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SCIENTIFIC ARTICLE

Use of tranexamic acid in primary total knee replacement: effects on perioperative blood loss

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Anesthesia;
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Abstract
Background and objectives: The use of tranexamic acid in primary total knee replacement surgeries has been the subject of constant study. The strategies to reduce bleeding are aimed at reducing the need for blood transfusion due to the risks involved. In this study we evaluated the use of tranexamic acid in reducing bleeding, need for blood transfusion, and prevalence of postoperative deep vein thrombosis in primary total knee replacement.
Method: 62 patients undergoing primary total knee replacement were enrolled in the study, from June 2012 to May 2013, and randomized to receive a single dose of 2.5 g of intravenous tranexamic acid (Group TA) or saline (Group GP), 5 min before opening the pneumatic tourniquet, respectively. Hemoglobin, hematocrit, and blood loss were recorded 24 h after surgery. Deep vein thrombosis was investigated during patient's hospitalization and 15 and 30 days after surgery in review visits.
Results: There was no demographic difference between groups. Group TA had 13.89% decreased hematocrit ($p = 0.925$) compared to placebo. Group TA had a decrease of 12.28% ($p = 0.898$) in hemoglobin compared to Group GP. Group TA had a mean decrease of 187.35 mL in blood loss (25.32%) compared to group GP ($p = 0.027$). The number of blood transfusions was higher in Group GP ($p = 0.078$). Thromboembolic events were not seen in this study.

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Conclusion: Tranexamic acid reduced postoperative bleeding without promoting thromboembolic events.

PALAVRAS-CHAVE
Anestesia;
Ácido tranexâmico;
Prótese do joelho;
Sangramento;
Transfusão de sangue

Uso do ácido tranexâmico em artroplastia total primária de joelho: repercussões na perda sanguínea perioperatória

Resumo
Justificativa e objetivos: O uso do ácido tranexâmico, em cirurgias de artroplastia total primária de joelho, tem sido objeto de constante estudo. As estratégias para redução de sangramento visam à redução da necessidade de transfusão de sangue devido aos riscos que apresentam. Neste estudo, propomos a avaliação do uso do ácido tranexâmico na redução do sangramento, na necessidade de transfusão de sangue e na prevalência de trombose venosa profunda (TVP) pós-operatória em artroplastia total primária de joelho.
Método: Foram estudados 62 pacientes submetidos à artroplastia primária total de joelho, de junho de 2012 a maio de 2013, randomizados para receber ácido tranexâmico 2,5 g endovenoso (grupo AT), em dose única, ou soro fisiológico (grupo GP), cinco minutos antes da abertura do torniquete pneumático, respectivamente. Foram feitas dosagens de hemoglobina e hematócrito e medida a perda sanguínea 24 horas após a cirurgia. A TVP foi pesquisada durante a internação do paciente, 15 e 30 dias após a cirurgia nas consultas de revisão.
Resultados: Não houve diferenças demográficas entre os grupos estudados. O grupo GT apresentou queda do hematócrito 13,89% (p = 0,925) comparado com o grupo placebo. O grupo GT apresentou diminuição de 12,28% (p = 0,898) da hemoglobina comparado com o grupo GP. O grupo GT apresentou uma diminuição média de 187,35 ml nas perdas sanguíneas (25,32%) quando comparado com o grupo GP (p = 0,027). O número de transfusões sanguíneas foi maior no grupo GP (p = 0,078). Eventos tromboembólicos não foram evidenciados neste estudo.
Conclusões: O ácido tranexâmico diminuiu o sangramento pós-operatório sem promover eventos tromboembólicos.

Introduction

The proposal to use tranexamic acid as a strategy to reduce blood loss in surgery of primary total knee replacement has been the subject of constant study, because it is a procedure associated with significant amounts of bleeding that can reach 20% of the volume in patients with significant comorbidities related to cardiovascular, cerebrovascular, and metabolic systems, due to the epidemiological characteristics of knee osteoarthritis/arthrosis.[1]

In these patients, blood loss leading to a perioperative anemia promotes high morbidity and mortality.[2] Patients with perioperative anemia have a longer hospital stay associated with a greater need for the use of resources, including blood transfusions, blood products, and admission to the intensive care unit.[3–5]

Strategies for reducing bleeding have been used to reduce the need for transfusion of blood and its products due to the associated risks.[4] Not only the transmission of viral and bacterial diseases, but the immunomodulation related to homologous transfusion has been a growing concern, especially as we evidence an increase in the prevalence of prostheses infections, immunosuppression, and the already seen relationship of neoplasms arising in patients receiving this type of transfusion.[4,6–8]

In this study, we propose to evaluate the use of tranexamic acid in reducing bleeding, need for transfusion of blood and blood products, and prevalence of postoperative deep venous thrombosis in primary total knee replacement.

Methods

After approval by the local Research Ethics Committee and obtaining written informed consent, 62 patients undergoing primary total knee replacement due to osteoarthrosis or rheumatoid arthritis, from June 2012 to May 2013, were randomized to receive intravenous tranexamic acid 2.5 g (Group TA) as a single dose or saline solution (Group P) 5 min before the opening of the pneumatic tourniquet, respectively. Exclusion criteria were patient's refusal to participate in the study, allergies to drugs used, changes related to coagulation, use of nonsteroidal anti-inflammatory or antiplatelet drugs seven days before surgery, kidney or liver failure,

pregnancy, and previous history of deep venous thrombosis or pulmonary embolism.

Randomization was performed using a software: the http://www.randomizer.org by the hospital pharmacist, not participating in the study and confidentially. To each patient of both groups, a 0.9% saline 100 mL was given without identification, with tranexamic acid or saline solution. All study participants were blind to what was inside the saline solution offered by the hospital pharmacy. Anesthetic technique was freely chosen by the anesthesiologists to be applied to study participants, as well as the surgical technique. Total knee replacement was performed with cemented prosthesis using pneumatic tourniquet inflated with compressed air with pressure of 150 mmHg above the systolic blood pressure of the patient. All patients received prophylaxis for deep venous thrombosis with unfractionated heparin at 5000 UI subcutaneously every 8 h after the first dose applied before pneumatic tourniquet inflation and used compression stockings on both legs during the seven days following surgery.

Postoperative blood loss was measured in drainage system installed by the surgeon in the surgical wound and recorded in the first 24 h after surgery. Hematocrit and hemoglobin values were measured 24 h after surgery. The need for blood transfusion was observed in both groups at 24 h following surgery. The criteria for transfusion were established according to the protocol used by the surgeon: bleeding greater than 20% of blood volume or postoperative hemoglobin less than 8 g dL^{-1}.

Postoperative deep vein thrombosis (DVT) was investigated through clinical history and physical examination during the patient's hospital stay, and Doppler ultrasound performed with flow analysis in the region with clinically suspected DVT. In the follow-up visit, 15 and 30 days after surgery, the systematic investigation was repeated by the surgeon.

Statistical analysis was performed with SPSS software version 22.0. Data were analyzed with the Student's *t*-test for quantitative variables and chi-square test for qualitative variables.

Results

Data from 62 patients were analyzed, 30 patients in placebo group (Group P) and 32 in tranexamic acid group (Group TA), where 30.64% ($n = 19$) of the patients were male and 69.35% ($n = 43$) female. There were no demographic differences between the two groups (Table 1).

Table 1 Demographic data.

	Group placebo $n = 30$	Group TA $n = 32$	*p*
Age (years)	63.96 ± 4	67.87 ± 5	0.180
Sex			
Male	9	10	
Female	21	22	
Weight (kg)	82.96 ± 3	83.46 ± 11	0.729
ASA			
I/II	3/27	0/22	0.212

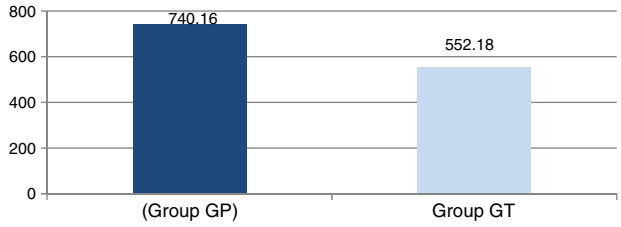

Figure 1 Graph showing the difference in bleeding volume (mL) in 24 h between groups ($p = 0.027$).

The mean initial hematocrit (Hti) was 40.03 ± 0.006% in group TA and the mean final hematocrit (Htf) was 31.19 ± 0.017%, demonstrating a hematocrit reduction of 22.08%. In group P, Hti was 42.08 ± 0.024% and Htf 31.27 ± 0.010%, presenting a hematocrit reduction of 25.64%. Group TA showed a hematocrit fall of 13.89% ($p = 0.925$) compared to placebo group.

Mean initial hemoglobin (Hbi) in group TA was 13.36 ± 0.05 g dL^{-1}. The mean hemoglobin after the procedure (Hbf) was 10.52 ± 1.342 g dL^{-1}, showing a decrease in Hb of 21.26% in this group after surgery. In group P, Hbi was 13.96 ± 1 g dL^{-1} and Hbf was 10.57 ± 0.95 g dL^{-1}, showing a decrease in Hb of 24.29%. The group TA showed a decrease in Hb of 12.28% ($p = 0.898$) compared to group P.

The mean postoperative bleeding in group TA was 552.81 ± 107 mL and in group P it was 740.16 ± 205 mL. Group TA showed a mean decrease of blood loss of 187.35 mL (25.32%) compared to group P ($p = 0.027$) (Fig. 1).

Group P needed the double packed red blood cells (RBC) units transfused (8) compared to group TA (4) ($p = 0.078$).

Deep venous thrombosis was not observed in both groups.

Discussion

The present study showed a reduction in postoperative bleeding in patients who received tranexamic acid because antifibrinolytic drugs promote reduction of fibrinolysis. Surgical trauma releases the tissue plasminogen activator (t-PA) and the fibrinolytic system is activated. The t-PA is the main enzyme responsible for plasminogen conversion to plasmin. Thrombin also activates fibrinolysis by vascular endothelium t-PA release.[9] Surgical stress increases plasmin release at the site of vascular damage and amplifies fibrinolysis.

Tranexamic acid (trans-4-(aminomethyl)cyclohexane carboxylic acid), which is a synthetic fibrinolysis inhibitor, acts through competitive inhibition of plasminogen activation in plasmin,[10,11] which results in a fibrinolysis delay due to non-plasmin formation, binding to fibrinogen or to fibrin monomers does not occur and results in a clot stabilization.[4] The choice of drugs for the study was based on the safety profile and its efficacy reported in the literature.

Among the strategies to reduce perioperative bleeding in knee replacement there is the use of pneumatic tourniquet during the perioperative period.[12] However, this tourniquet decreases intraoperative blood loss, but when deflated an increase in bleeding is seen, which is explained by the hyperfibrinolysis due to plasmin release from the surgical bed.[13,14]

Several authors studied tranexamic acid to establish its effect in reducing bleeding and need for transfusion of blood and blood products in primary total knee replacement.

However, there was no consensus regarding dose and time to administer the drug under study.[15–17]

Orpen et al. reported a significant blood loss reduction of 43.5% ($p = 0.006$) in the immediate postoperative period in the group receiving 15 mg kg^{-1} intravenous tranexamic acid at the time of cemented knee prosthesis placement compared to the group receiving saline solution at the same time. There were no reports of deep vein thrombosis in both groups.[12]

In a study of patients with hip fracture, the intravenous administration of tranexamic acid (15 mg kg^{-1}) at the time of skin incision and repeated 3 h later (total of 30 mg kg^{-1}) reduced the need for blood transfusion.[18]

Studying the efficacy of antifibrinolytic, Camarasa used intravenous tranexamic acid at a dose of 10 mg kg^{-1} before deflating the pneumatic tourniquet, and repeated it 3 h after the same intravenous dose and demonstrated a decreased blood loss in patients undergoing total knee replacement.[19]

Recent systematic review of randomized controlled trials concluded that the use of tranexamic acid as a bleeding reduction strategy reduced the need for blood transfusions by at least 50% and its complications, indicating that this drug reduces blood loss in at least 300 mL—such findings are similar to that found by the authors.[20]

In this study, we use tranexamic acid in equal dose (2.5 g) for all patients, which resulted in a mean of 30 mg kg^{-1} applied 5 min before opening the pneumatic tourniquet in rapid infusion. A study of bleeding reduction in surgeries in which there is fibrinolysis activation advocated the use of tranexamic acid doses between 2 and 7 g.[21]

Regarding hematocrit and hemoglobin levels in this study, although there was a greater decrease in Hb in group TA, it was not enough to require blood transfusion according to the protocol adopted by the surgeon. In the surgical protocol, patients who presented Hb <8 g dL^{-1} or postoperative blood loss >20% of blood volume would be submitted to blood transfusion.

This approach is consistent with the literature with regard to lower the patient's exposure to homologous blood transfusion. By using a simple protocol, similar to that proposed by the surgeon in the present study, Ballantyne et al. showed a 31% reduction in blood transfusions when adopted as a transfusion criterion a Hb of 8.5 g dL^{-1} compared to Hb of 11 g dL^{-1}.[22]

With the same purpose, Zadzilka et al. recommended as a strategy to reduce preoperative transfusion of blood and blood products the establishment of a tolerable Hb level in order to perform the transfusion.[23]

In this study, the need for units of blood transfused was double in group P. However, we cannot claim a relationship with or without the use of tranexamic acid because the result was not statistically significant.

Studies have reported the possibility of increased thromboembolic events related to the use of tranexamic acid in patients undergoing medium to major orthopedic procedures. This increase is based on the effects of antifibrinolytic drugs associated with prolonged bed rest and prothrombotic activity of the inflammatory response to surgical trauma. However, in the present study, in which the drug prophylaxis was used (subcutaneous unfractionated heparin 5000 IU every 8 h) associated with use of compression stockings for seven days perioperatively, there was no evidence of thromboembolic events in both groups of patients.

A study assessing the efficacy and safety of increasing doses of intravenous tranexamic acid (1000 mg; 2000 mg; and 3000 mg) in patients undergoing total knee replacement showed no thromboembolic events in studied groups.[24]

Several studies have failed to show an association between the use of tranexamic acid and the occurrence of thromboembolic events.[9,13] The likely explanation for these findings lies in the fact tranexamic acid does not affect fibrinolytic activity on the walls of the veins and promote no prothrombotic activity in the studied groups.[13]

In this study, we conclude that the use of tranexamic acid reduces postoperative bleeding in primary total knee replacement, with the absence of thromboembolic events. However, additional studies are needed to assess its impact on the need for transfusion of blood and blood products.

Conflicts of interest

The authors declare no conflicts of interest.

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