Tranexamic Acid Efficacy in Total Knee Arthroplasty (A prospective comparative study)

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Abstract

Background
To reduce bleeding after total knee arthroplasty (TKA), various strategies were developed; the usage of tranexamic acid (TXA) is one of these strategies. TXA administration, both systemic and local, is effective in the literature.
This study aimed to evaluate the effectiveness of local and combined TXA administration (systemic + local) in minimizing blood loss following TKA.
Patients and Methods
Between November 2017 and August 2020, we enrolled all patients who had a primary TKA in our department. Patients were categorized into three groups according to the TXA administration method: control group (without TXA), intra-articular (IA) group, and a group that received combined intravenous and intra-articular. Demographic data and age, sex, comorbidities, and preoperative hemoglobin levels were collected. The maximum hemoglobin decline was the primary outcome, while the drain's blood amount (cc/day), the rate of blood transfusion, and the duration of hospital stay were secondary outcomes.
Results
The sample was composed of 54 patients divided into a control group (18 cases), an IA group (18 cases), and an IV + IA combined group (18 cases). The postoperative hemoglobin drop rate was highly significant between the control group and the IA and combined groups. Also, there was a significant difference between the IA group and the combined group with a P value=0.023. The drain's amount of blood, the transfusion rate, and length of hospital stay showed significant differences between the control group and the IA and combined groups. There was no significant difference in the postoperative complication rate in the three groups.
Conclusion
TXA is a safe and efficient way to reduce overall blood loss in TKA patients, according to data from this study and the literature**.** Administration of combined protocol of intravenous with intraarticular seems to be significantly superior to the other administration protocols. The IA protocol had comparable results with the control group (without TXA) and without increasing the risk of thrombotic events.

Keywords
Tranexamic acid; Knee Arthroplasty; Blood loss; hospital stay; hemoglobin drop.
Evidence level
a prospective comparative study "Level II."

Introduction

Among the most common concerns in elective total knee arthroplasty (TKA) is perioperative bleeding.[1,2] Fibrinolysis caused by surgical trauma, which can be accelerated with tourniquet use, lowers the risk of venous thromboembolism while favoring postoperative blood loss.[3] blood donation and red cell salvage perioperatively are two methods for reducing perioperative blood loss. Besides, perioperative transfusions increase the patient's treatment costs and risks of allergy, infection, and disease transmission.[4]

Pharmacological approaches have become more prevalent in recent years. Antifibrinolytic drugs such as protein, aminocaproic acid, and tranexamic acid (TXA) have been suggested because, after TKA surgery, hyperfibrinolysis is considered to be the most common cause of postoperative bleeding. TXA is an anti-fibrinolysis agent that prevents clot lysis by suppressing plasminogen activators' proteolytic action. Five studies on the TXA's efficacy in minimizing perioperative blood loss in total joint arthroplasty have been published since the first study by Benoni et al.[1] TXA given intravenously (IV) is thought to increase the risk of thrombotic events. TXA has also been linked to allergic reactions in some people. TXA should not be used in patients with an al-

lergy history, arterial or venous thrombosis, thrombosis or thromboembolism inherent risk, acute renal failure, subarachnoid hemorrhage, or epilepsy, according to some authors. According to other research, common postoperative prophylactic regimens like aspirin, warfarin, low-molecular-weight heparin (LMWH), and even factor Xa inhibitors can reduce the risk of deep vein thrombosis (DVT).[7,8]

TXA topical IA administration before wound closure has been proposed by some researchers to reduce the risk of thrombotic events-related complications. TXA given orally was found to be more effective than placebo in patients undergoing primary TKA in some studies.[10] In the literature, the amount of TXA given and the time it was given (preoperative, intraoperative, postoperative, or a combination of these) differ greatly. Although the recommended IV TXA doses range from 10 to 20 mg/kg, some studies recommended a 1 g dose (ranging from 500 mg to 3 g). Continuous infusion doses range from 2 mg/kg/h for 20 hours to 10 mg/kg/h for 3 hours. TXA can be given as a single-dose bolus or as a continuous infusion intravenously (for 2-3 hours).[11] TXA topical doses, diluted in 75 to 250 mL saline solution, range from 250 mg to 3g.

Aim of the Work

This research aimed to evaluate the effectiveness of systemic, local, and combined systemic and local TXA in minimizing blood loss following TKA. The researchers hypothesized that combining the two treatments would be more effective at controlling blood loss.

Patients and Methods

Between November 2017 and August 2020, all patients in our department with a primary TKA were included in this analysis. We excluded patients with a history of cerebrovascular diseases, ischemic heart diseases, thromboembolic manifestations, and renal impairment. The TXA administration protocol was used to divide all enrolled patients into three groups: group I (control group), no TXA used; group II (topical group), intra-articular: Following the placement of the final components and wound closure, 1.5 g of TXA is injected intra-articularly., and group III (combined group), a combination of IV dose of TXA 1gm injected intravenous before inflation of tourniquet by 30-60 minutes and 1gm dose before the release of tourniquet in additional to topical 1.5gm of TXA intra-articular after wound closure.

All the patients received LMWH postoperatively and continued for 14 days. During the cementation phase, a standard medial parapatellar approach with cemented components and a tourniquet was used for all surgeries. An IA drain was clamped for 2 hours and then released in all of the patients. Between the first and second postoperative days, knee mobilization and weight-bearing were permitted. On the first postoperative day, a continuous passive motion was started. Age, sex, medical comorbidities, and preoperative hemoglobin level were all taken into consideration. Maximum hemoglobin loss was the primary outcome used to assess the efficacy of TXA. It was calculated as the difference between the preoperative and lowest postoperative hemoglobin levels. Secondary outcomes included the blood amount in the drain (cc/day), the transfusions rate, and the length of hospitalization. In symptomatic patients, 8 g/dl was the cut-off value of hemoglobin for transfusion. On the other hand, patients with cardiac disease may require transfusions even if their hemoglobin levels are higher.

Postoperative complications were recorded, including postoperative fever (>38.5°), bruising, wound dehiscence, hematoma, DVT, thrombotic events, and infections. The groups' differences were evaluated using a Student's t-test or a Chi-square test, with $P < 0.05$ indicates a significant difference.

Results

A total of 54 patients were included in the study. The mean age was 58.56 years with a standard deviation of 10.28 and ranged from 22–76. Mean BMI was 29.17 kg/m2, with a standard deviation of 4.82 and ranged from 16.8 to 38.9. Seventy-six percent were women (41 cases), and 24.1 % (13 cases) were men. Depending on how TXA was administered, the patients were categorized into three groups using the above-mentioned inclusion and exclusion criteria; not administered, 18 cases; IA, 18 cases; both IV and IA, 18 cases. The three groups were homogenous. All groups were comparable regarding age and gender, P values were 0.051 and 0.146, respectively. According to the preoperative hemoglobin level, no differences were shown between the groups (P=0.724). Also, medical comorbidities showed no significant differences between the groups, as illustrated in (Tab 1&2).

The combined group's maximum hemoglobin drop was significantly lower (3 g/dl, SD 0.62, range 0.1 - 3 g/dl) than IA group (3.6 g/dl, SD 0.87, range 0.3 - 3.6 g/dl) and control group (6.1 g/dl, SD 1.14; range 1.4 - 6.1 g/dl), P values were 0.023 and < 0.001, respectively. Also, the IA group's maximum hemoglobin drop was significantly lower than the control group, with a P-value of 0.003. (Tab. 3a &3b).

The median blood amount in the drain was 400 cc/day one (range 200 to 650) in the control group without TXA. In the IA group, it was 300 cc/day one (range from 100 to 400), while in the combined group, it was 175 cc/day one (range 50 to 300). Eight cases needed a blood transfusion in the control group (44.4%), three cases in the IA group (16.75), and no cases needed a transfusion in the combined group. All three groups were standardized for a hospital stay of 4 days. However, five days duration was required for those with blood transfusion or the drain to be retained. They were eight cases in the control group (44.4%), 3 cases in the IA group (16.7%), and zero cases in the combined group. Blood amount in the drain, transfusion rate, and length of hospitalization were secondary outcomes, and all showed statistically significant differences between the three groups (Tab. 4&5).

The difference in complication rates between the three groups was insignificant. There was no evidence of DVT or other thrombotic events. (Tab. 6).

Table 1: Age, sex, and preoperative Hb level differences in the three groups.

		Control group	Topical group	Systemic and topical group	Test value	P-value	Sig.
		No. = 18	No. = 18	No. = 18			
Age	Mean ± SD	55.17 ± 11.46	63.17 ± 8.03	57.33 ± 9.86	3.154•	0.051	NS
	Range	22 – 71	49 – 76	28 – 71			
Sex	Female	11 (61.1%)	14 (77.8%)	16 (88.9%)	3.850*	0.146	NS
	Male	7 (38.9%)	4 (22.2%)	2 (11.1%)			
Preoperative Hb level	Mean ± SD	12.36 ± 1.69	12.03 ± 0.96	12.12 ± 0.99	0.325•	0.724	NS
	Range	10.2 – 15.4	10.6 – 13.5	10.7 – 13.8			

**: Chi-square test; •: One Way ANOVA test*

Table 2: Medical comorbidities in the three groups and their significance.

		Control group	Topical group	Systemic and topical group	Test value	P-value	Sig.
		No. = 18	No. = 18	No. = 18			
Medical Co-morbidities	No	4 (22.2%)	7 (38.9%)	8 (44.4%)	2.111*	0.348	NS
	Yes	14 (77.8%)	11 (61.1%)	10 (55.6%)			
HTN	No	9 (50.0%)	9 (50.0%)	12 (66.7%)	1.350*	0.509	NS
	Yes	9 (50.0%)	9 (50.0%)	6 (33.3%)			
DM	No	12 (66.7%)	15 (83.3%)	16 (88.9%)	2.968*	0.227	NS
	Yes	6 (33.3%)	3 (16.7%)	2 (11.1%)			
Bronchial asthma	No	17 (94.4%)	16 (88.9%)	15 (83.3%)	1.125*	0.570	NS
	Yes	1 (5.6%)	2 (11.1%)	3 (16.7%)			
Rheumatoid arthritis	No	16 (88.9%)	17 (94.4%)	18 (100.0%)	2.118*	0.347	NS
	Yes	2 (11.1%)	1 (5.6%)	0 (0.0%)			
Hypothyroid	No	18 (100.0%)	18 (100.0%)	17 (94.4%)	2.038*	0.361	NS
	Yes	0 (0.0%)	0 (0.0%)	1 (5.6%)			
SLE	No	18 (100.0%)	18 (100.0%)	17 (94.4%)	2.038*	0.361	NS
	Yes	0 (0.0%)	0 (0.0%)	1 (5.6%)			
Septic knee and debridement	No	18 (100.0%)	18 (100.0%)	17 (94.4%)	2.038*	0.361	NS
	Yes	0 (0.0%)	0 (0.0%)	1 (5.6%)			
HCV	No	18 (100.0%)	18 (100.0%)	17 (94.4%)	2.038*	0.361	NS
	Yes	0 (0.0%)	0 (0.0%)	1 (5.6%)			
Alcohol addict	No	17 (94.4%)	18 (100.0%)	18 (100.0%)	2.038*	0.361	NS
	Yes	1 (5.6%)	0 (0.0%)	0 (0.0%)			

**: Chi-square test*

Table 3a: level of hemoglobin drop in the three groups.

Hb drop	Control group	Topical group	Systemic and topical group	Test value	P-value	Sig.
	No. = 18	No. = 18	No. = 18			
Mean ± SD	-2.48 ± 1.14	-1.41 ± 0.87	-0.81 ± 0.62	15.806	0.000	HS
Range	-6.1 – -1.4	-3.6 – -0.3	-3 – 0.1			
Post hoc analysis						
Control Vs. topical group		**Control Vs. systemic and topical**		**Topical Vs. systemic and topical**		
0.001		0.000		0.052		

•: One Way ANOVA test

Table 3b: Analysis of differences in hemoglobin drop between the three groups.

Hb drop	Topical group	Systemic and topical group	Test value	P-value	Sig.
	No. = 18	No. = 18			
Mean ± SD	-1.41 ± 0.87	-0.81 ± 0.62	-2.376	0.023	S
Range	-3.6 – -0.3	-3 – 0.1			
Hb drop	**Control group**	**Topical group**	**Test value**	**P-value**	**Sig.**
	No. = 18	**No. = 18**			
Mean ± SD	-2.48 ± 1.14	-1.41 ± 0.87	-3.168	0.003	HS
Range	-6.1 – -1.4	-3.6 – -0.3			
Hb drop	**Control group**	**Systemic and topical group**	**Test value**	**P-value**	**Sig.**
	No. = 18	**No. = 18**			
Mean ± SD	-2.48 ± 1.14	-0.81 ± 0.62	-5.452	0.000	HS
Range	-6.1 – -1.4	-3 – 0.1			

•: Independent t-test

Table 4: Differences in the amount of blood loss in the drain postoperative between the three groups.

		Control group	Topical group	Systemic and topical group	Test value	P-value	Sig.
		No. = 18	No. = 18	No. = 18			
Day one loss	Median (IQR)	400 (300 – 550)	300 (200 – 300)	175 (100 – 200)	28.881≠	0.000	HS
	Range	200 – 650	100 – 400	50 – 300			
Day two	Median (IQR)	250 (200 – 300)	125 (100 – 200)	125 (100 – 150)	24.077≠	0.000	HS
	Range	150 – 400	50 – 300	50 – 200			
Day three	Median (IQR)	100 (50 – 100)	50 (50 – 100)	50 (50 – 50)	13.081≠	0.001	HS
	Range	50 – 250	50 – 150	50 – 100			
Post Hoc analysis							
		Control Vs topical group	**Control Vs. systemic and topical**		**Topical Vs. systemic and topical**		
Day one loss		0.001	0.000		0.003		
Day two		0.000	0.000		0.397 (NS)		
Day three		0.021	0.001		0.198 (NS)		

≠: Kruskal-Wallis test

Table 5: Differences in blood transfusion rate and hospital stay between the three groups.

		Control group		Topical group		Systemic and topical group		Test value*	P-value	Sig.
		No.	%	No.	%	No.	%			
Need Blood Transfusion	Not need	10	55.6%	15	83.3%	18	100.0%	11.188	0.004	HS
	Need	8	44.4%	3	16.7%	0	0.0%			
Hospital Stay	4 days	10	55.6%	15	83.3%	18	100.0%	11.188	0.004	HS
	5 days	8	44.4%	3	16.7%	0	0.0%			

**: Chi-square test*

Table 6: Differences in complications between the three groups.

Complications	Control group	Topical group	Systemic and topical group	Test value	P-value	Sig.
	No. = 18	No. = 18	No. = 18			
No	14 (77.8%)	17 (94.4%)	18 (100.0%)	5.731*	0.057	NS
Yes	4 (22.2%)	1 (5.6%)	0 (0.0%)			

**: Chi-square test*

Discussion

TXA reduces total blood loss, rate of blood transfusion, blood amount in the drain, and hospital stay length without increasing the rate of complications, according to this study.

TXA IV in TKA is considered safe and beneficial by various authors, either as a single or doses intraoperatively or postoperatively. In a randomized controlled trial, Levine et al.[13] found that a typical intravenous dose of 1 g was as effective as weighted doses (20 mg/kg).[14] According to Iwai et al., a TXA double intravenous dose for reducing postoperative bleeding in TKA is more effective than a single dose[15], particularly when the doses were given before and during

surgery. In a similar randomized controlled trial, Maniar et al. found that a three-dose regimen (including an after-surgery dose) was even more useful.[16]

Patel et al. found that 10 mg/kg IV TXA and 2 g IA TXA reduced blood loss equally well in 89 patients with a primary TKA.[17] Similarly, IA TXA administration is effective in reducing blood loss after TKA in many recent studies.[18]

Furthermore, despite some authors' contradictory results, no difference was found between topical and IV TXA according to recent meta-analyses[18,19]. A few studies have looked at the relationship between the IA protocol and the combination protocol in patients undergoing TKA. Using a combined protocol rather than just IV administration, Jain et al. achieved promising results regarding hemoglobin drop, mean total blood loss, transfusion rate[22].

Lin et al. found that a combined protocol reduced hemoglobin drop, blood loss, total drain amount, and transfusion more significantly than IA administration alone in a study of 120 patients.[23] In bilateral TKA, Karaaslan et al. evaluated the effectiveness of a combination of three TXA administration routes: 15 mg/kg as a bolus dose, ten minutes before the tourniquet inflation, followed by 3gm IA, ten minutes before the tourniquet was deflated, and then, 10 mg/kg/h IV infusion for three hours after the operation. The authors stated that in patients with bilateral TKA, this method reduced total blood loss.[24] Huang et al. evaluated the outcomes of IV TXA (3gm) versus a combined strategy (1.5 g IA and 1.5 g IV). Both strategies were equally effective in lowering the rate of transfusion and total blood loss, but regarding maximum hemoglobin decline, drainage amount, postoperative knee swelling and pain, hospitalization length, and short-term satisfaction, the combined protocol produced better outcomes.[25]

In fifty-four patients, we conducted an initial prospective cohort study because TXA is effective in TKA regardless of the administration route. Patients were divided into a control group without TXA administration, IA administration, and a combination of IV and IA. This study aimed to confirm TXA's efficacy and see if one route of administration was superior to the others or if the combination was better. Our study results revealed that hemoglobin decline, transfusion rate, blood in the drain, and hospital stay were ideal with the combined group. The IA and control groups ranked 2nd and 3^{rd,} respectively.

In this study, to avoid any group distribution bias, demographic data was studied first to detect any significant differences in the distribution of age, sex, preoperative hemoglobin, and medical comorbidities. The statistics of all these variables revealed no significant differences between the study groups.

Finally, the preliminary experience with TXA in TKA described above contradicts what has been reported in the literature, particularly in the combination of IV and IA. Maximum hemoglobin drop showed significant differences between the treatment groups, with the combined group outperforming the others. However, as previously stated, this study has some confounding factors. To increase the power of the study, the sample size must be increased, and the patients must be randomly assigned. To summarise, TXA administration in TKA reduces hemoglobin drop, total blood loss, drain's amount of blood, and blood transfusion rate safely and effectively. Although intravenous TXA administration has been linked to an increased thrombotic risk, the literature does not fully support this claim. Instead, there is consensus on IA TXA's comparable efficacy, which is not linked to an increased risk of thrombosis.

Conclusion

In TKA patients, TXA minimizes total blood loss efficiently and safely, according to the findings of this study and the literature. The combined IV and IA protocol appear to be significantly much better than the other administration protocols.

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