RESEARCH ARTICLE

Comparison of Combined Intraarticular and Intravenous Administration of Tranexamic Acid with Intraarticular and Intravenous Alone in Patients Undergoing Total Knee Arthroplasty without Drainage Catheter: A Clinical Trial Study

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Received: 10 April 2022 *Accepted: 2 October 2022*

Abstract

Objectives: We aimed to assess the most effective route for Tranexamic acid (TXA) administration among Intraarticular (IA), Intravenous (IV), and combined IA/IV for Total Knee Arthroplasty (TKA) surgeries.

Methods: A double-blinded clinical trial was run on 147 TKA candidates. Blood loss and hemoglobin (Hb) drop were evaluated using the Gross and Nadler formula in three matched case groups administered TXA during the TKA through IV, IA, or combined IA/IV route. Tourniquet was used on all operations for controlling intraoperative blood loss. No drainage catheter was used for the cases.

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

Conclusion: The combined IA/IV route had a 28% and 19% reduction of blood loss, compared to the IV or IA methods, respectively. Therefore, using TXA via the combined IA/IV route may be more effective for reducing perioperative blood loss following TKA surgery using a tourniquet without drain placement.

Level of evidence: I

Keywords: Blood loss, , Surgical, Total knee arthroplasty, Tranexamic acid

Introduction

Total Knee Arthroplasty (TKA) is the method frequently opted 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 has undergone total knee or hip joint replacement,[2] and it is predicted that in 2020, almost 106,5000 primary TKA will 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 1,498 ml.[4] The blood transfusion following PBL may be associated with an 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 transfusion rate from approximately 33% to nearly 2% in TKA cases[5] and reduces the PJI by 50%.[5] Its administration also reduces the inpatient hospital cost from 15,110 $ to 14,890 $.[6]

There are different methods of TXA administration, including topical, intravenous (IV), intra-articular (IA), oral, and combined IV/IA. The 2019 published guideline of the American Association of Hip and Knee Surgeons, American Society of Regional Anaesthesia and Pain Medicine, American Academy of Orthopaedic Surgeons, Hip Society, and Knee Society has failed to conclude the best route for

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THE ONLINE VERSION OF THIS ARTICLE ABJS.MUMS.AC.IR

TXA administration.[7] Some studies proposed the combined IV/IA method to be associated with less PBL in TKA surgery.[8-10] However, to the best of our knowledge, most of the literature about the use of TXA in TKA surgery is performed in the presence of a drainage system. In the present study, we aimed to compare the IV, IA, and combined IV/IA methods in patients who have a tourniquet inflamed during TKA surgery but do not have a drain.

Materials and Methods

Trial design and participants

This double-blind clinical trial was conducted from September 2015 to June 2016 at our center. Before the study, written consent was obtained from all participants. After approving the study by the Tehran University of Medical Sciences ethical review board (Tehran University of Medical Sciences), it was registered at the Iranian Registry of Clinical Trials (www.irct.ir) (Tehran University of Medical Sciences). The Consolidated Standards of Reporting Trials (CONSORT) guidelines[11] were followed for reporting this study.

Patients were chosen based on the following inclusion and exclusion criteria. The inclusion criteria were more than 20 years of age, limited functionality, and severe knee pain due to degenerative knee osteoarthritis. Exclusion criteria were the patient's unwillingness to participate in the study or the postoperative follow-up, allergic reaction to TXA, Hemoglobin (Hb) level of less than 10, history of coagulopathy, coronary artery disease, cerebral vascular illness, diabetes mellitus, and renal or liver impairment. From a total number of 152 participants, 150 patients met the inclusion criteria, but we excluded three individuals from the study as they were unwilling to participate [Figure 1]. Therefore, a total of 147 individuals were involved in the study.

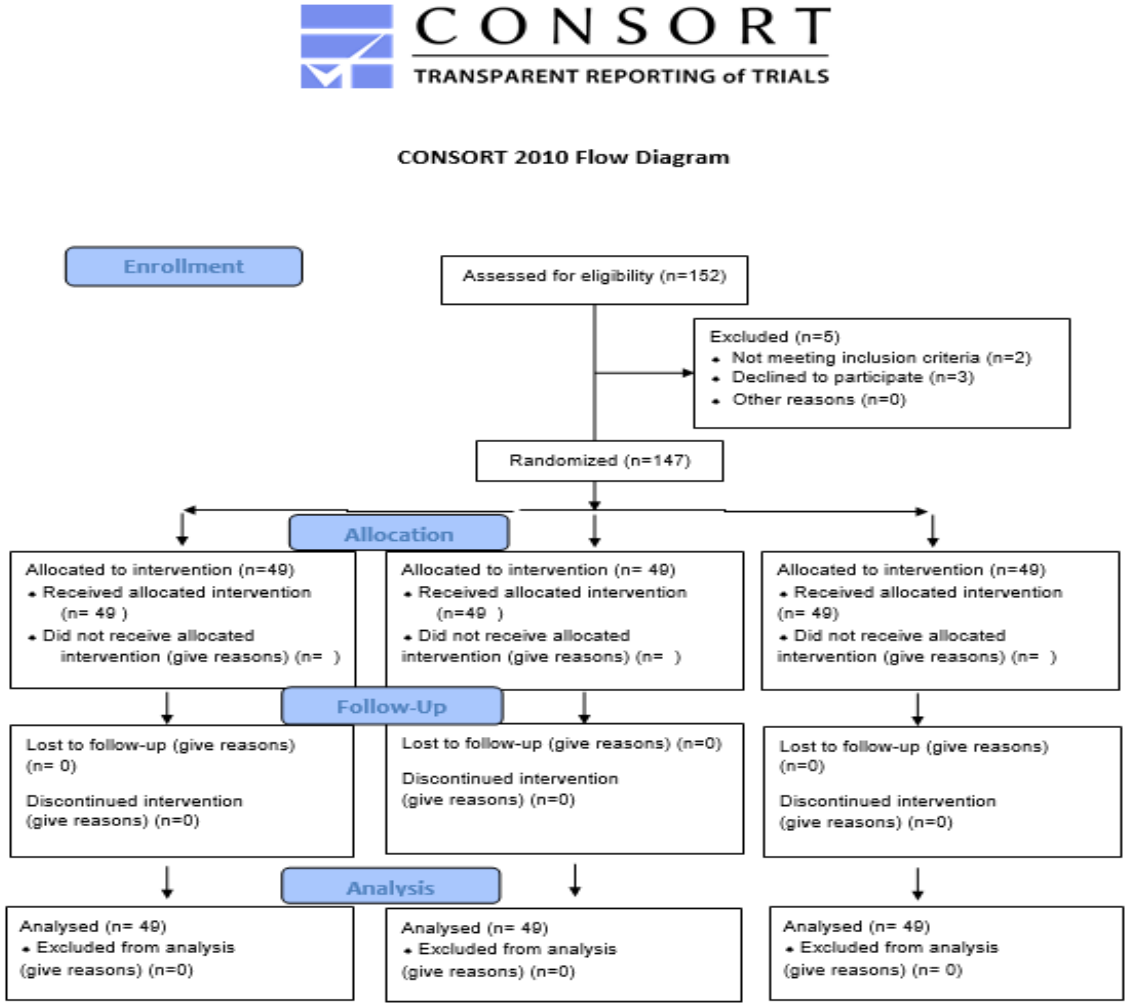

Figure 1. CONSORT diagram depicting the process of allocation and randomization. n: number of cases, IA: intraarticular, IV: intravenous, TXA:

tranexamic acid

Randomization and blinding

Patients were randomly assigned to three TXA administration groups (IV, IA, combined IV/IA) with a 1:1:1 ratio using size 6 blocks. Randomization was performed using computer-generated random numbers, by a researcher not involved in patient evaluation and surgery, or analysis of the patient's 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 mg/kg of the patient's weight (mg/dl) TXA (Tranexip®, Caspian Tamin Co, Rasht, Iran) intravenously 10 min before tourniquet inflation. In addition, 15 mg/kg TXA was injected into their knee at the end of the surgery after closing the joint capsule and 5 min before tourniquet deflation with a 23-gauge needle. In the IV group, 15 mg/kg TXA was injected intravenously only 10 min before tourniquet inflation. Finally, the IA group received the same dose by injection to their operated knee with a 23-gauge needle after capsule closure and 5 min before tourniquet deflation.

Perioperative and postoperative medications

Cefazolin 1 g (Kefzol®) was given to all participants one hour before the operation and every eight hours on the first day after the surgery, as a prophylactic measure. Acetylsalicylic acid tablet (Aspirin®) 325 mg was administered to all individuals twice daily postoperatively for thromboembolic prevention for six weeks. As a pain killer, a Celecoxib (Celexib®) capsule of 400 mg was given to the participants in two doses, 30 min before the surgery and then every 12 h 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 of deep vein thrombosis (wells score of at least 2) was present. Moreover, chest CT angiography was performed to rule out pulmonary embolism in the presence of any symptom suggesting the likelihood of pulmonary embolism, including dyspnea. Based on our transfusion protocol, in the presence of anemia symptoms (such as dizziness, tiredness, palpitation, or pallor), one unit of the 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 into 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, and patellar resurfacing was done for all individuals. Bone cutting and soft tissue balancing were performed according to the previous guidelines. All surgeries used a cemented posterior cruciate-stabilized prosthesis (Scorpio® NRG, Stryker). Spinal anesthesia with 0.5% Bupivacaine (Marcaine®) was used for pain management during the surgery, and a tourniquet was used in all cases. However, a drainage catheter was not used in any of them. After the operation, standard physiotherapy was performed for all participants.

Outcome measures

Demographic features (including age, gender, weight, height, and 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, and 72 h 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 the occurrence of thromboembolic events was also investigated and recorded.

The primary measure of this study was the amount of the PBL (from before the surgery till day three postoperatively) analyzed according to the Gross[13] and Nadler[14] formula [Figure 2]. Our secondary measures were the amount of Hb drop on the first, second, and third days postoperatively (compared to the amount of preoperative Hb), the incidence of thromboembolic events or other postoperative complications, and the number of PC transfused. All patients were followed for two years.

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

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

$$BVforwomen = 0.3561 \times H^3 + 0.03308 \times W + 0.1833$$

$$BVformen = 0.3669 \times H^3 + 0.03219 \times W + 0.6041$$

Figure 2. Blood loss Gross and Nadler formula

Statistical analysis

Data were analyzed using the SPSS software (version 25) for Windows. The statistical significance was set at $P<0.05$. Data normality was studied using the Shapiro-Wilk test. One-way ANOVA with post hoc Bonferroni was performed on normally distributed quantitative data (shown by mean±SD). Qualitative variables (shown by percentage frequency) were tested using the 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 the Shapiro-

Wilk test for normality, and the results confirmed they were normally distributed. No significant difference was observed among IV, IA, and combined IV/IA groups regarding age, gender, weight, height, and BMI. The Chi-squared test was not applicable for gender since the expected count in one of the groups was less than 5. However, the results of Fisher's exact test revealed no significant difference between groups in terms of gender (IA vs. IV: P=0.49, Combined vs. IA: P=0.33, Combined vs. IV: P=0.76). Preoperative Hb level, Hct level, and intraoperative tourniquet time were also not significantly different between the three groups.

Total blood loss was calculated using the Gross and Nadler formula [Figure 2], the results of which are shown in [Table 2].

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/m²)	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%)	0.76§	0.33	0.49
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

All quantitative data reported as mean ± standard deviation & analyzed with one-way ANOVA (Bonferroni post hoc). Qualitative data also reported as frequency (%) & analyzed by $\chi 2$ test.

* Combined vs. IV

† Combined vs. IA

‡ IA vs. IV

§ P value was calculated using Fisher exact test

Table 2. Hemoglobin & Hematocrit Drop and Postoperative Blood Loss

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

Data reported as mean ± standard deviation & analyzed with one-way ANOVA (Bonferroni post hoc

*Combined vs. IV

†Combined vs. IA

‡IA vs. IV

The mean±SD of total blood loss in the combined IV/IA groups was 630.51±252.85, which was significantly lower than the amount of blood loss in the IA and IV groups (P<0.05). On the other hand, the mean±SD of blood loss of IV and IA groups were 878.10±267.80 and 774.76±288.17 ml, respectively, which were not significantly different from each

other (P=0.18) [Figure 3].

There was no significant difference between the three groups in Hb drop at 24 h postoperatively [Figure 4]. However, Hb drop at 48 and 72 h postoperatively was significantly lower in the combined group, compared to the other two groups (P<0.05). There was no significant difference between the IA and IV groups in the amount of Hb drop at any given time [Figure 4].

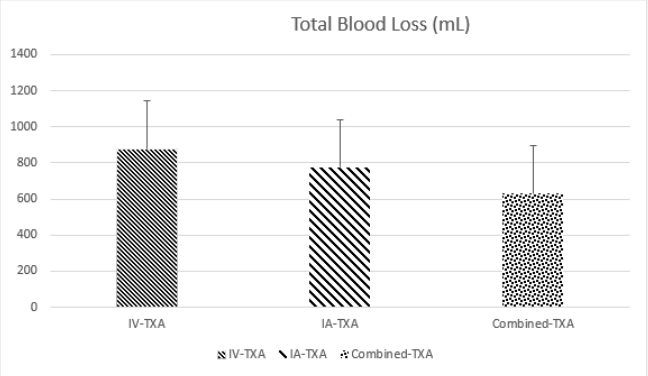

Figure 3. Estimated perioperative blood loss in IA, IV, and combined IA/IV groups for TXA administration. ml: milliliter, IV: intravenous, IA: intraarticular, TXA: tranexamic acid, SD: standard deviation

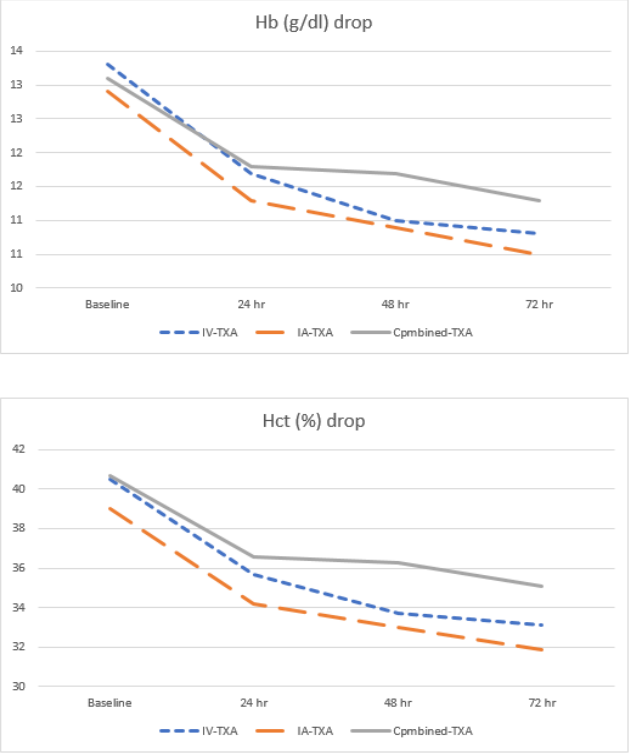

Figure 4. Haemoglobin (upper graph) and Haematocrit (lower graph) change for 72 hours postoperatively. Hb: hemoglobin, g/dl: gram per deciliter, h: hour, TXA: tranexamic acid, IV: intravenous, IA: intraarticular

Similar to the Hb drop, the Hct of the combined group demonstrated a significantly lower decline at 48 and 72 h postoperatively (P<0.05), compared to that in the IV and IA groups. On the other hand, no significant difference was observed between IV and IA groups in Hct drop at any time or between any of the three groups at 24 h postoperatively [Figure 3].

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, PBL is still one of the most important complications of TKA. Over 1790cc blood may be lost perioperatively by TKA surgery.[15] Blood transfusion, the subsequent increasing cost, and complications such as infections or allergic reactions, along with prolonged hospital stay, are possible consequences associated with PBL.[5]

TXA, an anti-fibrinolytic agent, is used in TKA surgeries to reduce blood loss and transfusion requirements. Different administration methods have been introduced and investigated, but the most efficient is still a matter of debate.[7] Several Randomized controlled clinical trials and meta-analyses have reported better results (among IA, IV, and combined IA/IV) using the combined IV/IA method.[8, 16-18] In contrast, Meshram et al.[19] and Lee et al.[10] studies suggest no significant difference between IA and combined IA/IV methods.[10, 19] one of the reasons for this discrepancy may stem from the PBL measurement method. It is demonstrated that the nadir of postoperative Hb occurs 3-4 days after the TKA.[20,21] Therefore, many studies measure the postoperative Hb on day three after surgery to subtract it from preoperative Hb and calculate the PBL according to the Nadler formula.[16, 21-25] However, Meshram et al.[19] and Lee et al.[10] studies used day five after surgery to analyze the PBL. This may lead to the 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 one. However, significantly less Hb loss was detected for the combined IA/IV method, compared to the other two methods (IA, IV), on postoperative days two and three.

Schnettler et al. found that the combined use of a tourniquet and IV TXA may be associated with more blood loss, compared to the IV TXA alone, suggesting that using a tourniquet may eliminate the effect of IV TXA by precluding its access to the site of hemorrhage.[26] Therefore, the use of IA TXA in these circumstances has can enhance the availability of the drug intraoperatively.

To the best of our knowledge, no study has simultaneously compared the three methods (IV, IA, and combined IV/IA) among those undergoing TKA with tourniquet placement and no use of a drainage catheter. Theoretically, using no suction tube may cause hematoma formation and

subsequently increase postoperative pain. On the other hand, it may be helpful in decreasing the blood loss following the surgery due to the tampon effect. Interestingly, a recent randomized trial in patients receiving IV TXA during knee replacement showed no significant increase in postoperative pain when no drain was used, except in the immediate six hours after the operation.[27] Furthermore, no difference was detected in PBL between those with and without drain. It may merit special attention that a suction drain might theoretically eliminate the TXA injected intraarticularly and, as a result, decrease the possible effect of IA TXA.

Our study demonstrated no significant difference in PBL between IA and IV administrations. This is in accordance with Chen et al. study capturing similar results in the presence of a drainage system. Furthermore, in our study, the combined IV/IA method had a superior effect on declining PBL. Several other studies using drainage catheters reached a similar conclusion.[8,9] Therefore, placing a drainage catheter, if clamped for enough time after the IA TXA administration, may not affect the efficacy of IA TXA.

PBL in our study in the group using a 15 mg/kg dose of TXA (via IV route) was similar to the study by Lee et al.[10] using 10 mg/kg of the TXA intravenously.[10] This is in accordance with the Xianhua Ye et. al. 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 with Yuan et al. demonstrating that 17%-39% of blood transfusions depend on the TXA administration route postoperatively.[17] Unlike our study, in which all TKAs were performed under spinal anesthesia, Yuan et al. used general anesthesia for the surgeries. Therefore, the higher percentage of transfusion in that study may have resulted from the type of anesthesia. In a previous study,[29] it was also noted that spinal anesthesia, compared to general anesthesia, may be associated with less PBL.

Our patients were followed for two 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 et al.,[16] Karampinas et al., [9] and Nielsen et al. [18] studies, we detected no thromboembolism after the surgery. In other studies, the rate of thromboembolism was reported at 0-4%, 0-2%, and 0.3-2%, using IA, IV, and combined IA/IV TXA, 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 872,416 patients in 510 US hospitals compared the rate of postoperative inpatient complications after total hip or knee replacement between those who received TXA perioperatively and those managed without TXA. They found that TXA administration was associated with fewer postoperative complications, 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 (such as those with a history of thromboembolism, active cancer, or other conditions).

Considering study limitations, patients undergoing bilateral TKA, general anesthesia, or surgical drain use were not included in this study. Therefore, the results might not apply to these subgroups. Our sample size was similar to many studies published in the literature.[8, 16] However, further concrete evidence with larger sample size are needed to analyze the likelihood of rare side effects following TXA use.

Conclusion

Combined use of IV and IA TXA in TKA surgeries may be associated with lower PBL, compared to IV or IA administration, without increasing the risk of thromboembolic complications.

Acknowledgement

The authors would like to thank Dr. Babak Sattartabar for his helps in data collection. Also, we appreciate the kind participation of our patients in this study.

Conflict of interest: None
Funding: None

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