doi: 10.53446/actamednicomedia.1146576

Acta Medica Nicomedia

Cilt: 5 Sayı: 3 Ekim 2022 / Vol: 5 Issue: 3 October 2022
https://dergipark.org.tr/tr/pub/actamednicomedia

Research Article | Araştırma Makalesi

PERIARTICULAR INJECTION OF RANAWAT SUSPENSION IN COMBINATION WITH TRANEXAMIC ACID REDUCES BLEEDING AND POSTOPERATIVE PAIN IN TOTAL KNEE ARTHROPLASTY

RANAWAT SÜSPANSİYONUNUN TRANEKSAMİK ASİT İLE KOMBİNE PERİARTİKÜLER ENJEKSİYONU TOTAL DİZ ARTROPLASTİSİNDE KANAMA VE AMELİYAT SONRASI AĞRIYI AZALTABİLİR

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ABSTRACT

Objective: The benefits of periarticular injections of local anesthetic agents or tranexamic acid have been previously evaluated in terms of their effects on postoperative pain in a number of orthopedic studies. However, data is lacking on the efficacy of local anesthetic and tranexamic acid combinations that may be used for this purpose. We aimed to investigate the effects of periarticular injection of both tranexamic acid and Ranawat suspension on postoperative pain and bleeding in patients undergoing total knee arthroplasty.

Methods: A total of 124 patients who underwent total knee arthroplasty were consecutively enrolled in this study. Patients were divided into two groups: those receiving the periarticular injection of a cocktail containing the combination of Ranawat suspension and Tranexamic acid and those receiving no injections. Postoperative pain, postoperative tramadol requirement and blood loss were compared between groups.

Results: Hemoglobin and hematocrit levels were significantly higher at third day postoperatively in recipients of periarticular Ranawat suspension and tranexamic acid combination (p=0.044 and p=0.047, respectively). In addition, the amount of drainage blood loss (p<0.001) and need for blood transfusions (p=0.009) were significantly higher in patients receiving no periarticular injections. Moreover, analgesic requirements were also significantly lower during the first 72 hours in recipients of periarticular injections compared to those receiving no injections.

Conclusion: Periarticular injection of a cocktail containing the combination of Ranawat suspension and tranexamic acid in patients undergoing total knee arthroplasty is effective in reducing blood loss, pain and additional analgesic requirement, without causing an increase in major complications.

Keywords: Ranawat suspension, tranexamic acid, postoperative pain, blood transfusion, postoperative analgesia

ÖZ

Amaç: Lokal anestezik ajanların veya traneksamik asidin periartiküler enjeksiyonlarının faydaları daha önce birçok ortopedik çalışmada postoperatif ağrı üzerindeki etkileri açısından değerlendirilmiştir. Ancak bu amaçla kullanılabilecek lokal anestezik ve traneksamik asit kombine kullanımının etkinliğine ilişkin veriler henüz ortaya koyulmamıştır. Bu çalışmada total diz artroplastisi uygulanan hastalarda hem traneksamik asit hem de Ranawat süspansiyonunun periartiküler enjeksiyonunun postoperatif ağrı ve kanama üzerine etkilerini araştırmayı amaçladık.

Yöntem: Bu çalışmaya total diz artroplastisi uygulanan toplam 124 hasta dahil edildi. Hastalar iki gruba ayrıldı: Ranawat süspansiyonu ve Traneksamik asit kombinasyonunu içeren bir kokteylin periartiküler enjeksiyonunu alanlar ve enjeksiyon yapılmayanlar. Gruplar arasında ameliyat sonrası ağrı, ameliyat sonrası tramadol ihtiyacı ve kan kaybı karşılaştırıldı.

Bulgular: Periartiküler Ranawat süspansiyonu ve traneksamik asit kombinasyonu uygulanlarda postoperatif üçüncü günde hemoglobin ve hematokrit seviyeleri anlamlı olarak yüksekti (sırasıyla p=0,044 ve p=0,047). Ayrıca periartiküler enjeksiyon yapılmayan hastalarda drenaj kan kaybı miktarı (p<0,001) ve kan transfüzyonu ihtiyacı (p=0,009) anlamlı olarak daha yüksekti. Ayrıca, periartiküler enjeksiyon alan hastalarda, enjeksiyon yapılmayanlara kıyasla ilk 72 saat içinde analjezik gereksinimleri de önemli ölçüde daha düşüktü.

Sonuç: Total diz artroplastisi uygulanan hastalarda Ranawat süspansiyonu ve traneksamik asit kombinasyonunu içeren bir kokteylin periartiküler enjeksiyonu majör komplikasyonlarda artışa neden olmadan kan kaybı, ağrı ve ek analjezik gereksinimini azaltmada etkilidir.

Anahtar Kelimeler: Ranawat süspansiyonu, traneksamik asit, postoperatif ağrı, kan transfüzyonu, postoperatif analjezi

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Submitted/Başvuru: 21.07.2022 • **Accepted/Kabul:** 07.10.2022 • **Published Online/ Online Yayın:** 15.10.2022

Introduction

Total knee arthroplasty (TKA) has become a common procedure worldwide. It improves the degree of motion of the joint, increases mobility and reduces pain during daily activities in advanced cases of osteoarthritis. Excessive blood loss and postoperative pain are major complications of this surgical procedure. Severe surgical pain in the early postoperative period primarily delays the restoration of range of motion as well as the whole rehabilitation process, which might lead to joint contractures and could limit daily activity.[1] In addition, pain relief following surgery and the improvement in knee function has been shown to be the main components of patient satisfaction in TKA surgery.[2] From this point of view, early postoperative pain is likely a major concern for patients and increased pain may also cause the overuse of non-steroidal anti-inflammatory drugs and oral and iv. narcotic agents, which could potentially lead to serious adverse events including impaired homeostasis, acute renal dysfunction, urinary retention, respiratory depression, hypoxia and delirium.[3] Therefore, adequate pain control is crucial to minimize the risk for postoperative pain and avoid its complications.

Severe bleeding, another serious complication of TKA is associated with anemia, poor wound healing, and increased risk for surgical site infections that may adversely affect outcome. Accordingly, substantial blood loss may necessitate blood transfusions which carry the risk of transfusion transmissible diseases, immunological transfusion reactions and mistransfusions.[4] Therefore, it is apparent that measures to decrease the frequency and volume of postoperative bleeding are essential.

Recently, periarticular injections have emerged as an option to decrease the level of postoperative pain.

A modified version of Ranawat's suspension containing ropivacaine, epinephrine, ketorolac and clonidine was shown to reduce the surgical pain particularly in the early postoperative period.[5] Tranexamic acid (TXA) is a plasminogen activator inhibitor, that inhibits the activation of plasminogen to plasmin and consequently improves hemostasis. Recent data indicates that periarticular injection of TXA during TKA might prevent bleeding and reduce the number of transfusions.[6]

Although the benefits of periarticular injections of local anesthetic agents or TXA is evaluated in a number of studies, there is very little data on the efficacy of periarticular use of local anesthetic and TXA combinations.

In the present study, we aimed to investigate the effect of periarticular injection of a cocktail containing TXA and Ranawat's suspension in terms of postoperative pain and bleeding in patients undergoing TKA. The primary outcome of the study was postoperative pain and the requirement for analgesics (Tramadol dose), and secondary outcome was blood loss and complications

Methods

This study received ethics committee permission from Bakırköy Dr. Sadi Konuk Education and Research Hospital Clinical Research Ethics Committee with the decision no. 2019-06-05 (dated 03.18.2019). Our study was retrospective and no written consent was attempted.

Retrospective data of all consecutive patients who underwent unilateral TKA in our Hospital at the Orthopedics and Traumatology Service between August 2014 and December 2018 were screened and patients who did not fulfil any of the exclusion criteria were enrolled in this retrospective study. A total of 23 patients were excluded as follows: those who underwent bilateral TKA (7 patients) or revision arthroplasty (8 patients), patients who required general anesthesia (4 patients) and those with previous knee surgery (5 patients). A final total of 124 patients were included in statistical analysis. Patients were divided into two groups: those receiving the periarticular injection of a cocktail containing the combination of Ranawat suspension and TXA (Group A) and those receiving no injections (Group B). We began to use periarticular injections of the aforementioned cocktail in July 2016; therefore, patients who underwent surgery after this date comprised Group A, while those which had undergone surgery before July 2016 comprised Group B. The surgical procedures, post-operative care and clinical follow-up of patients remained similar throughout this period. The primary outcome of the study was postoperative pain and the requirement for analgesics (Tramadol dose), and secondary outcome was blood loss and complications.

Surgical Procedure

All surgical procedures were carried out by the same surgical team with the same primary surgeon. Each procedure was performed with a uniform approach under spinal anesthesia and a tourniquet was applied from bone resection to skin closure in all patients to maintain adequate homeostasis. Through a medial parapatellar approach, a midline skin incision was executed. The Genesis II Complete Knee System (Smith &Nephew INC, Memphis, TN) was fixed with cement in all procedures. Patellar resurfacing and desensitization with electrocautery were not performed in any of the patients. In group A, 1000 mg TXA (25 mg/mL) in combination with a modified Ranawat suspension including 49.25 mL of ropivacaine (5 mg/mL), 1 mL of ketorolac (30 mg/mL), and 0.8 mL of clonidine (0.1 mg/mL) which was diluted with 48.85 mL of saline, was injected via 22-gauge needles into deep tissues including the capsule, collaterals, and extensor mechanism along with the subcutaneous tissue. A surgical drain was placed into the knee joint and clamped while the patients were transferred to the recovery unit. The clamp was removed at the second hour postoperatively and was left to spontaneous drainage up to 36 hours and was then removed. All patients received the same postoperative pain control protocol consisting of acetaminophen 1000 mg every 8 hours and tenoxicam every 12 hours for 24

hours. Fifty mg iv. Tramadol, which is a unique analgesic medication that inhibits monoaminergic reuptake and demonstrates opioid receptor agonist activity, was administered when the aforementioned protocol was insufficient in relieving pain. The amount of Tramadol administered to each patient was recorded. Allogenic blood transfusion was performed when postoperative hemoglobin levels dropped below 9 g/dL. Subcutaneous enoxaparin (40 mg/day) was administered to prevent deep venous thrombosis. Active range of motion exercises and full weight-bearing walking with the use of a walker or rails were allowed at post-op 24th hour.

Clinical Evaluation and Laboratory Measurements

Demographic features, preoperative and postoperative hematocrit and hemoglobin levels, amount of blood drainage, postoperative pain and the total dose of tramadol administered were retrieved from hospital records. Postoperative pain was evaluated using the visual analogue scale (VAS, 0: no pain, 10: severe pain).

Statistical Analysis

Statistical analyses were carried out using SPSS for Windows, version 17 (SPSS, Chicago, IL, USA). Normal distribution of the variables was studied with the Kolmogorov-Smirnov te

st. Continuous variables are presented as the mean ± standard deviation and categorical variables as percentage. Comparisons among groups with respect to demographic data, hemoglobin and hematocrit levels and VAS scores were performed using the student's t-test. Chi-square tests were used for univariate analysis of the categorical variables. Two-sided $p \leq 0.05$ was accepted to show statistical significance.

Results

A total of 124 patients (mean age 69 ± 8 years, 17 male) were enrolled in the study. Among these, 64 patients were recipients of the periarticular injection of Ranawat suspension and TXA (Group A) and 60 patients did not receive any injection (Group B). There were no significant differences between the groups with respect to age, sex, height, weight and BMI (Table 1).

Visual analogue scale scores indicating surgical pain were significantly lower at postoperative 6 hours (3.2 ± 0.7 vs. 5.2 ± 0.7, p<0.001), 24 hours (3.7 ± 0.8 vs. 4.9 ± 0.8, p<0.001), and 72 hours (3.0 ± 0.8 vs. 3.5 ± 0.7, p=0.002) in patients receiving periarticular injections compared to those receiving no injections (Table 2). Moreover, the number of tramadol injections were also significantly lower during the 72-hour follow-up in patients receiving periarticular injections compared to those receiving no injections (Table 2).

Table 1. Demographic features of the study population

	Group A PAI (+) n=64	Group B PAI (-) n=60	*p* value
Age, years	69±8	70±7	0.571
Sex (female/male)	58/6	(49/11)	0.145
Height, cm	165±4	163±4	0.465
Weight, kg	80±5	79±6	0.170
BMI, kg/m^2	29.6±2.1	29.6±1.8	0.860
Varus osteoarthritis, n	61 (95%)	58 (97%)	0.702

Data are presented as mean ± standard deviation. BMI: body mass index; PAI: periarticular injection

Table 2. Postoperative pain and need for additional analgesic

	Group A PAI (+) n=64	Group B PAI (-) n=60	p value
VAS score			
Preoperative	2.6±0.7	2.7±0.7	0.823
Postoperative 1st Hour	1.7±0.5	1.7±0.5	0.727
Postoperative 6th Hour	3.2±0.7	5.2±0.7	<0.001
Postoperative 24th Hour	3.7±0.8	4.9±0.8	<0.001
Postoperative 72nd Hour	3.0±0.8	3.5±0.7	0.002
Additional analgesic (Tramadol), n			
Postoperative 0-6 hours	1 (1%)	9 (15%)	<0.001
Postoperative 6-24 hours	8 (13%)	20 (33%)	0.006
Postoperative 24-72 hours	13 (20%)	21 (35%)	0.043

Data are presented as mean ± standard deviation. PAI: periarticular injection; VAS: visual analogue scale

Table 3. Parameters related to blood loss

	Group A PAI (+) n=64	Group B PAI (-) n=60	p value
Hemoglobin, g/dL			
Preoperative	12.3±1.4	12.7±1.5	0.197
Immediately postoperative	10.6±1.9	11.0±1.3	0.143
Postoperative 1st Day	10.7±4.4	10.1±1.2	0.234
Postoperative 3rd Day	10.7±3.9	9.3±1.0	0.047
Hematocrit, %			
Preoperative	38.4±3.7	38.6±3.9	0.781
Immediately postoperative	34.1±2.8	33.7±3.3	0.516
Postoperative 1st Day	30.4±5.0	30.7±3.4	0.721
Postoperative 3rd Day	30.2±2.8	28.1±2.9	0.044
Drainage blood (mL)	200±69	280±53	0.001
Allogenic blood transfusion, n	5 (8%)	14 (23%)	0.009

Data are presented as mean ± standard deviation. PAI: periarticular injection

While the preoperative hemoglobin and hematocrit levels were similar in the two groups, both parameters were significantly higher at third day postoperatively in those receiving periarticular injection of Ranawat suspension and TXA (30.2 ± 2.8 vs. 28.1 ± 2.9, p = 0.044 for hematocrit, and 10.7 ± 3.9 vs. 9.3 ± 1.0, *p*=0.047 for

hemoglobin level). In addition, blood drainage was significantly higher in patients receiving no periarticular injections (280 ± 53 mL vs. 200 ± 69 mL, p<0.001). Patients receiving the periarticular cocktail required fewer transfusions compared to those receiving no injections (8% to 23%, p=0.009, Table 3). During hospitalization, no severe complications such as DVT or localized infection and minor complications were observed in any group.

Discussion

The present study demonstrates that utilization of a cocktail containing both Ranawat's suspension and TXA not only improves pain control but also reduces postoperative blood loss. Our findings show that blood drainage and the need for allogenic blood transfusion are lower in patients receiving a periarticular injection of a combination of Ranawat suspension and TXA. Moreover, the cocktail reduces postoperative pain throughout the hospital course and minimizes the need for narcotic administration.

Total knee arthroplasty is increasingly being utilized as the treatment of choice in patients with osteoarthritis worldwide. However, postoperative pain continues to be of major concern both for patients and healthcare professionals.[7] Failure in pain control following TKA is related to several unpleasant consequences including delayed functional recovery, prolonged hospitalization and increased costs. Various strategies to control postoperative pain, such as peripheral nerve blocks, multimodal analgesia and epidural anesthesia have been established.[8] Multimodal analgesia in the form of periarticular injection has garnered much attention in recent years due to its positive effects on diminishing postoperative pain with minimal side effects. Opioids, non-steroidal anti-inflammatory drugs, steroid hormones and local anesthetic agents are commonly used in these cocktails.[9,10] However, there is still no consensus among surgeons regarding the content of the cocktails used in periarticular injections.

A few trials have been conducted to compare the efficacy of various cocktails or agents in reducing postoperative pain. In general, bupivacaine and ropivacaine based cocktails showed similar performance in decreasing the pain scores and opioid consumption.[11,12] In a recent prospective and randomized trial, Collins et al.[5] investigated the comparative efficacy of liposomal bupivacaine and a modified version of Ranawat Suspension containing ropivacaine, epinephrine, ketorolac and clonidine in 105 patients undergoing primary TKA. The authors demonstrated that both liposomal bupivacaine and modified Ranawat suspension showed similar efficacy in decreasing pain levels and reducing narcotic usage. Therefore, in our study, we used the validated and potent modified Ranawat suspension to address pain in our group of TKA patients. In accordance with the results of the study conducted by Collins et al., we found that the ropivacaine based cocktail used in the present study not only reduced the need for tramadol but also decreased pain scores up to 72 hours postoperatively.

An important aspect of the present study is that we used a cocktail combining modified Ranawat suspension and TXA in order to obtain an additional benefit in blood loss which occurs frequently in TKA. It has been shown that an excessive amount of bleeding ranging between 1000 mL to 2000 mL may occur during TKA and 10% to 38% of patients require transfusion of around 1–2 units of blood.[13,14] However, blood transfusions jeopardize the healing process due to the possibility of infections, hemolysis problems, immunological reactions and transfusion-related lung injury; furthermore, transfusions cause increased health costs.[15] Therefore, minimizing the requirement for blood transfusions is also an important target when performing TKA.

Tranexamic acid, a competitive inhibitor of plasminogen activation, is an antifibrinolytic agent that has been shown to be effective in reducing blood loss following TKA.[16] It has been investigated in recent years as a condition where blood values decrease beyond the visible known as hidden blood loss after major surgical operations. Likewise, inhibition of TXA plasminogen activation has been shown to prevent hidden bleeding that may occur after arthroplasty surgeries by providing a direct anti-inflammatory effect. In our study, despite the termination of the residual drain (visible blood loss) on the third day between the groups, the hemoglobin levels were significantly higher in the group using TXA, suggesting that the ongoing hidden bleeding was decreased.[17]

A Considerable amount of data reveals that the application of intravenous TXA reduces postoperative bleeding and demand for blood transfusions.[18] However, there are some concerns regarding the intravenous administration of TXA in the context that it may be associated with increased risk for deep venous thrombosis, cerebrovascular events and cardiovascular events which are common in the medical history of patients undergoing TKA. These clinical limitations led to the implementation of intraarticular and periarticular injections of TXA in TKA. Although periarticular injection of TXA appears safe, the efficacy of this method has only been reviewed in a few studies. Recently, Yozawa et al.[6] studied the efficacy of periarticular TXA (1000 mg) in combination with 40 mL of 0.25% ropivacaine and 1:200.000 epinephrine on blood loss in 82 patients undergoing TKA. They showed that hemoglobin and hematocrit reduction were less in patients receiving TXA compared to those not receiving TXA. They also noted that blood drainage was lower in the TXA group. Furthermore, no severe complications, including deep venous thromboembolism or infection were observed in those receiving TXA. In our study, we used a similar dose of TXA in our patients and found that TXA use was associated with less bleeding, less blood drainage, and fewer allogenic blood transfusions. In accordance with the previous results, there were no severe complications in the early postoperative period among patients

receiving the combination of Ranawat suspension and TXA cocktail in this study.

Local infiltration analgesia and intraarticular TXA is recommended by Enhanced Recovery After Surgery (ERAS®) Society.[19] We applied both in the same solution in our study.

Our findings show that periarticular injection of a single cocktail combining a modified Ranawat suspension and TXA is a safe method which is associated with less bleeding, less pain and reduced need for additional analgesics in patients undergoing TKA.

There are some limitations to be acknowledged. Firstly, the present study is a retrospective observational study and the sample size is relatively small to reach a definite conclusion. Secondly, the follow-up period of patients was quite short. A longer follow-up is required to accurately address the impact of the cocktail on bleeding and major complications such as deep venous thrombosis. In addition, data regarding the functional improvement of patients and the effects of healthcare costs were not evaluated. However, we believe that our results are satisfactory to provide sufficient information for the efficacy of the cocktail in the early postoperative period.

In conclusion, periarticular injection of a cocktail containing the combination of Ranawat suspension and TXA in patients undergoing TKA is effective in reducing blood loss, pain scores and additional analgesic requirements without increasing major complications in the early postoperative period. We suggest that the use of this cocktail might enhance recovery after surgery, will increase patient satisfaction and could decrease healthcare costs.

Compliance with Ethical Standards

Bakırkoy Dr. Sadi Konuk Research Hospital Clinical Research Review Board: Decision No:2019.06.05.123.

Conflict of Interest

The authors declare no conflicts of interest.

Author Contribution

ÜM: Hypothesis, study design, material preparation, data collection and analysis; ÇP: Study idea, writing the first draft of the article, critical review of the article finalization and publication process.

Financial Disclosure

None.

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