Comparison of the Effects of Intravenous and Topical Tranexamic Acid with the Combined Method in Reducing Blood Loss Following Total Knee Arthroplasty

Abstract

Introduction: Postoperative bleeding is a major concern in total knee arthroplasty (TKA), often leading to complications such as anemia and increased demand for blood transfusion. Tranexamic acid (TXA), an antifibrinolytic agent, is used intravenously and topically to reduce surgical blood loss. This study aimed to compare the efficacy of three administration methods of TXA (intravenous, topical, and combined) in reducing bleeding among Iranian patients.

Materials & Methods: This double-blind randomized clinical trial (RCT) was conducted on 135 patients undergoing TKA, between February 2021 and June 2021. Patients were randomly assigned to three groups of 45 each: intravenous, topical, and combined. Demographic data, postoperative drainage volume, hemoglobin changes, and other clinical variables were analyzed using SPSS software.

Results & Discussion: The combined TXA group showed a statistically significant reduction in intraoperative bleeding (524.0 ± 150.5 mL) compared to the intravenous (665.6 ± 136.3 mL) and topical (740.2 ± 141.5 mL) groups ($p<0.05$). This group also experienced a smaller postoperative drop in hemoglobin. No significant differences were observed among the groups in terms of edema or knee circumference ($p>0.05$).

Conclusion: The combined administration of intravenous and topical TXA was more effective in reducing postoperative drainage volume and hemoglobin drop, compared to either method alone. These findings support the superiority of the combined approach and highlight the importance of TXA use in managing bleeding in orthopedic surgeries.

Keywords: Postoperative hemorrhage, Total knee replacement, Tranexamic acid.

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Introduction

Postoperative bleeding is one of the primary concerns in total knee arthroplasty (TKA). Approximately one-third of patients undergoing total joint arthroplasty (TJA) require 1 to 3 units of blood postoperatively[1]. Intraoperative bleeding during knee arthroplasty often leads to postoperative anemia[2]. Acute postoperative anemia and blood transfusion are associated with increased complications, including angina pectoris, myocardial infarction, heart failure, and delayed rehabilitation[3, 4]. Various strategies are employed to control bleeding, such as the use of antifibrinolytics, desmopressin, preoperative anemia management, discontinuation of anticoagulant medications, deliberate hypotension, and tourniquet application during TKA to reduce blood loss[5–7].

Tranexamic acid (TXA) is one of the most widely known antifibrinolytic agents used to reduce bleeding. It is a lysine analog that binds to plasmin and inhibits its activity, thereby preventing the fibrinolysis process. TXA has been shown to significantly reduce overall blood loss during primary total knee arthroplasty procedures[8]. Tranexamic acid can be administered intravenously or topically. Intravenous administration of TXA varies significantly in timing (preoperative, intraoperative, postoperative, or in combination) and in dosage. There is no global consensus regarding the standard intravenous dose of TXA, and it is often left to the surgeon's discretion.

Reported intravenous TXA doses range from 10 to 20 mg/kg[9]. Theoretically, intravenous TXA may increase the risk of thrombotic events. It is contraindicated in patients with a history of allergy to the drug, arterial or venous thrombosis, an inherent risk of thrombosis or thromboembolism, acute renal failure, subarachnoid hemorrhage, or a history of seizures[10]. Topical tranexamic acid is administered as a diluted solution directly into the surgical site to act on the tissues and bleeding areas. Tranexamic acid, at a dose of 2-3 grams diluted in 100 ml of normal saline, is injected into the joint 5-10 minutes before opening the tourniquet at the end of surgery. This is done after suturing the fascia and subcutaneous tissue. [9]. Although intravenous tranexamic acid theoretically increases the risk of thrombosis, several studies have demonstrated that topical tranexamic acid is equally effective in reducing blood loss, with no significant difference in thrombotic events[11–13].

The need for blood transfusion in total knee arthroplasty (TKA) has been reported to decrease by up to 81% with intravenous TXA, 66% with topical TXA, and 61% with oral TXA[14]. The administration of tranexamic acid in gynecologic, orthopedic, urologic, and cardiac surgeries can reduce the need for blood transfusion by up to 35%[15].

The present study aims to compare postoperative blood loss following total knee arthroplasty among three methods of tranexamic acid administration: intravenous, topical, and a combination of both.

Materials & Methods

This study was conducted as a randomized, double-blind clinical trial (RCT) on patients undergoing total knee arthroplasty (TKA) at Fatemi and Qaem Hospital in Ardabil from February 2021 to June 2021. Simple random sampling was employed to allocate participants into groups for comparison. The sample size was calculated using Cochran's formula, with a significance level of $\alpha = 0.05$ and statistical power of 0.8, resulting in 135 participants. The patients were randomly divided into three groups: 45 patients received intravenous tranexamic acid, 45 received topical tranexamic acid, and 45 received a combination of both.

In the topical group, 2-3 grams of tranexamic acid diluted in 100 mL of normal saline was injected intra-articularly 5–10 minutes before deflating the tourniquet, after suturing the fascia and subcutaneous layers. In the intravenous group, 1 gram of tranexamic acid was administered before tourniquet inflation and another 1-2 gram during the operation via intravenous injection. In the combination group, 1 gram of intravenous tranexamic acid was given before tourniquet inflation and 1-2 gram of topical tranexamic acid was administered as in the topical group protocol.

All surgeries were performed by a single orthopedic surgeon using the medial parapatellar approach on one knee with a tourniquet pressure of 300-350 mmHg. The tranexamic acid administration method was strictly adhered to for each group. A surgical drain was inserted for all patients, which was clamped for 3 hours postoperatively and then released in the ward. Patients were discharged once they could independently ambulate using a walker. After discharge, all patients received 40 mg of subcutaneous enoxaparin every 24 hours for 20-25 days. Fluid resuscitation was performed for all patients. Hemoglobin levels were assessed the day after surgery, and postoperative blood loss was measured based on drain output 24-36 hours after surgery.

Data on surgical outcomes—including postoperative blood loss from the drain, joint motion limitations (flexion and extension range of the knee), and postoperative knee swelling (based on pre- and post-operative knee circumference)—were collected from patient records and clinical examinations.

Blood transfusion was administered to patients with hemoglobin levels below 8 g/dL, or below 10 g/dL in patients showing significant symptoms of anemia despite adequate volume replacement. Doppler ultrasound was routinely used at discharge and during six-month follow-ups or whenever deep vein thrombosis (DVT) was suspected.

Demographic data, including age, sex, comorbidities, and body mass index (BMI), were also collected. Continuous data were presented as mean ± standard deviation and analyzed using one-way analysis of variance (ANOVA) followed by post hoc comparisons. Categorical data were expressed as frequencies and percentages, and comparisons were made using the Chi-square test. A p-value of <0.05 was considered statistically significant. All analyses were performed using SPSS version 20.0.

All patients provided written informed consent to participate in the study. Their data were kept confidential and accessible only to the research team. Patients could withdraw from the study at any stage without any restrictions. All personal information was

stored securely by the physician and principal investigator, and no patient names were mentioned in the study. The study received ethical approval from the Ethics Committee of Ardabil University of Medical Sciences under code IR.ARUMS.REC.1399.597.

Results

In this experimental study, 135 patients who underwent total knee arthroplasty (TKA) were evaluated. The patients were divided into three groups: 45 patients in the intravenous tranexamic acid group, 45 in the topical tranexamic acid group, and 45 in the combined tranexamic acid group. The baseline characteristics of the patients—including age, sex, and body mass index (BMI)—were comparable across the three groups (Table 1). Of the total participants, 63 (46.7%) were female and 72 (53.3%) were male. The mean age of the patients was 64.3 ± 5.9 years, and the mean BMI was 29.0 ± 2.4 kg/m². No statistically significant differences were observed between the groups in terms of demographic variables ($p > 0.05$).

A total of 31 patients (23%) had underlying medical conditions, the most common of which were diabetes (7.4%), hypertension (7.3%), renal disease (7.3%), thyroid disorders (3%), cardiovascular disease (3%), pulmonary disease (1.5%), and rheumatologic disorders (0.7%). The distribution of comorbidities was similar among the three groups, and no statistically significant differences were observed between them ($p > 0.05$). The mean blood loss in the combined TXA group was 524 ± 150.5 mL, compared to 665.6 ± 136.3 mL in the intravenous TXA group and 740.2 ± 141.5 mL in the topical TXA group, which was statistically significant ($p < 0.05$). Postoperative blood loss was significantly lower in the combined TXA group compared to the intravenous and topical TXA groups. Table 2 presents the clinical and laboratory findings of the patients in the three groups.

Pre- and postoperative clinical and laboratory parameters, including hemoglobin level, knee circumference, drainage blood loss, need for blood transfusion, and length of hospital stay, were evaluated across the three groups. The difference in hemoglobin levels before and after surgery showed a statistically significant difference among the groups ($p < 0.05$). However, knee circumference and postoperative edema in the combined TXA group did not differ significantly compared to the intravenous and topical TXA groups ($p > 0.05$).

Analysis of gender distribution, body mass index, and comorbidities revealed no statistically significant differences among the three groups ($p > 0.05$). Postoperative blood loss was not significantly associated with gender, BMI, or presence of comorbid conditions in any group ($p > 0.05$). Pearson correlation analysis showed that postoperative blood loss was significantly correlated with the amount of drainage blood loss, and changes in hemoglobin levels before and after surgery across all groups ($p < 0.05$).

Table 1: Demographic Characteristics of Patients. There was no significant difference among the groups regarding demographic variables.

Variable (n = 135)	Topical Group (n = 45)	Intravenous Group (n = 45)	Combined Group (n = 45)	P value
Age				
Mean	64.0	64.0	64.7	0.817
Standard Deviation	6.5	5.6	5.7	
Body Mass Index (BMI)				
Mean	29.1	28.9	29.0	0.955
Standard Deviation	2.5	2.6	2.3	
Gender				0.915
Male – Frequency	25	24	23	
Male – Percentage	55.6%	53.3%	51.1%	
Female – Frequency	20	21	22	
Female – Percentage	44.4%	46.7%	48.9%	

Table 2: Comparison of clinical and laboratory findings of patients.				
Variable (N = 135)	Topical Group (n = 45)	Intravenous Group (n = 45)	Combined Group (n = 45)	P Value
Hemoglobin change before and after surgery (g/dL)	2.7 ± 0.9	2.5 ± 0.9	1.5 ± 0.5	*<0.05
Drainage blood loss (mL)	740.2 ± 141.5	665.6 ± 136.3	524.0 ± 150.5	*<0.05
Need for blood transfusion, number (%)	1 (2%)	1 (2%)	0	0.601
Knee circumference difference (pre/post-op) (cm)	1.3 ± 0.09	1.2 ± 0.1	1.3 ± 0.08	0.632
Length of hospital stay (days)	4.0 ± 0.9	4.4 ± 0.9	4.5 ± 1.3	0.175
In the comparison among the three groups, the combined TXA group demonstrated superior outcomes in terms of reduced blood loss. An asterisk (*) indicates statistically significant differences.				

Overall, the combined TXA group consistently demonstrated the lowest blood loss and hemoglobin reduction. No cases of deep vein thrombosis (DVT) and infection were observed during the study period or at the 6-month follow-up in any of the groups.

Discussion

This study demonstrated that the simultaneous use of intravenous and topical tranexamic acid has a greater effect on reducing intraoperative and postoperative bleeding during total knee arthroplasty (TKA) compared to the separate use of each type (intravenous tranexamic acid and topical tranexamic acid). The combined method led to a significant reduction in bleeding and smaller changes in hemoglobin levels, without increasing the risk of thrombotic complications. These results clearly show the superiority of the combined method and emphasize the importance of using tranexamic acid in controlling bleeding during orthopedic surgeries.

The use of tranexamic acid has been widely considered in various surgeries, particularly in single-joint knee arthroplasty (TKA), to reduce bleeding during and after surgery. In this study, the combined group, which received both intravenous and topical tranexamic acid, showed the best results in reducing bleeding and other surgical outcomes compared to the groups that received only one form of the drug. These findings are consistent with the results of similar studies, which have also demonstrated that combining these two methods can have more positive effects compared to using either method separately.

In the study by Jixiang Tan and colleagues, a meta-analysis of 19 studies, similar results were presented. The current study compares three different methods of tranexamic acid administration (intravenous, topical, and combined), showing that using the combination of both methods can lead to better results in reducing bleeding during TKA surgery compared to either method alone. On the other hand, the study by Jixiang Tan and colleagues focuses on the use and effect of intravenous tranexamic acid. Regarding sample size, the meta-analysis article includes 19 studies with a total of 1,114 patients, which increases the credibility and power of the data analysis[16].

Despite the alignment of most studies in this field, some previous studies have yielded different results. In the retrospective study by Guorui Cao, which investigated patients undergoing bilateral knee replacement surgery, the overall blood loss and hemoglobin drop were higher in the control group compared to the intravenous treatment group, but this difference was not statistically significant. The study concluded that confirming these results requires further research and the conduction of prospective studies, especially since the study was retrospective and focused on bilateral joint replacement surgeries[17]. In a systematic review and meta-analysis of randomized controlled trials (RCTs) conducted by Yu Fu and colleagues, the effectiveness and safety of topical tranexamic acid versus intravenous tranexamic acid were assessed. This study found no significant difference between the need for injection, blood loss, drainage blood loss, hemoglobin levels 24 hours post-operation, infection incidence, and deep vein thrombosis (DVT) between topical and intravenous tranexamic acid administration. The results of this study do not align with the present study, where bleeding levels in the topical, intravenous, and combined tranexamic acid groups were significant, and intravenous tranexamic

acid was more effective than the topical form. The combined form was also the most effective method in reducing surgery-related blood loss in TKA[18].

In a prospective randomized controlled trial by ZeYu Huang and colleagues, aimed at determining the effectiveness and safety of combined intravenous and topical tranexamic acid in comparison with intravenous tranexamic acid alone for unilateral total knee arthroplasty (TKA), patients were divided into two groups. The first group received 3 grams of intravenous tranexamic acid, while the second group received 1.5 grams of topical tranexamic acid along with 1.5 grams of intravenous tranexamic acid. The results showed that, compared to 3 grams of intravenous tranexamic acid, adding 1.5 grams of topical tranexamic acid to 1.5 grams of intravenous tranexamic acid in unilateral knee arthroplasty could provide similar effectiveness in reducing the need for blood transfusions and overall blood loss, without compromising safety. The most important point is that by adding topical tranexamic acid, patients experienced less hemoglobin (Hb) drop, lower drainage volume, less knee pain postoperatively, reduced knee swelling, shorter hospital stays, and greater short-term satisfaction. The present study did not investigate the effects of different doses of tranexamic acid, nor did it examine the combined use of intravenous and topical tranexamic acid[19].

This study demonstrates that intravenous tranexamic acid is more effective than the topical form, but the combined method is the most effective approach for reducing bleeding associated with knee arthroplasty. Apart from comparing the effects of different tranexamic acid combinations on bleeding related to knee arthroplasty surgery, identifying factors that affect their outcomes is also very important, as the effects of a single drug can vary among different patients. This is crucial for personalizing treatment for each patient. In this study, postoperative bleeding was statistically significantly associated with the drainage blood loss, and changes in hemoglobin, but no significant statistical relationship was found with variables such as age, body mass index, knee circumference before and after surgery, the need for whole blood transfusion, and the number of hospital days. In this study, no thromboembolic complications or deep vein thrombosis (DVT) and infection were observed in any of the groups. Further studies are recommended to explore such factors in future research and allow for comparison of results. Given that this issue has not been explored in previous studies, more research is suggested. The differences between the various methods of tranexamic acid use in these studies are also replicable, and the results can be generalized.

However, this study had limitations, including the lack of investigation into the effects of oral administration, the lack of examination of different tranexamic acid doses, and the absence of a control group. Additionally, the lack of long-term follow-up of patients was another limitation. Therefore, it is recommended that future studies address these issues to provide a more accurate comparison of different tranexamic acid methods and their long-term effects. Moreover, investigating the factors affecting treatment efficacy and the possibility of personalizing treatment for different patients is crucial and could improve clinical outcomes in knee arthroplasty surgeries.

Conclusion

This experimental study demonstrated that the combined use of tranexamic acid significantly reduces blood loss following total knee arthroplasty. The group that used both intravenous and topical methods (combined) showed the best results in reducing bleeding compared to the groups using intravenous or topical treatment alone. The combined group also had better outcomes in terms of reducing swelling and knee circumference, hemoglobin drop, and drainage blood loss after surgery.

Furthermore, the results showed that postoperative blood loss was more closely associated with the drainage blood loss and hemoglobin drop. However, no significant correlation was found with variables such as age, BMI, underlying diseases, knee circumference, the need for blood transfusion, and the number of hospital days. These findings highlight the superior effect of the combined method of tranexamic acid in comparison with other methods for reducing postoperative bleeding.

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