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EFFICACY OF EXTENDED ORAL TRANEXAMIC ACID ON BLOOD LOSS IN PRIMARY TOTAL KNEE ARTHROPLASTY

EFICÁCIA DO USO PROLONGADO DE ÁCIDO TRANEXÂMICO ORAL NA PERDA DE SANGUE NA ARTROPLASTIA TOTAL PRIMÁRIA DO JOELHO

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ABSTRACT

Introduction: Tranexamic acid is widely used for patients undergoing total knee arthroplasty (TKA). However, the duration of systemic tranexamic acid (TXA) administration varies in many reports. Hence, this study aims to compare blood loss between a single intravenous (IV) TXA dose, and one dose of IV TXA combined with oral TXA, during 48-hour postoperative care in primary TKA. Methods: Ninety-four patients with primary osteoarthritis, who underwent primary TKA, were randomized into two groups. The first group consisted of 47 patients and received a dose of 750 mg IV TXA and 750 mg oral TXA postoperatively at 8-hour intervals for 48 hours. In the second group, 47 patients received a single dose of IV TXA and a placebo at the same intervals for the same time duration. Hemoglobin (Hb) was measured at 4, 24 and 72 hours after operation. Results: The mean total blood loss were not different between the two groups (p=0.37). There was no difference in total Hb reduction or closed suction drainage outputs (p=0.9 and 0.07, respectively). Conclusion: The extended use of oral TXA for 48-hour postoperative care did not decrease the total blood loss following TKA compared with a single dose of IV TXA. ***Level Of Evidence I; High quality randomized trial.***

Keywords: Arthroplasty, Replacement, Knee. Tranexamic acid. Blood transfusion.

RESUMO

Introdução: O ácido tranexâmico é amplamente utilizado para pacientes submetidos à artroplastia total do joelho (ATJ). No entanto, a duração da administração de ácido tranexâmico sistêmico (ATS) varia em muitos relatórios. Assim, este estudo tem como objetivo comparar a perda sanguínea entre uma dose única intravenosa (IV) de ATS e uma dose de ATS IV combinada com ATS oral, no atendimento pós-operatório ao longo de 48 horas em ATJ primária. Métodos: Noventa e quatro pacientes com osteoartrite primária, submetidos a ATJ primária, foram randomizados em dois grupos. O primeiro grupo de 47 pacientes recebeu uma dose de 750 mg de ATS IV e 750 mg de ATS oral no pós-operatório, a cada 8 horas, durante 48 horas. No segundo grupo, 47 pacientes receberam dose única de ATS IV e placebo nos mesmos intervalos e pelo mesmo período de tempo. A hemoglobina (Hb) foi medida às 4, 24 e 72 horas de pós-operatório. Resultados: A média da perda sanguínea total não foi diferente entre os dois grupos (p = 0,37). Não houve diferença na redução da hemoglobina total ou saídas de drenagem de sucção fechada (p = 0,9 e 0,07, respectivamente). Conclusão: O uso prolongado de ácido tranexâmico oral por 48 horas de pós-operatório não diminuiu a perda total de sangue após ATJ em comparação com uma dose única de ATS IV. ***Nível de Evidência I; Estudo Clínico randomizado de alta qualidade.***

Descritores: *Artroplastia do Joelho. Ácido tranexâmico. Transfusão de sangue.*

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INTRODUCTION

Postoperative anemia, following primary total knee arthroplasty (TKA), is a problem related to postoperative allogeneic blood transfusions.[1] The drawbacks of allogeneic blood transfusions are associated with an increased risk of postoperative infection, transfusion reaction, and transfusion-transmitted viral infections; prolonged hospital stays; and increased costs of treatment.[2–4]

Presently, many strategies are being used to decrease blood loss and the rate of blood transfusions in patients undergoing TKA, including the use of tourniquets,[5] tranexamic acids (TXA),[6] topical fibrin sealant,[7] reinfusion drains,[8] and preoperative iron supplements,[9] or erythropoietin.[10]

Today, TXA is widely used by orthopedic surgeons to decrease postoperative blood loss in patients undergoing TKA.[11] The

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The study was conducted at Prince of Songkla University, Faculty of Medicine, Songkhla, Thailand.

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mechanism of action of TXA is antifibrinolytic function inhibiting clot lysis, which could decrease postoperative blood loss and the rate of allogeneic blood transfusions without increasing the risk of venous thromboembolism (VTE).[6] TXA could be administered in TKA patients through different routes, such as intravenous (IV),[12] oral,[13] intraarticular,[14] and soft tissue periarticular injections.[15] Several randomized control trials have shown no significant difference in the blood-sparing effect among the different forms of TXA.[16–18]
The duration of systemic TXA administration varies in many studies, from a single dose to an extended dose of 14 days,[19–21] because blood loss following TKA, including those from drainage and hidden blood loss, can occur for longer than 24 h postoperatively.[16] Thus, we hypothesized that extended duration of TXA administration could decrease the total blood loss and rate of allogeneic blood transfusions. However, a limited number of studies have compared single-dose TXA with multiple doses of TXA for up to 48 h of post-operative care. Thus, this study was conducted to compare the total blood loss and transfusion rates between a single dose of IV TXA and one dose of IV TXA combined with oral TXA for 48 h of postoperative care in patients undergoing primary TKA.

MATERIAL AND METHODS

This study was a prospective randomized controlled trial. The trial was conducted at a tertiary care hospital from January 2019 to March 2020. The procedures in this study were performed in compliance with the Declaration of Helsinki regarding ethical principles for medical research and experiments involving human subjects. This study was approved by the local Ethics Committee and Institutional Review Board. Written informed consent was obtained from each patient. This study was approved by the Ethics Committee and Institutional Review Board of the Faculty of Medicine, Prince of Songkla University (EC 61-228-11-1).
Thai Clinical Trials Registry (http://www.clinicaltrials.in.th) Registry number: TCTR20190114001

Participants

Patients with primary osteoarthritis aged less than 85 years scheduled for primary unilateral TKA were approached for possible inclusion in this study. The exclusion criteria were patients who were using anticoagulants, tretinoin, estrogen, or oral contraceptive pills before the operation; those with a history of deep vein thrombosis or pulmonary embolism and acute coronary syndrome or cerebrovascular accident; those with active cancer, end-stage chronic kidney disease, abnormal coagulation profile, and abnormal liver function test; those allergic to TXA; those who underwent previous knee surgery; patients required stemmed prosthesis; and those with a severe deformity that required extensive soft tissue release combined with a constrained implant or ligament reconstruction.

Accounting for all patients

One hundred and three patients were approached for possible inclusion in the study. Four patients declined to participate, and five patients were excluded because they had end-stage chronic kidney disease. Finally, 94 patients participated in the study. All patients completed the trial and were analyzed with intention-to-treat analysis.

Randomization

Block-of-four randomization was performed using computer-generated random numbers to randomize the patients into two groups. Sealed, opaque envelopes were used for allocating patients, and random allocation was conducted by a pharmacist, who was not associated with the study, at the inpatient hospital pharmacy before the patients went into the operating room. The first group, consisting of 47 patients, received 750-mg IV TXA 30 min before surgery and three capsules of 250-mg oral TXA 8 h at 8-h intervals for 48 h after surgery. The control group, consisting of 47 patients, received a single dose of 750-mg IV TXA 30 min before the operation and three placebo capsules, which looked identical to oral TXA capsules, after surgery at the same intervals for the same time (Figure 1).
All patients underwent the same surgical technique by a single surgeon and followed the same postoperative care protocol. A cemented, stabilized total knee prosthesis was used in all patients; additionally, the medial parapatellar approach was used in all patients. A pneumatic tourniquet was inflated from the skin incision until capsular closure was conducted. A femoral cut was performed with an intramedullary guide, while the proximal tibia was cut with an extramedullary guide. The patella was not resurfaced. A closed suction drain was applied before capsular closure. The drain tube was clamped for 3 h after the operation, released, and then removed on postoperative day 2. A rehabilitation protocol for ankle pumping, quadriceps isometric, and range of motion exercises was started immediately after the operation. On the day after the operation, the patients had ambulation training using a walker. All patients received a tablet of aspirin (81 mg) two times a day for VTE prophylaxis. Paracetamol (500 mg) tablets every 6 h were prescribed for all patients. If the patient had a verbal numerical pain score of more than 4, an injection of IV fentanyl (30 mcg) was administered as rescue pain medication every 2 h.
Postoperative hemoglobin (Hb) levels were measured 4, 24, and 72 h after surgery. The indication for allogeneic blood transfusion was Hb of less than 9 g/dL or if the patient had symptoms of anemia. Total blood loss was calculated from patient baseline characteristics, Hb level 72 h after surgery, and volume of blood transfusion using the Hb-balance method.[22] The number of units of allogeneic blood transfused and postoperative complications was recorded.

Statistical analysis

Patient demographic data, such as age, body mass index (BMI), preoperative Hb level, preoperative hematocrit (Hct), platelet count, tourniquet time, operative times, postoperative blood loss, postoperative Hb loss, Hct reduction, and closed suction drainage output, were compared between the groups using the independent t-test. Pearson's χ^2 test was used for evaluating gender, operative side, American Society of Anesthesiologists (ASA) classification, and transfusion rates.

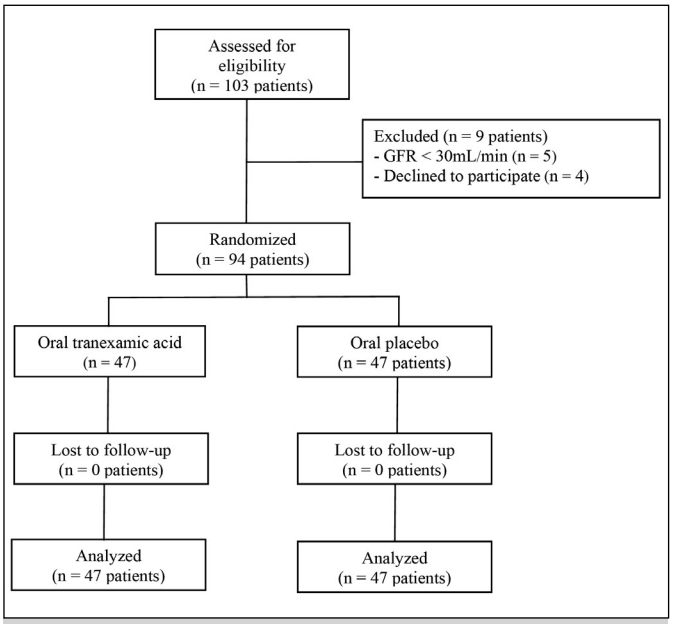

Figure 1. Flow study diagram.

The analyses were performed using R, version 3.1.0 (R Foundation for Statistical Computing, Vienna, Austria). A *p*-value of less than 0.05 was used to denote statistical significance. The sample size was calculated based on a previous TXA study involving patients undergoing TKA[15] for testing two independent means. Forty-seven patients per group were required to detect a significance level of 0.05, and power was set at 0.8 to detect a difference of 175 mL of postoperative blood volume.

RESULTS

No differences in patient demographic data, including age, gender, operative side, BMI, ASA classification, preoperative Hb level, preoperative Hct, platelet count, tourniquet time, and operative times, were observed between the two groups (Table 1).

Postoperative outcomes are shown in (Table 2). No differences in the mean total blood loss and blood loss during the first 24–72-hours after surgery were observed between the two groups ($p = 0.37$ and 0.76, respectively). Additionally, no differences in the total Hb reduction, Hb loss during the first 24–72 h postoperatively, and total Hct reduction were observed ($p = 0.9$, 0.84, and 0.97, respectively). Although the extended TXA group had lower closed suction drainage outputs than the control group, it did not reach statistical significance ($p = 0.07$). Among the patients in the extended TXA group, 8.5% (4/47) received blood transfusions, whereas no patient in the control group received blood transfusions; the difference was statistically significant ($p = 0.04$).

No postoperative complications, including deep vein thrombosis, pulmonary embolism, wound hematoma that required reoperation, prolonged wound discharge, and superficial or deep wound infections, were observed in both groups.

DISCUSSION

Currently, total blood loss and allogeneic blood transfusions in patients undergoing TKA could be decreased by several methods.

Table 1. Demographic data.

	Extended TXA group (n = 47)	Control group (n = 47)	p-value
Age (Year)	68.3 ± 7.9	67.6 ± 8	0.69
Gender (Male/Female)	7:40	2:45	0.08
Side (Left/Right)	20:27	22:25	0.68
ASA (1:2:3)	1:38:8	1:37:9	0.96
BMI (kg/m^2)	27.5 ± 4.6	28.7 ± 3.7	0.19
Pre-op Hb (g/dL)	12.9 ± 1.3	12.5 ± 1.1	0.20
Pre-op Hct (%)	39.5 ± 3.9	38.6 ± 3.1	0.21
Platelet count (x 10^3 / L)	262.57 ± 61.91	269.53 ± 55.29	0.57
Operative time (Min)	76 ± 24	73 ± 15	0.45
Tourniquet time (Min)	55 ± 18	54 ± 15	0.92

Table 2. Post-operative outcomes.

Outcome	Extended TXA group (n = 47)	Control group (n = 47)	P-value
Total blood loss (mL)	740 ± 295	691 ± 218	0.37
Blood loss during 24-72 hrs	166 ± 153	176 ± 164	0.76
Total Hb loss (g/dL)	2.4 ± 0.9	2.4 ± 0.8	0.90
Hb loss during 24-72 hrs	0.5 ± 0.5	0.5 ± 0.5	0.84
Total Hct reduction (%)	7.3 ± 2.7	7.3 ± 2.5	0.97
Closed suction drainage outputs (mL)	471 ± 215	547 ± 185	0.07
Transfusion (n)	4	0	0.04

One of these methods is TXA administration, which decreases postoperative blood loss and allogeneic blood transfusions without increasing the rate of VTE.[6]

In a study, Helito et al.[23] compared IV TXA, topical hemostatic agents, and placebo; and reported that TXA had results comparable to those of topical hemostatic agents in terms of postoperative Hb reduction, and TXA was associated with less blood loss compared with placebo.

While many studies support the efficacy of IV and oral TXA in patients who underwent TKA, most have used TXA for a short time. However, blood loss following TKA can continue for longer than 24 h postoperatively.[16] Therefore, we hypothesized that extended doses of TXA decreased both total blood loss and the rate of allogeneic blood transfusions. However, this study found that extended doses of oral TXA did not decrease postoperative blood loss or allogeneic blood transfusions.

Furthermore, this study found no differences in total blood loss and blood loss during the first 24–72 h following TKA between patients who had IV TXA combined with extended oral TXA and those who received a single dose of IV TXA. Our findings conform to those of the trial by Li et al.,[21] who compared patients receiving IV TXA before surgery and at the time of wound closure and then received supplemental IV TXA twice daily on postoperative days 1 and 2 with those who had only two doses of IV TXA. This study found no difference in total blood loss among the patients in both groups. However, another study contradicted our results. Wang et al.[20] reported that patients undergoing TKA who received IV TXA before surgery and then 3 h postoperatively with oral TXA from postoperative day 1 to 14 had less total blood loss than patients who had only two doses of IV TXA on an operative day.

Our results demonstrated that patients in the extended oral TXA and control groups had no difference in postoperative Hb reduction. This study reported results similar to those reported by Li et al.[21] and Wang et al.,[20] who reported that the extended use of TXA for 2 or 14 postoperative days did not outperform two doses of IV TXA. In addition, we found that close suction drain output in the extended oral TXA group was not significantly lower than that in the control group. Similarly, studies have found that patients who received extended TXA for two postoperative days did not have lower drain output than those who received two doses of IV TXA. [21]

In this study, the blood transfusion rates in the control group were lower than that in the extended oral TXA group with a statistical significance. We pondered this finding because we could not find any studies reporting on this issue. A randomized controlled trial by Iwai et al.[24] has reported no difference in blood transfusion rates in patients undergoing TKA who received a single dose of IV TXA compared with those in patients who received two doses of TXA. Besides, the studies by Li et al.[21] and Wang et al.[20] have reported that the extended use of TXA over 1 day did not show a reduction in the blood transfusion rate. In this study, four patients received blood transfusions, all of whom were from the extended oral TXA group. We hypothesized that this curious finding was caused by two reasons. First, the threshold for blood transfusion in this study (Hb < 9 g/dL) was lower than that in previous studies (Hb = 7–8 g/dL).[20,21,24] We considered using Hb < 9 g/dL as the threshold based on the study by Cardozo et al.[25] that set this Hb value as a minimum threshold for transfusion relative to clinical symptoms. In this study, one patient who received an allogeneic blood transfusion 4 h after surgery had Hb of 7.8 g/dL. However, the three remaining patients received blood transfusion 24 h after surgery because the Hb levels were 8.5, 8.6, and 8.8 g/dL,

respectively, 24 h after surgery. All four patients did not have anemic symptoms.

Second, three patients who received blood transfusions in the extended oral TXA group were in the top 4.23% of all patients who had the lowest Hb levels (9.0, 10.5, and 10.9 g/dL, respectively). Thus, we hypothesized that the reason why the extended oral TXA group had a higher rate of blood transfusion than the control group is by chance, but it might be because of an undiscovered reason. This study had some limitations. First, the threshold for blood transfusion in this study was lower than that in other studies. Therefore, patients who had lower baseline Hb might have a higher chance of receiving a blood transfusion, even though no anemic symptoms were observed. Second, this study was underpowered according to the post-hoc analysis due to the lower than expected differences in total blood loss. Nonetheless, we believe that this study provides valuable data, proposing further investigation on this subject.

CONCLUSION

In conclusion, this study demonstrated that the extended use of oral TXA for 48 h postoperatively did not decrease the total blood loss or the number of blood transfusions following TKA compared with a single dose of IV TXA.

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