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The role of intravenous tranexamic acid for blood loss in total hip arthroplasty secondary to femoral neck fracture

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ABSTRACT

Aim: The aim of the study was to compare the efficacy of intravenous (IV) administration of tranexamic acid (TXA) in terms of bleeding volume, allogeneic blood transfusion (ABT) requirement, and complications in total hip arthroplasty (THA) secondary to osteoporotic femoral neck fracture (FNF).

Material and Method: A total of 165 patients who underwent THA on the background of FNF in our clinic were included in the study. Patients' demographic data, preoperative and postoperative blood parameters, the amount of blood loss calculated according to the Nadler formula, amount of ABT, and complications at the 90-day follow-up were recorded. The patients were divided into two groups those who received 15 mg/kg preoperatively and 10mg/kg IV TXA at the end of the operation (TXA group-89 patients) and those who did not receive TXA (Control group-76 patients) and the two groups were compared.

Results: The total amount of bleeding calculated according to the Nadler formula was significantly less in the TXA group (1659,68±320,86ml) compared with the Control group (1774,43±365,24ml) (p=0.033). The need for ABT was 42.86% in the TXA group and 57.14% in the control group, and this difference was statistically significant (p=0.008).

Conclusion: In patients who underwent THA on the basis of osteoporotic FNF, preoperative and postoperative administration of 2 doses of IV TXA significantly reduced total blood loss and the need for ABT. We suggest that IV TXA administration can be safely performed, especially in this patient group, to reduce the amount of bleeding and therefore the need for ABT by not increasing any thromboembolic complications.

Keywords: Total hip arthroplasty, tranexamic acid, blood loss, allogeneic blood transfusion, nadler

INTRODUCTION

The incidence of hip fractures after simple falls is on the rise as the proportion of the elderly population increases and bone mineral density decreases with age (1). However, it is estimated that more than 6 million hip fractures will have occurred by 2050 (2). Femur neck fractures (FNF) constitute the majority of hip fractures in the elderly and are often treated with the surgical option of hemiarthroplasty (HA) or total hip arthroplasty (THA). Although THA provides better functional scores and pain reduction compared with hemiarthroplasty, it also has disadvantages such as the risk of dislocation, prolonged surgery time, and increased perioperative bleeding (3). It has been reported that the mean perioperative total blood loss in THA can be 700-2000 ml and allogeneic blood transfusion (ABT) rates can range from 16% to 68% (4,5). ABT may result in a variety of complications, including the transmission of blood-borne diseases, immunologic reactions, increased periprostatic infection, increased costs, acute lung injury, allergic reactions, and death.(4) Due to these reasons, despite numerous studies conducted to reduce perioperative bleeding and the need for ABT, the use of antifibrinolytic agents has become increasingly popular recently. Tranexamic acid (TXA), a synthetic analog of the amino acid lysine, prevents fibrinolysis by blocking the lysine binding sites of plasminogen and thus stabilizes the clot by reducing the proteolytic activity on fibrinogen and fibrin monomers (6). TXA has been reported as an effective and relatively safe agent in reducing blood loss among antifibrinolytic agents (7).

Although there have been studies and meta-analyses on the use of TXA in THA applications, the dose, form, and time of administration of TXA are still controversial (8–12). Although there are publications reporting that the use of intravenous (IV), oral or topical TXA is superior to each other in studies, there is no consensus on issues

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such as multiple-dose, single-dose, or combined use of TXA, except for the use of TXA (11,12).

Although there are many studies on the use of TXA in THA performed on elective grounds, the number of studies on the bleeding amount, need for ABT, and complications of TXA in patients who underwent THA for osteoporotic FNF in the elderly population is limited (13,14). This patient profile often consisted of patients who were often excluded from TXA studies due to cardiac diseases, previous cerebrovascular events, or comorbidities. However, it is well-documented that ABT applications are even riskier in the elderly population (15). Hence, ABT should be avoided as much as possible in this age group. Therefore, in this study, we aimed to compare the amount of bleeding, the need for ABT, and postoperative complications in the elderly population in whom THA was applied on the background of FNF by comparing patients who received IV TXA with patients who did not receive TXA.

MATERIAL AND METHOD

The study was carriedout with the permission of Aydın Adnan Menderes University Clinical Researches Ethics Committee (E-21559114-804.01-20/01/2023-301616). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. The archive records of our clinic between January 2013 and December 2020 were retrospectively reviewed, and patients over the age of 65 who underwent THA on the basis of FNF, patients who had at least 3 months of postoperative follow-up for symptomatic deep vein thrombosis (DVT) and had adequate records, and patients who underwent primary THA using the posterolateral approach were determined. Patients who underwent revision hip arthroplasty, patients with ischemic heart disease, cerebrovascular accident, known bleeding disorder, a history of thromboembolism such as DVT, chronic liver or renal failure, known sensitivity to TXA, incomplete archival records, and patients who could not be reached were excluded from the study. A total of 13 patients, 6 of whom were given TXA and 7 who were not given TXA, were excluded from the study because they died in the first 90 days of follow-up. A total of 165 patients who met these inclusion criteria were included in the study. Of these patients, 89 were in the group that received IV TXA and 76 were in the control group that did not receive TXA.

It was ensured that the preoperative hemoglobin (Hb) level was higher than 10 gr/dl in all patients for whom surgery was indicated. All patients underwent uncemented THA in the lateral decubitus position by surgeons experienced in arthroplasty through a standard posterolateral approach.

According to the TXA protocol we applied in THA, in the TXA group, the intravenous infusion was administered in 15mg/kg (Transamine®, 250 mg/2.5 mL IV Injectable Solution Teva Pharmaceuticals, Turkey) 100mL saline (0.9%) 30 min before the TXA skin incision, and again in the operating room, in 10mg/kg 100mL saline (0.9%) immediately after the fascia was closed. TXA was not administered in the other group.

40 mg/day enoxaparin sodium, which was started 12 h before the surgery prophylactically, was administered subcutaneously once a day to the patients and was used for 30 days after discharge. The patients were mobilized on the first postoperative day and followed up with the standard postoperative follow-up protocol. Demographic data, the amount of ABT, whether a drain was used or not, and operative risk according to the American Society of Anesthesiologists (ASA) classification were recorded. Preoperative and postoperative blood parameters on the 1st, 2nd, and 3rd days were recorded. The trigger point for ABT was determined as Hb < 8 g/dl (16).

The formula described by Nadler et al. (17) was used to calculate the amount of blood loss.

BBV-male(L)=(0,3669 × H3)+(0,03219 × W)+0,6041

BBV-female(L)=(0,3561 × H3)+(0,03308 × W)+0,1833

Hb loss was found by applying the estimated BBV, preoperative Hb, postoperative Hb and transfused Hb amount to the formula below.

Hb loss=BBVx(preoperative Hb–postoperative Hb)x10 dL/L+amount of transfused Hb

Patients were followed up for the presence of hematoma, infection, and DVT during hospitalization and the first three months after discharge.

Preoperative blood values, demographic data, estimated blood volume (EBV), ABT rates, estimated blood loss, length of hospital stay, and complications such as superficial or deep wound site problems, DVT, and pulmonary embolism (PE) in the first 90 days postoperatively were compared between the groups.

SPSS 22.0 for the Windows program was used for statistical analysis. Descriptive statistics were expressed as numbers and percentages for categorical variables and mean, standard deviation, minimum, and maximum for numerical variables. Comparisons of two independent groups were made with Student's t-test when numerical variables met the normal distribution condition and with the Mann-Whitney U test when they did not. Rates in independent groups were compared using the Chi-Square Test. The statistical significance level was accepted as $p<0.05$.

RESULTS

When the demographic data and general characteristics between the two groups were compared, no difference was observed between the groups. All these data are summarized in **Table 1**. Comparison of preoperative mean blood values is shown in **Table 2**. It was found that there was no significant difference between the groups in terms of these values.

Table 1. Demographic and general data of the patients.

	IV TXA group (n:89)	Control group (n:76)	P value
Age (years) ±SD	72.10±5.15	71.55±4.56	0.474
Gender (Female/Male)	54/34	48/38	0.651
Height (cm) ±SD	165.66± 6.91	165.46±6.32	0.964
Weight (kg) ±SD	73.11± 10.52	74.11± 9.21	0.518
Body mass index (kg/m²) ±SD	26.69± 3.72	27.03± 3.15	0.533
Surgery time (minutes) ±SD	146.68± 24.92	145.06± 29.92	0.705
Lenght of stay hospital (days) ±SD	5.34± 1.91	6.57± 2.74	0.001
ASA score			0.388
ASA 1	5 (5.62%)	3 (3.95%)	
ASA 2	48 (53.93%)	51 (67.11%)	
ASA 3	32 (35.96%)	20 (26.31%)	
ASA 4	4 (4.49%)	2 (2.63%)	

Abbreviations: IV, intravenous; TXA, tranexamic acid

Table 2. Comparison of preoperative blood parameters of patients.

	IV TXA group	Control Group	P value
APTT	27.43±4.04	27.23±2.89	0.153
Protrombin time	13.63±1.71	13.88±2.31	0.431
INR	1.06±0.13	1.08±0.15	0.470
Thrombocyte	260.66±85.05	276.65±85.05	0.230
Hemoglobin	12.97±1.04	13.15±1.44	0.345

Abbreviations: IV, intravenous; TXA, tranexamic acid; APTT, activated partial thromboplastin time; INR, internationel normalized ratio

The comparison of Hb and Hematocrit (Htc) values between the two groups on preoperative and postoperative days is shown in **Table 3**.

Table 3. The mean hemoglobin and hematocrit values of the patients preoperatively and postoperatively on 0, 1, 2 and 3 days.

	IV TXA group	Control Group	P value
Hemoglobin			
Preop	12.97±1.04	13.15±1.44	0.345
Postop day 0	10.55±1.33	10.92±1.72	0.126
Postop day 1	9.86±1.31	9.89±1.76	0.922
Postop day 2	9.21±1.27	9.16±1.55	0.848
Postop day 3	9.09±1.07	9.02±1.11	0.684
Hematocrit			
Preop	38.27±3.85	39.53±4.58	0.056
Postop day 0	35.13±9.21	33.10±5.15	0.577
Postop day 1	32.96±9.19	29.65±6.05	0.343
Postop day 2	27.93±3.93	27.65±4.48	0.665
Postop day 3	27.39±3.06	27.42±3.37	0.945

Abbreviations: IV, intravenous; TXA, tranexamic acid

Total blood loss, total blood volume, total Hb loss, total Hb loss, transfusion amount, and ABT values, which were calculated using the Nadler formula, were compared in **Table 4**, and total blood loss, ABT amount and the total amount of ES transfused were less in the group given TXA (p=0.033, p=0.008, p=0.007, respectively).

Table 4. Total blood volume, total blood loss, Hb loss calculated according to Nadler's formula and need for ABT and transfused ES amount

	IV TXA group	Control Group	P value
Total Blood Volume	4.42±0.49	4.39±0.53	0.703
Total Blood Loss	1659.68±320.86	1774.43±365.24	0.033
Hb loss	222.76±50.36	234.73±53.10	0.140
ABT amount	33/89 (42.86%)	44/76 (57.14%)	0.008
Transfused ES amount	0.62±0.90	1.05±1.07	0.007

Abbreviations: IV, intravenous; TXA, tranexamic acid; Hb, hemoglobin; ABT, allogeneic blood transfusion; ES, erythrocyte suspension

When evaluated in terms of complications, DVT was seen in 2 patients in the TXA group at the 90-day follow-up, whereas DVT was seen in 1 patient in the control group. There was no significant difference between the groups in terms of complications such as DVT or PE (p=1.000).

DISCUSSION

With increasing life expectancy, the incidence of hip fractures is increasing and is expected to reach up to 6 million per year in the USA alone in the near future (18,19). THA is a frequently preferred technique after hip fracture and is a major surgical option with a bleeding rate of approximately 2000 ml (4,5). Although there are many studies on reducing the amount of bleeding and the need for ABT with the use of TXA in patients who underwent THA on elective grounds, the number of studies with TXA applications in patients who underwent THA on FNF grounds is limited (13,14,20). For this reason, we think that our study will contribute to the literature. Our study showed that TXA significantly reduced the amount of bleeding and ABT in patients who underwent THA on the basis of FNF compared with the non-TXA group. In our study, it was found that TXA resulted in a decrease of approximately 115 ml in the amount of bleeding and 14.28% in the amount of ABT with 2 doses of 15mg/kg IV preoperatively and 10 mg/kg IV immediately after fascia closure.

In a study examining the efficacy of TXA in patients who underwent total hip surgery on the basis of intra-articular FNF, 58 patients who underwent TXA and 137 patients who did not undergo TXA were compared. It was found that there was approximately a 31% decrease in the transfusion rate and a 28% decrease in hemoglobin level in the TXA group (14). In this study,

we think that comparing the amount of bleeding only from hemoglobin levels without using a method such as the Nadler formula may not give accurate results. In their randomized clinical trial, Watts et al. (13) reported a decrease of approximately 9% in the need for blood transfusion in patients who underwent arthroplasty on the basis of FNF compared with the placebo group in patients who received TXA, but this value was not statistically significant. Meanwhile, in our study, we think that TXA can be used safely since the amount of transfusion was significantly reduced by approximately 14% and the amount of bleeding by approximately 115ml (15.4%) in the TXA group.

Additionally, Lee et al. (21), in their prospective randomized study, compared the placebo group with TXA administered in 2 doses of 15mg/kg at doses similar to our study. In the placebo group, the total blood loss was 1326ml and the need for ABT was 58.8%, while in the TXA group, blood loss was 674ml, and the need for ABT was 26.5%. However, in this study, blood loss was determined by calculating the amount coming from the drain and intraoperative bleeding. Based on the literature review, very different amounts of ABT and bleeding have been observed in applications of TXA. These differences may be caused by factors such as different methods used to calculate the amount of bleeding and different trigger points in Hb values for the need for ABT. Further, TXA has an approximately 2-hour half-life, and its plasma concentration reaches its maximum within one hour of administration. In the studies, TXA administered at different times and doses may also result in differences in ABT and bleeding amounts. There is no consensus on the dose and time interval of TXA, and there are different studies on this subject. In a study comparing 3 groups of 10mg/kg TXA, 15mg/kg TXA, and placebo group in THA, it was reported that 10mg/kg or 15mg/kg administration was also effective in reducing the amount of bleeding, but the need for ABT was significantly less in the 15mg/kg dose group than in the 10mg/kg group (22). In their study, Imai et al. (23) investigated the effect of TXA on intraoperative and postoperative bleeding amounts by dividing into 5 groups control group without TXA, single dose preoperative, single dose postoperative, double dose preoperative and 6 h postoperative, double dose postoperative and 6 hours postoperative. They emphasized that TXA administered preoperatively before anesthesia was effective in reducing the amount of bleeding, but double-dose administration of TXA, repeated at 6 h, was more effective in providing therapeutic plasma concentration. In this study, 2 doses, preoperatively and immediately after fascia closure, were not compared. In our study, we think that one of the reasons why iv TXA administration in the form of 2 doses before surgery and after fascia closure was significantly effective in reducing the amount of bleeding and the need for ABT was that we provided a sufficient amount of therapeutic plasma concentration by administering an appropriate dose and double dose.

Apart from the IV use of TXA, options such as oral, topical, or combined use are applied in the literature (9,20,24). In a meta-analysis of 964 patients comparing THA patients treated with topical and IV TXA, it was shown that there was no significant difference between the groups in total blood loss, the need for ABT, and the occurrence of DVT-like complications (24). Although it is thought that topical use may be safer in terms of side effects compared with IV use, there is no compelling evidence for this. When topical use options are considered, there are many options in the literature, such as application after fascia closure, through a drain, in the acetabular or femoral preparation. It is well-established that, intraoperative bleeding as well as postoperative bleeding causes significant blood loss. Therefore, it is evident that topical options such as fascia closure or drain applications may not have any impact on intraoperative bleeding. However, as in our study, we think that IV TXA administered preoperatively will be effective in reducing intraoperative bleeding. Furthermore, in a study conducted in healthy individuals, it was found that the plasma concentration of TXA reached the maximum level at the 1st hour after IV administration in individuals administered IV single dose TXA and that 30% of TXA was excreted in 1 hour, 55% was excreted in the 3rd hour and 90% in 24 hour (25). Hence, we think that in our study, effective plasma concentration that will reduce bleeding especially in the intraoperative process is achieved with IV TXA administration before anesthesia induction, while the effective plasma concentration of TXA, which started to decrease towards the end of the surgery, was achieved with the re-administration of TXA as a second dose, and the effective plasma concentration was reached for bleeding observed in the early postoperative period. For this reason, we are of the opinion that IV TXA, which we administer before and after surgery, is an effective and successful application in reducing blood loss.

Due to the retrospective design of our study, only patients who were diagnosed after clinical suspicion were evaluated in terms of thromboembolic events such as DVT and PE. Subclinical or clinically asymptomatic thromboembolic complications may not be diagnosed because vaso-occlusive events are not routinely screened by ultrasonography or any additional tests. One of the limitations of our study is the problems arising from this retrospective design. Moreover, the fact that the amount of intraoperative bleeding was not measured can be considered one of the shortcomings of the study.

CONCLUSION

We think that this study, which we have done in patients over 65 years of age who underwent THA after FNF in osteoporotic conditions, will contribute to the literature as it has compared the effectiveness of TXA in a more specific group. Our study suggests that TXA is effective and safe on blood loss and the need for ABT in FNF secondary THA applications in the osteoporotic background. Nevertheless, we believe that studies involving a large number of patients, in a prospective design, which evaluate all forms of TXA, including combined forms, may provide clearer results on its efficacy and safety.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Aydın Adnan Menderes University Clinical Researches Ethics Committee (E-21559114-804.01-20/01/2023-301616).

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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