Comparison of combined intraarticular (IA) and intravenous (IV) administration of tranexamic acid with IA and IV alone in patients undergoing total knee arthroplasty without drainage catheter: a clinical trial study

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Abstract

Purpose

we aim to determine the most effective route for TXA administration (among IA, IV, combined IA/IV) for TKA surgeries using tourniquet without drainage catheters

Methods

We performed a double-blinded clinical trial on a total of 147 TKA candidates. The amount of blood loss and hemoglobin drop were evaluated in three matched case groups administered TXA during the TKA either via IV, IA or IV plus IA route. Drainage catheter was used for none of the cases.

Results

The combined group showed an average blood loss of 630 ± 252 ml which was significantly lower than the IV group (878 ± 268 ml, P-value < 0.01) and the IA group (774 ± 288 ml, P-value = 0.03). Besides, the mean hemoglobin and hematocrit drop was significantly lower in the combined group compared to the other two groups, 48 and 72 hours postoperatively (P value < 0.05).

Conclusions

The TXA administration via IV plus IA route had 28% and 19% reduction of blood loss in comparison with using the TXA via IV alone and IA alone methods respectively. Therefore, given the surgery is performed with tourniquet application, TXA usage via IV plus IA route may be a more effective way for reducing the perioperative blood loss in TKA cases in patients undergoing TKA without drain placement.

Introduction

Total Knee Arthroplasty (TKA) is considered by many as the method of choice for the management of end stage knee degenerative osteoarthritis with a survival rate of 15–20 years[1]. In the United states (US), over 2% of the population have undergone total knee or hip joint replacement[2] and it is predicted that in the year 2020, almost 1065000 primary TKA would be performed in the US[3]. One of the most important complications of TKA like any other surgery is Perioperative Blood Loss (PBL). The average PBL in a TKA surgery has been estimated at 1498 milliliter (ml) respectively[4]. The blood transfusion following PBL may be associated with increased hospital stay, delayed wound healing, periprosthetic joint infection (PJI) and increased mortality within 90 days following TKA surgery[5].

Widespread application of Tranexamic acid (TXA) as a method for eliminating the PBL, decreases the rate of blood transfusion from approximately 33% to nearly 2% of TKA cases[5] and reduces the PJI by

50%[5]. Its administration also reduces the inpatient hospital cost from 15110\$ to 14890\$[6].

There are different methods of TXA administration including topical, intravenous (IV), intra-articular (IA), oral and combined IV/IA. The 2019 guideline has emphasized controversy about the best route for TXA administration[7]. Some studies have demonstrated the combined IV/IA method to be associated with less perioperative blood loss in TKA surgery[8–10]. However, to the best of our knowledge, most of the literature about the use of TXA in the TKA surgery are performed in the presence of drainage system. In the present study, we aim to compare the IV, IA and IV plus IA method in patients who have a tourniquet inflated during TKA surgery but do not have a drain.

Material And Methods

Trial design and participants:

This double blind clinical trial was conducted from September 2015 to June 2016 at Imam Khomeini Hospital. The Consolidated standards of Reporting Trials (CONSORT) guidelines[11] was followed for reporting this study.

Patients were chosen based on the following inclusion and exclusion criteria; Inclusion criteria were age of more than 20 years, limited functionality and severe knee pain due to knee degenerative osteoarthritis, having no history of thromboembolism, coronary artery disease or cerebral vascular illness, diabetes mellitus, renal or liver impairment. Exclusion criteria were patient's unwillingness to participate in the study or postoperative follow up, allergic reaction to TXA or Hemoglobin (Hb) level of less than 10. From a total number of 152 participants, 150 patients met the inclusion criteria. We excluded 3 individuals from our study as they were unwilling to participate in the study (Fig. 1). Thus, a total of 147 individuals were involved in the study.

Randomization and blinding

Patients were randomly allocated into three TXA administration groups (IV, IA, combined IV/IA) with 1:1:1 ratio using size-6 blocks. The randomization was performed using computer generated random numbers. Randomization was obtained by a researcher not involved in patient's evaluation, surgery or analysis of the patients' data. The route for TXA administration was written in a well-sealed envelope. The envelope was opened in the operating room and the administration was performed accordingly. The knee surgeon (S.M.J.M) did not know the allocation before opening the envelope. In addition, the data analyzer and the participants were blind to the route of administration before and after the surgery.

Interventions:

The combined IV/IA group received 15 milligrams per each kilogram of the patient's weight (mg/kg) TXA (Tranexip®, Caspian Tamin Co, Rasht, Iran) intravenously 10 minutes (min) before the skin incision and 15 mg/kg TXA was injected to their knee after closing the joint capsule with a 23-gauge needle. In the IV

group 15 mg/kg TXA was injected intravenously only 10 min prior to the incision, whereas the IA group received the same dose by injection to their operated knee with a 23-gauge needle after capsule closure.

Perioperative and postoperative medications:

Cefazolin 1 gram (g) (Kefzol®) was administered to all patients 1 hour (hr.) before the operation and every eight hrs. for the first day after the surgery as a prophylactic measure. Acetyl salicylic acid tablet (Aspirin®) 325 milligram (mg) was administered to all patients postoperatively for thromboembolic prevention for 6 weeks. As a pain killer, Celecoxib (Celexib®) capsule 200 mg was given to the participants two dose 30min before the surgery and then every 12-hr. post-surgery. After the operation, the individuals were screened for thromboembolism clinically according to the Wells criteria[12]. Doppler ultrasonography was performed when any suspicion to deep vein thrombosis (DVT) (wells score of at least 2) was present. Also, in the presence of any symptom suggesting the likelihood of pulmonary embolism including dyspnea chest CT scan was performed to rule out pulmonary embolism. Based on our transfusion protocol, in the presence of anemia symptoms (e.g. dizziness, tiredness, palpitation, pallor) 1 unit of packed cell (PC) was transfused to those with less than 8.5 mg/dl of blood Hb. In the absence of anemia symptoms, transfusion (1-unit PC) was injected to those having less than 7.5 mg/dl Hb.

Anesthesia, surgery and rehabilitation:

All operations were performed by the same surgeon (S.M.J.M). the TKA was performed by medial parapatellar approach. Patellar resurfacing was done for all individuals. Bone cutting and soft tissue balancing was performed according to the previous guidelines. Cemented posterior cruciate-stabilized prosthesis (Scoriop® NRG, Stryker) was used in all surgeries. During the surgery, spinal anesthesia with 0.5% Bupivacaine (Marcaine®) was used for pain management. Tourniquet was used in all cases. However, drainage catheter was not used in any of them. After the operation, standard physiotherapy was performed for all participants.

Outcome measures:

Demographic features (i.e. age, gender, weight, height, body mass index (BMI)) and laboratory data (Hb and hematocrit (Hct) levels) prior to surgery, intraoperative tourniquet time, Hb and Hct level at 24, 48 & 72 hours postoperatively and the number of PC transfused to participants during or after TKA were registered. History of any blood transfusion during the hospital stay or occurrence of thromboembolic events were also investigated and recorded.

The primary measure of this study was the amount of the perioperative blood loss (from before the surgery till day 3 postoperatively) analyzed according to the Gross [13] and Nadler[14] formula (Fig. 4). Our secondary measures were the amount of Hb drop at 1st, 2nd and 3rd days postoperatively (in comparison to the amount of preoperative Hb), incidence of thromboembolic events or other postoperative complications and the number of PC transfused. All patients were followed for a period of 2 years.

Statistical analysis:

Data were analyzed using SPSS version 25 for Windows. The statistical significance was set at P-value < 0.05. Data normality was studied using Shapiro-Wilk test. One-way ANOVA, with post hoc Bonferroni was performed on normally distributed quantitative data (shown by mean $\pm$ standard deviation). qualitative variables (shown by percentage frequency) were tested by means of chi-squared test.

Results

Demographic variables, preoperative Hb and Hct levels of patients within each of the three studied groups are shown in Table 1. Quantitative data were analyzed by Shapiro-Wilk test for normality and all were normally distributed. No significant difference was observed among IV, IA and Combined IV/IA groups with regards to age, weight, height, and BMI. Regarding gender, chi-squared test was not applicable since the expected count in one of the groups was less than 5. Preoperative hemoglobin level, hematocrit level and intraoperative tourniquet time was not significantly different between any two groups.

Table 1
Baseline Demographics & Preoperative Data

Characteristic	IV TXA(N = 49)	IA TXA(N = 49)	Combined TXA(N = 49)	P value*	P value[†]	P value[‡]
Age (y)	69.27 ± 8.73	69.94 ± 6.28	70.59 ± 7.71	1.000	1.000	1.000
Weight (Kg)	80.25 ± 12.02	77.15 ± 9.37	75.63 ± 12.34	0.142	1.000	0.424
Height (m)	1.59 ± 0.07	1.59 ± 0.06	1.58 ± 0.07	0.698	1.000	1.000
BMI (Kg/m ²)	31.43 ± 4.26	30.49 ± 3.99	30.37 ± 5.36	0.772	1.000	0.824
Gender (F vs. M)	43(89.6%) vs. 5(10.4%)	46(93.9%) vs. 3(6.1%)	42(85.7%) vs. 7(14.3%)	(-)§		
Hb (g/dL)	13.30 ± 1.26	12.91 ± 1.30	13.16 ± 1.22	1.000	0.818	0.312
Hct (%)	40.52 ± 3.61	39.00 ± 3.94	40.70 ± 3.65	1.000	0.079	0.145
Tourniquet time	69.04	68.71	68.35	0.45	1.00	1.00
<i>All quantitative data reported as mean ± standard deviation & analyzed with one-way ANOVA (Bonferroni post hoc). Qualitative data also reported as frequency (%) & analyzed by χ^2 test.</i>						
* Combined vs. IV						
† Combined vs. IA						
‡ IA vs. IV						
§ χ^2 was not applicable since the expected count in one of the groups was less than 5						

Total blood loss was calculated using Gross & Nadler formula (Fig. 4). The results are shown in Table 2.

Table 2
Hemoglobin & Hematocrit Drop and Postoperative Blood Loss

	<i>IV TXA(N = 49)</i>	<i>IA TXA(N = 49)</i>	<i>Combined TXA(N = 49)</i>	<i>P value*</i>	<i>P value[†]</i>	<i>P value[‡]</i>
Postoperative blood loss						
<i>Total blood loss</i>	878.10 ± 267.80	774.76 ± 288.17	630.51 ± 252.85	0.000	0.027	0.184
Hemoglobin (g/dL) Drop from baseline						
<i>24 hr. postop.</i>	1.61 ± 0.80	1.61 ± 0.97	1.30 ± 0.63	0.527	1.000	1.000
<i>48 hr. postop.</i>	2.29 ± 0.81	2.01 ± 1.05	1.39 ± 0.70	0.000	0.036	1.000
<i>72 hr. postop.</i>	2.49 ± 0.82	2.37 ± 1.03	1.79 ± 0.83	0.003	0.049	1.000
Hematocrit (%) Drop from Baseline						
<i>24 hr. postop.</i>	4.84 ± 2.41	4.83 ± 2.91	3.89 ± 1.99	0.179	0.184	1.000
<i>48 hr. postop.</i>	6.86 ± 2.43	6.02 ± 3.14	4.16 ± 2.09	0.000	0.002	0.341
<i>72 hr. postop.</i>	7.48 ± 2.45	7.12 ± 3.08	5.38 ± 2.49	0.001	0.005	1.000
<i>Data reported as mean ± standard deviation & analyzed with one-way ANOVA (Bonferroni post hoc</i>						
<i>* Combined vs. IV</i>						
<i>† Combined vs. IA</i>						
<i>‡ IA vs. IV</i>						

Mean total blood loss in the Combined IV/IA groups was 630.51 (± Standard Deviation [SD] 252.85) and was significantly lower than the amount of blood loss in IA and IV groups (P value < 0.05). On the other hand, the mean blood loss of IV and IA groups were 878.10 (± SD 267.80) and 774.76 (± SD 288.17) ml respectively and were not significantly different from each other (P value = 0.18) (Fig. 2)

Hb drop at 24 hours postoperatively was not significantly different between any of the three groups (Fig. 3). However, Hb drop at 48 hrs. and 72 hrs. postoperatively were significantly lower in the combined group compared to the other two groups (p < 0.05). IA and IV groups were not significantly different from each other according to the amount of Hb drop at any given time (Fig. 3).

Similar to the Hb drop, the Hct of the combined group demonstrated significantly lower decline at 48 and 72 hrs. postoperatively (P < 0.05) in comparison with IV and IA groups. No significant difference in Hct drop was observed between IV and IA group at any given time or between any of the three groups at 24 hrs. postoperatively (Fig. 2).

None of the patients in this study required blood transfusion or experienced thromboembolism or other postoperative complications during their hospital stay.

Discussion

Despite the latest advancements in surgical procedures and anesthesiology, perioperative blood loss is still one of the most important complications of the TKA. Over 1790cc blood may be lost perioperatively by TKA surgery[15]. Blood transfusion, and the subsequent increasing cost and complications such as infections or allergic reactions, along with prolonged hospital stay are a number of possible consequences associated with perioperative blood loss[5].

TXA as an anti-fibrinolytic agent, is used in TKA surgeries in order to reduce the blood loss and transfusion requirement. Different methods of administration have been introduced and investigated, but the most efficient method is still a matter of debate[7]. A number of RCTs and meta-analyses have reported better results (among IA, IV and combined IA/IV) using the combined IV/IA method[8, 16–18], whereas Meshram [19] and Lee [10] studies suggest no significant difference between IA and combined IA/IV use[10, 19]. One of the reasons for this discrepancy, may stem from the PBL measuring method. It is demonstrated that the nadir of postoperative Hb occurs 3–4 days after the TKA[20, 21]. Thus, many studies measure the postoperative Hb on day 3 after surgery in order to subtract it from preoperative Hb and calculate the PBL according to the Nadler formula[16, 21–25]. However, Meshram [19] and Lee [10] studies used day 5 after surgery to analyze the perioperative blood loss. This may lead to underestimation of blood loss and the effect of TXA on perioperative blood conservation. Our study also shows that the postoperative day with which preoperative Hb is compared, is important. As demonstrated, no significant Hb loss was noticed between IA, IV and combined IA/IV administration on postoperative day 1. However, significantly less Hb loss was detected for combined IA/IV method compared to the other two methods (IA, IV) on postoperative 2 and 3.

Schnettler found that the combined use of tourniquet and intravenous TXA may be associated with more blood loss compared to the intravenous TXA alone suggesting that using tourniquet may eliminate the effect of intravenous TXA by precluding its access to the site of hemorrhage[26]. Therefore, accompanied use of intraarticular TXA in these circumstances has the rationale of enhancing the availability of the drug intraoperatively.

To the best of our knowledge, no study has compared the three methods (IV, IA, combined IV/IA) simultaneously in those undergoing TKA with tourniquet placement and no use of drainage catheter. Theoretically, use of no suction tube may cause hematoma formation and subsequently increase the postoperative pain. On the other hand, it may eliminate the postoperative blood loss due to tampon effect. Interestingly, recent randomized trial in patients receiving Intravenous TXA during knee replacement, did not show any significant increase in postoperative pain when no drain is used except in the immediate 6 hrs. after the operation [27]. Furthermore, no difference regarding perioperative blood loss was detected between those with and individuals without drain. It may merit special attention, that

suction drain might theoretically eliminate the TXA injected intrarticularly and as a result might decrease the possible effect of intraarticular TXA.

Our study demonstrated no significant difference regarding perioperative blood loss between IA and IV administrations. This is in accordance with Chen et. al, study capturing similar result in the presence of drainage system. Furthermore, in our study, the combined IV/IA method had superior effect in declining PBL. Several other studies using drainage catheter arrived at similar conclusion[8, 9]. So, placing drainage catheter, if clamp for enough time after the TXA intraarticular administration, may not affect the efficacy of intraarticular TXA.

PBL in our study in the group using 15 mg/kg dose of TXA (via IV route) was similar to the lee study using 10 mg/kg of the drug intravenously [10]. This is in accordance with Xianhua Ye study which also found no statistically significant difference between 10 and 15 mg/kg IV administration of TXA, either in the amount of intraoperative blood loss or postoperative blood transfusion[28].

We had no case needing blood transfusion postoperatively. This is in contrast to Yuan et. al. demonstrating 17–39% of participants needing blood transfusion depending on the route of TXA administration postoperatively[17]. Unlike our study in which all TKAs were performed under spinal anesthesia, Yuan et. al. used general anesthesia for the surgeries. Thus, the more percentage of transfusion in that study may be a result of the type of anesthesia. Previous study [29], also noted that spinal anesthesia compared with general anesthesia may be associated with less blood loss perioperatively.

Our patients were followed for 2 years after the surgery. However, most previous papers had a follow up ranging from 7 days to 11 months[8–10, 16–19]. Similar to Iseki[16], Karampinas [9] and Nielsen[18] studies, We detected no thromboembolism after the surgery. In other studies, the rate of thromboembolism was reported 0–4%, 0–2%, 0.3-2% percent using IA, IV and combined IA/IV tranexamic acid respectively during TKA [10, 17, 19]. No statistically significant difference has been demonstrated between TXA administration and the control groups or between different TXA usage methods in many studies[8–10, 16–19]. A population based study on 872416 patients in 510 US hospitals compared the rate of postoperative inpatient complications after total hip or knee replacement between those received TXA perioperatively and those managed without TXA. They found that TXA administration was associated with less incidence of many complications postoperatively including blood transfusion, thromboembolic complications and intensive care unit admission[6]. However, further studies may be needed to evaluate the risk of thromboembolism after TXA consumption in high risk patients (e.g. those with a history of thromboembolism, active cancer, etc.)

Among study limitations, we can mention to the fact that patients undergoing bilateral TKA, general anesthesia or surgical drain use were not included in this paper. Therefore, the results might not be applicable to these subgroups. Our sample size was similar to many studies published in the literature [8, 16]. However, further larger sample size studies are needed to determine the likelihood of rare side effects following TXA use.

Conclusions

combined use of IV and IA TXA in TKA surgeries may be associated with lower perioperative blood loss in comparison with IV and IA administration, without increasing the risk of thromboembolic complications.

Declarations

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Ethics approval and consent to participate: informed written consent was obtained from the participants included in the study. The Institutional Review Board (IRB) of **Tehran University of Medical Sciences** (Imam Khomeini Complex Hospital) Reviewed and Approaved our study protocole and declared that there was no ethical Concern with the study in 15/07/2017 (Approval code: IR.TUMS.VCR.REC.1396.2879). The Study retrospectively was registered in Iranian Registry of Clinical Trials (IRCT) in 29/04/2020 (IRCT registration number: **IRCT20160809029286N6**) (www.irct.ir/trial/47313). We Confirmed that **all participants were above 16 years of age in present study.**

Informed consent: an informed consent signed by all the precipitants of study

Consent for publication: Written consent was obtained from our patient to publish his clinical information.

Availability of data and materials: The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

Competing interests: The authors declare that they have no conflict of interest.

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Authors' contributions: S.M.J.M and N.B supervised the study and revised the manuscript. M.A.A and A.P Gadering the Data and prepared the manuscript. A.M reviewed the literature, perfomed the IRCT registry. F.V reviewed the literature, Editted the Manuscript. **All authors have read and approved the manuscript**

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Figures

Figure 1

CONSORT diagram depicting the process of allocation and randomization. n, number of cases; IA, intraarticular; IV, intravenous; TXA, tranexamic acid.

Figure 2

the estimated perioperative blood loss in IA, IV and combined IA/IV groups for TXA administration. Abbreviations: ml, milliliter; IV, intravenous; IA, intraarticular; TXA, tranexamic acid; SD, standard deviation.

Figure 3

Hemoglobin (upper graph) and Hematocrit (lower graph) change during a 72 hours postoperatively. Abbreviations: Hb, hemoglobin; g/dl, gram per deciliter; hr, hour; TXA, tranexamic acid; IV, intravenous; IA, intraarticular

$$total\ blood\ loss(mL) = \frac{Hgb_{loss} \times 100(mL/dL)}{Hg}$$

$$Hgb_{loss} = BV \times (Hgb_i - Hgb_e) \times 10dL/L + Hgb_t$$

$$BV_{forwomen} = 0.3561 \times H^3 + 0.03308 \times W + 0.1833$$

$$BV_{formen} = 0.3669 \times H^3 + 0.03219 \times W + 0.6041$$

Figure 4

Blood Loss Gross & Nadler formula