The effect of early tranexamic acid on bleeding, blood product consumption, mortality and length of hospital stay in trauma cases with hemorrhagic shock: a randomized clinical trial

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Keywords

Tranexamic acid • Placebo • Trauma patients • Acute bleeding

Summary

Introduction. *Because no medication has been approved for coagulation support in trauma, the current study was aimed to evaluate the effectiveness of intravenous injection of Tranexamic acid (TXA) in patients with acute traumatic bleeding.*
Methods. *In the current randomized controlled clinical trial, 68 patients with acute bleeding and hemorrhagic shock presentation due to blunt trauma of the abdomen, pelvis, and thorax, randomly assigned into two groups of TXA and placebo.*
Results. *There was no statistically significant difference between the two groups in terms of Systolic blood pressure, pulse rate, Base excess, serum hemoglobin changes, bleeding volume, the incidence of thrombotic events, and the number*

of deaths (p > 0.05). But Systolic blood pressure, pulse rate, base excess, and serum hemoglobin, changed significantly within each group over time(p < 0.05). The median time for the length of hospital stay among the TXA group was lower than the Placebo group (6 days vs 10 days, p = 0.004). Also, there was a significant difference between the two groups about the median of pack cell, Platelet consumption, and bleeding Volume (p < 0.05).
Conclusion. *The use of TXA is associated with lower use of blood production and reduced length of hospital stay, however, thrombotic events incidence and mortality rates between the TXA and placebo groups were not different.*

Introduction

Acute bleeding is one of the leading causes of death globally, and the estimate of death related to blood loss is about 1.9 million cases annually, that most of them are due to injuries. Uncontrolled bleeding is the cause of approximately one-third of trauma-related deaths [1]. In the United States, about 60,000 deaths per year are caused by acute bleeding [2]. About 90% of injury-related deaths occurred in low and middle-income countries annually. In Iran, as a middle-income country, injury-related deaths and bleeding due to trauma are among the leading causes of mortality and burden of diseases [3, 4].

Due to decreased oxygen delivery, severe blood loss leads to widespread tissue ischemia [5], followed by a cascading inflammatory response that causes further tissue damage and cell deaths [6]. Concomitant abnormalities in blood coagulation can cause rapid bleeding, and Cerebral and myocardial hypo perfusion with bleeding can be fatal within minutes [7]. Current approaches to controlling acute bleeding are varied depending on the availability of treatment options and local expertise in critical care and trauma. In general, bleeding management aims is to achieve rapid homeostasis, restore tissue flow, treat blood clotting, and reduce inflammatory responses [1]. Recent studies have shown great interest in the role of fibrinolysis in hemorrhagic shock and the effect of

TXA in reducing fibrinolysis. TXA, discovered in 1962, has remained a treatment option in the management of surgical and gynecological hemorrhages for five decades [8, 9]. Recent researches focusing on the role of fibrinolysis in bleeding has paid close attention to the part of TXA in various clinical contexts [10, 11]. Although cessation of fibrinolysis appears to be the primary mechanism that TXA can reduce mortality, there is evidence for additional anti-inflammatory agents [12]. Numerous studies have described the use of TXA in patients after traumatic injury, administered as 1 g intravenously, with subsequent 1 gr injection for continuous or recurrent bleeding [13]. Due to the importance of controlling bleeding in patients with trauma, the current study was aimed to evaluate the effectiveness of early intravenous injection of TXA in patients with acute bleeding and hemorrhagic shock presentation due to severe trauma.

Methods

STUDY DESIGN AND PARTICIPANTS

The present study was a randomized and parallel clinical trial (Superiority Trial) performed on 68 traumatic

patients referred to Hazrate- Rasoul Akram Hospital in Tehran in 2020.

UNDER STUDIED PATIENTS AND SAMPLE SIZE

In the current study, The main inclusion criteria were patients with acute bleeding and hemorrhagic shock presentation due to blunt trauma of the abdomen, pelvis, and thorax with severe trauma(an injury severity score greater than 15) [8] were selected. The used sample size was 68 patients (34 cases in the TXA group versus 34 subjects in the placebo group) (Fig. 1). The sample size was determined according to following formula:

$$n= \frac{(Z_{(1-\alpha/2)}+Z_{(1-\beta)})^2(p_1(1-p_1) +p_2(1-p_2))}{d^2}$$

Where P_1 (death rate in Intervention group) was considered 17% and P_2 (death rate in control group) was considered 52%. $Z_{(1-\alpha/2)}$ and $Z_{(1-\beta)}$ was considered 1.96 and 0.84 respectively. In the current formula d (effect size) was 35%. The calculated sample size was 29 cases for each group and by considering the 15% attrition this amount increased to 34 cases per group.

INCLUSION AND EXCLUSION CRITERIA

Inclusion criteria were acute bleeding, due to blunt trauma of the abdomen, pelvis, and thorax with hemorrhagic shock presentation (unstable vital signs: systolic blood pressure less than 90 mm and pulse rate more than 110), Injry Severity Score of more than 15 and age more than 18 years old which were arrived to hospital in within 3 hour from the trauma. Individuals with renal insufficiency (serum creatinine greater than 1.5 mg/dL), pregnancy, hematuria, history of coagulation disorder, and anticoagulant use were excluded.

RANDOMIZATION AND MASKING

The patients were divided into intervention and control groups based on block randomization. For the block randomization, the blocks with size 4 were used for the block randomization. For this purpose, the desired treatment was named with A and the control treatment was named with B. Then all the cases in which these treatments could be put together were placed inside the blocks. The generated blocks were numbered and randomly selected. This selection of blocks continued until the sample size was completed. This process was applied and completed before the patient's recruitment. The intervention group was given 1 gr TXA of intravascular infusion in 100 ccs of normal saline and then 1 gr every 12 hours for up to 24 hours. TXA was used in 3 doses. The initial dose (1 gram) was injected within 10 minutes and the following two doses at 12-hour intervals. Patients in the control group were given a placebo (normal saline). The clinicians evaluated all patients during hospitalization about the number

Fig. 1. The consort 2010 flow diagram for the current study.
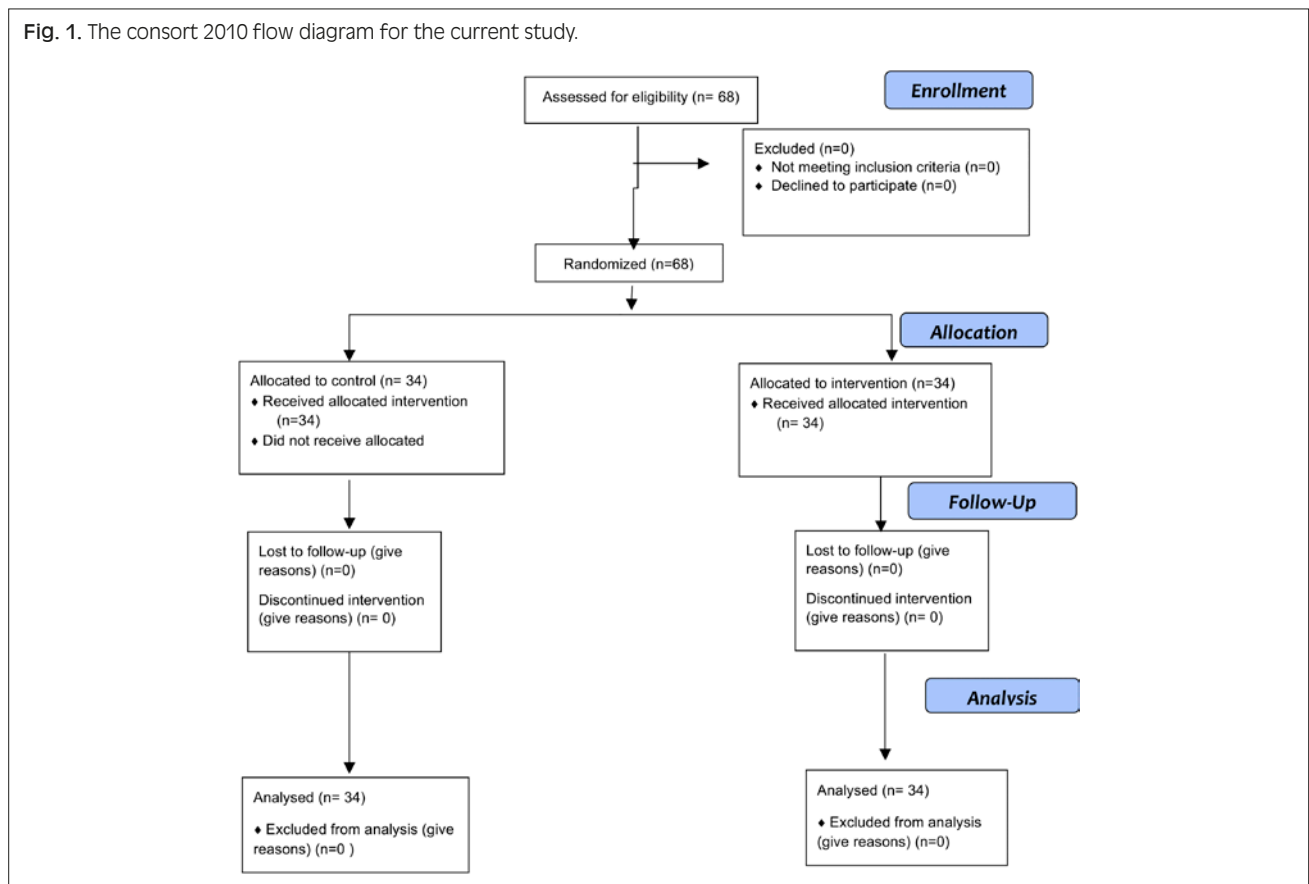
of blood products transfusion, serum hemoglobin, and vital signs. Patients were followed for one month for possible thrombotic events, including Deep Vein Thrombosis (DVT), Pulmonary Thromboemboly (PTE), Cerebrovascular accident (CVA), and myocardial infarction (MI). Also, the final status of the patient's (recovery or death status) and length of hospital stay were recorded in the designed checklist. The double blinding method was used to masking patients and physicians. In addition to the randomization number, the drug pack label was identical for TXA acid and placebo. In addition, the selected blocks were placed in opaque envelopes with no known contents. That is until the patients were assigned, the envelopes were closed and no one knew the order of interventions inside (randomization concealment).

This research conducted according to the World Medical Association Declaration of Helsinki. The recruitment of participants was initiated from the February to December 2020 and this process finished end of the 2020 year. But the follow up patients lasted until the beginning of 2021.

OUTCOME

The effect of TXA on Mortality, Hospital Length of Stay, and Use of Blood Production was the understudy's outcomes.

DATA ANALYSIS

Descriptive statistics such as mean ± standard deviation and median (interquartile range) were used to express quantitative findings, and frequency (percentage) was used to present qualitative findings. Data analyzed using the Independent sample t-test or Mann Whitney u test, chi-square, or Fisher exact test and repeated measure one-way ANOVA. The equation of variance (sphericity assumption) was assessed using Mauchly's test of sphericity. Due to the lack of this assumption, the difference between the means at the different times was evaluated using the Greenhouse-Geisser correction. The statistical significance level was considered as α:0.05. All data analyzed using the SPSS software Version 22.0. Armonk, NY: IBM Corp. IBM Corp. Released 2015.

Results

DESCRIPTIVE STATISTICS

The mean of age among the TXA and Placebo group was 37.76 ± 8.85 and 34.82 ± 7.37 years, respectively, and there was no statistically significant difference between the two groups about the age distribution (p = 0.14). The 26 (76.5%) of total cases among the TXA group were males, and this percent among the placebo group was 30 (88.2%) (p = 0.20). There was no statistically significant difference between the two groups about the variables such as Etiology of bleeding, Spleen rupture, Hemothorax, Retroperitoneal hematoma, Rupture of the intestinal mesentery, and Hepatic injury (Tab. I).

Tab. I. Comparison of demographic characteristics and etiology of bleeding in TXA and placebo group.

Variables	TXA	Placebo	P-value
Age	37.76 ± 8.85	34.82 ± 7.37	0.14
Males	26 (76.5%)	30 (88.2%)	0.20
Etiology of bleeding			
Spleen rupture	17 (50.0%)	13 (38.2%)	0.32
Hemothorax	3 (8.8%)	5 (14.7%)	0.33
Retroperitoneal hematoma	14 (41.2%)	18 (52.9%)	0.33
Rupture of the intestinal mesentery	4 (11.8%)	2 (5.9%)	0.33
Hepatic injury	11 (32.4%)	5 (14.7%)	0.08

BASELINE CHARACTERISTICS

The mean of baseline hemoglobin (g/dL) among TXA and placebo groups was 13.59 ± 1.20 and 13.34 ± 2.25, respectively (0.66). The mean of systolic blood pressure (mm/Hg) among TXA and placebo groups was 93.52 ± 16.21 and 97.64 ± 22.43 respectively (0.96). Also, there was no significant difference between the two groups in the mean of pulse rate, GCS and Base excess (mmol/L) (p > 0.05). More information was shown in Table II.

COMPARING THE OUTCOME OF INTEREST

Systolic blood pressure

The mean ± SD of Systolic blood pressure at the time of admission, 12,24 and 48 hours after the entry in the TXA group was 93.53 ± 16.21, 108.24 ± 15.27, 112.94 ± 7.40, and 115 ± 10.80 respectively. This increasing trend in the TXA group over time was statistically significant (p < 0.001). Also, the mean of Systolic blood pressure at the time of admission, 12, 24, and 48 hours after the entry in the placebo group was 97.65 ± 22.44, 102.35 ± 13.72, 113.53 ± 11.25, and 111.76 ± 5.76. This increasing trend in the TXA group over time was statistically significant (p < 0.001). The difference in mean of the systolic blood pressure between the two groups over time was not statistically significant (p = 0.12). Also, in overall, the difference of SBP between the TXA and Placebo group was not statistically significant (p = 0.59) (Tab. III, Fig. 2).

Tab. II. Baseline clinical and laboratory characteristics in TXA and placebo group.

Variables	TXA	Placebo	P-value
Baseline hemoglobin (g/dL)	13.59 ± 1.20	13.34 ± 2.25	0.66
systolic blood pressure (mm/Hg)	93.52 ± 16.21	97.64 ± 22.43	0.96
pulse rate (per minute)	124.71 ± 17.44	125.88 ± 28.93	0.35
GCS	14.41 ± 0.85	14.52 ± 0.99	0.35
Base excess (mmol/L)	-2.85 ± 3.00	-3.94 ± 4.47	0.57

Hemoglobin

The mean ± SD of Hemoglobin at time of admission and 12, 24 and 48 hours after entry in the TXA group was 13.49 ± 1.20, 10.82 ± 1.28, 9.87 ± 1.07, and 9.38 ± 1.04 respectively. This decreasing trend in the TXA group over time was statistically significant (p < 0.001). Also, the mean of Hemoglobin in time of admission and 12, 24, and 48 hours after entry in the placebo group was 13.34 ± 2.25, 10.86±1.42, 9.27 ± 1.62, and 8.59 ± 1.52. This decreasing trend in the TXA group over time was statistically significant (p < 0.001). The difference in mean of the Hemoglobin between the two groups over time was not statistically significant (p = 0.15). Also, in overall, the difference of Hemoglobin between the TXA and Placebo group was not statistically significant (p = 0.16) (Tab. III, Fig. 2).

Pulse rate

The mean of Pulse rate in time of admission and 12, 24, and 48 hours after entry in the TXA group were

124.71 ± 17.45, 114.12 ± 16.17, 104.47 ± 11.43, and 96.47 ± 9.01. This decreasing trend in the TXA group over time was statistically significant (p < 0.001). Also, the mean of Pulse rate in time of admission and 12, 24, and 48 hours after entry in the placebo group was 125.88 ± 28.93, 116.47 ± 10.41, 110.59 ± 10.70, and 99.38 ± 12.99. This decreasing trend in the TXA group over time was statistically significant (p < 0.001). The difference in mean of the Hemoglobin between the two groups over time was not statistically significant (p = 0.56). Also, in overall, the difference in Pulse rate between the TXA and Placebo group was not statistically significant (p = 0.29) (Tab. III, Fig. 2).

Base excess

The mean of Base excess in a time of admission and 12,24 and 48 hours after admission in the TXA group was -2.85 ± 3.01, -9.18 ± 3.32, -5.06 ± 3.78, and -2.29 ± 4.48. This decreasing trend in the TXA group over time was statistically significant (p < 0.001). Also,

Fig. 2. The trend of different clinical and laboratory factors between two groups duration the follow-up period.
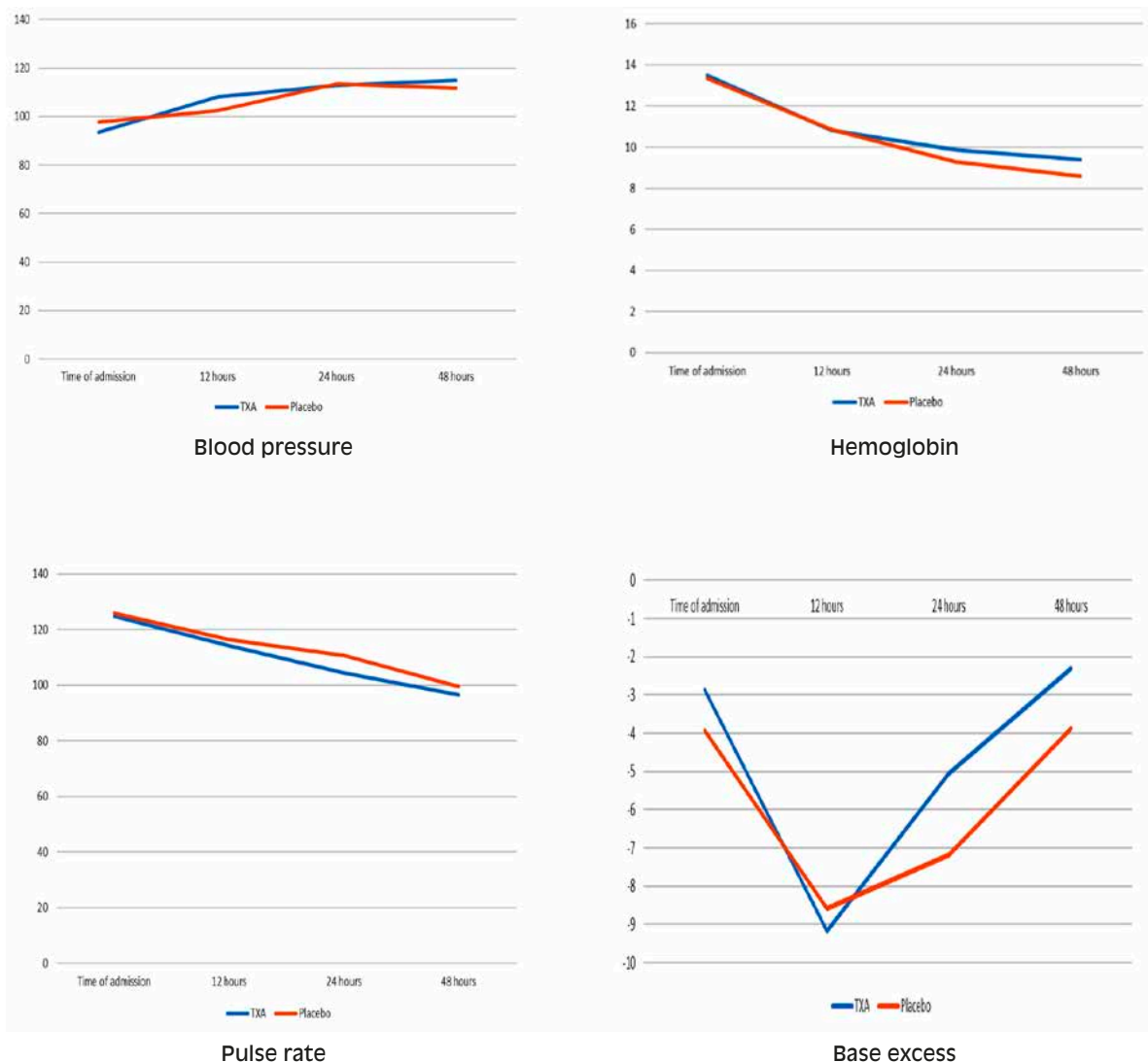
the mean of Base excess in a time of admission and 12,24 and 48 hours after admission in the placebo group was -3.94 ± 4.48, -8.59 ± 4.61, -7.18 ± 4.12, and -2.29 ± 4.48.

This decreasing trend in the TXA group over time was statistically significant (p < 0.001). The difference in mean of the Base excess between the two groups over

Tab. III. Comparison of different clinical and laboratory factors between two groups duration the follow-up period.

Group	Group	Mean	Std. deviation	Between-group	Time* group	Time
Blood pressure						
Admission Systolic BP	TXA	93.53	16.21	0.59	0.12	< 0.001
	Placebo	97.65	22.44			
	Total	95.59	19.54			
Systolic BP (12 hours)	TXA	108.24	15.27			
	Placebo	102.35	13.72			
	Total	105.29	14.71			
Systolic BP (24 hours)	TXA	112.94	7.40			
	Placebo	113.53	11.25			
	Total	113.24	9.45			
Systolic BP (48 hours)	TXA	115.00	10.80			
	Placebo	111.76	5.76			
	Total	113.38	8.74			
Hemoglobin						
Admission HB	TXA	13.49	1.20	0.16	0.15	< 0.001
	Placebo	13.34	2.25			
	Total	13.42	1.79			
HB (12 hours)	TXA	10.82	1.28			
	Placebo	10.86	1.42			
	Total	10.84	1.34			
HB (24 hours)	TXA	9.87	1.07			
	Placebo	9.27	1.62			
	Total	9.57	1.40			
HB (48 hours)	TXA	9.38	1.04			
	Placebo	8.59	1.52			
	Total	8.98	1.35			
Pulse rate						
Admission Pulse rate	TXA	124.71	17.45	0.29	0.56	< 0.001
	Placebo	125.88	28.93			
	Total	125.29	23.72			
Pulse rate (12 hours)	TXA	114.12	16.17			
	Placebo	116.47	10.41			
	Total	115.29	13.55			
Pulse rate (24 hours)	TXA	104.47	11.43			
	Placebo	110.59	10.70			
	Total	107.53	11.41			
Pulse rate (48 hours)	TXA	96.47	9.01			
	Placebo	99.38	12.99			
	Total	97.93	11.19			
Base excess						
Admission Base excess	TXA	-2.85	3.01	0.15	0.06	< 0.001
	Placebo	-3.94	4.48			
	Total	-3.40	3.83			
BE (12 hours)	TXA	-9.18	3.32			
	Placebo	-8.59	4.61			
	Total	-8.88	3.99			
BE (24 hours)	TXA	-5.06	3.78			
	Placebo	-7.18	4.12			
	Total	-6.12	4.06			
BE (48 hours)	TXA	-2.29	4.48			
	Placebo	-3.88	3.58			
	Total	-3.09	4.10			

Tab. IV. Comparison use of blood products and length of hospital stay in TXA and placebo group.

Variable	TXA, Median (IQR)	Placebo, Median (IQR)	P-value
Bleeding volume (cc)	1,000 (2,000-800)	1,500 (2,000-950)	0.03
Length of stay (day)	6 (12-6)	10 (26-8)	0.004
Pack cell (250 ml/unit)	3 (4-1)	3(5-3)	0.02
Fresh Frsh plasma (225 ml/unit)	2 (6-2)	10 (26-8)	0.08
Platelet (70 ml/unit)	0 (0-0)	0 (6.25-0)	0.008

time was not statistically significant (p = 0.06). Also, in overall, the difference in Pulse rate between the TXA and Placebo group was not statistically significant (p = 0.15) (Tab. III, Fig. 2).

USE OF BLOOD PRODUCTS AND MORTALITY

The number of deaths in TXA and placebo groups was 2(5.9%) and 4 (11.8 %), respectively (p = 0.33). The median (IQR) of bleeding volume for TXA group was significantly lower than the control group [1,000 (1,200) vs 1,500 (1,050), p = 0.03]. The median time for the length of hospital stay among the TXA group was lower than the Placebo group (6 days vs ten days, p = 0.004). Also, there was a significant difference between the two groups about the use of blood product consumption such as Platelet. More information was shown in Table IV.

THROMBOTIC EVENTS

The incidence of thrombotic events among TXA cases was 0, and this amount in the placebo group was 4 (11.8%). There was no statistically significant difference between the two groups (p = 0.06)

Discussion

In our study, the mortality rate in the intervention group (TXA) was lower than in the control group, but this difference was not statistically significant. For the first time, clinical evidence of the effect of early TXA administration on trauma-induced mortality was demonstrated in a CRASH-2 randomized clinical trial [14, 15]. A subsequent observational study (MATTERs) [16] showed that TXA administration in patients injured on the battlefield was associated with lower mortality (6.5% decrease in patients mortality), this finding was similar to the CRASH2 trial (2.2% mortality decrease among TXA admitted cases) [11, 15]. Also, another study showed that the TXA administration was associated with an 8% reduction in 28-day mortality [17]. In contrast, in the Goethe study, TXA administered before hospitalization did not significantly reduce 30-day mortality [18]. Other observational studies have shown a similar risk of death in patients receiving TXA and control groups [12, 19]. In another study, TXA was associated with an increased risk of mortality in individuals requiring emergency blood transfusion and surgery [20]. Such controversy can be due to different criteria for patient inclusion criteria. The CRASH-2 trial included patients with suspected persistent bleeding in which 50% of patients had a blood transfusion, because

inclusion factors in CRASH2 were all kinds of blunt or penetrating trauma with different amount of bleeding. In comparison, nearly 96% of the subjects in our study had any blood transfusion, which was higher than the CRASH-2 trial values [14, 15]. Another study showed that excessive mortality by TXA, also 97% of cases received blood transfusions [20]. The different sample size is another factor that can lead to different results. Studies with larger sample sizes have more reliable results.

According to our results the use of blood production in TXA group was fewer than placebo group. Despite the reported association between TXA administration and reduced need for blood transfusion in patients who undergo mainly elective surgery [21], it has been suggested that reduced tranexamic acid mortality may be along with the increasing demand for blood transfusion in injured patients [12, 16, 19, 22]. In particular, some researchers have identified a phenomenon called "fibrinolysis extinction," in which fibrinolysis observed on thromboelastographic is severely impaired in more than half of severely injured patients [23]. This could theoretically explain the contradictory effects of antifibrinolytic drugs in studies and indicate that TXA should be considered selectively [24, 25]. However, there is no evidence supporting the statistical interaction between TXA administration and the degree of fibrinolysis in clinical outcomes.

Some studies don't show significant association between the TXA administration and blood transfusion rate [12, 14, 20], but this association was showed in MATTERs study [16]. The results of the Tenxa study showed that early administration of TXA was not associated with a reduction in the use of blood products, and administration of TXA at an earlier time doesn't have any benefit to the patient [26]. Also, a multicenter observational study in Japan showed no significant difference between TXA and control groups in terms of the need for blood transfusion [17]. An observational study showed that TXA was associated with better survival in traumatized patients with unstable hemodynamic status [12].

According to our results, the hospital length of stay among TXA admitted cases was lower than the placebo group. It can be due to other factors such as less blood loss and so on.

LIMITATIONS

The current study had some limitations that include, due to time constraints as well as the outbreak of COVID-19 disease, which leads to a decrease in trauma patients

referred to the hospital and consequently decreases the sample size, so the insufficient sample size effects on study power and lead to insignificant results. Also because of few sample size, we cannot perform the subgroup analysis according to important variables.

Conclusions

Overall results of this study showed that TXA administration, was associated with better hemodynamic status, lower use of blood production, reduced bleeding and length of hospital stay but does not have a significant association with the incidence of thrombotic events, and mortality rate in trauma patients with severe acute bleeding.

Ethical approval

This study approved by ethical committee of Iran University of medical sciences with ID: IR.IUMS.FMD. REC.1399.603.

Acknowledgements

Conflict of interest statement

The authors declare no conflict of interest.

Authors' contributions

AN and TT collected data and analysis, provided initial drafting. MV Comments and development of the manuscript, YA data analysis. All authors approved the final draft.

References

[1] Gruen RL, Brohi K, Schreiber M, Balogh ZJ, Pitt V, Narayan M, Maier RV. Haemorrhage control in severely injured patients. Lancet 2012;380:1099-108. https://doi.org/10.1016/S0140-6736(12)61224-0.

[2] Cannon JW. Hemorrhagic shock. N Engl J Med 2018;378:370-9. https://doi.org/10.1056/NEJMra1705649.

[3] Abbasi H, Bolandparvaz S, Yadollahi M, Anvar M, Farahgol Z. Time distribution of injury-related in-hospital mortality in a trauma referral center in South of Iran (2010-2015). Medicine 2017;96(21). https://doi.org/10.1097/MD.0000000000006871

[4] Bolandparvaz S, Yadollahi M, Abbasi HR, Anvar M. Injury patterns among various age and gender groups of trauma patients in southern Iran: a cross-sectional study. Medicine 2017;96(41). https://doi.org/10.1097/MD.0000000000007812

[5] Barbee RW, Reynolds PS, Ward KR. Assessing shock resuscitation strategies by oxygen debt repayment. Shock 2010;33:113-22. https://doi.org/10.1097/SHK.0b013e3181b8569d

[6] Zhang Q, Raoof M, Chen Y, Sumi Y, Sursal T, Junger W, Brohi K, Itagaki K, Hauser CJ. Circulating mitochondrial DAMPs cause inflammatory responses to injury. Nature 2010;464:104-7. https://doi.org/10.1038/nature08780

[7] Tisherman SA, Alam HB, Rhee PM, Scalea TM, Drabek T, Forsythe RM, Kochanek PM. Development of the emergency preservation and resuscitation for cardiac arrest from trauma clinical trial. J Trauma Acute Care Surg 2017;83:803-9. https://doi.org/10.1097/TA.0000000000001585

[8] Moore HB, Moore EE, Liras IN, Gonzalez E, Harvin JA, Holcomb JB, Sauaia A, Cotton BA. Acute fibrinolysis shutdown after injury occurs frequently and increases mortality: a multicenter evaluation of 2,540 severely injured patients. J Am Coll Surg 2016;222:347-55. https://doi.org/10.1016/j.jamcollsurg.2016.01.006

[9] US Food and Drug Administration. Highlights of prescribing information.

[10] Kolev K, Longstaff C. Bleeding related to disturbed fibrinolysis. Br J Haematol 2016;175:12-23. https://doi.org/10.1111/bjh.14255

[11] Roberts I, Shakur H, Ker K, Coats T. Antifibrinolytic drugs for acute traumatic injury. Cochrane Database Syst Rev 2012;(12). https://doi.org/10.1002/14651858.CD004896.pub4

[12] Cole E, Davenport R, Willett K, Brohi K. Tranexamic acid use in severely injured civilian patients and the effects on outcomes: a prospective cohort study. Ann Surg 2015;261:390-4. https://doi.org/10.1097/SLA.0000000000000717

[13] Levy JH. Antifibrinolytic therapy: new data and new concepts. Lancet 2010;376:3-4. https://doi.org/10.1016/S0140-6736(10)60939-7

[14] Roberts I, Shakur H, Coats T, Hunt B, Balogun E, Barnetson L, Cook L, Kawahara T, Perel P, Prieto-Merino D. The CRASH-2 trial: a randomised controlled trial and economic evaluation of the effects of tranexamic acid on death, vascular occlusive events and transfusion requirement in bleeding trauma patients. Health Technol Assess Rep 2013;17:1. https://doi.org/10.3310/hta17100

[15] Collaborators C-: The importance of early treatment with tranexamic acid in bleeding trauma patients: an exploratory analysis of the CRASH-2 randomised controlled trial. Lancet 2011;377:1096-101. https://doi.org/10.1016/S0140-6736(11)60278-X

[16] Morrison JJ, Dubose JJ, Rasmussen TE, Midwinter MJ: Military application of tranexamic acid in trauma emergency resuscitation (MATTERs) study. Arch Surg 2012;147:113-9. https://doi.org/10.1001/archsurg.2011.287

[17] Shiraishi A, Kushimoto S, Otomo Y, Matsui H, Hagiwara A, Murata K, Hayakawa M, Maekawa K, Saitoh D, Ogura H. Effectiveness of early administration of tranexamic acid in patients with severe trauma. Br J Surg 2017;104:710-7. https://doi.org/10.1002/bjs.10497

[18] Guyette FX, Brown JB, Zenati MS, Early-Young BJ, Adams PW, Eastridge BJ, Nirula R, Vercruysse GA, O'Keeffe T, Joseph B. Tranexamic acid during prehospital transport in patients at risk for hemorrhage after injury: a double-blind, placebo-controlled, randomized clinical trial. JAMA Surg 2021;156:11-20. https://doi.org/10.1001/jamasurg.2020.4350

[19] Harvin JA, Peirce CA, Mims MM, Hudson JA, Podbielski JM, Wade CE, Holcomb JB, Cotton BA. The impact of tranexamic acid on mortality in injured patients with hyperfibrinolysis. J Trauma Acute Care Surg 2015;78:905-11. https://doi.org/10.1097/TA.0000000000000612

[20] Valle EJ, Allen CJ, Van Haren RM, Jouria JM, Li H, Livingstone AS, Namias N, Schulman CI, Proctor KG. Do all trauma patients benefit from tranexamic acid? J Trauma Acute Care Surg 2014;76:1373-8. https://doi.org/10.1097/TA.0000000000000242

[21] [Henry DA, Carless PA, Moxey AJ, O'Connell D, Stokes BJ, Fergusson DA, Ker K. Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion. Cochrane Database Syst Rev 2011(1). https://doi.org/10.1002/14651858.CD001886

[22] Shakur H, Roberts I, Fawole B, Chaudhri R, El-Sheikh M, Akintan A, Qureshi Z, Kidanto H, Vwalika B, Abdulkadir A. Effect of early tranexamic acid administration on mortality, hysterectomy, and other morbidities in women with post-partum haemorrhage (WOMAN): an international, randomised, double-blind, placebo-controlled trial. Lancet 2017;389:2105-16. https://doi.org/10.1016/S0140-6736(17)30638-4

[23] Moore HB, Moore EE, Gonzalez E, Chapman MP, Chin TL, Silliman CC, Banerjee A, Sauaia A. Hyperfibrinolysis, physiologic fibrinolysis, and fibrinolysis shutdown: the spectrum of postinjury fibrinolysis and relevance to antifibrinolytic therapy. J Trauma Acute Care Surg 2014;77:811. https://doi.org/10.1097/TA.0000000000000341

[24] Napolitano LM, Cohen MJ, Cotton BA, Schreiber MA, Moore EE. Tranexamic acid in trauma: how should we use it? J Trauma Acute Care Surg 2013;74:1575-86. https://doi.org/10.1111/jth.12878

[25] Moore EE, Moore HB, Gonzalez E, Chapman MP, Hansen KC, Sauaia A, Silliman CC, Banerjee A. Postinjury fibrinolysis shutdown: rationale for selective tranexamic acid. J Trauma Acute Care Surg 2015;78:S65. https://doi.org/10.1097/TA.0000000000000634

[26] Tencza E, Harrell IV AJ, Sarangarm P. Effect of tranexamic acid administration time on blood product use in urban trauma patients. Am J Health Syst Pharm 2020;77(Suppl. 2):S46-53. https://doi.org/10.1093/ajhp/zxaa074