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Research Article

The efficacy, safety, and cost-effectives of combined administration of Intravenous and Local Tranexamic Acid in the management of Patients Undergoing Primary Total Hip Arthroplasty: A prospective, blinded and randomized clinical study

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ABSTRACT

Objective: The aim of this study was to compare the efficacy, safety, and cost-effectiveness of combined administration of intravenous and local tranexamic acid with those of either intravenous or local administrations in patients undergoing primary total hip arthroplasty (THA).

Methods: This prospective, blinded, and randomized clinical study was performed on patients undergoing unilateral primary THA from September 2018 to December 2019. A total of 90 patients were included and prospectively allocated to one of three groups: the combined group (n= 30, 14 male, 16 female; mean age = 54.9 ± 12 years), intravenous (IV) group (n = 30, 13 male, 17 female; mean age = 54.9 ± 12.3 years), and local group (n = 30, 13 male, 17 female; 50.3 ± 12.3). Tranexamic acid was used systemically by IV application (15mg/kg) in IV group, locally in the surgical field (2g) in local group as well as combined systemic and local together in combined group. The amount of blood loss, number of erythrocyte suspension transfusion, and changes in hemoglobin and hematocrit levels were documented accordingly. The estimated mean tranexamic acid and erythrocyte suspensions cost, extra nurse care, monitoring and laboratory costs associated with blood transfusion, and total hospital costs were compared among groups.

Results: No differences existed in hemoglobin and hematocrit levels after surgery among the groups. The combined group required fewer blood transfusion compared to the local and IV groups, and the total amount of ES was statistically significantly lower ($P = 0.039$) in the combined group. Although the medication cost was higher in the combined group than in the other groups ($P < 0.001$), combined group was more cost-effective ($P < 0.001$) when the total costs related to blood loss were evaluated. No occurrence of deep vein thrombosis or pulmonary embolism was found in the study.

Conclusion: Combined administration of IV and local tranexamic acid seems to be more effective in reducing the requirement and amount of blood transfusion without increasing the risk of thromboembolic complications in primary THA compared to IV or local administrations. Despite increasing the prophylaxis costs, combined administration of TXA can result in lower total hospitalization costs by decreasing blood loss and consequent treatment costs in primary THA.

Level of Evidence: Level I, Randomized Controlled Trial

Introduction

Total Hip Arthroplasty (THA) is the most commonly performed and successful adult reconstructive hip procedure in the end-stage hip osteoarthritis.[1] Excessive blood loss, an important early complication in THA, can disrupt patients' hemodynamic condition and may require allogeneic blood transfusion (ABT).[2] ABT may cause serious complications such as blood-transmitted infections, immunological reactions as well as longer hospitalization and higher total treatment cost compared to non-transfused patients.[3,4] Several blood conservation techniques have been used to decrease blood loss and reduce ABT requirements, including induced hypotension, regional anesthesia, autologous blood transfusion, intraoperative blood salvage and the utilization of antifibrinolytic agents such as Tranexamic Acid (TXA).[2]

Plasmin is a proteolytic enzyme that degrades fibrin in the fibrinolytic system. TXA is a reversible and competitive inhibitor of plasminogen (plasmin precursor), inhibiting the formation of plasmin and consequently preventing fibrinolysis.[5] TXA has been shown to be effectively associated with reduced blood loss and decreased transfusion rates without increasing the risks of Deep Vein Thrombosis (DVT) and/or Pulmonary Embolism (PE).[6,7]

The ideal method of TXA application in THA is still controversial. It has been reported by many authors that the Intravenous (IV) use of TXA in THA significantly reduced blood loss and blood transfusion rates.[7-9] The local application of TXA has many benefits such as being easy to use, directly affecting the bleeding site, minimizing systemic drug absorption, and thus reducing the potential complications of IV TXA administration.[10–12] Yi et al. showed in their prospective,

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randomized control trial that combined IV and topical administration of TXA could reduce blood loss and the transfusion rate in patients undergoing THA.[7]

The aims of the present study are[1] to compare the efficacy of three TXA application methods, which are IV, topical and combined administration, in terms of intraoperative, hidden and total blood loss, transfusion rate, and hemoglobin and hematocrit drop,[2] to evaluate the safety of the combined application of TXA and[3] to investigate the effect of different TXA administration methods on the treatment cost.

Materials and Methods

This prospective, blinded and randomized clinical study included the patients undergoing unilateral primary THA planned to be performed between September 2018 and December 2019. Before starting the trial, the study protocol was approved by clinical research ethics committee (Protocol number: 85/8 date: 07/06/2018), and a written informed consent was obtained from all participants prior to surgery.

Patient selection

The adult patients who were diagnosed with hip osteoarthritis and scheduled for unilateral primary THA were included in the study. The patients were excluded from the study according to the following criteria: primary THA with osteotomy requirement, TXA contraindications (prior thromboembolic event), any hematological disease, use of anticoagulant, antiagregant or oral contraceptive drugs and preoperative hepatic or renal dysfunction. Before the surgery, 90 patients were divided in three groups and matched with a number between 1 and 90. The groups were randomly created using a website tool (www.randomizer.org). According to the sequence of numbers obtained by the randomization, TXA was administered systemically by IV injection in the IV group, locally in the surgical field in the local group and systemic and local combination in the combined group (Table 1). The ASA (American Society of Anesthesiologists) score that is associated with intraoperative blood loss, postoperative infections and other complications was determined in the patients included in the study.[13] Comorbid conditions were assessed by using the Charlson Comorbidity Index.[14]

Surgical technique

All surgeries were performed by the same surgeon (ET) under combined spinal–epidural anesthesia. Posterior approach was used with a lateral decubitus position. The M/L taper femoral stem (Zimmer, Warsaw, IN) and Trilogy® IT (Zimmer, Warsaw, IN) acetabular shell with a highly cross-linked polyethylene liner were used in all cases. Controlled hypotension was achieved during the surgery, and systolic blood pressure values were kept approximately at 80-90 mmHg. In all patients, the wound was closed with the same method without drain. The estimated intraoperative blood loss volume determined by the anesthesiologist included the definite suction volume and visual assessment of all blood-soaked materials and field in the operating room.

Table 1. Study Groups

IV group	15 mg/kg TXA (max 1 g) prior to surgery
Local group	2 g TXA in wound after closing of fascia locally
Combined group	15 mg/kg TXA(max 1 g) prior to surgery 2 g TXA in wound after closing of fascia locally

Note: Study groups and the treatments are shown in this table.

HIGHLIGHTS

- The medication cost due to bleeding prophylaxis was higher in the combined group.
- The combined group required fewer blood transfusions.
- The combined group was more cost-effective considering the total costs related to blood loss.
- The combined use of TXA results in lower total hospitalization costs by decreasing blood loss and associated treatment costs.
- The three tranexamic administration methods had similar reliability.

TXA administration

In the IV and combined groups, 15 mg/kg TXA (Transamine®, Teva İlaçları Inc., İstanbul, Turkey) diluted with 100 mL normal saline solution was infused five minutes prior to surgery. In the local and combined groups, at the end of the surgery, once the fascia was closed, 2 g of TXA was poured into the surgical field with a large tip injector. Additionally, the same volume of normal saline solution was poured into the surgical field at the end of the surgery in the IV group, and the local group patients received a 150 mL normal saline IV infusion administered five minutes before the skin incision. All treatments were administered by a case management nurse and an anesthesiologist who were not involved in this trial. The patients, the surgeon and the anesthesiologist performing the procedures were blinded in the study, and only the case management nurse knew about the patient randomization, medication and placebo treatments given to the patient.

Transfusion criteria

The use of blood transfusions was standardized according to a protocol based on the guidelines for perioperative transfusion by the National Institutes of Health Consensus Conference.[15] According to this protocol, a blood transfusion was indicated when the hemoglobin concentration was <8 g/dl or for the patients whose hemoglobin level was <10.0 g/dl with concomitant intolerable anemic symptoms or any anemia-related organ dysfunctions.

The use of intraoperative blood transfusion was determined by the anesthesiologist by following the physiological requirement of keeping the mean arterial pressure greater than 70 mmHg. Fluid need and intraoperative third-space loss were supplemented with balanced crystalloid solutions and hydroxyethyl starch.

Prophylaxis of venous thromboembolism

All patients received lower extremity strength training preoperatively and started passive and active physiotherapy postoperatively. They were required to walk with full weight-bearing at least twice a day before discharge. Low-molecular-weight heparin (4000 anti-Xa/0.4 mL of enoxaparin sodium, Clexane) was first administered 8 hours after surgery and then every 24 hours until hospital discharge. After discharge, 10 mg/day of rivaroxaban was prescribed for 15 days for prophylaxis against venous thromboembolism. All patients used antithromboembolic stockings postoperatively.

Monitoring of thromboembolism

The patients were examined daily in the hospital for any clinical symptoms of venous thromboembolism. A diagnostic Doppler ultrasound examination of both lower limbs was performed on all patients by the radiologist on the day the patient was discharged. An ultrasound examination, computed tomography (CT) pulmonary arteriography, and lower limb venography were planned to be performed at postoperative 6-month follow-up if a patient had venous thromboembolism symptoms.

Outcome measurements

The outcome measures were hemoglobin, hematocrit and platelet concentrations and their changes in the preoperative and postoperative three days, intraoperative blood loss (IBL) and total blood loss (TBL), transfusion requirement and frequency. The

amount of IV fluids administered per patient was recorded during the intraoperative and postoperative periods. Nadler's formula was used for the calculation of the patients' total blood volume.[16] The TBL was calculated using the formula described by Brecher at al.[17] Hidden blood loss (HBL) was determined by subtracting the amount of intraoperative blood loss from the total blood loss. DVT and PE were planned to be recorded in case of occurrence. In our study, the costs of TXA and Erythrocyte Suspension (ES) (350 mL) administered to the patient, the accommodation fee paid for hospitalization and the cost of the hip replacement prosthesis applied to the patient were calculated. Besides, the additional laboratory work, monitoring and nurse care costs due to transfusion were calculated and cost effectiveness was evaluated.

Statistical analysis

Categorical measurements were summarized as number and percentage, while numerical measurements as mean and standard deviation. The chi-square test statistics was used to compare categorical measurements between groups. Whether numerical measurements meet the normal distribution assumption was tested with the Shapiro–Wilk test. In comparison of numerical variables between the groups, the one-way analysis of variance was used if its assumptions are met; the Kruskal–Wallis test was used if the assumptions are not met. The Tukey HSD or Games & Howell tests were used depending on whether the within-group variances were homogeneous or not, if the assumptions were made in the binary comparisons of the groups for the situations that were found significant in these comparisons. If the assumptions were not met in the binary comparisons of the groups, the Mann–Whitney *U*-test with Bonferroni correction was used. All data management and statistical analysis were performed with SPSS, version 20.0 software (SPSS Inc., Chicago, IL). The level of significance was set at $P < 0.05$.

Results

Ninety patients were scheduled to have a THA in our hip surgery department. The study cohort was formed by randomly assigning 30 of the patients included in the study to the IV group, 30 to the local group and 30 to the combined group. The three groups were similar in terms of baseline characteristics such as age, gender, ASA score, Charlson Comorbidity Index, Body Mass Index (BMI), blood volume and preoperative hemoglobin and hematocrit and platelet counts (Table 2). All patients included in the study were followed for 6 months after THA surgery. DVT was not detected in diagnostic Doppler ultrasound examination of both lower limbs on discharge day.

Intraoperative results such as incision length, operation time, IBL, intraoperative transfusion requirement and amount in the surgery were statistically similar among the groups ($P > 0.05$) (Table 3). The postoperative blood loss data are presented in Table 4. The mean postoperative 3rd day hematocrit level was significantly higher in the combined group than the IV and local groups (33.9, 31.9, and 31.9, respectively; $P = 0.035$). There was no difference among the groups in terms of hemoglobin, hematocrit and platelet levels observed on the other days after surgery. The amount of IV fluids administered per patient was similar among all groups during the intraoperative and postoperative periods. More than 4000 mL of IV fluids were administered on the day of surgery in each group, and there was no significant difference among the groups ($P = 0.456$).

The mean TBL values in the IV, local and combined groups were 1436.2 ± 785.3, 1446.3 ± 702.9, and 1106.7 ± 482.1mL, respectively, with no significant intergroup differences. The mean HBL values in the IV, local and combined groups were 866.2 ± 547.4, 874.7 ± 536.0, and 626.7 ± 387.5 mL, respectively, with no significant differences among the groups (Table 3). In our study, regardless of the groups, the average HBL of all transfused patients ($n = 20$) was 1415.6 ± 502.8, while it was 789.2 ± 503 in patients without transfusion, and the difference was statistically significant ($P < 0.001$).

Although the requirement and amount of ES transfusion intraoperatively among the groups were similar ($P = 0.260$), in the postoperative follow-up, the total amount of ES replacement requirement in the combined group was statistically significantly lower compared to the IV and local groups ($P = 0.039$) (Table 4). None of the patients had a major perioperative complication such as blood transmission infections, immunological reactions or no sudden drop in blood values, and the patients were discharged on the 3rd day after the operation.

The estimated TXA, ES, additional laboratory work, monitoring and nurse care due to transfusion and hospital total cost are given in the Table 5. The mean TXA cost was significantly lower in the IV group than in the local and combined groups ($P < 0.001$). The mean cost of

Table 2. Characteristics of Patients in the Groups

	IV Group	Local Group	Combined Group	*P*
Age	54.1 ± 12.3	50.3 ± 11.8	54.9 ± 12	0.289
Gender				
Male	13 (43%)	13 (43%)	14 (47%)	0.956
Female	17 (57%)	17 (57%)	16 (53%)	
ASA Score				
ASA-1	22 (73.3%)	23 (76.6%)	22 (73.3%)	0.423
ASA-2	8 (26.6%)	7 (23.3%)	8 (26.6%)	
Charlson Comorbidity Index	2.6 ± 1.1	2.4 ± 1	2.6 ± 0.9	0.450
BMI (kg/m^2)	28.2 ± 4.1	27.3 ± 4.3	28.9 ± 4.6	0.370
Calculated blood volume (mL)	4745.5 ± 801.4	4573.7 ± 754.6	4751.7 ± 796.9	0.610
Preoperative hemoglobin (g/dL)	13.6 ± 1.3	13.8 ± 1.4	14.2 ± 1.4	0.190
Preoperative hematocrit (%)	39.8 ± 3.2	40.4 ± 3.3	41.7 ± 3.5	0.074
Preoperative platelet (10^3/μL)	252.6 ± 55.9	251.6 ± 64.3	259.2 ± 51	0.854

Characteristics of patients such as age, gender, ASA score, Charlson Comorbidity Index, body mass index, calculated blood volume, preoperative hemoglobin, hematocrit and platelet concentrations are given in this table.

Table 3. Intraoperative Results and Calculated Amounts of Blood Loss

		IV Group	Local Group	Combined Group	*P*
Incision length (cm)		13 ± 2.2	12.7 ± 2	12.9 ± 3.1	0.860
Operation time (minutes)		70.9 ± 14.4	70.8 ± 9.3	69.6 ± 12.8	0.907
Intraoperative blood loss (mL)		570 ± 369.7	571.7 ± 347.3	480 ± 205.8	0.695
Hidden blood loss (mL)		1436.2 ± 785.3	1446.3 ± 702.9	1106.7 ± 482.1	0.104
Total blood loss (mL)		866.2 ± 547.4	874.7 ± 536.0	626.7 ± 387.5	0.106
The amount of ES given intraoperatively	0	25 (83.3%)	24 (80%)	29 (96.6%)	0.333
	1	4 (13.3%)	4 (13.3%)	1 (3.3%)	
	2	1 (3.3%)	2 (6.6%)	0 (0%)	
No. of ES (%) given intraoperatively		6 (40%)	8 (53.3%)	1 (6.6%)	0.140
No. of patients (%) given transfusion intraoperatively		5/30 (16.6%)	6/30 (20%)	1/30 (3.3%)	0.240

Intraoperative results such as incision length, operation time, intraoperative blood loss and ES transfusion rates and amounts, and the total and hidden blood losses are given in this table.

Table 4. Perioperative Hemoglobin and Hematocrit Values and Given ES Amounts and Rates

			IV Group	Local Group	Combined Group	*P*
Preoperative	Hemoglobin		13.6 ± 1.3	13.8 ± 1.4	14.2 ± 1.4	0.190
	Hematocrit		39.8 ± 3.2	40.4 ± 3.3	41.7 ± 3.5	0.074
Intraoperative	No. (%) of ES given		6 (25%)	8 (33.3%)	1 (4.1%)	0.260
Postoperative 1st day	Hemoglobin		11.1 ± 1.5	11.2 ± 1.7	11.8 ± 1.3	0.171
	Hematocrit		32.9 ± 3.8	33.3 ± 3.8	34.8 ± 3.4	0.099
	No. (%) of ES given		3 (12.5%)	1 (4.1%)	0 (0%)	0.318
Postoperative 2nd day	Hemoglobin		11 ± 1.4	10.9 ± 1.5	11.5 ± 1.3	0.179
	Hematocrit		32.6 ± 3.6	32.5 ± 3.9	34.4 ± 3.6	0.100
	No. (%) of ES given		2 (8.3%)	1 (4.1%)	2 (8.3%)	0.310
Postoperative 3rd day	Hemoglobin		10.6 ± 1.2	10.6 ± 1.5	11.3 ± 1.3	0.071
	Hematocrit		31.9 ± 3.3	31.9 ± 3.8	33.9 ± 3.3	**0.035**
	No. (%) of ES given		0 (0%)	0 (0%)	0 (0%)	–
Total	No. (%) of ES given		11 (45.8%)	10 (41.6%)	3 (12.5%)	**0.039**
	Transfusion amount	0	21 (70%)	22 (73.3%)	27 (90%)	0.307
		1	7 (23.3%)	6 (20%)	3 (10%)	
		2	2 (6.7%)	2 (6.7%)	0 (0%)	

Follow-up of hemoglobin and hematocrit values before and after surgery and amounts of ES given in the perioperative period are given in this table.

Table 5. Treatment Costs

	IV Group (TL)	Local Group (TL)	Combined Group (TL)	*P*
The mean cost of TXA (Min–Max)	5.4 (5.4-5.4)	10.8 (10.8-10.8)	16.2 (16.2-16.2)	**<0.001**
The mean cost of ES (Min–Max)	79.8 (0.0-435.4)	72.6 (0.0-435.4)	21.8 (0.0-217.7)	**0.048**
The mean cost for extra laboratory, monitorization and nurse care due to transfusion (Min–Max)	63.8 (0.0-348.2)	58 (0.0-348.2)	17.4 (0.0-174.1)	**0.048**
The mean cost of blood loss prophylaxis and treatment (Min–Max)	149.1 (5.4-788.9)	141.4 (10.8-794.4)	55.4 (16.2-407.9)	**<0.001**
The meant total cost of hospitalization (Min–Max)	9179.1 (9035.4-9818.9)	9171.4 (9040.8-9824.4)	9085.4 (9046.2-9437.9)	**<0.001**

The mean cost of TXA, ES, extra laboratory, monitoring and nurse care due to transfusion, and the mean total cost of hospitalization are given in this table.

ES and the mean cost for additional laboratory work, monitoring and nurse care due to transfusion were lower in the combined group than in the IV group, and the difference was statistically significant ($P = 0.048$). Consequently, the mean cost of blood loss prophylaxis and its treatment was significantly lower in the combined group than in the local and IV groups ($P < 0.001$). In the combined group, blood loss–related costs were lower than the other groups, and as a result, the mean total cost of hospitalization was significantly lower ($P < 0.001$). The mean cost of hospitalization and hip prosthesis were the same for all patients in the study group (1054.5 and 4975.5 TL, respectively; $P > 0.05$).

A periprosthetic fracture was observed in two patients, one in the IV group and one in the combined group during the surgery. Four patients, one in the IV group, two in the local group and one in the combined group had superficial wound infection. They were treated with oral antibiotics. DVT and PE were not observed in any patient during 6 months of follow-up.

Discussion

TXA can be administered intravenously, locally and orally or combinations of these methods. There is no consensus on which way is the optimal in particular and on dosages in different modes of administration. In two separate studies examining topical 3 g TXA application in both THA and Total Knee Arthroplasty (TKA) patients, the mean blood loss was significantly higher in the non-TXA patients in both TKA and THA groups and postoperative ABT decreased dramatically with TXA.[10,18] In a prospective study, the topical application of TXA was shown to be as effective as systemic use, providing the prevention of possible side effects in IV use.[6] In another study, comparing two TXA groups (IV and local groups) showed that local (intraarticular injection) use of TXA was more effective than IV injection in terms of amount of blood loss and requirement for transfusion. However, IV application of TXA has the advantage of inducing partial microvascular homeostasis by stopping fibrin clot dissolution in the affected area.[12] Recent studies showed that, IV combined with local administration of TXA in patients undergoing a primary THA significantly reduced postoperative blood loss and the transfusion rate without increasing the risk of DVT and/or PE compared to IV use of TXA.[7,19] Therefore, in our study, IBL, HBL and TBL were statistically similar across the three groups although lower in the combined group.

It was shown in many studies that TXA application reduced total blood loss and decreased the requirement and frequency of ES transfusion.[10,12,19] In addition, some studies indicated that TXA administration, regardless of the application method, reduced the amount of perioperative blood loss.[7,20] However, Yamasaki et al. stated that perioperative blood loss was similar in both the TXA group and the control group.[5] Visual estimation, photometric analysis, gravimetric and volumetric methods are generally used to measure blood loss during surgery. Visual estimation methods may be inaccurate to estimate actual blood loss due to changes in blood loss status. Gravimetric and photometric measurement may be impractical and labor-intensive during surgery, and volumetric methods using non-calibrated collection bags may give inaccurate results.[21] Fedoruk et al. reported that there was no statistically significant difference among these methods used to measure blood loss.[21]

In our study, the perioperative blood loss during surgery was performed by a blinded anesthesiologist using visual estimation method and calculating the definite suction volume. We found that the use of different TXA administration methods (IV, local or combined) did not statistically affect the amount of perioperative blood loss. Although the intraoperative blood transfusion rates were lower in the combined group than in the IV and local groups, there was no significant difference among the three groups ($P > 0.05$). However, the total transfusion rate was lower in the combined group in our study, and the difference was statistically significant ($P = 0.035$).

The total blood loss during these procedures is generally found with the sum of intraoperative bleeding and post-operative drainage. However, hemoglobin values after the operation indicate more blood loss than expected. This undetected blood loss is called HBL. Many theories have been suggested as the possible causes of HBL, such as extravasations into the tissues, residual blood in the joint and blood loss due to haemolysis. Sehat et al. stated that HBL accounted for 26% of the total blood loss in THA and 49% in TKA.[22] In our study, the mean HBL was 59% of the total blood loss, and administration method of TXA did not cause a significant change in HBL value. We think that our HBL rates were high because we did not use drain. A small amount of hematoma in the

surgical field after surgery was observed in all patients, but this did not cause any serious problems in any patient.

The use of TXA in primary THA is well documented. However, the ideal method of administering TXA to patients undergoing THA remains controversial.[7,19,23] In the study comparing IV and combined (IV + local) TXA administration in revision THA, Wu et al. showed that the combined administration of IV and topical TXA effectively decreased the total blood loss and the number of blood transfusions required compared to IV TXA alone.[19] The studies conducted with the patients with primary unilateral THA revealed that the combined IV and topical administration of TXA significantly reduced postoperative bleeding and transfusion rate.[7,24] Similarly, the combination of IV and topical TXA was shown to significantly reduce blood loss and transfusion rates in primary total joint arthroplasty without increasing the risk of thrombotic complications.[23] In our study in which we evaluated the total blood loss in THA surgery, we found that combined TXA application decreased blood loss; however, the decrease was not statistically significant. Similarly, the combined TXA application significantly decreased transfusion rates and recruitments as stated in the previous studies.

Considering that thrombotic complications could lead to unacceptable consequences following THA, blood loss prophylactic treatment should not increase the rate of thrombotic complications. In our study, no symptomatic DVT and PE after THA surgery were observed during 6 months follow-up in all groups. This is consistent with the results reported in the previous studies.[7,19] However, the potential adverse effects of TXA are still unknown; thus, further studies are needed to examine the safety of TXA. In addition, blood transfusion during THA has potential complications such as immune suppression, transfusion reaction, or fluid overload.[25,26] In our study, no complication related to blood transfusion occurred in any patient.

In previous studies, it was shown that TXA use reduced treatment costs.[27–29] Despite increasing medication costs with TXA application; operating room, blood transfusion, laboratory and room costs contribute to cost savings.[27,28] Conservation of blood products, reduced laboratory costs and shorter hospital stays are likely the major factors behind the cost reduction associated with TXA use.[29] At the time of the study, the cost of ES is much higher than TXA (ES unit (350 mL) cost: 239.45, 1 gr TXA:5.4 TL). In addition to the cost of ES, it can be predicted that the total cost may increase exponentially considering the costs related to application, additional monitoring, laboratory and nurse care and the costs incurred in case of possible complications and blood replacement. In our study, significantly lower amount of ES replacement was performed in the combined group compared to the IV and local groups. Although blood loss prophylaxis (TXA) costs were higher in the combined group, when the total cost of blood loss prophylaxis and treatment was considered, the combined group was found to be significantly more cost-effective than the other groups. In addition, the application cost of transfusion as well as the costs of extra nurse care (include patient monitoring) and additional laboratory work were considered, and the combined use of TXA significantly reduced the total hospital costs. We have shown that the combined administration of IV and local TXA reduced the total ES requirements and costs; thus, the total hospitalization costs significantly decreased by reducing the costs of prophylaxis and the treatment of blood loss. Combined TXA administration in patients with appropriate indication is a safe prophylaxis that reduces the total hospital costs.

Concerning the use of TXA in primary THA, different methods and ranges of TXA dose have been reported. The TXA doses in the range of 10 to 30 mg/kg in IV application and up to 3g in topical application were recommended in the literature.[7,18,19,30,31] Although some studies indicated that multiple IV TXA administration was more effective than a single bolus administration,[23,31] satisfactory results were also obtained with a single bolus application in many studies.[7,18,19,30] They showed that a single 15 mg/kg IV administration of TXA before the skin incision provided an effective and reliable bleeding prophylaxis consistent with our experience.[7,19] In our study, the IV administration of TXA was conducted as a single bolus of 15 mg/kg TXA in 100 mL saline solution before the skin incision, and the local administration was applied by pouring 2 g TXA into the surgical field at the end of the surgery.

There are some potential limitations to the present study. Since the TXA effect was shown in many previous studies, we did not include the placebo group in our study. Our aim not to include the placebo group was that we wanted to investigate the superiority of the different TXA application methods. A second limitation was that the Doppler ultrasound examination was performed routinely on the postoperative 3rd day. In our study, if there were clinical findings of DVT or PE, radiological evaluation of the patients was planned. However, asymptomatic DVT could not be diagnosed by the outcome measures in this study. Third, the Doppler ultrasound procedure in our study was performed on the postoperative 3rd day, rather than at the peak time (between the 4th and 13th days) for clinically significant/evident thrombosis.[32]

The combined TXA administration in primary THA was more effective in reducing the requirement and amount of blood transfusion without increasing the risk of thromboembolic complications. Despite increasing the prophylaxis costs, combined TXA administration in primary THA resulted in lower total hospitalization costs by decreasing blood loss and consequent treatment costs.

Ethics Committee Approval: Ethics committee approval was received for this study from the Clinical Research Ethics Committee of Ortopedia Hospital (Protocol number: 85/8 date: 07/06/2018).

Informed Consent: Informed consent was obtained from each patient in the study.

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