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Using intra-articular tranexamic acid in total knee replacement surgery with and without bleeding control: a prospective randomized double blind study

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Abstract. – OBJECTIVE: To investigate the effectiveness of tranexamic acid (TA) application in two techniques: in the first one wound closure is performed before the tourniquet is released; in the second one, wound closure is performed after the tourniquet is released.

PATIENTS AND METHODS: The study is conducted on four groups of patients: (1) TA + TNR (tourniquet not released) where there is no bleeding control and TA is applied after wound closure without tourniquet release; (2) TA - TNR where placebo is applied after wound closure without tourniquet release; (3) TA + TR (tourniquet released) where tourniquet is released first and TA is applied after bleeding control and wound closure; and (4) TA - TR where tourniquet release is followed by bleeding control and placebo application.

RESULTS: The amount of hemorrhage in hemovac drains in each group was as follows: 217.4 ± 99.6 (100-590) ml in the TA + TNR group; 411.6 ± 133.7 (175-850) ml in the TA - TNR group; 291.2 ± 89.5 (160-650) ml in the TA + TR group; and 458.2 ± 138.6 (200-920) ml in the TA - TR group ($p<0.0001$). The TA + TNR group differed significantly from other groups in terms of the hemorrhage in drains. Similarly, the TA + TNR group was notably different from the TA - TNR and TA - TR groups with regard to the hemoglobin and hematocrit values.

CONCLUSIONS: The study reveals that the amount of blood in hemovac drains is reduced significantly after the application of tranexamic acid to the suprapatellar space in the technique where wound closure is performed without bleeding control and before the tourniquet is released.

Key Words:
Tranexamic acid, Bleeding, Knee.

Introduction

Patients undergoing total knee replacement (TKA) are at risk of serious bleeding. In previous trials, the reported amount of blood loss in TKA could be up to 2000 cc[1-5]. It is known that the prevention of blood loss through the use of anti-fibrinolytic agents in TKA is a preferred method against the risk of immunological reaction and disease transmission that may accompany blood product replacement[1]. Tranexamic acid (TA), a plasminogen activator-inhibitor, is known to reduce blood loss by inhibiting fibrinolysis[6]. However, the dosage and method of TA administration remains controversial[7]. On the other hand, despite reported complications of pneumatic tourniquets such as increased thrombotic complications, delays in wound healing and their potential to cause neurovascular injury, it is still routinely practiced by orthopedic surgeons. This is due to the facts that pneumatic tourniquets are capable of reducing bleeding and, in turn, blood loss and that they provide a better view for the surgeon and facilitate cement application[8-11]. However, in terms of complications and blood loss, whether it is advantageous to release tourniquet before or after wound closure is still a controversial issue[8]. In the literature, there are no comparative studies carried out between groups where wound closure is done before releasing the tourniquet and where wound closure is performed after tourniquet release and homeostasis, as to what extent intra-articular TA treatment reduces bleeding. Considering this, our objective at the outset was to compare the effectiveness of intra-articular TA with that of control groups and to explore which of the two different wound closure types would be more efficient.

Patients and Methods

Designed as a prospective randomized double-blind evaluation, our work includes four groups of 25 patients, two of which were set as control groups.

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Patients with hemorrhagic diathesis and those who were operated on in the presence of anticoagulant therapy were excluded from the study. Informed consent was obtained from all individual participants included in the study. This study was approved by Clinical Research Ethics Committee of Malatya (Turkey) (Protocol No.: 2016/80). The groups we worked with were as follows: (1) TA + TNR (tourniquet is not released, no bleeding control, tranexamic acid is applied after wound closure); (2) TA - TNR (placebo is applied after wound closure without releasing the tourniquet); (3) TA + TR (tourniquet release is followed by bleeding control, TA is applied after wound closure); and (4) TA - TR (tourniquet release is followed by bleeding control and placebo application is performed afterwards). Throughout the study, TA and placebo administrations were performed after wound closure in the suprapatellar space and the same injection was exercised before tourniquet release in TNR groups. TA application was performed with 6 ampoules of 250 mg TA (transamine % 10 ampoule, Actavis, Istanbul, Turkey) while placebo application comprised of 15 ml saline. The drains were opened after 1 hour of clamping after surgery and finally removed after 24 hours in all patients. A midline parapatellar approach was adopted for all of our patients. For infection prophylaxis, 1 g of cefazolin intravenous (Cezol, Deva, Istanbul, Turkey) was applied before operation and ankle pump exercise was initiated right after each operation. Isotonic and isometric knee exercises were started on post-operative day 1. Patients were assisted in walking with a walker starting from the first day after the removal of surgical drains. All patients were discharged after the fourth post-operative day. Subcutaneous 40 mg/0.4 ml enoxaparin sodium (Clexane, Sanofi Aventis, Istanbul, Turkey) was administered 12 hours after surgery for thromboembolism prophylaxis and continued daily for three weeks. Hemoglobin and hematocrit values were measured pre-operatively. The drains were kept active. The amount of blood in the drains was noted down. The changes in hemoglobin and hematocrit levels between the time before surgery and on post-operative day 3 were taken into account. We applied erythrocyte suspension transfusion if the hemoglobin value was measured to be below 8 g/dl during the post-operative period. For values between 8-10 g/dl, transfusion was applied if symptoms of anemia were present. Tourniquet application and operating times were recorded. The time elapsed from tourniquet inflation until wound closure was taken into consideration while calculating operation times. We used cemented cruciate retaining total knee prosthesis. Patients were asked to present themselves for control visits on post-operative 15th and 45th days and in three, six, and twelve-month intervals. Pre-operative and post-operative 1st year WOMAC scores of the patients were evaluated. The body-mass index of the patients was also calculated. Randomization was achieved by successive selection of patients from among those whose wounds were closed without tourniquet release and those who were applied wound closure after bleeding control and tourniquet release. In the same way, TA and placebo were also administered consecutively with the nurse notified about the order of succession and the surgeon not knowing the process. The statistical data evaluation was conducted according to the numbers appointed to patients on the nurse's list in which each group was designated with a capital letter from A to D.

Statistical Analysis

Statistical analyses were performed using SPSS for Windows, Version 21.0 (IBM Corp., Armonk, NY, USA). Whether the data were normally distributed was examined via the Shapiro-Wilk test. The comparisons between the groups were made by analysis of variance based on the Kruskal-Wallis test and we made use of the Mann-Whitney U-test for the pairwise comparisons. Power analysis suggested that at least 24 subjects should be taken from each group when α=0.05 and 1-β (power)=0.80. The p-value of <0.05 was considered statistically significant.

Results

Pre-operative and post-operative early stage evaluations were performed on all 25 patients included in each group. The demographic characteristics of the groups are shown in Table I.

Table I. Distribution of groups according to demographic characteristics.

	TA+TNR	TA-TNR	TA+TR	TA-TR	*p*
Number of patients	17F,8M (25)	19F,6M (25)	19F,6M (25)	18F,7M (25)	0.83
Age	65.1±7.9 (51-79)	68.5±6.8 (55-82)	67.1±6.7 (53-79)	68.5±5.9 (55-80)	0.41
BMI (kg/m²)	30.2±4.2(21.2-38.7)	31.2±4.8 (20.8-39.1)	29.8±5.7(19.7-36.9)	29.6±4.9 (20.1-39.9)	0.78

F: female, M: male, TA: Tranexamic acid, TNR: Tourniquet non released, TR: Tourniquet released, BMI: Body mass index.

The amount of hemorrhage in the TA + TNR group was 217.4 ± 99.6 (100-590) ml; this was 411.6 ± 133.7 (175-850) ml in the TA - TNR group; 291.2 ± 89.5 (160-650) ml in the TA + TR group; and 458.2 ± 138.6 (200-920) ml in the TA - TR group ($p<0.0001$). Table II shows the detailed values of the other parameters. The TA + TNR group differed significantly from the other groups in terms of the hemorrhage in drains (Table III). The TA + TNR group was notably different from the TA - TNR and TA - TR groups in terms of the 1st and 3rd post-operative day hemoglobin and hematocrit values. The same group did not display a significant difference when compared with the TA + TR group (Table III). None of the patients required erythrocyte suspension as per the 1st post-operative day hemoglobin counts results. When the groups were evaluated in terms of transfusion requirement on the third post-operative day, we observed that the TA + TNR group needed 2, the TA - TNR group 6, the TA + TR group 3, and the TA - TR group needed 8 units of erythrocyte suspension ($p<0.05$). Each patient who received transfusion was given 1 unit of erythrocyte suspension. The evaluation of transfusion requirement showed that the TA - TR group was significantly different from the others (Table III). Turning to tourniquet durations and operation times, we found out that tourniquet duration was longer in the TNR groups while the TR group displayed longer operation times ($p<0.05$) (Table II). There was no difference between the groups in terms of the 1st year WOMAC scores (Table II). One patient in the TA + TNR group had to be excluded from the WOMAC evaluation due to a change of address. Similarly, another patient in the TA - TR group with prosthetic joint infection could not be included in the one-year WOMAC evaluation due to elevated CRP and sedimentation rates on the 45th post-operative day. We applied washout, debridement, and insert replacement for this patient. During the follow-up, one patient in the TA - TNR group underwent aspiration for hemarthrosis on post-operative day 14. In one patient in each of the TA-TR and TA + TNR groups, we observed wound closure defects after sutures were removed. The wounds of these patients were debrided and sutured again. Besides this, we did not observe pulmonary thromboembolism or symptomatic deep venous thrombosis in any of our patients.

Discussion

Reduction of blood loss in total knee arthroplasty is a very important issue[12]. Although tourniquet application is controversial, it is still used in total knee arthroplasty operations[8,12]. However, it is still a matter of debate among surgeons whether tourniquet should be released before or after wound closure[8,12,13]. Some surgeons report that closing the wound after tourniquet release and achieving bleeding control reduce blood loss, post-operative pain and future complications while also providing a better assessment of patellar tracking and improved functionality[7,8, 14,15]. However, others suggest that releasing the tourniquet after wound closure is a more advantageous method since it shortens surgery duration and restrains blood loss[8,12,16,17]. The perioperative blood loss in TKA is primarily related to the surgical skill and technique of the surgeon, the draining technique, the application of pressure dressing, anti-fibrinolytic therapy, the duration of tourniquet application, and the time to start the rehabilitation process[8,18]. The majority of research on orthopaedics shows TA application to reduce blood loss in the post-operative period[5,19]. Yet there is no consensus on how to apply TA. Many investigations[1,5,20] suggest that, whether intravenous, intra-articular, or mixed, the TA application method does not significantly affect the outcome. We, therefore, adopted an intra-articular application of TA to avoid complications that may arise in patients at risk due to intravenous administration. In the present study, drain clamping was standardized in all patients for 1 hour post-operatively. Pressure dressing was not necessarily used in all patients. Comparing the TA + TNR and TA + TR groups, we noticed no difference so far as the hemoglobin and hematocrit levels as well as erythrocyte suspension transfusion rates were concerned. However, we observed that the TA + TNR group seemed to be more advantageous than the TA + TR group in terms of surgery duration and the amount of blood in the surgical drains. Likewise, we found significant differences in hemorrhage amounts, hemoglobin and hematocrit differences, and erythrocyte suspension transfusion levels in the two TA receiving groups when compared with the control groups. As for operation times, duration was much shorter for the groups wherein the tourniquet was released after wound closure. Our research did not display any significant differences in hemorrhage amounts, hemoglobin count, hematocrit differences or erythrocyte suspensions transfusion figures between the TA - TNR and TA - TR

Table II. Comparison of groups' parameters.

	TA+TNR	TA-TNR	TA+TR	TA-TR	*p*
Amount of bleeding in the drains (ml)	217.4±99.6 (100-590)	411.6±133.7 (175-850)	291.2±89.5 (160-650)	458.2±138.6 (200-920)	0.000
Preoperative hematocrit level (%)	40.7±3.9 (30.8-47.9)	41.1±4.4 (31.7-48.3)	40.4±3.4 (29.3-47.3)	41.4±3.6 (32.1-49.2)	0.97
Hematocrit level at day 1 postoperatively(%)	35.2±4.3(27-43.2)	33.7±3.9(26-44.2)	34.7±4.2(26.2-42.4)	33.2±4.1(24.1-41.2)	0.30
Hematocrit level at day 3 postoperatively(%)	33.4±4.1(26.2-41.5)	31.2±4.7(22-43.1)	31.7±3.8(21.6-41.7)	29.4±4.3(21.8-38.1)	0.005
Hematocrit difference (%)	7.4 ±2.7(3.1-12.3)	9.8±5.6(4.2-13.1)	9.2±6.1(3.9-14.1)	11.3±3.5(3.9-19.3)	0.001
Preoperative hemoglobin level (g/dl)	13.4±1.4(10.1-15.6)	13.7±1.8(11.7-16.8)	13.1±1.5(10.2-16.5)	13.3±1.7(10.3-16.1)	1.0
Hemoglobin level at day 1 postoperatively (g/dl)	11.7±1.6(8.3-14.4)	11.3±1.3(9.1-15.2)	11.6±1.6(8.5-14.9)	10.8±1.2(7.9-13.4)	0.12
Hemoglobin level at day 3 postoperatively (g/dl)	11.1±1.4(7.7-13.7)	10.3±1.2(8.1-13.2)	10.7±1.3(7.6-13.1)	9.9±1.3(7.4-12.9)	0.04
Hemoglobin difference (g/dl)	2.2±1.1(0.7-4.7)	3.1±1.5(0.9-7.2)	2.6±1.2(1-5.4)	3.3±1.4(1.3-7.5)	0.02
Erythrocyte suspension transfusion (unit)	0.08±0.2 (0-1)	0.24±0.43(0-1)	0.12±0.47 (0-1)	0.32±0.47(0-1)	0.04
Preoperative Womac score	81.5±12.8 (62-93)	78.1±17.5 (58-95)	83.58±15.2 (55-92)	77.9±12.89 (60-93)	0,41
Post-operative Womac score (1st year)	28.4±18.3 (6-75)				
(n=24)	22.4±19.4 (8-68)				
(n=25)	29.6±16.4(5-79)				
(n=25)	27.2±15.4(6-72)				
(n=24)		0.33			
Duration of hospitalization (days)	5.4±2.7(4-9)	4.7±1.9(4-11)	5.1±1.6 (4-12)	4.8±2.1(4-9)	0.78
Tourniquet duration (minutes)	63.1±18.2(55-102)	61.7±23.2(52-105)	54.3±16.3(40-87)	55.6±15.9(42-91)	0.03
Operation time (minutes)	63.1±18.2(55-102)	61.7±23.2(52-105)	74.7±25.3(52-110)	77.2±21.8(55-112)	0.02

TA: Tranexamic acid, TNR: Tourniquet non released, TR: Tourniquet released.

Table III. *p*-values of binary comparisons between groups.

	TA-TNR	TA+TR	TA-TR
TA+TNR	**a:0.000**	**a:0.02**	**a:0.000**
	b:0.03	b:0.18	b:0.001
	c:0.04	c:0.23	c:0.000
	d:0.04	d:0.31	d:0.16
	e:0.02	e:0.22	e:0.02
	f:0.12	f:0.64	f:0.03
TA-TNR		**a:0.000**	a:0.41
		b:0.46	**b:0.10**
		c:0.43	c:0.17
		d:0.20	d:0.36
		e:0.15	e:0.88
		f:0.27	f:0.53
TA+TR			**a:0.000**
			b:0.001
			c:0.002
			d:0.05
			e:0.02
			f:0.04

TA: Tranexamic acid, TNR: Tourniquet non released, TR: Tourniquet released. a,b,c,d,e,f : p-values of binary comparisons. (a: amount of bleeding in the drain, b: Hematocrit level at day 3 postoperatively, c: hematocrit differences, d: Hemogram level at day 3 postoperatively, e: hemoglobin differences f: erythrocyte suspension transfusion.

groups. In some previous studies has been reported that tourniquet release after wound closure causes certain complications, be it minor or major, such as the loosening of unnecessary lateral retinaculum, increased perioperative blood loss from cancellous bone due to increased fibrinolytic activity after tourniquet release and wound closure[8,12,21]. In our study, however, we were unable to detect any difference between the groups in terms of minor and major complications. Besides, there was no difference among the four groups in the post-operative 1-year WOMAC scores. As far as the power analysis is concerned, the number of patients included here may not be sufficient to compare complication rates since the amounts of blood in the drains are taken into consideration within the scope of this study. Still, we believe that the findings of our research are worth examining particularly because these results are that of a prospective randomized double blind study.

Conclusions

We showed that the application of tranexamic acid to the suprapatellar space after wound closure without bleeding control or releasing the tourniquet reduced the amount of blood in the drain when compared with a similar application wherein the tourniquet was released before wound closure.

Conflict of Interest

The Authors declare that they have no conflict of interest.

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