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Original Article

Comparative study of topical *vs.* intravenous tranexamic acid regarding blood loss in total knee arthroplasty☆

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ABSTRACT

Objective: To compare topical *vs.* intravenous tranexamic acid (TA) in total knee arthroplasty regarding blood loss and transfusion.
Methods: Ninety patients were randomized to receive TA intravenously (20 mg/kg in 100 mL of saline; group IV), topically (1.5 g in 50 mL of saline, sprayed over the operated site, before release of the tourniquet; topical group), or intravenous saline (100 mL with anesthesia; control group). The volume of drained blood in 48 h, the amount of transfused blood, and the serum levels of hemoglobin and hematocrit before and after surgery were evaluated.
Results: The groups were similar for gender, age, weight, laterality, and preoperative hemoglobin and hematocrit levels ($p > 0.2$). The hemoglobin level dropped in all groups when comparing the preoperative and the 48-h evaluations: the control group decreased 3.8 mg/dL on average, while the IV group had a decrease of 3.0, and the topical group, of 3.2 ($p = 0.019$). The difference between the control and IV groups was confirmed by Bonferroni test ($p = 0.020$). The difference between the control group and the topical group was not significant ($p = 0.130$), although there was less reduction in hemoglobin in the topical group; the comparison between the IV group and the topical group was also not significant ($p = 1.000$).
Conclusion: Using topic and IV tranexamic acid decreased blood loss and the need for transfusion in total knee arthroplasty. Topical application showed results similar to IV use regarding the need for blood transfusion, but without the possible side effects of IV administration.

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Estudo comparativo com uso do ácido tranexâmico tópico e intravenoso em relação à perda sanguínea na artroplastia total do joelho

Palavras-chave:
Ácido tranexâmico
Artroplastia
Artroplastia de substituição
Joelho
Moduladores de fibrina
Antifibrinolíticos

RESUMO

Objetivo: Comparar o uso de ácido tranexâmico (AT) tópico e intravenoso na artroplastia total de joelho com relação à perda de sangue e necessidade de transfusão.
Métodos: Foram randomizados 90 pacientes para receber AT por via intravenosa (20 mg/kg em 100 mL de solução salina; grupo IV), tópico (1,5 g em 50 mL de solução salina, antes de soltar o torniquete; grupo tópico) ou solução salina intravenosa (100 mL com anestesia; grupo controle). O volume de sangue drenado em 48 horas, a quantidade de sangue transfundido e as concentrações sérias de hemoglobina e hematócrito foram avaliados antes e depois da cirurgia.
Resultados: Os grupos eram semelhantes quanto a sexo, idade, lateralidade e concentrações pré-operatórias de hemoglobina e hematócrito (p > 0,2). A concentração de hemoglobina diminuiu em todos os grupos quando as avaliações pré-operatória e em 48 horas foram comparadas: o grupo controle teve redução média de 3,8 mg/dL, enquanto o grupo IV teve diminuição de 3,0 e o grupo tópico, de 3,2 (p = 0,019). A diferença entre os grupos controle e IV foi confirmada pelo teste de Bonferroni (p = 0,020). A diferença entre os grupos controle e tópico não foi significativa (p = 0,130), apesar de haver uma menor diminuição da hemoglobina no grupo tópico; a comparação entre os grupos IV e tópico também não foi significativa (p = 1,000).
Conclusão: O uso de AT tópico e IV reduziu as perdas sanguíneas e a necessidade de transfusão na artroplastia total do joelho. O uso tópico mostrou resultado semelhante ao uso IV em relação à necessidade de transfusão sanguínea, porém sem os possíveis efeitos colaterais da administração IV.

Introduction

Total knee arthroplasty is a major orthopedic operation involving considerable loss of blood. Despite the common use of tourniquets, it is estimated that the volume of blood loss during this surgery is between 800 and 1200 mL.[1–5]

Bleeding during surgical trauma induces activation of the coagulation cascade[3,6] and then fibrinolysis.[1,7–9] Tranexamic acid, an antifibrinolytic agent, has demonstrated in having the ability of reducing blood loss, but there is still controversy regarding the dosage and the type of administration. Tranexamic acid inhibits fibrinolysis by competing with the lysine molecule at fibrinogen binding sites.[7,10,11] It is used successfully in heart surgery, organ transplants and gynecological surgery, procedures involving a large amount of blood loss.[10–14] In knee arthroplasty, intravenous tranexamic acid has been shown to reduce blood loss and the need for blood transfusion.[1,15–19] However, the dosage and type of administration are still controversial, and possible side effects such as nausea, headache and hypercoagulation, although rare, may occur.[18,20–22] A study measuring the plasma levels of plasminogen in peripheral blood suggests that the effect of tranexamic acid is greater at the site of the surgical wound than in the peripheral blood.[7]

We designed this randomized controlled trial to observe if there was any difference between the topical and intravenous administration of tranexamic acid in total knee arthroplasty regarding the volume of blood loss and the need for transfusion. The hypotheses tested here were: (1) the blood loss would be higher in the control group when compared to the others; (2) topical and intravenous administrations of the drug should be equally effective in reducing blood loss and the need for blood transfusion.

Material and methods

Study design and scenario

This is a randomized, single-blind, simulation-controlled clinical study performed in a large hospital between June and November 2014. The Research Ethics Committee approved the study protocol (number 27270814.0.0000.0085) and the patients signed the free and informed consent form before scheduling the date of surgery, after being fully informed about the procedures and design of the study. The study is enrolled in clinicaltrials.gov (protocol register NCT02323373).

Participants and surgical technique

Patients with unilateral total knee arthroplasty (TKA) as a result of Ahlbäch grade III, IV and V arthrosis were eligible and recruited at private clinics of the authors of this study. All patients underwent the same surgical technique with total posterior cruciate ligament resection, patellar arthroplasty, and femoral canal closure with a bone plug. No

patient was submitted to lateral release of the patella. Exclusion criteria were: history or identified risk of deep venous thrombosis or pulmonary embolism or history of coagulation or cardiovascular disorders; vascular diseases or current use of anticoagulant drugs; orthopedic surgery in the lower limbs.

The same prosthesis was used in all cases (Genesys 2, Smith & Nephew, Memphis, USA). Tourniquets were used in all patients. All patients received intravenous bolus hydration (8 mL/kg) immediately prior to surgery and 4 mL/kg/h of saline during the operation. The same anesthesia team participated in all surgeries. The same knee surgery team, with experienced surgeons (that is, there was no resident surgeon or in team training) performed all the operations. Hemostasis was done after tourniquet release before tissue closure. A suction drainage device was installed and used for 48 h (3.2 mm, Portovac, Zammi), the drained volume was recorded every six hours.

Patients received either regional (double-block) or general (when lumbar puncture was not possible) anesthesia. The regional anesthesia protocol included spinal anesthesia (4 mL of 0.5% bupivacaine) and placement of an epidural catheter. A patient-controlled analgesia pump (PAC) allowed pain control for 48 h after surgery, with 165 mL of saline (0.9%), fentanyl (15 mL) and ropivacaine (20 mL, 1%) with administration of 4 mL per hour, 6 mL bolus, 20-min repeat interval, and maximum dose of 60 mL in 24 h. General anesthesia was performed with propofol, fentanyl and cisatracurium besilate for tracheal intubation. Intravenous infusion pumps were maintained with propofol and opioids. PAC for intravenous analgesia included saline solution (0.9%, 95 mL,), morphine (50 mL, 1–2 mL/h, bolus of 1 mg every 15 min) and a maximum dose of 6 mL/h.

All patients of the three groups received the same postoperative care protocol, including physiotherapy with continuous passive movement equipment (for 1 h, 3 times a day), with gradual increase of flexion, initiated with 60° of knee flexion; prevention of venous thrombosis with elastic stockings and sodium enoxiparin (Clexane®, Sanofi) given subcutaneously once daily for 10 days.

Outcomes

The primary outcome analyzed in this study was the volume of blood loss in total knee arthroplasty. This was determined by the suction drain, with recording of the total volume in milliliters, measured 48 h after the end of surgery, when drainage systems were removed. Secondary outcomes were: need for transfusion (patient received two units of packed red blood cells every time hemoglobin levels were below 8.0 g/dL). One month before surgery and 24 and 48 h after surgery, all patients underwent hemoglobin and hematocrit serum levels, and the normalized international ratio and coagulation time were calculated. The age and sex of the patients were also recorded. Therefore, the variables analyzed in this study were: hemoglobin level, hematocrit, partial thromboplastin time (PTT), international normalized ratio (INR), volume of blood loss through the portovac drain and need for transfusion.

Sample size

We used the primary parameters to detect the differences and to assume the standard deviations with value of $\alpha = 0.05$ and with power of 80%; the sample size for each group was calculated to be 26 (Table 1). Expecting withdrawal and exits of about 10%, we decided to enroll 30 patients in each group.

Randomization, allocation and interventions

Randomization was performed by the anesthesiologist drawing lots of sealed envelopes, previously placed in a container with 90 similar envelopes (30 in each group) prepared in advance with an allocation ratio of 1:1:1.

Each patient was allocated to one of three groups: the topical group consisted of patients receiving a solution of 1.5 g tranexamic acid (50 g mg/mL, Transamin®, Zydus Nikkho) diluted in 50 mL saline (at 0.9%), which covered the entire operated area, and maintained for 5 min for absorption before tourniquet release. The intravenous group received 20 mg/kg of tranexamic acid diluted in 100 mL at 0.9% saline solution, administered with anesthesia in 10 min. Finally, the control consisted of patients who received only 100 mL of saline, also administered at the time of anesthesia running in 10 min.

Statistical analysis

For statistical analysis, SPSS software version 13.0 was used. Significance was set at 5%. We used the *t*-test for the paired analyses, the Chi-square test and the non-parametric Kruskal–Wallis and Mann–Whitney tests. We also used the analysis of variance (Anova) with the Bonferroni multiple comparisons method.

Results

During the study period, 102 patients were invited to participate. However, we had to exclude four patients due to cardiomyopathy, five due to previous events of thromboembolism, and three previously submitted to tibial osteotomies (Fig. 1). Therefore, we concluded the evaluations with 90 patients, 30 in each group. Of these patients, 80 were operated with regional anesthesia (double block) and 10 with general anesthesia (due to previous spine arthrodesis or other anatomical problems that hindered the performance of a new puncture). There were no surgical complications, no lesions or side effects, and no patient perished nor where there are any withdrawals.

Most patients were women (24 in the intravenous group, 21 in the topical group and 25 in the control group). The average age was 65.7 years (from 48 to 88). The three groups were homogeneous in terms of age, gender, body weight, laterality ($p > 0.05$), preoperative concentrations of hemoglobin ($p = 0.549$) and hematocrit ($p = 0.295$) and coagulation time ($p = 0.143$). The international normalized ratio (INR) was slightly different between the groups (1.01 in the control group, 1.07 in the intravenous group and 1.03 in the topical group, $p = 0.020$). In the Mann–Whitney test, the normalized

Table 1 – Parameters for calculating sample size.

Parameters	Hb	Ht	PTT	INR
Difference	1	10	3.5	0.06
Deviation	1.2	4	6	0.10
Alpha	5%	5%	5%	5%
Test power	80%	80%	80%	80%
Sample	14	4	26	24

Hb, hemoglobin; Ht, hematocrit; INR, normalized international ratio; PTT, partial thromboplastin time.
Pairted *t* test (comparison of means).

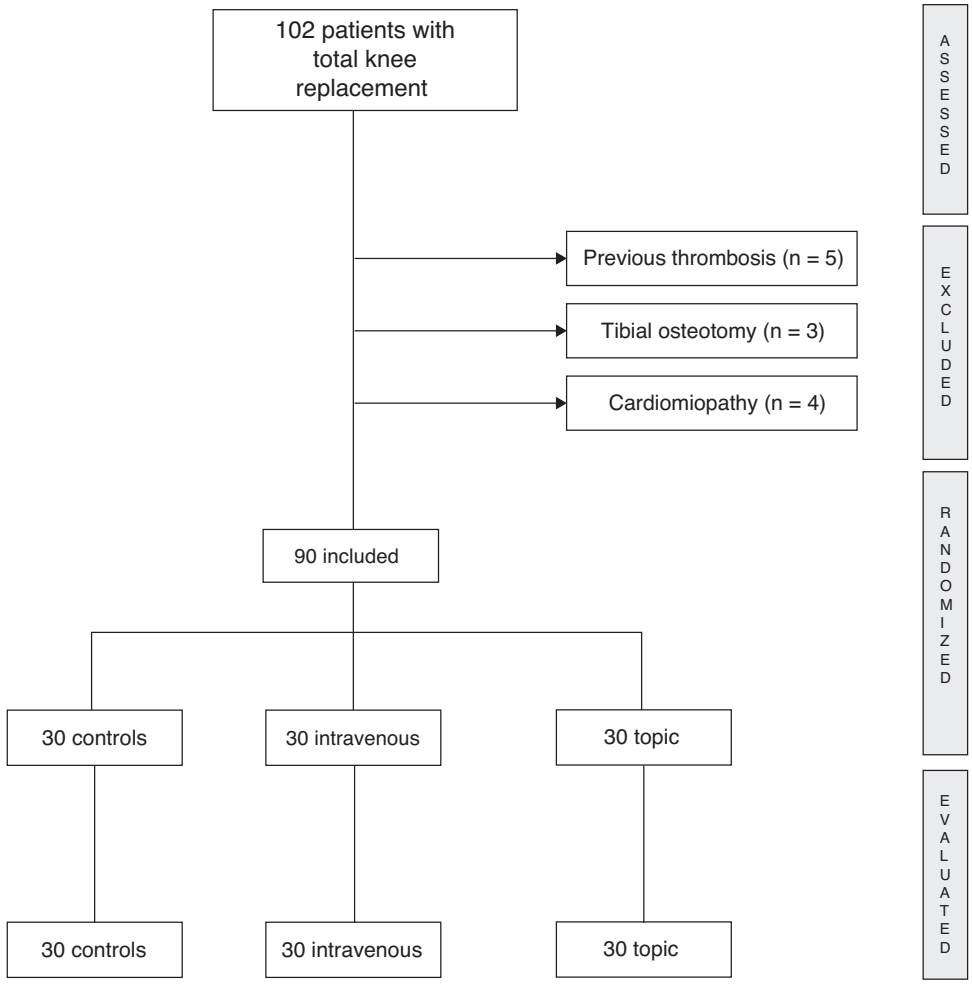

Fig. 1 – Flowchart for patient enrolment. One hundred and two patients with total knee prosthesis were evaluated.

international ratio was significantly different between the control and intravenous groups ($p = 0.008$) and between the intravenous and topical groups ($p = 0.042$), but it was similar in comparison to the topical and control groups ($p = 0.470$). Hematocrit and PTT were not significantly different between groups. Table 2 shows the mean values at the beginning of the study and the standard deviations in each group.

Hemoglobin concentration decreased in all groups when the preoperative evaluations were compared, and in 48 hours: there was a reduction of 27.40% in the control group, 23.18% in the topical group, and 22.30% in the intravenous group ($p = 0.001$ for all). The difference between the groups was significant: the control group decreased by 3.8 mg/dL on average, while the intravenous group had a reduction of 3.0 and the topical group, 3.2 ($p = 0.019$). Another Bonferroni comparison showed that there was a significant difference between the control and intravenous groups ($p = 0.020$), whereas there was no difference between control and topical groups ($p = 0.130$), and intravenous and topical groups ($p = 1.000$). Fig. 2 shows a box diagram with such comparisons.

The volume of blood in the drainage device 48 h after surgery was significantly different between the groups, as shown in Table 3. The Bonferroni test, which compared pairs showed that the difference between the control and

Table 2 – Mean basal values and standard deviation (SD) for each group and comparison among groups.

Variable	Group	Mean	Median	SD	Minimal	Maximum	p
Hb	Control	13.5	13.5	1.1	10.7	15.3	0.549[a]
	IV	13.9	13.5	1.2	11.9	16.7	
	Topical	13.8	13.7	1.3	10.6	16.5	
Ht	Control	41.1	41.2	3.0	32.3	46.2	0.295[a]
	IV	42.1	42.3	3.8	30.9	50.5	
	Topical	42.5	42.6	3.3	35.5	48.4	
PTT	Control	28.2	27.5	3.8	23.4	37.1	0.143[a]
	IV	29.8	29.5	3.3	24.7	40.0	
	Topical	29.9	29.3	3.8	24.4	39.4	
INR	Control	1.01	1.01	0.07	0.80	1.20	0.020[b]
	IV	1.07	1.07	0.08	0.99	1.32	
	Topical	1.03	1.02	0.06	0.86	1.18	

INR, normalized international ratio; IV, intravenous group; Hb, hemoglobin; Ht, hematocrit; PTT, partial thromboplastin time.

[a] Variance analysis – Anova.

[b] Kruskall–Wallis test.

Table 3 – Mean volume of blood drained and standard deviation (SD) for each group and comparison among the groups (variance analysis and Bonferroni multiple comparisons test).

Test	Group	Mean	Median	SD	Minimal	Maximum	p
Anova	Control	609	595	203	260	1.000	0.001
	IV	421	340	246	150	990	
	Topical	409	400	213	70	850	
Bonferroni	Control *vs.* IV						0.004
	Control *vs.* topical						0.004
	IV *vs.* topical						1.000

IV, intravenous group.

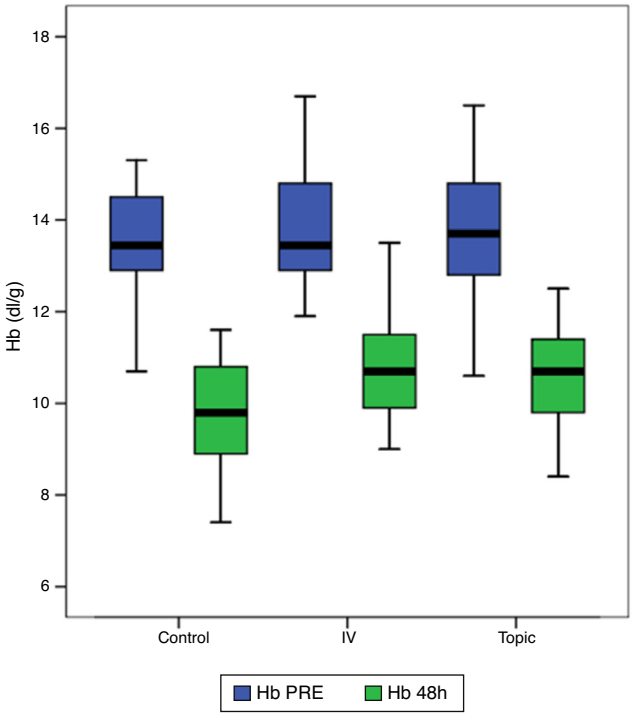

Fig. 2 – Graph shows the comparison of hemoglobin levels preoperatively (blue boxes) and 48 h after surgery (green boxes).

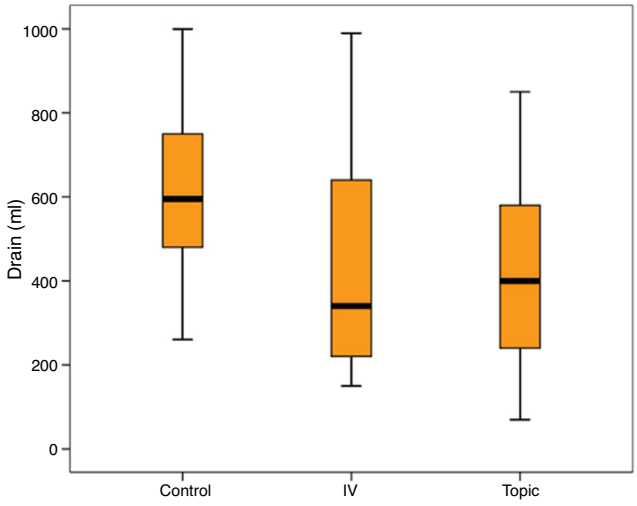

Fig. 3 – Graph showing the comparison of drain effective output in the three groups.

intravenous groups, and between the control and topical groups was significant, but the difference between the topical and intravenous groups was not significant. This is illustrated in Fig. 3.

Only six patients required blood transfusions, all belonging to the control group (20%).

Discussion

Most bleeding after total knee arthroplasty occurs after tourniquet removal.[9,23–26] Despite the controversies regarding postoperative outcomes, such as function and pain, tourniquets are widely used in total knee arthroplasty and actually reduce blood loss by half.[27] But they still carry risks of nerve damage and options for reducing blood loss are being investigated.

We conducted a randomized, controlled study in a Brazilian population study group that compared the topical and intravenous administration of an antifibrinolytic agent, tranexamic acid, which in some studies is administered prior to tourniquet application to slow the onset of fibrinolysis,[17] and has been shown to reduce postoperative blood loss in orthopedic surgery without thromboembolic events or other complications.[17,28–31] The drug was also studied in the Crash series of multicenter studies with trauma patients; it reduced the risk of death due to hemorrhage when administered within three hours of the trauma.[17,29,32,33]

In this study, we were able to confirm the hypothesis that blood loss would be greater in the control group, not treated with tranexamic acid, compared to two other groups that used the drug. This finding is consistent with the literature, confirming the antifibrinolytic effect of tranexamic acid.[1,15–19,30,34,35] In addition, we also confirm the second hypothesis: we have revealed that topical and intravenous administrations of the drug are equally effective in reducing blood loss.

The topical administration of tranexamic acid has some advantages, the main one being the possibility of using lower dosage.[36] In addition, it avoids the risks associated with the systemic absorption of the medication, with the possible risk of hypercoagulation,[37] with the use only of local action, and also slows the onset of fibrinolysis.[9,21] They can also be administered by intra-articular injection through the drain, shortly after closure, with clear effects on total blood loss and knee joint edema.[38] However, our study is one of the first to directly compare intravenous drug administration with local administration in total knee arthroplasty in a Brazilian population group. Our study demonstrated that the topical dose of 1.5 g was as effective as the intravenous dose of 20 g mg/kg of tranexamic acid in relation to the need for blood transfusion.

Maniar et al.[22] conducted a randomized, controlled trial comparing various tranexamic acid dosage schedules and included a group receiving a single local dose application of 3 g/100 mL saline solution in patients undergoing total knee arthroplasty. The authors compared local *vs.* intravenous administration of the drug, but it was a dosage study in which various intravenous administration schemes were compared with only one local administration regimen and dosage. The result of this study reported that to be effective, the use of IV tranexamic acid should be given in one initial dose at least during anesthetic induction. As in our study, they found significant differences between local administration of tranexamic acid and controls.

Options for minimizing bleeding in total knee arthroplasties are described in the literature, among them: local adrenaline use, the use of a navigation system for bone cuts and/or the use of hemostatic agents (Floseal®, Baxter).[39]

One of the limitations of our study is that it was not double-blind. Another limitation was the preoperative evaluations performed by different laboratories, but with the same methodology.

Conclusions

This randomized and controlled clinical study demonstrated that the IV use of tranexamic acid had the lowest blood loss regarding topical and control groups, but the topical use was sufficient to reduce the need for blood transfusions, without the possible side effects of the IV use in the total knee arthroplasty.

Conflicts of interest

The authors declare no conflicts of interest.

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