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ORIGINAL STUDY

Tranexamic acid use in simultaneous bilateral total knee arthroplasty : a comparison of intravenous and intra-articular applications, which is more effective?

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Patients applied with simultaneous bilateral total knee arthroplasty (SBTKA) with the administration of intravenous or intra-articular tranexamic acid (TXA) were compared in respect of blood loss and the need for allogenic blood transfusion.

Of a total 53 patients applied with SBTKA, 32(60%) were administered intravenous TXA and 21(40%) intra-articular TXA. The patients were evaluated in respect of age, gender, height, weight, body mass index (BMI), body blood volume, preoperative and 1,2,3 and 4 days postoperative levels of hemoglobin (Hb) and hematocrit (Htc) and the change in Hb levels, estimated blood loss, mean actual blood loss, the need for allogenic blood transfusion (ABT) and the use or not of a drain.

No difference was determined between the intravenous and intra-articular groups in respect of mean age, gender, height, weight, and body blood volume. No difference was determined between the groups in preoperative and postoperative mean Hb and Hct values, the reduction in mean Hb postoperatively, estimated blood loss, or the need for ABT. No deep vein thrombosis or pulmonary embolism was determined in any patient.

In the application of SBTKA, TXA can be safely administered by the intravenous or intra-articular route to reduce the need for ABT. The results of this study determined no difference in efficacy between the routes of application. For patients with a risk of intravenous use, intra-articular application can be preferred.

Keywords : simultaneous bilateral total knee arthroplasty ; blood loss ; allogeneic blood transfusion ; intra-articular ; intravenous ; tranexamic acid.

INTRODUCTION

Blood loss (BL) after TKA has been reported as 1685.0±571.4 mL and need for allogenic blood transfusion (ABT) at a rate of 23% *(1)*. As the

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vast majority of the patient population for TKA is >65 years, BL tolerance is lower because of cardiovascular diseases *(2)*. Complications of ABT such as increased cost, blood-borne and periprosthetic joint infections, febrile and allergic reactions, hemolysis, immunosuppression, circulatory overload, electrolyte imbalance, acid-based disorders, pulmonary problems and even death, could obviously result in higher rates *(3-5)*.

To reduce BL and ABT, tranexamic acid (TXA) usage, which inhibits fibrinolysis with reversible lysine blockage without increasing thromboembolic complications, has come widespread in recent years *(6)*. In studies showing that TXA reduced BL and ABT, successful results have been reported, but timing, route and dosage of TXA show great diversity *(7-11)*. Intra-articular (IA) versus intravenous (IV) methods have also been studied but no difference has been determined in terms of diminishing ABT and BL *(12)*.

Although studies related to the use of both IVTXA and IATXA and combined use in both unilateral and SBTKA have reported decreased BL and ABT, conflicting results have been reported related to administration route *(9,11,13,14)*. There are 2 studies that reported the results of IVTXA or IATXA in SBTKA *(15,16)*. One of them reported no difference but, it was a computer assisted SBTKA and additional to this, patients with a past history of thromboembolic episodes, cerebrovascular diseases, and chronic renal diseases were excluded from this study *(15)*. On the contrary, authors of the other one concluded IA administration was better than IVTXA in reducing blood loss and clinical outcome after SBTKA. But they also excluded patients with coagulapathy, history of thromboembolic disease, renal insufficiency *(16)*. It has been thought that TXA could increase thromboembolic events such as deep vein thrombosis (DVT) and pulmonary emboli (PE) because of potential hypercoagulability in situations where thromboprophylactic agents cannot be used *(17)*. Due to this theoretical risk of vascular thrombosis, an empirical trend towards not giving TXA to patients with a previous history or increased risk of DVT/PE, stroke, MI, cardiac stents or bypass surgery, or who have thrombophilia has existed *(18)*. Hovewer, considering the beneficial effect of TXA in reducing BL and ABT, we have started using IATXA instead of not using TXA for these patients with bypass surgery or vascular stent, stroke or MI, end stage renal disease and a history of DVT. As it is seen, there is no study on the use of TXA in SBTKA patients with a history of thromboembolism and the above mentioned comorbidities and there is also no consensus on the route of administration of TXA in SBTKA and the information on this subject is insufficient in the literature. For these reasons, BL and ABT were evaluated in SBTKA patients without a history of thromboembolism and who were given IVTXA, and SBTKA patients who had a history of thromboembolism, chronic renal failure, vascular stent and stroke who received IATXA in this study.

MATERIALS AND METHODS

Data of patients who underwent cemented SBTKA using IVTXA or IATXA to reduce postoperative BL and the need for ABT in our clinic between 2014 and 2019 were evaluated retrospectively. Patients with a history of bypass surgery or vascular stent, stroke or MI, end stage renal disease and a history of DVT were administered IATXA and constituted the IA group and the others who were administered IVTXA constituted the IV group. We did not exclude any patients with a history of those mentioned disorders. So, a total of 53 patients were identified who underwent SBTKA, of which 32 (60%) were given IVTXA and 21 (40%) were given IATXA. Approval for the study was granted by the Local Ethics Committee.

The patients were evaluated in respect of demographic characteristics [age, gender, height (H), weight (W), body mass index (BMI), body blood volume (BBV)], and preoperative and 1st, 2nd, 3rd, and 4th days postoperative hemoglobin (Hb) and hematocrit (Htc) levels, the change in Hb level, estimated BL, mean actual BL, the need for ABT. Preoperative Hb levels were not <10.0 in any patient. The perioperative BL was measured using the formula described by Nadler (19). According to Nadler’s formula, we first calculated the estimated BBV separately for men and female.

$$BBV\text{-}male(L)=(0,3669 \times H^3)+(0,03219 \times W) + 0,6041$$

BBV-female(L)=(0,3561 x H³)+(0,03308 x W)+0,1833

Hb loss was found by applying the estimated BBV, preoperative Hb, postoperative Hb and transfused Hb amount to the formula below.

Hb loss=BBVx(Preoperative Hb-Postoperative Hb)x10 dL/L+amount of transfused Hb

Theoretical BL and actual BL were found by calculating the Hb loss, preoperative Hb, and transfused blood volume as formulated below.

Theoretical BL=100 mL/dLx(Hb loss/Preoperative Hb)

Actual BL=Theoretical BL + Transfused Blood Volume

For patients with IVTXA, an infusion was administered of 15 mg/kg in 500 cc saline 15 mins before skin incision for 30 mins, and at 4 hours postoperatively, an infusion of 10 mg/kg in 500 cc saline for 30 mins. IATXA was administered to the proximal-medial surface of the patella with an injection after capsular closure before tourniquet deflation. IATXA was given as 1.5 g per knee. We have 250 mg/5 mL ampoules, and we filled 6 of them into a syringe and emptied them at 1.5 g TXA per knee.

We have not used hemovac drain for 2 years in TKA with TXA. Therefore, of the 53 cases in the study, hemovac drain was used in 30 (56%) cases and not in 23 (44%) cases. The operations were performed by the same surgeon. Following capsular closure of the first side TKA, before tourniquet deflation, the other knee was started. Operations were performed with regional anaesthesia under a pneumatic tourniquet (≤250 mm/Hg). Femoral canal was filled with a bone plug. Cemented PS TKA was implanted. In patients with hemovac drain, after IATXA, the drain was clamped and opened 2 hours later. Patients were encouraged to start exercises in bed, and mobilized on postoperative day 1. For DVT prophylaxis, 0.4 ml enoxaparin sodium was started 8 hours after surgery and used 10 days postoperatively. Hb level of 8.0 g/dl was determined as trigger for ABT but transfusion was also done when Hb values were 8-10 g/dl in patients with symptoms of hypotension, tachycardia, dizziness and loss of balance. Patients were discharged on postoperative day 3 with the exception of 2 patients who received ABT and were hospitalized for >7 days.

Patients with increased leg circumference, swelling and Homan's test positivity in the postoperative period were investigated with venous Doppler USG for the presence of DVT. The presence of any findings such as wound problem, hyperemia, temperature increase or sensitivity in the joint were recorded.

Data were analysed with SPSS 15.0 for Windows. Descriptive statistics were stated as number (n) and percentage (%) for categorical variables and as mean±sd, minimum and maximum values for numerical variables. In the comparison of two groups, Student's t-test was used for numerical variables showing normal distribution, and the Mann Whitney U-test for variables not showing normal distribution. Ratios in the groups were compared with Chi-square analysis. Significance level was accepted as 0.05.

Table I. — Age, gender, weight, height, BMI, body blood volume values of local and systemic groups

		Type of Application				
		Local(IATXA)		**Systemic(IVTXA)**		
		n	%	n	%	p
Gender	Male	6	28.6	6	18.8	0.507
	Female	15	71.4	26	81.3	
		Mean ±SD	Min-Max (Median)	Mean ±SD	Min-Max (Median)	p
Age (years)		68.8±7.1	54-85 (68)	65.2±6.9	53-81 (64)	0.075
Height (m)		1.64±0.07	1.53-1.78 (1.64)	1.63±0.08	1.51-1.83 (1.625)	0.828
Weight (kg)		75.8±9.5	59-93 (75)	74.4±8.7	57-91 (74.5)	0.587
BMI		28.2±2.9	21.9-33.2 (28.7)	27.9±3.3	21.2-35.1 (27.9)	0.771
Body blood volume		4.45±0.62	3.44-5.56 (4.46)	4.35±0.58	3.53-5.78 (4.20)	0.524

RESULTS

No difference was determined between the IVTXA and IATXA groups in respect of age, gender, height, weight, BMI and BBV (Table I). According to the American Society of Anesthesiologists (ASA) classification, there were 6 (18.8%) ASA-1, 22 (68.8%) ASA-2, and 4 (12.5%) ASA-3 patients in the IVTXA group. In the IATXA group, there were 3 (14.3%) ASA-1, 13 (61.9%) ASA-2, 4 (19.0%) ASA-3, 1 (4.8%) ASA-4 patients. There was no significant difference between the groups in terms of ASA classification (p=0,651). When the evaluation was made in terms of comorbidities between the IVTXA and IATXA groups, no significant difference was found between the groups (Table II). In the comparison of the TXA administration route, hemovac drain was not used in 13 patients (26 knees) applied with IVTXA and in 10 patients (20 knees) applied with IATXA. No difference was determined between the groups in respect of drain use (p=0.615). No difference was determined in preoperative and postoperative mean Hb, the reduction in mean Hb postoperatively, estimated BL, actual BL, or the need for ABT (Table III). A total of 13 units (U) ABT were applied to 8 (38.1%) patients in the IATXA group (2 patients 1U, 5 patients 2U, 1 patient 3U), and a total of 8U to 6 (18.8%) patients in the IVTXA group (4 patients 1U, 2 patients 2U).

Table II. — Comorbidities of local and systemic TXA groups

Comorbidities	Systemic (IVTXA)	Local (IATXA)	P value
Coronary artery disease	0 (%0,0)	2 (%9,5)	0,152
Chronic renal failure	0 (%0,0)	1 (%4,8)	0,396
Coronary artery surgery	0 (%0,0)	2 (%9,5)	0,152
Anemia	1 (%3,1)	1 (%4,8)	1,000
Hypertension disease	15 (%46,9)	12 (%57,1)	0,465
Diabetes mellitus	6 (%18,8)	3 (%14,3)	1,000
Thyroid diseases	4 (%12,5)	1 (%4,8)	0,637
Lung diseases	6 (%18,8)	4 (%19,0)	1,000
Psychiatric disorders	2 (%6,3)	2 (%9,5)	1,000
Hyperlipidemia	0 (%0,0)	2 (%9,5)	0,152
Rheumatoid arthritis	0 (%0,0)	2 (%9,5)	0,152
Peripheral venous insufficiency	1 (%3,1)	1 (%4,8)	1,000
Previous gastrointestinal surgery	2 (%6,3)	5 (%23,8)	0,099
Others	2 (%6,3)	5 (%23,8)	0,099

Venous Doppler USG examination was made in 5 patients in the IVTXA and 6 patients in the IATXA groups because of suspicion of DVT. No DVT or PE was determined in any patient. No revision was done in any knee because of superficial or deep infection. There was no wound problem in the follow-up of the patients.

We had 2 patients who received ABT and were hospitalized for >7 days. One of the patients was an elderly 67-year-old male patient with a history of left nephrectomy for renal failure. He was in IATXA group. Because his preoperative Hb value of 13.5 g/dL dropped to the level of 6.6 on the postoperative 1st day, 2 U ES transfusion was performed. The Hb level was 9 on 2nd and 9.2 3rd postoperative day. There was no problem in the mobilization of the patient and no additional problems developed. Other patient was a 76-year-old female patient who was administered IVTXA. Her Hb level was 11 g/dL before the operation. It was 10.5 on the 1st, 8.5 on the 2nd and 7.5 on the 3rd postoperative day, 2 U ES transfusion was performed because of Hb drop. Hb increased to 8.7 g/dL after ABT. Upon detection of a Felix Type 1 intraoperative fracture in the left tibia, it was fixed with 2 cannulated screws. For this reason, the patient was hospitalized for more than 7 days in order to learn about controlled rehabilitation. The postoperative course was uneventful.

DISCUSSION

Although TXA has been used to reduce BL and the need for ABT in SBTKA, no consensus has yet been reached on the ideal administration route *(1,9,20-22)*. The most significant finding of this study was that there was no difference between IVTXA and IATXA in SBTKA in respect of the amount of BL and the need for ABT. A secondary outcome was that in drainless SBTKA, there was advantage of either of the two routes of TXA. The results of the

Table III. — Local and systemic TXA preoperative and postoperative blood values, blood losses need for blood transfusion

		Application Type				
		Local(IATXA)		Systemic(IVTXA)		
		Mean±SD	Min-Max (Median)	Mean±SD	Min-Max (Median)	p
HGB	Preop	12.56±1.62	9.2-15.5 (12.4)	12.63±1.24	10.3-14.9 (12.8)	0.867
	PO 1	10.96±1.60	6.6-14.3 (10.9)	11.33±1.14	9.6-14.1 (11.05)	0.418
	PO 2	10.16±1.85	7-13.7 (9.5)	10.87±1.52	8.5-14.2 (11)	0.134
	PO 3	9.78±1.76	7.5-13.1 (9.2)	9.88±1.49	7.5-13 (10.1)	0.813
	PO 4	9.66±1.70	7-12.3 (9)	9.73±1.78	7-12.6 (9.45)	0.985
	Minimum	9.02±1.74	6.6-11.9 (8.3)	9.33±1.43	7-11.5 (8.95)	0.506
HTC	Preop	37.6±4.8	27.7-44.7 (38.1)	38.1±3.9	30.3-45.8 (38.5)	0.665
	PO 1	33.8±5.2	20.7-43.1 (32.8)	35.0±3.7	28.3-42.3 (33.8)	0.344
	PO 2	32.2±5.3	25.5-41.2 (31.8)	33.3±5.0	25.5-42.4 (33.45)	0.433
	PO 3	30.9±6.3	22.1-40.1 (30.1)	31.0±5.6	22.2-39.7 (31.85)	0.971
	PO 4	30.6±5.9	20.8-40.4 (29.6)	30.5±6.4	20.8-40.1 (31.2)	0.949
Hemoglobin loss (gr)		162.2±69.3	56.0-323.7 (154.5)	145.8±69.5	37.9-305.0 (128.9)	0.404
Theoretical blood loss (ml)		1282.8±497.4	462.6-2529.1 (1188.2)	1143.1±501.4	305.4-2323.5 (1072.6)	0.324
Actual blood loss (ml)		992.3±523.7	-445.2-1956.1 (1110.7)	946.2±469.6	246.7-1955.6 (917.7)	0.740
Blood transfusion	**No**	13 (61.9)		26 (81.3)		0.118
	Yes	8 (38.1)		6 (18.8)		
	1 Unit	2 (9.5)		4 (12.5)		
	2 Unit	5 (23.8)		2 (6.3)		
	3 Unit	1 (4.8)		0 (0.0)		

current study show that both IATXA and IVTXA can be used in SBTKA safely.

Although less BL has been reported with combined administration of IVTXA+IATXA than single IVTXA route in a non-randomised comparative study with tourniquetless SBTKA *(9)*, no benefit of combined administration has been found in recent prospective randomized studies in SBTKA *(1,11,20)*. These studies were all comparison of combined group vs single route of TXA administration. We did not have combined group in our study. However, there are few studies which compared the sole use of IVTXA or IATXA in SBTKA *(15,16)*. In a prospective study of 90 patients with computer-assisted SBTKA were evaluated in 3 groups of placebo, 1 g IVTXA and 1 g IATXA to each knee of TXA. Although the TXA groups were seen to have better results in respect of the postoperative decline in Hb level and need for ABT, no superiority of one route was determined. But, this study was based on computer-assisted SBTKA *(15)*. However, the administration of 15 mg/kg IATXA 10 mins before closure was seen to have relatively better results compared to 2 doses of IVTXA (15 mg/kg 30 mins before tourniquet deflation, and the same dose repeated 2 hours later) in a prospective study of 70 patients *(16)*. Additionally, patients with a history of bleeding disorders, thromboembolic episodes, cerebrovascular diseases, known allergy to TA and chronic renal or liver diseases were excluded from these above mentioned studies *(15,16)*. On the contrary, the decrease in Hb level in the first 4 days postoperatively was the same in IATXA and IVTXA groups in the current study. As it is seen there is no consensus on the better route of TXA administration. When combined group studies are taken into account that combined TXA administration had no advantage over sole use *(11,20)*, we suggest the IVTXA or IATXA to be appropriate for the reduction of BL and requirement for ABT in SBTKA despite the lack of a combined group in our study. Furthermore, we think that IATXA can be used safely in patients with a history of thromboembolism, stroke, vascular stents, CHD and chronic renal failure regarding that we had no complications related to IATXA in these patients.

There is no consensus not only the route of administration but also on the dose of TXA and the number of applications *(21-23)*. IVTXA is administered either single or multiple times and the amount of dose is also controversial *(1,9,11,15,18,20,24,25)*. Single dose of 1 g IVTXA has been found to be ineffective when compared to patients with no IVTXA in SBTKA *(26)*. IATXA is also administered with a variety of dosages (range, 1-3 g per knee) *(11,13,18,25)*. In a study where 1.5 g and 3 g IATXA doses were compared in unilateral TKAs, BL was determined to be reduced by 20% (300 mL) and 25% (400 mL) respectively compared to placebo group, but no difference was found between the 1.5 g and 3 g IATXA *(27)*. In the current study, IATXA was administered as 1.5 g to each knee, and IVTXA as 15 mg/kg just before skin incision+10 mg/kg after 4 hours postoperatively. Other than the aim of comparing the TXA doses, as no difference was determined between the IVTXA and IATXA in respect of decrease in Hb level, BBL, and ABT, we recommend that these doses can be used effectively in SBTKA.

Previous studies have found no difference between IVTXA and IATXA in respect of ABT *(15)*. However, in a prospective, randomized study with SBTKA, it was reported that while ABT was not required in IATXA group, transfusion was required in 7 out of 35 (20%) patients in IVTXA group, and thus IATXA administration was concluded to be more advantageous *(16)*. In the current study, we found no significant difference between groups in respect of ABT which was consistent with the literature.

Venous Doppler USG was made of a total of 11 patients in the current study, 6 in IATXA and 5 in IVTXA groups, who had increased leg circumference and complaints of pain. No DVT was detemined in any patient and the postoperative rehabilitation program was continued. No PE developed clinically in any patient and no superficial or deep infection was determined in any case. IVTXA and IATXA administration in computer-assisted SBTKA have caused no difference in respect of DVT, PE, infection or wound problems *(15)*. In a study which compared a combined IVTXA+IATXA group with a sole IVTXA in SBTKA, no thrombotic events was reported in either group, and 1 (2%) patient in the IVTXA group developed arrythmia for which a pacemaker was fitted *(9)*. In another study which compared 154 patients, distal DVT was detected in four of 43 patients (9%) in the combined IVTXA+IATXA group and four of 34 patients (12%) in the IVTXA group without any significance and no major thrombotic events other than distal DVT were determined between groups *(20)*.

In a study comparing 871 patients who were given TXA at a 2-hour interval with 874 patients who were not given TXA in SBTKA, the frequency of DVT was found in 18% in the group given TXA and 14% in the control group, and no significant difference was found *(25)*. In a randomized, controlled study, which compared IATXA only and combined IVTXA+IATXA in SBTKA, no symptomatic DVT or PE, and no superficial wound necrosis were seen in any patient, while wound leakage was observed in 6 (4%) cases in the IATXA group and 5 (3%) in the combined group, with no significant difference(11). TXA has been administered IV and IA in SBTKA operations and no complications have been reported *(16)*.

In recent years, the use of a hemovac drain in TKA has been shown to increase BL and its use is not recommended since it provides no advantage *(28-30)*. Nevertheless, the results of the cases where drain was or was not used were seen to be similar in the current study in both groups.

The main limitation of this study was the retrospective design. Major disadvantage is loss of data from patient files in retrospective studies. However, since 2011, for primary and revision arthroplasties, the data related to BL and ABT have been recorded on a pre-prepared chart in our clinic. Therefore, there were no incomplete or loss of data eliminates this disadvantage. In most studies these types of patients have been excluded, but in the current study, SBTKA patients were compared by admistering IATXA. Thus, the disadvantage of excluding patients can be considered to have been prevented.

CONCLUSION

In conclusion, when all the results are taken into consideration, TXA can be administered by IV or IA route to reduce BL and the need for ABT in SBTKA operations. In particular, as no major complications developed in patients with a history of thromboembolism, the administration of IATXA to each knee can be considered both practical and safe and can therefore be recommended.

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