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Research Article

Intravenous Injection of Tranexamic Acid in Patients with Pelvis or Acetabulum Fractures to Reduce Blood Loss: A Double-Blind, Randomized, Controlled Trial

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Abstract

Background: Despite their low incidence, pelvis and acetabular fractures have a high mortality rate due to extensive hemorrhage. Tranexamic acid (TXA) is an antifibrinolytic drug that inhibits the production of plasminogen. The aim of the current study is to evaluate the safety and efficacy of TXA use for blood loss reduction and the need for blood transfusion in patients with fractures of the pelvis or acetabulum.

Methods: 108 patients were recruited from two tertiary care hospitals and assigned evenly either to the intervention (TXA) or the control group. TXA group received 15 mg/kg TXA 30 minutes before the fracture reduction and fixation surgery. The number of transfused blood units before, during, and after the surgery was recorded. Blood loss was assessed by calculation of estimated blood loss (EBL), collected blood with drain, collected blood with suction, and weight of the used gauzes during the surgery. The time between fracture occurrence and the surgery, the duration of the surgery, and the days of admission were assessed.

Results: The mean age was 39.49 ± 15.81 years, and 69.4% were women. 6 patients had pelvic, and 102 patients had acetabulum fractures. The duration of the surgery was not significantly different. The time gap between the reconstructive surgery and fracture occurrence was significantly higher in the TXA group (P = 0.032). The mean postoperative hospitalization time was significantly lower among TXA group patients (P = 0.037). The mean hemoglobin (Hb) in the TXA group was significantly higher, postoperatively (P = 0.028). The mean EBL, the blood volume collected by suction or drain, the weight of the consumed gauze during the surgery, and the number of transfused blood units were significantly lower in the TXA group. The transfusion rate was significantly lower in patients with a shorter time gap between fracture occurrence and reduction surgery (P = 0.021).

Conclusion: TXA can decrease blood loss, the transfused blood units during and after the operation, and hospital admission days. Moreover, it did not increase the chance of pulmonary thromboembolism (PTE) or deep vein thrombosis (DVT) in the patients receiving TXA; thus, it can be assumed as a safe and efficient drug in patients with acetabulum or pelvis fractures.

Keywords: Randomized Controlled Trial; Tranexamic Acid; Hip Fractures; Blood Loss

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Background

Pelvic and acetabular fractures are not common and account for 1.5% of all fractures in adults and 2-5 percent of fractures that require hospitalization (1, 2). Despite the low incidence of these fractures, they are accompanied by a high mortality rate of 5-50 percent, which makes pelvic ring fractures one of the leading causes of mortality among all types of fractures (3). Given that the main non-central nervous system (CNS) cause of death in pelvic fractures is extensive hemorrhage, using methods to control this issue is a priority that can reduce mortality rates among patients with pelvic and acetabulum fractures (4, 5).

Tranexamic acid (TXA) (Cyklokapron, Pfizer, New York, USA) is an antifibrinolytic synthetic derivative of lysine that works by competitively inhibiting the conversion of plasmin to plasminogen, which leads to effectively preventing fibrin degradation and dissolution of the formed clot (6). The use of TXA has been approved and widely accepted in orthopedic surgeries, including joint arthroplasty and shoulder and hip fracture surgery, which can reduce intraoperative blood loss and the need for blood transfusion (7-17). Moreover, the safety and efficacy of TXA to control bleeding in spine surgeries have been approved in previously conducted studies (18, 19).

Despite the positive evidence provided by studies which evaluated the effect of TXA use in pelvic and acetabular fractures regarding its use to minimize blood loss, the dosage and the method of injection in these studies were different, and the effect of TXA use on reducing blood transfusion is still under debate (20-22). Additionally, implementing new studies to reach a consensus concerning the effect of TXA use in the pelvis and acetabular fractures is essential. Thus, the aim of this study is to investigate the efficacy of TXA on blood loss reduction and the requirement for blood transfusion in patients with fractures of pelvis or acetabulum.

Methods

This prospective double-blinded randomized controlled trial was conducted in two tertiary referral centers in

Tehran, Iran, namely Taleghani and Imam Hossein hospitals. This study has been approved by the Ethics Committee meeting at Shahid Beheshti University of Medical Sciences, Tehran, Iran (IR.SBMU.MSP.REC.1399.275), and the Iranian Registry of Clinical Trials (IRCT20180404039188N2), and written consent was collected from all patients.

To calculate the sample size, the effect size was considered 0.45 based on previously conducted studies (23). Power and αlevels were estimated as 0.9 and 0.05, respectively. A sample size of 54 per condition was calculated. We included all adult patients with acetabulum or pelvic fractures in this study. However, we excluded patients with a history of anticoagulant drug (except for aspirin) or oral contraceptive use, abnormal prothrombin time (PT), international normalized ratio (INR) or partial thromboplastin time (PTT) range, coagulopathy disorders, open fracture, renal insufficiency, cerebrovascular accident (CVA), intracranial hemorrhage (ICH), spinal column fracture, high-grade intra-abdominal solid organ injury, myocardial infarction (MI), traumatic brain injury (TBI), cardiopulmonary resuscitation (CPR), pregnancy, and breastfeeding to minimize confounding variables and remove the risk factors for pulmonary thromboembolism (PTE) and exclude patients with contraindications for PTE prophylaxis use.

From September 2018 until December 2020, a total number of 108 patients with pelvis or acetabulum fractures were recruited and randomly assigned either to the intervention group or the control group. One of the operating room nurses in each hospital was responsible for allocating the patients either to the intervention or control group, using a computer random number generator based on the generated random number being odd or even. Moreover, the nurses were responsible for the safety of the drugs and ensuring that the patients in each group received the proper drugs according to their allocation.

Neither the researchers nor the patients were aware of allocation results until the gathered data were analyzed. The intervention group patients received 15 mg/kg TXA added into 500 ml of 0.9% saline serum intravenously. The patients in the control group received 500 ml 0.9% saline serum, just like the intervention group.

The intervention and control group patients' background and demographic data, including age, sex, body mass index (BMI), history of coronary heart disease, deep vein thrombosis (DVT), diabetes mellitus (DM), and hypertension (HTN), were gathered and compared. Moreover, laboratory tests before the fracture reduction, including hemoglobin (Hb), PT, INR, PTT, platelet count (PLT), and hematocrit (HCT) were assessed. The number of infused packed cell bags, lost blood volume, Hb 24 hours after the fracture reduction surgery, and estimated blood loss (EBL) were assessed and analyzed.

All fractures were treated by one of two experienced orthopedic hip surgeons. In the operating room, before the induction of general anesthesia, the patients were continuously monitored with cardiac monitoring, evaluating blood pressure and pulse oximetry. General anesthesia was indicated with routine anesthetic agents. 30 minutes before the surgery, 15 mg/kg TXA was added to 500 ml of normal saline and was injected into the intervention group patients within 30 minutes. The control group patients received 500 ml of normal saline as well. During and after the surgery, the amount of lost blood was estimated based on suctioned blood volume, the weight difference of the used gauze, and blood volume collected by a drain 24 hours after the surgery.

The EBL was assessed using Hb differences before and after the surgery, the estimated total blood volume (TBV) (65 ml/kg for women and 75 ml/kg for men) of the patients, and the estimated amount of allogenic Hb transfused to the patient: EBL = 1000 × [(Hb before surgery-Hb after surgery) × TBV + transfused HB]/(Hb before surgery).

During the postoperative care, vital parameters were recorded. All patients were followed up for one day. At the end of the first day after surgery, Hb and HCT were measured. Patients were monitored for any side effects, such as allergic reactions to the drug or any clinical evidence of DVT or PTE.

The data were analyzed by SPSS software (version 22, IBM Corporation, Armonk, NY, USA). Quantitative data were reported using mean and standard deviation (SD). Analysis of variance (ANOVA) and t-test were used to analyze quantitative data. The chi-square test was used for qualitative data, and P-value less than 0.05 was considered significant.

Results

As demonstrated in figure 1, 108 patients with acetabulum or pelvis fractures were recruited and included for data analysis. Half of the patients were allocated to the intervention group, and the other patients were allocated to the control group.

The baseline and perioperative information of the study groups is reported in table 1.

The patients had a mean age of 39.5 ± 15.2, and the mean BMI was 25.20 ± 4.69 kg/m^2. 69.4% of the patients were men. Seven patients had a history of coronary disease, 3 patients had DM, 13 patients had HTN, 102 patients had acetabular fractures, and six had pelvis fractures. The mean Hb of the patients before the surgery was 11.41 ± 1.67 g/dl. The average time gap from fracture to surgery was 8.74 ± 5.74 days. No significant differences were found comparing the TXA group and control group concerning age, BMI, gender, underlying disease, fracture zone, and the Hb rate prior to the reduction surgery. However, the time gap from the fracture to the operation was significantly longer among TXA group patients (P = 0.032).

Table 1. Baseline characteristics of tranexamic acid (TXA) and control groups

Baseline characteristics	TXA group	Control group	P-value
Age (year) (mean ± SD)	39.25 ± 15.36	39.72 ± 16.39	0.968
Gender (female) [n (%)]	14 (25.9)	19 (35.2)	0.296
BMI (kg/m2) (mean ± SD)	24.28 ± 4.22	26.03 ± 5.00	0.072
Underlying disease [n (%)]	5 (9.3)	11 (20.8)	0.095
Hb before surgery (g/dl) (mean ± SD)	11.29 ± 1.43	11.70 ± 1.86	0.763
Transfused blood units before surgery (mean ± SD)	1.59 ± 1.28	1.75 ± 1.69	0.839
The time between fracture and surgery (day) (mean ± SD)	9.94 ± 5.72	7.54 ± 4.53	0.032
Fracture zone [n (%)]			
Acetabulum	3 (5.6)	3 (5.6)	> 0.999
Pelvis	51 (94.4)	51 (94.4)	

BMI: Body mass index; Hb: Hemoglobin; SD: Standard deviation; TXA: Tranexamic acid

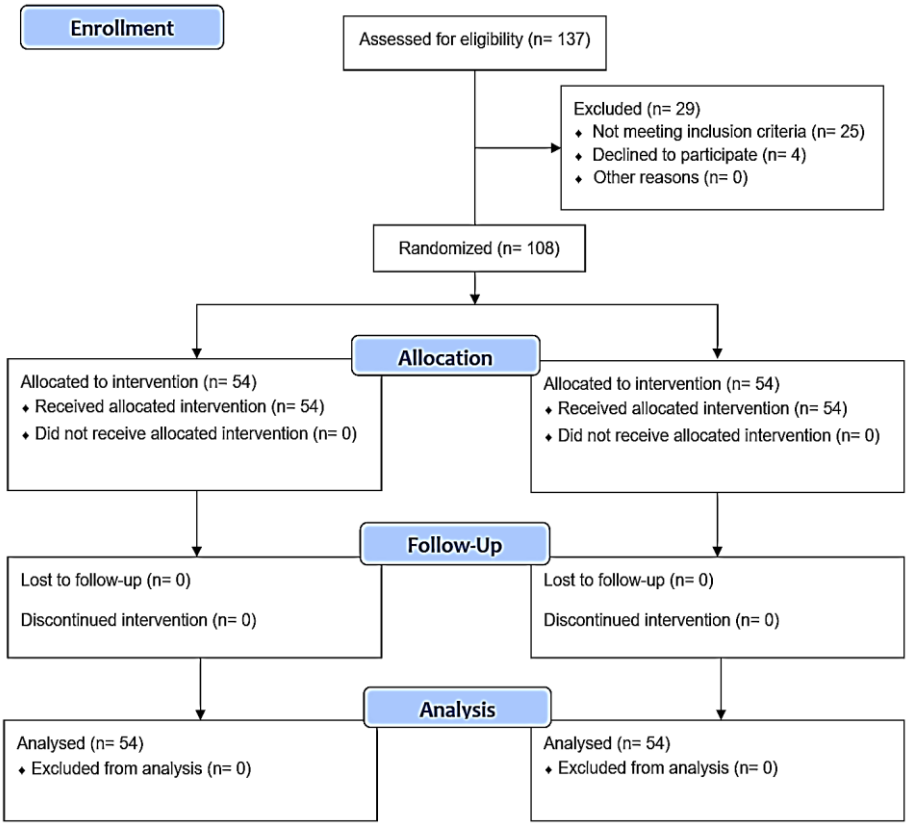

Figure 1. The Consolidated Standards of Reporting Trials (CONSORT) flow diagram of the evaluated and included patients

The surgical and postoperative information of the TXA and control groups is reported in table 2. The duration of the surgery was 183.7 ± 70.5 minutes. Since the current study was conducted in two referral hospitals, most of the admitted patients were referred to these hospitals by other healthcare centers due to the complexity of the cases. This led to long periods of hospitalization in the patients who participated in the current study. The mean hospitalization time after the surgery was 14.1 ± 6.2 days. No significant differences were observed between the groups concerning the operation time (P = 0.752), but the hospitalization time after the surgery was significantly lower in the TXA group (P = 0037). The results suggested that the difference between groups concerning the Hb rate after the surgery was insignificant (P = 0.418). The mean EBL (P = 0.025), the amount of collected blood volume by suction (P < 0.001), the weight of the used gauzes during the surgery (P < 0.001), and the blood volume collected by drain (P < 0.001) were significantly lower in TXA group patients (P < 0.001).

Thirty-four of the included patients had a blood transfusion. The mean transfused packed cell bags before surgery was 2.46 ± 1.12, while the mean number of transfused packed cells during or after surgery was 3.66 ± 1.87. The number of transfused blood units between the study groups before the reconstructive operation was not significantly different (P = 0.839); however, intervention group patients received a smaller number of blood-packed cells during and after the surgery (P = 0.039). By analyzing the number of patients that had blood transfusions along with the time gap between fracture occurrence and the reduction surgery, it was concluded that the need for blood transfusion was significantly lower in patients with a shorter time gap (P = 0.021) (Table 3).

Symptomatic PTE and DVT were observed in 4 patients each, two weeks after the surgery. There was no incidence of PTE or DVT 6 weeks and 3 months after the surgery in both control and intervention groups. The incidence of PTE (P = 0.495) and DVT (P > 0.999) was not significantly different among the study groups.

Table 2. Results in tranexamic acid (TXA) and control groups

Items	TXA group	Control group	P-value
Duration of surgery (minute) (mean ± SD)	185.75 ± 78.59	181.61 ± 61.82	0.752
Hb after surgery (g/dl) (mean ± SD)	10.03 ± 1.44	10.26 ± 1.66	0.418
Transfused blood units during and after surgery (mean ± SD)	1.23 ± 1.18	2.85 ± 1.69	0.039
EBL (ml) (mean ± SD)	728.83 ± 443.14	975.13 ± 447.95	0.025
Collected blood with suction (ml) (mean ± SD)	397.00 ± 54.54	1002.52 ± 91.00	< 0.001
Collected blood with drain (ml) (mean ± SD)	126.69 ± 99.07	837.90 ± 287.19	< 0.001
Weight of blood gauze (g) (mean ± SD)	178.03 ± 152.42	254.07 ± 66.76	0.017
Hospitalization after surgery (day) (mean ± SD)	4.68 ± 2.8	8.18 ± 3.24	0.037
Incidence of symptomatic DVT within 2 weeks after surgery [n (%)]	2 (3.7)	2 (3.7)	> 0.999
Incidence of symptomatic PTE within 2 weeks after surgery [n (%)]	0 (0)	2 (3.7)	0.495

DVT: Deep vein thrombosis; EBL: Estimated blood loss; Hb: Hemoglobin; PTE: Pulmonary thromboembolism; SD: Standard deviation; TXA: Tranexamic acid

Table 3. The association between the need for blood transfusion and the time gap between fracture occurrence and reduction surgery

The time gap between fracture and surgery	Blood transfused	Less than 10 hours [n (%)]	10 to 20 hours [n (%)]	More than 20 hours [n (%)]	P-value
All patients	Yes	7 (6.48)	10 (9.25)	17 (15.71)	0.021
	No	22 (20.38)	34 (31.49)	18 (16.68)	
TXA group	Yes	4 (7.40)	5 (9.26)	7 (12.96)	0.049
	No	10 (18.52)	17 (31.49)	12 (22.22)	
Control group	Yes	3 (5.56)	7 (12.96)	10 (18.51)	0.031
	No	12 (22.22)	17 (31.48)	6 (11.11)	

TXA: Tranexamic acid

Discussion

This study aimed to investigate the efficacy of TXA use for blood loss reduction in fractures of pelvis and acetabulum. No significant difference between the intervention and control groups was observed at baseline except for the time gap between fracture occurrence and the operation. Our results showed that TXA use significantly reduced EBL, the amount of collected blood volume by suction, the weight of the used gauze during the surgery, and the blood volume collected by a drain. Furthermore, the results of the current study demonstrated that using TXA reduced the number of transfused packed cells in patients in the TXA group in comparison to control group patients. TXA use did not increase the risk of PTE and DVT 2 weeks, 6 weeks, and 3 months after reduction surgery.

The current study demonstrated that using TXA reduced EBL, the collected blood volume from the suction, the weight of the used gauze during the surgery, and the amount of collected blood from the drain after the surgery. This result has been approved by previously conducted studies (24). Gumustas et al. performed a randomized controlled trial on 73 patients and concluded that the use of TXA reduced blood loss and Hb drops (20). Moreover, the results of the study of Spitler et al., which evaluated the effect of TXA on 93 patients with fractures of the pelvis, acetabulum, and proximal femur, demonstrated that TXA could reduce total blood loss (TBL) (21). Monsef Kasmaei et al. conducted a randomized clinical trial on 106 patients with pelvic trauma and concluded that TXA use reduced bleeding in 24, 48, and 72 hours after the reduction surgery (22). However, the results of the study performed by Lack et al. were in contrast with the results of the current study. They evaluated the efficacy of TXA in reducing blood loss in 88 patients with acetabulum fractures and claimed that it did not affect EBL and blood loss (25).

The differences in the outcomes of the Lack et al. study and the current study might be explained by the time of drug use. In the current study, the patients received 15 mg/kg of TXA 30 minutes before the reduction surgery; however, Lack et al. injected 10 mg/kg within 30 minutes before the surgery and a 10 mg/kg TXA infusion in 4 hours during the surgery. This dosage of TXA may not be sufficient to significantly decrease blood loss and the transfused blood units. A meta-analysis study demonstrated that increased administration of oral TXA reduced TBL and Hb decline in total hip or knee replacement surgeries (26).

The optimal dosage and method of TXA use for pelvis and acetabulum fractures have not been determined yet, and future studies should aim to determine the optimal TXA dosage and method of injection for pelvis and acetabulum fractures.

This study demonstrated that the use of TXA decreased the transfused blood units during and after the operation.

Concurrently, the findings of previously published research showed that TXA could decrease the number of transfused units (20, 27, 28). In 2013, Huang et al. published a systematic review and meta-analysis study that aimed to investigate the effectiveness of TXA use to reduce blood loss in patients undergoing major orthopedic surgeries and concluded that it could significantly reduce transfusion requirements (27). Furthermore, another meta-analysis study that aimed to evaluate the efficacy of TXA use to reduce transfusion rates in total knee arthroplasties (TKAs) concluded that infusion or topical TXA use could reduce transfusion rates (28); however, some previously published articles stated that TXA use might not reduce blood transfusion need in patients with acetabulum or pelvis fracture. Spitler et al. showed that unlike the reductive effect of TXA on TBL in patients with the fractures of pelvis, acetabulum, and proximal femur, it did not significantly affect the number of transfused blood units or the number of patients in need for postoperative transfusion (21). Furthermore, Lack et al. stated that the transfusion rates were associated with the duration of the surgery, the complexity of the fracture, and the Hb rate before surgery (25).

The use of TXA did not increase the chance of PTE or DVT until 3 months after the reduction surgery. Concurrent with previously published articles, this study confirmed the safety of TXA to be applied in pelvis and acetabulum fractures (20-22, 29).

This randomized double-blinded controlled trial was among the first efforts to investigate the safety and efficacy of TXA in acetabulum or pelvis fractures. The number of participants, no missing data, and the use of various methods to estimate the amount of blood loss could be assumed as strengths of the current study; however, every study has its limitations. The fractures of included patients were not classified. Additionally, the inclusion of patients with other acetabulum or pelvis fractures accompanied by other fractures was another limitation of the current study. This was due to the low number of patients with isolated pelvis or acetabulum fractures, and the exclusion of these patients would considerably reduce the sample size. The time gap between fracture occurrence and reduction operation difference among the study groups was another problem. However, the longer time gap in the TXA group and its association with increased blood loss did not affect the conclusions of this study concerning the efficacy of TXA in blood loss reduction. Another limitation of the current study was the low duration of follow-up as the adverse outcomes of the evaluated drug might occur weeks after the surgical procedure and drug application. Last but not least, some variables could not be evaluated in the current study, such as the optimal dosage and the method of TXA use in patients with pelvis and acetabulum fractures, which should be addressed in future studies.

Conclusion

This study investigated the safety and efficacy of TXA

intravenous injection for blood loss reduction in fractures of acetabulum and pelvis and suggested that TXA could reduce blood loss, the transfused blood units during or after the operation, and duration of postoperative hospital stay. Furthermore, TXA did not affect the chance of PTE or DVT; thus, TXA injection could be assumed as a safe and efficient method to reduce blood loss in acetabulum and pelvis fractures. Future studies should aim to address the optimal dosage, administration route, and timing of administration of TXA.

Conflict of Interest

The authors declare no conflict of interest in this study.

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