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Are systemic and topical tranexamic acid superior to each other in bleeding control in coronary bypass surgery?

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ABSTRACT

Objectives: Tranexamic acid significantly reduces postoperative bleeding and transfusion requirements in cardiac surgery. Intravenous administration has been associated with thromboembolism and seizures. The complex protocols and serious side effects associated with this administration increase interest in intrapericardial administration, and its preferability is being reviewed. The purpose of this prospective, randomized, double-blind study was to compare the effects of intrapericardial tranexamic acid administered following cardiac surgery with those of intravenous administration on postoperative bleeding and possible complications.

Methods: The study included 60 patients over the age of 18 who were undergoing elective coronary artery bypass grafting for the first time. The patients were randomized into intravenous and intrapericardial groups. Primary postoperative bleeding and transfusion requirements, and secondarily complications, reoperation and discharge times were evaluated.

Results: The 60 coronary artery bypass grafting patients included in the study, consisting of 30 patients in intravenous and intrapericardial groups, were not different from each other in terms of demographic data and Euroscore parameters. Postoperative 24-hour chest tube drainage was measured as 890±551 mL in the intrapericardial group and 708±504 mL in the intravenous group. The similar drainage amounts detected in the two groups did not create a statistically significant difference (P=0.190). Transfusion requirements were similar in both groups. No complications developed in any patient and no reoperation was required due to bleeding.

Conclusions: In conclusion; intrapericardial tranexamic acid application in coronary artery bypass grafting surgery reduces postoperative bleeding and transfusion requirement at an equivalent rate to intravenous. Intrapericardial application, which can provide the same effect without creating extra risk, may be a simpler and more practical method than systemic application, which includes complex protocols regarding dose and timing.

Keywords: Transfusion, antifibrinolytic, intrapericardial, postoperative bleeding, tranexamic acid, anesthesia, coronary artery bypass grafting

Open heart surgeries are major surgeries that frequently use cardiopulmonary bypass (CPB) pumps, have a high risk of bleeding [1]. Blood transfusion rates are 30-70%, and reoperation rates due to bleeding are 2-7%. 50-80% of bleeding is due to nonsurgical causes [2, 3]. The pump is held respon-

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sible for bleeding caused by fibrinolysis. Fibrinolysis accounts for 25-45% of serious bleeding and continues for 24 hours after the pump [4, 5]. Tranexamic acid (TXA), a synthetic lysine analog, prevents fibrin destruction and bleeding by inhibiting the conversion of plasminogen to plasmin on the fibrin surface [6]. Its effectiveness in controlling bleeding has also been shown in surgeries other than cardiac surgery [7, 8]. It is known that TXA reduces bleeding, transfusion requirements and reoperation rates after CPB. Its use is recommended with a high level of evidence by the American Society of Thoracic Surgeons, Transfusion Management Guidelines, and the Society of Cardiovascular Anesthesiologists. However, no consensus has been established on the optimum dose and method of use [6, 9-11]. Adverse effects such as thromboembolism and seizures seen with intravenous use have increased interest in topical application. Seizures associated with high intravenous (IV) doses are due to the antagonistic effect of TXA due to its similarity to β-aminobutyric acid (GABA) [12]. While previous literature focused on placebo-controlled efficacy studies, current literature focuses on comparisons of systemic and topical effects [10, 13-16]. The hypothesis of this study is that the effect of topical TXA on postoperative bleeding control is no different from systemic administration. For this purpose, we investigated the effect of IV and intrapericadial (IP) TXA on postoperative bleeding and transfusion requirement in coranary arteriy bypass grafting (CABG) surgery.

METHODS

A prospective randomized, double-blind study was conducted after receiving approval from the local Ethics Committee (2008/11-17), and included 60 patients aged >18 years who were undergoing CABG on pump for the first time. Patients with chronic renal failure (plasma creatinine level >2 mg/dL), hepatic dysfunction (active hepatitis, cirrhosis), history of pulmonary embolism, deep vein thrombosis, cerebrovascular disease, allergy, history of hematological disorders, use of fibrinolytics or antiplatelets within the last week, those who needed an intraaortic balloon pump at the end of the operation, and those who did not give consent for participation were excluded from the study. The 60 patients who were found suitable for

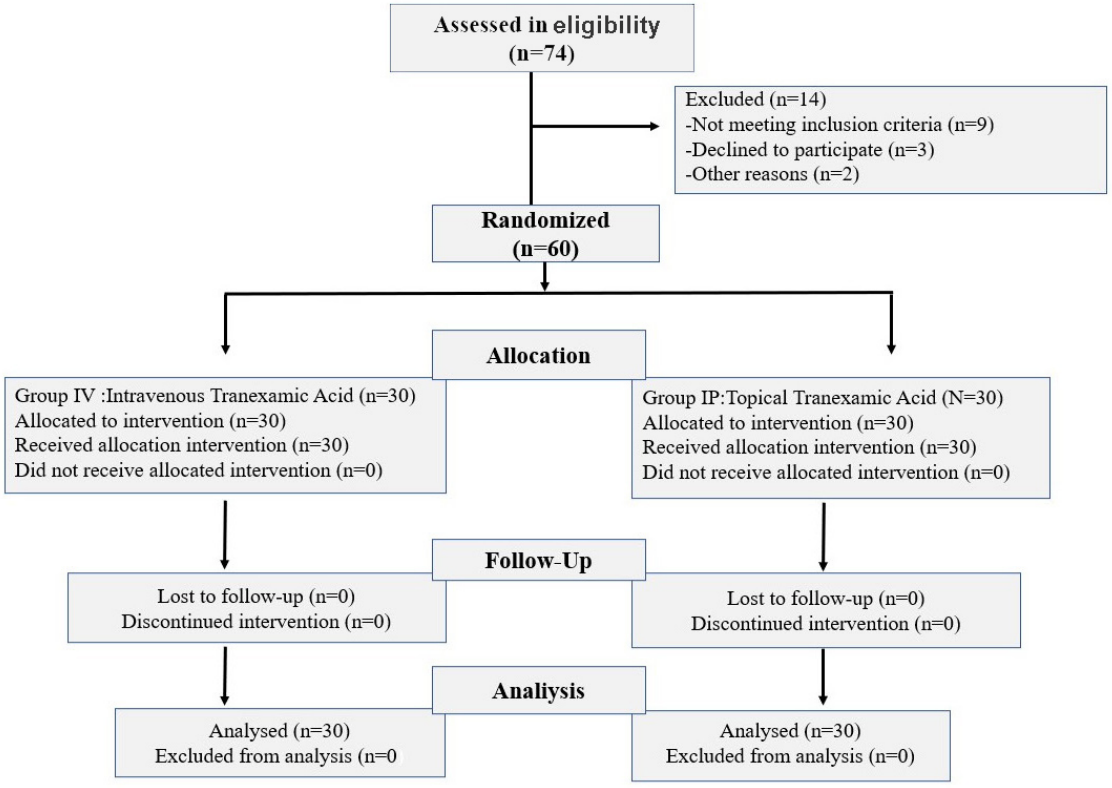

Fig. 1. Study protocol and intervention. IP=intrapericardial, IV=intravenous, TXA=tranexamic acid

the study were randomized into 2 groups using the sealed envelope method. The anesthesiologists and surgeons participating in the study were blind to the content of the 100 mL mixture administered and the patient groups. The determination of the patient groups and the preparation of the mixture were the responsibility of an anesthesiologist not involved in the study. Group IV: 100 ml of a mixture containing 40 mg kg-1 TA+ saline was administered IV (15 min), the pericardial cavity and mediastinal tissues were washed with 100 mL of physiological serum.

Group IP: 100 mL of physiological serum was administered IV (15 min). The pericardial cavity and mediastinal tissues were washed with 100 mL of the mixture (2 g TA+saline). (Fig.1.)

Procedure in Coronary Artery Bypass Grafting

Patients underwent routine anesthesia, perioperative care, and surgical procedures. Before CPB, 300 units/kg heparin was administered IV to ensure ACT>400 sec. Additional doses of heparin (100 units/kg) were administered if necessary. After CPB, antagonization was performed with protamine sulfate. Mediastinal and thoracic drains were clamped before sternum closure. IP and IV mixtures were applied after clamping. After sternum closure, clamped drains were opened. IV application was not continued in the intensive care unit.

Outcome Measures

Primary outcome

Postoperative bleeding amount was determined as the total bleeding amount between 0-3, 312, 12-24 hours in the intensive care unit and the first 24 hours.

Secondary outcomes

Transfusion amounts, Hematological data; Hemoglobine (Hb), Hematocrit (Htc), Platelets, coagulation parameters; Prothrombin time (PZ), Partial Tromboplastin time (PTZ), International normalized ratio (INR), ACT, demographic data, EuroScore, Complications (myocardial Infarction, thromboembolism, cerebrovascular ischemic attack, bleeding, seizure), intraoperative data (CPB and Cross Clamp time, heparin dose, protamine dose, number of bypassed vessels, Internal Mammarian Artery (IMA) use, time from protamine administration to sternum closure), reoperation rate, hospital stay and discharge time were determined.

According to the common transfusion protocol applied to the patients, erythrocyte suspension (Es) was given to patients with Hb<9 mg/dL as a result of arterial blood gas taken after the aortic cannula was removed or hemogram in the intensive care unit During intensive care follow-up, it was planned to give platelet suspension to patients with leakage type bleeding and platelet count <100,000 despite normal ACT values, and fresh frozen plasma (FFP) to patients with prolonged PT values (1.2 times the control value). Chest tubes were removed from patients with serous drainage of less than 100 mL for 8 hours.

Statistical Analysis

SPSS 15.0 program was used for statistical analysis of the data. In comparisons between two groups, Student t test was used for parametric data and chi-square test was used for nonparametric data. A P value of <0.05 was accepted as significant. Data were given as mean±standard deviation (Mean±SD).

RESULTS

The study was completed with 60 patients. The patients' Euroscore values were calculated. Demographic data and Euroscore scores were similar in both groups (Table 1).

There was no statistical significance between the groups in terms of operative data (number of bypass vessels, cross-clamp, CPB, sternum closure times, IMA usage status, amounts of heparin and protamine used) and postoperative data (reoperation, intubation, intensive care, discharge times). No complications developed throughout the study. No patients underwent reoperation (Table 2).

When preoperative and postoperative blood values (Hb, Htc, and Platelet), coagulation parameters (PZ, PTZ, INR) and ACT times were compared, no difference was found between the groups (Table 3). Postoperative Hb, Htc, ACT values of the 3rd, 12th, 24th days were similar in both groups. (Tablo 4).

When the amount of bleeding was examined between the 0-3, 3-12, 12-24th hours postoperatively, no significant difference was found between the groups (P=0.72, P=0.322, and P=0.975; respectively). The total amount of postoperative 24-hour bleeding was similar in both groups, and no statistical difference

Table 1. Demographic data and preoperative follow-up parameters of the groups

	Group IV (n=30)	Group IP (n=30)	P value
Age (years)	61±9.2	63.3±7.5	0.303
Gender (M/F)	27/3	27/3	
Body mass index (BMI)	26.1±2.52	25.8±2.66	0.206
EF (%)	43.3±9.5	47.5±11.7	0.135
EuroScore	2.7±1.8	2.9± 1.5	0.136

Data are shown as mean±standard deviation or number (n). IV=intravenous, IP=intrapericardial, M/F=Male/Female, EF=ejection fraction

was found between them. (P=0.190) (Table 5).

The amounts of ES and FFP used in the postoperative period were similar in both groups (P=0.220, P=0.388, respectively). Platelet suspension was not used in any of the patients included in the study.

DISCUSSION

This double-blind randomized clinical study has shown that the use of IP TXA in CABG surgery is equivalent to IV in terms of postoperative bleeding, transfusion requirement, complication and reoperation rates. The tissue plasminogen activator in the pericardial area is higher than that in the systemic circulation. The purpose of this is to prevent adhesion by increasing fluidity [17]. Surgical intervention increases fibrinolytic activity in this area [18]. Pericardium reduces the transfer of drugs applied to this area to the systemic circulation. The fact that IP-applied TXA remains below the detection level in blood is due to minimal systemic transfer [19, 20]. All these reasons

Table 2. Intraoperative and postoperative follow-up parameters for the groups

	Group IV (n=30)	Group IP (n=30)	P value
Number of bypassed vessels	3.1±1.1	3.1±0.8	0.847
Cross Clamp time (min)	69±25	62±27	0.397
CPB time (min)	80.4±32	77.3±19.2	0.289
Closure time (min)	38.1±5.1	39.5±4.3	0.062
Amount of heparin (mg)	232±25	238±35	0.262
Amount of protamine (mg)	305±60	312±53	0.088
IMA use	30/30	30/30	
Complication	0	0	
Number of reoperations	0	0	
Intubated stay (h)	12.6±3.4	13.1±4.1	0.246
ICU stay (h)	26.9±3.8	28.8±2.2	0.323
Discharge time (days)	7.3±2.8	8.1±1.9	0.412

Data are shown as mean±standard deviation or number (n). IV=intravenous, IP=intrapericardial, CPB=Cardiopulmonary bypass time, IMA=Internal Mammarian Artery, MI=Myocardial Infarction, CVA=Cerebrovascular ischemic attack, VTE=Venous thromboembolism, ICU=Intensive care unit.

Table 3. Blood values, coagulation parameters, ACT of the groups in the preoperative and postoperative periods

	Group IV (n=30)	Group IP (n=30)	P value
Preoperative			
Hemoglobin (gr/dL)	13±1.8	13.6±4.3	0.468
Hemotocrit (%)	37.7±5	36.6±6.4	0.493
Platelet ($\times 10^3$/mL)	256±179	204±81	0.158
PTT (sec)	38.03±16.1	33.57±7.9	0.179
PT (sec)	13.6±8.8	13±4.2	0.744
INR	1.01±0.9	1.01±0.11	0.710
ACT (sec)	146.7±17.5	141.8±11.9	0.214
Postoperative			
Hemoglobin (gr/dL)	10.3±0.8	10.4±1.2	0.586
Hemotocrit (%)	29.9±2.3	30.3±3.9	0.637
Platelet ($\times 10^3$/mL)	152±57	134±46	0.178
PTZ (sec)	39.4±17.75	38.6±18.05	0.853
PZ (sec)	13.4±1.25	13.5±1.28	0.706
INR	1.14±0.1	1.12±0.09	0.906
ACT (sec)	145.4±12.8	138.8±25.9	0.598

Data are shown as mean±standard deviation. IV=intravenous, IP=intrapericardial, ACT=Activated clotting time, PT=Prothrombin time, PTT=Partial thromboplastin time, INR=International normalized ratio, Hb=Hemoglobin, Htc=Hematocrit

support the use of IP TXA in terms of side effects. Although it is generally reported that topical TXA reduces bleeding and transfusion rates independently of the dose, it has been shown that low doses (10 mg/mL) are ineffective in cardiac surgery and the effect is dose-dependent [10, 21]. It is stated in the sources that topical TXA doses above 25-50 mg/mL may prevent re-epithelialization and cause bleeding [6]. It has also been reported that IV doses above 50 mg/kg are not superior to low doses in bleeding control and increase the risk of seizures [6, 22]. It has been shown that 2 g of TXA administered IP in CABG surgeries significantly reduces bleeding and blood product use [23]. The TXA doses we used in our study were determined using this information. It has been reported that 24-hour values are used in determining the amount of bleeding in cardiac surgeries and that Hb monitoring is not reliable due to hemodilution [24]. It has been shown in different placebo-controlled studies that IPapplied TXA reduces postoperative bleeding in the 24 hours without increasing the risk of thromboembolism and seizures [16]. In the literature, the effectiveness of topical TXA application in controlling bleeding in patients using oral anticoagulants or with a disturbed bleeding profile has been reported [25-28].

In our study, the amount of postoperative 24-hour bleeding was measured as 890±551 mL in the IP group. This amount is consistent with similar sources (791±483, 733±930) in IP applications [3, 25]. Our results show that the amount of bleeding is higher in the first 3 hours postoperatively. In fact, it has been reported that bleeding is higher in the first 3 hours after CPB and that antifibrinolytics used in this period reduce the transfusion requirement by 1-2 U [25, 29]. In a source similar to our study, it was reported that IP T·A was equivalent to IV in terms of postoperative 24-hour bleeding amounts, transfusion rates, complications and discharge time. This source, which is

Table 4. Postoperative Hb, Htc, ACT values at 3rd, 12th, 24th hours

		Group IV (n=30)	Group IP (n=30)	P value
Hb(gr/dL)	3rd hours	10.3±1.06	10±0.8	0.204
	12th hours	10.6±1.05	11±4.21	0.649
	24th hours	11±1.16	11.4±4.3	0.614
Htc (%)	3rd hours	30.5±3.1	29.3±2.3	0.107
	12th hours	31.9±2.7	30±2.1	0.212
	24th hours	32.1±2.8	30.4±2.6	0.303
ACT (sec)	3rd hours	146.5±13.6	138.3±13.6	0.598
	12th hours	134.5±11.18	138.4±10.7	0.707
	24th hours	131.6±8.4	133.9±7	0.729

Data are shown as mean±standard deviation. IV=intravenous, IP=intrapericardial, Hb=Hemoglobin, Htc=Hematocrit, ACT=Activated clotting time

consistent with our results, differs from our study in that surgeries other than CABG were also included, patients using anticoagulants were included, higher TXA doses (5 g) were used and different application protocols were followed [16]. Variable results in the literature regarding the amount of bleeding and transfusion need may be due to the type of cardiac surgery performed, TXA doses, application times, differences in case numbers, use of antithrombotics and application of different transfusion policies [16]. In studies reporting higher postoperative bleeding, it was reported that the bleeding-reducing effect of IP TXA was more pronounced [3, 25]. Survival rate with CABG surgery can be calculated with the Euroscore scoring system to get an idea about patient-specific mortality, morbidity, and hospital stay. In our study; similar results were recorded in both groups in terms of Euroscore values, characteristic features, and hemostatic parameters. For this reason, we think that we have fully ensured the reliability of the comparison by eliminating patient and surgical causes.

Limitations

Our study has some limitations. The first of these is the lack of a placebo group. This is because T·A is routinely applied for bleeding prophylaxis in our

Table 5. Postoperative bleeding amount, total transfusion values

	Group IV (n=30)	Group IP (n=30)	P value
Postoperative first 3 hrs (mL)	366±146	468±266	0.72
Postoperative 3-12.hrs (mL)	242±258	317±318	0.322
Postoperative 12-24.hrs (mL)	93±173	94±108	0.975
Postoperative first 24 hrs	708±504	890±551	0.190
Total (mL)			
ES (U)	1.3±1.3	1.8±1.5	0.220
FFP (U)	3.9±1.6	3.6±1.2	0.388
Platelet(U)	0	0	0

Data are shown as mean±standard deviation. IV=intravenous, IP=intrapericardial, FFP=Fresh frozen plasma, ES=Erythrocyte suspension

clinic. Our study may be insufficient to evaluate side effects. Because no complications were observed in any patient. Another limitation is that IP application inhibits fibrinolysis, causes adhesions, and may create a safety problem for reoperation. Although it is suggested that this situation can be balanced with a simultaneous anti-inflammatory effect, it is not clear how long patients should be followed for this purpose [30, 31]. The follow-up period limited to discharge in our study is weak in evaluating adhesions in IP applications. We believe that our study contributes to the literature due to the limited number of prospective studies comparing the effectiveness of IP and IV TXA with a single type of cardiovascular surgery and a similar patient profile (Euroscore).

CONCLUSION

As a result; IP TXA application in CABG surgery reduces postoperative bleeding and transfusion requirements at an equivalent rate to IV application. IP application, which can provide the same effect without creating additional risks, may be a simpler and more practical method than systemic application with complex protocols. Large randomized double-blind clinical studies are needed to confirm these findings.

Ethical Statement

This study was approved by the Dokuz Eylül University Medical Faculty Drug Research Local Ethics Committee (Decision no. 08/18-20, Date: 17.11.2008).

Authors' Contribution

Study Conception: FG, FM; Study Design: FG, FM; Supervision: FG, FM; Funding: FG, FM; Materials: FG, FM; Data Collection and/or Processing: FG, FM; Statistical Analysis and/or Data Interpretation: FG, FM; Literature Review: FG, FM; Manuscript Preparation: FG, FM and Critical Review: FG, FM.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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Editor's note

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