RESEARCH ARTICLE

The Efficacy of Intravenous Versus Topical Use of Tranexamic Acid in Reducing Blood Loss after Primary Total Knee Arthroplasty: A Randomized Clinical Trial

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Abstract

Background: Blood loss during and immediately after total knee arthroplasty (TKA) is among the most challenging concerns. It has been demonstrated that Tranexamic acid (TXA) can help to reduce perioperative blood loss. TXA can be used as an oral, topical or intravenous injection. Many studies evaluated the effectiveness of each route of administration but few works on a comparison between them. The current study aimed to compare the effectiveness of intravenous injection versus topical use of TXA in reducing perioperative blood loss after primary total knee arthroplasty.

Methods: Eighty-five patients who were a candidate for total knee arthroplasty were randomized into two groups: one group received Intravenous injection of 15 mg/kg TXA, 10 min before tourniquet inflation while the other group received 1 g diluted TXA during wound closure. The postoperative blood loss was estimated by measuring the whole drain output and also hemoglobin (HB) drops. Both groups compared based on the need for allogenic blood transfusion and also thromboembolic events.

Results: Patients who received topical TXA had a higher total drain output (*P<0.0001*) compared to intravenous injection. The hemoglobin drop also was more in the topical group although it was marginally significant (*P=0.05*).

Conclusion: Intravenous injection of TXA is more effective in reducing postoperative blood loss after primary TKA compared to topical administration.

Level of evidence: I

Keywords: Blood loss, Intravenous, Topical, Total knee arthroplasty, Tranexamic acid

Introduction

Blood loss during and after total knee arthroplasty (TKA) is among the most concerning complications and may increase the need for blood transfusion (1). Perioperative blood management help physicians to decrease the risk of postoperative anemia, thus decline the risk of morbidity and mortality. Furthermore, the morbidity and mortality associated with blood transfusion are attributed to increased susceptibility and

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transmission of infections, altered immune response, transfusion reactions, transfusion-related acute lung injury, circulatory overload, with resultant longer hospital stay and increased costs. Both anemia and blood transfusion are predictors of adverse outcome, so utilization of multimodal perioperative patient blood management (PBM) strategies are required during and after surgeries (2).

Several approaches have been performed to decline the perioperative blood loss, such as autologous blood transfusion, blood-salvaging techniques, low-pressure anesthesia and administration of recombinant human erythropoietin (3). However, some pharmacological strategies have been introduced for avoiding perioperative blood loss and result in improving the quality of care (4).

Recently, Tranexamic Acid (TXA) has been availed as a popular approach to aim this goal (5). TXA is a synthetic agent analog of lysine that can bind to lysine receptors on plasminogen to inhibits its fibrinolysis properties (6).

Several studies have supported the effectiveness of TXA in perioperative blood management and decreasing the need for blood transfusion and improving functional outcomes after total knee arthroplasty (1, 2, 4-7).

According to the literature, there are many effective routes for administration of TXA, however, intravenous and topical use is considered as the most effective (8). Although there are many studies on the effectiveness of each type of administration, however, controversy surrounds choosing the most appropriate route of TXA administration (9). Since now, few clinical trial studies have systematically compared the topical and intravenous drug consumption (10-13).

The current study aimed to compare the effectiveness of intravenous injection and topical use of TXA in reducing blood loss after primary total knee arthroplasty. The null hypothesis of the current study was that there is no significant difference between intravenous (IV) and topical TXA administration, while the alternative hypothesis was that the IV TXA is more effective in controlling blood loss after primary total knee arthroplasty.

Materials and Methods

This prospective, single-blinded, randomized clinical trial, was conducted to compare blood loss following the topical or IV administration of TXA in patients undergoing primary TKA. This study was registered at the Iranian Clinical Trials Registry. The registration identification number is IRCT20190427043390N1.

Nighty-seven patients with knee osteoarthritis, who admitted to our department of knee surgery for primary TKA from May 1st, 2017 to November 30th, 2018, were enrolled. All patients received written informed consent prior to enrollment. The exclusion criteria were: pregnancy, renal insufficiency (Cr> 2 and/or GFR <30), and history of anticoagulant medication or thromboembolic events (11, 14, 15). Revision surgeries, post-traumatic patients, simultaneous bilateral TKA, patients requiring more constrained prosthesis than posterior stabilizing, and those who died before the end of the follow-up period were also excluded. For patients who had staged bilateral TKA (5 patients), each joint was independently evaluated as a separate case.

All patients were randomly divided into two groups (with simple random number generator). Patients in the IV group received 15 mg/kg TXA through slow intravenous infusion, 10 minutes before tourniquet inflation. Topical administration in the control group was done by injecting 1g of TXA diluted in 10 cc normal saline into the joint after watertight closure of the joint capsule. All patients were followed for a minimum of 90 days following the operation.

We excluded twelve patients because of loss of data. The remaining eighty-five patients including 25 males and 60 females were included in the analysis (46 patients in the intervention group and 39 in the control group).

Before surgery, demographic data including age and gender and preoperative hemoglobin (Hb) levels were recorded. Prophylactic administration of 2g of intravenous Cefazolin was done for all patients 10 minutes before tourniquet application. All surgeries were performed under tourniquet control with a pressure of 150 mmHg above the patients' systolic blood pressures. A suction drain was used in all cases and were clamped for the first 6 hours after the surgery and removed after 24 hours. All operations were done by two fellowship-trained knee surgeons with the same methods.

To avoid thromboembolic events, LMWH (1 mg/kg of enoxaparin) was prophylactically used in both groups for 21 days. Blood Hb level was measured at 6 and 24 hours after surgery. Allogenic blood transfusion was done in any symptomatic patients with a blood Hb level less than 7g/dl during the hospital stay. All patients were routinely assessed for any clinical manifestation of venous thromboembolism during the hospital stay and 90 days after surgery. Any patient suspected of having a VTE was evaluated further by color Doppler ultrasound or computed tomographic angiography.

In all knees, the postoperative blood loss was measured based on the total drain output during the first 24 hours after surgery and the amount of Hb drop by subtracting the 24-hour postoperation Hb level from the preoperative Hb level. Both groups were assessed precisely for any thromboembolic events or need for an allogeneic blood transfusion during the hospital stay and 90-day post-admission period.

Sample size calculation

Using a priori to calculate the sample size, considering an effect size of 0.8, alpha error of 0.05, power of 95%, and allocation ratio of 1, the required total sample size was 80 knees with 40 knees in each group.

Statistical analysis

All data was collected and double-checked by two different researchers. According to the normal distribution of variables, independent t-test was used to compare the groups for determining the mean difference between hemoglobin drops, drain outputs, operation time, and length of hospital stay.

Results

Both groups were similar in terms of age, sex, preoperative

Table 1. Demographic variables

	IV TXA	Topical TXA	*P-value*
Sex, no. (%)			
Female	36(78.3)	24(61.5)	0.074
Male	10(21.7)	15(38.5)	
Age, mean (SD), years	68.28(7.4)	68.66(7.9)	0.83
Preoperative Hb, mean (SD), (g/dl)	12.61(2.3)	12.78(2.6)	0.73
Anesthesia, no. (%)			
General	30(65.2)	30(76.9)	0.173
Spinal	16(34.8)	9(23.1)	

IV=Intravenous, TXA=Tranexamic Acid, Hb=Hemoglobin/dl=gram/deciliter

Table 2. Comparison of different variables

	P-value	IV TXA	Topical
Hb drop, mean (SD), mg/dl	*0.048*	1.11 (0.17)	1.56 (0.19)
Drain output, mean (SD), ml	*0.001*	226 (107)	315 (114)
Operation time, mean (SD), minute	*0.52*	173 (28)	169 (27)
Hospital stay, mean (SD), days	*0.49*	4.7 (1.6)	4.4 (1.5)
Blood transfusion		None	None
DVT / TE		None	None

Hb= hemoglobin, SD=standard deviation, mg=milligram, dl=deciliter,ml=milliliter,DVT=deep vein thrombosis, TE=thromboemboly

Hb level, and type of anesthesia (all *P>0.05*) [Table 1].

The mean Hb drop was larger in the topical TXA group (1.56 (0.17) g/dl versus 1.11 (0.19) g/dl) which was marginally significant (*P=0.05*). The postoperative blood loss was also larger in the topical TXA group compared to the IV TXA group (*P=0.001*). Both groups were similar in terms of operation time and duration of hospital stay. No patients received an allogenic blood transfusion or readmitted because of VTE [Table 2].

Discussion

According to the result of this study, IV TXA was more effective in reducing the postoperative blood loss after primary TKA compared to the topical route. IV TXA also may play a more crucial role in preserving the post-operative Hb level than the topical use.

In support of our hypothesis, we provide preliminary data showing that by choosing the IV route, the drug is absorbed more into the surrounding blood vessels and the hemorrhagic bone surfaces compared to the intra-articular topical route. While by IV injection, the drug is widely distributed to the intracellular and extracellular spaces and will rapidly penetrate synovial fluid and synovial membranes, thus providing the same concentration in both synovial fluid and bloodstream (10).

Sarzaeem et al in the clinical trial study compared three routes of TXA administration including IV, Intraarticular (topical), and through the drain. They demonstrated that IV TXA had been more effective in controlling Hb drop and reducing the number of transfused units than other routes (14). Their results also support our findings, although we used a lower dosage of TXA.

Abdel et al in a clinical trial study showed that the IV route was more effective than the topical use to decrease Hb drop after total knee arthroplasty (15). A recent randomized double blinded study showed no major difference in the mechanism of action, coagulation, and fibrinolytic profile between topical TXA and a single dose of IV TXA. However, they showed lower calculated blood loss and shorter hospital stay with the IV TXA (16). On the other hand, Hamline et al showed that 3g of topical TXA was more effective than 1g of IV TXA in reducing the need for allogenic blood transfusion after primary TKA (17). Shin et al also in a meta-analysis study, demonstrated that topical and IV use of TXA had the same effect in reducing drainage blood loss in patients undergoing primary TKA (18).

Despite the beneficial effect of TXA in reducing blood loss and the need for allogenic blood transfusion, and even the infection rate (19), some surgeons may concern about thrombogenic effect of TXA especially by IV injection. Based on the current study, the rate of

thromboembolic events was not increased after IV or topical use of TXA that is supported by many studies in the English literature (2, 4, 7, 19).

This study has several strengths. First of all, it is an accurate clinical randomized trial study with precise randomization. The other strength is that both groups were comparable in terms of some confounding variables such as age, sex, pre-operative Hb level, and type of anesthesia. This study also was done by two fellowship-trained knee surgeons with the same techniques and methods.

Our study also has some limitations. The main limitation is that we did not evaluate the effect of some confounding variables such as body mass index and comorbidities. Besides, we did not consider the intraoperative blood loss which may be different between the groups. In the topical group, we used TXA after releasing the tourniquet that may interfere with the effect of TXA in reducing blood loss.

In conclusion, our result showed that the IV TXA is more effective in reducing the postoperative blood loss and probably hemoglobin drop after primary TKA.

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