Indian Journal of Orthopaedics Surgery 2023;9(3):162–167

Content available at: https://www.ipinnovative.com/open-access-journals

Indian Journal of Orthopaedics Surgery

Journal homepage: https://www.ijos.co.in/

Original Research Article

Combined intravenous and intraarticular tranexamic acid compared with intraarticular use alone in total knee arthroplasty: A randomized controlled trial

Seyed Morteza Kazemi[1], Seyyed Mehdi Hoseini[1], Alireza Mirahmadi[1], Pooya Hosseini-Monfared[1], Maryam Salimi[2], Reza Minaei[1,*]

[1]*Bone Joint and Related Tissues Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran*
[2]*Bone and Joint Diseases Research Center, Shiraz University of Medical Sciences, Shiraz, Iran*

ARTICLE INFO

Article history:
Received 05-07-2023
Accepted 21-07-2023
Available online 04-09-2023

Keywords:
Total knee arthroplasty
Tranexamic acid
Total blood loss

ABSTRACT

Background: Total knee arthroplasty is associated with high rates of blood loss during and after the surgery. Tranexamic acid is an antifibrinolytic agent that effectively reduces total blood loss in total knee arthroplasty and minimizes the need for blood transfusion and transfusion-related complications. However, the most efficacious route of tranexamic acid administration has not been established. Therefore, in this study, we aimed to compare combined intravenous and intraarticular tranexamic acid with intraarticular use alone in patients undergoing total knee arthroplasty.

Materials and Methods: In this randomized, double-blind clinical trial, 104 patients scheduled for primary unilateral Total knee arthroplasty were randomized to one of the two intervention groups. The combined intravenous and intraarticular group received 15 mg/kg (Max dose of 1 g) of intravenous tranexamic acid along with 15 mg/kg (Max dose of 1 g) of tranexamic acid administered intraarticularly after the capsule and retinaculum closure. Total blood loss was calculated using the drop in hemoglobin at post-operative day 3. The transfusion rate and incidence of thromboembolic events were evaluated.

Results: Total blood loss in patients receiving combined intravenous and intraarticular tranexamic acid was not significantly different from that in patients receiving only intraarticular tranexamic acid (926 ± 312 ml vs 905 ± 348 ml, p value= 0.824). There were no complications like thromboembolic events or wound infection.

Conclusion: In conclusion, the intraarticular administration of tranexamic acid is an equally effective route as combined intravenous and intraarticular use of tranexamic acid in total knee arthroplasty, and hence to avoid potential complications of systemic TXA use, we recommend using the intraarticular only tranexamic acid in total knee arthroplasty.

1. Introduction

Total Knee Arthroplasty (TKA) is an established safe procedure for people with knee arthritis. One of the most challenging aspects of TKA is the substantial blood loss. The amount of blood loss has been variable in different studies and has been reported to be up to 2000 mL.[1] The significant volume of blood loss leads to complications like anemia and the need for a blood transfusion which puts the patient at risk of blood transfusion complications, including transfusion-transmitted infections and immunologic reactions.[2] In order to limit the blood loss, several improvements over the perioperative management of bleeding have been proposed, including hypotensive anesthesia, use of cell salvage, drains, tourniquet application, and agents like tranexamic

* *Corresponding author.*
E-mail address: reza.minaie@gmail.com (R. Minaei).

https://doi.org/10.18231/j.ijos.2023.032

acid (TXA) and other antifibrinolytic agents like epsilon aminocaproic acid (EACA), and aprotinin.[3]

TXA, a synthetic derivative of lysin, is an antifibrinolytic agent that acts by competitively inhibiting plasminogen activation. It has been widely used to control bleeding in orthopedic surgeries like total hip arthroplasty and TKA. Several studies and meta-analyses have shown that TXA is a safe drug that can decrease the total amount of blood loss in TKA.[4] Different approaches have been suggested for the TXA administration in TKA concerning the dosage, timing, and route of administration. Various routes of administration like intravenous (IV), oral, topical spray to the joint surface, peri-articular injection, intraarticular (IA), or a combination of these methods have been discussed in several studies.[5] However, the most advantageous route and regimen of TXA administration have not been established.

The IV administration of TXA has some limitations, including relative contraindications in patients with a history of thromboembolic and ischemic events like deep vein thrombosis (DVT), pulmonary embolism (PE), or ischemic cerebrovascular accident. Therefore, topical administration of TXA can be a great option in these patients due to its minimal systemic effects.[6] In this double-blind, randomized clinical trial, we aimed to study the safety and efficacy of combined administration of IV+IA TXA compared to the intraarticular TXA alone.

2. Material and Methods

2.1. Study design

This randomized controlled trial involved patients with the age of 50 years and older who were scheduled for a primary unilateral TKA. We acquired the institutional review board approval before the start of this trial. Patients in the trial were informed about the surgery and informed consent was obtained.

2.2. Exclusion criteria

1. History of a thromboembolic event like DVT, PE, or arterial stenosis with or without concomitant coronary artery bypass grafting
2. History of cardiovascular diseases like myocardial infarction or atrial fibrillation or heart failure
3. History of cerebrovascular disease like the previous stroke
4. Clotting disorders including abnormal PT, PTT, or INR
5. History of allergic reaction to TXA
6. Being in pregnancy or during the lactation period
7. Drug abusers or alcoholics
8. Severe liver or kidney dysfunction
9. Severe infection
10. Preoperative hemoglobin < 10 g/dL
11. Diagnosis of inflammatory arthritis like rheumatoid arthritis, and pigmented villonodular synovitis

Enrolled patients were randomized into combined IV+IA group (group A) and IA only group (group B) in a 1:1 ratio consecutively. Assessment of the patients in the follow-up period was performed by an independent physician. The patients, trial investigators, data controller, and analyst were blinded. Group A: the patients received 15 mg/kg of TXA intravenously 10 min before the use of the tourniquet and a 15 mg/kg intraarticular dose after the capsule and retinaculum closure. Group B: the patients received a 15 mg/kg intraarticular dose of TXA after the capsule and retinaculum closure. The tourniquet was released at least 5 minutes after the IA injection of TXA in both groups. The study recruitment and progress steps are displayed in the Consolidated Standards of Reporting Trials (CONSORT) flow diagram template in Figure 1.

2.3. Surgical procedure and perioperative management

Patients taking aspirin or antiplatelet agents were asked to stop the medications one week prior to the TKA. Patients received standard spinal anesthesia using ropivacaine 0.5% (Molteni & C Dei Fratelli, Italy) and 25-50 μg of fentanyl and intraoperative sedation with 7-10 mL/h infusion of propofol 2% (Fresenius Kabi Austria Gmbh, Austria) was used at the discretion of the anesthesiologist.

All TKAs were carried out by the same experienced surgeon using the standard medial parapatellar approach following an anterior midline skin incision. A pneumatic tourniquet with a pressure of about 100 mmHg above the systolic blood pressure was applied to all patients. The tourniquet was inflated and deflated before the incision and after the skin closure, respectively. A cemented, posterior stabilized prosthesis (Stryker Triathlon, Mahwah, NJ) was used in all patients. Femoral bone cutting was performed with the aid of an intramedullary femoral resection guide. The femoral canal was sealed with an autologous bone plug. No vacuum drain or blood salvage was used. At the final stage of the surgery, 15 mg/kg (Max dose of 1g) of the IA TXA was injected after the capsule and retinaculum closure, and then the skin incision was closed by layer. The tourniquet was deflated at least 5 minutes after the injection of TXA. In the group A, in addition to the IA dose of TXA as described above, TXA with a dose of 15 mg/kg (Max dose of 1g) with 10 ml normal saline was slowly used intravenously and followed by the inflation of the tourniquet.

Patients were dressed with an elastic bandage and knee immobilizer after the surgery. Enoxaparin 40 mg once daily was administered subcutaneously from 12 hours after the surgery and continued for 14 days. Cefazolin was used as antimicrobial prophylaxis, given within 60 minutes before the surgical incision and repeated every 8 hours up to 24

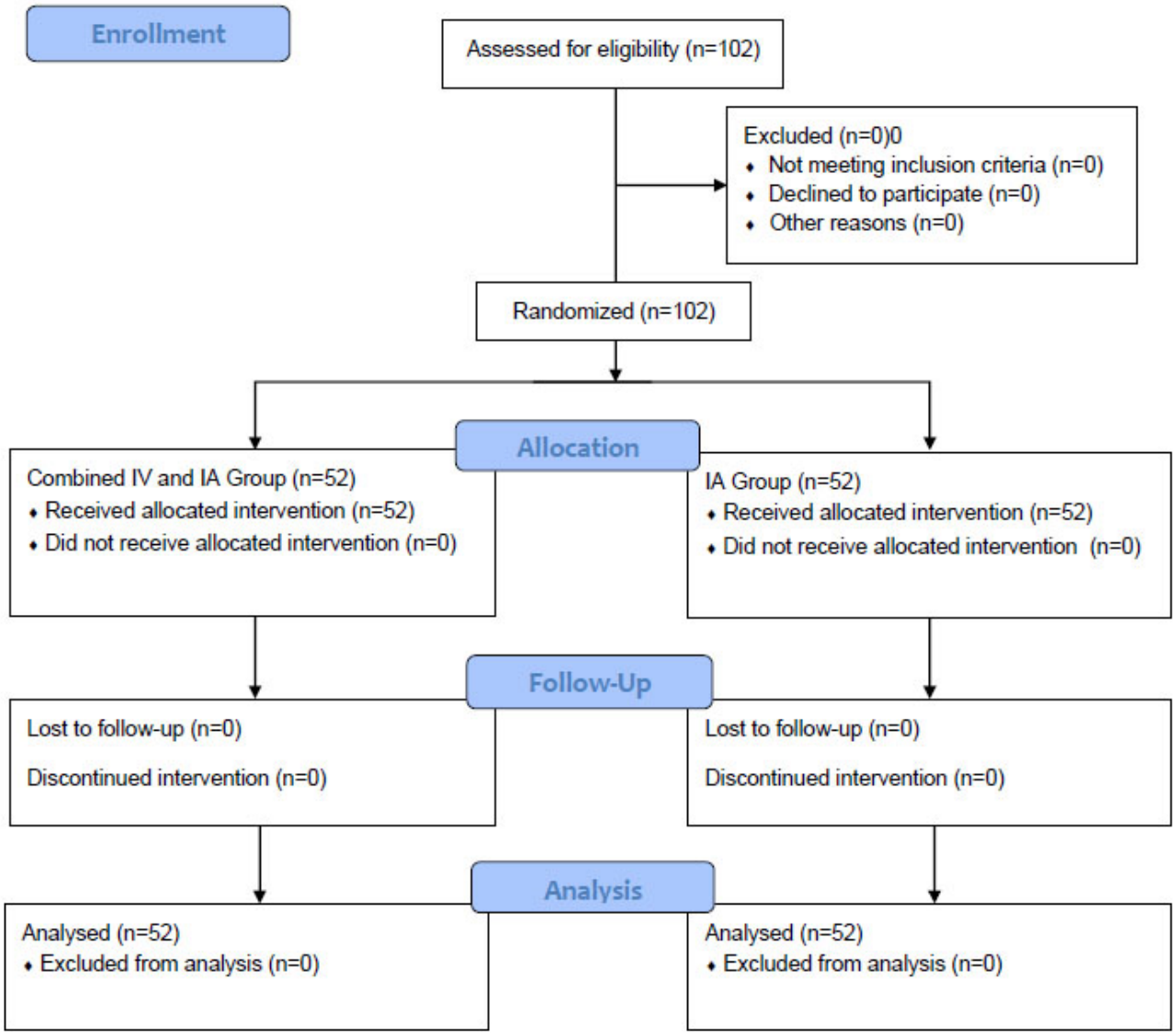

Fig. 1: CONSORT flow diagram of the study

hours after the surgery. All Patients were asked to follow a standard postoperative rehabilitation protocol, including walking exercises and lower extremity muscle strength training.

2.4. Outcome measures

The total amount of blood loss was estimated by the Gross formula, which uses the post-operative drop in hemoglobin (Hb) level and estimated blood volume adjusted for the weight and height of the patients using the formula described by Nadler et al.[7] The post-operative drop in Hb level was calculated using the Hb level in the first three days following the surgery. In patients who had received a blood transfusion, the lowest Hb level before the transfusion was utilized for calculation. Other outcomes were also assessed, such as the preoperative and post-operative Hb levels, transfusion rate, the incidence of thromboembolic events, and other post-operative complications.

Patients having a Hb level of less than 7 g/dL or for those with clinical features of anemia (defined as light-headedness, fatigue, palpitation, or shortness of breath), below 8 g/dL were assumed for blood transfusion.

The cases were followed up one week after the surgery in the outpatient department. Also, clinical evaluation for lower extremity edema, thromboembolic events, early infection, or wound healing disorders was performed in the follow up period.

2.5. Statistical analysis

The patients in the study were evaluated for the primary and secondary outcome variables. The data's normality was evaluated by means of the Kolmogorov-Smirnov Z-test and the Shapiro-Wilk test. The paired t-test was used for dependent, normally distributed continuous variables and the chi-square test was utilized to compare the categorical data. The statistical analyses were performed using IBM SPSS Statistics version 26 for Windows. The statistical significance level was assumed at less than 0.05 for P values.

The sample size was decided with regard to the previous studies results the and the expected Hb drop in the total knee arthroplasty.[8] For the sample size estimation, we used an alpha = 0.05 and power = 80%. The t-test indicated that each arm of the trial would require 47 patients. By considering the expected 10% dropout, 52 patients were needed in each arm. G-Power software (version 3.1.9.7, Kiel, Germany) was used for the statistical power calculation and 84% obtained.

3. Results

A hundred and four patients were included in this randomized controlled trial. The demographic data (age, sex, BMI) for the two groups were presented in Table 1.

No significant difference in demographic data was observed between the two groups. Lack of significant difference between the two groups concerning the length of the surgery was also observed (Table 1).

The lowest post-operative Hb in patients was 8.0 mg/dL, which was above the cut-off value for blood transfusion; therefore, none of the patients required a blood transfusion. The highest blood loss was 1618 ml. No signs of thromboembolic events, wound infection, need for knee aspiration, or other post-operative complications were detected during the follow-up period.

Based on linear models for repeated Hb measurement, considering sex, age, BMI, and surgery duration as cofounders, group A was comparable with group B, and the Hb drop in both groups were not statistically significant (Figure 2). Statistically significant differences in the Hb levels were evaluated using a mixed analysis of variance (ANOVA) (Table 2).

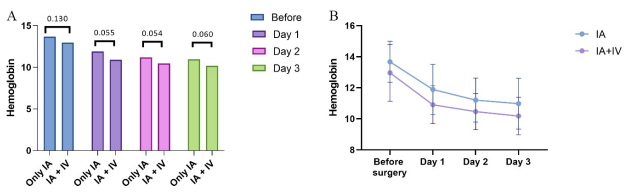

Fig. 2: A): The numbers above the bars are the P-Values of differences in Hb levels between IA and IV+IA groups. **B**): Hb level changes in different stages of the study

Despite persistent Hb decreases in the postoperative days, group A and group B was not significantly different based on the drop in the Hb levels (2.816±1.063 g/dL vs 2.812±1.043 g/dL, p-value=0.989) (Figure 2). Similarly, the estimated total blood loss that is based on the Hb drop was not significantly different in the group A compared to that in group B (926 ± 312 ml vs 905 ± 348 ml, p value= 0.824).

4. Discussion

The high volume of blood loss has been a challenging aspect of TKA, and several studies have been carried out to establish the best strategy in order to minimize the blood transfusion and total blood loss. Administration of TXA, as an effective agent to reduce the blood loss in TKA, have been suggested. TXA can be administered via various routes such as oral, intravenous, intraarticular, peri-articular, or a combination of these routes. In a large meta-analysis of 67 studies by Fillingham et al., it was found that the topical, IV, and oral use of TXA reduced blood loss in TKA in comparison to placebo.[9] Zhao et al. conducted a meta-analysis of 6 randomized controlled trials comparing the IA TXA use versus placebo. Their study showed that the IA administration of TXA significantly reduced the total blood loss in TKA without any significant difference in complication rates like thromboembolic events.[10] However, no advantage was discovered regarding the route and formulation, and dosing of the TXA, and conflicting data have been reported. Therefore, the most effective route and regimen for TXA use have not been established yet.

There are a few studies concerning the efficacy of combined IV+IA use of TXA in TKA. However, controversial results were reported. Nielsen et al. and Zhang et al. found lower blood loss in the combined IV+IA TXA group versus the IV TXA group.[11,12] Zhang et al. also reported that administration of combined IV+IA TXA can significantly reduce the total blood loss as opposed to the IA TXA.[12] Meshram et al. compared the combined IV+IA with the IA only TXA in the bilateral TKA and reported no significant difference in the blood loss in these two groups, which is consistent with our results.[13]

There is a concern over the IV use of TXA regarding the possibility of thromboembolic complications. However, the incidence of thromboembolic events like DVT or PE was not significantly different in the reported studies of the IV use of TXA. Medical conditions like cardiac and cerebrovascular disease, history of prior DVT, and renal insufficiency prevent the use of IV TXA. IA use of TXA does not have these same contraindications due to lower systemic absorption after topical use of TXA.[6,14] Therefore, IA use of TXA is especially beneficial for patients with contraindications for IV use of TXA.

This study shows that in reducing total blood loss in TKA, the efficacy of the IA use of TXA and the combined IV+IA TXA are equal.

Table 1: The basic characteristics of the included patients

Variable		Combined IV+IA Group	IA Group	P value
Number of Patients		52	52	
Gender	Male	4 (16.6%)	4 (16.6%)	1.000
	Female	20 (83.3%)	20 (83.3%)	
Age (years)		70.54 ± 6.02	69.54 ± 8.56	0.642
BMI (kg/m^2)		28.48 ± 4.71	29.46 ± 3.97	0.442
Operating Time (mins)		71.42 ± 3.06	70.46 ± 3.59	0.326
Pre-op Hb level (g/dL)		12.96 ± 1.82	13.67 ± 1.31	0.130

Notes: BMI: Body mass index, IV: Intravenous, IA: Intraarticular, Pre-op: Preoperation, Hb: Hemoglobin

Table 2: Hb level in different stages and groups

Hb level (g/dL)	Combined IV+IA Group	IA Group	P value
Pre-op	12.96 ± 1.82	13.67 ± 1.31	0.594
Day 1	10.90 ± 1.21	11.29 ± 1.61	
Day 2	10.46 ± 1.16	11.20 ± 1.41	
Day 3	10.17 ± 1.20	10.97 ± 1.63	

Notes: IV: Intravenous, IA: Intraarticular, Pre-op: Preoperation, Hb: Hemoglobin

Our study had some limitations including not assessing the cost-effectiveness of TXA use in TKA.

5. Conclusion

We have found that the efficacy of the IA use of TXA and the combined IV+IA TXA show the same efficacy in TKA. Therefore, we suggest the only intraarticular use of TXA for primary unilateral TKA, with the aim of avoiding the potential systemic adverse effects associated with the systemic use of TXA.

6. Abbreviations

TKA: total knee arthroplasty; TXA: tranexamic acid; IV: intravenous; IA: intraarticular; EACA: epsilon aminocaproic acid; PE: pulmonary embolism; DVT: deep vein thrombosis; Hb: hemoglobin

7. Source of Funding

None.

8. Conflicts of Interest

None.

References

1. Rosencher N, Kerkkamp HE, Macheras G, Munuera L, Menichella G, Barton DM, et al. Orthopedic Surgery Transfusion Hemoglobin European Overview (OSTHEO) study: blood management in elective knee and hip arthroplasty in Europe. *Transfusion*. 2003;43(4):459–69.
2. Bong MR, Patel V, Chang E, Issack PS, Hebert R, DiCesare PE. Risks associated with blood transfusion after total knee arthroplasty. *J Arthroplasty*. 2004;19(3):281–7.
3. Palmer A, Chen A, Matsumoto T, Murphy M, Price A. Blood management in total knee arthroplasty: state-of-the-art review. *J ISAKOS*. 2018;3(6):358–66.
4. Shemshaki H, Nourian SMA, Nourian N, Dehghani M, Mokhtari M, Mazoochian F. One step closer to sparing total blood loss and transfusion rate in total knee arthroplasty: a meta-analysis of different methods of tranexamic acid administration. *Arch Orthop Trauma Surg*. 2015;135(4):573–88.
5. Wu Q, Zhang HA, Liu SL, Meng T, Zhou X, Wang P, et al. Is tranexamic acid clinically effective and safe to prevent blood loss in total knee arthroplasty? A meta-analysis of 34 randomized controlled trials. *Eur J Orthop Surg Traumatol*. 2015;25(3):525–41.
6. Patel JN, Spanyer JM, Smith LS, Huang J, Yakkanti MR, Malkani AL, et al. Comparison of intravenous versus topical tranexamic acid in total knee arthroplasty: a prospective randomized study. *J Arthroplasty*. 2014;29(8):1528–31.
7. Nadler SB, Hidalgo JH, Bloch T. Prediction of blood volume in normal human adults. *Surgery*. 1962;51(2):224–32.
8. Lin SY, Chen CH, Fu YC, Huang PJ, Chang JK, Huang HT. The efficacy of combined use of intraarticular and intravenous tranexamic acid on reducing blood loss and transfusion rate in total knee arthroplasty. *J Arthroplasty*. 2015;30(5):776–80.
9. Fillingham YA, Ramkumar DB, Jevsevar DS, Yates AJ, Shores P, Mullen K, et al. The efficacy of tranexamic acid in total knee arthroplasty: a network meta-analysis. *J Arthroplasty*. 2018;33(10):3090–8.
10. Zhao-Yu C, Yan G, Wei C, Yuejv L, Ying-Ze Z. Reduced blood loss after intra-articular tranexamic acid injection during total knee arthroplasty: a meta-analysis of the literature. *Knee Surg Sports Traumatol Arthrosc*. 2014;22(12):3181–90.
11. Nielsen CS, Jans Ø, Ørsnes T, Foss NB, Troelsen A, Husted H. Combined Intra-Articular and Intravenous Tranexamic Acid Reduces Blood Loss in Total Knee Arthroplasty: A Randomized, Double-Blind, Placebo-Controlled Trial. *J Bone Joint Surg Am*. 2016;98(10):835–41.
12. Zhang YM, Yang B, Sun XD, Zhang Z. Combined intravenous and intra-articular tranexamic acid administration in total knee arthroplasty for preventing blood loss and hyperfibrinolysis: A randomized controlled trial. *Medicine (Baltimore)*. 2019;98(7):e14458.
13. Meshram P, Palanisamy JV, Seo JY, Lee JG, Kim TK. Combined intravenous and intraarticular tranexamic acid does not offer additional benefit compared with intraarticular use alone in bilateral TKA: A randomized controlled trial. *Clin Orthop Relat Res*. 2020;478(1):45–54.
14. Wong J, Abrishami A, ElBeheiry H, Mahomed NN, Davey JR, Gandhi R, et al. Topical application of tranexamic acid reduces postoperative blood loss in total knee arthroplasty: a randomized, controlled trial. *J Bone Joint Surg Am*. 2010;92(15):2503–13.

Author biography

Seyed Morteza Kazemi, Professor

Seyyed Mehdi Hoseini, Medical Doctor https://orcid.org/0000-0003-3693-9178

Alireza Mirahmadi, Medical Doctor https://orcid.org/0000-0003-3475-2692

Pooya Hosseini-Monfared, Medical Student https://orcid.org/0000-0003-4346-1029

Maryam Salimi, Medical Doctor https://orcid.org/0000-0001-9771-7048

Reza Minaei, Assistant Professor https://orcid.org/0000-0002-7851-842X

Cite this article: Kazemi SM, Hoseini SM, Mirahmadi A, Hosseini-Monfared P, Salimi M, Minaei R. Combined intravenous and intraarticular tranexamic acid compared with intraarticular use alone in total knee arthroplasty: A randomized controlled trial. *Indian J Orthop Surg* 2023;9(3):162-167.