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Tranexamic acid in knee arthroplasty: the effect of preoperative intravenous administration of together with postoperative intravenous maintenance and periarticular administration on bleeding, transfusion, and hospitalization time – a retrospective cohort study

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ABSTRACT

Objective: To compare patients who received preoperative intravenous (IV) plus postoperative maintenance IV tranexamic acid (TXA) therapy and perioperative periarticular TXA to those who did not receive TXA during total knee arthroplasty (TKA) in terms of blood loss, transfusion requirements, and length of hospital stay.

Material and Method: Data from 194 patients who underwent TKA between 2016 and 2019 were reviewed. A total of 106 patients were included. Twenty-one patients were male, and 95 were female. The patients were divided into three groups: Group 1 (n=37) that did not receive perioperative TXA, Group 2 (n=35) that received preoperative IV and postoperative maintenance TXA therapy, and Group 3 (n=34) that received preoperative IV and perioperative periarticular TXA. The groups were similar regarding demographic data. Statistical comparisons between the groups were made concerning the decrease in hemoglobin levels on postoperative days 1 and 3, the need for transfusion, and the length of hospital stay.

Results: The mean decrease in hemoglobin on the postoperative first and third days were 1.69(±1.13) and 2.94(±1.14)g/dl, in Group 1, 1.41(±0.99) and 2.44(±1.28)g/dl, in Group 2, and 1.24(±0.83) and 2.21(±0.84)g/dl in Group 3 respectively. The statistical comparison of the hemoglobin decrease revealed a significant difference between Groups 1 and 3 on the postoperative first day($p<0.05$). There was no other significant difference between the remaining group pairs. There was a statistically significant difference in the length of hospital stay and the amount of erythrocyte suspension used between Groups 1 and other groups ($p<0.05$). In Group 1, prolonged wound discharge was observed in four patients. No additional surgical intervention was performed in any of the three groups due to infection, and no vascular thrombosis or embolism was observed.

Conclusion: Our results showed that IV and periarticular TXA applications in TKA effectively reduced bleeding and bleeding-related complications without causing additional complications.

Keywords: Knee arthroplasty, tranexamic acid, transfusion, blood loss, intravenous, periarticular, maintenance therapy

INTRODUCTION

The increase in average human life expectancy, aging population, increased expectations concerning quality of life, and technological developments in orthopedics and traumatology have led to a significant increase in knee arthroplasty procedures. Blood loss during and after joint replacement surgery is one of the most critical problems to be addressed. Up to 1,000 ml of blood is lost during knee arthroplasty surgery, to which approximately 500 ml of unseen loss is added postoperatively (1,2). Therefore, 9-84 % of patients require a blood transfusion after knee arthroplasty surgery (3).

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Blood transfusions carry many risks, with the primary being blood-borne diseases, such as hepatitis B/C and human immunodeficiency virus. As a result of immunomodulation and immunosuppression that can occur after transfusion, postoperative infection rates increase, length of hospital stay is prolonged, recovery and return to function are slowed down, and mortality increases (4). Therefore, it is essential to reduce perioperative blood loss and the need for transfusion (5). In clinical practice, various methods are used to reduce blood loss (6), including antifibrinolytics. Tranexamic acid (TXA) is an antifibrinolytic drug, a synthetic lysine analog that acts as a plasminogen activator inhibitor. There is increasing scientific evidence that TXA, which has long been used to prevent blood loss during cardiothoracic and gynecologic surgery, can reduce perioperative blood loss during joint replacement surgery (7-9). TXA can be administered intravenously or periarticularly. Many studies have shown that both intravenous (IV) and periarticular administration of TXA significantly reduce blood loss while not increasing the risk of deep venous thrombosis (DVT) (10-12).

In the current medical literature, many articles discuss the use of IV and periarticular TXA in knee arthroplasty surgery. However, only a limited number of articles address the efficacy and safety of maintenance therapy with TXA after preoperative and periarticular TXA administration in knee arthroplasty surgery.

In this study, we compared the patients who received preoperative IV plus postoperative IV TXA or preoperative IV plus perioperative periarticular TXA with those who did not receive TXA during total knee arthroplasty (TKA) in terms of blood loss, transfusion requirements, and length of hospital stay.

MATERIAL AND METHOD

The study was carried out with the permission of Gaziosmanpaşa Training and Research Hospital Clinical Researches Ethics Committee (Date: 10.11.2021, Decision No: 372). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

This retrospective cohort study evaluated data from 194 patients operated on by a single arthroplasty surgeon between 2016 and 2019 with the same type of cruciate ligament preserving prosthesis (Genesis 2, Smith and Nephew, Memphis, TN, USA) diagnosed with primary gonarthrosis, who received preoperative IV TXA plus maintenance TXA for one day postoperatively, preoperative IV TXA plus perioperative periarticular TXA, and who were not administered perioperative TXA were retrospectively studied by reviewing patient records.

Patients with morbid obesity (body mass index > 35, n=21), history of deep vein thrombosis (n=5), renal dysfunction (n=12), cardiac problems (n=10), or rheumatologic diseases (n=8), those using anticoagulants (n=10), and those with severe soft tissue deformities [more than 20° varus (n=11)] or valgus (n=6) deformity, or 15° flexion contracture (n=5)] were excluded from the study.

A total of 106 cases that met the study criteria were included in the sample. Twenty-one of the patients were male, and 95 were female. The mean age was 64.79 (47-89) years.

Spinal or epidural anesthesia was performed in all patients. For prophylaxis, 2 grams of cefazolin sodium was administered intravenously as standard. Cruciate-retaining knee prosthesis was inserted via a parapatellar incision in all patients. For thromboembolism prophylaxis, 0.4 ml of Clexane was administered subcutaneously 12 hours after surgery and continued until ten days after discharge.

The patients in the study were divided into three groups:

- Group 1: surgery was performed with a pneumatic tourniquet without the administration of TXA.
- Group 2: the patients received 10 mg/kg IV TXA in 100 ml saline before incision and the same dose IV as an eight-hour infusion in the second hour after surgery.
- Group 3: the patients received 10 mg/kg IV TXA in 100 ml of physiological saline before incision, and the same dose was applied to the tissue around the joint at the end of surgery.

In Groups 2 and 3, the tourniquet was used only during cementation when the prosthesis was inserted.

A hemoglobin value below 70 mg/dl and a postoperative decrease of 30 mg/dl compared to the preoperative value were used as transfusion indications(13). In addition, changes in hemoglobin levels, length of hospital stay, and patients' blood transfusion requirements were assessed before surgery and on the postoperative first and third days.

Statistical Method: SPSS version 22 for Mac (SPSS Inc., Chicago, IL) was used for the statistical analysis. Mean, standard deviation, median, minimum and maximum values were used as descriptive statistics. The distribution of variables was checked using the Kolmogorov-Smirnov test. One-tailed analysis of variance was used to analyze data with a normal distribution, and the Kruskal-Wallis test was used to analyze data without a normal distribution. A p value of <0.05 was taken as the statistical significance limit.

RESULTS

Table 1 presents the decrease in hemoglobin levels on the postoperative first and third days. There was no statistically significant difference between Groups 1 and 2 and between Groups 2 and 3 in terms of the hemoglobin decrease on the postoperative first day ($p > 0.05$), while a significant difference was found between Groups 1 and 3 ($p < 0.05$) (**Table 2**).

The length of hospital stay of the groups and the number of erythrocyte suspensions applied are shown in Table 1. There was a statistically significant difference between Groups 1 and 2 and between Groups 1 and 3 in terms of the length of hospital stay ($p=0.005$). However, no statistically significant difference between Groups 2 and 3, although the length of hospital stay was lower in Group 2 (**Table 3**). The number of erythrocyte suspensions used statistically significantly differed between Group 1 and the remaining two groups. The number of erythrocyte suspensions used in Group 3 was lower compared to Group 2, albeit with no statistically significant difference (**Table 3**).

Prolonged serous discharge was observed in four patients in the early postoperative period in Group 1 and resolved with dressing control within ten days without the need for additional surgery. None of the patients in any of the groups required second surgery due to bleeding, serous discharge, or infection. No DVT, pulmonary embolism, or cardiac or cerebrovascular embolism was observed in any group.

DISCUSSION

This study compared the patients who received preoperative IV and postoperative IV TXA, preoperative IV, and perioperative periarticular TXA with those who did not receive TXA during TKA in terms of blood loss, transfusion requirements, and length of hospital stay. The decrease in hemoglobin levels was significantly lower in the patients administered periarticular TXA on the first day. Moreover, both TXA-administrated groups provided significantly better results than the non-TXA group in terms of erythrocyte suspension requirement and length of hospital stay. No thromboembolic complication was observed in any of the groups.

Table 1. Demographic data of the groups

	Group 1 (Non-tranexamic acid (n=37)	Group 2 IV tranexamic acid (n=35)	Group 3 Periarticular tranexamic acid (n=34)
Age (years)	65±9.24	65.05±7.77	64.82±6.72
Gender			
Female	30 (81%)	29 (83%)	26 (76%)
Male	7 (19%)	6 (17%)	8 (24%)
Average Hgb decrease on postoperative day 1 (g/dl)	1.69±1.13	1.41±0.99	1.24±0.83
Average Hgb decrease on postoperative day 3 (g/dl)	2.94±1.14	2.44±1.28	2.21±0.84
Average length of hospital stay (days)	5.2 ±1.50	3.77±1	3.88±0.76
Transfusion (U)	1.74±1.06	0.57±0.61	0.72±8.33

IV, intravenous; Hgb, hemoglobin

Table 2. Statistical data on hemoglobin decrease on the postoperative first and third days

Paired-samples Test								
First-day hemoglobin decrease	Paired differences					t	df	Sig. (2-tailed)
	Mean	SD	Std. error mean	95% CI				
				Lower	Upper			
Group 1 vs Group 2	0.240	1.42	0.240	-2.487	7.287	0.998	34	0.325
Group 1 vs Group 3	0.447	1.34	0.299	-0.208	9.149	1.944	33	0.060
Group 2 vs Group 3	0.200	1.24	0.212	-2.329	6.329	0.940	33	0.354
Third-day hemoglobin decrease								
Group 1 vs Group 2	0.422	1.58	0.268	-1.225	9.682	1.576	34	0.124
Group 1 vs Group 3	0.694	1.31	0.225	2.353	11.528	3.079	33	0.004*
Group 2 vs Group 3	0.294	1.57	0.270	-2.256	8.449	1.086	33	0.285

SD, standard deviation; CI, confidence interval; Group 1, non-tranexamic acid; Group 2, intravenous tranexamic acid; Group 3, periarticular tranexamic acid

Table 3. Statistical data on the length of hospital stay and erythrocyte suspension requirements

	Test Statistics[a]					
	Length of hospital stay			Erythrocyte suspension requirement		
	Group 1 vs Group 2	Group 1 vs Group 3	Group 2 vs Group 3	Group 1 vs Group 2	Group 1 vs Group 3	Group 2 vs Group 3
Z	-3.747[b]	-3.941[b]	-0.606[c]	-4.191[b]	-3.830[b]	-0.557[c]
Asymp. Sig. (2-tailed)	.000	.000	.000	.000	.000	.557

[a]Wilcoxon signed-ranks test, [b]Based on positive ranks, [c]Based on negative ranks Group 1, non-tranexamic acid; Group 2, intravenous tranexamic acid; Group 3, periarticular tranexamic acid

The use of TXA has recently gained popularity to reduce blood loss and transfusion requirement during knee arthroplasty surgery. Studies on the ideal dose and method of application have occupied an important place in the orthopedic literature in recent years. In this study, we investigated the efficacy of different administration methods of TXA.

Many studies have shown that TXA prevents blood loss in knee arthroplasty. For example, in a meta-analysis, Yang et al. (14) reported that IV TXA administration reduced blood loss by 504 ml transfusion and 1.43 units on average. In our study, we assessed blood loss based on the decrease in the hemoglobin level, which, we believe, is more valuable as a subjective assessment than the need for blood transfusion. In this regard, the statistically significant differences between Group 1 (no TXA), and Group 2 (preoperative TXA plus maintenance therapy) and Group 3 (preoperative IV and perioperative periarticular TXA) demonstrates the efficacy of TXA in preventing blood loss.

Although many studies have shown TXA to be effective in preventing blood loss, which of the administration methods is more effective is still a subject of research. Attempts are being made to increase the efficacy of TXA administered at the onset of anesthesia by different methods. In our study, no significant difference was found between the patients who received a single infusion in addition to the initial infusion and postoperative periarticular TXA. Both methods are effective in reducing the decrease in hemoglobin despite the absence of a tourniquet. This activity increases, especially after the first day. This can be attributed to the continuation of the efficacy of TXA in the postoperative period.

Previous studies have also investigated the efficacy of multiple postoperative TXA infusions (15,16). Tzatraitis et al. (15) found that the third dose of TXA infusion was more effective in maintaining hemoglobin levels. The authors observed a 2.33 mg/dL decrease in hemoglobin in patients who received the third TXA dose. In our study, the hemoglobin decrease was almost the same in both TXA groups. Therefore, it would be beneficial to further investigate whether a third dose of TXA infusion is really necessary.

In a 2017 study by Schnettler et al.(17), the use of tourniquets was reported to increase blood loss. In the current study, the tourniquet was inflated during cementation in Groups 2 and 3, while surgery was performed with a pneumatic tourniquet in Group 1.

, which was determined to be the group with the most negligible blood loss. However, to the best of our knowledge, there is no study on the paradoxical increase in blood loss in patients treated with a tourniquet.

In our study, except for the application of cement, a pneumatic tourniquet was not used in the patients administered TXA, whereas the operations in Group 1 were performed under the tourniquet. We can explain the lack of significant differences in hemoglobin decrease, especially in our measurements on the postoperative first day by the lower intraoperative bleeding in the patients who did not receive TXA. We believe that randomized clinical trials are needed to understand the impact of using a tourniquet on blood loss in the postoperative period.

In a retrospective study published by Saad et al. (18), 54 patients (31 revision knee arthroplasty/23 revision hip arthroplasty) who received 1 g IV TXA before incision and underwent wound closure were hospitalized for an average of 3.48 days postoperatively, and 46 patients who did not receive TXA (23 revision TKA/23 revision THA) were hospitalized for an average of 5.22 days postoperatively. This difference was statistically significant. The authors also reported that the use of TXA significantly reduced the need for postoperative transfusion. In our study, a statistically significant difference was found between Group 1 that did not receive TXA and both TXA-administered groups in terms of the length of hospital stay. However, there was no statistically significant difference between the groups receiving postoperative maintenance TXA and perioperative periarticular TXA.

In this study, we did not encounter any thrombotic complications associated with the use of TXA. The lack of diagnostic studies on thrombotic complications besides clinical evaluation may lead to overlooking subclinical complications. In the meta-analysis by Kerver et al. (19), examining 129 studies with 10,488 cases on the efficacy of TXA on bleeding, it was reported that the effect of TXA use on the incidence of DVT, pulmonary embolism, and myocardial infarction was inconclusive, but TXA statistically significantly reduced patient mortality. We believe that prospective randomized trials to be conducted in future will be helpful in clarifying this issue.

Despite the limitations of our study due to the retrospective design and relatively small number of patients, our results can be considered valuable because there were no differences in age, sex, weight, and preoperative hemoglobin levels between the groups. Standardization was achieved because the patients were operated on by the same surgeon with the same type of prosthesis. Although single-center trials have been shown to have higher treatment efficacy than multicenter trials in randomized clinical trials, there is no reason to believe that this would affects the results of the retrospective evaluation of case series, such as our study (20).

CONCLUSION

The results of this study showed that in TKA, in addition to preoperative IV TXA administration, postoperative IV maintenance therapy and perioperative periarticular TXA administration decreased the amount of bleeding and transfusion requirement during and after surgery and reduced the length of hospital stay. We believe that TXA administration in patients who have safely undergone arthroplasty is beneficial to prevent bleeding, long hospital stay, and transfusion-related complications.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Gaziosmanpaşa Training and Research Hospital Clinical Researches Ethics Committee (Date: 10.11.2021, Decision No: 372).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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