Comparison of intravenous, oral and intra-articular effects of tranexamic acid on reducing postoperative knee replacement bleeding

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Citation

ABSTRACT

Introduction: Complete knee replacement (Total knee) is one of the greatest surgical skills of the last century. Bleeding during and after this surgery is a major concern in selective knee replacement surgery. One of the most effective ways to reduce bleeding in this procedure is the use of antifibrinolytic drugs, especially tranexamic acid. However, the best use of this drug needs further investigation. Therefore, in this study, we compared the effect of intravenous, oral and Intra-articular tranexamic acid.

Materials and Methods: This study was a randomized, single-blind clinical trial with 135 patients undergoing knee replacement, referred to Amir al-Momenin Hospital and Qods Hospital, Arak, Iran, during 2019-2020. Participants were divided into 3 groups of 45 patients (intravenous tranexamic acid group, oral tranexamic acid group and Intra-articular tranexamic acid group). The mean of postoperative bleeding (up to 48 hours), mean return to operation room, mean hemoglobin in arthroplasty candidates, 8 hours and 48 hours after surgery, mean hospital stay and mean thromboembolic complications were compared. Results: The mean intraoperative bleeding was lower in the intravenous group than in the other two groups and in the Intra-articular group was lower than in the oral group (P = 0.01), but there was no significant difference (P = 0.4) in the mean bleeding after 72 hours. There was no significant difference in mean hemoglobin preoperatively, 8 hours and 48 hours postoperatively (P = 0.3, P = 0.7, P = 0.6). Also, there was no significant difference between the three groups in terms of mean hospital stay (P> 0.05 and P = 0.6). No postoperative or transfusion complications were seen in any of the groups, so no significant difference was observed (P> 0.05). Conclusion: Mean intraoperative bleeding was lower in the intravenous group than in the other two groups. The rate of postoperative bleeding, mean...
hemoglobin level decrease up to 48 hours postoperatively and the need for transfusion were similar in the three groups. Therefore, Intra-articular and oral tranexamic acid, are recommended as suitable substitutes for intravenous tranexamic acid.

Keywords: Tranexamic acid, Arthroplasty, Bleeding.

1. INTRODUCTION

The knee joint is one of the most important joints in the body which is affected by various inflammatory and degenerative diseases which ultimately destroys the cartilage and destroys the proper function of the joint and the patient has pain, joint instability, decreased range of motion and deformity (Minns et al., 2007). Complete knee replacement is one of the greatest surgical skills of the last century. In recent decades there have been advances in knee biomechanics that have improved techniques and practical results. As the elevation of population ages, and with better techniques and implants and increased success of knee replacement, the number of patients undergoing surgery has also increased (Jatin et al., 2017). Arthroplasty is also an effective treatment that helps relieve severe pain and defects in the knee joint (Tao-ping et al., 2017). Because this is a selective surgical procedure, reduces of pre, intra and postoperative problems (Jatin et al., 2017). High bleeding during surgery is a major complication following arthroplasty surgery that causes death and discomfort. Sometimes this bleeding results in a blood transfusion (Vamvakas & Blajchman, 2009). The risks associated with blood transfusion are high and proven, including the possibility of transmission of bloodstream infections and unwanted immunological reactions. It should also be noted that the costs of preparing each unit of packed red blood cells are very high (Spahn & Casutt, 2000). Due to the potential risks of bleeding and blood transfusions, there are many different methods of surgery today to reduce the amount of bleeding. One way to reduce bleeding and reduce the risk of transfusion is by the use of antifibrinolytic drugs such as aprotin, aminocaproic acid, and tranexamic acid (Eubanks, 2010). Tranexamic acid is an industrial fibrinolytic amino acid that binds reversibly to plasminogen-blocking lysine and prevents destruction of clotting (Aguílera et al., 2013). This drug is cost-effective and widely used in surgeries (Chen Wang et al., 2015). According to some studies and Meta-analyzes, tranexamic acid reduces bleeding without increasing complications (Tao-ping et al., 2017), and some clinical trials have shown that tranexamic acid reduces intraoperative bleeding and thus requires transfusion and blood transfusion (Fu et al., 2013). Despite the benefits of this drug, valuable information on its safety and safety is lacking (Juelsgaard et al., 2001).

Intravenous tranexamic acid may increase the likelihood of thrombotic events, such as Deep Venous Thrombosis (DVT) and pulmonary embolism (Chen Wang et al., 2015). There are also reports of an allergic reaction to tranexamic acid in some people. For this reason, they prohibit the use of tranexamic acid in those who have a history of allergies, arterial and venous thrombosis, an inherent risk of thrombosis and thromboembolism, acute renal failure, subarachnoid hemorrhage, or epilepsy (Tengborn et al., 2015). Therefore, many researchers have focused on Intra-articular use of this drug and this method has been suggested as an effective alternative that has a lower risk of intravenous tranexamic acid (Raveendran & Wong, 2013). Also, according to some studies, oral tranexamic acid has a much lower cost compared to its intravenous type, although the effect of both is similar in reducing postoperative bleeding (Francesco et al., 2016). In this study, we investigated the effects and side effects of intra-articular, oral and intravenous tranexamic acid after knee arthroplasty (Tao-ping et al., 2017).

2. MATERIAL AND METHODS

This study was a randomized single-blind clinical trial on patients undergoing knee arthroplasty referred to Amir al-Momenin Hospital and Qods Hospital, Arak, Iran, during 2019-2020. Patients candidate for knee arthroplasty were divided into three equal groups using random number table. The target population included all patients undergoing knee arthroplasty who met the inclusion criteria.

Inclusion criteria
1. All patients undergoing knee replacement surgery referred to the hospital
2. All patients with informed consent to participate in plan
3. All patients undergoing knee replacement surgery by one surgeon

Exclusion criteria
1. All patients undergoing knee replacement surgery in which spinal anesthesia failed and had to undergo general anesthesia
2. Patients with a history of thromboembolic events or liver disease or hypercoagulopathy
All patients entered the operating room after being approved by the anesthesiologist responsible for the plan and were placed on the bed in a supine position. Then complete monitoring including NIBP, PR, RR, SPO2 and E.C.G was performed. Then, a non-dominant hand patient received a suitable IV with Angiocath No. 18 and each was given 3–5 CC / kg of crystal fluid as Compensatory Volume Expands (CVE). Then all patients were seated and prepared for spinal anesthesia for surgery. Spinal anesthesia was performed for all the patients from L4-L5 or L5-S1 space using G-25 needle. For these patients, 5.0% bupivacaine (4 cc) was used for spinal anesthesia. After spinal anesthesia, patients were supine and ready for surgery. Patients were given tranexamic acid before, during or after surgery and knee replacement according to the type of study group. In all patients, surgery was performed using a tourniquet and 100 mmHg tourniquet pressure was adjusted above systolic pressure. Thus, in the first group (IV), intravenous infusion of 10 mg / kg tranexamic acid 15 minutes before inflated tourniquet and 10 mg / kg during skin repair was performed, and in the second (intra-articular) and third (oral) groups the same amount (10 cc) of distilled water was drawn into the syringe. The second group (Intra-articular group) was injected Intra-articular with 3 grams of tranexamic acid after retinaculum repair. In the third group, patients were given 1 gram of oral tranexamic acid, one hour before surgery, in the operating room, and one hour after surgery in the ward with a glass of water.

In order to observe blindness, the first group received syringes containing 10mg / kg equal to 10cc pre-prepared by the anesthesiologist in charge of the plan and the fellow anesthesiologist resident who was unaware of the content of the syringes was placed and in the second (Intra-articular) and third (oral) groups the same amount (10 cc) of distilled water was drawn into the syringe. The syringes, previously prepared by the anesthesiologist in charge of the plan, were labeled 1, 2, and 3 and made available to the resident in charge of the plan. Also, patients in the second group (Intra-articular) received 3 grams of tranexamic acid intra-articularly. For the first and third group patient, the joints were washed with 1000 cc normal saline only for blindness.

The surgeon then rinsed the articulated joint using these fluids. At the end of the surgery, all patients were dressed after surgery was completed and the position was closed. Patients were then transferred to recovery. Then, a questionnaire including questions about bleeding and intraoperative bleeding (up to 48 hours) and hemoglobin and return to the operating room up to 48 hours after surgery was completed for all patients. The questionnaires were then analyzed by SPSS 23 software.

Sample size

\[
 n = \frac{\left( z_{1-\frac{\alpha}{2}} + z_{1-\beta} \right)^2 (\delta_1 + \delta_2)^2}{(\mu_1 - \mu_2)^2}
\]

\[
\mu_1 = 367 \cdot 1 \quad \mu_2 = 306 \cdot 1 \\
\delta_1 = 50 \cdot 8 \quad \delta_2 = 72 \cdot 2 \\
z_{1-\frac{\alpha}{2}} = 1 \cdot 96 \quad z_{1-\beta} = 1 \cdot 28
\]

\[n = 45 \rightarrow \times 3 = 135\]

The total sample size was 135 persons divided into three groups of 45 persons.

Data analysis

The results of this study were recorded in the study questionnaires, the data obtained from the questionnaires were analyzed using SPSS 23 software, t-test and ANOVA statistical tests. Tables and charts were categorized.

Ethical considerations

In this study, the names and characteristics of the study subjects were kept confidential, no cost was imposed on the patient’s family, the form was completed and the patient’s education was completed with the consent of the patients and a written consent was obtained from the patients. At all stages of research, including proposal writing, sample collection and data analysis, researchers were required to adhere to the ethics of research approved by the Ministry of Health and the Helsinki Declaration. This research project, No. 2903, with code of ethics IR.ARAKMU.REC.1396.293, has been approved by the Ethics Committee of the Research Council of Arak University of Medical Sciences.

3. RESULTS

Comparison of age and sex of patients undergoing knee arthroplasty by spinal anesthesia was performed in three groups, intravenous, Intra-articular and oral tranexamic acid. Results showed that mean age and sex in intravenous group were 71.8±4.9,
23.3% male and 76.7% female, respectively. In the Intra-articular group were 72.2±6.8, 24.3% male and 75.7% female, and in the oral group were 72.6±5.4, 23.8% male and 76.2% female, respectively. According to these results, there was no significant difference between the three groups in terms of mean age and sex, and in almost all three groups the mean age was 72 years and the percentage of females in all three groups was 76% (P-value = 0.6, P-value =0.8).

Table 1 and figure 1 compares the mean intraoperative bleeding and 72 hours postoperatively in patients undergoing knee arthroplasty by spinal anesthesia in three groups of intravenous, Intra-articular and oral tranexamic acid. There was a significant difference in intraoperative blood pressure, with mean intraoperative bleeding lower in the intravenous group than in the other two groups and in the Intra-articular group less than the oral group (P-value = 0.01). However, there was no significant difference in mean bleeding after 72 hours of operation and bleeding rates were almost the same at 8 cc (P-value = 0.4).

Table 1 Comparison of mean bleeding during surgery and 72 hours after surgery

<table>
<thead>
<tr>
<th>P-value</th>
<th>Oral group</th>
<th>Intra-articular group</th>
<th>Intravenous group</th>
<th>Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>P=0.01</td>
<td>41.4±5.6</td>
<td>31.5±5.9</td>
<td>22.2±4.7</td>
<td>Average intraoperative bleeding (in cc)</td>
</tr>
<tr>
<td>P=0.4</td>
<td>8.4±1.7</td>
<td>9.3±2.1</td>
<td>7.8±1.1</td>
<td>Average bleeding 72 hours after surgery (in cc)</td>
</tr>
</tbody>
</table>

Figure 1 Mean bleeding during surgery and 72 hours after surgery

Mean hemoglobin preoperatively, 8 hours and 48 hours postoperatively, in patients undergoing knee arthroplasty by spinal anesthesia, were compared in three groups of intravenous, Intra-articular and oral tranexamic acid in Table 2 and according to the results there was no significant difference between the three groups in mean hemoglobin preoperatively, 8 hours and 48 hours postoperatively, so that the mean hemoglobin was almost the same in all three groups, preoperatively in all three groups 13, 8 hours after surgery 12.5 and two days after surgery 11. (P-value = 0.6, P-value = 0.7, P-value = 0.3).

Table 2 Mean hemoglobin preoperatively, 8 hours and 48 hours postoperatively

<table>
<thead>
<tr>
<th>P-value</th>
<th>Oral group</th>
<th>Intra-articular group</th>
<th>Intravenous group</th>
<th>Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>P=0.6</td>
<td>13.4±5.1</td>
<td>12.9±2.8</td>
<td>13.2±3.1</td>
<td>Mean hemoglobin preoperatively</td>
</tr>
<tr>
<td>P=0.7</td>
<td>13.1±4.3</td>
<td>12.6±3.6</td>
<td>12.8±4.7</td>
<td>Mean hemoglobin 8 hours postoperatively</td>
</tr>
<tr>
<td>P=0.3</td>
<td>11.3±3.4</td>
<td>11.1±2.9</td>
<td>10.9±4.1</td>
<td>Mean hemoglobin 48 hours postoperatively</td>
</tr>
</tbody>
</table>
Table 3 compares the mean length of hospital stay and return to the operating room in patients undergoing knee arthroplasty by spinal anesthesia in three groups, intravenous, Intra-articular and oral tranexamic acid. The mean hospital stay did not show a significant difference as the mean hospital stay was almost the same in all three groups and was approximately 5.3 days. There was also no return to the operating room in any of the groups (P-value≥0.05 and, P-value = 0.6).

Table 3 Comparison of mean hospital stay and return to operating room

<table>
<thead>
<tr>
<th>P-value</th>
<th>Oral group</th>
<th>Topical group</th>
<th>Intravenous group</th>
<th>Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>P=0.6</td>
<td>3.2±1.8</td>
<td>3.7±1.9</td>
<td>3.4±1.1</td>
<td>Average hospital stay (days)</td>
</tr>
<tr>
<td>P≥0.05</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>Average return to operating room</td>
</tr>
</tbody>
</table>

Mean postoperative complications and mean transfusion in patients undergoing knee arthroplasty by spinal anesthesia were evaluated in three groups, intravenous, Intra-articular and oral tranexamic acid. No significant difference was observed (P≥0.05).

4. DISCUSSION

One of the important goals of anesthesiologists and orthopedists in patients with knee arthroplasty is to find the right combination to reduce bleeding after arthroplasty. Knee replacement is one of the special skills of surgery in the last century and is an effective treatment to relieve severe pain and defects in the knee joint, which can be associated with complications such as bleeding during and after surgery (Soni et al., 2014). One of the most effective methods is the use of antifibrinolytic drugs, especially tranexamic acid (Juelsgaard et al., 2001). Therefore, in this study, we compared the efficacy and side effects of tranexamic acid in three intravenous, oral and Intra-articular forms in knee arthroplasty surgery. The results of this study showed that in all three groups, tranexamic acid significantly reduced intraoperative bleeding, but intravenous tranexamic acid had more effect on reducing bleeding than the other two groups. There was no significant difference between the three groups in terms of mean hemoglobin preoperatively, 8 h and 48 h postoperatively, and hemoglobin was almost the same in all three groups at the three mentioned times.

In this regard, several studies, including a Jashvant poerab study and colleagues in the United States in a retrospective study of 872416 patients undergoing knee arthroplasty in a retrospective study in 2014, concluded that the use of tranexamic acid in three doses; Intravenous administration of 1, 2 and 3 g was effective in reducing postoperative bleeding, but the use of lower doses of tranexamic acid was associated with fewer thromboembolic complications, acute renal failure (Jashvant et al., 2014). The results of our study were consistent with this study, so that in our study 10 mg / kg of tranexamic acid significantly reduced the amount of bleeding in the candidate patients.

In a similar study conducted by Jatin Parakah and colleagues in 2017, a randomized study of 50 patients undergoing knee arthroplasty, they compared the effect of intravenous and Intra-articular tranexamic acid. The results of this study indicated that the use of Intra-articular and intravenous tranxamic acid would both decrease bleeding and decrease hemoglobin levels in patients, but the rate of blood transfusion and possible demand for blood products in the Intra-articular group was higher than that of the intravenous group (Jatin et al., 2017). The results of this study were somewhat consistent with our study, in our study also reduced the amount of bleeding in both the intravenous and Intra-articular groups. However, in contrast to the above study, the rate of bleeding and hemoglobin in postoperative patients and the need for postoperative transfusions were similar in all three groups.

In another study by Eydan Kayupov and his colleagues in the USA in year 2017, 83 patients were candidates for total knee and divided into two groups, intravenous and oral tranexamic acid, and found that the mean total bleeding and mean blood transfusion requirement, were similar in both groups, with almost no significant difference between the two groups (Erdan et al., 2017). The results of this study were almost in line with our study, so that in our study the rate of intraoperative bleeding in intravenous group was lower in the two groups, but the rate of this bleeding at 72 hours postoperatively was similar in all three groups. The rate of transfusion and hemoglobin requirement was similar for patients up to 48 hours postoperatively.

And finally, in a study that Francesco and his colleagues in Italy on 34 patients in 2016, they examined the effect of tranexamic acid on Intra-articularly and intravenously. The results of this study showed that in the combination of intravenous and Intra-articular tranexamic acid, the rate of hemoglobin decrease was lower than in the other two groups, but the rate of bleeding in all three groups was similar (Francesco et al., 2016). The results of this study were not consistent with our study because in our study, intraoperative bleeding was significantly lower in the intravenous and oral groups, but there was no significant difference between the three groups in the amount of postoperative hemoglobin. There was no significant difference between the two groups after surgery and transfusion rate.
5. CONCLUSION
According to the results, it can be concluded that Intra-articular and oral tranexamic acid reduces bleeding and prevents postoperative hemoglobin loss and makes Intra-articular and oral tranexamic acid as an effective alternative to intravenous tranexamic acid. It is noteworthy that only in the tranexamic acid group; the mean intraoperative bleeding was lower than the other two groups, which may improve the surgeon's intraoperative vision, but no significant difference between the three groups in the mean postoperative bleeding. The operation, transfusion requirement, and hemoglobin reduction by 48 hours postoperatively were not observed between the three groups. Therefore, at the end, it is recommended that similar studies be performed with the same number of specimens or with other drugs to reduce bleeding during and after knee arthroplasty.

Acknowledgement
We thank all those who helped us in this research.

Author Contributions
All authors contributed to the design of the study, as well as data collection and analysis, and the writing of the manuscript. All authors read and approved the final manuscript.

Funding
This study has not received any external funding.

Conflict of Interest
There is no contradiction in the article.

Informed consent
Written & Oral informed consent was obtained from all individual participants included in the study.

Data and materials availability
All data associated with this study are present in the paper.

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Peer-review
External peer-review was done through double-blind method.

Article History
Received: 04 November 2020
Reviewed & Revised: 05/November/2020 to 08/December/2020
Accepted: 08 December 2020
E-publication: 19 December 2020
P-Publication: November - December 2020

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