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ORIGINAL STUDY

The effect of local and systemic application of tranexamic acid on the amount of blood loss and allogeneic blood transfusion after total knee replacement

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The effect of local and systemic Tranexamic Acid on blood loss and need for transfusion after total knee replacement was compared prospectively. Between 2012-2013, 90 patients with unilateral TKR were included. They were randomly divided into 3 and 15 mg/kg TXA was infused before and 10 mg/kg 1 hour after surgery in Group 1, 2 gr TXA was used topically in 2 and no TXA was applied in 3. Total blood loss and transfusion rate were used as outcome. Mean amounts of blood loss were 898.03 ± 298.21, 823.64 ± 224.33 and 1263.77 ± 298.79 ml in Groups 1, 2 and 3 respectively. There was a decrease in blood loss in TXA groups ($p < 0.001$). No difference was found between local and systemic groups ($p = 0.385$). Transfusion wasnot required in TXA groups but it was 8 in control group. No thromboembolic problem was seen in any patient. Since TXA decreased blood loss and lessen the need for transfusion significantly without increasing thromboembolic events in TKR, we suggest its usage in TKR either systemically or topically whenever possible.
Level of evidence : Prospective Randomized Controlled Trial, Level II).

Keywords : antifibrinolytic ; tranexamic acid ; total knee replacement ; allogeneic blood transfusion ; amount of bleeding.

INTRODUCTION

The amount of blood loss after total knee replacement (TKR) is approximately 800-1700 (ml) and 20-70% of these patients have been recorded to have allogeneic blood transfusion (ABT) (*18,21,32,45*). After such major and specific orthopedic interventions in elderly patients, the tolerance of them to these amounts of blood loss is relatively lower due to the lack of physiological reserves and the possible presence of accompanying diseases.

Although ABT is used when required, it has been reported to cause many complications as well. These include increase in cost, blood-borne

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infections, febrile and allergic reactions, haemolysis, immunosupression, circulatory overload, electrolyte disorders, periprosthetic joint infections, disorders of acid-base balance, transfusion associated acute lung damage and even death (*14,19,28,43,49*).

Recently, many methods have been developed to reduce the amount of blood loss in order to decrease these risks after TKR and to lower treatment costs. Among these methods are pharmacological agents such as preoperative erythropoietin (EPO) (*26*) and iron therapy (*11*), autologous blood donation, hemodilution, intraoperative and postoperative autotransfusion (*4,13,38*), hypotensive anesthesia (*5,48*), epinephrine (*53*), tissue binding fibrin (*31,34*) and methods like femoral intramedullary plug (*44*), flexion position of the operated knee joint in the first post-operative hours (*39*) and temporary closure of the drain (*27,46*). But, there is no standard widely accepted approach (*23,31,42*). While EPO is a costly treatment, iron supplement is difficult for patients to adapt because of its gastrointestinal side effects. The use of autologous blood donation, hemodilution and hypotensive anesthesia is limited in patients with ischemic heart disease and cardiac insufficiency. Some pharmacological agents have a limited area of use due to the difficulty in their supply, their high costs and side effects. In addition, applications such as femoral plug, keeping the knee joint in flexion (*3*) and temporary closure of the drain (*27*) have been reported not to lead to significant decrease in the amounts of blood loss.

Many studies have shown that antifibrinolytic agents used in blood loss during open heart surgery, dental interventions, tonsillectomy, prostatic surgery, menorrhagia, ophthalmologic traumas and hemophilia patients decrease blood loss (*6,12,15,24,50,56*). Especially in recent years, many studies have suggested that the antifibrinolytic agent, Tranexamic Acid (TXA) can considerably reduce blood loss and the need for blood transfusion after TKR surgeries (54,55). TXA has been applied locally (*3,10,17,29*) or systemically (*25,34*). However, the related literature includes very few studies comparing local and systemic applications of TXA (*20,51*).

The present study aimed to compare and evaluate the results of systemic and local TXA applications used to reduce the amount of blood loss and need for blood transfusion after primary TKR surgeries in our clinic.

MATERIALS AND METHODS

In this prospective randomized controlled study carried out in 2012-2013 upon obtaining the local ethic committee's approval, patients with degenerative knee osteoarthritis who did not respond to conservative treatment and underwent unilateral primary TKR were decided to be selected to participate in the study. Among them, patients with inflammatory arthritis, history of thromboembolism, myocardial infarction and stroke and TXA allergy were excluded from the study. Patient charts were designed in order to ensure record keeping and data security. Patients were examined before and after operations and the data collected were evaluated prospectively. In order to constitute the study population, we consulted with a statistician and assuming a standart deviation of 100 ml, 80% power and an alfa error of 0.05, it was calculated that there must be 30 knees when we accepted the difference in blood loss between groups being 75 ml. So, we started the study with an overall 90 patients having the above mentioned inclusion and exclusion criteria and they were divided into 3 groups of 30 as those given systemic TXA, local TXA and the non-TXA control group. Accordingly :

1. In Group 1, iv 15 mg/kg TXA was given 1 hour before the inflation of the tourniquet and 1 hour after the deflation of the tourniquet, iv 10 mg/kg TXA was given (in 100 ml isotonic sodium chloride) through one-hour infusion.
2. In Group 2, 2 gr TXA was applied locally on the proximal-medial surface of the patella with intra-articular injection after the joint capsule closure in the final stage of the operation before the tourniquet deflation (Fig. 1).
3. On the other hand, no TXA was applied in Group 3.

No other method or pharmacological agent was used to decrease the need for transfusion. One hour before the operation, 2 gr cefazolin sodium was given iv for antibiotic prophylaxis and continued for 48 hours. The patients were operated under combined spinal-epidural anesthesia with pneumatic tourniquet. The posterior cruciate ligament substituting primary total knee prosthesis was applied in all knees (61 knees : Depuy (Warsaw, Indiana), 29 knees : Stryker Scorpio (Mahwah, NJ)). All the prostheses were fixated with cement and patellar resurfacing was not done in any of the patients. A hemovac drain was placed inside the joint and anatomic layers

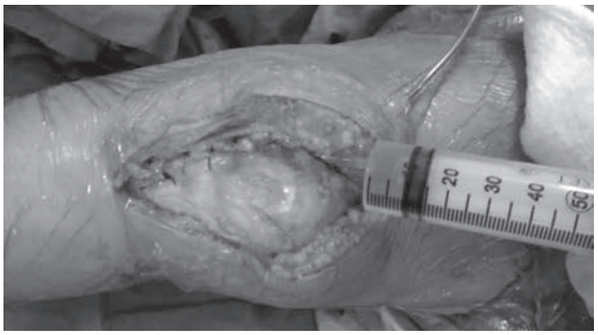

Fig. 1. — Tx local application technique

were closed accordingly. An elastic bandage was wrapped from fingers to the up of the thigh and the tourniquet was deflated afterwards. All patients were made to perform calf muscle pump exercises after surgery in order to decrease the risk of DVT.

Enoxaparin sodium 0.4 ml subcutaneous was started 8 hours after the operation and was continued once a day for 4 weeks. Hemovac drain was closed using clamps for 30 minutes after the closure of wound. After that, hemovac drain was opened as to have negative pressure and drains of all patients were observed and recorded in the postoperative 1st, 3rd, 6th, 12th and 24th hours. At the end of the 24th hour, drains were removed and full weight bearing was allowed for all the patients. Blood sample for the level of haemoglobin was drawn before the operation and 3 hours after the operation and on postoperative 1st, 2nd, 3rd and 10th days and the values were recorded as well. The amount of blood loss was calculated using the formula described by Nadler *et al* (*37*) and Good *et al* (*18*), which was proven to be effective.

Hb level of 8.0 g/dl was determined as the trigger value for allogeneic blood transfusion limit. Accordingly, ABT was given when Hb values were between 8 to 10 g/dl in patients with symptoms like hypotension, tachycardia, dizziness and balance loss. Total amount of blood loss calculated and the amount of ABT given were used as the evaluation criteria. Patients with stable performance status, biochemical and hematologic parameters and who developed no complications were discharged at the end of day 3 and were called for examinations at the outpatient clinic on the postoperative 10th day, and in the 1st and 3rd months after the operation. Patients who developed hematoma, superficial infection, deep infection and deep vein thrombosis (DVT) were followed. Patients' preoperative and postoperative demographic data, hemograms, coagulation values, amounts of blood loss, blood transfusions applied, complications and other parameters were recorded.

Statistical analysis was done on IBM SPSS statistics program version 21. Numeric variables were indicated as means ± standard deviation and categorical variables as percentages. In the comparison of the means between groups ; Student t test was used for the normally distributed data while Mann-Whitney U test was used for those without normal distribution. Categorical variables were compared with chi-square test. In all evaluations, $p < 0.05$ was accepted as the statistically significant value.

RESULTS

In our study, a total of 90 patients were included in the evaluations in groups of 30 with 5 men - 25 women (mean age 68.56 ± 5.38) in Group 1 given iv TXA, 4 men - 26 women (mean age 67.06 ± 6.54) in Group 2 of local TXA application and 5 men-25 women (mean age 67.03 ± 6.15) in the non-TXA Group 3. Patients' mean BMI (kg/m^2) and mean ASA scores were determined in Group 1, Group 2 and Group 3. No significant difference was found between groups in the statistical analysis of these data and the distribution was homogenous (Table I).

Preoperative mean Hb-Htc values of patients were determined for the groups 1, 2 and 3. In the statistical analysis of these values, no significant difference was observed between groups ; and no difference existed between groups in terms of patients' preoperative coagulation parameters (PT, APTT, INR) (Table I).

The total amount of blood coming out of drains was measured as 390.83 ± 151.7 ml in Group 1, 324.66 ± 126.49 ml in Group 2 and 777.43 ± 249.46 ml in Group 3. Although there was no statistical difference between the mean amounts of blood loss in the drains of patients in Group 1 and 2, the values of Group 2 patients were measured as relatively lower than Group 1. When Group 3 was compared to Group 1 and Group 2 separately, mean drain blood loss amounts were higher (Table II).

However, since the amount of blood accumulated in the drain does not reflect the total amount of blood loss, the formula described by Nadler *et al* (*37*) and Good *et al* (*18*) was used to calculate the total amount of blood loss. Accordingly, mean total amount of bleeding was measured as

Table I. — Demographic values and preoperative blood parameters

				p values		
	Group 1	Group 2	Group 3	Group 1-2	Group 1-3	Group 2-3
Gender [M/F]	5/25 (%16.7)	4/26 (%13.3)	5/25 (%16.7)	0.720	1.00	0.720
Age (years)	68.56 ± 5.38	67.06 ± 6.54	67.03 ± 6.15	0.337	0.309	0.984
Height (cm)	161.23 ± 5.41	162.40 ± 6.30	161.06 ± 7.18	0.445	0.920	0.448
Weight (kg)	79.46 ± 11.49	85.33 ± 14.04	84.16 ± 13.16	0.082	0.146	0.741
BMI (kg/m^2)	30.6 ± 4.52	32.4 ± 5.34	32.41 ± 4.55	0.164	0.126	0.991
ASA	2.1 ± 0.48	2.1 ± 0.40	2.23 ± 0.43	1.000	0.262	0.220
DM (-/+)	5/25	8/22	5/25	0.351	1.00	0.351
HT (-/+)	20/10	13/17	17/13	0.072	0.430	0.306
Preoperative-Hb (g/dl)	12.57 ± 1.01	12.74 ± 0.92	12.81 ± 1.31	0.588	0.585	0.919
Preoperative-Htc (%)	38.65 ± 2.75	38.77 ± 2.55	38.64 ± 3.91	0.862	0.988	0.876
PT (sec)	11.54	11.88	11.73	0.259	0.532	0.679
APTT (sec)	27.78 ± 2.71	26.68 ± 3.38	27.02 ± 3.19	0.167	0.323	0.688
INR	1.02 ± 0.06	1.01 ± 0.06	1.01 ± 0.07	0.445	0.517	0.956

BMI : Body Mass Index ; ASA : American Society of Anaesthesiology Status ; DM : Diabetes Mellitus ; HT : Hypertension ; Hb : Hemoglobin ; Htc : haematocrit ; PT : Prothrombin time ; APTT : Activated Partial Thromboplastin Time ; INR : International Normalized Ratio.

Table II. — Follow-up datas after surgery

				P values		
	Group 1	Group 2	Group 3	Group 1-2	Group 1-3	Group 2-3
Surgery Time (min.)	115.93 ± 6.26	111.40 ± 7.66	116.26 ± 6.16	0.167	0.836	0.116
Hospitalization (day)	3.26 ± 0.58	3.30 ± 0.95	3.36 ± 0.61	0.871	0.521	0.749
Drainage volume (ml)	390.83 ± 151.7	324.66 ± 126.49	777.43 ± 249.46	0.072	< 0.001	< 0.001
Infection	0/30	0/30	1/30	1.00	0.317	0.317
Deep Vein Thrombosis (DVT)	0/30	0/30	0/30	1.00	1.00	1.00
Allogenic Blood Transfusion (ABT)	0/30	0/30	8/30	1.00	0.003	0.003

898.03 ± 298.21 ml in Group 1, 823.64 ± 224.33 ml in Group 2 and 1263.77 ± 298.79 ml in Group 3. When mean amount of blood loss was compared with Group 3, it was observed to decrease by 30% in Group 1 and 35% in Group 2 ($p < 0.001$). In the comparison of groups 1 and 2, on the other hand, there was no statistically significant difference although the amount of blood loss in Group 2 was lower ($p = 0.385$) (Fig. 2).

None of the patients required ABT on the 1st postoperative day. On the 1st day after the operation, the decrease in Hb values of the patients in Group 2 was observed to be lesser than those in Group 1 and Group 3. This resulted in a significant difference with the control group ($p < 0.001$) whereas it was not significantly different from the systemic TXA group ($p = 0.129$). The decrease in the mean amount of Hb on the 1st postoperative day in patients in Group 1 was also less than that of control group, but this finding was not statistically significant ($p = 0.071$) (Fig. 3).

There was no need for ABT in the patients in systemic and local TXA groups in proportion to the amount of blood loss while 8 patients (26%) in the

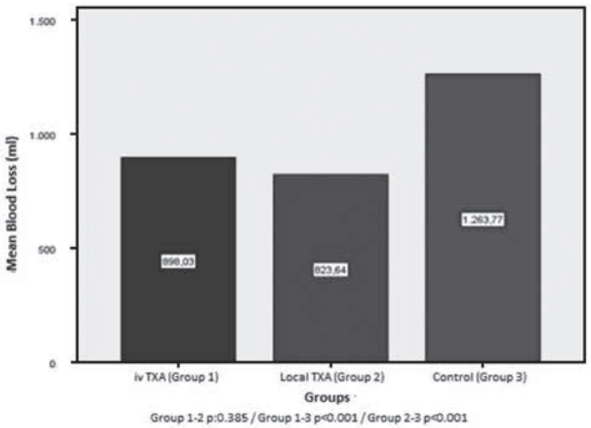

Fig. 2. — Average total amount of blood lost in the group

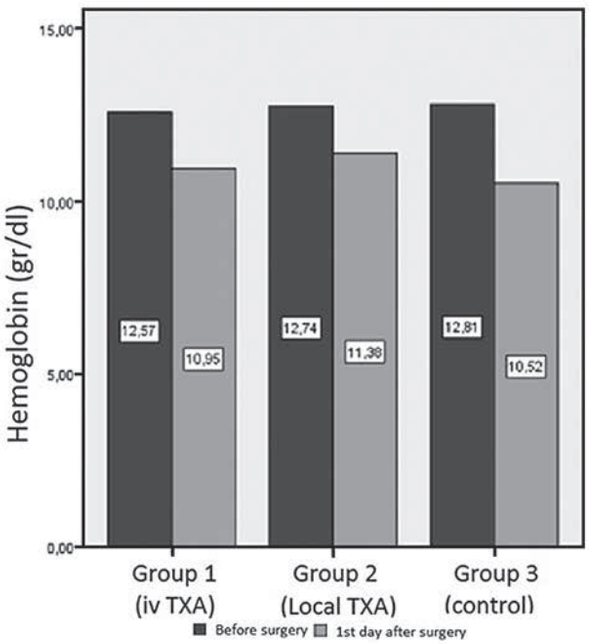

Fig. 3. — Pre-operative and post-operative day 1. average value of Haemoglobin.

control group were given ABT. One unite (U) of erythrocyte suspension was transfused to 3 patients, 2 U to 4 patients and 3 U to 1 patient ($p < 0.003$) (Table II). Mean preoperative hb value of the 8 ABT patients in the control group was 11.25 g/dl while mean preoperative hb value of the 22 non-ABT patients was 13.31 g/dl. This difference was found to be statistically significant ($p < 0.001$) (Fig. 4).

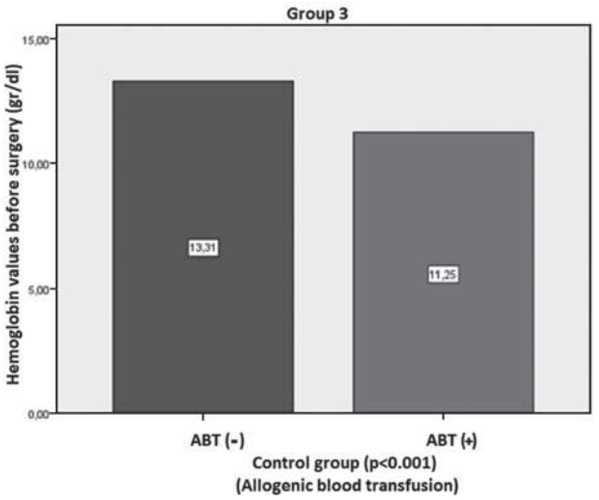

Fig. 4. — Allogeneic blood requirement, Preoperative hemoglobin values.

When the groups were compared in terms of durations of operation and hospitalization, no significant difference was found (Table II). A total of 7 patients (2 patients in Group 1, 3 patients in Group 2 and 2 patients in Group 3) developed complaints of edema and pain in calf area. The results of the lower extremity venous Doppler ultrasound given to these patients showed no finding of DVT. Prolonged serous fluid discharge was found in 6 patients, 2 patients from each group. While this discharge decreased in 5 of the patients, 1 patient in Group 3 was operated with irrigation and polyethylene insert was changed on the 13th postoperative day. The cultures of the joint gave no microorganism development and no findings of infection were present in the later follow-up and the clinical and laboratory tests in the 6th postoperative month showed no infection.

DISCUSSION

In the present study, it has been found that systemic and local TXA applications reduced amounts of blood loss and eliminate the need for ABT without increasing complication rates after TKR surgery. On the other hand, although no significant difference was found between systemic and local

applications, local application of TXA has been found to decrease the amounts of blood loss at relatively higher rates than systemic applications.

Local applications of TXA in TKR surgery led to a decrease in the amounts of blood loss and ABT rates (*10,17,22,29,36,40,52*). In a prospective, randomized, double blind designed study carried out with 124 patients, as a result of the comparisons of two groups with a placebo group, a significant level of decrease was observed in the amounts of blood loss in patients given TXA (*42*). Similarly, in another study conducted in 2013, it was reported that 3 g of local TXA decreased postoperative blood loss and the risk of transfusion significantly in patients of primary TKR and Total Hip Replacement (*29*). Still another study of 683 cases in the same year showed that 3 g of local TXA application reduced ABT and concurring morbidity rates and costs (*10*). A study carried out with 140 patients found that with clamping (closing with a clamp) the drain after a TXA injection done from the drain, total drainage, total blood loss, mean transfusion volume and transfusion rates all decreased in comparison with those who were not given injections (*36*). In our study, similar to the studies in the literature, it was found that the mean amount of blood loss decreased 440 ml in the local TXA group and that 26% of the patients were given ABT in the control group while none of them required ABT in the local TXA group. In a randomized and double blind study carried out by Georgiadis *et al* (*17*), 101 patients of unilateral TKR surgery were divided into 2 groups and after giving local TXA to one group and placebo to the other one, it was found that mean blood loss decreased by 350 ml in the local TXA group and no patient was given transfusion while an 8% need occurred in the placebo group, which did not result in a statistically significant difference. Despite this, they recommended the TKR patients to use local TXA regularly. Two other studies have been published reporting that amounts of blood loss during the postoperative period were reduced but that the level of decrease in transfusion rates was not significant (*22,40*). In our study, a significant decrease was found in the amounts of blood loss in the TXA group in comparison with the control group and no patient in the local TXA group required ABT. Therefore, we recommend local use of TXA in TKR surgery.

In TKR surgeries in which TXA has been infused systemically, decreases have also been reported in the amounts of blood loss and ABT rates in the postoperative period (*2,7-9,16,25,30,35,41*). In a prospective, randomized double blind study of 100 patients given 10 mg/kg of iv TXA before the operation and in per oral 250 mg capsules 3 times a day for 5 days after the operation, it was reported that TXA reduced the amount of postoperative blood loss and the need for transfusion without increasing the risk of thromboemboli (*9*). A prospective study which evaluated 71 unilateral primary TKR surgery patients found that as result of giving TXA at 10-15 mg/kg doses through infusion twice being 15 minutes before the inflation of the tourniquet and 3 hours after surgery, ABT rates fell from 37% to 0% (*41*). In another study, bilateral primary TKR surgeries were examined retrospectively in 87 patients by comparing 37 patients who were given TXA infusions of 20 mg/kg before incision to the 50 patients in the control group and ABT was found to fall from 50% to 11% (*25*). Since we obtained similar findings to these in the patients given systemic TXA in our study, we think that TXA can be used systemically.

Several studies have compared local and systemic applications of TXA as well and although they have concluded that amounts of blood loss and the need for ABT are reduced at similar rates in the postoperative period, controversial results have been reported with regard to local and systemic applications of TXA (*33,47,51*). In a prospective study, published in 2012 with 120 patients, Seo *et al* (*47*) gave 1.5 g local TXA to one group and 1.5 gr iv TXA to the other while covering the wound and compared these two groups with the non-TXA control group. They found that the local group reduced amount of blood loss significantly better than that of systemic group. However, there are two points of consideration in this study. The first one is the high rates of ABT given to all three of the groups (34% systemic TXA, 20% local TXA and 94% to patients in the control group) and the second point is the use of minimal invasive instrumentation set in the study. For these reasons, as the results obtained from this

study conflict with the literature, the reliability of the study is suspicious. In a retrospective study by Wind *et al* (*51*), 330 TKR cases were given 1 g preoperative iv TXA infusion and 130 TKR were given local TXA while 1838 TKR were not given TXA and called the control group. ABT was given at the rate of 6.5% (120/1839) in the non-TXA group, 0.3% (1/330) in the iv group while there was no (0/130) ABT in the local TXA group. Moreover, a difference was found in the systemic TXA group between the early postoperative period Htc values and the Htc values at discharge whereas no difference was observed in the local TXA group, which concluded that systemic application was better than local application in reducing blood loss. The authors associated this with the fact that the local TXA given before closing the wound could not be absorbed by tissues efficiently. In our study, TXA was applied both locally and systemically and was compared with the non-TXA control group. A 26% (8/30) ABT need occurred in the control group. In the other two treatment groups, however, amounts of blood loss were observed to be lesser than that of control group and neither group required ABT. Comparing local and systemic TXA, no significant difference was found between these two groups whereas we found 75 ml less bleeding in the local group. This finding is different from the study of Wind *et al* (*51*). This may be because we gave the local TXA application with an injector after the closure of the knee joint capsule. However, Wind *et al* (*51*) state that they conducted local medications into the knee before they closed the joint capsule. In this case, TXA may not be able to retain in the joint and may get out. In the study they carried out to determine the optimal TXA applications Maniar *et al* (*33*) examined five different dose regimens in which they looked at the total amount of drain and blood loss after TKR. They gave 10 mg/kg of TXA during the operation to group 1, before and during the operation to group 2, before, during and after the operation to group 3, during and after the operation to group 4 (different systemic applications of TXA in 4 groups) and locally to group 5. While blood loss decreased in all groups, single dose systemic TXA application during the operation was observed to be ineffective and it was found that 3 doses of intravenous application led to the highest decrease in blood loss. Different from this study, TXA was given in two doses both before (15 mg/kg) and after (10 mg/kg) the operation in the systemic TXA group in our study and a significant difference was found in comparison with the control group. Since there was no significant difference between local and systemic applications of TXA in our study, we recommend both local and systemic TXA applications in TKR surgery as they eliminate the need for ABT by reducing the amounts of blood loss.

Studies carried out with TXA have reported no increase in the number of complications such as DVT or Pulmonary emboli after TKR surgery (*1*,*54*,*55*). In the meta-analysis they reviewed 19 clinical studies, Alshryda *et al* (*1*) found significant decrease in blood transfusion need with TXA application and stated that there was no increase in the risk of DVT and Pulmonary emboli. Another meta-analysis which assessed the efficiency and reliability of TXA showed decreases in the amounts of blood loss without any increase in thromboemboli rates (*54*). Similarly, none of the patients in our study had these complications. These findings correspond with the literature. Local TXA applications could be considered to cause infection. However, the only case that was given debridement and insert change with suspected infection in our study was in the control group. In the local medication group, however, we did not encounter such a problem. Thus, we consider that TXA given under proper circumstances would not cause infection.

Our study has some advantages and disadvantages. Some of the major advantages of the study include the fact that there were 3 groups, no data was lost as none of the patients were excluded from follow-up, the data were collected prospectively and the study was carried out from a single center. The biggest disadvantage of our study, on the other hand, is the relatively few number of the cases. We recommend comparisons of local and systemic TXA applications with higher numbers of cases.

Considering all the findings of the present study, we recommend that TXA should be used locally or systemically in patients without contraindications since it reduced blood loss and the need for ABT without increasing complication rates after TKR

surgeries. Although there was no statistically significant difference between local and systemic applications of TXA in our study, we observed that local TXA reduced blood loss relatively better than systemic applications and we believe that local applications could be easier and more serviceable. Moreover, since local medication application is easier than systemic application and there are still doubts that TXA increases thromboembolic complications when given sistemically, we consider that local TXA application which is known to have a systemic absorption rate of 70% may be safer.

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