Original article

Bleeding reduction after topical application of tranexamic acid together with Betadine solution in total knee arthroplasty. A randomised controlled study

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A B S T R A C T

Introduction: Topical application of tranexamic acid to the knee joint before closure in total knee arthroplasty reduces postoperative bleeding without increase in complication. However, it is unknown the effectiveness of topical TXA performed with other topical medications, like povidone-iodine solution.

Materials and methods: One hundred and twenty-five patients were randomized to receive 100 mL of povidone-iodine solution (control: group A) or 1.5 mL (group B) and 3.0 g (group C) of topical TXA in povidone-iodine solution applied into the knee before closure in total knee arthroplasty.

Results: The patients in the TXA groups had higher mean postoperative hemoglobin levels (P<0.01 and P<0.03 in groups B and C, respectively) and a reduced postoperative blood loss in the TXA groups (P=0.07 and P=0.09 in groups B and C, respectively). No significant complications were observed.

Discussion: In this study, topical application of tranexamic acid after total knee arthroplasty together with povidone-iodine solution results in higher postoperative hemoglobin levels and lower blood loss compared with those in the control group without other complications.

Level of evidence: I – I: high-powered prospective randomized trial.

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1. Introduction

Several authors have published reports describing a reduction in blood loss and transfusion rates following total knee arthroplasty (TKA) after using an anti-fibrinolytic agent: tranexamic acid (TXA) [1]. This concern came to the fact that postoperative blood loss associated with TKA ranges from 1450 to 1790 mL, causing anaemia and other complications [2–5]. Blood transfusion is necessary in 10–38% of these patients [6–8]. The major cause of postoperative blood loss following TKA is attributable to both surgical trauma and local fibrinolysis, primarily after tourniquet release at the end of the procedure [9].

Topical TXA application is a medication with minimal systemic absorption and results in an important and effective decrease in bleeding [9–12]. However, it is unknown the effectiveness of topic TXA performed simultaneously with other topical medications, like povidone-iodine solution. Povidone-iodine solution is safe, inexpensive, simple to use, and readily available within most operating rooms; in addition, it has broad-spectrum bactericidal activity that includes methicillin-resistant Staphylococcus aureus [13–17]. Brown et al. reported that Betadine® (povidone-iodine solution) lavage may represent a reasonable way (0.97% to 0.15% P=0.04) of reducing acute postoperative deep infection in TKA [15].

The main objective of this study was to assess the efficacy of topical TXA application used together with povidone-iodine solution after TKA, secondarily analysing the effects of this agent on haematimetric indices and postoperative blood loss. Our hypothesis was that in conjunction with povidone-iodine solution, TXA had an antibibrinolytic effect.

2. Material and methods

A total of 125 patients undergoing TKA in Hospital Madre Teresa between 2012 and 2013 by a single surgeon (L.H.C. Jr.) were enrolled in this prospective, randomised, placebo-controlled...
The Ethical Committee of the Hospital Madre Teresa approved the details of this study, and written informed consent was obtained from each participant before starting this study (CAAE–Brazilian Ministry Health 05286512.0.0000.5127). No financial incentives were offered to encourage subjects to participate.

All adult patients who were scheduled for a primary TKA at Hospital Madre Teresa were eligible for inclusion. Exclusion criteria included the following: allergy to TXA or povidone-iodine solution, preoperative anaemia, refusal of blood products, preoperative use of anticoagulants (acetylsalicylic acid, enoxaparin, or any other, oral or intravenous, agent), fibrinolytic disorders, coagulopathy, arterial or venous thromboembolic disease and pregnancy. Moreover, the following patients were excluded from the study: patients with major comorbidities, such as ischaemic heart disease, patients with a history of myocardial infarction and those with severe pulmonary disease.

The doses chosen for the current investigation were based on previous studies of topical TXA in patients undergoing TKA, showing efficacy with doses of 1.5 g and 3 g for reducing the bleeding [9,10,12]. A diluted povidone-iodine solution (Betadine® solution – 0.35%) was used together and in the same time at the end of procedure for all groups, as shown by Brown et al. [15]. Patients in this study were randomised into three groups using a computerized program and were administered TXA as follows:

- group A patients (control) received Betadine® solution (0.35%) (200 ml – 0.35%);
- group B patients received 1.5 g (100 mg/mL) TXA (Transamin®, NIKKHO, Rio de Janeiro, Brazil) in Betadine solution (200 ml – 0.35%);
- group C patients received 3 g TXA (Transamin®, NIKKHO, Rio de Janeiro, Brazil) in Betadine solution (200 ml – 0.35%).

No control group was used with isolated TXA solution due to existence of data in the literature to substantiate the reduction in bleeding with this solution alone in the same doses used [9,11,12,18–21].

All patients received a spinal anaesthesia [12–15 mg isobaric bupivacaine (0.5%)] with a femoral and sciatic nerve block [125 mg ropivacaine (0.5%) associated to 75 μg of clonidine] guided by ultrasonography for postoperative analgesia. All the procedures were performed using pneumatic tourniquet around the upper part of the thigh with a pressure of 350 mmHg. A midline skin and medial parapatellar capsular incision was made to expose the knee joint. An identical type and appropriately sized, posterior stabilized knee prosthesis was used in every patient (NexGen – Zimmer®, Warsaw, Indiana, United States). After all components were implanted, the joint was thoroughly irrigated and the study medication (TXA) with Betadine solution (200 ml – 0.35%) was applied to the open joint surfaces and was left in contact with the tissues for five minutes, as described by Wong et al. [9]. The surgeon subsequently suctioned away excess of solution by placing the suction tip without touching the joint or the surrounding tissue surfaces. The wound was closed and a 3.2 mm-diameter drains without suction was utilized. The tourniquet was released only after wound closure. To prevent venous thromboembolism, patients received enoxaparin
(40 mg/day/subcutaneous) for 10 days. The first dose started 6h after the procedure.

Demographic characteristics of patients in this study are presented in Table 1. Measured outcomes were haematimetrics indices (haemoglobin, haematocrit, prothrombin time, activated partial thromboplastin time and international normalised ratio), drain volume (mL), allogenic blood transfusion, thromboembolic events, total calculated blood loss and acute postoperative infection. The evaluation of these parameters was made by a single examiner (E.F.T.) blinded to the patient group in question. The calculation of blood loss was done according to the formula described by Good et al. [4]. This formula analyses the difference between the preoperative haemoglobin and the lowest postoperative haemoglobin during the hospital stay or the lowest postoperative haemoglobin prior to blood transfusion. Based on haemoglobin total the calculated blood loss was estimated.

The criteria for transfusion of blood products included haemoglobin levels < 8.5 g/dL, intolerable symptoms of anaemia or any organ dysfunction, or all together. Daily postoperative haemoglobin levels were measured for three days, and the lowest levels were utilized for total calculated blood loss. Patients were examined daily for clinical symptoms of deep vein thrombosis. If a patient was symptomatic, a Doppler ultrasound was performed for both legs. Surgical drains were used for 24h after surgery, and all the volume collected was registered. All patients were followed for 12 weeks after surgery to assess for clinical symptoms of deep vein thrombosis and acute infection.

### 3. Statistical analyses

The distribution of potential confounders between study groups and the primary and secondary outcomes were assessed using summary statistics to include means, weighted means, standard deviations and 95% confidence intervals for quantitative data and frequencies and percentages for qualitative data. Continuous variables were compared using one-way analysis of variance, and categorical variables were compared with the use of the chi2 and ANOVA test. The following were assumed: standard effect size (d)=0.36; the level of alpha (two-tailed)=0.05; and power=0.8. In addition, we assumed the standard deviation within each group to be 14 g/dL, described by previous studies [9]. The sample size was increased by 20% to compensate for expected dropouts, which were a minimum of 33 patients per group.

### 4. Results

Patients in low-dose and high-dose TXA groups presented higher mean postoperative haemoglobin levels compared with those in the control group (P<0.01 and P=0.03 in groups B and C, respectively). There was no difference between the low-dose (1.5 g) and high-dose (3 g) TXA groups regarding postoperative haemoglobin levels (P=0.3). Any other significant difference was observed in haematimetrics indices between the three groups. There was a trend toward better results in postoperative haematocrit levels in the TXA groups as compared with the control group (P=0.07 and P=0.09 in groups B and C, respectively; Table 2), although no statistically difference exists.

The mean drain volume was similar for all the groups. However, the mean of total calculated postoperative blood loss was significantly reduced in the 1.5 g and 3 g TXA groups when compared with the corresponding value in the control group. There was no difference between the low-dose (1.5 g) and high-dose (3 g) groups. Further, the mean of drainage, the frequency of thromboembolic manifestations and allogenic blood transfusion was similar in the three groups. None acute infection was observed in the three groups (Table 3).

### Table 1
Demographic and clinical characteristics of the patients.

<table>
<thead>
<tr>
<th>Group</th>
<th>Site (right/left)</th>
<th>Sex (male/female)</th>
<th>Age (year)</th>
<th>Weight (kg)</th>
<th>Height (cm)</th>
<th>Body mass index (kg/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>R25 L15</td>
<td>M 10 F 30</td>
<td>69.3 ± 6</td>
<td>80.6 ± 13</td>
<td>1.64</td>
<td>29.9</td>
</tr>
<tr>
<td>B</td>
<td>R16 L26</td>
<td>M 17 F 24</td>
<td>70.8 ± 6.5</td>
<td>81.3 ± 11.9</td>
<td>1.66 ± 0.9</td>
<td>29.5</td>
</tr>
<tr>
<td>C</td>
<td>R22 L16</td>
<td>M 7 F 31</td>
<td>70 ± 8.2</td>
<td>79.4 ± 13.7</td>
<td>1.62 ± 0.09</td>
<td>30.2</td>
</tr>
</tbody>
</table>

The P value represents the result of one-way analysis of variance for independent means for continuous variables or the chi² test for independent proportions which included the three groups. The values are presented as means ± standard deviation; ns: not significant and P < 0.05 = significant.

### Table 2
Hematimetrics indices.

<table>
<thead>
<tr>
<th>Group</th>
<th>Pre-haematocrit</th>
<th>Post-haematocrit</th>
<th>Pre-platelet count</th>
<th>Post-platelet count</th>
<th>Pre-haemoglobin</th>
<th>Post-haemoglobin</th>
<th>Pre-APT</th>
<th>Post-APT</th>
<th>Pre-PT</th>
<th>Post-PT</th>
<th>Pre-INR</th>
<th>Post-INR</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>41.5 ± 2.6</td>
<td>33 ± 2.9</td>
<td>240.562 ± 54.700</td>
<td>200.937 ± 50.409</td>
<td>13.8 ± 0.8</td>
<td>10.9 ± 0.9</td>
<td>29.3 ± 4</td>
<td>31.6 ± 1.4</td>
<td>13.6 ± 1.3</td>
<td>16.4 ± 0.9</td>
<td>1.1 ± 0.8</td>
<td>1.2 ± 0.08</td>
</tr>
<tr>
<td>B</td>
<td>41.8 ± 3.9</td>
<td>34.8 ± 3.7</td>
<td>223.833 ± 55.825</td>
<td>188.285 ± 45.263</td>
<td>14 ± 1.4</td>
<td>12.5 ± 1.0</td>
<td>28.9 ± 5.5</td>
<td>32.6 ± 2.4</td>
<td>14 ± 3.7</td>
<td>16.3 ± 1.0</td>
<td>1.1 ± 0.08</td>
<td>1.2 ± 0.09</td>
</tr>
<tr>
<td>C</td>
<td>41.8 ± 3.5</td>
<td>34.7 ± 3.0</td>
<td>219.315 ± 55.703</td>
<td>189.473 ± 53.695</td>
<td>13.9 ± 1.5</td>
<td>11.7 ± 1.2</td>
<td>30.7 ± 4.46</td>
<td>32.7 ± 1.9</td>
<td>13.4 ± 1.4</td>
<td>16.3 ± 1.3</td>
<td>1.0 ± 0.05</td>
<td>1.2 ± 0.1</td>
</tr>
</tbody>
</table>

The P value represents the result of one-way analysis of variance for independent means for continuous variables or the chi² test for independent proportions which included the three groups. The values are presented as means ± standard deviation. ATP: activated partial thromboplastin time; PT: prothrombin time; INR: international normalized ratio; ns: not significant and P < 0.05 = significant.

5. Discussion

To our knowledge, this is the first study analysing both topical solutions together in TKA and the effects of TXA on haematometric indices and postoperative blood loss. The most important finding of this study is that topical application of TXA after TKA together with Betadine solution results in higher postoperative haemoglobin levels and lower blood loss compared with those in the control group without other complications, as seen in studies using isolated topical TXA [9,11,12,18–21]. A significant difference was noted in the haematometric indices, with 10.2% higher postoperative haemoglobin levels in both TXA groups with Betadine solution compared with those in the control group. Moreover, a decreased blood loss of 20% was observed in both TXA groups when compared with the control group. Attention should be given to the fact that these values have been found despite similar drainage for all. This may due to loss of other fluids than blood through the drain. However, the need for blood transfusion was similar in the three groups (but there was only one or two transfusions according to the groups) and no increase was observed in symptomatic thromboembolism. It is difficult to assess the rate of infection on such short series, although no acute infection was observed.

The mode of action of TXA is through competitive, reversible blockade of lysine-binding sites on plasminogen. In addition, the blockade induced by this agent results in the dissociation of plasminogen from fibrin and thus the inhibition of fibrinolysis. In the specific case of topical application, the TXA acts directly on the microvasculature and clot stabilization, thus reducing local bleeding. Changes in prothrombin and activated partial thromboplastin time must be measured when this agent is administered [18–23]. Wu et al. published the results of a meta-analysis evaluating the safety and efficacy of venous TXA in patients undergoing TKA. In their report, 15 randomised controlled trials met their inclusion criteria and were reviewed. They reported that the amount of blood loss and number of blood transfusions decreased significantly with intravenous TXA administration. Furthermore, TXA administration did not produce any significant differences in the prothrombin time, activated partial thromboplastin time, deep vein thrombosis or pulmonary embolism [23]; moreover, Alshryda et al. reached similar conclusions as well. They identified 19 clinical trials satisfying their admission criteria and reviewed their results. Their conclusion was that intravenous TXA significantly reduced the proportion of patients requiring blood transfusion (RR 2.56; P < 0.001) [20].

However, concerns regarding the safety of systemic TXA administration, the increased risk of thromboembolic events and interactions with others medications have hindered the wide adoption of this medication in the setting of TKA [23,24]. Despite these safety concerns, topical TXA application to the knee joint before TKA closure might be a route of administration, which will reduce postoperative bleeding without increasing the hypercoagulable state, associated with this surgical procedure. Our report is not the first to attribute a potential benefit to topical TXA administration during primary TKA. Wind et al. reviewed their experience with 2269 consecutive primary TKA procedures performed in 2009 patients over a period of 3.5 years. Intravenous TXA infusion demonstrated a statistically significant decrease in blood transfusion (P = 0.001), as did topical TXA application (P = 0.019). The transfusion rate without TXA was 6.5% (120/1839) but was only 0.3% (1/330) with TXA infusion. There were no transfusions (0/130) observed with the topical TXA use application [21]. Wong et al. reported a similar study with topical TXA; in their study, topical TXA application directly into the surgical wound reduced postoperative bleeding by 20–25% (300–400 mL), resulting in 16–17% higher postoperative haemoglobin levels compared with that in the placebo group. No clinically significant increase in complications could be identified in both groups [9]. Seo et al. also reported that intra-articular administration of TXA seems to be more effective in terms of reducing blood loss and transfusion frequency compared to intravenous administration, reducing the chance of transfusion-associated side effects and complications [11]. Li et al. [25] also reported that other topical product (fibrin sealant) in TKA was effective and safe, reducing haemoglobin decline, postoperative drainage volume, incidence of haematoma and need for blood transfusion, and did not increase the risk of complications, the same is not being reported by Massin et al. [26]. In this study, fibrin sealant was used in 31 patients who were compared to the other 31 patients. In the control group, 48% of patients required blood transfusions and the mean number of units per patient used was 0.9 ± 1. In the fibrin sealant group, 29% of patients required blood transfusions and the mean number of units was 0.6 ± 0.9. Despite these numbers, the differences (calculated blood loss, blood transfusion and mean number of red blood cell units used per patient) in fibrin sealant group were not statistically significant [26].

The present study had several limitations. Besides the fact that it was conducted with a relatively larger number of patients than previous studies, the study did not have the statistical power to evaluate the assumption that TXA can decrease the frequency of transfusion, despite decreased blood loss. With larger series of patients, we may be able to find the impact on the rate of transfusion. Another limitation was that screening for pulmonary embolism or deep vein thrombosis was performed only using Doppler ultrasound for symptomatic patients. We did not specifically assess the postoperative functional recovery to investigate the relationship between hemoglobin levels and the outcome of rehabilitation. Finally, the number of patients analyzed was small to have significance of the risk of acute infection after the TKA with application of topical solution of TXA together with Betadine.

This study is important from a practical standpoint because surgeons can consider incorporating the use of povidone-iodine solution with topical TXA in their blood-saving protocols, due to the fact that no interference with the effects of TXA has been noted when the combined use of povidone-iodine solutions is used. Larger series of patients may be able to find impact on the rate of infection with povidone-iodine solution. Those benefits can compensate the extra time spend on it.

6. Conclusions

In this study, topical application of tranexamic acid after total knee arthroplasty together with povidone-iodine solution results in higher postoperative hemoglobin levels and lower blood loss compared with those in the control group without other complications.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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