Case Series

Efficacy and safety of systemic tranexamic acid administration in total knee arthroplasty: A case series

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A R T I C L E   I N F O

A B S T R A C T

INTRODUCTION: Total knee arthroplasty (TKA) are associated with significant postoperative blood loss. Tranexamic acid (TXA) is a potent agent with antifibrinolytic activity, that can be administered via the intravenous (IV) and/or topical (intra-articular, IA) route, which can possibly interrupt the cascade of events due to hemostatic irregularities close to the source of bleeding. However, the literature contains scarce scientific evidence related to IV only TXA usage in TKA. The current study aims to compare the outcome between patients who were administered IV TXA and a control group in terms of blood loss, transfusion rate, and incidence of deep vein thrombosis (DVT) and thromboembolism (TE).
METHODS: 110 patients, who underwent TKA were placed into two groups: 1) 34 patients who received IV TXA; and 2) 76 patients in the control group. In the TXA group, patients received an IV TXA dose of 1 g, 30 min before incision. Two drains were placed.
RESULTS: Usage of IV TXA showed better results when compared to the control group in terms of mean blood transfusion (0.5 less transfusion during hospital stay), hemoglobin drop (10%). No cases of DVT or TE were noted among the two study groups.
CONCLUSION: Use of IV TXA provided significantly better results compared to no TXA use with respect to all variables related to postoperative blood loss in TKA. Moreover, TXA use is safe in terms of incidence of symptomatic DVT and TE.

1. Introduction

Large quantity of perioperative blood loss and large transfusion rates are associated with total joint replacement surgeries. The rate of transfusions for total knee arthroplasty (TKA) patients ranges between 11% and 21% [1]. TKA remains the most cost-effective operative management for patients with debilitating knee arthritis. However, TKA is associated with substantial blood loss in the postoperative period [2] which may be consequently complicated by significant anemia [3], increased risk of cardiopulmonary events, transfusion reactions, and increased health-care costs [4]. Moreover, the patient is at increased risk of allogeneic blood transfusion-related complications such as immunological reaction, transmission of certain blood-borne diseases, and postoperative infection [5]. Every operation stimulates the fibrinolytic process transiently [6], and TKA is often associated with the use of pneumatic tourniquet, which is associated with local fibrinolysis [7]. Therefore, the resulting hyperfibrinolysis can result in increased blood loss after TKA. Via hypotensive anesthesia [8], the use of intramedullary femoral plug [9], drain clamping [10], preoperative autologous blood donation [11], and the use of antifibrinolytic agents, surgeons are able to reduce the risk of blood loss.

Tranexamic acid (TXA) is a potent antifibrinolytic agent, which may interrupt the cascade of events due to hemostatic irregularities close to the bleeding source. It reaches a concentration of 90%–100% in joints compared with its plasma concentration [12]. In addition, TXA concentrations of up to 10 mg/mL of blood do not influence platelet counts, coagulation times, or various coagulation factors in whole blood or citrated blood from healthy subjects [13].

However, isolated case reports of thrombus formation have been reported in the literature, leading to concerns regarding the risk of thromboembolic complications in a population of patients

that is already at high risk for deep vein thrombosis (DVT) and pulmonary embolism (PE). This prevented widespread acceptance of intravenous (IV) antifibrinolytics in full joint replacement surgeries [14,15].

Furthermore, multiple studies [16–18] including a meta-analysis [19] showed the potential of topical (IA) TXA to be equivalent or even better than IV TXA. In addition, a recent study by Lin et al. [20] found that the efficacy of combined TXA administration is higher than topical use alone. Thus, it is imperative to say that a combined administration of TXA may prove to be more effective compared with topical or intravenous (IV) TXA use alone. While the study was based on patients who underwent total hip arthroplasty, the combined use of IV and IA TXA showed significantly lower levels of blood loss as compared to patients that received no TXA [21].

The present study was conducted to compare the efficacy of IV TXA usage with that of no use of TXA in terms of total blood loss and allogeneic transfusion rate and in terms of assessment of the safety profile of each regimen in terms of DVT and thromboembolism (TE) incidence. To note, this article has been reported in line with the PROCESS criteria [22].

2. Materials and methods

For this study, written informed consent was obtained from all the patients recruited. This manuscript is registered in the national registry UIN5696 [23].

A retrospective study of a single institution was conducted. All patients aged 50–98 diagnosed with knee osteoarthritis and scheduled for elective primary arthroplasty performed by the senior author at St. George Hospital University Medical Centre (Beirut, Lebanon) were eligible for the purpose of this study. The study excluded patients with history of renal impairment, cardiovascular disease (previous myocardial infarction, atrial fibrillation) or cerebrovascular disease (previous stroke or peripheral vascular surgery). Patients with history of thromboembolic disease, allergy to TXA, bleeding disorder, or receiving anticoagulant drug treatment were also excluded. Between January 2018 and December 2019, 110 patients were successfully recruited after meeting the inclusion and exclusion criteria, and subsequently divided into two groups: 1) 76 IV TXA; and 2) 34 no TXA.

30 min prior to incision, 1 g of IV TXA was given. Under spinal anesthesia, all TKA surgeries were performed using the standard medial parapatellar quadriceps splitting approach with patella eversion under tourniquet control at 300 mmHg. The distal femur was prepared using an intramedullary rod while the proximal tibia was prepared using an extramedullary jig. A bone plug was used to block the femoral medullary cavity after the femoral cuts. Two drains were placed, and the closure of wound was performed in a standard fashion in all cases. The tourniquet was deflated only after dressing had been applied to the operated knee at the end of the surgery. Postoperatively, all patients underwent a standard institution thromboembolic prophylaxis protocol. Pneumatic calf pumps were given immediately postoperatively until the patient started ambulating. In January 2010, the National Institute for Health and Care Excellence (NICE) introduced a recommendation to use low-molecular-weight heparin in joint replacement surgeries; hence, subcutaneous Lovenox (Enoxaparin sodium) 40 mg once daily (Sanofi, Paris, France) was given to all patients on the first postoperative day (POD) and continued until discharge from hospital and then at home or rehabilitation facility for a total of 35 days postop. All patients underwent inpatient postoperative physiotherapy with the aim of early mobilization. No deep vein thrombosis screening was done in the postoperative period to detect asymptomatic occurrence. For symptomatic patients, they were evaluated with ultrasonography of the lower limb deep veins and CT scan of the chest (PE protocol). The patients were considered fit for discharge once they had achieved at least 90° of knee flexion and were able to ambulate independently with or without walking aids. The length of hospital stay was on average five days

The primary outcomes of this study were transfusion incidences, postoperative drop in serum hemoglobin level while the secondary outcomes include duration of surgery, wound complications, and thromboembolic events within 30 days of surgery.

At the institution where this study was performed, a serum hemoglobin level of less than 8.0 g/dl was considered the transfusion trigger. For patients presenting with anemic symptoms or any anemia-related organ dysfunctions, the transfusion trigger was less than 10.0 g/dl.

2.1. Statistical analysis

Statistical analysis was carried out in consultation with the in-house biostatistician, using SPSS® 25.0 (IBM, Armonk, New York, United States). Statistical significance was defined as a p-value of ≤ 0.05. Testing for normality was done with the Shapiro-Wilk test. We used the Levene's test for equality of variances and the Student t-test for equality of means. Pearson's correlation coefficient was used to assess any correlation between TXA use and blood transfusions.

3. Results

Our results show a decrease in transfusion rates among patients in the TXA group. Our patients in both groups had no statistical difference in age or body mass index (BMI) (Table 1).

Table 2 shows a statistically significant negative Pearson correlation between TXA and blood transfusions ($p < 0.05$) and a positive Pearson correlation between TXA and the 1st postoperative day hemoglobin levels. Furthermore, a negative Pearson correlation exists between preoperative hemoglobin levels and blood transfusions ($p < 0.01$), and a positive correlation between preoperative and postoperative hemoglobin levels at day 1 and day 5 ($p < 0.01$).

We used the Levene's test for equality of variances and the student t-test for equality of means shown in Table 3. Our findings show no statistically significant difference in preoperative hemoglobin levels and hemoglobin at day 4 postoperatively, while statistically significant difference between the two groups was noted in the 1st postoperative hemoglobin levels and total amount of transfusion used intraoperatively and postoperatively. Since $p < .05$ is less than our chosen significance level $\alpha = 0.05$, we can reject the null hypothesis, and conclude that the day 1 postoperative hemoglobin levels and total amount of transfusion is significantly different. IV TXA use appears to have better results when compared to the control group in terms of mean blood transfusion (0.5 less transfusion during hospital stay) and hemoglobin drop (10%).

4. Discussion

The results of the presented study show that the IV administration of TXA in TKA surgeries was associated with significant reduction in the postoperative risk for bleeding and the need for transfusions. The drop in hemoglobin levels on the 1st postoperative day was 10% higher among patients when TXA was not used. This translated into a much lower risk of requiring a blood transfusion in the TKA patients in which IV TXA was administered. Patients with TXA required less transfusions as compared with required blood transfusion when TXA was not used.

Currently, TXA is FDA (Food and Drug Administration) approved only for certain procedures in a certain population such as tooth

Table 1

Population demographics in the current study. HbPREOP = preoperative hemoglobin levels, HbPOSTOP1 = hemoglobin levels on the 1st postoperative day, HbPOSTOP4 = hemoglobin levels on the 4th postoperative day. TXA (0) = TXA not used, TXA (1) = IV TXA used.

Group Statistics					
	TXA	N	Mean	Std. Deviation	Std. Error Mean
HbPREOP	0	34	12.041	1.8268	.3133
	1	76	12.746	1.9281	.2010
HbPOSTOP1	0	34	10.065	1.1903	.2041
	1	76	11.199	1.3436	.1401
HbPOSTOP4	0	34	10.106	.8790	.1508
	1	76	10.500	1.0943	.1141
Transfusion	0	34	.82	.521	.089
	1	76	.33	.494	.052
Age	0	34	70.82	16.67	1.30
	1	76	73.96	13.38	1.43
Hbpreop-Hbpostop1	0	34	1.976	0.63	0.11
Hbpreop-Hbpostop1	1	76	1.547	0.58	0.06

Table 2

Correlations. HbPREOP = preoperative hemoglobin levels, HbPOSTOP1 = hemoglobin levels on the 1st postoperative day, HbPOSTOP4 = hemoglobin levels on the 4th postoperative day.

Correlations		HbPREOP	HbPOSTOP1	HbPOSTOP4	transfusion	TXA
HbPREOP	Pearson Correlation	1	.531**	.390**	−.618**	.164
	Sig. (2-tailed)		.000	.000	.000	.067
	N	110	110	110	110	110
HbPOSTOP1	Pearson Correlation	.531**	1	.604**	−.454**	.363**
	Sig. (2-tailed)	.000		.000	.000	.000
	N	110	110	110	110	110
HbPOSTOP4	Pearson Correlation	.390**	.604**	1	−.184*	.167
	Sig. (2-tailed)	.000	.000		.039	.062
	N	110	110	110	110	110
Transfusion	Pearson Correlation	−.618**	−.454**	−.184*	1	−.406**
	Sig. (2-tailed)	.000	.000	.039		.000
	N	110	110	110	110	110
TXA	Pearson Correlation	.164	.363**	.167	−.406**	1
	Sig. (2-tailed)	.067	.000	.062	.000	
	N	110	110	110	110	110

** Correlation is significant at the 0.01 level (2-tailed).
* Correlation is significant at the 0.05 level (2-tailed).

Table 3

Student *t*-test and Levene's test. HbPREOP = preoperative hemoglobin levels, HbPOSTOP1 = hemoglobin levels on the 1st postoperative day, HbPOSTOP4 = hemoglobin levels on the 4th postoperative day.

Independent Samples Test		Levene's Test for Equality of Variances		t-test for Equality of Means					95% Confidence Interval of the Difference	
		F	Sig.	T	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	Lower	Upper
HbPREOP	Equal variances assumed	0.154	0.695	−1.846	108	0.067	−0.7045	0.3817	−1.4599	0.0510
	Equal variances not assumed			−1.893	61.959	0.063	−0.7045	0.3722	−1.4486	0.0396
HbPOSTOP1	Equal variances assumed	0.243	0.623	−4.332	108	0.000	−1.1342	0.2618	−1.6524	−0.6160
	Equal variances not assumed			−4.581	66.079	0.000	−1.1342	0.2476	−1.6285	−0.6399
HbPOSTOP4	Equal variances assumed	1.875	0.173	−1.886	108	0.062	−0.3941	0.2090	−0.8078	0.0196
	Equal variances not assumed			−2.085	72.951	0.041	−0.3941	0.1891	−0.7709	−0.0173
Transfusion	Equal variances assumed	1.394	0.240	4.944	108	0.000	0.497	0.101	0.298	0.697
	Equal variances not assumed			4.826	56.372	0.000	0.497	0.103	0.291	0.704

extraction in hemophilia patients. TXA distributes widely in the extracellular and intracellular compartments when given IV [24]. It spreads rapidly into the synovial fluid until the TXA concentration in the synovial fluid and the serum equalize [24]. The biological half-life of TXA in the joint fluid is 3 h, and glomerular filtration eliminates 90% within 24 h [24,25].

Antifibrinolytics have been in use since the 1960s as a class of drugs [25]. TXA is an amino acid lysine analogue. It competitively inhibits the activation of plasminogen and the binding of plasmin to fibrin, inhibiting the degradation of fibrin [14]. Since it works by increasing the breakdown of fibrin when created, it is not necessarily a procoagulant, but promotes coagulation already in progress [26]. This makes it potentially suitable for use in reducing post-operative bleeding, where surgical hemostasis has been achieved and fibrinolytic activity needs to be suppressed to help maintain hemostasis without promoting the formation of venous thrombus.

In a meta-analysis of all operations, tranexamic acid was associated with a 33% reduction in the risk of transfusion [27,28]. It was used successfully through an intravenous route in orthopedic surgery, with several studies showing significant reductions in bleeding and transfusion risk following TKA [2–5]. Nevertheless, the possibility of thromboembolic complications following systemic administration TXA remains a concern for many surgeons [14,15]

Cid and Lozano [29] conducted another meta-analysis assessing TXA efficiency in TKA in which nine trials were eligible and the results showed that TXA use is effective in reducing allogeneic blood transfusion requirements. Kagoma et al. [30] studied the impact of antifibrinolytics on blood transfusion reduction, showing a decrease in blood transfusion rate after total knee and hip arthroplasties.

Gill and Rosenstein reported IV TXA use in different doses significantly reduced intraoperative and total blood loss during the review of 13 randomized controlled trials [31].

In a study by Chen et al., whereby 120 patients undergoing bilateral total knee replacement were divided into control and tranexamic acid groups. The tranexamic acid group had reduced total blood loss and reduced blood transfusions rate with no change in thromboembolic safety [32].

No significant difference in safety between the different methods was noted after a comprehensive review of the literature [33]. For TKA, Amin et al. suggest administering a dose of 15 mg/kg IV 10 min before incision and 3 g in 100 mL of saline soak after wound closure [33].

Based on the evidence in the literature, Melvin et al. recommend a regimen consisting of a 1 g IV dose of TXA to be administered before incision or tourniquet inflation with an additional 1 g IV dose given at closure [34].

Based on the current evidence-based medicine, clinicians and patients need to be familiarized with the possible clinical benefits and risks of TXA, when deciding on their therapy management following TKA. Regarding efficacy and safety, our study suggests that TXA should be indicated in patients undergoing TKA. In view of our data, our protocol of 1 g IV tranexamic acid 30 min before incision seems to be effective and safe. This comes in accordance with the literature as a meta-analysis conducted by Fu et al. (2013) reported the beneficial use of UV TXA in TKA patients. Their results showed reduction in total blood loss, postoperative blood loss, transfusion rate, and transfusion volume. Furthermore, no statistically significant difference was found between the TXA group and the control group regarding the development of DVT or TE [35].

It is important to note that this study has several limitations. First, the participants included in our study excluded high risk patients since the exclusion criteria comprised a history of cardiovascular disease, cerebrovascular disease, thromboembolic events, renal failure, allergy to TXA, bleeding diathesis, and those on anti-

coagulation therapy. Second, this is a retrospective study. Third, differences in surgical techniques and blood transfusion protocol are likely to have contributed to the differences observed among studies. Few studies reported the type of surgical hemostasis utilized; these techniques are known to reduce bleeding during surgery [36].

5. Conclusion

After thorough review of the literature and according to the data of this study, it is our recommendation that 1 g of TXA in IV be given 30 min prior to incision. As this is seen to be beneficial in terms of blood loss, blood transfusions, and postoperative hemoglobin drop without increasing thromboembolic complications.

Declaration of Competing Interest

The authors declare no conflict of interest regarding the publication of this article.

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Ethics committee has given approval for publication and patient consent has been obtained.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

No identity identifiers are present whatsoever in the manuscript.

Author contribution

Joseph Maalouly: contributed to the writing and editing of this article.

Antonios Tawk: contributed to the writing and referencing of this article.

Dany Aouad: contributed to the writing of this article and the submission process.

Rami Ayoubi: contributed to the editing of the figures and of the text.

Donna El Assaad: contributed to the radiological images, and editing of the final text.

Georgio Lati: Contributed with data collection and editing of the article.

Mohammad Darwish: Contributed with data collection and editing of the article.

Georges El Rassi: contributed with the cases, writing and editing of the article.

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