RESEARCH ARTICLE

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Decreased Blood Loss with Systemic and Intraarticular Tranexamic Acid Administration after Total Knee Arthroplasty

ABSTRACT

Objective: Perioperative bleeding during total knee arthroplasty (TKA) is a lasting problem for surgeons. Intravenous or intra-articular administration of tranexamic acid (TXA) can effectively stop bleeding, but there is still no uniform standard for the best administration and dosing.

Methods: Between October 2017 and September 2019, ninety patients with unilateral primary knee osteoarthritis requiring knee replacement were retrospectively evaluated and investigated in three groups according to the route of TXA administration: Group 1 (n=30) intravenous (IV) injection, Group 2 (n=30) intra-articular injection (IAI), and Group 3 (n = 30) combined IV and IAI. Demographic characteristics, hematological indices, and the incidence of deep vein thrombosis (DVT) and pulmonary embolism (PE) were studied.

Results: Of the patients included in the study, 86% were female (n=78), and 14% were male (n=12). The gender distribution of the groups was homogeneous (p=0.749). The mean hemoglobin values of Group 2 were significantly lower than those of Group 1 and Group 3 (p=0.002 and p=0.045, respectively). Less postoperative blood loss was observed in the group receiving combined IV and IA TXA. The mean blood loss from the drain in Group 3 was significantly lower than that in Group 1 and Group 2 (p=0.001). Postoperative infection, DVT, and PE were not seen in any group.

Conclusions: This study demonstrated that the use of intraarticular and intravenous tranexamic acid in primary unilateral TKA significantly reduced postoperative blood loss and consequently decreased the need for blood transfusion without an increase in adverse events, particularly thromboembolic complications.

Keywords: Total Knee Arthroplasty, Tranexamic Acid, Efficacy, Bleeding

Total Diz Artroplastisi Sonrası Sistemik ve İntraartiküler Traneksamik Asit Uygulaması ile Kan Kaybının Azalması

ÖZET

Amaç: Total diz artroplastisi (TDA) sırasında perioperatif kanama cerrahlar için devam eden bir problemdir. Traneksamik asidin (TXA) intravenöz veya intra-artiküler uygulanması kanamayı etkili bir şekilde durdurabilir, ancak en iyi uygulama ve doz yöntemi için hala bir standart yoktur.

Gereç ve Yöntem: Ekim 2017 ile Eylül 2019 arasında diz replasmanı gerektiren tek taraflı primer diz osteoartriti olan 90 hasta retrospektif olarak değerlendirildi ve üç grup olarak incelendi. Grup 1 (n = 30) intravenöz(IV) , grup 2 (n = 30) intra-artiküler enjeksiyon (IAE) ve grup 3 (n = 30)) TXA'nın hem IV hemde IA kombine enjeksiyon uygulanmıştır. Demografik özellikler, hematolojik indeksler, derin ven trombozu (DVT) ve pulmoner emboli(PE) görülme insidansı araştırıldı.

Bulgular: Çalışmaya dahil edilen hastaların %86'sı kadın (n=78) ve %14'ü erkektir (n=12). Gruplara göre cinsiyet dağılımı homojendir (p=0,749). Grup 2'nin Hemoglobin(Hb) ortalamaları Grup 1 ve Grup 3'ün Hb ortalamalarından istatistiksel olarak anlamlı derecede düşük bulunmuş (p=0,002, p=0,045), Kombine IV ve IA TXA alan grupta postoperatif daha az kan kaybı gözlendi. Grup 3'ün Drenden Kan Kaybı ortalamaları Grup 1 ve Grup 2'nin Drenden Kan Kaybı ortalamalarından istatistiksel olarak anlamlı derecede düşük bulunmuş (p=0,001). Hiçbir grupta ameliyat sonrası enfeksiyon, DVT ve PE görülmemiştir.

Sonuç: Bu çalışma primer tektaraflı TDA'da intraartiküler ve intravenöz traneksamik asidin kullanılmasının postoperatif kan kaybını anlamlı derecede azalttığını ve bunun sonucu olarak advers olaylarda, özellikle tromboembolik olaylarda bir artış olmadan kan transfüzyonu ihtiyacını azalttığını göstermiştir.

Anahtar Kelimeler: Total Diz Artroplastisi, Traneksamik Asit, Etkinlik, Kanama

INTRODUCTION

The incidence of osteoarthritis increases with age. Today, TKA is frequently used to reduce pain and increase range of motion for patients with advanced osteoarthritis (1). Bone and soft tissue bleeding (600-1500 cc) represent the most common cause of postoperative morbidity after TKA (2), increase transfusion requirements by up to 50%, and prolong hospital stay (3). Additionally, the increase in the need for transfusion brings problems like added financial costs, hemolytic reaction risks, and the transmission of viral diseases (4).

The amount of bleeding is significantly reduced with the use of TXA, which is claimed to minimize hypovolemic side effects, delayed wound healing, and intra-articular hematoma formation (5). All these positive effects enable the administration of early rehabilitation after surgery (6). As an analog of the amino acid lysine, TXA can competitively intercept plasminogen activation and plasmin binding to fibrin, and, thus, inhibit fibrinolysis (7). Many previously published studies have confirmed that the use of TXA can significantly reduce blood loss and transfusion requirements, as well as effectively prevent postoperative inflammatory response and reduce postoperative pain (6). Besides, a multimodal analgesia regimen is required to decrease postoperative inflammatory response and pain. Tranexamic acid is a fibrinolysis inhibitor and plasminogen activator, which has been applied in various surgical branches for a long time and has been applied in the field of orthopedic surgery in recent years. Both intravenous and intra-articular tranexamic acid administration aim to reduce blood loss and the need for blood transfusion (9). Although there are many studies in the literature about the efficacy of intravenous and intraarticular administration, there are fewer studies on joint administration. We thought that it would be a reliable parameter to compare the effectiveness of both intravenous and intraarticular tranexamic acid in patients undergoing total knee arthroplasty in our clinic. Total knee arthroplasty was performed to find the best way to minimize the risk of bleeding.

MATERIAL AND METHODS

This study was approved by the Düzce University Clinical Research Ethics Committee (IRB number: 2019/205). After the consent of the institutional review board, 90 patients aged 50-75 years with unilateral total knee arthroplasty due to stage 4 primary knee osteoarthritis in Düzce University Medical Faculty Hospital Department of Orthopedics and Traumatology were retrospectively evaluated between September 1, 2017, and September 1, 2019. Patients who underwent unilateral knee arthroplasty under spinal-epidural anesthesia were divided into three groups. The groups were composed of 30 patients in each group. In Group 1, two doses of 10 mg/kg intravenous tranexamic acid (Transamine®, Bilim Pharmaceuticals, Turkey) were administered to each patient in 100 mL saline. The first dose was administered 15 minutes before tourniquet application, and the second dose was administered 3 hours after the tourniquet was lowered. In Group 2, 10mg/kg tranexamic acid was diluted with 100 mL of saline, and applied into the joint via a Hemovac drain after the arthrotomy area was closed, just before the tourniquet was lowered; the system was kept closed for 1 hour. On the other hand, in Group 3, tranexamic acid was administered both systemically and intraarticularly.

The following data were collected from the medical records, and compared between the groups: age, sex, weight, body mass index (BMI), American Society of Anesthesiology (ASA) score, operation time, tourniquet time, hemoglobin (Hb) levels, total 24-hour drainage amount, transfusion requirement within 24 hours after surgery, visual analog scales (VAS) score, and the presence of preoperative and postoperative complications (thromboembolic events , acute renal failure, myocardial ischemia, allergy, and transfusion reactions). All patients were operated in a single center by the same surgeon applying a medial parapatellar approach. A tourniquet was used before surgery and inflated to a pressure of 360 mmHg.

Tourniquet was applied to all groups, and Hemovac drains were placed. The amount of bleeding was monitored at three-hour intervals for 24 hours. The indication for blood transfusion was defined as postoperative hemoglobin level dropping below 10 g/dL. Patients' Hb, hematocrit (hct), Prothrombin Time (PT), International Normalized Ratio (INR), Activated Partial Thromboplastin Time (APTT), and platelet levels were routinely measured preoperatively and at 6, 24, and 48 hours postoperatively. Preoperative drainage was removed at postoperative 24th hour, and the amount was recorded. All patients were routinely given intravenous patient-controlled analgesia for pain control and low molecular weight heparin for thromboembolic prophylaxis. Postoperative complications were recorded while patients were followed up in outpatient treatment centers, four to six weeks after the operation. The following patients were excluded: patients with a history or presence of coagulopathy or bleeding disorder, renal dysfunction, anticoagulant usage, acute infection, coronary artery disease, history of DVT, PE, cerebrovascular event, TXA allergy, preoperative Hb <8 mg/dl, bilateral arthroplasty, or arthroplasty revision. Patients receiving general anesthesia were excluded too, to prevent confounding due to general anesthesia.

Statistical Evaluation: In this study, statistical analysis was performed by the NCSS (Number Cruncher Statistical System) 2007 Statistical Software (Utah, USA) package program.

The Shapiro-Wilk normality test, as well as descriptive statistical methods (mean, standard deviation, median, and interquartile range), were used to evaluate the data. The paired one-way analysis of variance was used for time comparisons of normal-distributed variables, and the Newman Keuls Multiple Comparison Test was used for subgroup comparisons. The one-way analysis of variance was used for intergroup comparisons with the Newman Keuls multiple comparison test for subgroup analyses. The Kruskal Wallis test with Dunn's multiple comparisons was used for between-group comparisons of variables that did not show normal distribution, and the Chi-square test was used for the comparison of qualitative data. The results were evaluated at p<0.05 level of significance.

RESULTS

This retrospective study included 60 patients who underwent THA for degenerative arthritis of the knee. The demographic and clinical characteristics of the patients are shown in Table 1. The mean age of the patients in the intravenous, topical, and combined group was 64.37±6.12 years, 63.3±6.39 years, and 62.73±6.03, respectively. There was no significant difference between the three groups regarding age, sex, height, weight, body mass index, prothrombin time, hemoglobin, American Society of Anesthesiologists score, or the presence of comorbidity. However, there was a statistically significant difference in the mean drain-originated blood loss between Group 1, Group 2, and Group 3 (p=0.001). The mean drain-originated blood loss of Group 3 was significantly lower than that of Group 1 and Group 2 (p=0.001 and p=0.019, respectively). On the other hand, the mean drain-originated blood loss of Group 1 was significantly lower than that of Group 2 (p=0.001). There was a statistically significant difference in blood usage between Group 1, Group 2, and Group 3 (p=0.031). Blood use in Group 2 was higher than in Group 1 and Group 3.

Table 1. Demographic and clinical characteristics of the patients

		Group 1		**Group 2**		**Group 3**		**p**
Age		64.37±6.12		63.3±6.39		62.73±6.03		0.585*
Sex	**Male**	4	13.33%	5	16.67%	3	10.00%	0.749+
	Female	26	86.67%	25	83.33%	27	90.00%	
Weight (kg)		84±7.59		83.03±6.81		84±7.59		0.841*
Height (cm)		165.37±5.62		165.03±5.33		165.37±5.62		0.964*
BMI		30.83±3.51		30.62±3.61		30.83±3.51		0.967*
Side	**Right**	16	53.33%	16	53.33%	14	46.67%	0.837+
	Left	14	46.67%	14	46.67%	16	53.33%	
ASA	**II**	18	60.00%	22	73.33%	24	80.00%	0.220+
	III	12	40.00%	8	26.67%	6	20.00%	
Drain-induced blood loss		211.67±52.41		321.67±68.77		156.83±26.83		**0.001***
Blood Used	**None**	21	70.00%	16	53.33%	24	80.00%	**0.031+**
	1.00	9	30.00%	10	33.33%	6	20.00%	
	2.00	0	0.00%	0	13.33%	0	0.00%	

*One-way Analysis of Variance +Chi Square Test

The Hb distributions of the groups are displayed in Table 2. Statistically, no significant difference was observed between the mean hemoglobin values preoperatively, at 24 hours, and at 48 hours between Group 1, Group 2, and Group 3 (p>0.05). A statistically significant difference was observed between the mean hemoglobin values of at 6 hours between Group 1, Group 2, and Group 3 (p=0.002). The mean hemoglobin values of Group 2 were significantly lower than the hemoglobin values of Group 1 and Group 3 (p=0.002, p=0.045). The mean hemoglobin values of Group 1 and Group 3 did not differ statistically (p=0.444) (Figure 1).

Table 2. Hemoglobin distributions between the groups

Hemoglobin	**Group 1**	**Group 2**	**Group 3**	**p***
Preoperative	12.93±1.32	12.62±1.08	12.70±1.35	0.611
6th Hour	12.42±1.07	11.09±1.61	11.96±1.57	**0.002**
24th Hour	12.70±1.35	11.65±1.18	11.98±1.20	0.691
48th Hour	12.12±0.94	11.60±1.08	11.87±1.18	0.180
p‡	**0.001**	**0.001**	**0.001**	

* One-way Analysis of Variance ‡Paired One-way Analysis of Variance

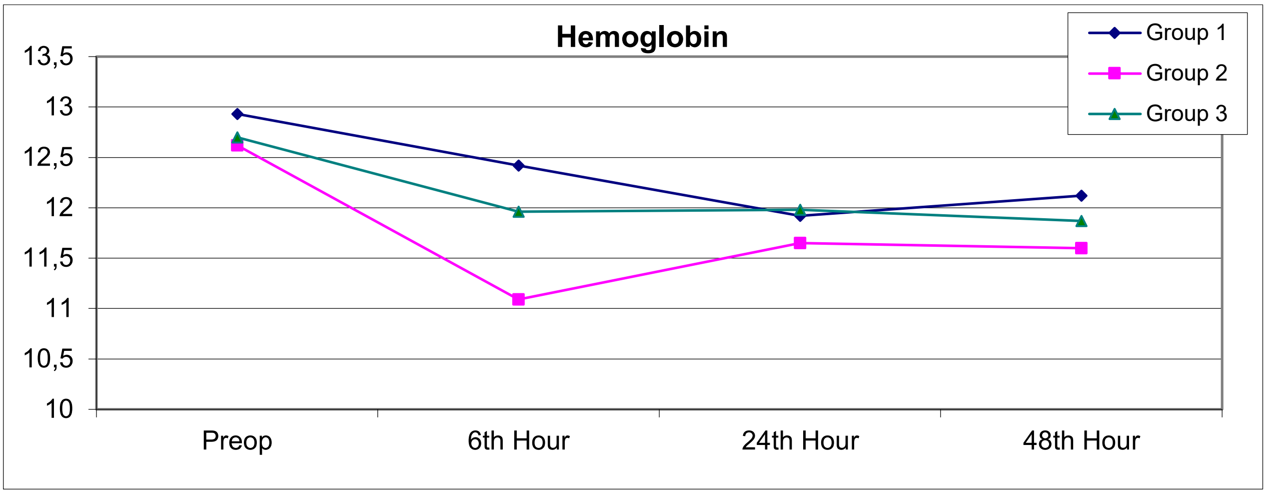

Figure 1. Hemoglobin distribution between groups

Hematocrit distributions of the groups are displayed in Table 3. Statistically, no significant difference was observed between the mean hematocrit values preoperatively, at 24 hours, and at 48 hours between Group 1, Group 2, and Group 3 (p>0.05). A significant difference was observed statistically in the mean hematocrit values at 6th hour between Group 1, Group 2, and Group 3 (p=0.014). The mean hematocrit values of Group 2 were significantly lower than the mean hematocrit values of Group 1 and Group 3 (p=0.049 and p=0.019, respectively). The mean hematocrit values of Group 1 and Group 3 did not differ statistically (p=0.925) (Figure 2).

Table 3. Hematocrit distributions between the groups

Hematocrit	Group 1	Group 2	Group 3	p*
Preoperative	38.90±2.63	37.30±2.77	37.90±2.50	0.065
6th Hour	37.40±2.30	33.17±4.48	36.03±3.58	**0.014**
24th Hour	36.23±3.56	34.73±3.39	36.00±3.18	0.187
48th Hour	35.73±4.63	34.70±3.20	36.23±2.92	0.260
p‡	**0.001**	**0.001**	**0.001**	

* One-way Analysis of Variance ‡Paired One-way Analysis of Variance

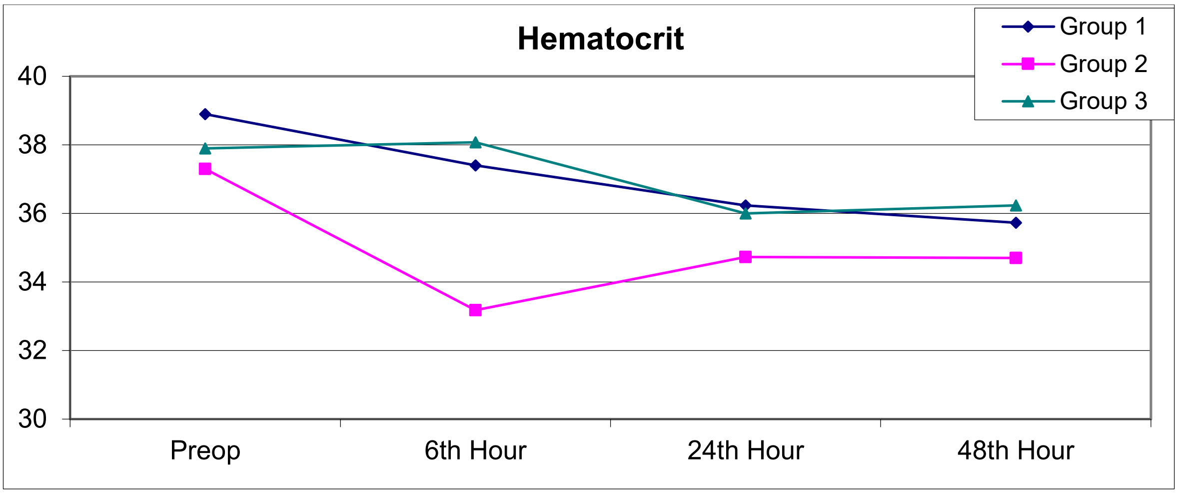

Figure 2. Hematocrit range between the groups

VAS distributions of the groups are displayed in Table 4. Statistically, no significant difference was observed in the mean VAS values at 6th hour between Group 1, Group 2, and Group 3 (p>0.05). A statistically significant difference was observed between the mean VAS values at 24 hours between Group 1, Group 2, and Group 3 (p=0.014). The mean VAS values of Group 3 were statistically lower than the mean VAS values of Group 1 (p=0.017). The mean VAS values of the other groups did not differ statistically (p>0.05) (Figure 3).

Table 4. VAS distributions of the groups

VAS	Group 1	Group 2	Group 3	p*
Preoperative	8.10±0.66	8.13±0.63	8.10±0.65	0.974
6th Hour	8.93±0.25	8.90±0.31	8.87±0.35	0.698
24th Hour	7.17±0.65	7.03±0.76	6.67±0.66	**0.018**
48th Hour	5.63±1.00	5.50±0.94	4.97±0.96	**0.022**
p‡	**0.001**	**0.001**	**0.001**	

* One-way Analysis of Variance ‡Paired One-way Analysis of Variance

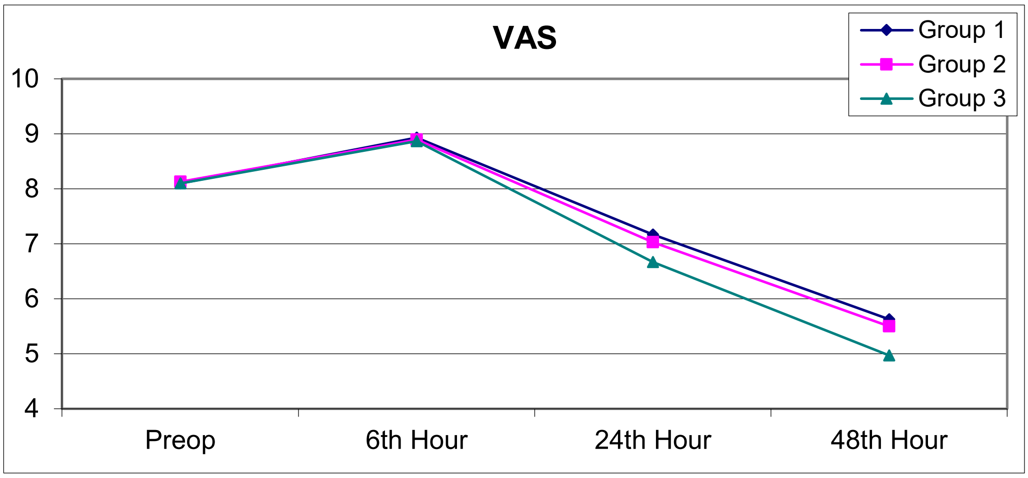

Figure 3. VAS distribution between the groups

DISCUSSION

The most essential finding of this study was was to reduce the need for blood transfusion after TKA in both intravenous and intraarticular groups. This is a method that is simple, easy to adopt, and suitable for patients and comprehensible for clinicians. In patients undergoing TKA, the effect of clamping after intravenous TXA and intraarticular TXA from the drain was similar to previous studies. The most important finding of this study was to reduce the need for blood transfusion after TKA in both intravenous and intraarticular groups.

Right after the administration of the surgical operation, the fibrinolytic system is temporarily activated (11). TXA is an amino acid that inhibits fibrinolysis by conversely blocking the lysine connection spots on the plasminogen molecules (12). This prevents plasma from connecting with fibrinogen and fibrin structures (13). Due to its antifibrinolytic effects, there are concerns about increasing venous thromboembolism while using TXA (14). Besides, TXA does not affect the fibrinolytic activity on venous walls (15). Therefore, an increase in the incidence of venous thrombosis was not observed in previous studies, or in ours (16). One of the most critical issues after TKA is the need for blood transfusion. Even though its incidence is low, serious complications, including allogeneic blood transfusions (e.g., viral infections, graft-versus-host disease) were reported (17). Because the need for blood transfusion decreased with our method, complications concerning the transfusion decreased as well. Intraarticular TXA administration after TKA was recently introduced, and it is proven to significantly reduce blood loss and knee swelling after surgery (18). Furthermore, it might also decrease the TXA dose, which is necessary to lower the postoperative blood loss (19). In our study, the intraarticular injection of TXA retrogradely by drain and compressing the system for 1 hour decreased the postoperative blood loss and the need for blood transfusion after TKA effectively.

Orthopedic surgeries are usually operations that need large amounts of blood transfusion. They are estimated to constitute 10% of the total transfusions (20). Forty-five percent of the patients with large surgical procedures require transfusions due to perioperative blood loss (21). Approximately 40% of these transfusions are related to joint replacement surgery (22). Complications of blood transfusion are rare. However, it may cause serious consequences for the patient. Thus, efforts are made to decrease blood loss and, thereby, reduce transfusion rates. The administration of TXA seems to be an appropriate treatment to reach this goal. Some studies showed that TXA may decrease bleeding ratio in orthopedic procedures (23-25). Lately, various studies compared the activity of drain clamp combined with TXA administration following TKA to control bleeding (26). Temporary drain clamps are reported to be able to decrease postoperative drainage at 24th and 48th hours significantly (27, 28).

Furthermore, patients with temporary drain clamps for more than 4 hours had higher hemoglobin levels and less blood transfusion in 24 hours following the operation compared to patients with no drain clamps (29). Also, a similar study showed that intravenous administration with drain clamp causes less blood loss and less decrease in the Hb values (30). We, too, found that intravenous administration with drain clamp causes less blood loss and a smaller decline in the Hb values.

It is known that patients who underwent TKA may develop DVT or PE (31). The risk of thromboembolic events in TXA is becoming more and more concerning (32). Our study indicated that thromboembolic complications do not differ widely when comparing the combined group with the IA and IV groups. This conclusion complied with the studies suggesting using combined TXA in TKA (33).

Another significant finding of the study was the lower opioid consumption in the first 6 hours after surgery in the group administrated combined treatment. Reducing opioid use after the operation will cause a decrease in the prevalence and morbidity of the adverse effects related to opioids. This observation was supported by VAS.

The study has some limitations. First, it was retrospective. Although the patient features didn't differentiate between the three groups, selection bias could not be excluded entirely. Secondly, to determine the dose and administration, controlled randomized studies are necessary. Also, studies that are executed by using thromboembolism screening tests such as ultrasonography might be needed.

Conclusion

This study indicated that using intraarticular and intravenous tranexamic acid in one-sided TKA decreases postoperative blood loss significantly, and, consequently, it decreases the need for blood transfusion without an increase in adverse effects, especially in thromboembolic activities.

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