Article published online: 2023-05-25



# Comparison of Blood Loss with the Use of Intravenous and Intraarticular Tranexamic Acid *Versus* Isolated Intraarticular in Primary Knee Arthroplasty*

## *Comparação da perda sanguínea com a utilização do ácido tranexâmico endovenoso e intra-articular versus intra-articular isolado em artroplastia primária de joelho*

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Rev Bras Ortop 2023;58(2):320–325.

**Abstract**

**Objective** The objective of this work is to compare blood loss during primary knee arthroplasty with the use of intravenous and intraarticular (IV + IA) tranexamic acid *versus* intraarticular (IA) tranexamic acid alone.

**Methods** This is a randomized, double-blind clinical trial. Patients with indication for primary total knee arthroplasty were recruited in a specialized clinic, where they were operated by the same surgeon, always using the same surgical technique. Thirty patients were allocated in the IV + IA tranexamic acid group and 30 patients in the IA tranexamic acid group, according to randomization. Blood loss was compared through hemoglobin, hematocrit, drain volume, and blood loss estimation (Gross and Nadler calculus).

**Results** After collection, data from 40 patients were analyzed, 22 in the IA group and 18 in the IV + IA group. There were 20 losses due to collection error. Between groups IA and IV + IA, there were no significant differences in 24 hours between hemoglobin levels (10.56 vs. 10.65 g/dL; $F_{1.39} = 0.63$, $p = 0.429$), erythrocyte (3.63 vs. 3.73 million/mm$^3$; $F_{1.39} = 0.90$, $p = 0.346$); hematocrit (32.14 vs. 32.60%; $F_{1.39} = 1.39$,

**Keywords**
- arthroplasty, replacement, knee
- tranexamic acid
- blood loss

* *Work developed at Regina Hospital, Novo Hamburgo, RS, Brazil.*

**received**
December 29, 2021
**accepted**
September 12, 2022

**DOI** https://doi.org/10.1055/s-0042-1757958.
**ISSN** 0102-3616.



Thieme Revinter Publicações Ltda., Rua do Matoso 170, Rio de Janeiro, RJ, CEP 20270-135, Brazil

$p = 0.240$); drainage volume (197.0 vs. 173.6 mL; $F_{1.39} = 3.38$ $p = 0.069$); and estimated blood loss (1,002.5 vs. 980.1; $F_{1.39} = 0.09$, $p = 0.770$). The same occurred in comparisons conducted after 48 hours postoperatively. Time was a significant factor for the change of all outcome variables. However, the treatment did not modify the effect of time on these outcomes. No individual presented any thromboembolic event during the work period.

**Conclusions** The use of IV + IA tranexamic acid showed no advantage in reducing blood loss when compared to the use of IA tranexamic acid alone in primary knee arthroplasties. This technique proved to be safe, since no thromboembolic event occurred during the development of the work.

## Resumo

**Objetivo** O objetivo desse trabalho é comparar a perda sanguínea durante a artroplastia primária de joelho, com a utilização do ácido tranexâmico endovenoso e intra-articular (EV + IA) *versus* intra-articular (IA) isolado.

**Métodos** Trata-se de um ensaio clínico randomizado, duplo cego. Pacientes com indicação de artroplastia total primária de joelho foram captados em clínica especializada, onde foram operados pelo mesmo cirurgião, utilizando sempre a mesma técnica cirúrgica. Trinta pacientes foram alocados no grupo ácido tranexâmico EV + IA e 30 pacientes, no grupo IA, conforme randomização. Foi comparada a perda sanguínea através dos níveis de hemoglobina, hematócrito, volume do dreno e estimativa da perda sanguínea (EBL) (cálculo de Gross e Nadler).

**Resultados** Após a coleta, foram analisados os dados de 40 pacientes, sendo 22 do grupo IA isolado e 18 do grupo EV + IA. Ocorreram 20 perdas por erro de coleta. Entre os grupos IA e EV + IA, não ocorreram diferenças significativas em 24 horas entre os níveis de hemoglobina (10,56 vs. 10,65 g/dL; $F_{1,39} = 0,63$, $p = 0,429$), eritrócito (3,63 vs. 3,73 milhões/mm$^3$; $F_{1,39} = 0,90$, $p = 0,346$), hematócrito (32,14 vs. 32,60%; $F_{1,39} = 1,39$; $p = 0,240$), volume de dreno (197,0 vs. 173,6 mL; $F_{1,39} = 3,38$; $p = 0,069$) e estimativa de perda sanguínea (1.002,5 vs. 980,1; $F_{1,39} = 0,09$; $p = 0,770$). O mesmo ocorreu nas comparações realizadas 48 horas pós-operatório. O tempo foi fator significativo para a mudança de todas as variáveis de desfecho. Porém, o tratamento não modificou o efeito do tempo nesses desfechos. Nenhum indivíduo apresentou qualquer evento tromboembólico durante o período do trabalho.

**Conclusões** O uso do ácido tranexâmico EV + IA não demonstrou vantagem em redução de perda sanguínea quando comparado ao uso de ácido tranexâmico IA isolado nas artroplastias primárias de joelho. Esta técnica demonstrou-se segura, visto que nenhum evento trombo-embólico ocorreu durante o desenvolvimento do trabalho.

**Palavras-chave**
- artroplastia do joelho
- ácido tranexâmico
- perda sanguínea

## Introduction

Intra and postoperative bleeding remains an essential issue in total knee arthroplasty (TKA) , because, in addition to impacting on hospitalization time and economic aspects, it can cause pain, edema, anemia, and risk of blood transfusion need, which, in turn, can generate disorders such as immune reaction, transmission of pathogens, and cardiac and pulmonary complications.[1–4] Several strategies have already been proposed to reduce allogeneic blood dependence in major surgeries. These include preoperative autologous blood storage, normovolemic hemodilution, hypotensive anesthesia, use of the cell recovery machine, and use of drugs with antifibrinolytic properties, such as aprotinin, epsilon-aminocaproic acid and tranexamic acid (TXA).[2]

Tranexamic acid is a synthetic antifibrinolytic drug, the effect of which results from the formation of a reversible complex with plasminogen and plasmin, inhibiting fibrinolysis and preventing fibrin clot lysis. In addition to also acting on partial block age of plasmin-induced platelet aggregation.[4–6]

Several studies have been carried out to prove the efficacy and safety of this medication during TKA procedures.[5] In a recent meta-analysis,[7] it was demonstrated that the amount of blood loss and the number of transfusions per patient

were lower, and the proportion of patients requiring a blood transfusion was lower in the group using tranexamic acid compared with the placebo group. Likewise, no significant difference was found in prothrombin time, partial thromboplastin time, deep vein thrombosis, and pulmonary embolism.[7] A prospective randomized study concluded that the use of TXA can reduce not only blood loss, but also postoperative joint effusion.[8] Similarly, in a retrospective study[9] in which the use or not of tranexamic acid was compared between knee or hip arthroplasty patients with a previous history of deep vein thrombosis (DVT), there was no clear increased risk of recurrence in those who used TXA

Also, different study methodologies have already been used to prove the efficacy of TXA. Most of these studies have not demonstrated superiority of technique when comparing IA or IV application.[10–15]

In a 2018[16] metaanalysis, strong evidence was found to support the efficacy of TXA to decrease blood loss and transfusion risk after primary TKA. However, no formulation, dosage, or number of doses provided an obvious advantage. In this same metaanalysis, the authors reported that moderate evidence supports preincision administration of TXA to improve efficacy.

The objective of this work is to compare blood loss in patients submitted to TKA, using intravenous and intraarticular (IV + IA) tranexamic acid versus isolated intra-articular (IA) tranexamic acid. Thus, we intend to verify if there is a difference in blood loss markers between treatment groups and to collaborate in the knowledge about the use of this important drug for the improvement of knee arthroplasty surgery

## Materials and Methods

The design of the present study consists of a randomized double-blind clinical trial.

The research protocol and free and informed consent form were submitted and approved by the ethics committee of Hospital Moinhos de Vento de Porto Alegre (CAEE n°: 63283216.6.0000.5330). Patients with indication for primary knee arthroplasty, without complex deformities, who require prostheses with higher degrees of constriction (primary prosthesis used) were included. These were recruited in a specialized clinic, always evaluated by the same professional. The procedures were performed in the operating room of our hospital, by the same surgeon, using the same surgical technique, using pneumatic tourniquet, and portovac drain in the postoperative period.

During the procedure, a medial patellar approach was used, followed by soft-tissue balancing and bone cuts (the same instrumental and the same type of prosthesis were always used), to achieve the equalization of the flexion and extension spaces and the stability of the prosthesis. Bone cap in the femoral canal was used in all procedures. In no case, the release of the lateral retinaculum was performed, and in all procedures the patella was replaced.

The maximum tourniquet time considered was 120 minutes. Loosening always occurred after the final closure of the skin.

The patients were submitted to the same postoperative protocol, already with the beginning of physiotherapy and mobilization on the first day. The Portovac drain, which was kept closed for 2 hours and then opened, was removed and quantified in 24 hours, always by the same evaluator. This approach does not present strong support in the literature, since there is no strong evidence regarding the use of the drain, or the amount of time that it should be kept closed and when it should be opened.[17–19]

The selected individuals were randomized, using the *RESEARCH RANDOMIZER* (www.randomizer.org) website for two groups: The IA + IV was subjected to the application of IV tranexamic acid, 15 mg/kg, after anesthetic induction and before surgical incision, and IA infiltration of 2 g (8 ampoules) after the closure of the articular retinaculum. The isolated IA group was subjected only to the application of IA transexamic acid, 2 g, after the closure of the medial retinaculum. It is noteworthy that neither the surgeon nor the patient knew about the composition of the groups. The doses used were based on the literature, where there is no absolute consensus on exact doses. Studies show that IA doses of 1 to 3 g have similar effects, as well as doses of 10 to 20 mg/kg.[20,21]

Randomization was controlled by an auxiliary technique, which informed the anesthesiologist about which patients should have the IV medication.

There was no need to use a control group because the benefit of tranexamic acid during the knee arthroplasty procedure is well-established, so the only doubt was regarding the methodology of its use.[7,8,10,15,16]

For data collection, a questionnaire was applied to the patients, 24- and 48-hours blood counts were requested, and portovac drain volume was measured at 24 hours postoperatively, always by the same evaluator.

Blood loss was compared by preoperative and postoperative blood count (24 and 48 hours), quantification of total volume of blood drained in 24 hours postoperatively, and blood loss estimation (GROSS and NADLER calculations). For standardization, the approach of tolerating a time difference in the collection of the blood count examination 24 and 48 hours postoperatively of 2 hours before or after the expected time was adopted.

Sixty patients met the requirements for performing the procedure, but only 40 individuals had all the data available at the end of the collection to perform the necessary comparations. Twenty patients were excluded due to data collection problems, generated by errors in the collection. Of these, 8 patients had a 24-hour blood count examination after the tolerance period, 6 of the 48-hour tests were collected out of time, and 6 patients had the portovac drain content incorrectly disregarded or measured by another professional. Sample calculation was not performed to determine the number of participants.

The exclusion criteria were history of neurovascular injury, history of thromboembolic event, coagulopathies, continuous use of medication that interfere in coagulation cascade, and diagnosis of secondary degenerative joint disease, in addition to any error caused in data collection.

For statistical analysis, a *t*-test was performed to evaluate the differences between preoperative variables, to evaluate the conditions of equality of the groups by weight, height, hemoglobin level, erythrocytes, and hematocrit.

To evaluate the difference between the treatment groups, as well as the interaction between treatment and time, an analysis of variance (ANOVA) was performed. The probability value (*p*-value) was set at $\alpha = 0.05$.

## Results

Among the 40 patients in the sample, 18 were allocated in the IA + IV group, and 22 in the isolated IA group.

►**Table 1** shows the sample data before the procedures, showing that there were no differences between the groups regarding height ($t_{46} = -0.585$; $p = 0.562$), weight ($t_{44} = -0.306$; $p = 0.761$), hemoglobin level ($t_{48} = -0.536$, $p = 0.595$), erythrocytes ($t_{48} = -0.925$, $p = 0.360$), and hematocrit ($t_{48} = -0.616$, $p = 0.541$).

►**Table 2** shows the differences in outcomes between the treatment groups in the postoperative period.

No differences were found between the IA and IA + IV groups when hemoglobin levels were compared, both in the 24-hour postoperative (PO) and in the 48-hour PO periods ($F_{1.39} = 0.63$, $p = 0.429$). Similarly, there was no difference in hematocrit levels in the period of 24 and 48 hours PO ($F_{1.39} = 1.39$, $p = 0.240$), EBL in the period of 24 and 48 hours PO ($F_{1.39} = 0.09$, $p = 0.770$), erythrocyte levels in the period 24 hours PO ($F_{1.39} = 0.90$, $p = 0.346$), and volume of blood drained in the period of 24 hours PO ($F_{1.39} = 3.38$ $p = 0.069$).

An analysis of variance was also performed to verify the interaction between time and treatment groups. Time was a significant factor for the change in mean hemoglobin levels ($F_{1.39} = 116.45$; $p < 0.001$), hematocrit ($F_{1.39} = 132.78$; $p < 0.001$), erythrocytes ($F_{1.39} = 99.61$; $p < 0.001$), and EBL ($F_{1.39} = 4.00$; $p = 0.049$). However, there was no interaction between the time and treatment factor, demonstrating that the treatment did not modify the effect of time to change mean hemoglobin levels ($F_{1.39} = 0.02$; $p = 0.877$), hematocrit ($F_{1.39} = 0.01$; $p = 0.928$), erythrocytes ($F_{1.39} = 0.00$; $p = 0.990$), and EBL ($F_{1.39} = 0.00$ $p = 0.990$).

During the period of work, there was no occurrence of embolic thrombus or need for blood transfusion in the individuals involved.

## Discussion

The present research aimed to compare the effect of the application of IV + IA tranexamic acid, with the application of isolated IA during primary knee arthroplasty procedure. As a result of the work, no difference was found in the parameters of blood loss, evaluated within the combined application group, when compared with the isolated IA application.

During the last decade, greater attention has been paid to the management of blood loss in TKA procedures due to the potentially associated unfavorable outcomes.[21]

**Table 1** Sample description before the procedure

| | Average (±SD) | | |
|---|---|---|---|
| | IA | IA + IV | *P*-value |
| Height (m) | 1.63 (±0.096) | 1.64 (±0.093) | 0.761 |
| Weight (Kg) | 81.36 (±11.26) | 83.48 (±13.27) | 0.562 |
| Hemoglobin (g/dL) | 13.23 (±1.20) | 13.43 (±1.41) | 0.595 |
| Erythrocytes (millions/mm$^3$) | 4.48 (±0.38) | 4.59 (±0.45) | 0.360 |
| Hematocrit (%) | 39.92 (±3.43) | 40.54 (±3.77) | 0.541 |

Abbreviations: IA, intraarticular infiltration of tranexamic acid; IA + IV, intravenous and intraarticular infiltration of tranexamic acid.
The differences between the groups were analyzed using t-tests.
Source: authors.

**Table 2** Postoperative results

| | IA | IA + IV | IA | IA + IV |
|---|---|---|---|---|
| | 12:00 p.m. | | 48h | |
| Hemoglobin (g/dL) | 10.56 (±1.00) | 10.65 (±1.27) | 10.31 (±1.22) | 10.49 (±1.07) |
| Hematocrit (%) | 32.14 (±3.10) | 32.60 (±3.57) | 30.91 (±3.43) | 31.86 (±3.25) |
| EBL | 1,002.46 (±226.59) | 980.092 (±429.89) | 1,161.92 (±279.00) | 1,137.51 (±466.85) |
| Erythrocytes (millions/mm$^3$) | 3,627 (±0.37) | 3,734 (±0.46) | | |
| Drainage volume (mL) | 197.0 (±81.32) | 173.6 (±76.66) | | |

Abbreviations: IA, intraarticular infiltration of tranexamic acid; IA + IV, intraarticular plus intravenous application of tranexamic acid.
The difference between groups was analyzed using ANOVA with repeated measures with interaction of groups by time.
Source: authors.

Blood loss during the procedure is estimated to range from 1,450 to 1,790 mL leading many patients to anemia and the need for postoperative transfusions.[23] Studies may confirm the hypothesis that blood loss is higher in patients undergoing knee arthroplasty not treated with tranexamic acid.[24]

In recent research, the efficacy and safety of TXA in reducing blood loss and the need for transfusions was evidenced,[25] which came in agreement with meta-analyses on the subject.[7,16,26] Numerous methodologies have already been used to evaluate the effect and safety of the medication. Topical application compared to control group demonstrated a 20 to 25% reduction in blood loss, without increasing the risk of thromboembolic events.[10] This result corroborates the finding of a randomized double-blind study that made the same comparison and demonstrated a reduction in the need for blood transfusion, and a reduction in blood loss, without significantly altering adverse effects.[11] When comparing IV application with IA application alone, no superiority was demonstrated between the two methodologies.[12]

In one study,[28] the use of Isolated IV acid, and the use of isolated IA was compared with oral formulation. This randomized controlled study indicated that 2 g of oral TXA resulted in similar blood loss when compared with 20 mg/kg of IV TXA or 2 g of IA TXA without closed suction drain and tourniquet.

A study compared the use of IV + IA application with isolated IA or IV alone. It was found that the combined application had a lower total blood loss, occult loss, lower reduction of postoperative hemoglobin, as well as reduction in fibrin and d-dimer degradation products, indicating a superiority in the prevention of blood loss and hyperfibrinolysis during TKA.[29]

When compared to the combined application, IV + IA, dividing the group into a dose of 1 or 2 g of IA application, a randomized double-blind study showed no enhanced efficacy with increased dose.[30]

In a recent study, it was stated that topical administration of tranexamic acid has some advantages, the main one being the possibility of using lower doses. In addition, it can avoid the risks associated with systemic absorption of the medication, with the possible risk of hypercoagulation status.[27]

Regarding its safety, in a metaanalysis already mentioned, it was demonstrated that TXA did not cause differences in prothrombin time, activated partial thromboplastin time and in the prevalence of deep venous thrombosis and pulmonary thromboembolism.[7] However, the same study cites that higher quality randomized controlled trials are needed to strengthen the conclusion that TXA does not increase complication rates in TKA.

In the present study, the outcomes were similar to those of the available literature. In the 40 patients evaluated, none of them had an unfavorable outcome, such as DVT, pulmonary thromboembolism, or the need for blood transfusion. Also, when the groups were compared, there were no differences in the parameters evaluated: drain volume, estimated blood loss at 24 and 48 h PO, hemoglobin levels at 24 and 48 h PO, hematocrit at 24 and 48 h PO, and erythrocytes at 48 h PO.

However, this study should be interpreted in the light of its limitations. First, the fact that this study does not present a placebo control group may limit the interpretation of TXA efficacy. However, extensive previous literature demonstrates its efficacy, and generating a placebo-only treatment group can be considered an ethical problem, in the sense of having a group to determine the benefit of an already established treatment. According to this clinical trial, there is a sample of only one research center with a limited sample size, since no sample size calculation was applied. It is possible that the size of the IV TXA group is small and that a larger sample would be required to detect a difference.

Thus, it can be concluded that it is likely that the isolated use of IA tranexamic acid, at a dose of 2 g, infiltrated after the closure of the medial knee retinaculum, can be used safely, and without the need for adding an IV dose, to reduce bleeding in arthroplasty procedures, avoiding the possible systemic effects of IV use of the substance.

## Conclusion

Tranexamic acid is a drug that has been studied more frequently in recent decades to minimize blood loss in major orthopedic surgeries. Several studies with different methodologies have already demonstrated its efficacy and safety. This study contributes to the literature by demonstrating that the isolated use of IA TXA can be used to reduce blood loss in primary knee arthroplasties, minimizing the need for additional IV dose during the procedure.

Financial Support
There was no financial support from public, commercial, or non-profit sources.

Conflict of Interests
The authors declare that there is no conflict of interests.

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