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Comparison of weight-based versus standard dosing of tranexamic acid for blood loss and transfusion amount in knee arthroplasty without tourniquet

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The aim of the study is to compare weight-based versus standard dosing of intravenous (IV) tranexamic acid (TXA) for blood loss and transfusion amount in total knee arthroplasty (TKA) without a tourniquet.

A total of 99 patients were divided into two groups: Group 1 (standard): 1 g of IV TXA 30 min before skin incision, and 1 g at postoperative 30 min and 3 h. Group 2 (weight-based): 10 mg/kg IV TXA 30 min before the skin incision, and 10 mg/kg at postoperative 30 min, and 3 h. Hemoglobin levels, before, and 1, and 2 days after the operation, postoperative amount of decrease in hemoglobin levels, and amount of erythrocyte transfusion were recorded. Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) and Knee Society Score (KSS) were applied in the evaluation of TKA results preoperatively, and at 1., 3., 6., and 12. months, postoperatively.

In both study groups, hemoglobin levels in male patients dropped significantly more deeply than female patients. Also, in both study groups, hemoglobin levels were significantly lower in patients with comorbid illnesses. A statistically significant difference was not detected between both groups in terms of pre- and postoperative WOMAC scores, KSS knee scores, and KSS function scores.

Our study showed that standard and weight-based dosing of IV TXA treatments were similar in efficacy and safety. Both treatments reduce blood loss and the need for transfusion. Also, there was no significant difference in terms of reliability between two groups.

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INTRODUCTION

Total knee arthroplasty (TKA) is frequently used today in patients with advanced-stage osteoarthritis to reduce pain and increase range of motion *(1)*. In studies conducted, blood loss during TKA has been reported as 1000-1790 mL and the requirement for blood transfusion as 10-38 % *(2)*. Increases

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in transfusion requirements are associated with additional financial costs, risks of hemolytic reactions, and the risk of transmission of viral disease.

It has been suggested that with the use of tranexamic acid (TXA), the amount of bleeding is significantly reduced resulting in decreases in hypovolemic side effects, delayed wound healing, and reduced intra-articular hematoma formation. All these positive effects allow early postoperative rehabilitation *(3)*. TXA is a fibrinolysis inhibitor and plasminogen activator that has been applied in various surgical fields for a long time. In recent years, it has been started to be also used in the field of orthopedic surgery. Both intravenous (IV) and intra-articular TXA administration aim to reduce blood loss and blood transfusion requirements.

Although there are numerous studies in the literature on the efficacy of IV administration of TXA, only a few studies have compared different IV applications *(4)*. In the present study, we aimed to compare weight-based versus standard dosing of IV TXA for blood loss and transfusion amount in TKA without a tourniquet.

MATERIALS AND METHODS

This retrospective study has been conducted in accordance with the principles of the Helsinki Declaration and approved by the local Institutional Review Board. Written informed consent was obtained from all subjects.

Between January 2014 and January 2017, 99 patients who underwent TKA with the diagnosis of primary osteoarthritis were enrolled in the study. Until April 2015, standard dosing was preferred in IV TXA use in our clinic, after May 2015 this application was replaced by weight-based dosing. Patients were divided into two groups according to the application of IV TXA (Transamin, Fako Pharm Co AS, Istanbul, Turkey).

Group 1 (standard dosing) (n=48): Intravenous administration of 1 g of TXA 30 min before skin incision, and 1 g at postoperative 30 min and 3 h

Group 2 (weight-based dosing) (n=51): Intravenous administration of 10 mg/kg TXA 30 min before the skin incision, and 10 mg/kg, at postoperative 30 min, and 3 h.

Patients who had undergone revision or simultaneous bilateral TKA surgery, those with > 30° flexion deformities or > 30° valgus-varus, preoperative anemia, renal or hepatic dysfunction, severe cardiac or cerebrovascular disease, congenital or acquired disease hematologic disease, DVT or pulmonary embolism, patients with contraindications to TXA use were excluded from the study.

Age, gender, body mass index (BMI), planned side of surgery, and presence of comorbid diseases of the cases included in the study were recorded. Hemoglobin levels, before, and 1, and 2 days after the operation, postoperative amount of decrease in hemoglobin levels, and the amount of erythrocyte transfusion were recorded.

Two scoring systems Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) and Knee Society Score (KSS) were applied in the evaluation of knee arthroplasty results preoperatively, and at 1., 3., 6., and 12. months, postoperatively.

Western Ontario and McMaster Universities Osteoarthritis Index: WOMAC consists of sections of pain, stiffness, physical function, social function and emotional function. The questions for these sections are graded from 1 to 5. Then the scores of each section are summed up to estimate the score of this section. In this system pain, joint stiffness and functions are questioned, and the low score indicates better outcomes.

Knee Society Score: The patients are investigated in three categories: A. Unilateral or bilateral procedures, but successfully applied to the contralateral knee, B. Ipsilateral and contralateral knees are symptomatic, C. Multiple arthrotic involvement. The scoring results are evaluated as follows: weak, <60 pts; 60-69, moderate; 70-84 pts, good; 85-100 pts, excellent.

Statistical Analysis: Comparisons were made with parametric (Student's t-test) and nonparametric (Friedman, Wilcoxon, and Mann-Whitney) tests. The distribution of categorical variables in both groups was compared using Fisher's exact test. To calculate correlation coefficients, partial correlation test was used. Correlations between continuous

variables were determined nonparametrically using Spearman's rho.

RESULTS

A total of 99 patients met the eligibility criteria for the study. Of the 99 patients (32 males, 67 females), the mean age was 66.7±6.2 (range, 57 to 79) years. Group 1 included 48 patients (14 males, 34 females) with a mean age of 66.1±6.5 (range, 57 to 78) years, and a mean BMI of 28.25±1.64 (range, 24.6 to 31.7) kg/m^2. Group 2 included 51 patients (18 males, 33 females) with a mean age of 67.3±5.9 (range, 58 to 79) years, and a mean BMI of 28.39±2.44 (range, 24.4 to 36.6) kg/m^2. Both groups did not differ from each other by means of age, gender, and BMI (p=0.127, p=0.528, and p=0.782, respectively). There was no statistical difference between groups in terms of the operating sides (p=0.544) and comorbidity (p=0.987).

There was a statistically significant intragroup difference between preop, day 1 and day 2 in terms of hemoglobin levels in both groups (Table I). The amount of hemoglobin reduction was 2.37±0.47 gr/dl in Group 1 and 2.33±0.75 gr/dl in Group 2 (p=0.769). The number of erythrocytes transfused has not statistically significant intragroup, and intergroup difference (p=0.913).

The comparison of the groups in terms of pre- and postoperative WOMAC scores, KSS knee scores, and KSS function scores in different time points is shown in Table II. A statistically significant difference was detected between groups, as for preop, 1., 3., 6., and 12-month. WOMAC, KSS knee, and KSS function scores (p<0.05).

The results of post-hoc pairwise comparisons are shown in Table III. According to these results, there was a statistically significant difference between all binary measurements (Wilcoxon p<0.001 Bonferroni correction).

In terms of postoperative complications, 1 patient in Group 1 and 1 patient in Group 2 had wound drainage (p=1.00). Duration of hospital stay was 5.4 (range, 4 to 8) days in Group 1 and 5.2 (range, 4 to 8) days in Group 2 (p>0.05).

DISCUSSION

In the present study, we aimed to compare weight-based versus standard IV dosing of TXA for blood loss in knee arthroplasty and revealed that both dosing regimens have similar effects.

Results of systematic reviews indicate that TXA reduces blood transfusion requirements whatever its etiology may be *(3)*. Tammachote et al. investigated the efficacy of high dose (3 g) compared with low

Table I. — Comparison of hemoglobin level, amount of hemoglobin reduction and number of transfused erythrocytes between two groups

	Group 1 (standard dosing) (n=48)	Group 2 (weight-based dosing) (n=51)	p Value
Preoperative hemoglobin (gr/dl)	12.24±1 10.8-14.7)	12.18±1.13 (10.4-14.5)	0.718
Postoperative 1. day hemoglobin (gr/dl)	9.87±0.92 (7.3-11.7)	9.86±1.26 (7.1-12.7)	0.883
Postoperative 2. day hemoglobin (gr/dl)	10.98±0.66 (10.1-12.7)	11.16±0.71 (10.1-12.9)	0.239
p Value	< 0.001	< 0.001	
Amount of hemoglobin reduction (gr/dl)	2.37±0.47 (1.5-3.7)	2.33±0.75 (0.7-4)	0.769
Number of transfused erythrocytes (U)	0.65±0.6 (0-2)	0.65±0.66 (0-2)	0.913

Table II. — Comparison of two groups in terms of pre- and postoperative Western Ontario and McMaster Universities Osteoarthritis Index and Knee Society Score

		Group 1 (standard dosing) (n=48)	Group 2 (weight-based dosing) (n=51)	p Value
WOMAC score	Preoperative	73.08±7.52 (61-85)	72.82±7.46 (61-86)	0.919
	Postoperative 1 month	53.27±5.01 (45-64)	52.94±5.19 (45-64)	0.693
	Postoperative 3 months	28.9±4.52 (22-40)	29.08±4.32 (22-40)	0.598
	Postoperative 6 months	14.17±2.75 (10-20)	14.14±3.05 (10-22)	0.821
	Postoperative 12 months	11.54±1.5 (9-14)	11.2±1.43 (9-14)	0.204
p Value		< 0.001	< 0.001	
KSS knee score	Preoperative	35.04±2.82 (30-40)	34.82±2.96 (30-40)	0.756
	Postoperative 1 month	56.71±4.98 (48-68)	56.84±5.7 (48-68)	0.930
	Postoperative 3 months	67.83±4.23 (60-79)	67.61±5.3 (59-79)	0.743
	Postoperative 6 months	77.73±4.15 (71-83)	78.2±4.88 (70-89)	0.465
	Postoperative 12 months	86.85±3.92 (81-93)	86.2±4.65 (72-93)	0.510
p Value		< 0.001	< 0.001	
KSS function score	Preoperative	30.21±7.99 (20-50)	29.41±9.88 (15-50)	0.480
	Postoperative 1 month	46.98±7.56 (30-60)	46.86±8 (30-60)	0.847
	Postoperative 3 months	61.71±6.3 (50-70)	61.18±7.04 (50-75)	0.723
	Postoperative 6 months	76.04±4.72 (65-85)	75.39±5.9 (60-85)	0.536
	Postoperative 12 months	84.9±4.44 (75-90)	84.12±6.38 (70-90)	0.883
p Value		< 0.001	< 0.001	

WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index; KSS: Knee Society Score

dose (500 mg) of intra-articular tranexamic acid in postoperative blood loss after primary TKA and showed that high-dose TXA was 43% more effective in reducing postoperative blood loss compared with low dose *(4)*. Tille et al. aimed to evaluate if blood loss and transfusion rate can be reduced in primary TKA by intraarticular application of TXA and revealed that 2 g TXA resulted in a significant reduction of blood loss and transfusion rate after primary TKA without increased complication rates *(5)*. Cao et al. aimed to evaluate whether TXA administration could reduce blood loss after bilateral TKA and

Table III. — Post-Hoc binary comparison of time points between groups for Western Ontario and McMaster Universities Osteoarthritis Index and Knee Society Score

Post-Hoc binary comparison	WOMAC score		KSS knee score		KSS function score	
	Group 1	Group 2	Group 1	Group 2	Group 1	Group 2
Preop. vs. Postop. 1st month	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Preop. vs. Postop. 3rd month	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Preop. vs. Postop. 6th month	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Preop. vs. Postop. 12th month	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Postop. 1st month vs. Postop. 3rd month	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Postop. 1st month vs. Postop. 6th month	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Postop. 1st month vs. Postop. 12. month	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Postop. 3rd month vs. Postop. 6th month	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Postop. 3rd month vs. Postop. 12th month	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Postop. 6th month vs. Postop. 12th month	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
	Hemoglobin					
	Group 1	Group 2				
Preop. vs. Postop. 1st day	<0.001	<0.001				
Preop. vs. Postop. 2nd day	<0.001	<0.001				
Preop. vs. Postop. 3rd day	<0.001	<0.001				

WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index; KSS: Knee Society Score; Preop: Preoperative; Postop: Postoperative

assigned 575 patients into three groups on the basis of TXA usage, including IV group, combined group (IV TXA combined with intra-articular TXA) and control group (no TXA use). The study indicated that TXA could reduce blood loss with no apparent increase between IV and combined groups *(6)*.

Many studies have been conducted on the application of IV TXA. Intravenous TXA dosing recommendations vary tremendously between surgical procedures and between published dosing regimens. There are literally dozens of clinical trials yielding widely different dosing recommendations. Analysis of appropriate dosing and timing of TXA administration was limited in the literature as no standard protocol has been determined: In the literature, reports of IV TXA used weight-based dosing *(7-14)* or standard dosing *(15-29)*. When weight-based dosing was used, cases received ranging between 10 and 20 mg/kg. Standard dosing ranged from 0.5 to 3 g for IV TXA. Patients received a single *(7, 8, 12-15, 17, 18, 22-24, 26-28)* double *(7, 9, 15, 16, 21, 22)* or triple *(10, 11, 19, 30)* dosing of TXA, depending on the study. Finally, the timing of IV administration differed amongst the reports. The IV administration of TXA was achieved at the time of incision, before the tourniquet inflation or deflation, after the tourniquet deflation, after cementing the prosthesis, or after wound closure. Legnani et al.

retrospectively compared pre- and post-operative infusion of TXA 15 mg/kg to a single pre-operative infusion and revealed that double infusion is more effective compared to single infusion in reducing need for transfusion requirements *(31)*. Tzatzairis et al. compared three different dosages of intravenous (IV) TXA in TKA without tourniquet. Group A received 15 mg/kg of IV TXA given on induction, Group B received an additional dose of IV TXA (15 mg/kg) 3 h after incision and Group C received an additional (third) dose 3 h later (15 mg/kg). According to their results, three doses of IV TXA have effectively and safely reduced blood loss *(32)*. In the present study, we aimed to compare weight-based versus standard dosing of IV TXA. Until April 2015, standard dosing was preferred in IV TXA use in our clinic, after May 2015 this application was replaced by weight-based dosing. Weight-based dosing group received IV administration of 10 mg/kg TXA 30 min before the skin incision, and 10 mg/kg, at postoperative 30 min, and 3 h; while standard dosing group received IV administration of 1 g of TXA 30 min before skin incision, and 1 g at postoperative 30 min and 3 h.

Limited clinical trials have concentrated on determining the ideal time and dosing for the administration of TXA. Iwai et al. performed a prospective analysis evaluating cases who had a single dosing of IV TXA 10 minutes before tourniquet deflation and the ones who had an extra dosing 3 hours postoperatively and revealed that the 2-dose group had significantly lower blood loss and transfusion amount *(33)*. Maniar et al. evaluated different 10 mg/kg IV dosing of TXA and revealed a statistically significant decrease in total blood and drain loss in cases who had 3 doses (pre-, intra-, and postoperatively) compared with cases receiving either a single or double dosing of TXA *(4)*. Wong et al. compared cases who had either 1.5 g or 3 g of IV TXA and revealed no statistically significant difference in total blood loss between 2 study groups *(34)*. Since the administration of TXA might have a dose-dependent consequence on decreasing the amount of blood loss, it is likely that the dosing and timing of administration might influence the amount of drain output, blood loss, and transfusion. In our study, no statistically significant difference was found in terms of efficacy and safety between the different forms of IV administration in TXA during TDA.

The most important consideration in patients who will be given IV TXA is patient selection. Care should be exercised to avoid IV administration of TXA to patients with a history of DVT or PE and with thromboembolic and cardiological problems. In their meta-analysis Brown et al. reported that the use of TXA did not cause significant increases in mortality, stroke, myocardial infarction, renal insufficiency, and reoperation rates *(35)*. Previous literature has demonstrated that the risk of venous thromboembolism is not increased by TXA, but given its mechanism of action, patient history and risk factors should still be strongly considered when choosing the administration route and dosage *(36)*. None of the patients participating in the study had any complication that could be caused by the use of TXA, and no reoperation was needed.

Limitations of our study include the retrospective design and relatively small number of our series. Also, some details of history and factors that may influence the outcome may not be thoroughly documented. Another limitation is that there is no separate control group that uses a placebo in our study. Due to these restrictions, associations should be interpreted with caution.

CONCLUSION

In conclusion, our study showed that weight-based and standard dosing of IV TXA treatments were similar in efficacy and safety. Both treatments reduce blood loss and the need for transfusion. However, there was no significant difference in terms of reliability between the two groups.

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