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INTRAARTICULAR EPSILON AMINOCAPROIC ACID VERSUS TRANEXAMIC ACID IN TOTAL KNEE ARTHROPLASTY

ACIDO ÉPSILON AMINOCAPROICO INTRA-ARTICULAR VERSUS ACIDO TRANEXÂMICO NA PRÓTESE TOTAL DO JOELHO

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ABSTRACT

Objective: To examine and compare the clinical efficacy of intraarticular epsilon aminocaproic acid (EACA) and tranexamic acid (TXA) in total knee arthroplasty (TKA). Methods: This study was a prospective, single-center, double-blinded randomized controlled trial, including sixty patients with osteoarthritis of the knee divided into two groups of 30 patients. In the TXA group, 1 g of TXA (0.05 g/ml) was applied intraarticularly, and in the EACA group, 4 g of EACA (0.2 g/ml) was applied intraarticularly. Serum hemoglobin (Hgb) and hematocrit (Htb) were measured during the preoperatively and 24 and 48 hours postoperatively. The range of motion and pain were evaluated by clinical examination. To evaluate knee function before and 2 months after surgery, the Western Ontario and McMaster Universities Index (WOMAC) questionnaire was used. Results: In total, 56 (93.3%) patients were evaluated up to the second postoperative month. No significant difference between the groups ($p > 0.05$) was found in the decrease in Hgb or Htb at 24 or 48 hours. Regarding assessment of the pain, WOMAC score and gain in knee flexion, no significant advantages up to 60 days after surgery ($p > 0.05$) were found. Conclusions: The decrease in Hgb and Htb during the first 48 hours postoperatively and the risk of transfusion were similar with the intraarticular use of 1 g of TXA and 4 g of EACA in TKA. The possible benefits regarding knee pain, gain in flexion and function were also similar for the two drugs. ***Level of Evidence II, Randomized, Double-Blinded, Single-Centre, Prospective Clinical Trial.***

Keywords: Total Knee Arthroplasty. Bleeding. Pain. Tranexamic Acid. Epsilon Aminocaproic Acid.

RESUMO

Objetivo: Avaliar e comparar a eficácia clinica do uso intra-articular do ácido épsilon aminocaproico (AEAC) versus o ácido tranexâmico (ATX) na prótese total do joelho. Métodos: Estudo clínico prospectivo, centro-único, duplo-cego e randomizado. Sessenta pacientes com osteoartrose de joelho foram incluídos. Os participantes foram divididos em dois grupos de 30 pacientes. No grupo ATX, foi aplicado 1 g de ATX (0.05 g/ml) intra-articular e, no grupo AEAC, foram aplicados 4 g de AEAC (0.2 g/ml) intra-articular. Valores séricos da hemoglobina (Hb) e hemtatócrito (Ht) foram dosados no pré-operatório e com 24 e 48 horas após a cirurgia. A amplitude de movimento e a dor também foram avaliadas no exame clínico. O índice WOMAC foi utilizado para avaliar a função do joelho antes e após dois meses da cirurgia. Resultados: Foram avaliados 56 (93.3%) pacientes até o segundo mês pós-operatório. Depois da cirurgia, não houve diferenças entre os grupos ($p > 0.05$) na queda do valor de Hb e Ht com 24 ou 48 horas. Com relação à avaliação da dor, WOMAC e ganho de flexão do joelho, não houve vantagem significativa para nenhum dos grupos até os 60 dias depois da cirurgia($p > 0.05$). Conclusão: A queda do valor da Hb e do Ht durante as primeiras 48 horas pós-operatórias e o risco de transfusão foram similares com o uso intra-articular de 1 g de ATX e 4 g de AEAC na artroplastia total do joelho. Os possíveis benefícios com relação ao controle da dor, ganho de flexão e função foram similares entre as duas drogas. ***Nível de Evidência II, Ensaio-Clínico Prospectivo, Randomizado, Duplo Cego, Centro-Único.***

Descritores: *Artroplastia Total do Joelho. Sangramento. Dor. Ácido Tranexâmico. Ácido Épsilon Aminocapróico.*

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INTRODUCTION

Antifibrinolytics have already been successfully used to reduce the need for transfusion in total knee arthroplasty (TKA).[1-3] TKA is associated with considerable blood loss.[3] Besides the risk of transfusion, excessive bleeding can impair the success of TKA through hematoma, swelling, stiffness, prolonged hospitalization, and delayed functional recovery and rehabilitation.[3] Epsilon aminocaproic acid (EACA) and tranexamic acid (TXA)

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are synthetic amino acid derivatives that interfere with fibrinolysis and promote hemostasis. Although the clinical efficacy of TXA in decreasing blood loss, improving the hemoglobin (Hgb) level and improving some functional parameters, such as pain and flexion, have been well demonstrated in TKA,[4] data on the effects of EACA in TKA have been reported in few published studies to date, and those studies have only investigated the intravenous use of EACA.[2,5,6] Due to the scarcity of this data, most surgeons prefer TXA over EACA, despite its higher cost in many countries.[1,6]

To our knowledge, this was the first trial of intraarticular EACA and TXA in TKA to determine if apparent differences in efficacy can be found.

The primary aim of this prospective, randomized trial was to examine and compare the clinical efficacy of intraarticular EACA and TXA in TKA. The study questions were if EACA and TXA were similar regarding blood conservation (defined by the transfusion rate and drop in Hgb and hematocrit [Htb]), postoperative pain control and postoperative gain in knee flexion; possible associations that have not yet been described were identified using a functional questionnaire.

Our hypothesis was that intraarticular TXA would be similar to intraarticular EACA in terms of antifibrinolytic effects after TKA.

MATERIALS AND METHODS

This study was a prospective, single-center, double-blinded randomized trial. The project was approved by Institution Ethics and Research Committee in July 2017 and was assigned the clinical trial in December 2017. All patients provided written informed consent to participate in the study.

Study population

During recruitment, between July 2017 and December 2018, patients (of both sexes) that had three-compartment osteoarthritis of the knee as an indication for TKA and were awaiting scheduling of the procedure, had no diagnosis of inflammatory disease, had no history of atrial fibrillation, pulmonary embolism, deep vein thrombosis, or surgery on the same knee, had no coagulopathy and were not using anticoagulant medications were eligible for inclusion. The TKA procedures were performed between October 2017 and July 2019. Inadequate closure of the joint capsule at the end of surgery, with identified leakage of the drug applied to the joint, was considered an exclusion criterion. The last follow-up was in September 2019.

Interventions

The blood of the patients was collected for serum Hgb and Htb measurements before surgery, in the operating room. Knee arthroplasty was performed with a standard medial parapatellar approach by two surgeons from the same hospital. A tourniquet was used in all subjects during the surgery until the wound was dressed. Cemented cruciate-substituting implants without patellar resurfacing were used in all procedures. After joint capsule closure, the surgeon left the operating room, and the random group assignment of the patient, determined using an electronic randomization program to divide the participants into 2 groups of 30 patients, was revealed. No patient was informed of the group assigned. In the TXA group, the auxiliary surgeon applied 1 g of TXA (0.05 g/ml) intraarticularly using a 20 ml syringe and a 40 × 1.2 mm needle before the operative wound was sutured (Figure 1). In the EACA group, the auxiliary surgeon applied 4 g of EACA (0.2 g/ml) intraarticularly using a 20 ml syringe and a 40 × 1.2 mm needle before the operative wound was sutured (Figure 1).

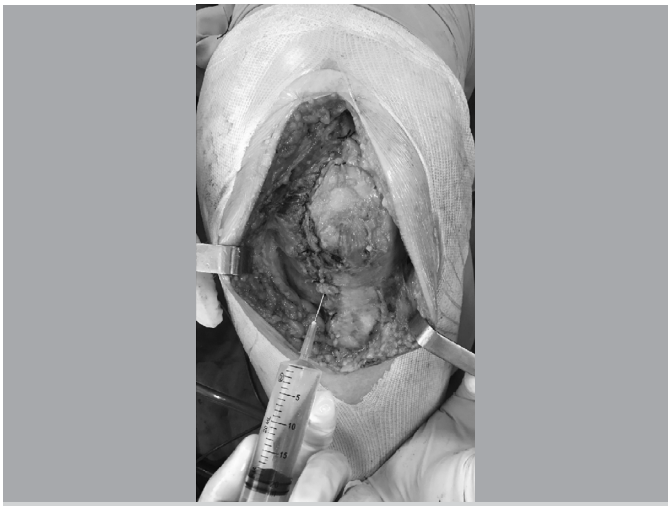

Figure 1. Application of drug in the joint cavity after joint capsule closure.

Data collection

Data were collected before and after surgery, as follows (Table 1):

Table 1. Model of the worksheet used for data collection at the different time points (before and after surgery).

	Before	24 h		48 h	20 days	60 days
Hgb	x	x		x		
Htb	x	x		x		
Knee flexion		x		x	x	x
Pain		x		x	x	x
WOMAC	x					x
Transfusion		x		x		
Surgical site		x		x	x	x
Signs of infection					x	x

Hgb: hemoglobin; Htb: hematocrit; pain: evaluation of pain on a numerical scale; WOMAC: evaluation of the Western Ontario and McMaster Universities Index; transfusion: assessment of the need for blood transfusion; surgical site: observation of the healing status; signs of infection: assessment of serum test results and the need for antibiotic therapy, surgical debridement or implant removal.

1. Serum Hgb and Htb were measured during the preoperative period and also 24 and 48 hours after surgery. The need for transfusion was evaluated for patients with values below 7 mg/dL and clinical signs of acute anemia.
2. The patients underwent clinical examinations at the following postoperative time points: 24 hours, 48 hours, between 15 and 25 days, and 2 months after surgery. a) Range of motion was evaluated using a goniometer. b) Pain was evaluated using an 11-point (0-10) numerical scale, on which zero indicated no pain, and 10 indicated the most intense pain ever felt. Each patient selected a single number that best represented the intensity of their pain at the time of the evaluation. c) The surgical site was evaluated by clinical examination.
3. To evaluate knee function before and 2 months after surgery, the Western Ontario and McMaster Universities Index (WOMAC) questionnaire was used.

Postoperative protocol used

1. During hospitalization, the following analgesics were prescribed: 1 g of intravenous dipyrone every 6 hours and 50 mg of tramadol hydrochloride every 8 hours.
2. Patients with pain equal or above 7 on the numerical pain scale received 4 mg of intravenous morphine every 4 hours, and this grade was considered in the evaluation for that period.
3. At the time of discharge, 1 g of dipyrone was given orally every 6 hours if there was pain, and 50 mg of tramadol hydrochloride

was given orally every 8 hours if pain persisted despite the use of dipyrone.
4. All patients received 40 mg of subcutaneous enoxaparin as prophylaxis for deep venous thrombosis in the hospital at 8, 24 and 48 hours after surgery, and 10 mg of rivaroxaban daily was prescribed for another 10 days at home.
5. Antibiotic prophylaxis was performed with 2 g of intravenous cefazolin during anesthetic induction, and 1 g of cefazolin was administered every 8 hours for 24 hours.

Statistical analysis

The statistical power of the sample was calculated using the sampsi command of STATA software (version 11, 2011, College Station, Texas, USA) for a comparative design of groups with repeated measures and using the reduction in Hgb as the parameter, and we found that 20 patients per group would guarantee a power of at least 95% for comparisons.
Comparisons between the two groups at all times with respect to all variables were performed using mixed-effects (random and fixed effects) linear regression models. Post-test orthogonal contrasts were used for comparisons. Intergroup comparisons regarding changes in Hgb and Htb at certain times were performed using Student's *t*-test. The significance level adopted for all comparisons was 5%.

RESULTS

In this study, 60 patients, including 30 in the TXA group and 30 in the EACA group, were followed until the second postoperative day (Figure 2). In total, 56 (93.3%) patients were evaluated up to the second postoperative month, including 27 (90%) in the TXA group and 29 (96.6%) in the EACA group. The mean patient age was 67.97 (41-85) years in the TXA group and 68.67 (46-83) years in the EACA group. In total, 22 women in the TXA group and 20 women in the EACA group were included. The two groups were statistically similar preoperatively regarding Hgb, Htb, knee flexion and WOMAC score (Table 2).

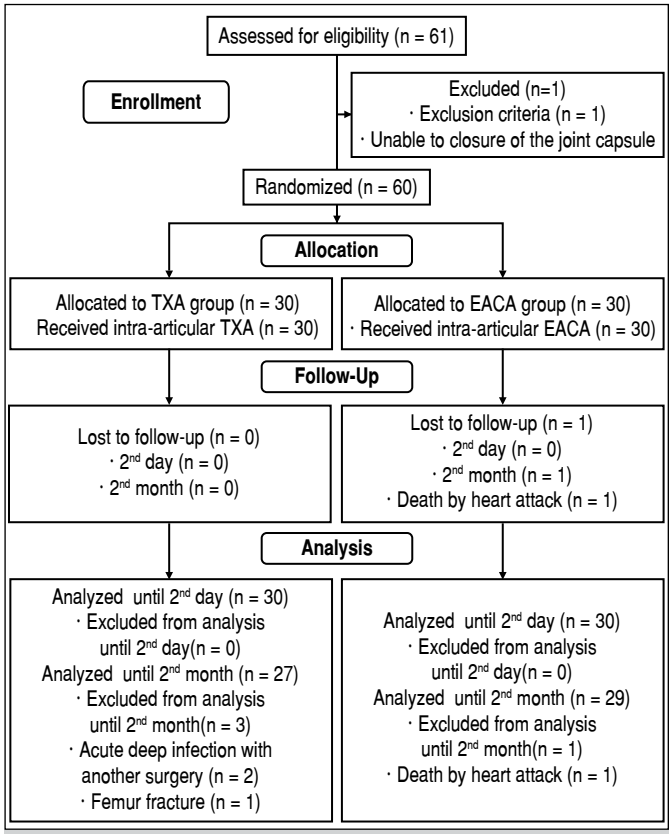

Figure 2. CONSORT flowchart.

Table 2. Demographic data.

	TXA group	EACA group	P value
Number of surgical patients	30	30	> 0.05
Number of patients followed to the 2nd day	30	30	> 0.05
Number of patients followed to the 2nd month	27 (90%)	29 (97%)	> 0.05
Mean age	67.97 (41-85)	68.67 (46-83)	> 0.05
Sex (man/woman)	8/22	10/20	> 0.05
Preoperative hemoglobin value (mean and standard deviation)	13.24 (1.48)	12.47 (1.6)	> 0.05
Preoperative hematocrit value (mean and standard deviation)	38.49 (4.15)	37.95 (5.34)	> 0.05
Preoperative knee flexion (mean and standard deviation)	106.5 (13.84)	98.33 (10.77)	> 0.05
Preoperative WOMAC score (mean and standard deviation)	66.93 (19.96)	68.57 (20.72)	> 0.05

Table 3 shows that no significant difference ($p > 0.05$) was found in the Hgb or Htb decrease at 24 or 48 hours after surgery between the groups.

Table 3. Hgb and Htb.

	TXA group (mean and standard deviation)	EACA group (mean and standard deviation)	P-value
Hgb drop at 24 hours	1.59 (1.11)	1.19 (0.82)	> 0.05
Hgb drop at 48 hours	2.54 (1.18)	2.48 (1.22)	> 0.05
Htb drop at 24 hours	4.82 (3.37)	3.68 (3.01)	> 0.05
Htb drop at 48 hours	7.29 (3.42)	7.04 (4.05)	> 0.05

Table 4 shows that no significant advantage was detected in either group regarding either pain or gain in knee flexion at 24 hours, 48 hours, 20 days or 60 days after surgery ($p > 0.05$).

Table 4. Evaluation of pain and flexion gain.

	TXA group (mean and standard deviation)	EACA group (mean and standard deviation)	P value
Mean pain at 24 hours	3.37 (2.58)	4.07 (3.17)	> 0.05
Mean pain at 48 hours	3.1 (2.75)	3.31 (3)	> 0.05
Mean pain at 20 days	2 (1.82)	2.24 (2.47)	> 0.05
Mean pain at 60 days	1.36 (1.81)	1.59 (1.86)	> 0.05
Flexion gain at 24 hours	66.17 (18.37)	74.17 (24.74)	> 0.05
Flexion gain at 48 hours	74.83 (17.88)	76 (24.26)	> 0.05
Flexion gain at 20 days	91.67 (12.89)	91.55 (15.18)	> 0.05
Flexion gain at 60 days	97.96 (17)	98.1 (12.57)	> 0.05

Regarding the WOMAC score, no differences between the two groups were found up to 2 months after surgery (Table 5).

Table 5. Comparison of WOMAC score between groups.

	TXA group (mean and standard deviation)	EACA group (mean and standard deviation)	P-value
WOMAC score at 2 months	19.96 (8.5)	20.72 (11.71)	> 0.05

During the follow-up of the 60 patients, four cases (6.7%) of wound dehiscence and superficial infection were successfully treated with dressings and oral antibiotics (two in the TXA group and two in the EACA group). Two cases (3.3%) of acute deep infection were treated; one required debridement, and one required implant removal (both in the TXA group). One (1.7%) manipulation was performed to treat arthrofibrosis (in the EACA group). In total, one (1.7%) diagnosed case of thrombosis in the TXA group was identified. One (1.7%) case of mortality due to a heart attack in the EACA group were detected. No patients required a blood transfusion (the transfusion criterion was an Hgb value less than 7 mg/dL in symptomatic patients). The identified complications were not significantly associated with EACA or TXA use (Table 6).

Table 6. Complications.

	TXA group	EACA group	Total
Wound dehiscence and superficial infection	2 (3.3%)	2 (3.3%)	4 (6.7%)
Acute deep infection	2 (3.3%)	0	2 (3.3%)
Manipulation due to arthrofibrosis	0	1 (1.7%)	1 (1.7%)
Thrombosis	1 (1.7%)	0	1 (1.7%)
Death	0	1 (1.7%)	1 (1.7%)
Transfusion	0	0	0
Total patients	5 (8.3%)	4 (6.7%)	9 (15%)

DISCUSSION

EACA and TXA function by a similar mechanism. Supported by robust scientific evidence, TXA is widely routinely used in TKA at many orthopedic surgery centers, reducing the risk of transfusion and costs.[7] However, fewer studies have analyzed EACA or compared the two drugs.[3]

We found only two clinical prospective studies in the literature, both of which were small trials showing similar efficacy for TXA and EACA.[1,5] We found only a prior retrospective study including a large number of patients that showed the same results.[6] The doses of EACA were at least 5 times higher than the doses of TXA in these studies, and EACA was administered intravenously in all of them.[1,5,6] This study was the first to compare 1 g of TXA with 4 g of EACA administered intraarticularly in TKA. In some situations, EACA is less expensive than TXA[1,6]; proving that the effects are comparable providing additional justification for its use, and this justification becomes even more robust if an even lower dose can be used with the same efficacy. Several publications have shown the noninferior effect of topical TXA over intravenous TXA.[8,9] When given intravenously, minor gastrointestinal symptoms, such as nausea and vomiting, have been reported.[10] Antifibrinolytic drugs are known to decrease perioperative bleeding and prevent premature clot dissolution.[11] Surgeons can apply the drug by themselves when administering it intraarticularly, and lower doses can be used with less risk of systemic side effects.[12,13]

We determined pain control, knee flexion gain and knee function by the WOMAC questionnaire in the groups up to two months postoperatively, in addition to evaluating the drop in Hgb and Htb. This study also shows that the possible benefits in pain control, flexion gain and knee function demonstrated in some previous studies using TXA were similar when using EACA.[12,14]

This study has some limitations. First, although we performed a power analysis to determine the size of the study population, our study was a small clinical trial at a single center. Second, we estimated bleeding using only serum Hgb and Htb levels without calculating the blood volume using the weight and height of the patients. Third, since we did not use drains because we considered that a portion of the drug applied intraarticularly could be lost through the drain, we could not directly measure bleeding. Fourth, we did not determine the serum drug levels achieved in the patients, and therefore, although we did not observe any clinically evident side effects, we cannot determine a difference in the safety of these drugs administered intraarticularly.

CONCLUSIONS

The drop in Hgb and Htb in the first 48 hours postoperatively and the risk of transfusion were similar for 1 g of TXA and 4 g of EACA administered intraarticularly in TKA. The possible benefits regarding knee pain, flexion and function were also similar for the two drugs.

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