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Original Article

Effect of Intravenous Administration of Tranexamic Acid During Surgery on Blood Loss in Patients with Femoral Fracture Surgery

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Abstract

Introduction: In major operations such as hip surgery, the volume of blood loss is high, and patients require blood transfusion. The current study aimed to assess the effect of Tranexamic Acid on reducing blood loss and the need for blood transfusion during and after surgery.

Methods: Assessed patients with concher femoral insertion surgery were randomly divided to intervention and control groups. After anesthesia, the intervention group received Tranexamic Acid (10 mg/kg) 15 minutes before infusion. The infusion was performed at a rate of 1 mg/kg/hr until the end of surgery. In the control group, equal volumes of normal saline were used.

Results: The mean blood loss during surgery was 1081.67±298.70 cc In the placebo group; and was 557.00±00.76 cc in the intervention group. The mean blood loss during surgery was significantly higher in the placebo group than in the intervention group (P<0.001). The mean blood loss after surgery was 427±000.7032 in the placebo group, and was 249.67±66.37 in the control group (P<0.001). Blood transfusion, during and after surgery was significantly different between the two groups (P<0.001).

Conclusion: Single dose Tranexamic Acid (10 mg/kg) 15 minutes before the infusion to patients scheduled for femoral fracture surgery can reduce blood loss and the need for blood transfusion during and after surgery.

Keywords: Femoral fracture, Blood loss, Blood transfusion, Tranexamic Acid.

Introduction

Due to increased trauma and increased frequency of such surgeries, orthopedic surgeries may cause serious complications such as blood loss and the need for blood transfusion. However, blood transfusion also has consequences, including the transmission of viral diseases, blood group incompatibility, increased rate of bacterial infections, and sensitization of the immune system[1-3]. On the other hand, interventions planned by blood banks to reduce these complications are costly. Hence, interventions to reduce blood loss during and after surgery are affordable. Several techniques are developed for this purpose, including autologous blood transfusion, storing compatible blood for surgery, using surgical tourniquets for lower limbs, and the drug agents against fibrinolysis during surgery (e.g., aprotinin, Tranexamic Acid, and Aminocaproic acid). However, each of these techniques has its complications[4,5]. According to the literature, Tranexamic Acid can reduce the need for blood transfusion, compared to the placebo,

without causing a significant increase in complications such as thromboembolism events. However, there are concerns regarding the increased risk of coagulation in surgeries with a high risk of thromboembolism, such as orthopedic surgeries[6-8]. Tranexamic Acid is commonly used as an anticoagulant to reduce blood loss in maxillofacial surgery, heart surgery, and rhinoplasty in women, and in most cases, its effectiveness has been confirmed[9,10]. However, few studies are conducted in the field of orthopedics. Tranexamic Acid increases the reliability of the clot by preventing the activation of plasminogen and preventing further blood loss[11]. Considering that evidence regarding the effect of Tranexamic Acid on reducing blood loss is still controversial, particularly concerning its consequence, safety, and consequences, most studies have investigated the effects of tourniquets. Besides, most studies have examined total knee or hip surgeries, and the results concerning other organs are incomplete and not widespread. In addition, various studies have used different time and drug administration methods. Hence, in the present study, we aimed to clarify the effect of intravenous Tranexamic Acid injection on reducing blood loss in femoral fracture surgery.

Methods

Study Design

In this randomized, double-blind clinical trial, 60 patients, after evaluating against inclusion and exclusion criteria, admitted to an Orthopedic Hospital (Iran-Tabriz) during 2019 are investigated. To estimate the sample size, primary information, including mean and standard deviation of intraoperative blood loss variable, were extracted from the study by Gustav Ekba[12]. By considering a 95% confidence interval, test power of 90%, 20% change in the significant variable, and using the following formula, the minimum sample size in each group was calculated as 26 cases. By considering attrition of 20%, the sample size of each group was increased to 30 cases.

$n = [(Z1-\alpha/2 + Z1-\beta) 2\times (SD12 + SD22] / (Mean1 – Mean2)2$

Participants were selected using the convenience sampling technique. Then, subjects were allocated to the groups of intervention and control using the random block with sizes of 2 and 4. A random sequence was generated using the RAS software. The groups were matched concerning demographic variables. In this study, the main researcher and statistical advisor were not aware of the allocation of patients, and data were collected by the assistant researcher.

Inclusion and Exclusion Criteria

Inclusion criteria were at least 18 years old, candidates for femoral fracture surgery with concher insertion, and patients with physical classes 1 and 2 based on the American Anesthesiology Society. Also, exclusion criteria were sensitivity to Tranexamic acid (based on the patient's medical history), pre-existing anemia (hemoglobin<8 g/ml), avoiding blood transfusion, history of anticoagulant drugs, coagulation disorders, history of thromboembolism, history of cerebrovascular damage, ischemic heart disease, pregnancy, major underlying diseases such as pulmonary or heart disease, liver, and renal failure, history of seizures, and need for re-surgery.

Implementations

After obtaining the approval of the surgeon, the pre-surgery consultation was performed, and the necessary information was recorded. Heparinization was started the day before surgery by injecting heparins with low molecular weight. All necessary tests were registered in patients' records, including hemoglobin, hematocrit, fibrinogen, PT, PTT, urea, creatinine, INR, platelet count, and CBC. Anesthesia was induced after performing necessary checkups, including NIBP, HR, and SaO^2. Anesthesia indications were Propofol (2-2.5 mg/kg, Fentanyl (1-2 mcg/kg), Midazolam (.03-.05 mg/kg), and Atracurium (0.5-0.6 mg/kg). Patient monitoring included: NIBP, HR, SaO^2, urinary extraversion, $ETco^2$, TOF, along with Hb & Hct, if necessary. After choosing the appropriate position and performing prep and drep, Tranexamic Acid (10 mg/kg) was administered for subjects in the intervention group 15 minutes before infusion. The infusion continued at a dose of 1 mg/kg/hr until the end of surgery. The control group received normal saline, with equal volume, as the placebo. The drugs were prepared in similar syringes and delivered to the anesthesiologist, who was unaware of the content. Syringes were coded, then the volume of blood loss during surgery was estimated by careful examination of the blood in the suction, the amount of blood poured at the site of the operation, and the number of gases impregnated with blood. Intraoperative blood

transfusion was performed using the MABL (Maximum Allowable Blood Loss) formula of different references [ABL= [EBV x(Hi-Hf)]/Hi. The following variables were investigated both during and after surgery: blood loss during surgery (primary outcome), secondary consequences (postoperative hemorrhage in the drainage tank, transfusion during and after surgery, and urinary extraversion). Necessary tests, including Hb, Hct, PT, PTT, aPTT, Fibrinogen, urea, creatinine, INR, PLT, and CBC, both before and after surgery, as well as the need for post-surgery transfusion (in cases with hemoglobin< 8 gr/dl in healthy patients and <10 gr/dl in patients with ischemia-induced symptoms) were investigated. Besides, symptoms of thromboembolic events in cases with a WELLS score were examined. Doppler sonography was performed for DVT diagnosis.

Statistical Analysis

Data were analyzed using descriptive statistics (mean ± SD and percentage). The independent t-test was used to compare the mean of two groups (quantitative), and the chi-square test was applied for qualitatively comparing the two groups. The Kolmogorov-Smirnov test was applied to test normal distribution. Data were analyzed using SPSS version 22. Statistical significance was considered when p-value<0.05.

Results

The placebo group comprised 7 (23.3%) female and 23 (76.6%) male patients, while the intervention group comprised 8 (26.7%) female and 22 (73.3%) male patients. The groups were not significantly different concerning gender (I,e. were gender-matched (p=0.984)). There was no statistically significant difference between the mean height of patients in the placebo (171.67±6.74) and Tranexamic Acid (171.63±6.21) groups (P=0.984). Concerning the age structure of both groups, there was no statistically significant difference between the mean age of patients in the placebo (47.40±12.55) and Tranexamic Acid (43.77±15.65) groups (P=0.325). There was no statistically significant difference between the mean weight of the patients in the placebo (76.67±6.40) and Tranexamic acid (74.53±6.68) groups (P=0.264).

Before surgery, the mean urinary extraversion of the placebo group (131.00±69.45) was lower than the Tranexamic Acid group (186.00±92.61) (p=0.012). Besides, in the placebo group, the mean urinary extraversion in the first hour (161.38±±70.34) was lower than that of the Tranexamic Acid group (225.83±.90.42) (p=0.003). In the placebo group, the mean urinary extraversion in the second hour (75±193.97) was lower than the intervention group (273.67±99.29) (p=0.001). Also, the mean urinary extraversion in the third hour of the placebo group (256.71±69.73) was lower than the Tranexamic Acid group (335.83±96.53). On the other hand, the mean urinary extraversion at the end of surgery in the placebo group (372.24±73.11) was lower than the Tranexamic Acid group (415.83±93.85) (p=0.052).

In the placebo group, the mean blood loss during surgery was 1081.67±298.70, and for the intervention group, it was 557.00±128.76 cc. The mean blood loss during surgery was significantly higher in the placebo group than in the Tranexamic Acid group (p<0.011). The mean blood loss after surgery in the placebo and control groups was 427.00±83. 32 and 249.67±66.36, respectively (p<0.001) (Table 1). There was a significant difference concerning blood transfusion during and after surgery (p<0.001).

Table 1: Comparison of blood loss and transfusion during and after surgery between the two groups

Blood ;oss	**Tranexamic acid**	**Control**	**P Value**
During surgery(CC)	557.00±128.76	1081.67±298.70	0.001
after surgery(CC)	249.67±66.36	427.00±83. 32	0.001
Transfusion			
1 Unit	0	3 (10%)	0.001
2 Unit	0	6 (20%)	
3 Unit	0	7 (23.33%)	
No Transfusion	30(100%)	14 (46.66%)	

Laboratory tests during and after surgery were as follow: platelet changes before (P=0.604) and after surgery (P=0.271), hemoglobin before (P=0.167) and after surgery (P=0.001), hematocrit before (P=0.157) and after surgery (P=0.001), prothrombin time before surgery (P=0.241) and after surgery (P=0.001), relative thromboplastin time before (0.999) and after surgery (P=0.001), level of INR before surgery (P=0.332) and after surgery (P=0.001), fibrinogen before (P=0.597) and after surgery (P=0.019), urea before (P=0.974) and after surgery (P=0.065), and creatinine before (P=0.237) and after surgery (P=0.001).

In the Tranexamic Acid group, surgeon satisfaction was as follows: 29 (96.6%) cases were "good" one case, or 3.3% was moderate, and no one was dissatisfied. In the placebo group, surgeon satisfaction was as follows: eight cases (26.6%) had a "good" opinion, and 19 cases (63.3%) were moderate, and 3 (10%) were dissatisfied. Surgeon satisfaction was significantly higher in the Tranexamic Acid group than in the placebo group (p=0.001).

After providing the intervention, no complication was observed in both groups (e.g. thromboembolic events, sonographic symptoms of deep vein thrombosis, and complications of Tranexamic acid injection).

Discussion

The current study aimed to investigate the effect of Tranexamic Acid administration on preventing blood loss after femoral surgery to prevent complications of blood transfusions. This study demonstrated that the administration of 10 mg/kg Tranexamic Acid 15 min before infusion could reduce blood loss during surgery. Therefore, the volume of blood loss and the amount of blood transfused for patients with Tranexamic Acid infusion were lower than the control group. Tranexamic Acid was first proposed to prevent blood loss in adults at high risk of blood loss in a clinical trial conducted in 274 hospitals in 40 different countries. In this extensive trial study, patients were divided into two groups of intervention (1g initial dose of Tranexamic Acid and another 1g after 8 hours) and the placebo. Tranexamic Acid could effectively reduce blood loss. Besides, no significant complication related to clotting was reported[13,14,15]. Camarasa et al. reported that administration of Aminocaproic acid and 10 mg/kg of Tranexamic Acid before tourniquet opening could reduce blood loss during Knee arthroplasty. Besides, it reduced the need for blood transfusion[16]. Rajesparan et al. found that intravenous administration of 10 mg/kg Tranexamic Acid at the beginning of surgery was not associated with reduced blood loss and the need for blood transfusion. But doses of 15 and 20 mg/kg reduced blood loss and the need for blood transfusion after surgery but did not affect during-surgery blood loss. Husted et al., in a study on Pelvic arthroplasty, showed that a single dose of 10 mg/kg and infusion of 1 mg/kg/h Tranexamic Acid 10 hours before surgery was associated with reduced post-surgery blood loss and the need for blood transfusion[17]. The dose and type of administered drugs are similar to the present study. However, in the present study, 10 mg/kg Tranexamic Acid was injected 15 minutes before infusion, which

resulted in a significant reduction of blood loss. Choi et al. showed that a single dose of 20 mg/kg Tranexamic Acid before surgery had reduced blood loss in bilateral maxilla osteotomy. In this study, the volume of blood loss in the control group was 422 ml more than the Tranexamic acid group[18, 19]. In this context, it can be argued that when a fibrin clot is formed, the therapeutic effects of Tranexamic Acid appear. Tranexamic Acid prevents clot-dissolving by the proteolytic consequence of plasmin. By blocking the lysis site on the plasminogen molecular, Tranexamic Acid delays the clot lysis time. Therefore, it prevents the bonding of active plasmin on the fiber surface; surgery and venous stasis release the active tissue plasminogen, which causes activation of the fibrinolytic system. If Tranexamic Acid is administered before clot formation, it inhibits the lysis of the clot, and its effect reduces after clot formation. It indicates the reason for less affection of Tranexamic Acid in reducing blood loss at the end of surgery. Moreover, it can explain the ineffectiveness of continuous administration of Tranexamic acid (infusion) in preventing blood loss after cardio surgeries.

Limitations and Recommendations

The current study has limitations including not considering long-term complications and not evaluating different doses of the drug. According to the findings of the present study and other studies, as well as the mechanism of Tranexamic acid in preventing clot-dissolving, it is necessary to investigate the effect of this drug on reducing the amount of blood loss during and after surgery, the need for the blood transfusion on different doses of the drug, various times of administration, and surgical operations with different extents.

Conclusion

The results demonstrated that administering a single dose of Tranexamic Acid (10 mg/kg) at 15 minutes before the infusion to patients, and also intake one mg/kg/hr of it until the end of surgery to patients with femoral fracture was associated with reduced blood loss and reduced need for blood transfusion.

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Conflict of Interest Disclosures

None

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Authors' Contributions

MP: Study design and study managing. AS: Intervention. NA: Manuscript preparation and submission. AM: Data Analysis. SA: Data Collection.

Ethical considerations

Once ensuring the confidentiality of the information, patients were aware that all methods and measures used in hemorrhagic surgery are planned to save the life of the patient via maintaining the function of vital organs. The goal was to reduce the amount of blood loss during surgery and prevent complications related to blood loss, as well as the patient's need for blood transfusion. Informed written consent was obtained from all participants. The current study is approved by the ethics committee of the Tabriz University of Medical Sciences (NO: IR.TBZMED.REC.1398.946) And Iranian Registry Of clinical Trial (NO: IRCT20191208045664N1).

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