Effect of Tranexamic Acid on Prevention of Hemorrhagic Mass Growth in Patients with Traumatic Brain Injury

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BACKGROUND: **Intracranial hemorrhage is a common complication of traumatic brain injury (TBI). The purpose of this study is evaluation of the effect of tranexamic acid (TXA) on hemorrhagic mass growth in TBI patients.**

PATIENTS AND METHODS: **In this randomized, double-blind clinical trial, 149 patients with TBI and any kind of blood on their computed tomography scan enrolled in the study and were randomly allocated to receive TXA or placebo. After 24 hours, computed tomography scan was repeated for assessing the changes in hemorrhage, new bleeding, and mass effects of blood on brain tissue. The primary outcome was growth of the hemorrhagic lesion. Data were analyzed by SPSS software using Fisher exact, chi-square, and Mann-Whitney U tests, as well as linear and logistic regression models.**

FINDINGS: **The incidence of hemorrhagic lesion growth was 20.5% in the TXA group and 22.7% in the placebo group. The difference was not significant ($P = 0.87$, RR = 0.89). The mean (standard deviation) of hemorrhagic lesion growth was 9.4 (15.3) in the TXA group and 10.2 (10.1) in the placebo group without significant difference ($P = 0.27$). The frequency of deaths (2.7% vs. 4%), adverse outcome at discharge (10.8% vs. 17.3%), and 3 months later (6.8% vs. 14.7%) in the TXA group were lower than the placebo, but the difference was not statistically significant. No side effect was observed with the administration of TXA.**

CONCLUSION: **Administration of a short dose of TXA does not lead to significant prevention of growth of posttraumatic hemorrhagic lesion or improvement of clinical outcomes.**

INTRODUCTION

Traumatic brain injury (TBI) is one of the major causes of death and disability in the world. It is estimated that 1.5 million patients die annually due to TBI.[1] The annual incidence rate of TBI in the United States is between 180 and 250 per 100,000 population,[2] and this figure is calculated between 15.3 and 144 per 100,000 population in Tehran, Iran.[3] TBI is classified into 3 categories based on the Glasgow Coma Scale (GCS): severe (10%); moderate (10%); and mild (80%).[4]

Intracranial hemorrhage (ICH) is a common complication of TBI, which may progress and worsen after admission to the hospital.[5] About three fourths of patients with TBI have intracranial hemorrhage,[6] which may get larger while admitted to the hospital in about half of patients.[7,8] It is told that this bleeding is associated with a high risk of coagulopathy, and this may lead to increase in hemorrhage size, higher mortality, and disability. Increase in fibrinolysis, which implies high levels of fibrin degradation products, is a common pattern of coagulopathy in TBI. Therefore antifibrinolytic agents such as TXA may reduce ICH due to trauma.[5]

Several clinical trials have confirmed the efficacy and safety of TXA.[9-11] In CRASH-2, an international study on the effects of TXA, 20,211 cases of trauma in 40 countries received an early injection of TXA. This resulted in reduced mortality of those who bled or were at risk of bleeding without any side effects. The researchers also concluded that TXA is a cost-beneficial drug in low- and

Key words
- Intracranial hemorrhage
- Tranexamic acid
- Traumatic brain injury

Abbreviations and Acronyms
CT: Computed tomography
GCS: Glasgow Coma Scale
GOS: Glasgow Outcome Scale
ICH: Intracranial hemorrhage
SDH: Subdural hemorrhage
TBI: Traumatic brain injury
TXA: Tranexamic acid

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middle-income countries.[9] Later, this drug joined the World Health Organization's list of essential medicines.[12]

TXA administration in patients with aneurysmal subarachnoid hemorrhage has reduced the chance of rebleeding but increased brain ischemia probably due to vasospasm or microvascular thrombosis.[13] Because many patients with trauma-related bleeding also have TBI, there will be apprehension about the risk of brain ischemia for these patients.[5] Another study in nontraumatic intracerebral hemorrhages showed that TXA is effective in stabilizing the hematoma.[14] Studies about TXA and TBI are limited. A subgroup of the CRASH-2 study including 270 cases with TBI had ICH, and their mean hemorrhagic growth was lower in the TXA in comparison with the placebo group, although the difference was not statistically significant. It was also found that TXA had no effect on mortality and disability of these patients.[5] Yutthakasemsunt et al,[11] in a study of 238 patients with severe and moderate TBI, concluded that the difference between the 2 groups was not significant for progressive ICH, mortality, and unfavorable outcome. Jokar et al[15] concluded in their study that in spite of an increase in bleeding volume in both the TXA and placebo groups, the increment in the TXA group was significantly lower than the control. In a systematic review of CRASH-2 and the Yutthakasemsunt study, it was concluded that TXA significantly reduced the progression of ICH and improved the clinical outcomes of patients. Finally, in this study, the researchers suggested that more studies and evidence were needed to support the routine use of this drug in TBI patients.[16]

Therefore due to limited studies about the effect of TXA on TBI-induced bleeding and the various effects of this drug on the outcomes of traumatic patients, this study was conducted to investigate the effect of TXA in prevention of increase in bleeding volume in TBI patients. If its effect was proven, it could be used as one of the routine drugs in the trauma emergency ward for reducing the mortality and morbidity of TBI.

PATIENTS AND METHODS

This is a double-blind, randomized clinical trial on 150 patients with TBI admitted to Shahid Beheshti University Hospital, Kashan University of Medical Sciences, Kashan-IR during 2014–2016.

Participants

Patients with isolated TBI or multiple trauma patients, with TBI as the main problem, who arrived at the hospital within 8 hours of trauma, aged 15 and older, with nonpenetrating injury and any kind of traumatic intracranial bleedings (subdural hemorrhage [SDH], subarachnoid hemorrhage, contusion, intraventricular hemorrhage, and epidural hematoma) in admission CT scans, no need for brain surgery during the first 8 hours, no coagulation disorder, serum creatinine <2 mg, and nonpregnancy were enrolled to the study. Major organ damage requiring surgical intervention within the first 8 hours, receiving any medication that disturbs homeostasis, those who do not have a secondary CT scan, and those who missed follow-up were excluded.

Intervention

The patients complying the inclusion criteria were divided randomly into 2 intervention and control groups on the basis of 4 blocks. In the intervention group, intravenous TXA was administered with the first dose of 1 g in 100 mL of normal saline in 10 minutes and then with a maintenance dose of 1 gram per 1000 mL of normal saline for 8 hours.[5] In the control group, 0.9% normal saline was used in the same order. Other treatment protocols and care were routinely done for all patients. Data were recorded in the checklist by interview and patients' charts.

In order to blind the study, the syringes containing TXA and normal saline were coded by 1 of the study contributors and supplied to the wards. The physicians and nurses who cared for the patients were unaware of the content of the syringes supplied. The drug code could be broken in case of a problem or complication. Within 24–48 hours of intervention, CT scan was repeated and the size of the hemorrhagic lesion, new bleeding in the scan,

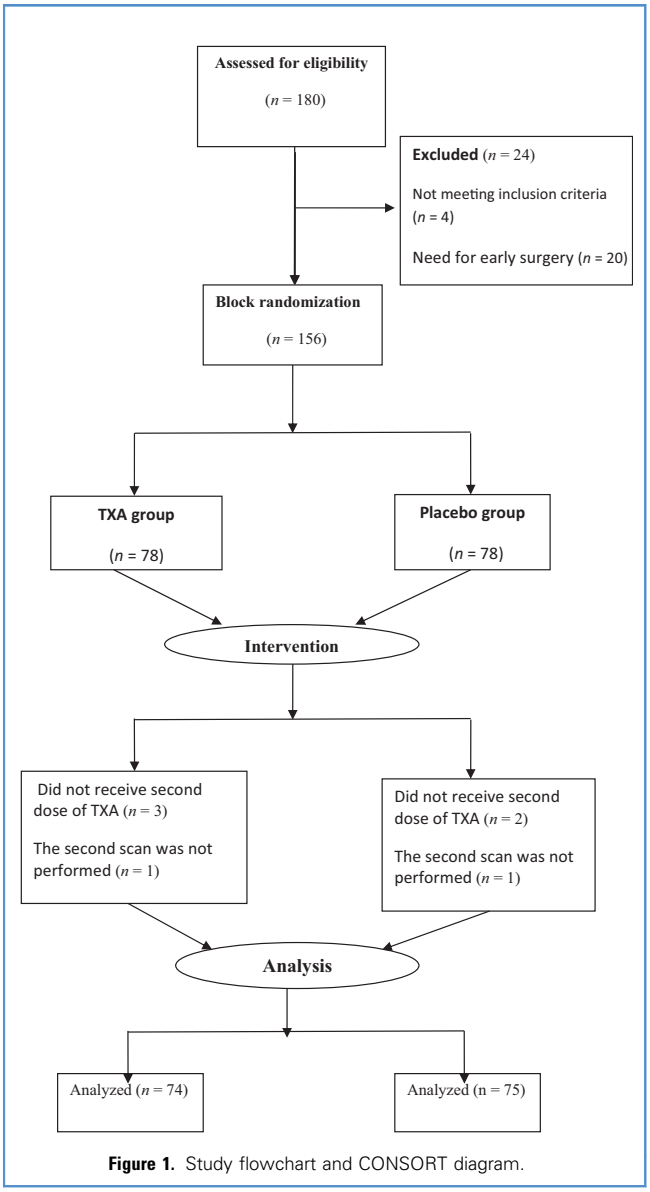

Figure 1. Study flowchart and CONSORT diagram.

and effects of the hemorrhagic lesion on the brain tissue were examined. To calculate the volume of bleeding, the following formula was used: multiplying the maximum length of bleeding and its maximum width by the number of cuts in centimeters divided by 2.

The primary outcome was assessment of any increase in the volume of hemorrhagic lesion in comparison with the initial size and secondary outcomes including the need for brain surgery, death, functional status based on the Glasgow outcome scale, new bleeding, and mass effects. At the time of discharge and 3 months later, functional outcome was assessed by the neurosurgeon based on the GOS, with a score of 1–5 points on the basis of the patient's functional status. A higher score indicates better recovery. Also, patients were evaluated for the complications of TXA including nausea and vomiting, abdominal pain, and deep vein thrombosis.

Ethical Consideration

This study was approved at the Ethics Committee of Kashan University of Medical Sciences. Written consents were obtained from all patients. This study was also registered on IRCT with the following number: IRCT2010112028 54N6.

Statistical Analysis

The Kolmogorov-Smirnov test showed that some of the data do not have normal distribution. Therefore for statistical analysis Fisher exact, chi-square, and Mann-Whitney U tests, as well as linear regression and logistic regression models, were used to eliminate the possible effects of confounding variables. Data were analyzed by SPSS software and the significance level was considered 0.05.

RESULTS

Out of 180 patients selected for this study, 20 were excluded due to the need for surgery (brain or other organs) during the first 8 hours, 4 cases were younger than the age of 15 years, 5 did not receive the second dose of TXA, and the second scan was not performed for 2. Finally, 149 patients were analyzed in 2 groups (TXA = 74 and placebo = 75) (Figure 1).

In this study, the patients were matched in 2 groups according to the variables of age, gender, nationality, cause of trauma, GCS, systolic blood pressure, duration of hospital stay, admition to ICU and its duration (Table 1).

There is no statistically significant difference in the rate of skull fracture, mass effects on brain tissue, the occurrence of new bleeding, and type of hemorrhage between the 2 groups (Table 2).

Table 3 shows a statistically significant difference between the 2 groups in terms of changes in volume of hemorrhagic lesion ($P = 0.03$).

The prevalence of hemorrhagic lesion growth in the TXA group was 20.5% versus 22.7% in the placebo group. This difference between the 2 groups was not significant (Table 4). The mean and standard deviation of the volume of hemorrhagic lesion in the TXA group was 9.4 ± 15.3 mL and in the placebo group 10.2 ± 10.1 mL. This difference was not significant ($P = 0.27$). Although the frequency of deaths and unfavorable outcomes at hospital discharge and 3-month follow-up in the TXA group is less than

Table 1. Demographic and Clinical Characteristics of Patients in 2 Groups

Group	TXA	Placebo	*P* Value
Age*	42.3 ± 18.3	39.3 ± 18.1	0.31
Gender†			
Male	67 (90.5)	66 (88)	0.62
Female	7 (9.5)	9 (12)	
Nationality†			
Iranian	70 (94.6)	65 (86.7)	0.1
Non-Iranian	4 (5.4)	10 (13.3)	
Trauma cause†			
Traffic accidents	64 (86.5)	62 (82.7)	0.43
Fall	8 (10.8)	8 (10.7)	
Conflict	2 (2.7)	2 (2.7)	
Others	0 (0)	3 (4)	
GCS at the time of arrival*	12.7 ± 2.83	11.65 ± 3.71	0.14
Systolic blood pressure (mm Hg*)	118.2 ± 16.3	120 ± 15.6	0.24
Duration of hospital stay*	13.5 ± 14.3	14.5 ± 11.2	0.14
Admission to ICU†			
Yes	41 (55.4)	49 (65.3)	0.21
No	33 (44.6)	26 (34.7)	
Duration of ICU stay*	11.9 ± 13.7	10.2 ± 9.9	0.46

TXA, tranexamic acid; GCS, Glasgow Coma Scale; ICU, intensive care unit.
*Data are presented as mean and standard deviation.
†Data are presented as numbers (%).

Table 2. Comparison of Computed Tomography (CT) Scan Findings in 2 Groups

Group Variable*	TXA	Placebo	*P* Value
Skull fracture	29 (39.2)	30 (40)	0.92
Mass pressure effects on brain tissue in primary CT scan	12 (16.2)	14 (18.7)	0.43
New bleeding	17 (23.33)	14 (18.7)	0.21
Type of hemorrhage			
Contusion	36 (48.6)	38 (50.7)	0.80
SDH	22 (29.7)	20 (26.7)	0.67
EDH	16 (21.6)	15 (20)	0.80
SAH	43 (58.1)	35 (46.7)	0.16

TXA, tranexamic acid; SDH, subdural hemorrhage; EDH, epidural hematoma; SAH, subarachnoid hemorrhage.
*Data are presented as number (%).

Table 3. Comparison of Changes in Volume of Hemorrhagic Mass in 24 Hours in 2 Groups

Group Change the Mass Volume*	TXA	Placebo	*P* Value
Volume reduction	50 (68.5)	38 (50.7)	0.03
Increasing volume	15 (20.5)	17 (22.7)	
Without change	8 (11)	20 (26.7)	

*Data are presented as number (%).

in the placebo group, their difference is not statistically significant. The majority (60%) of those who needed surgery had SDH, and in all deaths (5 cases), SDH was observed with other types of bleeding.

Linear regression analysis of the effect of age and type of drug and GCS on the increment of hemorrhagic lesion size showed that if other variables remain constant, the only factor that has a significant effect on the volume of bleeding is the age, so for each year increase in the age, mean of the hemorrhage decreases by 0.153 ($P = 0.013$).

Multiple logistic analysis of the effect of the drug on the outcome of the patients, along with age, GCS, and the increase in hemorrhagic lesion, showed that although the treatment had no significant effect on the unfavorable outcome, if other variables remain constant, for each year increase in patient age, the odds for unfavorable outcome increased by 1.1 times ($P = 0.015$). Also for each unit increase in GCS, the odds for unfavorable outcome decreased by 0.62 ($P < 0.001$). The effects of increasing the volume of hemorrhagic lesion in this analysis were not significant.

DISCUSSION

The study showed that TXA reduced the growth of hemorrhagic lesion due to TBI without any evidence of increased risk of thromboembolic events. However, this difference was not statistically significant. This finding is similar to other studies.[5,11] However, Zehtabchi et al,[16] in their systematic review of the previously mentioned studies, with pooled analysis showed a significant difference in the growth of hemorrhagic lesion between the 2 groups and in favor of TXA.

In total, 21.4% (33 people) of the patients had increased volume of hemorrhagic lesion. This rate has been reported between 7% and 68%.[8,17,18] in various studies. In Yutthakasemsunt's study, this rate was similar to the current study (22.2%)[11] and CRASH-2 study 37%.[5]

In this study, there was a significant difference between the 2 groups in terms of volume changes in the hemorrhagic lesion within 24 hours ($P = 0.03$). In the TXA group, the volume decreased in 68.5% of the cases, increased in 20.5%, and remained unchanged in 11% of the subjects after 24 hours.

Increased hemorrhagic lesion in the TXA group was seen in 15 out of 74 (20.5%) and in the placebo group in 17 of 75 (22.5%) patients. The mean and standard deviation of hemorrhagic lesion volume in the TXA group was 9.4 ± 15.3 mL and in the placebo group 10.2 ± 10.1 mL. The difference between the 2 groups was not significant. In a study in Thailand, although the increase in hemorrhagic lesion in the TXA and placebo group was 18% and 27%, respectively, however, the difference was not significant.[11] In CRASH-2 study, hemorrhagic lesion growth was 36% in the TXA and 44% in the placebo group. The mean and standard deviation of hemorrhagic lesion in the TXA group was 5.9 ± 26.8 mL and 8.8 ± 29.2 mL in the placebo group, and the difference between the 2 groups was not significant.[5] Jokar et al,[15] in their single blind study on 80 patients with TBI, showed a significant difference in increasing size of bleeding in the 2 groups. Differences in the growth of hemorrhagic lesion in various studies may be due to the differences in timing of CT scanning, difference in measurement of the volume, and other diagnostic criteria, as well as the research methodology.

Death rate in the TXA group in this study was 2.7% versus 4% in the placebo, and the difference between the 2 groups was not significant ($P = 1$). This finding is consistent with the CRASH-2 study, where the death rate was 11% in the TXA group and 18% in the placebo group, without significant difference, and it was found that TXA does not reduce mortality.[5] In a Yutthakasemsunt et al[11] study (2013), death rates were 10% in the TXA and 14% in the placebo group, without difference between the groups. The lower percentage of death in our study may be due to differences in the criteria for entry of individuals into the study. In this study, patients with mild traumatic hemorrhage and any bleeding volume were enrolled, while Yutthakasemsunt et al.[11] studied patients with moderate to severe TBI.

There were no significant differences between the 2 treatment groups in terms of other adverse effects concerning GOS at

Table 4. Comparison of Patients Outcomes in 2 Groups

Group Outcome*	TXA	Placebo	*P* Value	RR (95% CI)
Growth of hemorrhagic mass	15 (20.5)	17 (22.7)	0.87	0.89 (0.55–1.74)
Need for surgery	8 (10.8)	12 (16)	0.35	0.67 (0.29–1.55)
Death	2 (2.7)	3 (4)	1	0.67 (0.12–3.93)
Unfavorable outcome at discharge (GOS)	8 (10.8)	13 (17.3)	0.25	0.62 (0.22–1.46)
Unfavorable outcome 3 months after discharge (GOS)	5 (6.8)	11 (14.7)	0.12	0.46 (0.16–1.26)

TXA, tranexamic acid; RR, relative risk; CI, confidence interval; GOS, Glasgow Outcome Scale.
*Data are presented as number (%).

discharge and 3 months' follow-up. The CRASH-2 study did not show any difference in posttraumatic disability of patients, based on the Oxford Modified Disability Scale (mOHS) (22% in the TXA group and 26% in the placebo group).[5] Also in the study by Yutthakasamsunt et al,[11] this rate was 18% and 23% for TXA and placebo, respectively, and there was no difference in unfavorable outcomes based on GOS between the 2 groups. In the Zehtabchi et al[16] study, there was no improvement in clinical outcomes in patients with TXA.

In this study, the prevalence of vegetative life in the TXA group was 4.1% and in the placebo group it was 3.9%. No significant difference was found. The rate in the CRASH-2 study was 22% for the TXA group and 26% in the placebo, without any significant difference.[5] The reason for higher vegetative life in the mentioned study was in the inclusion of more severe brain trauma patients.

In the TXA group, 10.8% ultimately underwent surgical intervention with craniotomy and hematoma evacuation in all cases, and in the placebo group, it was 16%. The difference was not significant in the 2 groups. In the CRASH-2 study,[5] the rate of surgery in both groups was 15%. In the Yutthakasamsunt et al[11] study this was 3% for the TXA group. However, in the 2 mentioned studies, the difference was not significant.

The hemorrhagic mass effects on brain tissue were not significantly different between the 2 groups, although they were lower in the TXA group (16.2%) than in the placebo group (18.7%). The rates were 47% and 60% in CRASH-2 study for TXA and placebo, respectively, and the difference between the 2 groups was significant.[5] This finding is much higher than in our study because of the higher average volume of hemorrhagic mass in the study in comparison with ours. However, in another study, the rates were 10% and 8% for TXA and placebo, respectively.[11]

Within 24 hours of the initiation of treatment, new bleeding was seen in 23.3% of the patients in the TXA group and 18.7% of the placebo group, but no significant difference was found. The amounts in the CRASH-2 study[5] were 11% and 16% for TXA and placebo, respectively, although the difference between 2 groups was not significant like ours.

No side effects with TXA were seen in this study. In the study of Roberts et al,[10] the safety of this drug has been reported in a wide range of patients with traumatic bleeding. In several other studies, it was also found that TXA was not associated with an increased risk of thromboembolic events.[11,15,16]

In linear regression analysis, the patient's age is the only factor with a significant effect on the volume of bleeding, so by increasing age, mean hemorrhage volume decreases. This finding is in contrast with the concept of increased fragility of vessels by age and higher incidence of bleeding in the elderly; however, to our knowledge there is no report or explanation of such a finding. It may be due to the younger age of the trauma population in our country, and the incidence happens in an overall younger age group who may be physiologically resistant to trauma. Adversely, those in a lower limit of age may be at a higher risk for their specific physiologic state. This finding may need further consideration and comparison of different age groups with each other in larger case controlled studies.

Multiple logistic analyses showed that administration of TXA had no significant effect on the unfavorable outcome. Also, the odds for unfavorable outcome will increase with increasing age and decrease with increasing GCS. The effect of increase in volume of hemorrhagic lesion on the patients' outcome was not significant in this analysis. In the CRASH-2 study, it was found that after the elimination of the effects of age, GCS, and the type of treatment (as confounders), the increase in hemorrhagic lesion size was associated with disability.[5] The finding of unfavorable outcome with increasing age and lower GCS is a well-known fact; however, the former is in contrast with the previously mentioned finding of decreasing hemorrhage size with increasing age.

The limitations of this study were the small sample size and elimination of patients with coagulopathy, which should be considered in subsequent studies. Its strengths include double-blind design, randomized block allocation, precise tomographic data, and 3-month patient follow-up for outcome assessment. None of the patients were excluded from the follow-up period.

CONCLUSION

Although TXA prevented hemorrhagic mass growth, the difference was not statistically significant. No improvement in clinical outcomes was observed with the drug. Arrangement of further studies with larger sample sizes and consideration of the present study with different doses of TXA is recommended.

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