Original Article

The Impact of Tranexamic Acid on Brain Contusion and Intraparenchymal Hemorrhage in Patients with Head Injury

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Abstract

Background and Objectives: Traumatic brain injuries (TBIs) are among leading causes of debility and death at a global scale. The current study aimed at investigating the possible advantage of administrating tranexamic acid (TXA) in patients with post-TBI brain contusion and intraparenchymal hemorrhage (IPH). **Materials and Methods:** This double-blind randomized clinical trial was conducted on patients who had brain contusion/IPH according to their on-admission brain computed tomography (CT) scan, referring to Shahid Beheshti Hospital, Kashan University of Medical Sciences, during 2018-2021. The patients were randomly allocated to either the intervention group (receiving TXA through an antecubital vein access) or the control group (receiving Normal Saline via a similar route). TBI severity, ICH volume, and compressive effects of hemorrhagic mass on admission, 24 h, and 72 h after treatment were assessed. Then 3-month outcome estimated by Glasgow Outcome Scale (GOS). **Results:** There was no significant difference between patients' age, gender, TBI etiology (traffic collision or fall from height), and skull fracture between the study groups. Compressive effects of hemorrhagic mass, new bleeding and brain edema during 24 and 72 hours after intervention were not significantly different between the TXA and placebo groups. The alterations in ICH volume from preintervention to 24/72 h postintervention were similar between the intervention and placebo subgroups ($P > 0.05$). Majority of participants (82.5%) showed a good 3-month neurological outcome according to GOS, but that was not significantly different between the study groups. One case of death occurred in each subgroup, and both of them died after hospital discharge. **Conclusion:** TXA neither has a preventive effect against in-hospital post-TBI hemorrhage enlargement nor on neurological outcomes three months after hospital discharge.

Keywords: Contusion, intraparenchymal hemorrhage, tranexamic acid, traumatic brain injury

Introduction

Traumatic brain injury (TBI) is one of the main causes of disability/death in the world, with a rough annual estimation of millions of hospitalization and 1.5 million deaths, globally.[1] An annual incidence of 56.3 per 100,000 populations is estimated for TBI in Iran.[2] Intracranial hemorrhage (ICH) is a common complication of TBI that can progress/enlarge during the course of hospitalization.[3] More than 50% of TBI cases develop ICH,[4] half of them experiencing in-hospital volume expansion of the ICH.[5,6] ICH incidence and chance of progression is closely associated with coagulopathy, which highly increases morbidity and mortality in these patients. Induced fibrinolysis, with a surge in the level of substances related to fibrin degradation, is a common pattern of coagulopathy in TBI.[3]

Secondary brain injury due to ICH expansion, brain edema, raised intracranial pressure, and consequent brain ischemia

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are main causes of post-TBI morbidity and mortality. Coagulopathy-related injuries in brain tend to exacerbate with TBI; for instance, one-third of TBI cases show a 10 times higher rate of mortality.[7]

Antifibrinolytic medications might reduce the chance of post-TBI ICH. TXA, as an antifibrinolytic agent, has been proposed in recent studies as an effective medication for post-TBI ICH.[8] An international study, CRASH-2, has investigated the impact of early intravenous TXA injection on the rate of hemorrhage after TBI in 20211 patients recruited from 40 countries. Based on the findings of that study, TXA causes no major complication and lowers the mortality rate in patients with TBI who have or are at the risk of hemorrhage, and its early administration is recommended in TBI cases, especially in low- or medium-income countries as a cost-effective therapeutic approach.[9]

Some previous randomized clinical trials have reported the low risk and high efficacy of TXA administration in TBI, concluding that TXA is capable of significantly decreasing the possibility of ICH volume expansion.[7-12] Contrarily, some other studies did not confirm the effectiveness of TXA in hindering post-TBI ICH expansion.[3,13-15]

There is a dispute on the effect of TXA on post-TBI morbidity, mortality, and unfavorable outcomes. Some investigations have reported no significant difference in the rate of TBI-related mortality or unfavorable outcomes,[8,11,13,15-17] but some other clinical trials concluded that TXA improves the final neurological outcome in TBI.[3,7,18]

The impact of TXA administration on post-TBI intraparenchymal hemorrhage (IPH) and contusion, as primary brain injuries, has not yet been separately studied. Given the controversies on the effect of TXA on post-TBI ICH volume and neurological outcomes in previous papers, we aimed to investigate the impact of TXA on IPH and contusion in patients with TBI.

Materials and Methods

Study setting

This double-blind randomized clinical trial was conducted on patients with TBI, referring to a Shahid Beheshti Hospital of Kashan University of Medical Sciences (KAUMS) from 2019 to 2021.

Participants

For having 80% power at the 0.05 level of significance (two-sided test) to detect a significant difference of 20% in the proportion of patients with IPH growth at 24 h, we planned to randomize 80 patients (40 to each group). Hence, we estimated that we would need 96 patients in total for anticipated 20% attrition.

Inclusion criteria were: patient age more than 13 years. than 13 years, isolated blunt head trauma or those with multiple trauma whose head injury was their first priority, admitted to hospital in <3 h of the injury, and evidence of IPH/contusion on admission brain computed tomography (CT) scan. Patients with major multiple organ trauma who needed surgical intervention at the first 3 h posttrauma, those who used anticoagulant medications, or had known history of coagulopathy, patients who could not undergo second brain CT scan for any reason, patients with admission creatinine level of >2 mg/dl, and pregnant women were excluded from this investigation.

Intervention

All enrolled patients underwent brain CT scan using a 16-detector CT scanner for confirming IPH/contusion in brain CT scan and measurement of its volume. Patients in the intervention group received a stat dose of 1 gr TXA in 100 ml normal saline infused over 10 min and via an antecubital venous access, followed by a maintenance dose of 1 g in 1000 ml N/S infused over 8 h. The placebo group received normal saline with the same volume, through the same route.[19] On admission, prothrombin time (PT) and partial thromboplastin time, complete blood cell count, serum level of blood urea nitrogen, and creatinine were measured for all participants.

A randomization list was provided in permuted blocks of size four. Randomization numbers were stored in sequentially numbered, sealed opaque envelopes. In order to blind the study, one of the researcher prepared similar looking syringes of normal saline and TXA , coded them and allocated to encoded patient IDs. All investigators, clinicians, nurses, and participants were blinded to the treatment allocation. On-admission and 24/72 h postintervention CT images were inspected and interpreted by a radiologist and a neurosurgeon, neither of whom were aware of the medication used for the patients. Images were evaluated for ICH volume, progression, mass effect from ICH, or any appearance of new ICH focus. To calculate the volume of hemorrhage, maximum length of hemorrhage and peri-hemorrhage edema was multiplied by its maximum width and height divided by 2.[13]

Patients' level of consciousness, on admission and 24/72 h after intervention and also at hospital discharge, was determined by Glasgow Coma Scale (GCS) score (scored from 3 to 15, with higher scores denoting better initial neurological status and neurological recovery). In this study, the primary outcome was an increase in ICH volume compared to the initial size and secondary outcomes were new ICH, mass effect from ICH, and functional status. To evaluate the functional status, Glasgow Outcome Scale (GOS) was utilized and patients were assessed by physicians for their GOS score after 3 months of intervention in an outpatient setting in a neurosurgery clinic. Patients, who did not manage to attend an in-person appointment after 3 months, were contacted through phone call.

Ethical consideration

This study was approved by the Ethics Committee of Kashan University of Medical Sciences with the ethics code IR.KAUMS.MEDNT.REC1398.004. Written informed consent was obtained from all conscious patients. If the patient's level of consciousness decreased, written informed consent was obtained from their relative or representative. This

study was also registered on the IRCT site under the number IRCT20190422043339N1.

Statistical analysis

Data were analyzed by SPSS v. 16.0 (IBM Inc., Chicago, IL, USA). Qualitative data were described and presented as frequencies and percentages, and quantitative data were analyzed and their central tendency/dispersion was reported. Significance level was considered at $P < 0.05$. Chi-square (or Fisher's exact) test was implemented for analyzing categorical variables, while *t*-test (or MannWhitney *U*-test for not normally distributed variables) was used to analyze continuous variables. To evaluate the impact of TXA on the ICH volume and mass effect, GCS before and 24/72 h after intervention, as well as 3-month GOS, and considering other factors such as age, gender, head injury mechanism, and the presence of skull fracture in admission brain CT scan, linear and ordinal logistic regression models exploiting generalized estimating equations (GEEs) were designed and attested.

Results

Ninety-seven patients were enrolled for this investigation. After excluding 9 patients from the intervention group, and 8 patients from the control group, 40 patients in either group remained eligible to undergo investigation [Figure 1].

As per our results, no significant difference in age, gender, TBI etiology, ICU length of stay, hospital length of stay, and skull fracture was found between the intervention and control groups ($P > 0.05$)

According to GCS scores, TBI severity on admission was recorded as mild, moderate, and severe in 53.8%, 40%, and 6.2% of cases, respectively, while TBI severity on hospital discharge was reported as mild, moderate, and severe in 88.8%, 8.8%, and 2.5% of cases. Table 1 shows that neither on-admission nor on-hospital discharge GCS score was different between the intervention and placebo groups ($P > 0.05$).

Table 2 demonstrates that changes in the size of hemorrhagic mass over time after TXA/placebo injection did not differ significantly between the study subgroups.

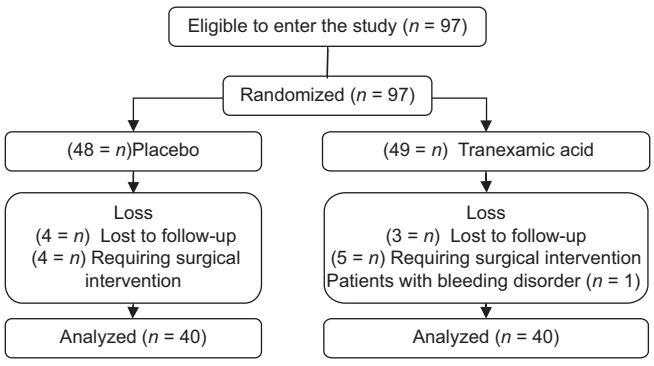

Figure 1: CONSORT flowchart for study groups

Nearly 98.8% of study subjects had contusion in their initial brain CT scan, 2.5% of those showing compression effect from ICH. Compression effect from ICH was noted in 10% of patients receiving TXA and 12.5% of patients receiving placebo 72 h after TBI. Moreover, new ICH was noted in 10% of participants (17.5% of patients receiving TXA and

Table 1: Frequency distribution of data in patients receiving tranexamic acid or placebo

Variables	Groups		Total	*P*
	TXA	Placebo		
Age[a] (years)	45.55±21.12	40.30±18.24	-	0.24
Sex[b]				
Male	35 (87.5)	36 (90)	71 (78.9)	1
Female	5 (12.5)	4 (10)	9 (11.2)	
TBI etiology[c]				
Traffic accidents	33 (82.5)	36 (90)	69 (86.2)	0.33
Fall	7 (17.5)	4 (10)	11 (13.8)	
ICU admission[c]				
Yes	16 (40)	11 (27.5)	27 (33.8)	0.23
No	24 (60)	29 (72.5)	53 (66.2)	
GCS at admission[c]				
Severe (<8)	1 (2.5)	4 (10)	5 (6.2)	0.13
Moderate (8-13)	20 (50)	12 (30)	32 (40)	
Mild (>13)	19 (47.5)	24 (60)	43 (53.8)	
GCS at discharge[c]				
Severe (<8)	0	2 (5)	2 (2.5)	0.4
Moderate (8-13)	3 (7.5)	4 (10)	7 (8.8)	
Mild (>13)	37 (92.5)	34 (85)	71 (88.8)	
Skull fracture[b]				
Yes	5 (12.5)	4 (10)	9 (11.2)	0.24
No	35 (87.5)	36 (90)	71 (88.8)	
ICU length of stay[d] (days)	1.93±4.94 0 (0–2)*	2.63±6.85 0 (0–1.75)*	-	0.46
Hospital length of stay[d] (days)	7.68±6.76 6 (5–8)*	9.1±10.22 5 (4–6.5)*	-	0.57

*Median (IQR), [a]*t*-test, [b]Fisher's exact test, [c]Chi-square tests, [d]Mann-Whitney test. Data are presented as *n* (%) or mean and SD. SD: Standard deviation, IQR: Interquartile range, TXA: Tranexamic acid, TBI: Traumatic brain injury, ICU: Intensive care unit, GCS: Glasgow Coma Scale

Table 2: Hemorrhagic mass size changes over time in patients receiving tranexamic acid or placebo

Mass size change time	Group		*P**
	TXA, *n* (%)	Placebo, *n* (%)	
Before intervention compared to 24 h later			
Volume increase	29 (72.5)	22 (55)	0.10
No change	11 (27.5)	18 (45)	
Before intervention compared to 72 h later			
Volume increase	30 (70)	26 (65)	0.32
No change	10 (30)	14 (35)	

*Chi-square tests. TXA: Tranexamic acid

2.5% of those taking placebo) 24 h after TBI (P = 0.06). Peri-hemorrhage edema was noted in 56.2% of participants 24 h after TBI. Generally, no significant difference was found in compression effect from ICH, new ICH, and peri-hemorrhage edema between the study subgroups either in premedication scans or in brain CT scans performed 24/72 h after TXA/placebo injection ($P > 0.05$).

Based on 3-month GOS scores, 82.5%, 6.2%, 6.2%, 2.5%, and 2.5% of patients showed a good neurological recovery, moderate disability, severe disability, entered vegetative state, and died, respectively. The neurological outcome 3 months after hospital discharge did not differ significantly between the intervention and placebo subgroups (P = 0.09) [Table 3].

Linear regression modeling using GEE revealed that none of the investigated variables significantly affect the size of hemorrhage over time [Table 4].

Ordinal logistic regression of GCS scores showed that GCS score over time is significantly related to TBI etiology (P = 0.001) and patients' age (P = 0.014), although it was not associated with treatment groups (TXA or placebo), patients' gender, and presence of skull fracture on admission. Traffic collision patients had a 5.9-fold more odds for having a higher on-admission GCS score compared to those fallen from height [Table 5].

Results of the logistic regression using GEE method showed that none of the investigated variables is meaningfully associated with the compression effect from ICH over time.

Linear regression analysis showed that on-admission GCS score ($P < 0.001$) and TBI etiology (P = 0.04) are significantly associated with the length of hospital stay. With every unit increase in on-admission GCS score, hospital stay length became 2 days shorter. In addition, traffic collision patients were admitted about 4 days less than those fallen from height [Table 6].

Table 3: Comparing Glasgow Outcome Scale scores after three months of hospital discharge between the study subgroups

GOS score	TXA, *n* (%)	Placebo, *n* (%)	Total, *n* (%)	*P**
Death	1 (2.5)	1 (2.5)	2 (2.5)	0.09
Vegetative	0	2 (5)	2 (2.5)	
Severe disability	2 (5)	3 (7.5)	5 (6.2)	
Moderate disability	5 (12.5)	0	5 (6.2)	
Good recovery	32 (80)	34 (85)	66 (82.5)	
Total, *n* (%)	40 (100)	40 (100)	80 (100)	

*Chi-square test. TXA: Tranexamic acid, GOS: Glasgow Outcome Scale

Table 4: Hemorrhagic mass size over time in a linear regression model using the generalized estimating equation method

Variable	*B*	95% Wald, CI		*P*
		Upper	Lower	
Intercept	−2.551	6.291	−11.394	0.572
Group				
TXA	2.870	5.887	−0.148	0.062
Placebo	0[a]	.	.	.
Sex				
Male	0.471	2.335	−1.392	0.620
Female	0[a]	.	.	.
TBI etiology				
Traffic accidents	3.102	7.989	−1.785	0.214
Fall	0[a]	.	.	.
Skull fracture				
Yes	−1.586	0.832	−4.003	0.199
No	0[a]	.	.	.
Age (years)	0.062	0.176	−0.052	0.287

CI: Confidence interval, TXA: Tranexamic acid, TBI: Traumatic brain injury

Discussion

This study showed no significant difference between patients' age, gender, TBI etiology, presence of skull fracture, on-admission GCS, and CT findings (as new ICH, compression effect from ICH, and peri-hemorrhage edema) before or 24/72 h after receiving TXA in the intervention and placebo subgroups. These findings are in keeping with the results of a previous study by Fakharian *et al*.[13]

Primary outcome

The intervention and control subgroups showed no meaningful difference in hemorrhage volume alteration before and 24/72 h after receiving medication/placebo. Previous studies have also confirmed the ineffectiveness of TXA for hindering ICH enlargement.[3,15,16] Mahmood *et al*. also found that TXA cannot prevent ICH enlargement;[14] however, Fakharian *et al*. reported that TXA prevents ICH from enlargement.[13] This discrepancy in reported results can be due to the type of ICH investigated, as in the latter study, authors enrolled patients with any type of ICH, but in the current study, only brain contusion and IPH were included. Some previous studies have concluded that TXA significantly decreases the rate at which ICH grows in size.[7,8,10-12] Other factors that can explain the literature controversies on TXA impact on TBI include time interval between brain injury and TXA injection, the dosage and frequency of TXA administration, duration of TXA use, TBI to brain CT or TXA injection to brain CT interval, and the method of calculating the ICH volume.

Secondary outcomes

According to GOS scores, the majority of study subjects (82.5%) showed a good neurological recovery after 3 months, with no significant difference between the intervention and placebo subgroups. This is in keeping with the results of the previously published papers.[3,13,15-17] Chakroun-Walha *et al*. reported no difference in 28-day mortality rate between the intervention and control subgroups.[20] Nonetheless, Nelson *et al*. found a better neurological outcome based on GOSE (Glasgow Outcome Scale Extended) in patients with traumatic subdural hematoma who have received TXA on hospital discharge, and 30 days post-TBI.[11] Remarkable differences in study sample size, time

Table 5: Ordinal logistic regression of Glasgow Coma Scale scores through time based on generalized estimating equation method

Parameter	*B*	95% CI for Exp (B)		Exp (B)	*P*
		Lower	Upper		
GCS					
Severe (<8)	−1.579	0.030	0.206	0.109	1.426
Moderate (8-13)	0.790	0.320	2.203	0.422	15.149
Group					
TXA	−0.070	0.426	0.933	0.861	2.042
Placebo	0[a]	.	1	.	.
TBI etiology					
Traffic accidents	1.770	2.108	5.872	0.001	16.357
Fall	0[a]	.	1	.	.
Age (years)	0.027	1.005	1.027	0.014	1.049
Sex					
Male	−0.857	0.137	0.424	0.137	1.315
Female	0[a]	.	1	.	.
Skull fracture					
Yes	−0.503	0.112	0.605	0.559	3.265
No	0[a]	.	1	.	.

CI: Confidence interval, TXA: Tranexamic acid, TBI: Traumatic brain injury, GCS: Glasgow Coma Scale

Table 6: Regression modeling of the investigated variables based on the length of hospital stay

Model	Unstandardized coefficients		Standardized coefficients (β)	*P*
	SE	*B*		
Constant	6.712	42.655		0.000
Group	1.486	0.627	0.037	0.674
Age (years)	0.044	0.035	0.079	0.435
Sex	2.429	−0.211	−0.008	0.931
GCS at admission	0.226	−1.95	−0.704	0.000
TBI etiology	2.034	−4.227	−0.170	0.041
Skull fracture	2.260	−2.589	−0.095	0.256
Mass size after 24 h	0.359	−0.251	−0.067	0.487
Mass effect after 24 h	5.073	0.395	0.007	0.938

TBI: Traumatic brain injury, GCS: Glasgow Coma Scale, SE: Standard error

of neurological recovery assessment, the time of TXA first dose injection, and study inclusion criteria such as injury severity can explain different results of our study compared to others.

The current study showed a 2.5% mortality rate, not differing meaningfully between the intervention and control groups. This is in line with the findings of Perel *et al*.'s study, which has reported a mortality rate of 11% and 18% for those who received TXA and those who did not, respectively, while no statistically significant difference was found between them.[3] Additionally, another investigation did not report a significant difference between mortality rate in TBI patients who have received TXA (10%) and that of patients who were given placebo (14%).[15] Fakharian *et al*. reported a mortality rate of 2.7% and 4% for patients receiving TXA and placebo, respectively, again with no meaningful difference between them.[13] Moreover, the CRASH-3 study reported that TXA prescription decreases the mortality rate in mild-to-moderate TBI patients, but not in severe cases.[18]

Compression effect from ICH after 72 h of TBI was nearly 10% in patients who received TXA and 12.5% in the placebo subgroup; however, the difference was not significant. The CRASH-2 study found the same feature in 47% of the TXA group and 60% of the placebo group, and reported the difference statistically significant.[3] The higher figures of that study compared to our study can be linked to the higher mean volume of the hemorrhage in their study. Another study found that 10% of patients from the TXA group and 8% of patients from the placebo group showed compression effect from ICH in their brain CT scan; however, the difference was not significant.[15] Fakharian *et al*. reported an ICH compression effect of 16.2% in the TXA group and 18.7% in the placebo group, again with no significant difference between them.[13]

The current study revealed that after 24 h of TXA/placebo injection, a new ICH occurs in 17.5% of cases in the intervention subgroup, and 2.5% of patients in the placebo subgroup, not differing significantly. The CRUSH II study reported a new ICH in 11% and 16% of patients receiving TXA and placebo, respectively,[3] and Fakharian *et al*.[13] reported the same measures at 23.3% of the TXA group and 18.7% of the placebo group. Both of these studies similarly reported that the difference between the rates of new ICH is not significant between the intervention and placebo subgroups.

Hospital or ICU length of stay did not significantly differ with prescribing TXA, which is in keeping with the results of a previous study by Fakharian *et al*.[13] To the best of our knowledge, no other study in literature included these factors.

This investigation showed that TBI severity (according to GCS scores) does not differ between the TXA and placebo groups at any TXA/placebo to brain CT time interval. Linear regression analysis revealed that TXA administration, gender, and finding skull fracture in admission brain CT scan are not associated with GCS at any time post-TXA/placebo injection, as opposed to TBI etiology and gender, which were associated with GCS score through time. Furthermore, the mean GCS score was higher in patients with traffic collision than those fallen from height

Linear regression analysis showed that from all of the variables studied, only on-admission GCS score is associated with hospital length of stay. The size of hemorrhagic mass did not differ between traffic accident patients and those fallen from height. Traffic collision patients stayed in hospital 4 days less than those fallen from the height, which can be related to the higher mean on-admission GCS score in the former, as mentioned previously. With every unit increase in on-admission GCS score, patients were likely to experience a 2-day shorter hospital stay.

This study has some limitations worthy of note. First, the investigation was single center and the study sample was relatively small, which may affect the study power and generalizability of findings. Small sample size also made it impossible to evaluate the adverse outcomes related to TXA and its independent impact on the mortality rate. Second, the time interval between TBI and TXA injection in the intervention group was 3 h. Future studies might shorten this period and achieve new or even opposite results. Finally, including mild cases of TBI might result in a falsely improved final neurological recovery. However, this study followed the subjects for 3 months after TBI with no participant loss during the course of investigation.

Conclusion

According to the findings of this study, TXA prescription does not affect the ICH size and will not improve the 3-month neurological outcome in TBI patients. Conducting populous studies on cases collected from multiple centers, accounting for the effect of different doses of TXA, and further shortening the time interval between TBI and drug injection is warranted.

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Conflicts of interest

There are no conflicts of interest.

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