ARAŞTIRMA MAKALESİ / *RESEARCH ARTICLE*

Tranexamic Acid in Total Knee Arthroplasty: A Comprehensive Examination of Double-Dose Strategies for Hemostasis

Total Diz Artroplastisinde Traneksamik Asit: Hemostaz için Çift Doz Stratejilerinin Kapsamlı Bir İncelemesi

Muhammed Kazez[1], Mustafa Yalin[1], Sefa Key[2]

[1]Department of Orthopaedics and Traumatology, Health Sciences University, Elazig Fethi Sekin City Hospital;
[2]Department of Orthopaedics and Traumatology, Firat University, Elazig, Türkiye

ABSTRACT

Aim: *The current study aimed to evaluate the impact of administering tranexamic acid (TXA) through intravenous (IV) or intraarticular (IA) routes, in double doses, in conjunction with postoperative drain clamping (DC), on postoperative bleeding, transfusion requirements, and thromboembolic complications in patients undergoing total knee arthroplasty (TKA).*

Material and Methods: *A retrospective review of 96 patients undergoing unilateral primary TKA for gonarthrosis between 2021 and 2022 was conducted. Patients received either double-dose IV TXA (n=52), double-dose IA TXA (n=26), or no TXA (n=18) along with postoperative DC. Various parameters were compared among groups, including preoperative and postoperative hemoglobin (Hb) levels, blood transfusion requirements, and length of hospital stay (LOS).*

Results: *Both IV and IA double-dose TXA significantly reduced postoperative bleeding compared to no TXA administration. The need for blood transfusion was lowest in the double-dose IV TXA group. No significant differences were observed in thromboembolic complications among the groups. Length of hospital stay (LOS) was significantly shorter in the TXA groups compared to the no TXA group.*

Conclusions: *Administration of double-dose TXA, either IV or IA and postoperative DC effectively reduced postoperative bleeding in TKA patients. Double-dose IV TXA demonstrated the lowest transfusion rates, suggesting a potential advantage in reducing transfusion requirements. Both IV and IA TXA administrations were safe and efficacious, with no significant increase in thromboembolic complications, emphasizing their overall safety profile in TKA patients.*

Key words: *total knee arthroplasty; double-dose tranexamic acid; transfusion rate*

ÖZET

Amaç: *Bu çalışma, total diz artroplastisi (TDA) uygulanan hastalarda, intravenöz (IV) veya intra-artiküler (IA) yollarla çift dozda uygulanan traneksamik asidin (TXA) ve ameliyat sonrası dren klempajının (DC), ameliyat sonrası kanama, transfüzyon gereksinimleri ve tromboembolik komplikasyonlar üzerindeki etkisini değerlendirmeyi amaçladı.*

Gereç ve Yöntem: *2021 ve 2022 yılları arasında gonartroz nedeniyle tek taraflı primer TDA uygulanan 96 hastanın retrospektif bir incelemesi yapıldı. Hastalar, çift doz IV TXA (n=52), çift doz IA TXA (n=26) veya TXA uygulanmayan (n=18) gruplarına ayrıldı ve ameliyat sonrası DC uygulandı. Preoperatif ve postoperatif hemoglobin (Hb) seviyeleri, kan transfüzyon gereksinimleri ve hastanede kalış süresi (HKS) gibi çeşitli parametreler gruplar arasında karşılaştırıldı.*

Bulgular: *Hem IV hem de IA çift doz TXA, TXA uygulanmayan gruba kıyasla ameliyat sonrası kanamayı önemli ölçüde azalttı. Kan transfüzyon gereksinimi en düşük olan grup çift doz IV TXA grubuydu. Gruplar arasında tromboembolik komplikasyonlarda anlamlı bir fark gözlenmedi. Traneksamik asit gruplarında, TXA uygulanmayan gruba kıyasla HKS anlamlı ölçüde daha kısaydı.*

Sonuç: *Çift doz TXA'nın, IV veya IA olarak uygulanması ve ameliyat sonrası DC ile birlikte, TDA hastalarında ameliyat sonrası kanamayı etkili bir şekilde azalttığı tespit edildi. Çift doz IV TXA, en düşük transfüzyon oranlarını gösterdi ve transfüzyon gereksinimlerini azaltmada potansiyel bir avantaj sundu. Hem IV hem de IA TXA uygulamaları güvenli ve etkili bulundu, tromboembolik komplikasyonlarda anlamlı bir artış olmaması, TDA hastalarında genel güvenlik profilini vurgulamaktadır.*

Anahtar kelimeler: *total diz protezi; çift doz traneksamik asit; transfüzyon oranı*

İletişim/Contact: *Mustafa Yalın, Health Sciences University, Elazığ Fethi Sekin City Hospital, Department of Orthopaedics and Traumatology, Elazığ, Türkiye* • ***Tel:*** *0424 606 60 00* • ***E-mail:*** *mustiyalin1988@gmail.com* • ***Geliş/Received:*** *25.08.2024* • ***Kabul/Accepted:*** *11.02.2025*

ORCID: *Muhammed Kazez: 0000-0002-7344-1064* • *Mustafa Yalın: 0000-0001-8281-9885* • *Sefa Key: 0000-0003-3620-936X*

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Introduction

Total knee arthroplasty (TKA) is a frequently conducted surgery to address severe knee joint degeneration. The primary objective of prosthesis implementation is to facilitate normal kinematics and joint range of motion. Despite the medial pivot knee prosthesis (MPTKP) simulating natural knee kinematics, a consensus on the prosthesis that completely represents these characteristics has yet to be developed[1]. Enhancing patient safety and satisfaction during and post-TKA is crucial. Despite significant advancements in anaesthetic and surgical methodologies, TKA continues to be linked with substantial perioperative blood loss[2]. Total knee arthroplasty would trigger the fibrinolysis system, potentially resulting in significant haemorrhage[3]. Allogenic blood transfusion carries the risk of negative outcomes, including hemolytic responses, antigenic responses, transfusion-related severe kidney failure, and cardiovascular problems. These complications may lead to costly burdens and possibly fatal consequences for patients[4]. So far, many techniques have been used to reduce blood loss, such as pharmaceutical therapy, autologous donation, and allogenic transfusions of blood[5]. Furthermore, other techniques have been effectively used to manage bleeding, minimize blood loss, and reduce the need for transfusions after surgery. These procedures include the use of drain clamping (DC), the administration of tranexamic acid (TXA), and the application of tourniquets[6,7].

Prior research has shown that the intravenous (IV) and intraarticular (IA) applications of TXA effectively decrease blood loss and the need for transfusions in primary TKA without elevating the risk of thrombosis[8]. Drain clamping is a suggested technique to minimize blood loss during the initial postoperative phase after TKA. The frequent application of clamps to drains used in TKA has been supported by several individuals; however, it continues to be an issue of dispute even among physicians who continue to employ postoperative drains[7,9,10]. Various methods have been reported to minimize the loss of blood and the requirement for blood transfusions after TKA. However, the most effective approach is still uncertain. Both DC and TXA treatments are relevant to us as straightforward approaches to hemostasis[11]. Nevertheless, the studies published so far have not reached a unanimous agreement regarding the IV or IA dosage of TXA in TKA. The objective of the study was to examine the impact of TXA administration and the different methods of administration (double dose IV or double dose IA) on the overall blood loss and blood volume in the drains (1), the need for blood transfusion (2), and the occurrence of thromboembolic complications (3) in patients undergoing TKA with postoperative DC.

Material and Methods

Following obtaining ethical approval from the local ethics committee (approval date: 13/02/2024, approval number: 2024/03-75), a thorough retrospective review was carried out by examining hospital records by scanning. Written informed consent was obtained from all participants, thereby ensuring voluntary participation and authorization to utilize their anonymized data in the current study. The current study included patients who underwent unilateral primary TKA for gonarthrosis between 2021 and 2022. Inclusion criteria comprised patients aged between 50 and 85 years, with a preoperative hemoglobin level of ≥11 g/dL, and with at least one year of follow-up data. Patients were excluded if they underwent bilateral or revision TKA, had active infections, hematological disorders such as coagulopathies, or significant cardiovascular complications. The study was conducted by the principles outlined in the Declaration of Helsinki.

To ensure the reliability of the results, potential confounding factors were minimized by excluding patients with known coagulopathies, hematological disorders, or significant cardiovascular diseases, as these conditions were part of the exclusion criteria. However, minor comorbidities not meeting exclusion thresholds, such as controlled hypertension or type 2 diabetes mellitus, were documented and adjusted for during data analysis when necessary. Anticoagulants or antiplatelet medications were discontinued at least seven days before surgery, as per institutional protocols, and patients with deviations from these protocols were excluded.

A retrospective investigation was conducted to examine the impact of various administration methods of TXA (double dose IV administration or double dose IA administration) on bleeding in 96 patients who underwent unilateral primary TKA for gonarthrosis between 2021 and 2022. Preoperative haemoglobin (Hb) levels, postoperative Hb levels (postoperative 8th hour, 24th hour, and 72nd hour), need for blood transfusion, and length of hospital stay (LOS) were compared among each other and with patients who did not receive TXA. The IV administration of TXA was conducted as a gradual infusion 30 minutes before the surgical procedure.

The dosage of the application was established at 15 mg/kg TXA. A duplicate dosage of TXA was administered 15 minutes before the release of the tourniquet. In IA administration, following the closure of the arthrotomy, a dosage of 30 mg/kg of TXA (double dose) was administered into the joint after diluting it with 10 ml of saline. This entire volume was carefully injected into the joint space after ensuring the injection did not exceed the joint's maximum injectable capacity. The technique was standardized to maintain consistency across patients.

The same surgeons performed the surgical procedures, utilizing tourniquets and haemovac drains. The haemovac drains remained closed for 2 hours during the postoperative phase. Subsequently, the drains were opened, and the bleeding volume was observed for 24 hours. The drains were removed 24 hours after the surgery. Each patient received a standard surgical procedure, including a midline incision, medial parapatellar arthrotomy, and unilateral TKA. The criterion for blood transfusion was a postoperative Hb level <8 g/dL. All patients were monitored for one year after the surgery to detect potential complications. Patients were monitored for thromboembolic complications for one year postoperatively. In cases where clinical findings raised suspicion of deep vein thrombosis (DVT) or pulmonary embolism (PE), Doppler ultrasonography and computed tomography angiography (CTA) were performed to confirm the diagnosis. Routine follow-ups included clinical evaluations at 1, 6, and 12 months, during which patients were assessed for symptoms such as leg swelling, pain, or shortness of breath, which could indicate potential thromboembolic events.

Statistics

The statistical analyses in the study were conducted using the IBM Statistical Package for Social Sciences (SPSS) program version 22 (IBM Corp., Armonk, NY, USA). An assessment was conducted to determine the conformity of the parameters to a normal distribution using the Shapiro-Wilks test. Descriptive statistical methods were employed, such as mean, standard deviation, and frequency. The Student t-test was used to compare two groups for parameters with a normal distribution, while the Mann-Whitney U test was employed for parameters without a normal distribution. The Wilcoxon Signed Ranks test was employed to compare parameters within the same group that did not exhibit a normal distribution. The Fisher-Freeman-Halton test was used to compare qualitative data. The significance level was assessed at $p < 0.05$.

Table 1. *Patient characteristics and postoperative data*

		Min-Max	Mean ± SD
Age		52–81	66.44±4.03
Blood collected in the drain (cc)		300–1200	512.5±212, 88 (400)
Length of stay		3–6	3.78±0.67 (4)
		n	%
Gender	Female	80	83.3
	Male	16	16.7
Tranexamic acid use	Absent	18	18.8
	Intraarticular	26	27.1
	Intravenous	52	54.2
Transfusion requirement	Yes	12	12.5
	No	84	87.5

Table 2. *Haemoglobin levels in the general participants*

Haemoglobin	Min-Max	Mean ± SD (median)
Preoperative	10–16	12.41±1.25 (13)
Postoperative 8th hour	9–14	10.65±1.13 (11)
Postoperative 24th hour	8–12	9.49±1.11 (9)
Postoperative 72nd hour	6–12	9±1.15 (9)

Results

The patients' ages varied from 52 to 81 years, averaging 66.44±4.03. The majority of the patients (83.3%) were female, while the remaining 16.7% were male. Out of the total of 96 patients, a double dosage of IV TXA was administered to 52 patients, a double dose of IA TXA was administered to 26 patients, and no TXA was administered to 18 patients. The mean amount of time for LOS was estimated to be 3.78±0.67 days. No instances of DVT or PE were found in any patient. 12.5% of patients needed blood transfusions, whereas 87.5% did not necessitate them (Table 1).

The average Hb assessments of the patients before the surgery and 72 hours after the surgery are shown in Table 2. Upon analyzing the Hb values based on the administration of TXA, there was no notable disparity between the groups at the 8th hour after surgery. However, at the 24th and 72nd hours after surgery, the Hb values of patients who were not administered TXA were considerably lower than those who were administered TXA ($p<0.05$). No significant differences were

Table 3. *Parameters that vary according on tranexamic acid's usage or administration method*

	Tranexamic acid use			
	Absent	Intraarticular	Intravenous	p
	(Min-Max)-(Mean ± SD)	(Min-Max)-(Mean ± SD)	(Min-Max)-(Mean ± SD)	
Age	(61–73)-(65.67±2, 83)	(52–81)-(66.85±5, 11)	(60–79)-(66.5±3, 8)	[1]0.630
Blood collected in the drain (cc)	(400–1200)-(677.78±315.4 (500))	(300–1000)-(476.92±181.79 (400))	(400–1000)-(473.08±152.26 (400))	[3]0.015*
Length of stay	(4–6)-(4.44±0.62 (4))	(3–5)-(3.69±0.62 (4))	(3–5)-(3.6±0.57 (4))	[3]0.000*
Preoperative	(10–16)-(12.5±1.69 (13))	(10–15)-(12.38±1.13 (12))	(10–15)-(12.38±1.14 (13))	0.948
Post-operative 8th hour	(9–14)-(10.5±1.54 (10))	(9–13)-(10.58±1.14 (10))	(9–13)-(10.73±0.97 (11))	0.403
Post-operative 24th hour	(8–11)-(8.67±1.14 (8))	(8–12)-(9.62±1.2 (9))	(8–11)-(9.71±0.94 (10))	0.001[3]
Post-operative 72nd hour	(6–9)-(7.67±0.91 (8))	(7–12)-(9.19±1.27 (9))	(7–11)-(9.37±0.79 (9))	0.000[3]
Preoperative-postoperative 8th hour p[4]	0.000*	0.000*	0.000*	
Preoperative-postoperative 24th hour p[4]	0.000*	0.000*	0.000*	
Preoperative-postoperative 72nd hour p[4]	0.000*	0.000*	0.000*	
	n (%)	n (%)	n (%)	
Gender				
Female	15 (83%, 3)	21 (80%, 8)	44 (84%, 6)	[1 2]0.932
Male	3 (16%, 7)	5 (19%, 2)	8 (15%, 4)	
Transfusion requirement				
Yes	7 (38%, 9)	4 (15%, 4)	1 (1%, 9)	-
No	11 (61%, 1)	22 (84%, 6)	51 (98%, 1)	

[1]Student t Test; [2]Fisher Freeman Halton Test; [3]Mann-Whitney U Test; [4]Wilcoxon Sign Test; *p<0.05
The number of intravenous tranexamic acid administrations in those who required transfusion was not suitable for statistical comparison due to being only 1.

observed between IV and IA applications when comparing them in various periods (p>0.05) (Table 3).

The amount of blood extracted from the haemovac drain in patients who did not receive TXA was considerably greater than that of patients who received IA and IV TXA (p1:0.021; p2:0.031; p<0.05). The current study found no significant difference in the quantity of blood extracted from the haemovac drain between patients who had IA and IV TXA doses (p>0.05) (Table 3).

The LOS values of those who did not receive TXA were shown to be considerably greater than those who received IA and IV TXA (p1:0.002; p2:0.000; p<0.05). The LOS values did not show any statistically significant difference between patients who received IA and IV TXA treatments (p>0.05) (Table 3).

Upon analyzing the need for transfusion among the different groups, it was shown that only 1 out of 52 patients who received IV TXA needed a transfusion, whereas 4 out of 26 patients who received IA TXA required a transfusion, and 7 out of 18 patients who were not administered TXA needed a transfusion (Table 3). Statistical analysis was not possible due to the small sample size of one patient needing transfusion in the IV TXA group.

Discussion

The study's key discovery was that using IV or IA double-dose TXA, in conjunction with postoperative DC, effectively decreased postoperative bleeding at comparable rates. Furthermore, when assessing the need for blood transfusion during the postoperative period, it was noticed that the administration of double-dose IV TXA resulted in the lowest transfusion rates. Although a statistical analysis could not be conducted, this finding suggests a potential benefit of double-dose IV TXA in reducing the need for transfusion. Both applications demonstrated high safety and efficacy in terms of complications and overall safety.

A substantial body of literature supports the use of IV TXA in TKA. In a study conducted by Akgül et al.[12],

it was found that administering 20 mg/kg of IV TXA before the skin incision within primary TKA resulted in a significant decrease in total blood loss and reduced drainage volume, as in line with the current study. In a retrospective study conducted by Pitta et al.[7], involving 610 patients over 4 years, it was observed that the IV administration of TXA led to a notable reduction of 9.4% in blood loss during TKA. However, no significant difference was observed in the incidence of DVT between the TXA and the control groups. Topical delivery of TXA has gained increasing attention as a means to avoid bleeding, particularly when compared to the safety issues associated with IV administration. With a systemic absorption rate of less than 70%, it is a potential option for systemic use. In a randomized controlled study by Ishida et al.[13], a group of patients undergoing TKA were injected with 2000 mg/20 mL of topical TXA, while another group received a placebo. The results showed a significant reduction in postoperative Hb levels in the TXA group compared to the control group, similar to the findings in the present study.

Several studies have shown the use of varying dosages of TXA during the perioperative phase of TKA to achieve improved outcomes[14–16]. The Mohammad meta-analysis[17] found that administering high doses of IV TXA (≥2 g or ≥30 mg/kg as a single push) resulted in decreased transfusion needs in comparison with standard doses (≤1 g TXA), as in line with the current study. However, the impact on thromboembolic complications and mortality remained unclear. A study conducted by A. Fígar et al.[18] revealed that administering one single injection (1 g) of IV TXA effectively decreased the need for transfusion following total hip arthroplasty while maintaining a low incidence of adverse events. In a study conducted by Kang et al.[19], it was shown that administering three doses (3 g) of IV TXA following TKA in older patients resulted in lower blood loss, less postoperative inflammation, and fewer fibrinolytic responses compared to a single dosage (1 g) or two doses (2 g). Importantly, this treatment approach did not lead to increased adverse events. A recently published randomized controlled trial demonstrated that the single-dose schedule was as effective as the two-dose strategy[20]. Based on the findings of a meta-analysis performed in 2023[21], it was concluded that the blood transfusion rate did not differ significantly between the single-dose and double-dose TXA groups. Within the existing literature, there is a noticeable lack of reference to the various modalities of administration (IV or IA) of high-dose (double-dose) TXA despite several cases comparing different TXA dosages. The current investigation examined different ways of administering high-dose TXA (IV or IA) to address this research gap. The current study determined that the double IV dose of TXA was the most effective approach to reducing transfusion rates.

Several recent studies have compared the effectiveness of combining DC with TXA administration for controlling bleeding after TKA. Chareancholvanich et al.[22] discovered that the combination of DC and TXA administration resulted in a substantial decrease in postoperative bleeding and blood transfusion following TKA, compared to utilizing TXA or DC individually, as in line with the current study. In theory, DC may provide transient hemostasis by providing a tamponade impact in the joint, reducing blood loss and decreasing the need for transfusion[23]. In addition, Sangasoongsong et al.[24] discovered that using a relatively low dosage of TXA in conjunction with a 2-hour DC technique successfully decreased postoperative bleeding and the need for transfusions in traditional TKA. The current research examines several administration techniques for a double dosage of TXA combined with a 2-hour DC technique. Consequently, significant enhancements were observed in postoperative bleeding and transfusion rates, which aligns with the existing literature.

The LOS is a significant factor in determining the overall expenses associated with TKA surgery. According to a meta analyse[21], administering a double-dose of TXA may decrease the LOS following joint arthroplasty[25–27]. Nevertheless, only three studies in the meta-analysis documented LOS, rendering the aggregated data somewhat contentious. Additional research is required to validate these findings. Moreover, the aggregated findings indicated no substantial difference in the LOS between those receiving double doses and those receiving single doses[21]. In the current investigation, we observed that the administration of double dosage TXA with postoperative DC greatly reduced the LOS time, according to the literature. Furthermore, as a contribution to the existing body of research, we found that the LOS remained similar regardless of whether the double dosage of TXA was administered IV or IA.

Limitations and Strengths

The data presented in this study are limited, as is common for any research conducted using a retrospective data review. First, the data was not collected systematically or prospectively. Second, all the subjects included

in the research were exclusively managed at a single facility in Türkiye. Third, the absence of a comprehensive long-term follow-up may result in underestimating potential complications. Fourth, the analysis did not consider the cost burden of using double-dose TXA. A significant limitation of the study is the failure to compare the additional cost associated with double-dose TXA with the potential cost savings resulting from reduced LOS. As a result, a comprehensive conclusion could not be drawn.

Moreover, using a specific criterion, such as a Hb value below 8 g/dL, as a transfusion threshold, it is evident that this current research may provide varying interpretations on transfusion rates compared to other publications available in the field that use different criteria. This study focused solely on evaluating double-dose TXA via intravenous and intraarticular routes without direct comparison to single-dose TXA. This design choice limits the generalizability of our findings regarding dose-specific efficacy. Future studies with larger sample sizes and direct comparisons between single- and double-dose regimens are warranted to validate and expand upon these results. Also, the study employed a 2-hour drain clamping duration, which differs from the 3-hour duration used in some previous studies, such as Chareancholvanich et al. This discrepancy in timing was based on institutional protocols and surgeon preference. However, the potential impact of different clamping durations on outcomes was not systematically investigated, representing a limitation of this study. The study's relatively small sample size limited the ability to perform robust statistical analyses for transfusion rates, particularly in subgroup comparisons. This limitation reduces the generalizability and statistical power of the findings related to transfusion requirements. The study's most influential conclusion is that administering high-dose (double-dose) TXA, either IV or IA, in conjunction with postoperative DC has beneficial effects on postoperative bleeding and the need for transfusions. This work addresses the existing knowledge gap in the literature by investigating several methods for administering a double dosage of TXA using the postoperative DC approach.

Conclusion

The study found that utilizing IV or IA double dosage TXA and postoperative DC significantly reduced postoperative bleeding at similar rates. In addition, during the evaluation of blood transfusion requirements in the postoperative period, it was observed that a double dose of IV TXA led to the lowest transfusion rates. This finding indicates a potential advantage of using a double dose of IV TXA to decrease the requirement for transfusion. Both applications showcased exceptional safety and efficacy, with no complications and a strong focus on overall safety.

Conflicts of Interest

The authors have no conflicts of interest to declare relevant to this article's content.

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Ethics Approval

The study was approved by the local institutional ethical review board of the local ethics committee (Firat University Ethics Committee) (approval date: 13/02/2024, approval number: 2024/03–75).

Informed Consent

Informed consent was obtained from all participants included in the study.

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