 Acta Chir Orthop Traumatol Cech., 91, 2024, No. 3, p. 151–155
DOI: 10.55095/achot2024/019

ORIGINAL PAPER
PŮVODNÍ PRÁCE

Intraarticular TXA Administration with Appropriate Timing of Clamping and Appropriate Dose is More Effective Than IV Administration

Intraartikulární podání TXA s vhodným načasováním uzavírání a vhodnou dávkou je účinnější než IV podání

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ABSTRACT

PURPOSE OF THE STUDY
Our aim was to compare the effects of intraarticular and intravenous (IV) tranexemic acid (TXA) application on bleeding and complication rates in patients who underwent total knee arthroplasty (TKA).

MATERIAL AND METHODS
Between 2017 and 2021, 406 patients who underwent TKA with 2 g of IV TXA and retrograde 1.5 g of TXA applied through the drain were included in the study. Of the patients, 206 were in the IV TXA group. Preoperative and postoperative hemoglobin levels, drain output, BMI, ASA score, blood loss, and the number of transfused patients were recorded. Complications such as symptomatic venous thromboembolism were also recorded.

RESULTS
There was no significant difference between the two groups in terms of age, sex, American Society of Anesthesiologists (ASA) score, or BMI ($p = 0.68, 0.54, 0.28, 0.45$). Total drain output and blood loss were significantly higher in the IV TXA group than in the intraarticular TXA group ($p < 0.0001$, $p < 0.0001$). Eighteen patients in the IV TXA group and 1 patient in the intraarticular TXA group received a blood transfusion ($p < 0.0001$). There was no difference between the two groups in terms of preoperative hemoglobin or platelet count ($p = 0.24$). However, postoperative hemoglobin level was higher in the patients who received intraarticular TXA ($p=0.0005$). More thromboembolism events were seen in the IV TXA group ($p < 0.0001$).

CONCLUSIONS
Intraarticular TXA application reduces blood loss more than IV application, reduces the blood transfusion rate, and causes fewer complications.

Key words: tranexemic acid, total knee arthroplasty, intraarticular injection, blood loss, blood transfusion.

INTRODUCTION

Blood loss is an important complication in total knee arthroplasty (TKA) and may increase the need for blood transfusion (8). Perioperative blood management reduces the risk of morbidity and mortality (20). Autologous blood transfusion, blood salvage techniques, hypotensive anesthesia and administration of recombinant human erythropoietin have been applied to reduce perioperative blood loss (19). Recently, some pharmacological drugs have been developed to prevent blood loss.

Recently, tranexemic acid (TXA) has become a popular method used for this purpose (10). There are many effective ways to administer TXA, but intravenous (IV) and intraarticular use are considered the most effective (24). Currently, intraarticular application is recommended to provide maximum effect in the compressed area such as the knee joint capsule and to avoid the side effects of systemic application (4, 6, 23). In addition, intraarticular applied TXA in TKA has also been reported to reduce swelling, which may have the advantage of earlier mobility and less pain (11). Intraarticular TXA can be applied in different ways (1, 14).

Our aim in the present study was to compare the hemostatic efficiencies (blood loss, drain output, preoperative and postoperative hemoglobin levels, and the number of patients who received a blood transfusion) of the retrograde intraarticular method through the drain and the IV method in TXA application.

MATERIAL AND METHODS

The study was planned as a retrospective evaluation of medical data. A total of 406 patients who underwent

primary TKA and received IV and intraarticular TXA between 2017 and 2021 were included. The patients were divided into two groups according to whether they received IV or intraarticular TXA. We compared blood loss, drain output, preoperative and postoperative hemoglobin levels, complication rates, and the number of patients who received a blood transfusion between the two groups. All data used in the study were obtained from hospital records. Included in the study were patients who had undergone primary elective unilateral TKA after a diagnosis of osteoarthritis. The exclusion criteria were TXA allergy; preoperative liver or kidney dysfunction; severe heart or respiratory disease, including coronary artery stenting; coagulopathy; thrombocytopenia defined by preoperative platelet count <150,000/mm^3; a history of a thrombotic condition; pregnancy; breast-feeding; diagnosis of inflammatory arthritis; <18 years or >100 years; and/or preoperative hemoglobin level <10 g/dL.

The number of patients who received IV TXA was 206 and the number of patients who received intraarticular TXA was 200. Of the 406 patients, 250 (61.5%) were female. The mean age of the patients was 64.2 (range 52 to 89). The mean body mass index (BMI) was 29.5 kg/m^2 (range, 20 to 40 kg/m^2).

Preoperative and postoperative hemoglobin levels were recorded. The hemoglobin levels of the patients were measured at the postoperative 24th hour, 1st day, 2nd day and 3rd day. The lowest hemoglobin levels before the postoperative blood transfusion (if performed) were recorded.

According to the formula given by Nadler et al., blood loss was determined from the difference between the preoperative hemoglobin level during the hospital stay (before transfusion) and the lowest postoperative hemoglobin level (16).

The total drain output in 24 hours and the number of patients who underwent a postoperative blood transfusion were recorded. Complications such as symptomatic venous thromboembolism (VTE), cerebrovascular accident, and myocardial infarction were recorded. The criteria for blood transfusion were hemoglobin <8 g/dL and hemoglobin <10 g/dL in a patient with symptomatic anemia or considered at high risk for significant underlying cardiac comorbidities. One unit of blood was administered at a time and the presence of symptoms or signs was reassessed.

Surgical technique

All operations were performed by an experienced surgeon (Author CI). A tourniquet was used in all patients from the beginning of the surgical procedure. The tourniquet was deflated after the skin was closed. A cemented prosthesis (NexGen, Zimmer, Warsaw, IN, USA) was used in all patients. Drains were also used in all patients. A standard midline skin incision and medial parapatellar arthrotomy approach was used. Standard surgical techniques were used for intraoperative hemostasis. A jones bandage was applied to all patients. Low molecule weight heparin at a dose of 4000 IU (0.4 mL)/day was used for deep vein thrombosis (DVT) prophylaxis in all patients.

Patients in the IV TXA group were administered 1 g of IV TXA before the tourniquet was inflated. A second dose of 1 g of TXA was administered to the patients in this group after the tourniquet was deflated.

For the intraarticular TXA group, 1.5 g of TXA diluted in 50 mL of normal saline solution (total volume 65 mL) was sent retrogradely through the drain after the fascia was tightly closed. It was checked that there was no fluid leakage from the fascia. The drain was kept closed for 1 hour in patients who received intraarticular TXA. The drain was opened 1 hour after the injection. The first 65 cc of drainage from the drain was not taken into account in the calculation. All outputs were measured and recorded in milliliters. All drains were removed 24 hours after the operation.

Statistical analyses

The statistical analysis was performed using SPSS (Version 23.0, SPSS Inc., Chicago, IL, USA). If continuous variables were normal, they were described as the mean±standard deviation ($p > 0.05$ in the Kolmogorov–Smirnov test or Shapiro–Wilk test ($n < 30$)), and if the continuous variables were not normal, they were described as the median. The continuous variables were compared by the use of the Mann-Whitney U test. The categorical variables between the groups were analyzed by using the chi square test or Fisher's exact test. The level for statistical significance was predetermined at $p < 0.05$.

RESULTS

There was no significant difference between the two groups in terms of age, sex, American Society of Anesthesiologists (ASA) score, or BMI (Table 1).

Total drain output was significantly higher in the IV TXA group than in the intraarticular TXA group (150 compared to 480 mL; $p < 0.0001$) (Table 2).

There was no difference between the two groups in terms of preoperative hemoglobin or platelet count ($p=0.24$). When evaluated in terms of postoperative hemoglobin, the hemoglobin level was higher in the patients who received intraarticular TXA ($p = 0.0005$) (Table 2).

In terms of blood loss, a significantly higher level was found in patients who received IV TXA compared to those who received intraarticular TXA ($p < 0.0001$).

Eighteen patients in the IV TXA group and 1 patient in the intraarticular TXA group received a blood transfusion ($p < 0.0001$). One unit of blood was given to the patients who received a blood transfusion; no more was needed.

In the IV TXA group, 8 (3.8%) of the patients had symptomatic VTE (6 patients) and thrombotic cerebrovascular disease (2 patients) in hospital or after discharge, whereas, in the intraarticular TXA group, symp-

Table 1. Patient demographics

	IV TXA(N:206)	Intraarticular TXA(N:200)	P value
Age (min–max)	63.5 (52–89)	64.7 (55–85)	0.68
Gender			0.54
male	82	76	
female	126	124	
BMI (min–max)	29.3 (20–39)	29.6 (20–40)	0.45
Preop. hemoglobin (g/dL)	14.2 (10.4–15.3)	14.0 (11–16.1)	0.24
Postop. hemoglobin (g/dL)	10.1(7.6–12.2)	12.9 (10–15.0)	0.0005
Preop. platelet count (platelets/mL)	245 (159–488)	241 (164–500)	0.09
Preop. ASA score			0.28
I or II	131	127	
III or IV	75	73	

(IV = intravenous, TXA = tranexamic acid, BMI = body mass index)

Table 2. Results

	IV TXA(N:206)	Intraarticular TXA(N:200)	P value
Total drain output at 24 hr (mL) (min–max)	480 (150–650)	150 (50–250)	p <0.0001
Thrombotic event	8 (3.8%)	1 (0.5%)	p <0.0001
Number of transfused patients	18	1	p <0.0001
Blood loss (mL)	432 (180–2,459)	171 (82–1,242)	p <0.0001

(IV = intravenous, TXA = tranexamic acid)

tomatic VTE was seen in 1 (0.5%) ($p < 0.0001$). None of the patients in either group had a coronary arterio-occlusive event.

DISCUSSION

Most important finding in the present study was that retrograde TXA administration via a drain prevents blood loss more than IV TXA, and therefore blood transfusion is less necessary in TKA. In addition, the systemic side effects of TXA are significantly reduced by intraarticular application.

Blood loss during TKA remains a problem due to soft tissue dissection and bone cuts. After excessive blood loss, blood transfusion is required to prevent morbidity and mortality. However, there are risks such as transfusion reactions, intravascular hemolysis, infection, renal failure and excessive fluid overload after transfusion (5, 23). Recently, studies have been conducted to reduce blood loss to reduce these risks.

TXA has gained popularity due to its effectiveness and ease of implementation. Numerous studies have shown that IV TXA acts as a potent antifibrinolytic, reducing perioperative blood loss and postoperative transfusion rates after TKA (5, 12). Despite a few recent studies reporting the safety of IV TXA, there are still concerns about its safety profile (2, 4, 7). Orthopedic surgeons prefer local TXA for this reason. However, some studies have shown that local TXA is not as effective as IV in preventing blood loss or has results similar to those of IV (2, 22). In a meta-analysis, it was reported that blood loss parameters, including transfusion requirement, blood loss through the drain, estimated blood loss, total blood loss, and change in hemoglobin levels, as well as the incidence of postoperative complications, did not differ significantly between patients who received IV and those who received intraarticular TXA during primary TKA (18). In our study, retrograde TXA administration through the drain reduced blood loss more than IV TXA and drain output was less.

Intraarticular TXA administration has been applied in different ways and at doses ranging from 0.25 g to 3 g (15). In conclusion, it has been shown that intraarticular TXA reduces blood loss. Studies on the optimal dose are ongoing. Wang et al. applied retrograde 1 g of TXA via a drain to a group of patients undergoing TKA. They administered IV TXA and intraarticular saline to the other group. They closed the drain for 2 hours and removed it after 48 hours. The mean drain output was 145 mL in patients who underwent retrograde TXA through the drain (21). In the present study, we applied retrograde 1.5 g of TXA through the drain and closed it for 1 hour. We removed the drain at 24 hours. We observed that the average drain output was 150 mL. In previous studies, it was reported that the duration of drain clamping ranged from 1 to 24 hours postoperatively (13). Drain clamping without TXA was not sufficient to control blood loss (13). In one study, a single dose of IV TXA was compared with 1 g of intraarticular TXA. They clamped the drain for 6 hours. As a result, they showed that IV TXA was more effective (20). Hamline et al. showed that 3 g of intraarticular TXA

was more effective than 1 g of IV TXA in reducing the need for allogeneic blood transfusion after primary TKA (9). We think that the clamping time and TXA dose are important. It has also been reported that a long clamping time is associated with a number of different problems such as skin necrosis, hematoma, and DVT, as well as delayed wound healing (3). We did not administer intraarticular saline to the patients in the IV TXA group, as it may increase these complications.

In a meta-analysis, it was shown that a single dose of IV TXA did not fully cover the period with the highest bleeding risk in the first few hours after the operation (18). It has been shown that a double IV TXA dose is the minimum to reduce blood loss from the drain, and a single intraarticular TXA dose is sufficient if tissue contact time is extended by using the clamped drain technique (18). It was reported that intraarticular TXA doses ranging from 1.5 to 3.0 g may be more effective in reducing drain blood loss in patients undergoing primary TKA (18). Panteli et al. showed that allogeneic transfusion requirements decreased with ≥2 g doses given topically (17). In our study, we applied a single dose of 1.5 g of intraarticular TXA and a double dose (1 g + 1 g) of IV TXA. We observed that this practice significantly reduces blood loss. We think that it is not necessary to administer more doses of intraarticular TXA.

In terms of complications, many studies have shown that IV TXA does not increase complications such as DVT (18). Abdel et al. found that IV and intraarticular TXA thromboembolism events were 1.6% and 0.6%, respectively, in TKA (2). They reported that there was no significant difference. However, in the present study, IV TXA (3.8%) was significantly higher risk than intraarticular TXA (0.5%) in terms of thrombosis.

The limitation of our study was that it excluded at risk patients with co-morbidity. These patients were excluded due to concerns about the safety of TXA. In the second IV group, no clamping was done at the drain outlet and the same amount of fluid (such as saline) was not applied to the joint. This was due to the complications mentioned above. However, to avoid calculating the amount of fluid administered to the joint, the same volume of fluid from the drain was neglected in the intraarticular group.

CONCLUSIONS

Intraarticular TXA administration reduces blood loss more than IV administration, reduces the blood transfusion rate, and causes fewer complications, although the dose is smaller.

Ethics approval: *Ethics committee approval was obtained from our institution.*

Consent to participate: *Informed consent forms were obtained from all patients for both their participation in the study and for publications.*

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