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Original article

Evaluation of efficacy and safety of early tranexamic acid therapy inpatients with trauma: A double-blinded randomized clinical trial

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ABSTRACT

Background: Previously, the effect of early tranexamic acid (TXA) infusion has been reported inconclusively in patients with trauma hospitalized in developed countries. We aimed to investigate the effectiveness and side effects of TXA infusion in patients with trauma.
Method: The present study was a blinded parallel-designed randomized clinical trial (RCT) on 140 patients with trauma. The first group ($n = 70$) received early TXA(1 g/stat, for 10 min) and the second group ($n = 70$) received normal saline as placebo. Needing blood infusion and surgical procedures, the number of needed pack cells, thrombosis and mortality were compared between the two groups.
Results: No difference has been shown in outcomes between the two groups. Men required 41.1 times more blood transfusion than women ($p = 0.01$). Coincidence of pneumothorax and abdominal injury increased the blood requirement by 7.6 and 26.3 times, respectively ($p = 0.002$ and $p = 0.005$). The TXA group required 1.9 times more blood transfusions than the placebo. Men showed a 3.9 times higher risk of venous thrombosis than women. Also, patients who had trauma and pneumothorax had a 2.87 times higher risk of venous thrombosis. Abdominal trauma and organ fractures increased the risk of venous thrombosis by 2.5 and 2.2 times, respectively. In addition, the risk of venous thrombosis was 62% lower in the TXA than in the placebo.
Conclusion: The sex of patients and co-morbidities along with trauma affected the blood requirements. Men and patients with co-morbidities are more susceptible to the venous thrombosis, adjusting for grouping. Further studies with larger sample sizes are needed to confirm these results.
Trial registration: The present study has been registered in the Iranian randomized clinical trials under the number of IRCT20220507054758N1 that is submitted on 24 May 2022.

Evaluación de la eficacia y seguridad del tratamiento precoz con ácido tranexámico en pacientes con traumatismo: Ensayo clínico aleatorizado doble ciego

Palabras clave:
Ácido tranexámico
Traumatismo
Mortalidad
Trombosis

RESUMEN

Antecedentes: Previamente, el efecto de la infusión temprana de ácido tranexámico (ATX) se ha reportado de forma no concluyente en pacientes con trauma hospitalizados en países desarrollados. Nuestro objetivo fue investigar la efectividad y los efectos secundarios de la infusión de ATX en pacientes con trauma.
Método: El presente estudio fue un ensayo clínico aleatorizado (ECA) paralelo, ciego, con 140 pacientes con trauma. El primer grupo ($n = 70$) recibió ATX temprana (1 g/h durante 10 min) y el segundo grupo ($n = 70$) recibió solución salina normal como placebo. Se compararon la necesidad de infusión sanguínea y procedimientos quirúrgicos, el número de glóbulos rojos necesarios, la trombosis y la mortalidad entre los dos grupos.
Resultados: No se observaron diferencias en los resultados entre los dos grupos. Los hombres requirieron 41,1 veces más transfusiones sanguíneas que las mujeres ($p = 0,01$). La coincidencia de neumotórax y lesión abdominal incrementó el requerimiento sanguíneo 7,6 y 26,3 veces, respectivamente ($p = 0,002$ y $p = 0,005$). El grupo tratado con ATX requirió 1,9 veces más transfusiones sanguíneas que el grupo placebo. Los hombres mostraron

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un riesgo 3,9 veces mayor de trombosis venosa que las mujeres. Asimismo, los pacientes con traumatismo y neumotórax tuvieron un riesgo 2,87 veces mayor de trombosis venosa. El traumatismo abdominal y las fracturas de órganos incrementaron el riesgo de trombosis venosa 2,5 y 2,2 veces, respectivamente. Además, el riesgo de trombosis venosa fue un 62% menor en el grupo tratado con ATX que en el grupo placebo.
Conclusión: El sexo de los pacientes y las comorbilidades, junto con el traumatismo, afectaron el requerimiento sanguíneo. Los hombres y los pacientes con comorbilidades son más susceptibles a la trombosis venosa, ajustando por agrupamiento. Se necesitan estudios adicionales con muestras más grandes para confirmar estos resultados.
Registro de prueba: El presente estudio se ha registrado en los ensayos clínicos aleatorizados iraníes con el número IRCT20220507054758N1, presentado el 24 de mayo de 2022.

Introduction

Trauma is a cause of death in population of all countries.[1] Bleeding is the main cause of early death in these patients due to the initiation of coagulopathy reactions that finally lead to hemorrhagic shock and multi-organ failure.[2–5] Fibrinogen, the first factor needed in the coagulation process, is severely decreased in trauma patients that it has been shown in more than 40% of trauma patients who are hypotensive.[6,7-] According to the recent trauma guidelines, restoration of blood and coagulation status to the physiological levels are suggested in addition to the stabilization of oxygenation and perfusion.[8,9] Strong evidences suggest that early death after trauma can be minimized by early treatment of acute coagulation and hemorrhagic shock.[10,11] However, it is not clear that whether the fibrinolysis resulted from a disturbance in the activation of the fibrinolytic system or an inhibition beyond the physiological level after the activation of the fibrinolytic system led to its shutting down.[12] Tranexamic acid (TXA) is an antifibrinolytic drug derived from lysine that was introduced as early as 1968 for menorrhagia treatment,[13] which works by slowing down the conversion of plasminogen to plasmin, subsequently reducing fibrinolysis and stabilizing the blood clot. The beneficial effect of TXA for severely injured patients who are undergoing shock and require massive blood transfusions is established[14]; however, more studies in this area were carried on civil countries and showed inconclusive results that cannot be generalized to the developing countries due to the different care and treating systems.[15–20] The object of the present study was to evaluate the effect of early TXA administration in Iranian patients who were hospitalized due to the trauma in Ayatollah Mousavi Hospital in Zanjan City, as a trauma center.

Methods and patients

Patients and intervention

The present study was a double-blindedparallel-design randomized controlled clinical trial (RCT) that was ethically approved by the ethical committee of Zanjan University of Medical Sciences, Zanjan, Iran (IR.ZUMS.REC.1401.044) and registered in the Iranian randomized clinical trials under the number of IRCT20220507054758N1. All procedures were performed according to the CONSORT clinical trial guidelines and Helsinki guidelines for human studies. This study was performed on trauma patients who were referred to the Ayatollah Mousavi hospital, Zanjan, Iran, from 2022 to 2023. All patients more than 15 yr. who sustained blunt or penetrating trauma with signs of hemorrhagic shock were randomly assigned to the TXA treatment or placebo (control) after being admitted to the hospital. The randomization unit was the person, and the block randomization method was used to categorize patients using allocation software, with five participants in each block. Randomly coded envelopes were used for covering the grouping. The researcher who evaluated the final outcomes and patients was blinded about the grouping. Our inclusion criteria were systolic blood pressure less than 90 mmHg at the scene of injury, heart rate <120, estimated blood loss of 0.5 L in the field, bleeding without control by direct pressure or tourniquet, and major amputations were included in the present study. Patients younger than 15 yr, with active thromboembolic events including active stroke, myocardial infarction and pulmonary embolism, traumatic arrest or who were receiving anticoagulant drugs, were excluded. Moreover, cranial injury, traumatic brain injury with brain contusion and those who had not consent were not included in this study. Patients with the estradiol intake, chlorpromazine and other anti-inhibitor coagulants were excluded due to drug interaction. First, an informed consent form was gathered from all patients or their families. Two-hundred patients with trauma were checked for eligibility whom 167 participants had the criteria and were categorized randomly into the TXA, who received 1 g TXA/stat, dissolved in normal saline, or placebo who received normal saline. Infusions were administered for 10 min. The drug and placebo were placed in similar drug packages, and the therapist did not know the type of prescribed drug; only the drug code was recorded in the patient's file for blinding. The flow diagram of the study is shown in Fig. 1. No change was occurred to the trial after it commenced, including any outcomes or analyses.

Outcomes

The patient's age, gender, mechanism of trauma (penetrating or blunt), the presence of other injuries such as long bone or hip fracture, initial vital signs, hemoglobin and hematocrit were recorded upon arrival, and then, the patient's need for blood transfusion, the number of blood product units, the occurrence of venous thrombosis, the amount of hemoglobin and hematocrit, the need for surgical procedures were assessed as the primary outcome. The venous thrombosis was diagnosed by the clinical examination through the presence of clinical symptoms including erythema, edema, pain and tenderness of the limbs. Primary outcomes were assessed for 48 h. The 24-h mortality status was evaluated as the secondary outcome. Side effects including blood clots, deep vein thrombosis, pulmonary embolism, retinal artery or vein occlusion and kidney disorder were assessed during the study.

Sample size and statistical analysis

The sample size was computed according to the previous study[21] for comparing differences in mortality; based on the below formula, 66 patients were computed in each group in which $\mu_1 = 1.22$, $\mu_2 = 1$, $\sigma_1 = 0.5$ and $\sigma_2 = 0.4$.

$$n = \frac{\left(Z_1 - \frac{\sigma}{2} + Z_1 - \beta\right)^2 \left(\sigma_1^2 + \sigma_2^2\right)}{\left(\mu_1 - \mu_2\right)^2}$$

Data were analyzed using descriptive statistical methods and analytical statistics using univariate and multivariate statistical tests using SPSS software V.22. In order to check the statistical distribution of the data, the Kolmogorov–Smirnov test was used and all quantitative

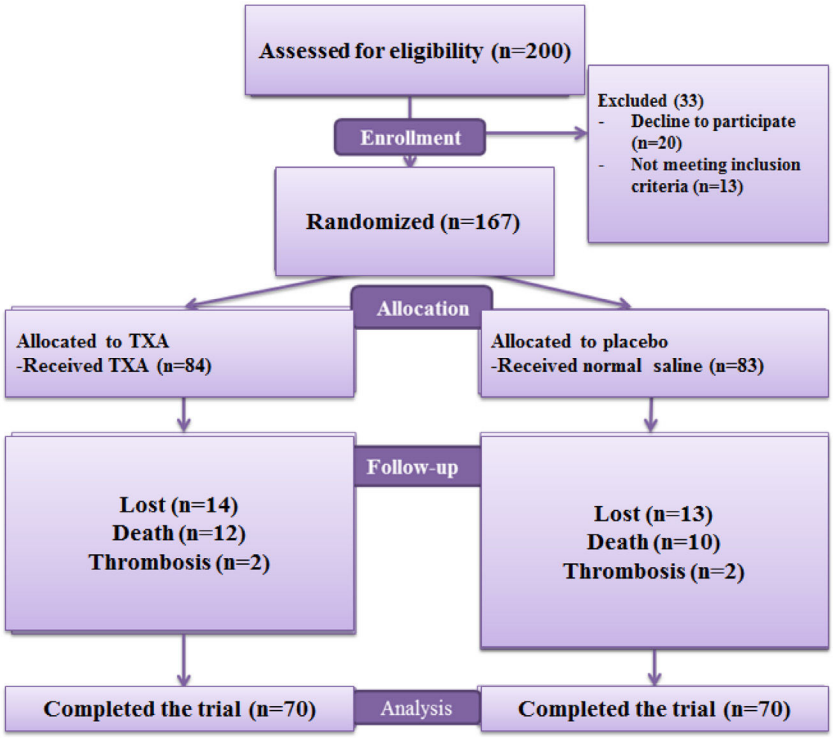

Figure 1. Summary of CONSORT flow diagram.

variables did not have a normal distribution ($p < 0.05$). Therefore, all non-parametric statistical tests were used for evaluation. Linear regression and logistic tests were used to adjust the effect of primary factors on the investigated outcomes.

Results

In total, seventy patients completed the trial in each group. Participant's demographic data are explained in Tables 1 and 2. The vital signs and severity of injury were not statistically significant between the two studied groups.

As shown below, no significant difference has been shown between the two studied groups on hemoglobin and hematocrit, as well as their reductions after interventions (Table 3).

As shown in Table 4, qualitative outcomes showed no significant difference between the two studied groups.

According to the results of the logistic regression model, sex showed a significant effect on the need for blood infusion (OR = 41.1, 95% CI = 2.03–831.1, $p = 0.015$). Moreover, systolic (OR = 1.32, 95% CI = 1.08–1.6, $p = 0.005$) and diastolic (OR = 0.77, 95%CI = 0.63–0.94, $p = 0.012$) blood pressure showed a significant effect on the patient's need for blood infusion. Patients with pneumothorax and injury to the abdomen need 7.6- and 26.3-times higher blood infusion than others, respectively (95% CI = 2.1–27.1, $p = 0.002$ and 95%CI = 2.7–253, $p = 0.005$, respectively) adjusted for the baseline parameters. The baseline hemoglobin showed a significant effect on the patient's need for blood transfusion (OR = 23.9, 95%CI = 4.97–114.7, $p < 0.001$). Adjusting for all variables, systolic (OR = −0.57, 95%CI = −0.09, −0.02, $p = 0.002$) and diastolic (OR = 0.51, 95% CI = 0.02–0.1, $p = 0.004$) blood pressure showed a significant effect on the number of needed pack cells. Injury to the abdomen (OR = −0.2, 95%CI = −0.97, −0.12, $p = 0.01$) and other organs (OR = 0.23, 95% CI = 0.27–1.1, $p = 0.001$) showed a significant effect on the number of needed pack cells. In addition, the baseline hemoglobin negatively affected the number of needed

Table 1
Patient's quantitative characteristics at the start of the study.

Variables	Groups	TXA ($n = 70$)	Placebo ($n = 70$)	P value[†]
Age, yr		38.5 ± 11.5	41.7 ± 13	0.131
SBP, mmHg		94.1 ± 6.6	93.1 ± 19.2	0.2
DBP, mmHg		66.4 ± 6.5	67.2 ± 15.2	0.1
SPO2, mmHg		91.4 ± 1.9	92.3 ± 1.6	0.5
HR, beat/min		108.2 ± 8.7	105.8 ± 9.1	0.2
Hemoglobin, mg/dl		13.9 ± 1.3	13.9 ± 1.6	0.7
Hematocrit, %		41.9 ± 4	42 ± 5.05	0.6

[†] Evaluated by Man-Whitney test, SBP; systolic blood pressure, DBP; diastolic blood pressure, SPO2; oxygen saturation pressure.

Table 2
Patient's qualitative characteristics at the start of the study.

Variables	Groups	TXA ($n = 70$) Number (%)	Placebo ($n = 70$) Number (%)	P value[†]
Sex	Male	46 (65.7)	43 (61.4)	0.7
	Female	24 (34.3)	27 (38.6)	
Trauma	Blunt	62 (88.6)	60 (85.7)	0.6
	Penetrate	8 (11.4)	10 (14.3)	
Pulmonary CT	Pneumothorax	11 (15.7)	7 (10)	0.4
	Fracture	28 (40)	44 (62.9)	
	Pneumothorax + fracture	10 (14.3)	0	
	Normal	21 (30)	19 (27.1)	
Hip graph	Normal	66 (94.3)	64 (91.4)	0.5
	Non-normal	4 (5.7)	6 (8.6)	
Abdomen graph	Normal	35 (50)	36 (51.4)	0.8
	Non-normal	35 (50)	34 (48.6)	
Organs	Normal	43 (61.4)	44 (62.9)	0.6
	Fracture	27 (38.6)	26 (37.1)	

[†] Evaluated by chi-square test, SBP; systolic blood pressure, DBP; diastolic blood pressure, SPO2; oxygen saturation pressure.

Table 3
Quantitative outcomes assessed in the studied groups.

Variables	Groups	TXA ($n = 70$)	Placebo ($n = 70$)	P value[†]
Hemoglobin, mg/dl		11.2 ± 2.05	11.48 ± 1.99	0.4
Hematocrit, %		33.4 ± 6.1	34.5 ± 5.9	0.3
Hemoglobin reduction		-2.8 ± 1.3	-2.4 ± 0.96	0.1
Hematocrit reduction		-8.4 ± 3.9	-7.3 ± 2.8	0.1

[†] Evaluated by Man-Whitney test.

pack cells ($OR = -0.6, 95\%\ CI = -0.76, -0.44, p < 0.001$). None of the assessed parameters had a significant effect on thrombosis and mortality adjusted for all variables. No side effect was observed in any participant.

Discussion

The present RCT showed that the baseline hemoglobin, systolic and diastolic blood pressure, as well as injury to other organs, include lung, abdomen and fracture effect on the patient's need for blood transfusion and the number of needed pack cells. Men were more likely to need blood transfusion than women by 41.1 times. Patients in the TXA need 1.9-times higher blood transfusion than the placebo; however, this was not statistically significant. Coincidence of abdominal trauma with trauma in other parts of the body increased the need for blood transfusion by 26.3 times. The risk of death in patients with blunt trauma was 2.3-times higher than that of penetrating trauma. Compared to women, men showed 3.9-times higher risk of venous thrombosis, however, these differences were not statistically significant. Our results are inconsistent with the previous studies in developed countries.[15–20] One of the most important reasons for not observing a statistically significant difference between some results can be due to the sample size in the present study. On the other hand, the injection of TXA in stat form in the present study was after the patient arrived from the scene of injury to the hospital. TXA is a time-dependent drug, and the scene injection affects the results. According to the European guidelines, there is an opportunity for TXA infusion up to three hours after the injury, but perhaps an hourly infusion has more benefits than a 3-hourly infusion.[22] It is interesting to note that in 2019, a systematic review study was conducted to investigate the effect of TXA administration on mortality and the incidence of complications such as thromboembolism, the need for blood transfusions, and the number of cell packs required. This study was conducted on the results of clinical trial studies. Since the methodology and the type of trauma studied were not homogeneous, only two clinical trial studies were eligible for meta-analysis, both of which were conducted in developed countries.[21] The results show that TXA administration reduces 24-h mortality by about 50%. In addition, it reduced the risk of 30-day death and thromboembolic events by 14% and 26%, respectively. The important thing is that these countries were developed, which can affect the results. To confirm this point, the largest study that was recently conducted in this field in Germany in a multi-centered manner reminds the importance that there is a need to conduct studies in developing countries and the results of studies conducted in advanced countries in this field cannot be generalized to developing countries because of different care systems and available facilities.[23] The results of the present study differ from the previous study by Menyar etal., which was conducted retrospectively in 2019 with the aim of investigating the effect of TXA administration before the hospital in trauma patients in terms of the need for blood transfusions and thromboembolic events, but is similar in mortality outcome.[21] In the mentioned study, the shock index and serum lactate level were significantly higher in the controls than in the TXA group. This factor can explain the differences in results. In addition, the design of the current study is a double-blindedRCT that can predict the results with the least amount of error. Also, the results of our study are consistent with two other studies, one retrospective and the other a clinical trial, in order to investigate the benefit of TXA on mortality, the need for blood transfusions, and the occurrence of side effects such as venous thrombosis, pulmonary embolism, and cardiac arrest in trauma patients. In these studies, there was no advantage of early administration of TXA in these patients.[24,25] In another study in adults with trauma, the 28-day mortality and the length of hospital stay were lower in the group receiving TXA, and patients required less blood products compared to the control group.[26] The results of this study are inconsistent with our study. One of the reasons for this inconsistency is that in the aforementioned study, the control group was selected retrospectively. That is, the patients receiving TXA were included in the study as the drug-receiving group, without the same time as the control group. The control group was selected retrospectively from the hospitalized patients in previous years. However, the TXA significantly reduced bleeding volume, only in patients with traumatic brain injury who had a contusion. In this RCT, the researchers concluded that bleeding volume responds differently to TXA injection depending on the type and location of bleeding.[27] This was the first study conducted in Iran and in Zanjan city on trauma patients caused by accidents and falling. More than 80% of the participants in this study had trauma caused by an accident, which has not been investigated in Iran until now. In addition to the civilization of the countries, another important reason for the differences between various studies is the type of studied trauma and the study design. Cross-sectional, retrospective studies have been conducted in this field, and the number of double-blinded RCTs is very limited. Similar to all studies, the present study also has some limitations. One of the limitations is the sample size, which is recommended to conduct studies with a larger sample size in the future. In addition, long-term mortality (one month or until discharge) was not evaluated in this study, which is recommended to be evaluated in the future. Also, venous thrombosis was diagnosed by the presence of clinical symptoms including erythema, edema, pain and tenderness of the limbs and through clinical examination, which is suggested to be assessed with color Doppler ultrasound to confirm or reject this complication. TXA was administered after patients were received at the hospital that affected its effectiveness. In addition, most of the patients participating in the current study were hospitalized due to trauma caused by an accident, which suggests that future studies should investigate the effect of early administration of TXA on specific types of trauma with a larger sample size. Timing of TXA administration and duration of intervention are other effective factors which must be assessed and compared in future studies. The present study was a single-center clinical trial whose results are not generalizable to other centers and countries due to various care systems.

Table 4
Qualitative outcomes assessed in the studied groups.

Variables	Groups	TXA ($n = 70$) Number (%)	Placebo ($n = 70$) Number (%)	P value[†]
Thrombosis	Yes	1 (2.9)	2 (5.7)	0.69
	No	68 (97.1)	66 (94.3)	
Need to blood infusion	Yes	20 (28.6)	17 (24.3)	0.7
	No	50 (71.4)	53 (75.7)	
Number of pack cells	0	50 (71.4)	53(75.7)	0.4
	2	5 (7.1)	6 (8.6)	
	3	11 (15.7)	0	
	4	4 (5.7)	11 (15.7)	
Need to surgery	Yes	10 (14.3)	7 (10)	0.78
	No	60 (85.7)	63 (90)	
Mortality	Yes	12 (17.1)	10 (14.3)	0.6
	No	58 (82.9)	60 (85.7)	

[†] Evaluated by chi-square test.

Conclusions

In the present study, TXA infusion did not show a beneficial effect on mortality, the number of pack cells, the need for blood transfusion, and venous thrombosis. Further studies with larger sample sizes are needed to confirm these results.

Consent to participate

Informed consent was obtained from all individual participants included in the study.

Ethics approval

The ethics committee of Zanjan University of Medical Sciences (ZUMS), Zanjan, Iran (IR.ZUMS.REC.1401.044).

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CRediT authorship contribution statement

Amin Esfandyari: Conceptualization, Investigation, Project administration, Writing – original draft, Writing – review & editing. **Mir Ali Mousavi:** Data curation, Formal analysis, Investigation, Project administration, Writing – review & editing. **Ali Ammari:** Conceptualization, Methodology, Supervision, Writing – review & editing. **Mohammad Arbati:** Methodology, Validation, Writing – review & editing. **Naser Keikhali:** Project administration, Validation, Writing – review & editing. **Farzaneh Karami Tanha:** Data curation, Formal analysis, Writing – review & editing.

Declaration of competing interest

The authors have no relevant financial or non-financial interests to disclose.

Data availability

Data are available from the corresponding author on reasonable request.

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