The effect of tranexamic acid in traumatic brain injury: A randomized controlled trial

Abolfazl Jokar a, Koorosh Ahmadi b, Tayyebeh Salehi a, Mahdi Sharif-Alhoseini c, Vafa Rahimi-Movaghar c,d,*

a Department of Emergency Medicine, Arak University of Medical Science, Arak, Iran
b Department of Emergency Medicine, Alborz University of Medical Sciences, Karaj, Iran
c Sina Trauma and Surgery Research Center, Tehran University of Medical Sciences, Tehran, Iran
d Department of Neurosurgery, Shariati Hospital, Tehran University of Medical Sciences, Tehran, Iran

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ABSTRACT

Purpose: Traumatic brain injury (TBI) is a leading cause of death and disability. Intracranial hemorrhage (ICH) secondary to TBI is associated with a high risk of coagulopathy which leads to increasing risk of hemorrhage growth and higher mortality rate. Therefore, antifibrinolytic agents such as tranexamic acid (TA) might reduce traumatic ICH. The aim of the present study was to investigate the extent of ICH growth after TA administration in TBI patients.

Methods: This single-blind randomized controlled trial was conducted on patients with traumatic ICH (with less than 30 ml) referring to the emergency department of Vali-Asr Hospital, Arak, Iran in 2014. Patients, based on the inclusion and exclusion criteria, were divided into intervention and control groups (40 patients each). All patients received a conservative treatment for ICH, as well as either intravenous TA or placebo. The extent of ICH growth as the primary outcome was measured by brain CT scan after 48 h.

Results: Although brain CT scan showed a significant increase in hemorrhage volume in both groups after 48 h, it was significantly less in the TA group than in the control group (p = 0.04). The mean total hemorrhage expansion was (1.7 ± 9.7) ml and (4.3 ± 12.9) ml in TA and placebo groups, respectively (p < 0.001).

Conclusion: It has been established that TA, as an effective hospital-based treatment for acute TBI, could reduce ICH growth. Larger studies are needed to compare the effectiveness of different doses.

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Introduction

Traumatic brain injury (TBI) is a leading cause of death and disability. Each year about 1.5 million persons die and more than 10 million persons are hospitalized following a TBI worldwide.1 A study showed an annual incidence rate of 56.3/100,000 population for TBI in Tehran, Iran.2 One of the most important and devastating parts of the secondary pathologic cascade that may occur after the initial brain injury is the progression of intracranial hemorrhage (ICH), especially within the first 24 h.3 Its frequency varies according to TBI severity.

ICH is also associated with a high risk of coagulopathy which leads to increased risk of hemorrhage growth and higher mortality.4 Therefore the antifibrinolytics agents might reduce traumatic ICH. Tranexamic acid (TA), as an antifibrinolytic, has recently been shown to be an effective treatment of traumatic hemorrhage. In a recent mega-trial (CRASH-2) in more than 20,000 trauma patients with major bleeding, TA significantly reduced mortality, with no increase in vascular occlusive events.5 Analysis of a TBI sub-group (n = 270) showed a trend toward less mortality with TA.6,7 A systematic review demonstrated statistically significant reduction in ICH progression with TA and a non-statistically significant improvement of clinical outcomes in TBI patients.8 To date, there has been no study to determine the extent of ICH expansion after TA administration and also the optimal dose of TA in TBI patients.

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The present study aims to investigate the extent of ICH growth after TA administration in TBI patients.

Materials and methods

The patients with acute traumatic ICH were successively enrolled in this single-blinded, controlled, randomized trial at the emergency department of Vahid Asr Hospital, Arak, Iran in 2014. The study was approved by Research Ethics Committee, Arak University of Medical Sciences. The TBI patients aged 15 years and more, within 2 h of injury onset, and with acute ICH (volume of less than 30 ml) based on CT scan findings, were eligible for the trial. The exclusion criteria were: (1) Glasgow coma scale (GCS) total score <8; (2) unknown onset time; (3) ICH volume more than 30 ml as measured by CT scan; (4) need for surgery; (5) presence of focal neurologic deficits; (6) subarachnoid hemorrhage; (7) the cerebral edema with midline shift; (8) use of TA within the previous 14 d; (9) hereditary or acquired hemorrhagic diathesis or coagulation factor deficiency; (10) creatinine > 20 mg/L; (11) pregnancy (women of child bearing potential must be tested); (12) history or current evidence suggestive of venous or arterial thrombotic events, including deep vein thrombosis, pulmonary emboli, cerebral vein thrombosis, cerebrovascular accident; (13) history of hypersensitivity to TA; and (14) history of acquired color blindness or visual vascular problems.

Informed consent was obtained from patients or their relative or representative. Initial brain CT scan was done immediately after admission and routine care. The baseline data including demographic data, mechanism of injury, and findings of initial brain CT scan (especially ICH volume) were entered. Then, included patients were randomized to get either the intervention or placebo treatment based on a computer-generated code list (40 patients in each group). Multiplicity adjustment was also done regarding to age, gender, and systolic blood pressure. All patients received a conservative treatment for ICH, and either intravenous TA (a bolus of 1 g in 100 ml 0.9% NaCl over 10 min followed by a continuous infusion of 1 g in 500 ml 0.9% NaCl over 8 h) or unobvious placebo.

The extent of ICH growth as the primary outcome at 48 h after admission was measured by brain CT scan. We estimated a 60% rate of ICH growth in placebo patients, according to the previous studies. We planned to randomize 80 patients, 40 to each group. This trial would have about 80% power at the 0.05 level of significance (two-sided test) to distinguish a significant increase in hemorrhage volume in both groups.

An emergency medicine specialist who was blind to treatment allocation and clinical findings evaluated the first and second scans. Both baseline and 48 h ICH volumes were compared between treatment and placebo groups adjusted for baseline volume. Any intraventricular hemorrhage components were excluded in ICH volumes.

Results

We recruited 80 patients (40 allocated to TA and 40 allocated to placebo) in 2014. Baseline characteristics of the included patients are shown in Table 1. Brain CT scan taken at 48 h after TBI showed a significant increase in hemorrhage volume in both groups (p < 0.001). But the increased ICH volume in the TA group was significantly less than that in the control group (p = 0.04, Table 2). The mean total hemorrhage expansion was (1.7 ± 9.7) ml and (4.3 ± 12.9) ml in the TA and placebo groups, respectively (p < 0.001).

### Table 1
Baseline characteristics of patients with ICH who were allocated to TA or placebo groups.

| Characteristics | TA (n = 40) | Placebo (n = 40) | p value |
|-----------------|-------------|-----------------|---------|
| Gender*         |             |                 | 0.30    |
| Male            | 32 (40.0)   | 28 (35.0)       |         |
| Female          | 8 (10.0)    | 12 (15.0)       |         |
| Age: mean ± SD (years) | 35.4 ± 14.6 | 36.2 ± 14.9        | 0.79    |
| Systolic blood pressure (mmHg) | 160.1 ± 21.3 | 161.9 ± 18.1 | 0.68    |
| Initial ICH volume (ml) | 21.6 ± 5.37 | 22.2 ± 4.9  | 0.83    |
| ICH type*       |             |                 | 0.83    |
| Epidural hematoma | 6 (7.5)    | 6 (7.5)         |         |
| Subdural hematoma | 6 (7.5)    | 8 (10.0)        |         |
| Cerebral hematoma | 28 (35.0)  | 26 (32.5)       |         |
| Hospital stay days* | <15       | 28 (35.0) |         |
|                 | 15–30       | 22 (27.4)       |         |
|                 | >30         | 9 (11.3)        |         |

Note: ICH: intracranial hemorrhage; TA: tranexamic acid. *: Data are expressed as n (%).

### Table 2
Effect of TA on total hemorrhage expansion in the patients with ICH in two groups.

| Group       | ICH volume (ml) | p value |
|-------------|-----------------|---------|
|             | Initial | After 48 h | Expansion |
| TA          | 21.6 ± 5.37    | 23.3 ± 6.4 | 1.7 ± 9.7 |
| Placebo     | 22.2 ± 4.9     | 26.5 ± 6.4 | 4.3 ± 12.9 |

Note: ICH: intracranial hemorrhage; TA: tranexamic acid.

Discussion

Our study showed that TA could reduce ICH growth after TBI. Other studies demonstrated reduction in ICH progression, too.6,8,11,12 The release of thromboplastin after TBI is followed by the activation of the coagulation and fibrinolytic pathways.13 Increased fibrinolysis, distinguished by high levels of fibrinogen degradation products, is a main cause of coagulopathy in TBI, raising the probability that TA can decrease traumatic ICH.14 Therefore, the earlier TA is administered, the more likely it will stop complete activation of fibrinolysis.15

On the other hand, other studies demonstrated no improvement of clinical outcomes in TBI patients with TA.3,11 CRASH-2 collaborators although reported that TA significantly reduced all-cause mortality,7 in a subgroup analysis of traumatic ICH patients, TA showed non-significant trend to reduce mortality or dependency.7 They found that neither moderate benefits nor moderate harmful effects of TA can be excluded after TBI. Also, Harvey et al16 showed that there was no evidence of TA benefit in TBI patients. Valle et al17 reported that TA increased mortality in high injury acuity patients which can probably be attributed to the rapid availability of fluids and emergency operative interventions at the trauma centers.

In our study, the patients in TA group received two doses of TA (a bolus and a continuous infusion) as soon as possible after admission and routine care. The timing of TA administration and the existing status of the coagulation system (anticoagulation or procoagulation state) would determine whether thromboembolism formation is prevented or facilitated.18 Gruen and Mitrail confirmed that the benefit was only seen when TA was administered within 3 h of injury. Also, Lipsky et al19 reported that sooner administration of TA improved the survival further. Valle et al17 reported that mortality associated with TA was influenced by the timing of administration. In the present study, there was not any side effect of TA administration. Robert et al20 confirmed the safety of TA in a wide spectrum of patients with traumatic bleeding, even the most severely injured. A study showed that TA had no significant...
increase in serious prothrombotic complications if administered within 3 h of injury.\textsuperscript{10} Zehtabchi et al\textsuperscript{15} declared the use of TA was not associated with significant (clinically or statistically) increase in the possibility of thromboembolic events compared with placebo or standard therapy in TBI.

There are some limitations that must be considered. This study was a single-blinded trial, whereas a double or triple-blinded trial would be more accurate. Meanwhile, the time period between trauma occurrence and TA administration had to be considered more precisely. Further, markers of coagulopathy were not measured. In conclusion, it has established that TA as an effective hospital-based treatment for acute TBI could reduce ICH growth. Larger studies are needed to compare the effectiveness of different doses.

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