RESEARCH

EFFECT OF TRANEXAMIC ACID AND CELL SALVAGE SYSTEM USE IN TOTAL HIP ARTHROPLASTY ON ALLOGENEIC BLOOD TRANSFUSION AND HOSPITAL COSTS IN GERIATRIC PATIENTS: A RETROSPECTIVE COHORT STUDY

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■ Gökhan SERTÇAKACILAR[1, 2]
■ Yaser PEKTAŞ[2]
■ Malik ÇELİK[3]
■ Güneş Özlem YILDIZ[2]

CORRESPONDANCE
[1, 2] Gökhan SERTÇAKACILAR

Phone: ++905053130818
e-mail: drgokhansertcakacilar@gmail.com

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[1] Cleveland Clinic, Department of Outcomes Research, Cleveland, ABD

[2] Bakirkoy Dr. Sadi Konuk Training and Research Hospital, Department of Anesthesiology and Reanimation, Istanbul, Turkey

[3] Bakirkoy Dr. Sadi Konuk Training and Research Hospital, Department of Orthopedics and Traumatology, Istanbul, Turkey

Abstract

Introduction: Cell salvage and tranexamic acid are used in total hip arthroplasty to reduce allogeneic blood transfusions. This study aimed to determine the effect of tranexamic acid used before surgery on the volume of intraoperative and postoperative allogeneic blood transfusions, hospital costs, and postoperative complications in geriatric patients undergoing total hip arthroplasty by comparing it with that of the cell salvage and control treatment.

Materials and Methods: The data of 1408 patients in who underwent primary total hip arthroplasty at a single center between January 2012 and October 2021 were retrospectively analyzed. Patients were classified into three groups according to the treatment used cell salvage (n=227), tranexamic acid (n=485), and control treatment (n=533). Blood loss, volume of allogeneic blood transfused, hospitalization, cost parameters and thromboembolic complication rates were evaluated.

Results: Patients in the TXA group received the least volume of blood transfusions during the intraoperative and postoperative periods (p=0.001, p=0.004 respectively). The volume of autologous blood transfusion in the cell salvage group was similar to the volume allogeneic blood transfusions in the tranexamic acid group (p=0.92). The cost was significantly lower in the tranexamic acid group (p<0.001), whereas it was significantly higher in the cell salvage group compared to that in the other groups.

Conclusion: In total hip arthroplasty, a common procedure in the geriatric population, preoperative use of tranexamic acid is associated with less intraoperative and postoperative blood loss, less allogeneic blood transfusion, and lower hospital costs, without increasing the risk of thromboembolic events.

Keywords: Tranexamic acid, operative blood salvage, arthroplasty, hip, cost-benefit analysis

INTRODUCTION

In recent years, due to the increase in life expectancy, the number of total hip arthroplasties (THAs) performed for osteoarthritis, rheumatoid arthritis, hip bone metastasis, and fractures has been gradually increasing. In the United States (US) the total number of patients estimated to undergo THA by 2025 is 652,000 (1) THA is considered a major orthopedic surgery associated with the risk of massive blood loss (2). Perioperative anemia (hemoglobin [Hb] level <12.0 g/dl in women and <13.0 g/dl in men) is associated with increased morbidity and mortality (3). The standard approach for the treatment of perioperative anemia is allogeneic blood transfusion (ABT), which is required in 10%–32% of THAs (4).

However, the use of ABT is associated with various complications such as febrile transfusion reactions caused by leucoagglutinin, infection, transfusion-associated sepsis, transfusion-related acute lung injury, hemolytic transfusion reactions, and transfusion failure (4,5). Furthermore, the increased costs and supply shortage associated with ABT have led to the development of various perioperative blood management strategies to reduce intraoperative blood loss and the requirement of ABT (5). In addition, the use of ABT prolongs the length of hospital stay, such as age, implant use, duration of surgery, and comorbid diseases (6).

Various studies have shown that tranexamic acid (TXA) can successfully reduce blood loss in THA through an antifibrinolytic mechanism and can help reduce hospital costs (2,7). In addition, there is no increase in the risk of developing thromboembolic complications such as deep vein thrombosis and pulmonary embolism when TXA is used (8). However, there is no definite standard regarding its use and dosage (9).

Cell salvage (CS) is the intraoperative collection and reinfusion of autologous blood. The main goal of using this system is to reduce the need for ABT and related complications (10). The use of a CS system in orthopedic surgery can restore up to 70% of the intraoperative blood loss and significantly reduce the need for ABT (11). However, the results of some randomized controlled trials and meta-analyses on the intraoperative use of CS systems in reducing the need for ABT in hip and proximal femur surgeries are controversial (12,13).

This study aimed to determine the effect of TXA used before surgery on the volume of ABT, costs, and postoperative complications in geriatric patients who underwent THA by comparing it with that of CS and control treatment.

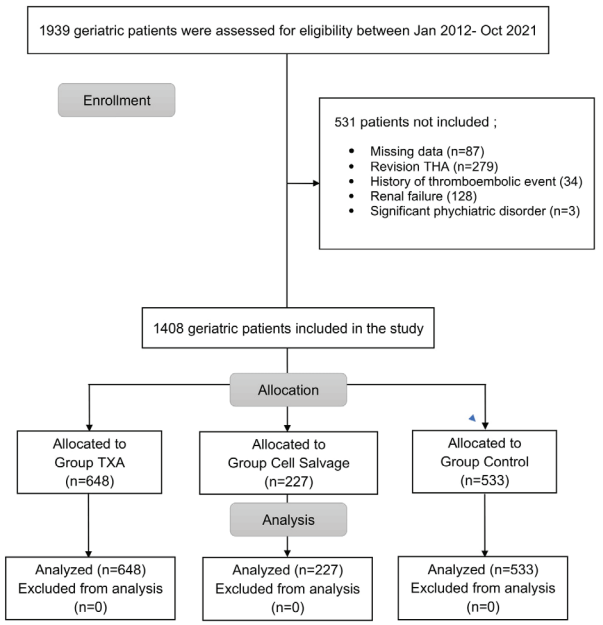
METHODS AND MATERIALS

Study design and patient selection

After obtaining approval from the clinical research ethics committee of the training and research hospital where the study was conducted (Protocol code: 2021/29, Decision number: 2021-02-18), the data of 1939 patients who underwent primary THA at a single center between Jan 2012 and Oct 2021 were retrospectively analyzed. For this purpose, the data of geriatric patients who underwent THA over a nine-year period were obtained from the hospital database. A total of 531 patients were excluded owing to reasons such as missing data, revision arthroplasty, and anesthesia performed by different physicians. Finally, 1408 patients were included. We then evaluated the patients' demographic data, comorbidities, surgery and anesthesia data, perioperative laboratory findings, bleeding and transfusion data, and length of hospital stay data. Figure 1 shows the flowchart of the study.

Patients aged ≥ 65 years who underwent THA and were in the American Society of Anesthesiologists (ASA) I–IV risk group were included. In addition, patients in whom anesthesia was administered

Figure 1. CONSORT flow diagram of the study



by the same anesthesiologist were included to provide a standard and homogeneous group comparison in the retrospective review. All consecutive patients who met the inclusion criteria were included.

Patients with a history of thromboembolic events, those with renal insufficiency (creatinine level >200 μmol/l), those who did not consent to allogeneic blood transfusion due to their religious beliefs (for example, Jehovah's Witnesses), and those who underwent preoperative donated autologous blood transfusion or received erythropoietin were excluded. This study was conducted in accordance with the ethical principles of the 2013 Brazilian revision of the Helsinki Declaration.

Anesthesia procedure

Patients received general anesthesia or regional anesthesia (spinal or combined spinal epidural) according to the preference of the anesthesiologists (GS and YP). The general anesthesia group generally consisted of patients who did not want regional anesthesia; had a history of lumbar stabilization or had a history of cardiac failure, such as heart failure and previous myocardial infarction; and in whom sudden hypotension should be avoided. Anesthesia induction was performed using midazolam, fentanyl, propofol, and rocuronium at doses appropriate for the patient's weight and age. Anesthesia was maintained using sevoflurane (MAC 0.5–1) and remifentanil infusion (0.05–0.2 mcg/kg/min). Regional anesthesia was performed using isobaric bupivacaine (10–15 mg) and fentanyl (10 mcg) as an adjuvant agent in accordance with the age, height, and cardiac function of the patient. Heart rate (beats/min) and mean arterial pressure (mmHg) were recorded during the perioperative period.

In patients receiving TXA, 15 mg/kg tranexamic acid was administered in 100 cc saline at an infusion rate of 10 ml/h as a standard preoperatively. Routine postoperative thromboprophylaxis included low molecular weight heparin starting six h after skin closure and stockings to prevent thromboembolism. There was no change in routine surgery or anesthesia techniques during the study period.

Surgical technique

THA was performed using the Hardinge (direct lateral) approach while the patients were in the lateral decubitus position under general or regional anesthesia. Femoral and acetabular cementless components were inserted, and a polyethylene liner was used. Negative pressure drainage was performed during wound closure.

ABT protocol

Hb and hematocrit (Hct) measurements were performed in each patient, in line with the standard preoperative examinations of the anesthesia clinic. Intraoperative Hb and Hct values were measured using blood gas analyses, with a measurement frequency determined by the rate of blood loss and the patient's hemodynamic status. Hb and Hct

measurements were routinely performed in each patient on the morning of the day after surgery.

All patients were transfused according to the national protocol recommended by the Turkish Society of Anesthesiology and Reanimation transfusion guidelines. Accordingly, Hb level = 8 g/dl (4.96 mmol/l) in patients aged ≥65 years in the standard risk group and Hb level = 10 g/dl (6.21 mmol/l) in the high-risk patient group, regardless of age, were accepted as the transfusion limit. For this purpose, arterial blood gas analyzes were performed at regular intervals from the patients. Furthermore, to Hb levels, clinical markers supporting the signs and symptoms of anemia, such as decreased urine volume (< 30 ml/h) , tachycardia (>100 beats/min), and hypotension (mean blood pressure <60 mmHg), contributed to blood transfusion decisions in patients with intact cardiac function and ensured adequate fluid replacement. During surgery, the decision for ABT was made by the anesthesiologist. Packed red blood cells were provided by the local blood bank in a buffy coat-removed erythrocyte suspension with a mean volume of 200 ml, Hb level of 15 g/dl, Hct level of 65%–75%, and leukocyte count of 0.4×10^9/l.

All patients who underwent THA were followed up in the postoperative intensive care unit for 24 h after surgery. During this period, the same parameters were valid for blood transfusion, and the decision for transfusion was made by the anesthesiologist. On postoperative day 1 (POD1), patients with stable hemodynamics were transferred to the orthopedic ward, where the decision for transfusion was made by the surgeon during follow-up. Although the surgeons' criteria for performing ABT may have varied, data on postoperative ABT volumes were included, and the volume of intraoperative blood transfusions in the three groups was compared.

Cost analysis

Costs related to the volume of ABT used, the dose of TXA used, and the CS system used during the evaluation process were calculated for each patient. Daily bed charges for the patients were also included in the cost analysis. A cost comparison study was then conducted to determine the most economical perioperative blood management strategy. The CS equipment used in our hospital was the OrthoPAT blood salvage system developed by Haemonetics Corp.(Braintree, MA, USA).

Outcomes

The primary objective of this study was to evaluate the effect of TXA used before surgery on the volume of ABT in geriatric patients undergoing THA by comparing it with the that of CS and control treatment. The secondary objective was to evalute the cost–benefit, total blood loss, intraoperative blood loss, transfusion rate, and thromboembolic complications during the first 3 months postoperatively.

Statistical analysis

The data collected in the study were evaluated using the International Business Machines® Statistical Package for the Social Sciences® Statistics version 22 software program for Windows 10. The Kolmogorov–Smirnov test was used to check the normality of the data distribution. For descriptive statistics, categorical variables are presented as percentages (%), and numerical variables are presented as means ± standard deviations. One-way analysis of variance (ANOVA) and the Welch test (no homogeneity between groups) were used for comparing the numerical data between the three groups, and the Tukey test was used for post hoc analysis. When one-way ANOVA assumptions could not be achieved, the Kruskal–Wallis test was used. The Mann–Whitney U test was used to determine the group that caused the difference between the groups according to the results of the Kruskal–Wallis test. Statistical significance level of alpha was set at $p < 0.05$. Additionally, receiver operator characteristic (ROC) analysis was performed to determine

the cutoff values for the volume of bleeding that was presumed to reduce blood loss.

RESULTS

In total, 67.2% (887) patients were women, and the mean patient age was 74.3 ± 7.27 years. The mean body mass index was 24.3 ± 5.47 kg/m^2. Further, 63.5% patients were in the ASA III risk group. The mean surgery time was 90.9 ± 42.9 min. Surgery was performed on the right side, with a rate of 57.32%. The demographic characteristics of the patients classified into groups according to the method of preventing ABT use are shown in Table 1. The ASA score and other descriptive variables were similar between the groups (Table 1).

During the intraoperative period, the blood loss was 368.2 ± 131.4 ml, which was significantly lower in the TXA group than that in other groups (p=0.018). In contrast, postoperative blood loss was similar between the groups (p=0.054) (Table 2). There were no differences between the groups in terms of Hct values during the preoperative period, on POD1, and at discharge (p=0.156, p=0.334, and p=0.091, respectively). When compared with the preoperative period, the amount of decrease in Hct values on POD1 and at the time of discharge was similar in the groups (p=0.068 and p=0.062, respectively, Table 2).

There were no statistically significant differences between the groups in terms of hemodynamic parameters during the preoperative, intraoperative,

Table 1. Demographic characteristics and surgical data of groups

	TXA (n=648)	Cell Salvage (n=227)	Control (n=533)	p-value
Age (yr)	72.4±6.4	74.7±7.3	73.8±8.9	0.761*
Gender				
Female	412 (63.5%)	140 (61.7%)	335 (62.8%)	0.817†
Male	236 (36.4%)	87 (38.3%)	198 (37.1%)	
BMI	24.2±5.2	23.8±6.6	25.1±5.8	0.224‡
ASA				
I	44 (6.7%)	15 (6.6%)	34 (6.4%)	0.842†
II	189 (29.1%)	68 (29.9%)	161 (30.3%)	
III	413 (63.7%)	144 (63.4%)	335 (63.0%)	
IV	2 (0.3%)	0 (0%)	3 (0.5%)	
Anesthesia type				
Regional	428 (66.0%)	153 (67.4%)	367 (68.8%)	0.923†
General	220 (33.9%)	74 (32.5%)	166 (31.1%)	
Duration of anesthesia (min)	117.4±73.8	112.6±65.3	110.5±92.6	0.275†
Duration of surgery (min)	89.1±34.4	92.3±45.8	88.6±48.7	0.284†
Operation side				
Right	375 (57.9%)	129 (56.8%)	309 (57.9%)	0.937†
Left	273 (42.1%)	98 (43.2%)	224 (42.0%)	
Length of stay (day)	8.6±4.8	9.6±5.7	10.3±5.2	**0.004***
PO thromboembolic incidence	6 (1.86%)	3 (1.88%)	6 (1.50%)	0.877**

TXA: tranexamic acid; BMI: body mass index; ASA: American Society of Anesthesiologists; PO: postoperative
Data are presented as the mean ± standart deviation and number of patients (%). *Welch Test / †Kruskal-wallis Test / ‡AnovaTest / **chi-square

Table 2. Perioperative blood loss and hemoglobin-hematocrit levels comparisons

	TXA (n=648)	Cell Salvage (n=227)	Control (n=533)	*P*-value
IO blood loss (ml)	368.2±131.4	628.7±257.3	598.7±219.6	**0.018**[*]
PO blood loss (ml)	418.6±205.7	446.3±216.2	485.1±223.8	0.054[*]
Hemoglobin (mg/dl)				
Preoperative	12.4±1.2	12.2±1.6	12.2±1.8	0.142[*]
POD 1	9.7±1.6	9.7±1.4	9.8±1.9	0.682[†]
Discharge	9.6±1.7	9.4±0.9	9.6±1.7	0.686[a]
Hematocrit				
Preoperative	37.2±4.2	36.6±4.3	36.6±4.9	0.156[*]
POD 1	30.4±3.7	29.7±4.2	29.4±4.7	0.334[†]
Discharge	29.9±3.0	28.6±2.7	29.1±2.9	0.091[†]
Hemoglobin decrease (mg/dl)				
POD 1	2.6±1.4	2.5±1.3	2.6±1.4	0.748[‡]
Discharge	2.8±1.7	2.8±1.2	2.9±1.8	0.108[*]
Hematocrit decrease				
POD 1	6.8±3.4	6.9±3.2	7.2±3.5	0.068[†]
Discharge	7.4±4.8	7.9±3.9	7.5±4.3	0.062[*]

TXA: tranexamic acid; IO: intraoperative; PO: postoperative; POD 1: postoperative day 1
Data are presented as the mean ± standart deviation. [*]Welch Test / [†]AnovaTest / [‡]Kruskal-wallis Test

and postoperative periods after extubation (Table 3). Patients in the TXA group received the least volume of blood transfusions during the intraoperative and postoperative periods ($p < 0.001$ and $p=0.004$ respectively). The number of patients who received ABT was significantly higher in the control group than in the other groups ($p < 0.001$ and $p < 0.001$, respectively; Table 3).

The length of hospital stay was shorter in the TXA group than in the other groups ($p=0.003$); there was no difference in the length of hospital stay between the CS and control groups. The average cost was 139.5 ± 77.1 US dollars ($) in the TXA group and 419.3 ± 91.2 $ in the CS group. The cost was significantly lower in the TXA group ($p < 0.001$), whereas it was significantly higher in the CS group than in the other groups.

ROC analysis was performed to determine the cutoff value at which the difference in intraoperative blood loss occurred between the methods used. The cut-off value for the TXA and control groups was 420 ml (AUC, 0.829; $p < 0.001$). Accordingly, the use of TXA in patients in whom bleeding > 420 ml was predicted was considered beneficial in terms of reducing intraoperative bleeding, with 78.5% specificity and 78% sensitivity. The cutoff value for the CS and TXA groups was 380 ml. The use of TXA was considered more beneficial for bleeding >380 ml, with 62% specificity and 60% sensitivity, and TXA used with bleeding below this volume to avoid the cost burden was associated with the use of CS (Figure 2).

The incidence of postoperative venous thromboembolic complications, such as deep venous

Table 3. Perioperative hemodynamic and transfusion data

	TXA (n=648)	Cell Salvage (n=227)	Control (n=533)	*P*-value
Hearth rate (beats/min)				
T0	85.33±12.87	88.63±16.10	87.28±13.12	0.392*
T1	73.94±11.88	71.68±15.92	72.67±13.35	0.339*
T2	87.92±13.56	90.42±14.83	89.24±15.71	0.514*
Mean arterial pressure (mmHg)				
T0	90.8±14.25	92.32±15.8	94.16±10.76	0.128*
T1	66.04±11.51	66.30±10.39	68.26±9.16	0.312*
T2	82.53±10.08	84.34±7.79	86.15±9.81	0.394*
Crystalloid solution (ml)	413.28±49.12	427.55±39.34	444.20±54.72	0.413†
IO Blood Tranfusion				
Allogeneic n (%)	174 (%26.9)	73 (%32.1)	255 (%47.8)	**< 0.001***
Volume (ml)	326.4±208.3	348.6±278.2	592.5±286.2	**< 0.001†**
Otolog n (%)	-	227(%100)	-	-
Volume (ml)	-	339.2±207.2	-	-
Total n (%)	174 (%26.9)	227(%100)	255 (%47.8)	**< 0.001***
Volume (ml)	326.4±208.3	687.4±287.5	592.5±286.2	**< 0.001†**
PO ABT				
n (%)	110 (%16.9)	49 (%21.5)	170 (%31.8)	**< 0.001***
Volume (ml)	136.3±184.1	182.7±233.8	220.3±160.2	**0,004†**
Total ABT (n-%)	223 (%34.4)	97 (%42.7)	303 (%56.8)	**0,011***
Cost ($)	139.5±77.1	419.3±91.2	179.9±64.8	**< 0.001***

ASA: American Society of Anesthesiologists; IO: intraoperative; PO: postoperative; ABT: allogeneic blood transfusion
Data are presented as the mean ± standart deviation and number of patients (%). *Kruskal-wallis Test / †Welch Test.

thrombosis, pulmonary embolism, and stroke, was compared between the groups, and no significant difference was found between the groups (p=0.877) (Table 1).

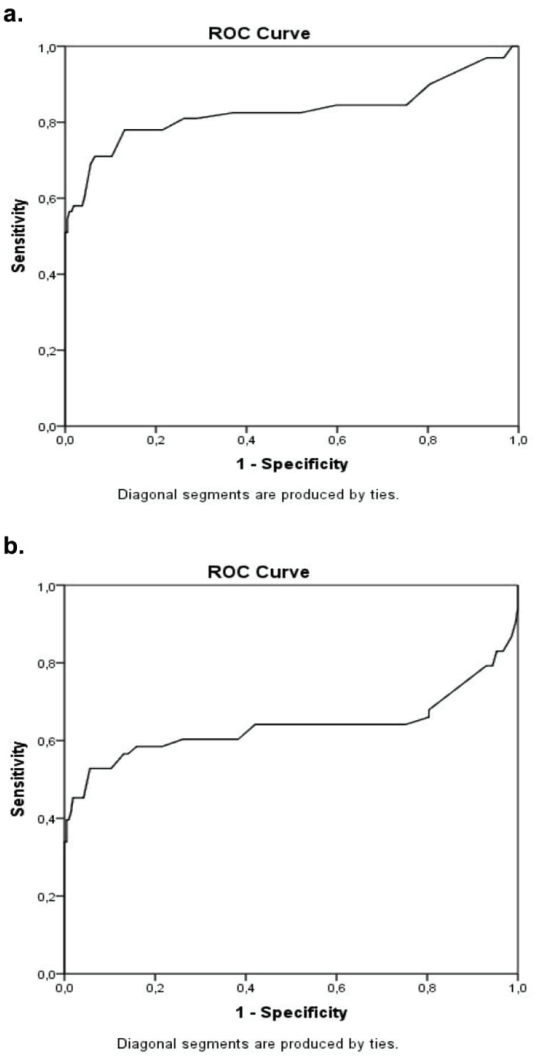
DISCUSSION

TXA and CS are commonly used to reduce the need for ABT during major surgeries, including cardiopulmonary bypass, total hip and knee replacement, and radical prostatectomy (14-16). These methods help maintain hemodynamics without increasing thromboembolic events such as postoperative deep vein thrombosis (DVT), pulmonary embolism, and stroke (17).

In this retrospective study, the use of TXA reduced the need for intraoperative ABT without increasing the risk of thromboembolism in geriatric patients. In addition, it significantly reduced intraoperative blood loss, the need for ABTs, and hospital costs. The use of CS reduced the need for ABT, but significantly increased costs.

The two most commonly used methods to re-

Figure 2. Receiver operating characteristic (ROC) analysis curves of tranexamic acid (TXA) and blood loss according to two different study groups.



a. TXA group vs. Control group
b. TXA group vs. Cell salvage group

duce the need for intraoperative ABT in THA, are TXA a pharmacological agent, and CS treatment. Although many studies have compared both these methods with control treatment, to the best of our knowledge, no study has compared these methods in geriatric patients (10,13,17).

In different studies performed with TXA and CS, a significant decrease was found in need for blood transfusion, Hct levels, and the volume of ABT compared to that in the control group (8,18). In the present study, similar to the literature, the volume of ABT was similar in both groups and lower than that in the control group. In this respect, both TXA and CS are clinically effective.

However, the volume of total intraoperative blood transfusion was significantly lower in the TXA group than that in the other groups. The most important study result was that the volume of ABT in the TXA group was similar to the volume of autologous blood transfusion in CS. It has been observed that using high-cost CS can only meet the volume of autologous blood transfusion provided by preoperative TXA, but it cannot prevent the need for intraoperative ABT.

During the postoperative period, although the volume of ABT was the lowest in the TXA group, there was no statistical difference between the groups. We thought that this was because the dose was not repeated in the postoperative period, especially in the TXA group.

The half-life of 1 g of TXA administered as an intravenous bolus is approximately 2 h. The volume of distribution is approximately 9–12 L, and 95% of TXA is excreted through the kidneys via the urine and is chemically unchanged. The plasma TXA concentration required for approximately 80% inhibition of fibrinolysis is 10 µg/ml (19). The maximum concentration is achieved approximately 1 h after IV administration, and its anti-fibrinolytic effect lasts up to 17 hours. However, pharmacokinetic studies have reported that the efficacy of drug clearance and, thus, the therapeutic window can slightly change with age (20). In the first hours of surgery, tissue plasminogen factor (t-PA) release increases, which causes increased fibrinolytic activity and anemia. Therefore, TXA can be used in the preoperative or

early intraoperative phase to reduce increased t-PA release during surgery (4).

Although there was no significant difference between the three groups in terms of ABT in the postoperative period, the lowest volume of transfusion was found in groupTXA. In this study, TXA was administered to patients after anesthesia induction and before skin incision. Previous studies have suggested the use of TXA in the preoperative or early intraoperative phase to combat increased t-PA release during surgery (4,21). TXA administered 24 h after surgery may cause excessive inhibition of fibrinolytic activity due to the combined effects of TXA and t-PA inhibitor (t-PAI), possibly leading to vaso-occlusive events such as DVT and pulmonary embolism (4,21). The incidence of thromboembolic events in the TXA group was similar to that in the CS and control groups, supporting the current hypothesis. However, in some studies, the incidence of thromboembolic events in the groups that received an additional dose in the postoperative period was similar to that in the groups that did not (22,23).

Although TXA has a statistically better performance than CS, it seems to have a similar effect in terms of clinical outcomes such as perioperative ABT, postoperative Hb, and Hct values. Currently, the method of choice is determined by efficacy, cost, and postoperative complications.

Considering the cost analyses of both methods, it was determined that the total hospital cost, including daily bed charges, was the lowest in the TXA group. The volume of ABT and the length of hospital stay were lower in the TXA group than in the other study groups.

THA is a surgical procedure in which intraoperative blood loss is high due to increased tissue fragility, especially in geriatric patients, and ABT is associated with postoperative morbidity and high cost (2). Authors of this study found that the use of TXA might be beneficial for blood loss of >420 ml. In a similar study, TXA reduced intraoperative blood loss (15). In our study, there was no significant difference between TXA and CS treatment in bleeding <380 ml. However, from a cost point of view, although the use of CS significantly reduced the need for intraoperative ABT, it did not provide an advantage over TXA.

The limitations of this study are its retrospective nature and the lack of randomization to account for differences between groups. All surgeries were performed at a single hospital, and the TXA dose used in this study might not reflect the results of other hospitals with different dosing protocols. This study was also conducted in geriatric patients undergoing unilateral THA, and the benefits of TXA use might not extend to the emergency care setting or to bilateral THA or revision arthroplasty procedures where more extensive bleeding is expected. It was suggested that age could significantly affect TXA clearance. Therefore, additional pharmacokinetic and dosing studies should be performed in geriatric populations. In addition, the lack of a standard protocol for ABT in the postoperative period in our hospital may prevent us from reaching a definite judgment on the postoperative blood transfusion results. The strength of the study was the evaluation of three groups—TXA, CS, and control.

CONCLUSION

The study data showed that TXA reduced the need for ABT better than CS during the perioperative period by preventing blood loss in geriatric patients. Although they have similar success in terms of performance during the intraoperative period, TXA seems to be the most appropriate option than CS in terms of cost-effectiveness.

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