**Evaluation of Antifibrinolytic Use in Anterior Cruciate Ligament Arthroscopic Reconstruction. A Prospective Clinical Trial**

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**SUMMARY**

**Objective.** To evaluate the effectiveness of two antifibrinolytic drugs (tranexamic acid and epsilon-aminocaproic acid) in reducing postoperative hemarthrosis after anterior cruciate ligament reconstruction.

**Methods.** 45 patients diagnosed with primary anterior cruciate ligament tears were randomly placed into 3 groups: control, tranexamic acid (TXA) and epsilon-aminocaproic acid (EAC). The first group was operated on without the use of the drugs, and for the other two, the dose was adjusted by weight. The evaluation was conducted for 1 and 7 postoperative days to assess the degree of hemarthrosis, assess the visual pain scale and measure the range of motion (ROM) in degrees. The patients were then assigned a subjective functional score at 14 and 28 postoperative days.

**Results.** The TXA group showed improvement on the postoperative pain scale after 7 days compared to the control group. When evaluated with the Lysholm functional score, the TXA group showed improvement compared to the control group. No significant statistical difference emerged in the parameter evaluated for the EAC group.

**Conclusions.** The tranexamic-acid group showed reduced pain and improved function after arthroscopic reconstruction of the ACL. Up to this point, the use of Epsilon-aminocaproic acid yielded no benefit. A follow-up study with more participants may confirm our findings or present new relevant findings.

**KEY WORDS**

Knee; anterior cruciate ligament reconstruction; hemarthrosis; antifibrinolytics; arthroscopy.

**INTRODUCTION**

Arthroscopic reconstruction is a reliable procedure with good outcomes for the treatment of lesions of the anterior cruciate ligament (ACL). Despite the great advances in the development of techniques, improvement of implants and graft-related studies, management of the intra-articular bleeding inherent to the procedure remains a point of discussion (1, 3-5, 11). The use of antifibrinolytic drugs has helped control bleeding in several surgical areas, including orthopedics (2, 6-10, 16). Tranexamic acid and epsilon-aminocaproic acid are two of the most used drugs in this context and are commonly available in tertiary-care service in the public health-care system (PHCS) (16).

The current study aims to assess the reproducibility of good results with the use of these drugs in the reduction of hemarthrosis after ACL arthroscopic reconstruction (ACLR) and to evaluate improvement in rehabilitation in the short and long term. Thus, we can verify the possibility of a faster dehospitalization with the administration of these drugs.
MATERIALS AND METHODS

The current study is characterized as a randomized prospective clinical trial. To date, 43 patients diagnosed with anterior cruciate ligament lesions employed our service between April and October 2017 and were included in the study. Furthermore, we intend to increase the number of participants to increase our study’s impact. This study was approved by the hospital ethical committee under number 2.045.499 in May 2017.

As inclusion criteria, we selected patients older than 18 with indication of ACLR. As exclusion criteria, we considered patients presenting with any of the following features: coagulation disorders, currently attending anticoagulant therapy, altered preoperative coagulation tests, vasculopathies, pregnant or lactating woman, renal disease or renal insufficiency (15), sickle cell anemia, allergy to anesthetics, allergy to epsilon-aminocaproic acid, important preoperative pain (Visual Analog Scale for Pain > 5) (13) and large preoperative edema (grade 3 or 4) (12). Patients submitted to meniscal suture or review cases of previous surgeries were also excluded from the study along with those who did not agree to sign the free informed term of consent (FITC). An examiner, who was not the surgeon in each case, randomly assigned patients to 3 groups.

The same team operated on all patients. We utilized the anatomical reconstruction technique of the ACL with flexor tendons, with an endobutton for the fixation in the femur and an interference screw in the tibia. We applied the tourniquet in all the groups. All the cases were operated on by group members with similar numbers of years of experience (> 5 years). An aspiration drain was not employed (3-5). All patients executed the same physiotherapy rehabilitation protocol.

One group was operated on without using the studied drugs. This group was classified as the control group. In another group, 1 dose of 10 mg/kg of tranexamic acid (Transamin R) was used during the anesthetic induction, adding 10 mg/kg/h in the 3 hours after the initial dose (Bula Transamin. Lab Nikkho 2012). This group was the TXA group.

Finally, in the last group, epsilon-minocaproic acid (Ipsilon R) was used at a dosage of 100 mg/kg in 250 ml of sodium chloride 0.9% running for 2 hours, starting at the induction. These participants also received 1 g/h in the 2 hours after the loading dose (Bula IPSILON. Lab Nikkho 2012). This group was the EAC group.

As variables in the study, we evaluated gender, age, score on the pain scale, hemarthrosis graduation on the Coupens and Yates scale, degrees of range of motion at 1 and 7 days postoperative, and score on the Lysholm scale at 14 and 28 postoperative days.

Results analysis

Patients were seen during their visits on the first postoperative day (with a similar time interval from the end of procedure to the time of visit). They underwent an assessment of their knees’ range of motion in degrees of total flexion and extension using a digital goniometer (figure 1; iGaging R, San Clemente, CA). Joint effusion was assessed and stratified according to the classification proposed by Coupens et al. (12) (table I), and pain degree to the passive ROM by visual analogue scale (VAS). The evaluation was repeated in outpatient care 7 days after surgery. Patients underwent subjective evaluation of functionality with the Lysholm questionnaire (11, 15) at the 14th and 28th postoperative days.

Statistical analysis

To analyze the partial results, we used the Kruskal-Wallis Test to verify the difference between the three groups in the studied variables. The groups were then compared pairwise with the Mann-Whitney Test adjusted by Bonferroni’s Correction. A P value of 0.05 (5%) was used as the level of significance.

Table I. Clinical Scale of hemarthrosis (12).

<table>
<thead>
<tr>
<th>Degree</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No palpable effusion</td>
</tr>
<tr>
<td>1</td>
<td>Palpable effusion with fluid</td>
</tr>
<tr>
<td>2</td>
<td>Palpable effusion in the suprapatellar space</td>
</tr>
<tr>
<td>3</td>
<td>Evident patellar rejection</td>
</tr>
<tr>
<td>4</td>
<td>Strained hemarthrosis</td>
</tr>
</tbody>
</table>

Figure 1. Digital goniometer used for range of motion measurement.
RESULTS
Two of the 45 initially included patients in the study were excluded due to a failure to follow-up in the 4 weeks of postoperative analysis. To date, 15 patients have been evaluated in the control group, 14 in the TXA group, and 14 in the EAC group. All three studied groups were statistically similar for the age and gender variables.

The control and TXA groups presented a significant difference in the Visual Analog Scale for Pain on the 7th postoperative day (0.011).

Regarding the Lysholm score variable, the TXA and EAC groups and control groups presented significant differences on the 14th postoperative day (0.012 and 0.025, respectively) (table II).

Despite not being statistically significant, comparison of the control group with the TXA group and then the EAC group showed statistically significant differences in the Lysholm analysis at 2 weeks postoperation (0.021 and 0.028, respectively). The remaining results have shown no statistically relevant differences.

DISCUSSION
Tranexamic acid and epsilon-aminocaproic acid are antifibrinolytic drugs that block the lysine binding site on plasmin and plasminogen molecules, thereby preventing clot dissolution (2). The use of these drugs for peri and postoperative bleeding control has been shown to reduce blood loss in cardiac surgeries, digestive tract surgeries, and transplants and in patients presenting with coagulation disorders (6, 7, 9).

Some studies in our survey show these drugs’ effectiveness in reducing blood loss and the need for hemotransfusion in the primary knee arthroplasty (7, 9, 10). However, these drugs do not show a difference between one another regarding control of bleeding in the primary knee arthroplasty (2).

Karaaslan et al. (1) demonstrated the existence of good outcomes in the arthroscopic reconstruction of the ACL by using a tranexamic acid dose of 10 mg/kg/h for 3 hours in 105 operated knees. He also noted hemarthrosis reduction (better bow of early movement in rehabilitation, less need for relief punctures) postoperation (1); however, that study compared the use of an antifibrinolytic with the use of a suction drain.

Even though the hemarthrosis content aspirated through the drain would be an objective value to evaluate the studied drugs’ efficacy, we have not made use of this artifice. The use of a drain was evaluated in several studies regarding its efficacy in the ACLR postoperation, with most of the studies showing the benefit of its nonuse (3-5). As our goal is to evaluate the drugs’ clinical outcomes, we chose not to use the aspiration drain.

We did not find in the literature studies comparing tranexamic acid with epsilon-aminocaproic acid in ACL reconstruction, which motivated us to start our trial. We also believe most of surgeons don’t use drugs to minimize hemarthrosis for two main reason: usually it’s not a major complication and unfamiliarity on the part of many surgeons.

Although we plan to include a larger number of participants in a follow-up study, the use of TXA was shown to be effective in reducing patients’ pain one-week post-operation and improving knee function in the same period.

We believe that a larger number of studied cases is needed along with a follow-up on our study to increase the current findings’ reliability and confirm other trends, as well as other studies on this topic.

The use of TXA and EAC in the management of postoperative ACLR hemarthrosis is a viable option with low economic and morbidity impact. These results will allow us to evaluate, in a forthcoming study, these drugs’ applicability to the earliest safe dehospitization in the ACLR.

We had some limitations in this present study more than one surgeon was performing the surgeries, follow up was limited to the first month and despite of finding some significant statistical differences between the groups the number of patients could be higher.

CONCLUSIONS
According to the parameters evaluated in the present study, the use of TXA in the ACLR proved to be more effective than the administration of EAC and the control group in the first postoperative weeks. The study meets the ethical standards of the journal (17).
CONFLICT OF INTERESTS
The authors declare that they have no conflict of interests.

REFERENCES