Comparison of weight-based versus standard dosing of tranexamic acid for blood loss and transfusion amount in knee arthroplasty without tourniquet

olcay guler (✉ olcayguler77@gmail.com)

Istinye Universitesi <https://orcid.org/0000-0002-0022-0439>

Engin Çarkçı

Istanbul Training Hospital

Mehmet Halis Çerci

Nisa Premier Hospital

Gürkan Gümüşsuyu

Istinye Universitesi

Çağatay Öztürk

Istinye Universitesi

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Abstract

Background To compare weight-based versus standard dosing of intravenous (IV) tranexamic acid for blood loss and transfusion amount in total knee arthroplasty (TNA) without tourniquet. **Methods** A total of 99 patients who underwent TNA with the diagnosis of primary osteoarthritis were enrolled in this retrospective case-control study. Patients were divided into two groups according to the application of tranexamic acid. Group 1 (weight-based dosing): 10 mg/kg IV TA 30 min before the skin incision, and 10 mg/kg, at postoperative 30 min, and 3 h. Group 2 (standard dosing): 1 g of IV TA 30 min before skin incision, and 1 g at postoperative 30 min and 3 h. Hemoglobin levels, before, and 1, and 2 days after the operation, postoperative amount of decrease in hemoglobin levels, and amount of erythrocyte transfusion were recorded. Two scoring systems Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) and Knee Society Score (KSS) were applied in the evaluation of TNA results preoperatively, and at 1., 3., 6., and 12. months, postoperatively. **Results** Both groups did not differ from each other by means of age ($p=0.127$), gender ($p=0.528$), BMI ($p=0.782$), operating sides ($p=0.544$), existing comorbidities ($p=0.987$), preoperative hemoglobin level ($p=0.718$), the amount of hemoglobin reduction ($p=0.769$), and the amount of erythrocytes transfused ($p=0.913$). In both study groups, hemoglobin levels in male patients dropped significantly more deeply than female patients. Also, in both study groups, hemoglobin levels were significantly lower in patients with comorbid illnesses. A statistically significant difference was not detected between Groups 1 and 2 in terms of pre- and postoperative WOMAC scores, KSS knee scores, and KSS function scores. **Conclusion** Our study showed that weight-based and standard dosing of IV tranexamic acid treatments were similar in efficacy and safety. Both treatments reduce blood loss and the need for transfusion. Also, there was no significant difference in terms of reliability between the two groups.

Background

Total knee arthroplasty (TNA) is frequently used today in patients with advanced stage osteoarthritis to reduce pain and increase range of motion.¹ In studies conducted, blood loss during TNA has been reported as 1000-1790 mL and requirement for blood transfusion as 10-38 %.^{2,3} Increases in transfusion requirements are associated with additional financial costs, risks of hemolytic reactions, and the risk of transmission of viral disease.⁴

It has been suggested that with the use of tranexamic acid (TA), the amount of bleeding is significantly reduced resulting in decreases in hypovolemic side effects, delayed wound healing, and reduced intra-articular hematoma formation. All these positive effects allow early postoperative rehabilitation.⁵ TA is a fibrinolysis inhibitor and plasminogen activator that has been applied in various surgical fields for a long time. In recent years, it has been started to be also used in the field of orthopedic surgery. Both intravenous (IV) and intra-articular tranexamic acid administration aim to reduce blood loss and blood transfusion requirements.

Although there are numerous studies in the literature on the efficacy of IV administration of tranexamic acid, only few studies have compared different IV applications.⁶⁻⁸ In the present study, we aimed to compare weight-based versus standard dosing of IV TA for blood loss and transfusion amount in TNA without tourniquet.

Methods

Study Design: This retrospective case-control study has been conducted in accordance with the principles of the Helsinki Declaration. Written informed consent was obtained from all subjects.

Between January 2014 and January 2017, 99 patients who underwent TNA with the diagnosis of primary osteoarthritis were enrolled in the study. Patients were divided into two groups according to the application of IV TA (Transamin, Fako Pharm Co AS, Istanbul, Turkey)

Group 1 (weight-based dosing): Intravenous administration of 10 mg/kg TA 30 min before the skin incision, and 10 mg/kg, at postoperative 30 min, and 3 h.

Group 2 (standard dosing): Intravenous administration of 1 g of TA 30 min before skin incision, and 1 g at postoperative 30 min and 3 h. Patients who had undergone revision knee total endoprosthesis (TEP) or bilateral knee TEP surgery, those with $> 30^\circ$ flexion deformities or $> 30^\circ$ valgus-varus, preoperative anemia, renal or hepatic dysfunction, severe cardiac or cerebrovascular disease, congenital or acquired disease hematologic disease, DVT or pulmonary embolism, patients with contraindications to tranexamine use were excluded from the study.

Surgical procedure: All patients underwent total knee prosthesis under the spinal anesthesia performed by the same surgeon (O.G.). Midline skin incision was performed, and through parapatellar incision, the joint was accessed. Bicompartamental cementless knee prosthesis which spared the ligament without altering the patella and was applied without using tourniquet. Half an hour prior to administration, prophylaxis was started with 1 g cefazolin and the postoperative 1st day antibiotic was discontinued. Postoperative PCA and nerve block were not performed. Patients were started on percutaneous injections of low molecular weight heparin (enoxaparin sodium, Clexane[®] Sanofi-Aventis Turkey) at daily doses of 0.4 to 0.6 kg beginning 8 hours after the procedure which was maintained for 40 days.

In addition, the patients' ankles were positioned in passive ROM and socks were put on as a mechanical prophylaxis. Patients with symptoms of deep vein thrombosis (DVT) underwent Doppler US, instead of routine Doppler US. Thorax CT was performed for patients with clinical findings of pulmonary embolism (PE). The patients were encouraged to walk with the aid of a cane on the first postoperative day, and passive exercises were started using a "continuous passive motion" device.

Outcome Parameters

Age, gender, body mass index (BMI), planned side of surgery and presence of comorbid diseases of the cases included in the study were recorded. Hemoglobin levels, before, and 1, and 2 days after the operation, postoperative amount of decrease in hemoglobin levels, and amount of erythrocyte transfusion were recorded. Two scoring systems Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) and Knee Society Score (KSS) were applied in the evaluation of knee arthroplasty results preoperatively, and at 1., 3., 6., and 12. months, postoperatively.^{9,10} KSS is a system based on physical examination. It is an evaluation system providing information about dynamics of prosthesis, whereas WOMAC evaluates mostly knee function and postoperative pain.

Western Ontario and McMaster Universities Osteoarthritis Index: WOMAC consists of sections of pain (5 questions), stiffness (2 questions), physical function (17 questions), social function (7 questions) and emotional function (10 questions). The questions for these sections are graded from 1 to 5 (1: no, 2: mild, 3: moderate, 4: severe, 5: very severe). Then scores of each section are summed up to estimate the score of this section.

WOMAC is actually a scoring system that is used to evaluate the efficacy of anti-inflammatory drugs. However, since it is effective in evaluating the patient functions during postoperative period, it has been found a place in the clinical use. In this system pain, joint stiffness and functions are questioned and the low score indicates better outcomes (0-14 excellent, 15-28 good, 29-38 moderate, > 39 insufficient).⁹

Knee Society Score: It consists of two parts as Knee Score and Knee Functional Score, and the patients are investigated in three categories: A. Unilateral or bilateral procedures, but successfully applied to the contralateral knee, B. Ipsilateral and contralateral knees are symptomatic, C. Multiple arthrotic involvement. The scoring results are evaluated as follows: weak, <60 pts; 60-69, moderate; 70-84 pts, good; 85-100 pts, excellent.¹⁰

Statistical Analysis: Non-parametric statistical methods were used for values with skewed distribution. For comparison of two non-normally distributed variables Wilcoxon test was used. For comparison of more than two non-normally distributed variables Friedman test was used.

For comparison of two normally distributed groups Student t test was used. For comparison of two non-normally distributed groups Mann Whitney U test was used.

The χ^2 test (Fisher's Exact test) was used for two categorical variables and expressed as observation counts (and percentages).

Pearson correlation coefficient was used to determine the relationship between two normally distributed variables. Spearman's rho correlation coefficient was used to determine the relationship between two non-normally distributed variables.

Statistical significance was accepted when two-sided p value was lower than 0.05. Statistical analysis was performed using the MedCalc Statistical Software version 12.7.7 (MedCalc Software bvba, Ostend, Belgium; <http://www.medcalc.org>; 2013).

Results

A total of 99 patients met the eligibility criteria for the study. Of the 99 patients (32 males, 67 females), the mean age was 66.7 ± 6.2 (range, 57 to 79) years. Group 1 included 51 patients (18 males, 33 females) with a mean age of 67.3 ± 5.9 (range, 58 to 79) years, and a mean BMI of 28.39 ± 2.44 (range, 24.4 to 36.6) kg/m^2 . Group 2 included 48 patients (14 males, 34 females) with a mean age of 66.1 ± 6.5 (range, 57 to 78) years, and a mean BMI of 28.25 ± 1.64 (range, 24.6 to 31.7) kg/m^2 . Both groups did not differ from each other by means of age, gender, and BMI ($p = 0.127$, $p = 0.528$, and $p = 0.782$, respectively).

In Groups 1, and 2 respective number of patients were operated on the left ($n = 24$; 47.1 % vs 19: 39.6 %), and right ($n = 27$: 52.9 % vs. 29: 60.4 %) knees. There was no statistical difference between the groups in terms of the operating sides ($p = 0.544$). In Groups 1, and 2 the existing comorbidities consisted of diabetes mellitus ($n = 2$: 3.9 % vs 2: 4.2 %), hypertension ($n = 8$: 15.7 % vs 7: 14.6 %), while any comorbidities were not found in 41 (80.4 %) patients in Group 1, and 39 (81.3 %) patients in Group 2. There was no statistical difference between the groups in terms of comorbidity ($p = 0.987$).

Preoperative hemoglobin level was 12.18 ± 1.13 gr/dl in Group 1 and 12.24 ± 1.0 gr/dl in Group 2 ($p = 0.718$). There was a statistically significant intragroup difference between preop, day 1 and day 2 in terms of hemoglobin levels ($p < 0.05$) (**Table 1**). The amount of hemoglobin reduction was 2.33 ± 0.75 gr/dl in Group 1 and 2.37 ± 0.47 gr/dl in Group 2 ($p = 0.769$). The amount of erythrocytes transfused has not statistically significant intragroup, and intergroup difference ($p = 0.913$).

Comparison between the amount of hemoglobin reduction with other parameters is shown in **Table 2**. There was a statistically significant difference between Groups 1 and 2 in terms of distribution of the amount of hemoglobin reduction according to age of the patient, and comorbidities ($p < 0.05$). In both study groups, hemoglobin levels in male patients dropped significantly more deeply than female patients. Also, in both study groups, hemoglobin levels were significantly lower in patients with comorbid illnesses.

The comparison of the groups in terms of pre- and postoperative WOMAC scores, KSS knee scores, and KSS function scores is shown in **Table 3**. A statistically significant difference was not detected between Groups 1 and 2 in terms of pre- and postoperative WOMAC scores, KSS knee scores, and KSS function scores. A statistically significant difference was detected between groups, as for preop, 1., 3., 6., and 12-month. WOMAC, KSS knee, and KSS function scores ($p < 0.05$). The results of post-hoc pairwise comparisons are shown in **Table 4**. According to these results, there was a statistically significant difference between all binary measurements (Wilcoxon $p < 0.001$ Bonferroni correction). In terms of postoperative complications, 1 (2.0 %) patient in Group 1 and 1 (2.1 %) patient in Group 2 had wound

drainage ($p = 1.00$). Duration of hospital stay was 5.2 (4-8) days in Group 1 and 5.4 (4-8) days in Group 2 ($p > 0.05$).

Discussion

In the present study, we aimed to compare weight-based versus standard IV dosing of TA for blood loss in knee arthroplasty and revealed that both dosing regimens have similar effects.

Various methods are being used to reduce postoperative blood loss in total knee arthroplasty. Direct hemostasis without using tourniquet; when tourniquet is used, termination of tourniquet application before wound closure, hemodilution, hypotensive anesthesia and use of antifibrinolytic agent are some of these methods. Differences in methodological adjustments between studies do affect the rates in some parameters but do not seem to affect the results. Results of systematic reviews indicate that TA reduces blood transfusion requirements whatever its etiology may be.¹¹

Many studies have been conducted on the application of IV TA. However, the study protocols of these studies involve differences. Analysis of appropriate dosing and timing of TA administration was limited in the literature as no standard protocol has been determined: 12 reports^{7,12-22} of IV TA received weight-based dosing while 23²³⁻⁴⁵ studies received standard dosing. When a weight-based dosing was used, cases received ranging between 10 and 20 mg/kg. Standard dosing ranged from 0.5 to 3 g for IV TA. Patients received a single^{13,16,19,20,22-24,26,27,31,33-41,43,45}, double^{12,17,21,24,25,30,35,44}, or triple^{7,14,15,18,28} dosing of TA, depending on the study. Finally, the timing of IV administration differed amongst the reports. IV administration of TA was achieved at the time of incision, before the tourniquet inflation or deflation, after the tourniquet deflation, after cementing the prosthesis, or after wound closure. In the present study, we aimed to compare weight-based versus standard dosing of IV TA. Weight-based dosing group received IV administration of 10 mg/kg TA 30 min before the skin incision, and 10 mg/kg, at postoperative 30 min, and 3 h; while standard dosing group received IV administration of 1 g of TA 30 min before skin incision, and 1 g at postoperative 30 min and 3 h.

Limited clinical trials have concentrated on determining the ideal time and dosing for administration of TA. Iwai et al. performed a prospective analysis evaluating cases who had a single dosing of IV TA 10 minutes before tourniquet deflation and the ones who had an extra dosing 3 hours postoperatively and revealed that the 2-dose group had significantly lower blood loss and transfusion amount.⁶ Maniar et al. evaluated different 10 mg/kg IV dosing of TA and revealed a statistically significant decrease in total blood and drain loss in cases who had 3 doses (pre-, intra-, and postoperatively) compared with cases receiving either a single or double dosing of TA.⁷ Wong et al. compared cases who had either 1.5 g or 3 g of IV TA and revealed no statistically significant difference in total blood loss between 2 study groups.⁸ Since administration of TA might have a dose-dependent consequence on decreasing the amount of blood loss, it is likely that the dosing and timing of administration might influence the amount of drain output, blood loss, and transfusion. In our study, no statistically significant difference was found in terms of efficacy and safety between the different forms of IV administration in TA during TDA.

The most important consideration in patients who will be given IV TA is patient selection. Care should be exercised to avoid IV administration of TA to patients with a history of DVT or PE and with thromboembolic and cardiological problems. In their meta-analysis Brown et al. reported that the use of TA did not cause significant increases in mortality, stroke, myocardial infarction, renal insufficiency, and reoperation rates.⁴⁶ Previous literature has demonstrated that the risk of venous thromboembolism is not increased by TA, but given its mechanism of action, patient history and risk factors should still be strongly considered when choosing the administration route and dosage.^{47,48} None of the patients participating in the study had any complication that could be caused by the use of TA and no reoperation was needed.

Limitation of our study include the retrospective design and relatively small number of our series. In addition, some details of history and factors that may influence the outcome may not be completely documented. Another limitation is that there is no separate control group that uses placebo in our study. Due to these restrictions, associations should be interpreted with caution.

Conclusion

Our study showed that weight-based and standard dosing of IV TA treatments were similar in efficacy and safety. Both treatments reduce blood loss and the need for transfusion. However, there was no significant difference in terms of reliability between the two groups.

Declarations

-Ethics approval and consent to participate:

The ethical committee approval was not taken because of retrospective case control design of our study. Written informed consent was obtained from all subjects.

-Consent for publication:

-Availability of data and material:

-Competing interests: The authors declare no competing interests.

-Funding: No financial support was received for this paper

-Authors' contributions: All authors have read and approved the manuscript

OG: Performed operations

GG, EÇ: performed data collecting, statistical analysis

OG, ÇÖ, MHÇ: Editing and study design

-Acknowledgements: None

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Table Legends

Table 1. Comparison of hemoglobin level, amount of hemoglobin reduction and amount of transfused erythrocytes between groups.

Table 2. Parameters that have a significant effect on the amount of hemoglobin reduction.

Table 3. Comparison of groups in terms of pre- and postoperative Western Ontario and McMaster Universities Osteoarthritis Index and Knee Society Score.

Table 4. Post-Hoc binary comparison of time points between groups for Western Ontario and McMaster Universities Osteoarthritis Index and Knee Society Score.

Supplementary Files

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