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Intra-Articular versus Intravenous Tranexamic Acid in Controlling Blood Loss during Primary Total Knee Replacement

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Abstract

Objective: This prospective randomized controlled study was performed to evaluate the efficacy and safety of topical intra-articular compared with intravenous Tranexamic acid (TXA) to reduce blood loss in primary total knee replacement (TKR).

Background: Many trials in the literature were done regarding the use of intravenous tranexamic acid (TXA) in primary TKR. Randomized controlled studies have confirmed the efficacy of topical intra-articular TXA compared with placebo. The comparison between topical intra-articular and intravenous TXA is unclear.

Patients and Methods: A randomized controlled clinical study was performed to compare topical intra-articular TXA (3 g of TXA in 100 mL of physiological saline solution) with intravenous TXA in the form of two doses (each was 15 mg/kg in 100 mL of physiological saline solution, one dose before tourniquet release and another dose 3 hours postoperatively). The primary outcome measure was the blood transfusion rate and the secondary outcome measures included blood loss through the drain at 24 hours after surgery and blood loss measured by the Nadler formula at 48 hours postoperatively. Fifty patients were included in the study. Twenty five patients were allocated to receive topical intra-articular TXA (the experimental group) and another twenty five patients were allocated to receive intravenous TXA (the control group). Demographic data and preoperative laboratory values were comparable in both groups.

Results: The transfusion rate was zero in both groups; thus, no significant difference was demonstrated between the two groups for the primary outcome measure. In addition, no significant differences were also demonstrated for the secondary outcome measures. Mean drain blood loss at twenty four hours was 310.2 mL in the experimental group and 300.7 mL in the control group.

Conclusion: Intra-articular administration of TXA according to the described protocol in terms of efficacy and safety was comparable to intravenous TXA.

Keywords: TXA; TKA; Intra-articular tranexamic acid; Intravenous tranexamic acid; Blood loss

Introduction

Tranexamic acid (TXA) is an anti-fibrinolytic agent [1]. Its use in primary TKR is supported by many studies that confirmed its efficacy for decreasing blood loss [2-4]. Safety concerns in studies comparing TXA treatment against placebo, showed equivalent safety [5-8]. Though proved to be effective, still there are concerns regarding intravenous (IV) administration of TXA in some settings, and topical administration may be considered an encouraging alternative that is potentially less risky than systemic administration. Topical TXA administration in dental surgery even in patients receiving oral anticoagulation has confirmed the safety and efficacy of topical intra-articular administration of TXA [9]. The results of many randomized controlled trials [10-14], a meta-analysis [15] and retrospective and cohort studies [16-20] containing a large number of patients involving primary TKR confirmed efficacy in the form of significantly lower transfusion rates and blood loss in patients treated with topical TXA compared with placebo. Intravenous TXA is formally contraindicated in cases with a history of a thromboembolic or ischemic event such as deep venous thrombosis (DVT), pulmonary embolism (PE), acute myocardial infarction, ischemic cerebrovascular accident or ischemic retinopathy [20]. The level of TXA in peripheral blood was significantly lower with topical intra-articular administration than with IV administration [14], and this may increase safety. IV administration achieves high level of TXA into the synovial fluid of the target joint, but topical Intra-articular administration achieves the same result without a high systemic distribution, potentially reducing the thromboembolic risk [14]. Trials with various dosages and routes of administration, including tissue impregnation with 1.5 g or 3 g of TXA before knee closure [14], delivery of 2 g into the wound [13] or intra-articular delivery of 2 g through the drain [11] have confirmed the efficacy of topical TXA administration compared with placebo during TKR. However, in one study, 2 g of topical TXA in the joint before closure failed to achieve a significant reduction in blood transfusion [21]. This has raised concerns regarding possible differences in efficacy according to the route of administration. Based on this, it still remains unclear whether the topical intra-articular TXA administration in TKR is equally or less effective than that of IV administration. The objective of the present randomized controlled trial was to compare topical intra-articular TXA with intravenous TXA during primary unilateral TKR.

Patients and Methods

All patients were given written informed consents, and ethical Institute approval has been obtained. All patients planned to undergo primary unilateral TKR with cemented implants in our hospital from January to November 2014 were eligible for inclusion. The exclusion

criteria were absence of the consent, allergy to TXA, coagulopathy (preoperative international normalized ratio (INR) >1.5, prolonged partial thromboplastin time (PTT) of >1.5 times normal or platelet count <150,000/mm3), a history of arterial or venous thromboembolic diseases, hematologic disorders, retinopathy and breastfeeding. All patients were instructed to discontinue anti-platelet agents and aspirin at least seven days prior to surgery. Patients were randomly allocated to the experimental (Topical intra-articular) group (25 patients) or the control (IV) group (25 patients). Patients in the experimental group received a topical intra-articular dose of 3 g of TXA (Hemoxamine; CID) in 100 mL of physiological saline solution (0.9%sodium chloride solution) based on previous studies that confirmed the high efficacy of this dosage [14]. On the basis of previous efficacy studies [22,23], patients in the control group received a slow IV infusion of 100 mL of physiological saline solution containing a 15 mg/kg dose of TXA fifteen minutes before tourniquet release and a second similar dose three hours after surgery. All patients had spinal type of anesthesia. A pneumatic tourniquet was inflated to 100 mmHg above systolic arterial pressure after limb elevation and extremity exsanguination. An anterior midline incision followed by a parapatellar medial approach was utilized in all patients. A cemented posterior-stabilized NexGen prosthesis (Zimmer) was implanted. After all components were cemented, the joint was thoroughly irrigated and aspirated. Half of the volume of the topical medication was applied to the open joint surfaces with a syringe and was left in contact with the tissue for five minutes. The remaining half of the study medication was administered into the joint through the 12-mm drain after joint closure with the knee in fully extended position; then closed. It was then opened after two hours (at atmospheric pressure without vacuum) and removed after 24 hours. Prophylaxis against thromboembolism in all patients consisted of daily subcutaneous injection of 40 mg of enoxaparin (Clexane; Sanofi-Aventis) for three weeks, starting six hours postoperatively. Antibiotic prophylaxis included 2 g of Cephalosporin one hour before surgery and 1 g every eight hours for twenty-four hours. Patients with a Cephalosporin allergy received a slow infusion of 1 g of Vancomycin before surgery and 500 mg every twelve hours for twenty-four hours. Physical therapy was started on the first post operative day. All patients remained hospitalized for a minimum of five days.

Outcome measures

The primary outcome measure was postoperative blood transfusion. Blood loss through the drain was measured at three and twenty-four hours and served as one of the secondary outcome measures. The postoperative hemoglobin level was measured at twenty-four hours, forty-eight hours, and five days. The estimated blood loss was determined by the difference between the preoperative hemoglobin level and the lowest postoperative level. The estimated blood loss was calculated with use of the Nadler formula [24]. Blood transfusion was given for patients with a hemoglobin level of <8.0 g/dL even if they were asymptomatic. Other secondary outcome measures included safety assessment on basis of presence or absence of complications, the length of hospital stay, and postoperative changes in active range of motion of the knee (which was measured before surgery and thirty days postoperatively). Patients were clinically examined daily for DVT while hospitalized. A Doppler US examination was performed when there was a clinical suspicion of a DVT. The patient was instructed to return to hospital if limb swelling or calf pain happened after discharge.

Statistical methods

Distributions of demographic data, baseline data, surgical characteristics, and primary and secondary outcomes were assessed with measures of central tendency (mean ± standard deviation) for quantitative variables and with percentages for qualitative variables. The Student t or its non-parametric equivalent, Mann-Whitney test was used to compare continuous variables and the Chi-square test was used for categorical variables. In all applied tests, the P-values associated with test statistics indicated the significance level at which the null-hypothesis (the hypothesis of no difference) is rejected and it was set at 0.05 so that p-values ≥ 0.05 are statistically non-significant.

Results

From January to December 2014, fifty patients planned for primary unilateral TKR at our hospital were found to meet the inclusion criteria and were approved for participation in this trial. They were randomized to receive either topical TXA (the experimental group, n=25) or IV TXA (the control group, n=25). None of the patients was lost or excluded during follow-up. No statistically significant differences between the groups were found regarding age, sex, weight, height, body mass index, preoperative laboratory values (hemoglobin, platelet count), or surgical characteristics (site, surgical time, tourniquet time) Table 1.

No transfusion was performed in either group, confirming no statistically significant difference for the primary efficacy end point (transfusion rate). Similarly, when secondary efficacy end points involving blood loss were analyzed, there were no statistically significant differences in drain blood loss at twenty-four hours or in estimated blood loss at forty-eight hours or five days Table 2. Decreases in the hemoglobin level were similar in both groups and statistically insignificant Table 3, Figure 1. In the topical intra-articular TXA group, the decreases at twenty-four hours, forty-eight hours, and five days were -2.4, -3.2, and -2.1 g/dL, respectively, and the decreases were -2.5, -3.3, and -2.4 g/dL in the IV TXA group. The mean length of stay in the hospital was similar; five days in both groups. The range of motion of the knee forty-eight hours postoperatively was 89 degrees ± 11.1 degrees in the experimental group and 91 degrees ± 7.8 degrees in the control group (p=0.465). The range of motion one month postoperatively was 107 degrees ± 11 degrees in the experimental group and 108 degrees ± 10 degrees in the control group (p = 0.738) indicating no statistically significant difference. There were no differences between groups in the safety outcome; with no related complications reported.

Table 1: Baseline patient characteristics

Variable	Topical Group A (n=25)	IV Group B (n=25)	P-value*
General characteristics			
Age (yr)	69.2 ± 9.3	70.1 ± 10.4	0.748
Female / Male	16 / 9	15/10	1.000 †
Weight (kg)	76.5 ± 13.1	75.4 ± 13.3	0.770
Height (m)	1.6 ± 0.2	1.6 ± 0.1	1.000
BMI (kg/m2)	30.2 ± 3.9	30.1 ± 3.8	0.927
Side (left / right)	13 / 12	14 / 11	1.000 †
Pre-op. Laboratory values			
Hemoglobin (g/dL)	13.6 ± 1.1	13.5 ± 1.0	0.738
Platelet count (x1000/mcL)	220.2 ± 45.7	232.2 ± 48.1	0.370
Surgery characteristics			
Tourniquet time (min)	84.2 ± 14.7	86.3 ± 13.2	0.598
Operative time (min)	81.1 ± 13.9	81.7 ± 13.6	0.878

*Student t-test. - p- values ≥ 0.05 are statistically non-significant
† Chi-square test

Table 2: Postoperative blood loss

Variable	Time	Topical Group (ml)	IV Group (ml)	P-value*
		Mean ± SD	Mean ± SD	
Drain blood loss	24 hr	200.3 ± 310.2	180.2 ± 300.7	0.846
Estimated blood loss	48 hr	435.1 ± 1251.2	431.5 ± 1309.2	0.637
	5 d	502.3 ± 803.7	500.3 ± 984.6	0.208
Total blood loss	48 hr	528.4 ± 1561.4	502.7 ± 1609.9	0.741
	5 d	514.7 ± 1072.2	571.5 ± 1277.3	0.188

*Mann-Whitney test

Table 3: Postoperative Hemoglobin (Hb) level

Variable	Time	Topical Group (ml)	IV Group (ml)	P-value*
		Mean ± SD	Mean ± SD	
Postop. Hb (g/dl) level	24 hr	1.1 ± 11.2	1.1 ± 11.0	0.523
	48 hr	1.0 ± 10.4	1.0 ± 10.2	0.483
	5d	1.1 ± 11.5	1.2 ± 11.1	0.225
Change from Preop.Hb	24 hr	0.8 ± -2.4	0.8 ± -2.5	0.661
	48 hr	1.0 ± -3.2	0.9 ± -3.3	0.712
	5 d	1.2 ± -2.1	1.2 ± -2.4	0.381

*Student t-test

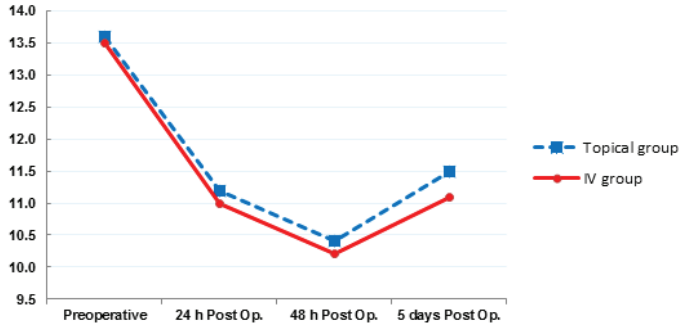

Figure 1: Hemoglobin concentration in g/dL according to time in each treatment group

Discussion

In this randomized controlled clinical trial, the results of topical administration of 3 g of TXA were comparable to the standard protocol involving IV administration of two 15-mg/kg doses. The results in patients treated with topical intra-articular TXA were consistent with those in other several studies [10-15] in which topical TXA was compared to placebo. Seo et al reported a high rate of transfusion of 20% in patients, who received topical intra-articular TXA, but the transfusion rate in that trial was also 34% after IV TXA and 94% after placebo; all the three rates were above the typical rate with use of blood loss prevention techniques [25]. In contrast, our work had no transfusion in either group, which may be due to the smaller numbers of patients in our study. Another factor may be that our higher dose of intra-articular TXA (3gm), compared to (1.5gm) in Seo et al study. However, we used these high doses of topical intra-articular TXA as absorption from the joint is clinically negligible [14]. Wider use of topical TXA during surgery may be facilitated because of the ability of the surgeon to administer a single TXA dose, rather than the two IV doses often administered by the anesthesiologist. Prevention of blood loss has a major implication on TKR costs [26,27], through decreasing morbidity and mortality, complications, and subsequently length of hospital stay. Blood transfusion is considered as the most important predictor of increased length of hospital stay after TKR [28,29]. In a previous study in which the mean length of hospital stay following "fast-track" knee replacement was only 3.8 days, while the length of stay for the patients who required a transfusion was threefold greater [28]. Retrospective clinical and economical evaluations have indicated significant savings per primary TKR performed with use of topical intra-articular TXA [20], with significant decreases in length of stay, blood bank costs, and total direct costs to the hospital for the TKR. Our results were consistent with that fact. The overall risk of a venous thromboembolic event (VTE) or the risk of DVT following TXA use in TKR has been thoroughly studied. Data on thousands of patients have not revealed an increase in overall VTE or DVT rates [2,3,5]. Even with less aggressive thromboprophylaxis protocols [5] such as the one used in the present study, low DVT and PE rates have been confirmed. Our study has some limitations. As no transfusion was needed in either group, the analysis was likely underpowered for confirming superiority of either treatment regarding blood loss and larger studies may be needed. Another limitation is that this trial could have had an additional third arm in which only placebo could have been used. However, ethical issues regarding placebo use have been raised because of the results of prior TXA studies [26]; including a placebo arm showing increased risk of transfusion. In summary, this randomized controlled trial indicated that the results of a single topical intra-articular dose of 3 g of TXA, administered for prevention of blood loss, were comparable to two 15-mg/kg IV TXA doses. Both regimens were equal regarding efficacy and safety with respect to avoiding blood transfusion and both achieved equal control of blood loss without significant complications.

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