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Original Article

Effects of single high dose topical tranexamic acid administration on bleeding and complications after total knee arthroplasty surgery:A retrospective clinical study

Tek seferlik yüksek doz topikal traneksamik asit uygulamasının total diz artroplastisi sonrası kanama ve komplikasyonlar üzerine etkisi: Retrospektif klinik çalışma

Ekin Kaya SİMSEK[1], Bahtiyar HABERAL*[2]

[1] Beypazarı State Hospital, Department of Orthopaedics and Traumatology, Ankara/TURKEY

[2] Baskent University Faculty of Medicine, Department of Orthopaedics and Traumatology, Ankara/TURKEY

Abstract

Aim: There is no consensus on the optimal method of Tranexamic acid (TA) usage in orthopaedic surgery in the literature. The aim of this study is to evaluate the effects of single high dose (3g) topical TA application on postoperative bleeding and complications in total knee arthroplasty (TKA) surgery.

Material and Methods: We retrospectively evaluated patients who underwent TKA in our clinic between January 2016 and June 2018. The patients were divided into two groups according to TA administration: Group 1 (topical TA, n=105/242) and Group 2 (non-TA, n=137/242). Demographic parameters, comorbidities, high-risk factors, preoperative hemoglobin (Hb) level, lowest postoperative Hb level, change in Hb, total drainage output, presence or absence of a transfusion, amount of blood transfused, length of stay, and complications were evaluated.

Results: In group 1, postoperative first- and second-day Hb levels were significantly higher than those in group 2. The blood loss on the day of surgery, the blood loss on the first postoperative day and total drain blood loss were significantly lower in group 1. It was determined that the patients in group 2 needed significantly more blood transfusions and had more length of hospital stay. There was no statistical difference in complications between the two groups.

Conclusion: Topical TA application effectively and significantly reduces blood loss and transfusion rates after surgery, without serious side effects, in patients undergoing primary TKA. This also reduces the length of the hospital stay.

Keywords: Total knee arthroplasty; tranexamic acid; blood loss; transfusion; complication

Corresponding author*: Bahtiyar Haberal, Baskent University Faculty of Medicine, Department of Orthopaedics and Traumatology, Ankara/TURKEY
E-mail: bahtiyarhaberal@hotmail.com
ORCID: 0000-0002-1668-6997
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Öz

Amaç: Literatürde ortopedik cerrahide Traneksamik asit (TA) kullanımının optimal yöntemi konusunda fikir birliği yoktur. Bu çalışmanın amacı, total diz artroplastisi (TDA) cerrahisinde tek yüksek doz (3g) topikal TA uygulamasının postoperatif kanama ve komplikasyonlar üzerine etkilerini değerlendirmektir.

Gereç ve Yöntemler: Ocak 2016 - Haziran 2018 tarihleri arasında kliniğimizde TDA uygulanan hastalar retrospektif olarak değerlendirildi. Hastalar TA uygulamasına göre iki gruba ayrıldı: Grup 1 (topikal TA, n = 105/242) ve Grup 2 (TA olmayan, n = 137/242). Demografik parametreler, komorbiditeler, yüksek risk faktörleri, preoperatif hemoglobin (Hb) düzeyi, postoperatif en düşük Hb düzeyi, Hb'deki toplam değişiklik, toplam dren çıkışı, transfüzyon varlığı veya yokluğu, transfüzyon yapılan kan miktarı, hastanede kalış süresi ve komplikasyonlar değerlendirildi.

Bulgular: Grup 1'de postoperatif birinci ve ikinci gün Hb seviyeleri grup 2'ye göre anlamlı olarak yüksekti. Grup 1'de ameliyat günü kan kaybı, ameliyat sonrası ilk gün kan kaybı ve toplam dren kan kaybı anlamlı olarak daha düşüktü. Grup 2'deki hastaların anlamlı olarak daha fazla kan transfüzyonuna ihtiyaç duydukları ve hastanede kalış sürelerinin daha uzun olduğu belirlendi. İki grup arasındaki komplikasyonlarda istatistiksel olarak anlamlı fark saptanmadı.

Sonuç: Bu çalışmada, TA'nın yara kapatıldıktan sonra diz eklemine topikal uygulaması; primer TDA yapılan hastalarda tromboembolik riskte bir artış yaratmadan, postoperatif Hb kaybını ve kan kaybını önemli ölçüde azaltmıştır. Bu durum hastanede kalış süresini de azaltmaktadır.

Anahtar kelimeler: Total diz artroplastisi; traneksamik asit; kan kaybı; transfüzyon; komplikasyon

Introduction

Osteoarthritis (OA), also known as degenerative joint disease, is a cartilage disease characterised by the progressive loss of the structure and function of articular cartilage, where the synovial joints are involved. The treatment of OA is multifaceted and includes patient education, lifestyle changes, rehabilitation, painkillers, intra-articular injections, needle lavage, and surgical treatment. Total knee arthroplasty (TKA) is the most common method in the surgical treatment of OA in orthopaedic practice.[1]

Trauma during TKA surgery triggers the coagulation cascade and local fibrinolysis. The deflating of the tourniquet, which is used to prevent bleeding during surgery, increases the fibrinolysis and increases the bleeding. Thus, bleeding can increase after surgery, and 10-38% of patients require a blood transfusion. The average blood loss per patient can be 1,450-2,000 ml.[2]

Anaemia causes hypovolemic shock, renal failure, cardiac problems, and wound healing problems. Complications, such as allergic reactions, bacterial/viral infections, transfusion-related acute lung injury, blood type incompatibility, hemolysis, and impaired metabolic balance due to blood transfusion for the treatment of acute anaemia, significantly increase mortality and morbidity. Medical expenses also increase as a result of blood transfusion and prolonged hospital stay, which is caused by these morbidities. For this reason, in the literature, the number of studies has been increasing recently to find ways to minimise blood loss and the need for blood transfusion.[3]

Tranexamic acid (TA), a synthetic anti-fibrinolytic agent, prevents fibrinolysis by blocking plasmin formation from plasminogen. The clot becomes stabilised due to reduced numbers of fibrin monomers and decreasing fibrinogen degradation.[4] Although TA has been used in cardiothoracic surgery, gynecologic bleeding and acute trauma for more than 40 years, its use in orthopaedic surgery has become widespread only in recent years. TA has intravenous, oral, and topical administration routes.[5] In the literature, it is reported that TA, which is applied after TKA, decreases the bleeding significantly without increasing the thromboembolic risk. However, patients with a history of renal failure, thromboembolic disorder, previous stroke, myocardial infarction, deep vein thrombosis, or pulmonary embolism are considered to be at high risk, and intravenous administration is considered to be contraindicated. Topical TA application is an alternative in these patients.[6] Although many studies have compared the efficacy of intravenous and topical administration of TA, there is no consensus on the optimal method of administration in the literature.

The purpose of this study is to evaluate the effects of single high dose topical TA application on postoperative bleeding and identify possible complications in healthy and high-risk patients.

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Material and Methods

Topical TA has been routinely applied with TKA in our clinic since 2017. Patients who underwent TKA in our clinic between January 2016 and June 2018 were retrospectively analysed. After exclusion of revision arthroplasties, unicompartmental knee replacements, oncological cases, traumas, patients with anticoagulant allergies, and patients with previous knee surgeries and hardware removal, 242 of the 266 patients were included in the study (Table 1). Data were collected from patients' electronic medical records. Demographic parameters (age, sex, and side of the surgery), comorbidities (e.g., hypertension, diabetes mellitus, arrhythmia, and coronary artery disease), high-risk factors (chronic heart failure, venous thromboembolism, stroke, myocardial infarction, deep vein thrombosis, and pulmonary embolism), preoperative hemoglobin (Hb) level, lowest postoperative Hb level, change in Hb, total drainage output, presence or absence of a transfusion, amount of blood transfused, length of stay, and complications (e.g., wound healing problems, effusion, and infections) were evaluated. This study was approved by our Institutional Review Board (Project no.KA18/355). Informed consent was obtained from all patients and the principles of the Helsinki Declaration were followed.

The patients were divided into two groups according to TA administration: Group 1 (topical TA, n=105/242) and Group 2 (non-TA,n=137/242).Both groups were compared statistically.

All patients received TKA surgery after standard pre-operative preparation and under regional spinal/epidural anaesthesia. A prophylactic antibiotic regime was given perioperatively with intravenous injection of cefazoline sodium (1 gr) (Cezol; Deva Holding AŞ, İstanbul, Turkey) 30 minutes before tourniquet inflation and every 8 hours afterward until the suction drain was removed. During surgery, patients were in a supine position with a tourniquet on the thigh. All the surgeries were performed by the medial parapatellar approach using two different cemented knee prostheses:(1) Scorpio+ single-axis system posterior stabilized, Stryker Howmedica Osteonics, Allendale, NJ, and (2) Sigma Primary Knee System posterior stabilized, DePuy Synthes Inc., Warsaw, IN. After all components were cemented in place,the tourniquet was deflated. Following bleeding control, the joint was irrigated with normal saline and suctioned out. Intra-articular suction drains were routinely applied. Then the wound was closed, and, for group 1 (topical TA), 3g of TA was applied via the suction drain without any dilution with saline. The negative suction drain was clamped for 30 minutes to obtain the full effect of topical TA application and then opened in group 1. The same procedure was applied to Group 2 without TA administration. Total drain output, haemoglobin, and hematocrit levels were recorded daily postoperatively. The criteria for blood transfusion were a haemoglobin concentration of <8 g/dl or a haemoglobin level of <10 g/dl if the patient had any signs of anaemia (e.g., unexplained tachycardia or hypotension unresponsive to fluid replacement). For every 1g/dl of haemoglobin drip, one unit of packed red cells (330 ml) was transfused. Enoxaparin sodium (40mg) (Oksapar; Koçak Farma İlaç ve Kimya Sanayi, İstanbul, Turkey) and deep vein thrombosis stockings were used during the hospital stay for coagulation prophylaxis. After discharge, coagulation prophylaxis was provided with oral rivaroxaban (10 mg) (Xarelto; Bayer AG, Leverkusen, Germany) therapy for 21 days. Isometric exercises, passive, and active mobilization exercises with full weight-bearing were started immediately after surgery. Sutures were removed at 2 weeks postoperatively. Patients were examined daily during hospitalization and examined every 15 days after discharge for any complications.

The data were analyzed using SPSS Statistics for Windows Version 25.0 (released in 2017, IBM Corp., Armonk, NY). Continuous variables were represented by numbers and percentages; continuous variables were presented with their mean and SD values. To compare categorical and continuous variables between groups,the Chi-square test and independent samples t-test were used,respectively. The statistical significance was set at $p<0,05$.

Results

Demographics

A total of 242 patient results were evaluated. Table 1 shows the demographic characteristics of the patients. There were no statistically significant differences in demographics.

Hemoglobin levels and blood loss

The preoperative Hb levels of the patients was 13,04 ± 1,15 mg/dl (mean ± SD) in group 1 and 13,23 ± 1,42 mg/dl in group 2. Hemoglobin levels were recorded postoperatively on the day of surgery and for the following 3 days. In group 1, postoperative first- and second-day Hb levels were significantly higher than those in group 2 ($p<0,001$). The difference between the highest and lowest Hb values obtained after surgery was termed as the maximum Hb decrease and it was significantly higher in group

2 (3,33 ± 0,90 mg/dl) than group 1(3,89 ± 1,19 mg/dl) (p<0,001). When the records of the amount of blood loss through the drain were examined, it was determined that both the blood loss on the day of surgery (p<0,001), the blood loss on the first postoperative day (p=0,033) and total drain blood loss (p<0,001) were significantly lower in group 1(Table 2).

Table 1: Demographic Characteristics of the Study Population

Variables*	Group 1 [N(%)]	Group 2 [N(%)]
Sex		
• Female	94 (%89.5)	110 (%80.3)
• Male	11 (%10.5)	27(%19.7)
Co-Morbidities		
• Arrhythmia	16 (%15.2)	13 (%9.5)
• DM	24 (%22.9)	48 (%35)
• HT	81 (%77.1)	105 (%76.6)
• CHD	19 (%18.1)	17 (%12.4)
High Risk Factors		
• CRF	4 (%3.8)	2 (%1.5)
• DVT	0 (%0.0)	2 (%1.5)
• MI	2 (%1.9)	3 (%2.2)
Side		
• Right	58 (%55.2)	75 (%54.7)
• Left	47 (%44.8)	59 (%43.1)
• Bilateral	0 (%0.0)	3 (%2.2)
Complications		
• WHP	2 (%1.9)	3 (%2.2)
• Effusion	3 (%2.9)	6 (%4.4)
• Pneumonia	1 (%1.0)	2 (%1.5)
• Amputation	0 (%0.0)	1 (%0.7)

*DM=Diabetes Mellitus, HT=Hypertension, CHD=Coronary Heart Disease, CRF=Chronic Renal Failure, DVT=Deep Vein Thrombosis, MI=Myocardial Infarction, WHP=Wound Healing Problems

Blood Transfusion

A total of 46 units of erythrocyte suspension (ES) were given to 30 of 105 patients (28,5%) in group 1, and 82 of 137 patients (59,8%) in group 2 received 186 units of ES (Table3).When the number of blood transfusions was evaluated statistically, it was determined that the patients in group 2 needed significantly more blood transfusions (p<0,001). When the average cost of the ES to the social security system was calculated, it was determined that the application of tranexamic acid lowered the cost of blood products for the patients included in this study by approximately 5,600 USD (Table 3).

Hospital Stay

Patients in group 1 had a mean hospital stay of 4,94 days compared with 5,27 days for patients in group 2, and there were statistically significant differences between the two groups (p=0,034) (Table 2).

Table 2: Comparison of Outcomes

	Group 1 (Mean ± SD)	Group 2 (Mean ± SD)	P* Value
Age	72,21 ± 7,41	69,96 ± 7,63	0.022
Pre-op. Hemoglobin (mg/dl)	13,04 ± 1,15	13,23 ± 1,42	0.269
Postop. Hemoglobin 0 (mg/dl)	11,5 ± 1,34	11,45 ± 1,41	0.785
Postop. Hemoglobin 1 (mg/dl)	10,84 ± 1,23	10,24 ± 1,07	<0.001
Postop. Hemoglobin 2 (mg/dl)	10,41 ± 1,11	9,97 ± 1,01	<0.001
Postop. Hemoglobin 3 (mg/dl)	10,31 ± 0,93	10,11 ± 0,87	0.088
Postop. Hemoglobin 4 (mg/dl)	10,36 ± 0,86	10,42 ± 1,01	0.678
Max. Hemoglobin decrease (mg/dl)	3,33 ± 0,90	3,89 ± 1,19	<0.001
Postop. 0 Drain Blood Loss (ml)	245,19 ± 149,42	786,53 ± 444,56	<0.001
Postop. 1 Drain Blood Loss (ml)	178,16 ± 84,53	212,57 ± 159,74	0.033
Total Drain Blood Loss (ml)	423,35 ± 193,92	997,91 ± 516,45	<0.001
Transfusion (number)	0,44 ± 0,74	1,36 ± 1,58	<0.001
Length of Stay (Day)	4,94 ± 0,86	5,27 ± 1,51	0.034

*p<0.05 was statistically different

Table 3: Transfusion Data and approximate costs

	TNP	NPUBT	NES (Unit)	Approximate Costs (USD)
Group 1 (TXA+)	105	30	46	1800
Group 2 (TXA-)	137	82	186	7500
Total	242	112	232	9300

TNP: Total Number of patients, NPUT: Number of patients undergoing blood transfusion, NES: Number of ES

Complications

There were 6 complications in group 1 (2 wound healing problems, 3 cases of articular effusion, and 1 case of pneumonia) and 12 in group 2 (3 wound healing problems, 6 cases of articular effusion, 2 cases of pneumonia, and 1 acute arterial thrombosis of the lower extremity resulting in amputation) (Table 1). No coagulation-related complications were found in any patient included in the study. There was no statistical difference in complications between the two groups.

Discussion

In our clinic, as indicated in the literature, a topical administration is preferred to minimize systemic absorption

of TA and thus prevent thromboembolic side effects.[6,7] In previous studies, both low-dose (500 mg) and high-dose (3 g) TA administration has been shown to be effective in reducing blood loss after surgery.[8,9] Recent studies have shown that high-dose topical TA administration is more effective.[4,10] For this reason, we preferred high-dose TA application in our clinical practice.

In this study, topical administration of TA via suction drain to the knee joint after wound closure significantly reduced post-operative Hb loss and blood loss in patients having a primary TKA. In the topical TA group, Hb values were significantly higher than in the non-TA group on the first and second post-operative days, which is consistent with reports in the literature [11,12]. However, no significant difference was found between the post-operative Hb values obtained on the day of surgery. Hemodilution due to intravenous fluid and drug administration, which is applied more intensively during and soon after surgery, may cause this result. Similar to the results obtained in previous studies, the blood loss through the drain on the day of surgery and the first post-operative day and the total drain blood loss in the topical TA group were significantly lower than in the non-TA group.[4,13] After primary TKA surgery, bolus blood loss occurs due to tourniquet use.[14] In the topical TA group, both TA administration and closure of the suction drain for 30 minutes after application may prevent bolus blood loss and result in decreased total drain output.

Previous studies have shown that intravenous TA protocols, both during and after surgery [11, 14, 15] and topical TA applications, including periarticular injections.[5, 9, 16] reduce blood transfusion rates compared with a placebo after primary TKA surgery. However, in the studies, different topical doses of TA (1g, 1,5g, 2g, and 3g) were not superior to each other.[4, 9, 10] In this study, 3g of TA was applied topically and there was a statistically significant decrease in blood transfusion rates compared with the non-TA group, which isconsistent with reports in the literature.

TA application reduces blood loss after surgery and affects the recovery period both locally and systemically. Decreased intra-articular hemorrhage reduces hematoma formation and joint swelling, and thus fewer wound healing problems occur. This increases compliance with isometric exercises and passive and active mobilization exercises, and generally accelerates mobilization. Consequently, local complications that prevent mobilization, such as joint contracture, are avoided. When systemic effects are evaluated, decreasing blood loss reduces the incidence of postoperative anemia and thus prevents anemia-related symptoms that reduce early mobilization, such as dizziness, shortness of breath, and fatigue. As a result of these effects, as shown in our study, the duration of hospital stay was significantly reduced in patients treated with TA.

Previous studies in the literature have shown that topical TA can be used safely even in patients with high thromboembolic risk. Abdel et al. compared the effects of topical and intravenous TAadministration after primary TKA and found thromboembolic disorder in 2 of 320 patient (0,6 %).[13] Wong et al. examined the effect of topical TA application on blood loss after surgery and reported thromboembolic disorder in 3 of 31 patients treated with 1,5g of TA and 1 of 33 patients treated with 3g of TA. They observed thromboembolic disorder in 2 of 35 placebo patients and reported that there was no statistically significant difference between the groups. [9] We encountered thromboembolic disorder in only 1 of the 242 patients included in our study, and this patient was in group 2 (non-TA group). In addition, we did not find any statistically significant difference between the groups when all the complications were evaluated.

The present study had several limitations. First, our study is a retrospective study and no power analysis was performed to determine the size of the study population. Second, in our clinic, we only administer a single high dose (3g) of topical TA after primary TKA. Therefore, we could not compare the results to other reported results using different administration procedures. Third, our data reflect short-term results and therefore we could not evaluate the effects of TA application in the long-term follow-up period.

Conclusions

In conclusion,our clinical practice and results support that topical TA application effectively and significantly reduces blood loss and transfusion rates after surgery,without serious side effects, in patients undergoing primary TKA. This reduces the length of the hospital stay.In addition, further studies are needed to determine the optimal dose range and route of administration of TA and thus establish “gold standard” treatment protocols.

Declaration of conflict of interest

The authors received no financial support for the research and/or authorship of this article. There is no conflict of interest.

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