Rev Bras Anestesiol. 2020;70(4):318–324

Brazilian Journal of ANESTHESIOLOGY
Revista Brasileira de Anestesiologia

Sociedade Brasileira de Anestesiologia

CLINICAL RESEARCH

# Comparison of two doses of intra-articular tranexamic acid on postoperative bleeding in total knee arthroplasty: a randomized clinical trial

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Received 24 September 2019; accepted 27 March 2020
Available online 20 June 2020

**KEYWORDS**
Hemorrhage;
Hemostasis;
Intra-articular;
Intravenous;
Topical;
Total knee arthroplasty;
Tranexamic acid

**Abstract**
*Introduction:* Tranexamic Acid (TXA), an antifibrinolytic that inhibits the fibrinolytic activity of plasmin is used to decrease perioperative blood loss and transfusion requirements in orthopedic surgery. The aim of our study was to compare postoperative bleeding in two intra-articular doses (1 g and 2 g) of tranexamic acid in adult patients undergoing unilateral total knee replacement.
*Method:* We conducted a single-operator, randomized, and controlled, double-blind study in two groups. The G1 group received 1 g of intra-articular TXA and the G2 group 2 g of intra-articular TXA. Both groups received 15 mg $kg^{-1}$ IV before the surgical incision (TXA induction dose) and then 10 mg $kg^{-1}$, orally, 6 and 12 hours after the induction dose of TXA.

The primary endpoint was bleeding measured by blood loss in postoperative drainage. Secondary outcomes were change in hemoglobin and hematocrit levels on the first and third postoperative days, and the need for transfusion during hospitalization.
*Results:* In total, 100 patients were randomized, and 100 were included in the analysis. Blood loss in postoperative drainage was similar in both groups (200 ± 50 vs. 250 ± 50 mL, G1 and G2 groups respectively). Change in hematocrit and hemoglobin values (% of change) between preoperative and day 3 were not statically significant between groups G1 and G2 (18 ± 5 vs. 21 ± 4; 21 ± 7 vs. 22 ± 5 respectively). No patients received blood transfusion.
*Conclusions:* Our study did not show superiority of 2 g of intra-articular tranexamic acid compared to 1 g.

ClinicalTrials.gov Identifier NCT04085575


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https://doi.org/10.1016/j.bjane.2020.03.004

**PALAVRAS-CHAVE**
Hemorragia;
Hemostasia;
Intra-articular;
Intravenosa;
Tópico;
Artroplastia total do joelho;
Ácido tranexâmico

## Comparação entre duas doses de ácido tranexâmico intra-articular no sangramento pós-operatório de artroplastia total do joelho: estudo clínico randomizado

### Resumo

*Introdução:* O Ácido Tranexâmico (TXA), agente antifibrinolítico que inibe a atividade fibrinolítica da plasmina, é usado para reduzir a perda sanguínea perioperatória e a necessidade de transfusão em cirurgia ortopédica. O objetivo do estudo foi comparar o efeito de duas doses intra-articulares (1 g e 2 g) de ácido tranexâmico no sangramento pós-operatório de pacientes adultos submetidos a prótese total unilateral de joelho.

*Método:* Realizamos estudo com operador único, randomizado, controlado e duplo-cego em dois grupos. O grupo G1 recebeu 1 g de TXA intra-articular e o grupo G2, 2 g de TXA intra-articular. Os dois grupos receberam 15 mg $kg^{-1}$ IV antes da incisão cirúrgica (dose de indução de TXA) e 10 mg $kg^{-1}$ por via oral, 6 e 12 horas após a dose de indução de TXA. O desfecho primário foi o sangramento medido pela perda sanguínea na drenagem pós-operatória. Os desfechos secundários foram alteração nos níveis de hemoglobina e hematócrito no primeiro e terceiro dias de pós-operatório e necessidade de transfusão durante a hospitalização.

*Resultados:* 100 pacients foram randomizados e 100 pacientes foram incluidos na análise. A perda sanguínea pela drenagem pós-operatória foi semelhante nos dois grupos (200 ± 50 mL *vs.* 250 ± 50 mL, grupos G1 e G2, respectivamente). A variação nos valores de hematócrito e hemoglobina (% de variação) entre o pré-operatório e o dia 3 não foi estatisticamente significante entre os grupos G1 e G2 (18 ± 5 *vs.* 21 ± 4; 21 ± 7 *vs.* 22 ± 5, respectivamente). Nenhum paciente recebeu transfusão de sangue.

*Conclusões:* O estudo não mostrou superioridade na dose de 2 g de ácido tranexâmico intra-articular em comparação à dose de 1 g. ClinicalTrials.gov Identifier NCT04085575



## Introduction

Since 1860, when Verneuil performed an interpositional arthroplasty, the number of patients needing knee replacement surgery has increased dramatically because of the aging population.[1] Total Knee Arthroplasty (TKA) is widely used as an effective treatment for end-stage osteoarthritis and other knee joint diseases. Improvements in surgical components and techniques have greatly enhanced TKA outcomes. However, TKA is an orthopedic surgical method that presents substantial perioperative blood loss.[2]

Traditional methods for reducing both blood loss and transfusion rates include the use of pneumatic tourniquet, intraoperative cell saver, hypotensive anesthesia, erythropoietin, autologous blood transfusion, intramedullary femoral canal plugging, cementing, drain clamping, navigation and minimally invasive surgery.[1,2]

Tranexamic Acid (TXA), an antifibrinolytic that develops its anti-hemorrhagic action by inhibiting fibrinolytic activity of plasmin has been used as an adjuvant for such measure and many studies have confirmed its effectiveness in decreasing blood loss.[3,4]

Fibrinolysis is stimulated by blood loss that follows surgical trauma and TKA may be associated with increased fibrinolytic activity.[4–6] TXA inhibits fibrinolysis by blocking the lysine-binding sites of plasminogen to fibrin.[4–6] This inhibits plasmin formation and displaces plasminogen from the fibrin surface.[4–7] Data from several studies show that, in vivo, tranexamic acid at high doses seems to slow down the activation of the complement system. So, TXA reduces bleeding in TKA and its functional repercussion has also been confirmed in trials testing several dosages and routes of administration.[4–9]

In the literature, efficacy of intra-articular TXA has also been confirmed, but the right dosage remains unclear.[4–6,9]

## Objective

The aim of our study was to measure postoperative bleeding with intravenous and oral tranexamic acid administration combined with two intra-articular doses (1 g and 2 g) of tranexamic acid (Sanofi-Aventis® Gentilly, France).

## Method

After obtaining approval from the hospital's ethics committee and informed consent, we conducted a single-operator, randomized, controlled, double-blind study in adult patients undergoing unilateral Total Knee Replacement (TKR) surgery from January to July 2019.

Exclusion criteria were absence of consent, tranexamic acid allergy, major comorbidities (severe ischemic heart disease, severe lung disease, severe renal failure, or liver failure), coagulopathy (preoperative platelet count < 150,000 $mm^3$, International Normalized Ratio – INR > 1.4, or prolonged partial thromboplastin time > 1.4 times normal), a history of arterial or venous thromboembolic disease (cerebrovascular accident, deep vein thrombosis or pulmonary thromboembolism), hematological

disorder (a hematopoietic, hemorrhagic or thrombogenic disease), retinopathy (severe limitation of the field of vision and/or color distortion), refusal to receive blood products, pregnancy, history of convulsions and participation in another clinical trial.

Patients with preoperative anemia (hemoglobin < 13 g $dL^{-1}$) were not excluded; instead, they were offered the current standard preoperative protocol at our institution (intravenous administration of iron and/or subcutaneous 40,000 IU erythropoietin), and surgery was postponed until the hemoglobin level was 13 g $dL^{-1}$.

All patients were instructed to discontinue anticoagulants and antiplatelet agents (except aspirin), according to ''Société Française d'Anesthésie et de Réanimation – SFAR'' recommendations (https://sfar.org/welcome-the-sfar-website/).

Recruited patients (Fig. 1) were randomized before the operation by generating random numbers with Microsoft Excel 2007 (Microsoft Corporation, Seattle, Washington, USA).

They were assigned to two groups: The G1 group received 1 g of intra-articular Tranexamic Acid (TXA) and the G2 group received 2 g of intra-articular tranexamic acid. Both groups received 15 mg $kg^{-1}$ IV before skin incision and then 10 mg $kg^{-1}$ orally at 6 and 12 hours after IV induction dose of tranexamic acid.

Treatment allocation was blinded to those involved (patient, anesthesiologist and surgeon). Double blinding was maintained during the study unless the anesthesiologist in charge needed to unblind allocation for clinical reasons (though no patients were unblinded). The coordinating investigator remained blinded until the study was completed and ready for analysis.

The primary endpoint was bleeding represented by blood loss in postoperative drainage. Secondary outcomes were changes in hemoglobin and hematocrit levels on the first and third postoperative days, and the need for transfusion during hospitalization.

## Total knee arthroplasty (TKA) and anesthetic technique

Perioperative antibiotic prophylaxis using first-generation cephalosporin was administered to all patients to prevent infection before spinal anesthesia. We did not use tourniquet during surgery.

A longitudinal midline skin incision was made. Mid vastus arthrotomy was performed for genu varum deformities and a lateral arthrotomy (Keblish procedure) for genu valgum deformities.

An Anatomic® primary total knee arthroplasty implant (AMPLITUDE®, Valence, France) with Computer Assisted Surgery (AMPLIVISION®, Valence, France), was implanted using the same surgical technique in all patients.

Intramedullary guide hole inside the femur was closed by impaction of an autologous structural bone graft into the entry point in all patients. Both femoral and tibial prostheses were implanted without cement.

Intra-articular infiltration of the mixture (150 mL infiltrated before implant placement) was done with an epidural anesthesia kit: ropivacaine (146 mL with the 2 mg $mL^{-1}$ solution) with 30 mg of ketoprofen (3 mL) and 0.5 mg of adrenaline (1 mL). We finished the procedure with a subcutaneous infiltration (50 mL of ropivacaine). The epidural catheter was left for reinjection on postoperative day 1.

On postoperative day 1, another intra-articular infiltration of 20 mL of the mixture ropivacaine 7.5% (17 mL with the 2 mg $mL^{-1}$ solution) with 30 mg of ketoprofen (3 mL) was administered and the catheter was removed at the end of the injection.

The suction drain, placed inside the knee capsule, was clamped until eight hours after the end of the surgery. One gram (2 mL) or 2 g (4 mL) of TXA in saline solution (end volume of 50 mL for both groups) was administered directly into the joint cavity.

All patients were normotensive during the perioperative period and cell savers and bipolar sealers were not used during surgery. Pre- and postoperative cryotherapy was performed for both groups.

Patients were mobilized, and continuous active motion was started 3 hours after the end of surgery, and the bandage and suction drain were removed 24 hours after surgery.

Postoperative blood drainage was recorded for all patients by pouring blood from the suction drain into a measuring jar. The external scale of the measuring jars was the same for all patients.

Hemoglobin and hematocrit values were recorded at preoperative and on postoperative days 1, 2 and 3.

The blood volume of the patient was calculated according to the formula of Nadler et al.,[10] and blood loss was estimated according to the method proposed by Mercuriali and Inghilleri.[11] In our study, we chose to use the three-day postoperative hematocrit for calculation of blood loss, instead of the five-day originally described.

$$\text{Blood volume} = \text{Males} : 604 + 0.0003668 \times \text{height}\ (\text{cm}^3) + 32.2 \times \text{weight}\ (\text{kg}).$$

$$\text{Blood volume} = \text{Women} : 183 + 0.000356 \times \text{height}\ (\text{cm}^3) + 33 \times \text{weight}\ (\text{kg})$$

$$\text{Estimated blood loss} = \text{blood volume} \times (\text{Hematocrit} - \text{pre} - \text{Hematocrit} - \text{post})$$

If the patient was transfused before the three-day postoperative hematocrit, we added the volume (in milliliter) of red-blood-cell transfused.

Blood transfusion was performed by the anesthesia team according to the French Society of Anesthesia & Intensive Care Medicine recommendations (https://sfar.org/welcome-the-sfar-website/) or if clinical condition or symptoms like tachycardia, hypotension evidenced anemia. The total blood transfusion volume was also recorded and all blood transfusions were performed within 3 days postoperatively. The same analgesic protocol was administered in both groups.

Enoxaparin sodium (Lovenox®, Sanofi-Aventis, Gentilly, France) was administered subcutaneously 6 hours after the end of the procedure to all patients and continued for 4 weeks postoperatively to prevent deep vein

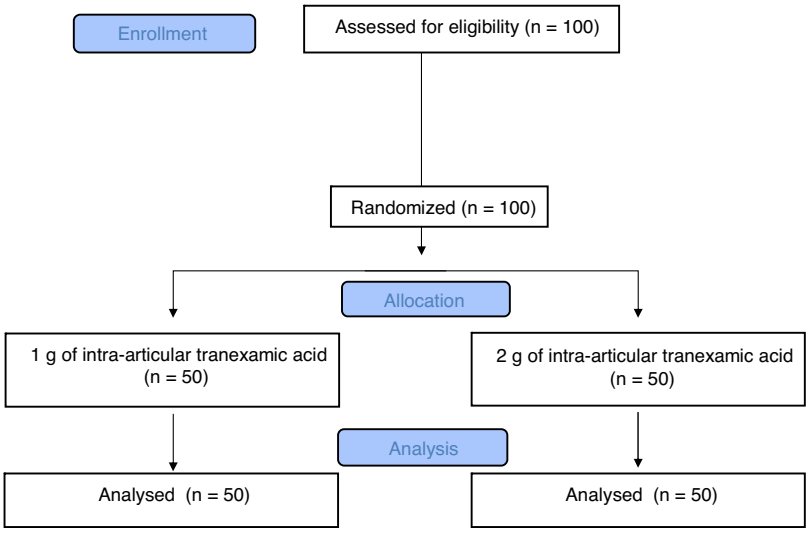


**Figure 1** Comparison of two doses of intra-articular tranexamic acid on postoperative bleeding in total knee arthroplasty: a randomized clinical trial, Consort flow diagram.

thrombosis. Static compression stockings were worn on non-operated lower extremities during the post-operative period, in addition to prophylactic low-molecular-weight heparin treatment. All patients were on regular follow-up at 1, 3, 6 and 12 months postoperatively. Complications were evaluated and recorded during regular follow-up.

## Statistical analysis

The Mann-Whitney U test was performed to compare quantitative variables (age, weight, and body mass index). Qualitative variables were compared by Fisher's exact test. The non-parametric Kruskal-Wallis test, associated with the Mann-Whitney U test, was used to compare values of hematocrit and hemoglobin between groups in the preoperative period and for days 1, 2 and 3. The non-parametric Friedman test, associated with the Wilcoxon matched-pairs test corrected for multiple comparisons, was used to compare changes in hematocrit and hemoglobin between successive periods within each group in the preoperative period and for day 1, 2 and 3.

Power analysis showed that 98 participants would be required in order to show a 30% absolute difference in blood loss in postoperative drainage between groups with an alpha risk of 0.05, a power of 80% using a two-sided test. Results were expressed in median ± median absolute deviation. The median absolute deviation is a variation of the average absolute deviation that is even less affected by outlying values because these values have less influence on the calculation of the median than they do on the mean. In general, for data with extreme values, the median absolute deviation or inter-quartile range can provide a more stable estimate or variability than the standard deviation.

*P*-values lower than a 0.05 chosen level were regarded as statistically significant. All statistical analyses were performed using the StatView® software for Windows (Abacus® Concepts Inc., Berkeley, CA, USA, 1996, version 4.57).

## Results

From January to July 2019, one hundred patients scheduled for primary unilateral total knee replacement at our hospital were assessed for participation in this trial. We obtained two groups of 50 patients, statistically comparable in terms of age, sex, body mass index and ASA score, operation time, intraoperative bleeding and antiplatelet use (Table 1). Blood loss analysis showed no significant differences between groups whether under aspirin or without treatment ($p = 0.48$).

The preoperative hemoglobin level, hematocrit level and platelet count were within the normal range in all patients. The preoperative mean hemoglobin and hematocrit level of groups G1 and G2 was 14 g dL$^{-1}$ and 42% for both groups (Tables 2 and 3). Decreases in hematocrit and hemoglobin levels were similar in the two groups and were not statically significants between days 1, 2 and 3 (Tables 2 and 3).

No patients were transfused. The criterion used to determine transfusion was a hemoglobin value of less than 7 mg dL$^{-1}$ or a compromised clinical condition as evidenced by tachycardia, hypotension or symptoms of anemia during or after surgery in consultation with the anesthesia team.

The mean length of hospital stay was similar and less than four days in both groups with a median (and standard deviation of the median) of less than four days (2.5 ± 0.9 days in G1 group and 2.9 ± 1.0 days in G2 group).

During regular follow-up, no patients included in this study had a symptomatic thromboembolic event or deep surgical site infection.

## Discussion

Major orthopedic surgeries, like total knee arthroplasty. are often associated with blood loss and provide a challenge with regard to fluid, transfusion and coagulation management.[2] Requiring blood transfusion could be associated with complications like viral infections, transfusion

**Table 1** Demographic characteristics, surgical data, drainage and calculated blood loss (mL) of the subjects included in the study.

| | G1 | G2 | *p*-value |
|---|---|---|---|
| Number | 50 | 50 | |
| Age (years) | 73 ± 6.5 | 73 ± 6 | 0.59 |
| Weight (kg) | 78 ± 7.0 | 75 ± 10 | 0.13 |
| Height (m) | 1.65 ± 0.11 | 1.65 ± 0.05 | 0.93 |
| BMI (kg m$^{-2}$) | 30 ± 3 | 27 ± 3.0 | 0.12 |
| Gender (Female/Male) | 28/22 | 30/20 | 0.32 |
| Side (right/left) | 27/23 | 27/23 | 0.22 |
| ASA (I/II/III/IV) | 3/35/12/0 | 5/38/7/0 | 0.51 |
| Patients taking ASA (n) | 10 | 8 | 0.18 |
| Duration of surgery (minutes) | 60 ± 4 | 60 ± 5 | 0.20 |
| Postoperative drainage (mL) | 200 ± 50 | 250 ± 50 | 0.82 |
| Calculated blood loss (mL) | 321 ± 116 | 371 ± 104 | 0.57 |

The G1 group received 1 g of intra-articular tranexamic acid and the G2 group received 2 g of intra-articular tranexamic acid. Both groups received 15 mg kg$^{-1}$ IV at 20 minutes of induction and then 10 mg kg$^{-1}$ in oral administration 6 and 12 hours after induction dose IV of tranexamic acid. Results were expressed in median ± median absolute deviation. ASA, Acetylsalicylic Acid lysine treatment; BMI, Body Mass Index; D, Day; Hb, Hemoglobin; Ht, Hematocrit; kg, Kilogram; m, meter; NS, Not Significant.

**Table 2** Preoperative and postoperative hematocrit values.

| | G1 | G2 | *p*-value |
|---|---|---|---|
| Number | 50 | 50 | |
| Preoperative Ht (%) (D0) | 42 ± 3 | 42 ± 2 | 0.55 |
| Ht at D1 (%) | 37 ± 3 | 37 ± 2 | 0.51 |
| Ht at D2 (%) | 33 ± 6[b] | 34 ± 2[b] | 0.99 |
| Ht at D3 (%) | 33 ± 3[c] | 33 ± 3[c] | 0.72 |
| Ht (% of change) between D0–D1 | 12 ± 3 | 12 ± 4 | 0.48 |
| Ht change (% of change) between D0–D3 | 18 ± 5 | 21 ± 4 | 0.85 |

The G1 group received 1 g of intra-articular tranexamic acid and the G2 group received 2 g of intra-articular tranexamic acid. Both groups received 15 mg kg$^{-1}$ IV at 20 min at induction and then 10 mg kg$^{-1}$ in oral administration 6 and 12 hours after induction dose IV of tranexamic acid. Results were expressed in median ± median absolute deviation. D, Day; g dL$^{-1}$, grams per deciliter; Ht, Hematocrit; NS, Not Significant.
$p < 0.05$, [a] Preoperative vs. D1, [b] Preoperative vs. D2, [c] Preoperative vs. D3.

**Table 3** Preoperative and postoperative hemoglobin values.

| | G1 | G2 | *p*-value |
|---|---|---|---|
| Number | 50 | 50 | |
| Preoperative Hb (g dL$^{-1}$) (D0) | 14 ± 1 | 14 ± 0.8 | 0.39 |
| Hb at D1 (g dL$^{-1}$) | 12 ± 1 | 12 ± 1 | 0.37 |
| Hb at D2 (g dL$^{-1}$) | 10 ± 2[b] | 11 ± 1[b] | 0.88 |
| Hb at D3 (g dL$^{-1}$) | 11 ± 1[c] | 11 ± 1[c] | 0.82 |
| Hb (% lost) between D0–D1 | 11 ± 4 | 12 ± 4 | 0.69 |
| Hb change (% of change) between D0–D3 | 21 ± 7 | 22 ± 5 | 0.71 |

The G1 group received 1 g of intra-articular tranexamic acid and the G2 group received 2 g of intra-articular tranexamic acid. Both groups received 15 mg kg$^{-1}$ IV at 20 min at induction and then 10 mg kg$^{-1}$ in oral administration 6 and 12 hours after induction dose IV of tranexamic acid. Results were expressed in median ± median absolute deviation. D, Day; g dL$^{-1}$, grams per deciliter; Ht, Hemoglobin; NS, Not Significant.
$p < 0.05$, [a] Preoperative vs. D1, [b] Preoperative vs. D2, [c] Preoperative vs. D3.

related reactions and fluid overload. In addition, transfusions increase the length of hospital stay and hospital costs.[12] The risks and costs of blood transfusion have generated interest in blood conserving strategies. These include hypotensive anesthesia, intraoperative blood salvage as well as the use of erythropoietin and antifibrinolytic agents.[3,13]

Tranexamic Acid (TXA) is an antifibrinolytic that competitively inhibits the activation of plasminogen to plasmin.[3] TXA

can also directly inhibits plasmin activity, but higher doses are required.[3] As a result, there is a decrease in proteolytic action on fibrin monomers and fibrinogen, which results in clot stabilization.[3] TXA has been used to decrease blood loss and transfusion rates without increasing of thrombotic events.[3–5,8,13]

Despite several clinical studies with TXA proving the efficacy of TXA in total knee arthroplasty, no consensus has been reached regarding the optimal regimen for TXA administration.[14–19] Study differences could be explained by different surgical techniques; differences in dosing regimens for TXA; and in indications for blood transfusion across hospitals.[14–19] However, besides safety, efficiency and costs are the crucial parameters to achieve the best administration method for any drug.[20,21]

Systemic (IV), intra-articular and oral are the most routinely used TXA regimens and they have been shown to be safe and effective.[5,16,18,21] In a meta-analysis done by Li et al.,[20] they demonstrated that combined administration of TXA in patients with total knee arthroplasty was associated with significantly reduced total blood loss, transfusion requirements, postoperative hemoglobin decline and length of hospital stay compared to single application.[20] Moreover, no adverse effects, such as superficial infection, Deep Venous Thrombosis (DVT) or Venous Thromboembolic Events (VTE) were associated with TXA.[20] The risk of DVT or overall risk of a VTE following TXA use in total knee arthroplasty has been thoroughly addressed and until now studies have not revealed an increase in DVT or overall VTE rates with using TXA.[19,22]

Concerning plasma levels after TXA administration, studies done in healthy volunteers demonstrated that the time taken for maximum plasma levels of TXA to be reached has been reported to be 30 minutes for intramuscular, two hours for oral administration, and 5 to 15 minutes for intravenous injection.[23,24] Plasma levels after topical TXA are around 70% lower than those after IV administration. The levels of TXA in the plasma after low (1.5 g) and high (3.0 g) doses were 4.5 mg $L^{-1}$ and 8.5 mg $L^{-1}$, respectively, whereas the plasma level 1 hour after 10 mg $kg^{-1}$ of IV TXA was 18 mg $L^{-1}$.[25]

The timely administration of TXA varied from one single preoperative loading TXA dose to continuous infusion after surgery.[3,4] Blanie et al. assessed the extent of postoperative hypercoagulability by measuring the association between elevated thrombin generation and increased thromboembolic risk. This study showed that fibrinolysis peaked 6 hours after the end of surgery and maintained for about 18 hours after surgery. They concluded that when administered for up to $16 \pm 2$ hours after surgery, TXA reduced postoperative fibrinolysis.[26]

In our protocol we used a combined regimen of TXA administration because it has been shown to be more effective than the single regimen without increase in complications.[5,6,16,19] Combined regimens of administration of TXA may be responsible for equivalent reductions in blood loss and blood transfusion requirements shown in the G1 and G2 groups without significant increase in postoperative complications. Decreases in the levels of hematocrit and hemoglobin were similar in both groups and there were no statistically significant differences between days 1, 2 and 3 (Tables 2 and 3).

Patients taking aspirin represented 20% and 16% of patients in G1 and G2, respectively, and there were no statistically significant differences in blood loss between both groups. These results suggest that there are no benefits to using the higher dose of intra-articular TXA.

## Conclusion

This randomized controlled trial does not show superiority of 2 g of intra-articular tranexamic acid compared to 1 g. As part of a multimodal protocol, both regimens allowed equal control of blood loss. The absence of difference in blood loss for patients using aspirin suggests that the lower dose of intra-articular TXA could be also used in these patients. Further studies will be required to confirm these results.

## Conflicts of interest

The authors declare no conflicts of interest.

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