$). The platelet variable was evaluated in the two groups of placebo and TXA, the mean and standard deviation in the TXA group were 1 and 1.13%, and 1.94 and 1.63% in the placebo group, respectively. The difference in platelet transfusion was significant between the 2 groups ($P = 0.011$). Furthermore, the mean and standard deviation of FFP were 0.65% and 0.66% in the TXA group and 2.03% and 1.76% in the placebo group, respectively. The difference in FFP was also significant among these groups. ($P = 0.0001$). In the case of surgery duration, the mean and standard deviation values were 4.13% and 0.40% in the TXA group and 4.85% and 0.46% in the placebo group, respectively, which shows a statistically significant difference between the placebo and TXA groups ($P = 0.0001$).

Table 1: Comparison of grafts in patients undergoing CABG

Study group	Tranexamic acid number (%)	Placebo group (%)	P
Graft 1	0 (0)	1 (3.2)	678.0
Graft 2	2 (6.5)	4 (12.9)	
Graft 3	11 (3.5)	12 (38.7)	
Graft 4	17 (54.8)	14 (4.2)	
Graft 5	1 (3.2)	0 (0)	

Table 2: Comparison of bleeding rates after CABG

Study group	Tranexamic acid number (%)	Placebo Number (%)	P
Score 1	20 (64.5)	4 (12.9)	0001.0
Score 2	7 (22.6)	2 (6.5)	
Score 3	2 (6.5)	15 (48.4)	
Score 4	2 (6.5)	8 (25.8)	
Score 5	0 (0)	2 (6.5)	

Table 3 compares the return to the operating room of the candidate patients (CABG) in the placebo and TXA groups. As seen in this table, there is no significant difference between the 2 groups ($P = 0.195$).

The number and percentage of discharge in the TXA group were found to be 31 and 100, and 29 and 93.5 in the placebo group, respectively, where there was no significant difference between the two groups ($P = 0.495$).

Discussion

Coronary artery disease is the most common heart disorder and the most common cause of death in developed countries.^[12] It is one of the most common diseases in human societies, that could be responsible for thousands of deaths annually. The treatment and control of the disease and its resulting disability impose a great deal of monetary burden on individuals and society.^[13,14] Since bleeding is one of the complications of this surgery, obtaining a suitable drug to prevent post-operative bleeding (CABG) is one of the important goals of anesthesiologists and cardiac surgeons. In the present study, we studied a population of patients who were candidates for CABG to evaluate the effects of TXA in surgery without high blood loss. The result of this study showed a significant difference between the placebo and TXA groups in terms of postoperative hemorrhage, received packed cell, platelet transfusion, duration of surgery and received FFP.

This difference was that postoperative bleeding in CABG, received packed cell, platelet transfusion, duration of surgery and received FFP were found to be lower in the TXA group than in the placebo group. This demonstrates the success of topical TXA therapy in controlling post-CABG hemorrhage. In our study, there were no significant differences in age, sex, return to operating room and discharge. This indicates that the results of our study did not correlate with the age and gender of the patients; as a matter of fact, the results were not influenced by the gender and age of the patients. A study by Hosni *et al.*, 2012 examined the effect of TXA on CABG bleeding, where 150 patients scheduled for primary coronary revascularization in patients subjected to CABG surgery. They were divided into three groups. In group A, TXA was injected before after cardiopulmonary bypass at 10 mg/kg and group B received the same amount after the pump. In group

C, only an equivalent volume of normal saline was given to the placebo. They found a higher blood loss in the placebo group after the operation (501 ± 288 vs. 395 ± 184 in group B and 353 ± 181 mL in group A, $P = 0.004$). This is consistent with the findings of our study. Besides, the mean and standard deviation of the mean packed cell volume in our study were 1.42 and 0.92 in the TXA group and 3 and 1.13 in the placebo group, respectively, showing a significant relationship between the groups ($P = 0.0001$). These results were in line with the study by Hassni *et al.*, where the mean and standard deviation of packed cell volume in the CABG group was 57.1 ± 1.25 and in groups B and C were 21.1 ± 1 and 69 ± 0.92 , respectively. The packed cell volume was significantly higher in the placebo group.^[15]

Fawzy *et al.* in 2009 also reported that platelet transfusion was significantly lower in the TXA group, which is consistent with our study, indicating higher platelet transfusion in the placebo group. Besides, the length of stay in the intensive care unit was also higher within the placebo group.^[11]

In a similar study by Abul-Azm *et al.* (2006), the effect of topical use of TXA in the pericardial cavity on postoperative bleeding was evaluated after open-heart surgery which consisted of two groups of 50 patients undergoing open-heart surgery. A significantly lower postoperative blood drainage rate and blood transfusions were found in the TXA group, which is in line with the results of our study. Contrary to our results, platelet and FFP levels were not significantly different between the two groups. On the other hand, mortality was not significantly different between the two groups that were in agreement with our findings but patients in the TXA group experienced a significantly lower duration of ICU admission and return to the operating room compared to the other group.^[16]

Conclusion

The results of our study indicate that the use of topical TXA not only has a significant effect on the reduction of bleeding after CABG but also was able to reduce the blood product transfusions, however, no significant effect was seen for mortality reduction and return to the operating room due to bleeding.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published

Table 3: Comparison of return to the operating room

Study group	No	Yes	P
	Number (%)	Number (%)	
Tranexamic acid	30 (96.8)	1 (3.2)	195.0
Placebo	26 (83.9)	5 (6.1)	

and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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