Comparison of the application of intra-articular and intravenous tranexamic acid to reduce blood loss during primary total knee arthroplasty

Comparação da aplicação de ácido tranexâmico intra-articular e intravenoso para reduzir a perda sanguínea durante a artroplastia total primária do joelho

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Abstract
Tranexamic acid (TXA) is frequently administered intravenously because it is recognized as a safe and effective procedure. This study's objective is to evaluate the effectiveness of intravenous and intra-articular TXA treatments in patients who have had primary unilateral knee joint replacement. Patients were divided into groups based on TXA applications. Group A patients, those who received intravenous TXA, Group B patients, those who received intraarticular TXA, and Group C patients were intended to serve as the control group. Age, gender, ASA scores, length of hospital stay, preoperative, postoperative, and discharge hemoglobin and hematocrit levels, and the quantity of blood product transfusion given to the

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patients was analyzed retrospectively. Analysis of the patient’s postoperative Hb values revealed that group C patients had lower Hb values (p < 0.05). Postoperative Hct levels were also seen to be significantly lower in group C individuals (p < 0.05). When the patients' Hb levels were measured at discharge, it was discovered that group C patients had lower Hb levels (p < 0.05). The Hct values of group C patients at discharge were also found to be considerably lower (p < 0.05). It was found that group C patients received significantly more blood transfusions than the other groups (p < 0.05) when the number of patient blood transfusions was compared between the groups. Intravenous and intra-articular TXA successfully minimize blood loss in primary TKA. The benefits of intra-articular administration over intravenous administration include convenience of administration, local application, and a higher level of safety.

**Keywords:** Tranexamic Acid. Blood Loss. Total Knee Arthroplasty.

**Resumo**

O ácido tranexâmico (TXA) é frequentemente administrado por via intravenosa porque é reconhecido como um procedimento seguro e eficaz. O objetivo deste estudo é avaliar a eficácia dos tratamentos com TXA intravenoso e intra-articular em pacientes submetidos à artroplastia unilateral primária do joelho. Os pacientes foram divididos em grupos com base nas aplicações de TXA. Os pacientes do Grupo A, aqueles que receberam TXA intravenoso, os pacientes do Grupo B, os que receberam TXA intra-articular e os pacientes do Grupo C foram destinados a servir como grupo controle. Idade, sexo, escores ASA, tempo de internação, níveis pré-operatórios, pós-operatórios e de alta de hemoglobina e hematócrito, e a quantidade de transfusão de hemoderivados dada aos pacientes foram analisados retrospectivamente. A análise dos valores de Hb pós-operatório dos pacientes revelou que os pacientes do grupo C apresentaram valores de Hb mais baixos (p < 0,05). Os níveis pós-operatórios de Hct também foram significativamente menores nos indivíduos do grupo C (p < 0,05). Quando os níveis de Hb dos pacientes foram medidos na alta, descobriu-se que os pacientes do grupo C tinham níveis de Hb mais baixos (p < 0,05). Os valores de Hct dos pacientes do grupo C na alta também foram consideravelmente mais baixos (p < 0,05). Verificou-se que os pacientes do grupo C receberam significativamente mais transfusões de sangue do que os outros grupos (p < 0,05) quando o número de transfusões de sangue do paciente foi comparado entre os grupos. O TXA intravenoso e intra-articular minimiza com sucesso a perda sanguínea na ATJ primária. Os benefícios da administração intra-articular
Introduction

Total knee arthroplasty (TKA), one of the most popular elective procedures carried out by orthopedic surgeons in everyday practice, is connected to considerable rates of transfusion and huge volumes of postoperative blood loss. Reduced blood loss during this procedure will lessen the demand for autologous and allogeneic blood transfusions as well as morbidity (Diamond, 2000; Carson, 1998). Both allogeneic and autologous blood transfusions are more expensive, linked to an increase in the prevalence of periprosthetic infections, and pose a risk of disease transmission and transfusion reactions (Friedman et al., 2014). Autologous blood transfusion, intraoperative blood-saving procedures, hypotensive anesthesia, use of modified drains, and antifibrinolytic drugs are only a few of the blood-saving strategies that have been discussed to limit blood transfusion in TKA (Royston, 1995; Martin & Von Strempel, 2006; Kiss et al., 2005; Juelsgaard et al., 2001; Dramis et al., 2006; Callaghan et al., 2005; Boether et al., 2009; Benoni et al., 1997).

An artificial antifibrinolytic substance called tranexamic acid (TXA) binds to the lysine binding site of plasminogen and prevents it from attaching to the surface of fibrin. Plasminogen activation is stopped, and fibrinolysis is postponed as a result (Hoylaerts et al., 1981). It is thought that TXA works in this way to help the body fight blood clots more successfully, which lessens bleeding. TXA has a lower price than aprotinin and has significantly higher efficacy than aminocaproic acid when compared to other anti-fibrinolytic medications (Henry et al., 2011). TXA, however, penetrates the main joints well, resulting in a drug concentration in the joint fluid that is about equal to the serum drug concentration (Alhberg et al., 1976).

In several disciplines, including cardiac surgery, gynecologic surgery, liver surgery, urologic surgery, and dental surgery (Coffey et al., 1995 & Sekhevat et al., 2009). TXA has been utilized to lessen postoperative blood loss. Since TXA was first used for TKA (Hiipala et al., 1995; Benoni et al., 1996), numerous studies have shown that its use reduces blood loss and the subsequent need for allogeneic transfusions without raising the risk of deep vein thrombosis (DVT) or pulmonary embolism (PE), although these complications are
theoretically a possibility because of the drug's antifibrinolytic effect (Veien et al., 2002; Seo et al., 2013; Mainar et al., 2012; Lin et al., 2011; Ido et al., 2000; Alvarez et al., 2008). Additionally, following investigations, it has been revealed that topical TXA application is just as efficacious as, or even more so, than intravenous TXA delivery (Seo et al., 2013, Mainar et al., 2012; Wong et al., 2010; Roy et al., 2012).

TXA is frequently administered intravenously because it is recognized as a safe and effective procedure. Numerous studies have demonstrated that this procedure minimizes blood loss and, hence, the need for blood transfusions while also having fewer side effects (Wang et al., 2017; Tan et al., 2013; Sabatini et al., 2015). Intra-articular TXA injection provides a longer duration of blood loss reduction than intravenous treatment because it reaches a larger concentration at the surgical site. Additionally, there is reduced systemic absorption, which lowers the frequency of thromboembolic events (Konig et al., 2013). The safety of intra-articular TXA is increased by the absence of thrombo-embolic events that are contraindicated for intravenous TXA, such as myocardial infarction (MI), pulmonary embolism (PE), and deep vein thrombosis (DVT) (Konig et al., 2013). The efficacy of TXA has been proven by various studies, however, discussions about its optimal regimen and dose continue (KoWang et al., 2017; Tan et al., 2013; Sabatini et al., 2015; Konig et al., 2013; Soni et al., 2014).

This study's objective is to evaluate the effectiveness of intravenous and intra-articular TXA treatments in patients who have had primary unilateral knee joint replacement in terms of postoperative hemoglobin and hematocrit levels decline and blood transfusion requirements.

**Methodology**

Following approval from the institutional review board, we looked back at the records of patients who underwent primary total knee arthroplasty between January 2021 and January 2023. Patients with hepatitis B and C infections, those who had bilateral total knee replacements, those who had TXA allergies, renal dysfunction, cardiovascular disease (like MI), stroke, DVT, cases with a history of thromboembolic disease like PE, and those who had used anticoagulants up to seven days prior to surgery were all excluded from the study. We also did not include cases involving revisions, single-compartment knee replacements, tumors, fractures, or hardware removal.
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On the patient charts, the following information was analyzed: age, gender, ASA scores, length of hospital stay, preoperative hemoglobin and hematocrit levels, postoperative 1st day hemoglobin and hematocrit levels, hemoglobin and hematocrit levels at discharge, and the quantity of blood product transfusion given to the patients.

Throughout the trial period, there was no modification to the anesthetic method. Patients received spinal anesthesia on a regular basis. Within 24 hours of surgery, low molecular weight heparin (40 mg enoxaparin sodium) was routinely started and continued in all patients for 45 days postoperatively. Preoperatively, prophylactic antibiotics (cefazolin sodium 1 g) were given and stopped 24 hours following surgery.

Patients were divided into groups based on TXA applications. Group A patients, those who received intravenous TXA, Group B patients, those who received intraarticular TXA, and Group C patients were intended to serve as the control group.

Drains were used in every patient because this was our standard procedure before employing tranexamic acid, and they were taken out 48 hours after surgery on average. Additionally, tourniquets were always routinely used. The same consultant orthopedic surgeon used the medial parapatellar technique for all of the procedures. A total knee-cemented prosthesis that replaces the posterior cruciate ligament was employed. Two intravenous doses of TXA (15 mg/kg body weight) were administered to participants in group A. 10 cc of ordinary saline was used to dilute each dose. A dose was administered 15 minutes before the tourniquet was inflated, and another dose was administered 15 minutes later. Before the wound was closed, Group B was infiltrated with 2 g of intra-articular TXA diluted with 100 ml of normal saline. No TXA applications were made during or after the operation, as group C patients served as the control group. The tourniquet was lowered when the wound was being dressed after hemostasis was achieved. Each wound was filled with a 12G drain and then closed in layers. Within 48 hours of surgery, the drain outlet was noted and eliminated. After surgery, blood transfusions were only done when Hb levels dropped below 8 mg/dl. Immediately following knee replacement surgery as well as 12 and 24 hours later, both groups were monitored for drain outlet, decreases in Hb and Hct, and blood transfusion requirements.

All study participants followed a predetermined postoperative procedure. After surgery, ankle pump exercises were started right away. Patients were made to stand on the second postoperative day, and continual passive motion exercises were introduced. Machines with continuous passive motion weren't employed. Additionally, the patients' Hb and Hct
levels on the first postoperative day and their Hb and Hct values at the time of discharge were assessed.

2.1 Statistics

The study's data were statistically analyzed using IBM SPSS Statistics 22.0 (IBM Corp., Armonk, New York). The Kolmogorov-Smirnov test was used to determine if the data adhered to the normal distribution. The mean and standard deviation (SD) data were used to present descriptive statistics. Quantitative data were compared between groups using the Repeated measure ANOVA, and non-normally distributed parameter comparisons between groups were done using the Friedman test. It was agreed that a p value of 0.05 was statistically significant.

2.2 Results

<table>
<thead>
<tr>
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<th>Group A</th>
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<th>Group B</th>
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<th>Group C</th>
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<tbody>
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<td>%</td>
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<td>Gender</td>
<td></td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>Female</td>
<td>14</td>
<td>18.71</td>
<td>11</td>
<td>14.7</td>
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</tr>
<tr>
<td>Male</td>
<td>61</td>
<td>81.3</td>
<td>64</td>
<td>85.3</td>
<td>58</td>
<td>78.4</td>
</tr>
<tr>
<td>Mean Age (year)</td>
<td>64.07</td>
<td>6.21</td>
<td>69.32</td>
<td>7.58</td>
<td>69.30</td>
<td>8.91</td>
</tr>
<tr>
<td>Mean Hospitalization Length (day)</td>
<td>5.53</td>
<td>0.89</td>
<td>5.67</td>
<td>1.42</td>
<td>6.04</td>
<td>1.63</td>
</tr>
</tbody>
</table>

Table 1: Demographic characteristics of the participants
Source: Research Results

The results of 256 patients were acquired as a result of the retrospective screening. 224 patients in total (75 patients from group A, 75 from group B, and 74 from group C) were included in the study after the exclusion criteria were used. 41 patients (18.3%) were female and 183 (81.7%) were male among the study's subjects. The patients' average age was 69.3±8.9 years, and their average length of stay in the hospital was 6±1.6 days. The people in the three groups are comparable in terms of all demographic characteristics, with the exception of mean age, when the demographic structures of the groupings are evaluated. The mean age of patients in Group A was found to be lower than that of the other two groups (p < 0.05) (Table 1).
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<table>
<thead>
<tr>
<th></th>
<th>Group A</th>
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<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>Preoperative Hb (gr/dL)</td>
<td>13.27</td>
<td>1.34</td>
<td>12.94</td>
<td>1.47</td>
<td>13.15</td>
<td>3.60</td>
</tr>
<tr>
<td>Preoperative Hct (%)</td>
<td>39.84</td>
<td>3.72</td>
<td>38.02</td>
<td>4.26</td>
<td>37.85</td>
<td>5.62</td>
</tr>
<tr>
<td>Postoperative Hb (gr/dL)</td>
<td>11.33</td>
<td>1.54</td>
<td>11.40</td>
<td>1.44</td>
<td>10.09</td>
<td>1.57</td>
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<td>Postoperative Hct (%)</td>
<td>33.70</td>
<td>4.29</td>
<td>33.74</td>
<td>4.25</td>
<td>33.53</td>
<td>31.75</td>
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<tr>
<td>Discharge Hb (gr/dL)</td>
<td>11.02</td>
<td>1.36</td>
<td>10.89</td>
<td>1.27</td>
<td>9.93</td>
<td>1.00</td>
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<tr>
<td>Discharge Hct (%)</td>
<td>32.71</td>
<td>4.02</td>
<td>31.92</td>
<td>3.71</td>
<td>29.50</td>
<td>3.22</td>
</tr>
<tr>
<td>Blood Transfusion Amount</td>
<td>0.11</td>
<td>0.39</td>
<td>0.12</td>
<td>0.43</td>
<td>0.43</td>
<td>0.66</td>
</tr>
</tbody>
</table>

Table 2: Comparison of Hb, Hct and blood transfusion amounts between groups
Source: Research Results

There was no discernible difference between the groups when they were compared based on their ASA scores (p > 0.05). The preoperative Hct values of group A patients were found to be greater than those of the other two groups (p < 0.05), despite there being no statistically significant difference in preoperative Hb values between group A, group B, and group C (p > 0.05).

When the patients' postoperative Hb values were analyzed, it was found that group C patients' Hb values were lower (p < 0.05). Likewise, group C patients' postoperative Hct values were seen to be considerably lower (p < 0.05).

When the Hb values of the patients were tested at discharge, it was found that the group C patients' Hb values were lower (p < 0.05). Similarly, it was noted that group C patients' Hct values at discharge were significantly lower (p < 0.05).

When the amount of patient blood transfusions was compared across the groups, it was discovered that group C patients received considerably more blood transfusions than the other groups (p < 0.05).

The average length of hospitalization for group C patients was longer, even though there was no statistically significant difference between the groups (p > 0.05) when the length of hospital stays of the patients were reviewed at the conclusion of the study.
**Discussion and Conclusion**

The intraoperative and postoperative blood loss related to the procedure is one of the key issues with TKA (Park et al., 2013; Kim et al., 2016). Between 800 and 1800 ml of blood may be lost as a result (Maniar et al., 2017). Due to the expense and morbidity involved with blood transfusions, TXA has been used to decrease their frequency. Delivery methods include intravenous infusion and topical application to intra-articular surfaces during wound healing. This study aimed to compare the outcomes of patients who used TXA intravenously and intraarticularly with those of individuals who did not.

The main conclusion of the current study is that TXA use, whether intravenously or intraarticularly, dramatically lowers the requirement for blood transfusions and the decline in Hb and Hct values when compared to patients who never used it. The Hb value, one of the parameters assessed in the current study, decreased in all groups when compared to preoperative values when it was measured after surgery and at the time of discharge, but it was found that the patients who did not receive TXA had significantly lower postoperative and discharge Hb values than the other two groups. The outcomes were consistent with a Fu et al. study that discovered intra-articular and intravenous doses of TXA were equally effective in lowering Hb levels (Fu et al., 2016). In contrast to the current study’s findings showed that intra-articular TXA patients saw considerably less Hb reduction than intravenous TXA patients (Pispati et al., 2013).

In their research, Bradshaw et al. and Alipour et al. assessed the decrease in Hct in the patients and found a statistically significant difference between the TXA-treated patients and the control group (Bardshaw et al., 2012; Alipour et al., 2013). Irwin et al.’s investigation, however, found that in patients who underwent TKA and total hip arthroplasty, the administration of TXA had no appreciable impact on Hct value (Irwin et al., 2013). Although all groups in the current study had lower postoperative and discharge values than their preoperative Hct values, it was discovered that the control group, which did not use TXA during the postoperative period and discharge, had a statistically significant decrease.

Blood transfusion is a significant contributor to the expense of knee replacement surgery (Demos et al., 2017) and the lengthening of hospital stays following TDA (Gomez et al., 2014). In a study by Husted et al., the average hospital stay following TKA was 3.8 days, but in 12% of patients who required blood transfusions due to substantial blood loss, the hospital stay was 3 times longer (Husted et al., 2008). Patients receiving TXA did not have a shorter length of stay, according to studies by Wong and Ellis (Wong et al., 2010; Ellis et al.,
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Shorter periods of stay were linked to the use of TXA, according to a meta-analysis by Alshryda and research by Ralley (Alshryda et al., 2011; Rallet et al., 2010). Additionally, the quantity of blood transfusion required following TXA results in a decline in complications linked to transfusion, which significantly lowers hospital expenses. The patients' easier mobility is another potential factor in the TXA group's reduced length of stay. Patients can move more easily because they do not experience anemia symptoms and do not need to stop their physical treatment to receive transfusions. This enables early patient discharge. The mean hospital stay of the patients who got intravenous and topical TXA was shorter than that of the patients who did not get TXA, despite the fact that there was no statistically significant difference between the length of hospital stay of the patients in the current study.

There are a few restrictions on this study. Retrospective observational research is being done in small patient groups at a single facility. Another drawback of the study is that the patients who took part in it were unaware of the illnesses that could cause bleeding disorders and were not routinely checked. Another flaw in the study is the absence of a cost analysis of the TXA application and the failure to assess its impact on patient functional outcomes.

In conclusion, intravenous and intra-articular TXA are quite successful at minimizing blood loss in primary TKA. The benefits of intra-articular administration over intravenous administration include convenience of administration, local application, and a higher level of safety.

References


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