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ORIGINAL STUDY

Tranexamic acid in total knee replacement which protocol? which application form? A prospective randomised study

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The aim of this study was to prospectively compare different delivery forms, doses and combined application forms of TXA for the reduction of blood loss and prevention of the allogeneic blood transfusion in patients with TKA and evaluate the results. The study included patients with knee joint osteoarthritis who were unresponsive to conservative management and 168 patients met the inclusion criteria. They were divided into 5 groups randomly as, Control (1), Local (2), Systemic+short infusion (3), Systemic+long infusion (4) and Systemic+oral TXA (5). When compared with the Control group, blood loss was significantly reduced in Groups 2, 3 and 4 (p=0.001, 0.001, 0.003) but not in Group 5. Twenty-four hour drainage output was lower in all treatment groups (p=0.001, 0.001, 0.001, 0.004). Although TXA groups had no difference in terms of blood loss, 24-hour drainage outputs of the local TXA group were less than Group 4 and 5 and it yielded similar amounts in comparison with group 3. It was determined that TXA use whether local or systemic gave rise to decreased blood loss and prevent allogeneic blood transfusion. But, regarding the results above, local TXA seemed to have favorable effects when compared with systemic+long infusion and systemic+oral TXA usage, whereas local use had similar results with systemic+short infusion. Additionally, there found no difference between systemic+short, systemic+long infusion and systemic+oral combined TXA usage with respect to blood loss, transfusion rates and drain follow-up. We recommend further prospective randomized controlled studies to make clear these differences. Systemic+oral combined TXA use have promising results when compared with other systemic multiple deliveries.

Keywords : Knee ; total knee arthroplasty ; prospective ; tranexamic acid ; bleeding ; allogenic blood transfusion ; systemic tranexamic acid ; local tranexamic acid ; oral tranexamic acid.

INTRODUCTION

It has been reported that there is 800-1700 ml blood loss in Total Knee Arthroplasty (TKA) applications and allogeneic blood transfusion is applied to approximately 20% of patients *(1)*. There are

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reports of transfusion rates as high as 70% *(2)*. As the vast majority of the patient population for TKA is >65 years of age, blood loss tolerance is lower because of comorbidities such as cardiovascular diseases, which are commonly seen in this patient population.

Allogenic blood transfusions have some undesired effects such as febrile reactions, allergies, immunosuppression, fluid-electrolyte imbalance and the risk of hemolysis and blood-transferred infection in addition to increasing periprosthetic infection rates *(3)*. In order to overcome this problem, the autologous blood donation *(4,5,6)*, preoperative iron supplementation *(7)* and erythropoietin treatment *(8)* in anemia, normovolemic haemodilution during the operation with the application of hypotensive anaesthesia *(4,9)*, tourniquet use *(10)*, cell-saver *(11,12)* have been recommended. But, most of these are expensive and need preoperative planning. Keeping the knee in flexion for a period postoperatively and temporary closure of the drain has been also reported to reduce blood loss rates *(13,14)*.

In addition to all these precautions and methods, tranexamic acid (TXA) has become more widely used in the last 10 years. Although it has been used in different surgical disciplines for a long time, it is relatively new in orthopaedic surgery. In particular, studies directed to reducing blood loss in TKA and Total Hip Arthroplasty (THA) have focussed on TXA in recent years. There have been more than 400 studies in the last 10 years that have researched the protocols of TXA use in different forms and at different doses against blood loss *(15)*. Local/topical versus systemic intravenous (iv) methods have been studied and no difference has been announced with regard to the prevention of allogeneic blood transfusion and diminishing the blood loss *(16)*. In recent years, it has been realized that multiple applications were more effective rather than single-use. Furthermore, combined applications have been studied and found to be effective *(17)*. There have been some studies comparing oral with systemic TXA use after TKA reporting comparable blood saving effects of oral TXA *(18,19,20,21,22)*. But, there are few studies on the use of oral TXA preparations and its combinations with other forms of TXA in TKA applications *(15,21,22)*. Unfortunately, there have also been conflicting results especially with oral TXA *(23)*. Additionally, there is still no consensus on TXA dose, the delivery form or the number of applications and debate continues *(24,25)*. In a recent systematic review comparing systemic and local administrations, authors aimed whether blood saving effects differed by doses and timings of administration, and whether the use of TXA was safe at all reported doses, timings, and routes of administration and concluded that no consensus has been found *(26)*. Regarding all of these studies, the widely accepted delivery form, dose and timing of administration has been unanswered, yet. Because of that reason, we decided to design a prospective "randomized" study comparing local and systemic combined forms including oral TXA combined systemic use with the hypothesis that there is no difference between different TXA protocols with regard to the TXA form, dosage and application route in reducing blood loss and the need for allogenic blood transfusion. Hence, the aim of this study was to make a prospective, randomised comparison of different doses of TXA applied in different forms in TKA operations.

MATERIALS AND METHODS

Approval for the study was granted by the Local Clinical Research Ethics Committee. Between November 2012 and June 2016, consecutive patients with degenerative knee joint disorder unresponsive to conservative management and scheduled for unilateral primary TKA after signed an informed consent in the outpatient clinic were invited to participate in the study. Patients with a history of rheumatoid arthritis, thromboemboli, cerebrovascular accident, myocardial infarction, revision knee arthroplasty and tumor cases were excluded.

The patients included in the study were randomly assigned to one of 5 groups with envelope method and were prospectively followed up. Patients in the Control group (Group 1), a preoperative saline infusion was administered. In the Local TXA group (Group 2), patients were administered with 2 gr TXA intraarticularly for a period of 5 minutes (min) in the final stage of the operation, following patellar

tendon repair and before wound closure. Patients were administered with an IV infusion of 15 mg/kg TXA in 100 ml saline for a period of 30 mins in the Systemic+short infusion (Group 3), Systemic+long infusion (Group 4) and Systemic+oral (Group 5) groups before inflation of the pneumatic tourniquet. But, at 3 hours after deflation of the tourniquet, 10mg/kg TXA in 500 ml saline IV infusion was applied for 1 hour in Group 3, 1 mg/kg/hr TXA in 1000 ml saline IV infusion was applied for 12 hours in Group 4 and with the first dose at the 3rd hour postoperatively, oral TXA treatment was applied for 3 days at a dose of 1.5 g/day (500 mg every 8 hrs) in Group 5.

On a prepared follow-up form for each patient, demographic data, blood parameters, American Society of Anesthesiologists (ASA) scores, operated side and drain follow-up were recorded. At postoperative 12 and 24 hours, drain follow-up was applied and the drain was removed after 24 hours. All blood transfusions were recorded. Postoperatively, the patients were followed up in the clinic for 3 days, and were then discharged. In order to prevent the formation of deep vein thrombosis, all patients were administered mechanical and pharmacological prophylaxis (0.4 ml enoxaparin subcutaneously for 6 weeks with the first dose applied at 6 hours postoperatively). In the follow-up examinations preoperatively and at 1, 2, 3 and 15 days postoperatively, hb values were recorded and the patient follow-up form was completed. The estimated blood loss (ml) was calculated with the formula defined by Nadler et al. *(27)*, based on the preoperative and follow-up hb values (gr/dl).

The sample size was calculated by applying a power analysis before the study. For the power of 80% and the significance level of 5%, units of 70 were acceptable between the treatment groups for the amount of blood loss and when the standard deviation was 100, the necessary sample size was determined as 33.

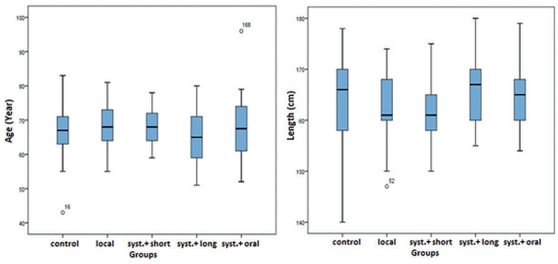
Statistical Analysis

Statistical analyses were carried out with SPSS v.21.0 software (SPSS Inc., IBM Corporation, Armonk, New York, USA). The groups were compared with respect to demographic data, preoperative blood parameters, estimated blood loss calculated with the Nadler et al. *(27)* formula and transfusion rates. The groups were examined with respect to the conformity of the data to the normal distribution and variance homogeneity. Data in homogenous variance with normal distribution were examined with parametric tests (ANOVA) and data not conforming to normal distribution or not of homogenous variance were examined with non-parametric tests (Kruskal Wallis, Mann Whitney U). The Chi-square test was applied in the comparison of categorical variables. As there were a total of 10 paired comparisons, Bonferroni correction was applied because of the group analysis, the p value was calculated as 0.05/10=0.005.

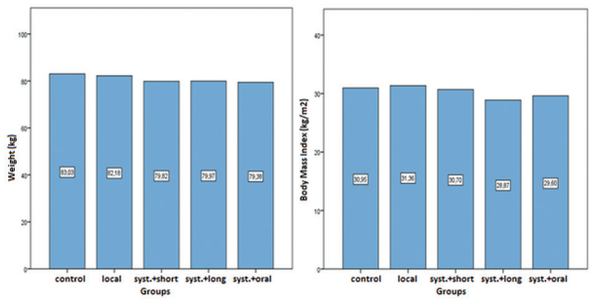
RESULTS

Overall, 170 patients who were applied with TKA for degenerative knee joint disease in the current study. As 2 patients, 1 male and 1 female, withdrew from the study during follow-up, the evaluations were completed with a total of 168 patients, comprising 34 in Group 1, 33 in Group 2, 34 in Group 3, 33 in Group 4 and 34 in Group 5. There were 143 (85.1%) females and 25 (14.9%) males, operated on the right side in 76 (45.2%) cases and the left side in 92 (54.8%). The median age at the time of surgery was 68 years (43-96), median height 164 cm (140-180), mean weight 80.88±12.41 kg, mean BMI 30.29±4.91 (kg/m^2), mean hb concentration 12.8 gr/dl (10.0-15.6), mean htc rate 39.2% (28.1-48.1) and median body blood volume was 4.48 L (3.16-5.85). The distributions of these parameters are shown in the graphs (Graph 1-4).

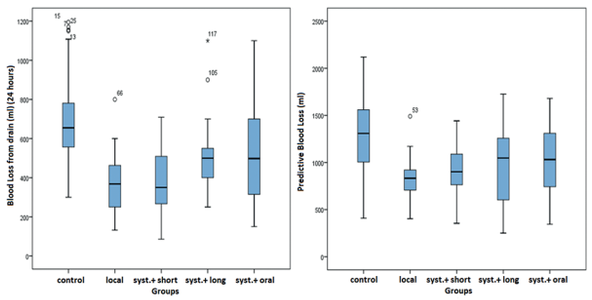
When the data were compared between the groups, no statistically significant difference was determined with respect to age (p=0.582), body weight (p=0.686), BMI (p=0.215) or operated side (p=0.651) ; a significant difference was determined in height (p=0.020). In the paired comparisons made with Bonferroni correction, the height of the patients in Group 4 were determined to be taller than that of Group 3 patients (p=0.001).



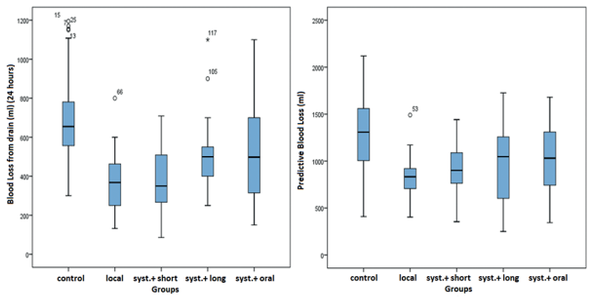
Graph 1. — Distribution of age and height of patients are shown.



Graph 2. — Body weights and distribution of BMI of patients in 5 groups are shown.



Graph 3. — Preoperative hb concentration (ml) and blood volume (L) of patients are shown.



Graph 4. — Estimated blood loss (ml) and 24-hour drain follow-up data (ml) of patients in 5 groups are shown.

No statistically significant difference was determined between the groups with respect to preoperative hb concentrations (p=0.374) (gr/dl), htc rates (p=0.167) (%), plt concentrations (p=0.276) (103/ml), prothrombin times (p=0.234) (secs), and body blood volume (p=0.369) (L). ASA scores were categorized as low (ASA I+II) or high (ASA III+IV). No difference was determined between the groups in terms of ASA score (p=0.451). The descriptive statistics related to the demographic data and the blood parameters are given in Table 1.

The basic parameters examined in the study were the amount of blood loss calculated according to the formula described by Nadler et al. *(27)*, transfusion rates and 24-hour drain follow-up. When the estimated blood loss amounts were compared between groups, any groups where a statistically significant difference was determined were compared as pairs with Bonferroni correction. In Groups 2, 3 and 4, the amount of blood loss was significantly reduced compared to Group 1 (p=0.001,0.001,0.003) but no significant difference was determined between Groups 1 and 5 (p=0.012). In the comparison between the TXA protocols, no statistically significant difference was determined between the groups 2, 3, 4 and 5. P values calculated as a result of the intra-group comparisons are shown in Table 2.

As statistically significant differences were determined between the groups in the comparison of the 24-hour drain follow-up, paired comparisons were made with Bonferroni correction. The drain follow-up values were determined to be statistically significantly lower in all the TXA protocol groups compared to Group 1 (p=0.001,0.001,0.001,0.004). Group 2 was determined to have statistically significantly low drain follow-up values compared to Group 4 and 5 (p=0.002, 0.004). The p values calculated as a result of the intra-group comparisons are shown in Table 2.

A statistically significant difference was determined between the groups with respect to transfusion rates (p=0.042) (Table 1). As no problem was observed with the expected value (20%) in any of the analyses in the paired comparisons of the groups, the Fisher Chi-square test was used. When all the groups were categorized into 2 groups as TXA

Table 1. — Demographic data and blood parameters of the patients in 5 groups are shown

	Group 1 (control)	Group 2 (local)	Group 3 (syst.+ short inf)	Group 4 (syst.+ long inf)	Group 5 (syst.+oral)	P values
Gender [M/F]	8/26	4/29	5/29	3/30	5/29	KS 0.544
Age (year)	67 (43-83)	68 (55 - 81)	68 (59 - 78)	65 (51 - 80)	67.5 (52-96)	KW 0.582
Length (cm)	166 (140-178)	161 (147 - 174)	161 (150 - 175)	167 (155 - 180)	165 (154-179)	KW 0.020
Weight (kg)	83.03±12.87	82.18 ± 12.53	79,82 ± 11.39	79.97 ± 11.96	79,38±13.48	AN 0.686
BMI (kg/m^2)	30.94 ± 5.06	31.35 ± 5.21	30.69 ± 4.31	29.41 ± 4.23	29.60 ± 5.47	AN 0.215
Side (Right/Left)	18/16	16/17	16/18	14/19	12/22	KS 0.651
ASA (I+II/III+IV)	6/28	4/29	5/29	2/31	2/32	KS 0.451
Preoperative hemoglobin value (g/dl)	13.25 (10.9-15.6)	12.5 (11.0-15.6)	12.5 (11.1-15.6)	13.0 (10.0-14.8)	12.8 (10.0-15.4)	KW 0.374
Preoperative hematocrit value (%)	40.23 ± 3.65	38.81 ± 2.75	38.60 ± 2.78	39.46 ± 4.01	38.36 ± 3.79	AN 0.167
Preoperative platelet count (10^3/ml)	260.5 (153-439)	253 (144-321)	269.5 (129-498)	272 (146-519)	284.5 (146-541)	KW 0.276
Preoperative Protrombin Time(PT)(sn)	11.4 (9.7-14.6)	11.5 (9.7-14.0)	11.4 (9.9-14.2)	12.1 (10.2-14.5)	12.15 (10.5-14.3)	KW 0.234
Body Blood Volume(L)	4.65 (3.38)-5.73)	4.36 (3.56-5.64)	4.35 (3.24-5.85)	4.49 (3.16-5.18)	4.39 (3.3-5.49)	KW 0.369
Blood Transfusion	6/34 (%17.64)	0/33 (%0)	1/34 (%2.94)	2/33 (%6.06)	2/34 (%5.88)	KK 0.048
Blood loss from drain (ml)	702 (300-195)	368 (132-800)	350 (86-709)	500 (250-1100)	498 (86-1195)	KW 0,001
Predictive Blood Loss (ml)	1309 (408-2119)	832 (403-1490)	900 (354-1441)	960 (250-1726)	1051 (344-1679)	KW 0.001

Table 2. — P values (p<0.005) between groups with blood loss* and 24-hour drainage follow up

P values	Group 1 (control)	Group 2 (local)	Group 3 (syst.+short)	Group 4 (syst.+long)	Group 5 (syst.+oral)
Group 1	1.000*/1.000	0.001*/0.001	0.001*/0.001	0.003*/0.001	0.012*/0.004
Group 2	0.001*/0.001	1.000*/1.000	0.219*/0.543	0.122*/0.002	0.014*/0.004
Group 3	0.001*/0.001	0.219*/0.543	1.000*/1.000	0.506*/0.013	0.131*/0.022
Group 4	0.003*/0.001	0.122*/0.002	0.506*/0.013	1.000*/1.000	0.437*/0.749
Group 5	0.012*/0.004	0.014*/0.004	0.131*/0.022	0.437*/0.749	1.000*/1.000

protocols and the control group, the transfusion rate of the TXA protocols was determined to be statistically significantly reduced (p=0.010) and no significant difference was determined in the comparison between the TXA groups.

DISCUSSION

The results of this study showed that the blood transfusion rates in TKA were reduced with the use of all TXA applications. The application of local TXA was determined to be as effective as the systemic combined applications (systemic+short and long infusion and systemic+oral). Additionally, with respect to blood loss, transfusion rates and drain follow-up, the systemic+short and long infusion applications were not determined to be superior to the systemic+oral combined usage. To the best of our knowledge, this is the first study to have compared the systemic+short, systemic+long infusions, systemic+oral combined applications and local application.

The local use of TXA in TKA has been reported to be an effective method in the reduction of blood loss *(28,29,30,31,32)*. In a meta-analysis by Georgiadis et al. *(29)* of 101 patients, a patient group applied with local TXA of 2 gr in a 75 ml saline solution for a 5 min period during cementing was compared with a control group. Total blood loss was found to be significantly lower in the TXA group. In a retrospective study of 683 cases by Chimento et al. *(33)*, a control group was compared with a group applied with local 3 gr TXA in a 100 ml saline solution during cementing. The local group was

reported to have higher hb values postoperatively, a lesser need for transfusion and a shorter hospital stay. In another study by Huang et al. *(34)*, the use of local TXA (1.5 gr) was compared with local and systemic combined use (1.5 gr local + 1.5 gr iv) and a significant difference was determined between the protocols in terms of blood loss and transfusion rates. In the current study, a significant reduction was determined in the local group compared to the control group with respect to blood loss (832 vs 1309 ml), drain follow-up (368 vs 702 ml) and transfusion rates (0% vs 17.64%). Thus, the results of the current study are consistent with those of Georgiadis et al. *(29)* and Chimento et al. *(33)*. But, local TXA did not have any difference when compared with systemic+short and systemic+long infusion. Additionally, in terms of blood loss, local use had no superiority but, 24-hour drainage values were less when compared with systemic+oral use. The reason for this difference might be the relatively low serum concentration of TXA when used orally as proposed *(22)*.

There are few studies related to the oral use of TXA *(21,22)*. In a study by Alipour et al. *(18)*, patients were given 1 gr oral TXA 2 hours preoperatively and this was continued for 18 hours postoperatively with a dose administered every 6 hours. Blood loss in the oral group was less than that of the control group. In a study by Irwin et al. *(21)*, 2698 patients applied with 15 mg/kg iv TXA before induction were compared with 302 patients administered with 25 mg/kg oral TXA before induction. The transfusion rate was determined to be lower in the oral TXA group than in the systemic group with no difference in complication rates between the groups. Fillingham et al. *(20)* designed a double blind placebo controlled prospective randomized study with 71 patients. One group of patients was given 1.95 gr oral TXA 2 hours before surgery and the other group was given 1 gr iv TXA before wound closure and they stated that total blood loss, transfusion rates and hb levels did not differ. In another prospective randomized study with 100 patients designed by Çankaya et al. *(19)*, one group was given 1.5 gr TXA (topical) and the other one was given 25 mg/kg oral TXA together with 1.5 gr local TXA during surgery (oral+topical). They found that the postoperative drainage amounts, measured blood loss volume and transfusion rates were lower in the combined oral+local group. In our study, since we did not have an oral+topical combined group ; so, we cannot compare our systemic+oral group findings with Çankaya et al. *(19)*. But, it may be said that we did not find the similar superior effect of our combined systemic+oral use against our local group. Furthermore, we found favorable results in local group compared with systemic+oral group which was the opposite of the above study. In a prospective randomized single-blinded study with 80 patients by Zohar et al. *(22)*, TXA efficacy was compared in 3 groups. In Group 1, 15 mg/kg TXA was given before tourniquet inflation and then after deflation, 10 mg/kg/hr continuous IV infusion was administered for 12 hours. In Group 2, 15 mg/kg TXA was given before tourniquet inflation and then after deflation, 10 mg/kg/hr continuous IV infusion was administered for 2 hours with the addition of 1 gr oral TXA at 6 and 12 hours postoperatively. In Group 3, 1 gr oral TXA was administered pre-operatively and at 6 and 18 hours postoperatively. Although a statistically significant reduction was seen in all 3 groups with respect to blood loss from the drain and transfusion rates, the efficacy of the oral group was determined to be the lowest. In our study, when the systemic+oral group was compared with the control group, no significant difference was determined with respect to the amount of blood loss (1051 vs 1309 ml) but significant reduction was determined with respect to drain follow-up (498 vs 702 ml) and transfusion rates (5.88% vs 17.64%). When the systemic+oral group was compared with the systemic+short infusion and the systemic+long infusion groups, no difference was determined between them with respect to blood loss (1051, 900, 960 ml), transfusion rates (5.88%, 2.94%, 6.06%) and drain follow-up data (498, 350, 500 ml). Although the results related to the use of oral TXA in the current study are not consistent to the results of Irwin et al. *(21)* and Çankaya et al. *(19)*, they are consistent with those of Zohar et al. *(22)* reporting higher amounts of 24-hour drainage values in their oral TXA group and reported the efficacy of oral TXA to be lowest between systemic, systemic+oral and oral only groups. It might be related with the

lower concentration of oral TXA in blood since its antifibrinolytic effect starts 2 hours after drug digestion. This might be why the blood loss was higher in systemic+oral group than other TXA groups in our study.

Debate continues about the dosages of IV TXA. In a meta-analysis that investigated the use of TXA in different surgical disciplines, the dose for parenteral TXA was defined as in the range of 5.5 - 300 mg/kg *(35)*. In studies which have studied to lessen blood loss and prevent transfusion need in THA and TKA, TXA at doses of 10-20 mg/kg has been determined to be effective, while other studies have reported that the use of 1 gr IV TXA regardless of bodyweight is effective *(10,16,18,26,28,30,33,34)*. In one meta-analysis, the use of parenteral TXA reduced blood loss by 408 ml compared to the control group and reduced the need for transfusion to 0,78 units per patient *(15)*. Maniar et al. *(17)*, investigated 4 different IV TXA protocols in their randomized controlled study being preoperative only, preoperative and intraoperative, intraoperative and postoperative and lastly preoperative and postoperative. All the TXA applications were seen to be effective in the reduction of blood loss from the drain and transfusion rates but the single dose regime in the control group was determined to be the least effective. In 4 studies which evaluated the timing of the use of TXA, 20 mg/kg IV TXA was applied preoperatively, intraoperatively and preoperatively and intraoperatively (each application as half dose 10 mg/kg) in 3 groups and the combined use was determined to be the most effective *(17,22,36,37)*. There are studies reported that the efficacy of TXA varies depending on the dose and duration of use *(23,26)*. Kim et al. *(26)* reviewed 28 randomized controlled studies evaluating the efficacy and safety of the use of TXA in TKA applications. According to this meta-analysis, significant reductions were determined to be associated with the use of TXA in drain follow-up (65-785 ml) in 18 of the studies evaluated, in total blood loss (191-942 ml) in 7 studies and in transfusion rates (10%, 60%) in 14 studies. In the same meta-analysis, the transfusion rates were examined in 19 of the studies, and while a significant reduction compared to the control group was determined in 14 studies, no statistically significant difference was determined in 5 studies. In a prospective randomized study, Chen et al. *(23)* examined the efficacy and safety of TXA applied to patients undergoing bilateral TKA in the same session. The TXA group was compared with the control group. To the patients in the TXA group, irrespective of body weight, 1 gr TXA in 100 ml saline solution was administered intravenously within 10 minutes preoperatively. The total blood loss and transfusion rates were determined to be significantly low in the TXA group. In the current study, in the comparison of the systemic+short infusion, systemic+long infusion and the control groups, it was determined that a significant reduction had been provided by TXA with respect to blood loss (900, 960, 1309 ml), drain follow-up (350, 500, 702 ml) and transfusion rates (2.94%, 6.06%, 17.64%) and thus these results were consistent with those of the previously mentioned studies.

In 2 studies which compared systemic and local TXA use, while Seo et al. *(38)* determined a significant reduction in blood loss from the drain and transfusion rates in the local group compared to the systemic group, Maniar et al. *(17)* determined no difference. In a randomized, controlled study of 90 patients conducted by Oztaş et al. *(31)*, a local group (2 gr TXA), a systemic group (preoperative 15 mg/kg+postoperative 10 mg/kg IV infusion) and a control group were compared. With respect to blood loss (823, 898, 1263 ml), drain follow-up (324, 390, 777 ml) and transfusion rates (0%, 0%, 26.6%), a statistically significant difference was determined between the TXA groups and the control group, but there was no difference between local and systemic application of TXA. In the current study, in the comparison of the local, systemic+short and systemic +long infusion and systemic+oral groups, no difference was determined with respect to blood loss (832, 900, 960, 1051 ml) and transfusion rates (0%, 2.94%, 6.06%, 5.88%), whereas a significant reduction was determined in the local and systemic+short infusion groups compared to the systemic+long infusion and systemic+oral group with respect to drain follow-up (368, 350, 500, 498 ml). The results of the current study are not compatible with the findings of Seo et al. *(38)* or Manier et al.

(17), but they are consistent with the results reported by Oztaş et al. *(31)* and Zohar et al. *(22)*.

As TXA is a potent antifibrinolytic agent, there are concerns that it could increase venous thromboembolic (VTE) complications when used in TKA applications. In a meta-analysis by Kim et al. *(26)* which investigated VTE complications apart from bleeding parameters, no statistically significant difference was determined between the control groups and TXA groups in terms of the risk of deep vein thrombosis (DVT) and pulmonary embolism. Januel et al. *(39)* reviewed 47 studies in literature, 41 of which were randomized controlled and 6 of which were observational. Symptomatic VTE complications associated with the use of TXA in THA and TKA were examined in this meta-analysis of 44844 patients. The incidence of symptomatic VTE was determined as approximately 1% in TKA and approximately 0.5% in THR. When examined by year, symptomatic VTE incidence in TKA applications was determined as 0.94% in the period 1996-2005 and this reduced to 0.50% in the period 2006-2011. In THA, the incidence of symptomatic VTE was determined as 0.43% for 1996-2005, which reduced to 0.09% in the period 2006-2011. With evidence of this reduction in incidence in current orthopaedic studies, it has not been determined that the use of TXA has caused an increase in VTE complications compared to control groups *(26,39,40,41,42,43,44)* In the current study, symptomatic VTE was not determined and the results are consistent with the literature.

There were some strengths and some limitations to this study. The greatest advantage was that as the study was prospective, there was no loss of data. As there are few studies which have researched oral TXA efficacy in TKA applications, this study can be considered of value for the reader by adding to current knowledge in the literature *(21,22)*. A limitation of the study could be thought that the TKA operations were performed by different surgeons. However, a standardized TKA surgical technique is applied in our clinic, and as all the operations were performed with the same method, this should not be considered to have an impact on the study results.

Our study showed that the application of local TXA was as effective as systemic combined applications, significantly reduced blood loss from the drain compared to systemic+long and systemic+oral applications and that these systemic combined applications had no superiority to the systemic+oral combined application in terms of blood loss, transfusion rate and drain follow-up. Local TXA administration in TKA applications is an effective and safe alternative. That no superiority was determined of the systemic combined protocols over the systemic+oral protocol was significant with respect to the efficacy of oral TXA. To the best of our knowledge, this is the first study to have compared systemic+oral combined use with other protocols and routes. Therefore, we think that our study is valuable to the readers.

Authorship declaration

Compliance with ethical standards : approval for the study was granted by the Local Clinical Research Ethics Committee. All authors listed meet the authorship criteria according to the latest guidelines of the International Committee of Medical Journal Editors, and all authors are in agreement with the manuscript.

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