—Case Reports—

Effect of Tranexamic Acid for Traumatic Brain Injury: A Case Report

Toru Miike, Yuichiro Sakamoto and Satoshi Inoue

Center for Emergency and Critical Care Medicine, Saga University Hospital, Saga, Japan

Traumatic brain injury (TBI) often results in coagulopathy, which increases mortality risk. The Clinical Randomization of an Antifibrinolytic in Significant Head injury (CRASH)-2 and CRASH-3 trials confirmed that tranexamic acid (TXA) was effective after trauma. Herein, we report a unique coagulation change in a patient with TBI given TXA after point-of-care assessment. Coagulation functions were impaired on admission. At 1 hour after TXA administration, clotting time was further prolonged in the extrinsic coagulation pathway but shortened in the intrinsic coagulation system. The results of a test of the total thrombus-formation analysis system showed improved blood clot formation ability. Intrinsic coagulation and clot formation improved after TXA administration in a TBI patient with coagulopathy. (J Nippon Med Sch 2020; 87: 227–232)

Key words: traumatic brain injury, tranexamic acid, coagulation function

Introduction

Coagulopathy is related to poor prognosis in trauma patients[1]. Traumatic brain injury (TBI) frequently causes coagulopathy[2], which is associated with increased mortality and worse neurological outcomes[3]. The Clinical Randomization of an Antifibrinolytic in Significant Head injury (CRASH)-2 trial confirmed the effectiveness and safety of tranexamic acid (TXA) for trauma patients[4], and the CRASH-3 trial showed that mortality risk related to head injury was reduced after TXA administration in patients with mild-to-moderate head injury[5].

TXA inhibits fibrinolysis by binding to plasminogen and plasmin, thus preventing collapse of the hemostasis mechanism. In addition to its use in trauma patients, TXA has been used in cardiovascular surgery[6], orthopedic surgery[7], pediatric surgery[8], and obstetrics/gynecology[9] and was reported to be effective in controlling intraoperative bleeding. Despite evidence regarding the effect of antifibrinolytic agents on hemostasis, such as that reported in CRASH-2 and CRASH-3, the mechanism by which TXA induces hemostasis is not well understood. No study has reported that hyperfibrinolysis is present in all patients with successful clinical outcomes after TXA administration. Moreover, a previous study utilizing an animal model of TBI did not show that TXA affects intrinsic or extrinsic coagulation functions[10]. Herein, we report a newly discovered coagulation change in a TBI patient given TXA after point-of-care assessment.

Case Presentation

While cycling, a healthy 87-year-old Japanese man was struck by a car traveling at a speed of 40 km/h. A doctor at the accident scene was unable to intubate the trachea and therefore performed cricothyroidotomy and inserted an intravenous line. The patient was transported to the hospital by ambulance, and his Glasgow Coma Scale score on admission was 3 (1 = eye opening, T = verbal, 1 = motor). He presented with anisocoria (right > left), and his cardiopulmonary status was physiologically stable, as there were no severe injuries other than head trauma. After a blood sample was collected, TXA 1 g was administered by intravenous bolus injection 1 hour after the injury, after infusion of 100 mL of Lactated Ringer's solution. A cranial CT scan revealed acute subdural hematoma, diffuse brain injury, and severe secondary brain injury caused by hypoxia and intracranial hypertension (**Fig. 1**). The patient was taken to the operating room for emergency surgery. Another blood sample was collected at 1 hour after TXA administration, and before surgery, when the patient received about 300 mL of intravenous

Correspondence to Toru Miike, MD, PhD, Assistant Professor, Department of Emergency and Critical Care Medicine Faculty of Medicine, Saga University, 5–1–1 Nabeshima, Saga, Saga 849–8501, Japan
E-mail: miike@cc.saga-u.ac.jp
https://doi.org/10.1272/jnms.JNMS.2020_87-409
Journal Website (https://www.nms.ac.jp/sh/jnms/)

Lactated Ringer's solution. No blood-derived products were given to the patient during this interval. Craniotomy was performed for removal of hematoma and cerebral decompression; however, overwhelming brain edema resulted in death, which was confirmed at 30 hours after the injury.

Past History and Medication

Gastric ulcer treated with rabeprazole sodium; no other significant medical history.

Results of Blood Testing

Blood collected from the patient on admission showed a low fibrinogen level, normal platelet count, and abnormally high levels of some biological markers, including metabolites produced by the activated coagulation/ fibrinolysis system (**Table 1**).

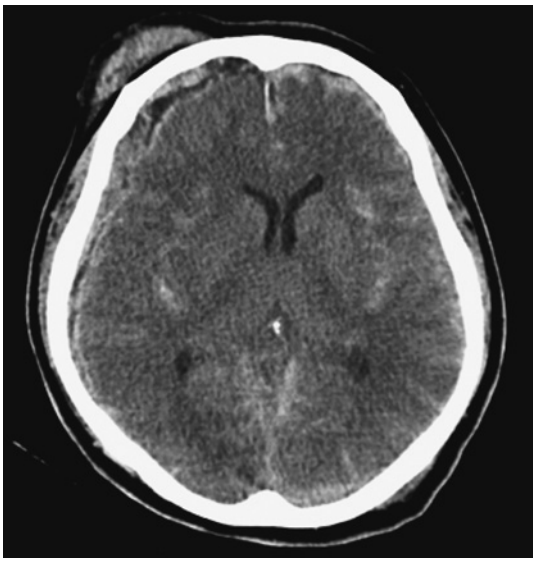

Fig. 1 Cranial computed tomography scan showing acute subdural hematoma with a midline shift and brain contusions.

Rotational Thromboelastometry

Rotational thromboelastometry (ROTEM delta; Tem International GmbH, Munich, Germany) is a point-of-care test used to evaluate blood viscosity[11]. Data obtained from the ROTEM channels INTEM, EXTEM, and FIBTEM reflect the intrinsic coagulation system, extrinsic coagulation system, and fibrin polymerization ability, respectively; APTEM can be used to identify hyperfibrinolysis. The results of ROTEM analysis of blood samples collected immediately before and 1 hour after TXA administration are shown in **Figure 2**. At admission, intrinsic and extrinsic coagulation were impaired, and fibrin polymerization ability was greatly impaired. At 1 hour after TXA administration, EXTEM showed further prolongation of clotting time and diminished clot firmness. INTEM showed shortening of clotting time but no change in clot firmness. There was little change in APTEM, as compared with EXTEM, which suggests the absence of hyperfibrinolysis.

Thromboelastography

Thromboelastography (TEG6s; Haemoscope Corporation, Niles, IL, USA) is a point-of-care device that, like ROTEM, can evaluate the viscosity of whole blood. The TEG6s device can be used to measure kaolin (CK: citrated kaolin), rTEG (CRT: citrated rapid TEG), functional fibrinogen (CFF: citrated functional fibrinogen), and kaolin with heparinase (CKH: citrated kaolin with heparinase). CK is influenced by the intrinsic coagulation system, CRT reflects intrinsic and extrinsic coagulation function, CFF represents fibrin polymerization ability,

Table 1 Laboratory findings

Test	Result	Normal value
Hematocrit	37.5	36.0-48.0%
Lactate	2.3	0.5-1.6 mmol/L
Platelet	233	131-362 10^3/mm
Fibrinogen	0.69	2-4 g/L
Prothrombin time	62	70-130%
Partial thromboplastin time	93.9	70-130%
FDP	735.4	0-5 μg/mL
D-dimer	326.4	0-1 μg/mL
PIC	59.4	0-0.8 μg/mL
TAT	2,373	<3.0 ng/mL

Low fibrinogen level and abnormally high levels of biological markers.
FDP: fibrin degradation product
PIC: plasmin-α2-plasmin inhibitor complex
TAT: thrombin-antithrombin complex

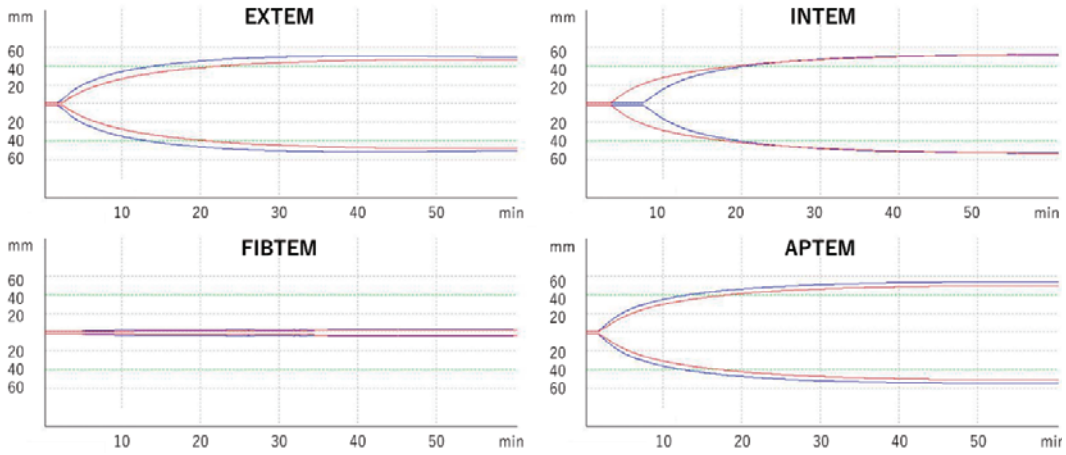

Fig. 2 Rotational thromboelastometry measurement
Time-course (x-axis) and clot firmness (y-axis). The graphs show the results of measurements before (blue line) and after (red line) TXA administration. INTEM showed that TXA shortened clotting time; no significant changes were seen in other parameters.
TXA: tranexamic acid

Table 2 Thromboelastography measurement

TEG6s	R (min)	K (min)	Angle (deg)	MA (mm)	LY30 (%)
CK (Pre TXA)	6.8	3.3	40	50.3	0
CK (Post TXA)	3.7	6	38	48.2	0
CRT (Pre TXA)	1.4	2.9	57.8	49.1	0
CRT (Post TXA)	2.1	3.3	62.2	45.9	0
CKH (Pre TXA)	7.6	3.1	44.7	49.2	
CKH (Post TXA)	3	6.2	36.9	48.8	
CFF (Pre TXA)				10.7	
CFF (Post TXA)				12.6	

Clotting time of CK was shortened after TXA administration. There was a gradual decline in clot firmness of CK.
TXA: tranexamic acid CK: citrated kaolin
CRT: citrated rapid TEG CKH: citrated kaolin with heparinase
CFF: citrated functional fibrinogen

and CKH is used to exclude the possible effects of heparin and heparinoid. CRT testing showed prolongation of clotting time and decreased clot firmness after TXA administration (**Table 2**). However, the clotting time of CK was shorter after TXA administration, as indicated by the INTEM channel of ROTEM. The decline in clot firmness of CK was gradual. CKH testing, in which heparinase is added to the sample, yielded results similar to those obtained for CK.

The Total Thrombus-formation Analysis System

The total thrombus-formation analysis system device (T-TAS; Fujimori Kogyo Co., Ltd., Japan) allows whole blood to flow through collagen and artificial blood vessels coated with tissue factor and measures pressure from the start of thrombus formation until occlusion. A pump is used to force blood into the artificial vessel. The process of thrombus formation is similar to that present in vivo, and the T-TAS device is better than other devices for investigating the process of thrombus formation. T-TAS results before and after TXA administration are shown in **Figure 3**. The time until the start of occlusive thrombus formation decreased from 573 seconds to 410 seconds, and thrombotic occlusion time decreased from 689 seconds to 508 seconds.

Discussion

After a head injury, breakdown of the blood-brain barrier causes an influx of brain tissue factor into the blood stream, which results in activation of factor VII and overreaction of the coagulation cascade[12]. Depletion of coagu-

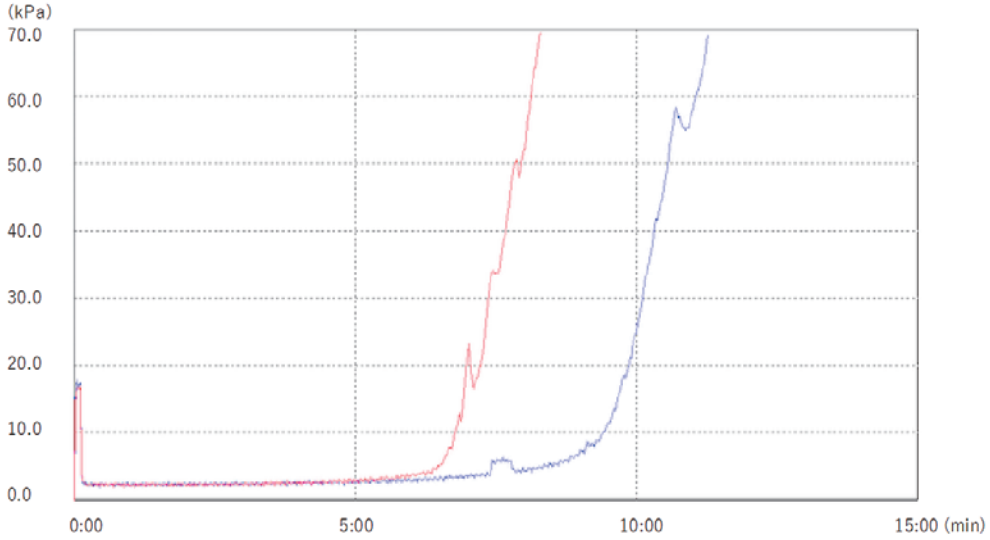

Fig. 3 Measurement of thrombus formation with a total thrombus-formation analysis system
Time-course (x-axis) and pressure measurements (y-axis). The graph shows measurements before (blue line) and after (red line) TXA administration. Thrombotic occlusion time was decreased from 689 seconds to 508 seconds by TXA administration, suggesting that TXA improved clot formation ability.
TXA: tranexamic acid

Table 3 Characteristics of patients who underwent ROTEM measurement before and after TXA administration

Case	Situation	Cranial CT findings	GCS	Severity of head trauma	Clotting time of INTEM (Before TXA → After TXA)	Percentage change in Clotting time of INTEM	Outcome
1	Traffic accident	Brain contusion	E1VTM1	severe	440 → 196 (sec)	56%	Dead
2	Fall	Brain contusion	E3V3M5	moderate	130 → 116 (sec)	11%	Survived
3	Traffic accident	Traumatic-SAH AEDH	E4V4M6	mild	309 → 285 (sec)	8%	Survived

Case 1 is the present patient. The clotting time of the intrinsic coagulation system was also shortened in two previously reported cases (cases 2 and 3).
CT: computed tomography GCS: Glasgow coma scale
SAH: subarachnoid hemorrhage AEDH: acute epidural hematoma
TXA: tranexamic acid

lation factor, caused by the excessive coagulation reaction and subsequent platelet dysfunction[13], results in progressive hemorrhagic injury and worse outcomes[14].

In our patient, ROTEM showed declines in intrinsic and extrinsic coagulation ability and fibrin polymerization ability. The TEG6s assay revealed a decline in extrinsic coagulation ability and fibrin polymerization ability and absence of effects by heparin and heparinoid. Levels of fibrin/fibrinogen degradation products and D-dimer were abnormally high, suggesting that blood clots had formed in the vessel and that thrombolysis occurred later. Thus, coagulopathy at admission was likely attributable to depletion of coagulation factor caused by over-reaction of the coagulation cascade. Abnormally high levels of plasmin-α2 plasmin inhibitor complex and thrombin-antithrombin complex were confirmed in this observation. At 1 hour after TXA administration, clotting time for the extrinsic coagulation pathway was further prolonged and intrinsic clotting time was shortened.

Two other TBI patients have undergone ROTEM analysis, as shown in **Table 3**; one had mild TBI, and the other had moderate TBI. The data showed a shortening of clotting time in the intrinsic coagulation system in both cases, without improvement in the extrinsic coagulation system. TXA was given 1 hour after the injury, and blood samples were collected at 1 hour after TXA administra-

tion. The tendency—ie, shortening of clotting time in the intrinsic coagulation system—was very similar to that in severe cases. On the basis of these findings, we presume that the improvement in intrinsic coagulation function by TXA was reproduceable. However, the shortening of clotting time in the intrinsic coagulation system is difficult to explain, in light of the course of extrinsic coagulation. TXA administration may improve intrinsic coagulation in TBI patients after depletion of clotting factor. To our knowledge, this finding has not been reported previously. TXA may have both a simple fibrinolysis suppressant effect and an inhibitory effect on coagulation consumption. Coagulation factors such as kallikrein, factor XII, factor XI, factor IX, factor VIII, and von Willebrand factor (which stabilizes factor VIII) have specific effects on intrinsic coagulation. When factors are replenished or depletion is suppressed, intrinsic coagulation is improved. However, the direct effect of TXA on these factors has not been reported. Although several studies examined the antifibrinolytic effect of TXA[15], its effect on coagulation factors is poorly understood. TXA has anti-inflammatory effects believed to be caused by direct or indirect inhibition of the kinin system[16], and a recent study reported that TXA administration inhibited bradykinin[17]. Kallikrein, which activates factor XII, produces bradykinin by breaking down high-molecular-weight kininogen. Therefore, TXA might suppress factor XII activation by inhibiting kallikrein upstream of the kallikrein-kinin system, thus resulting in reduced depletion of intrinsic coagulation factor. The shortened clotting time of the intrinsic coagulation system observed by the TEG6s assay might be attributable to preservation of intrinsic coagulation factor.

Several previous studies demonstrated the utility of point-of-care devices in trauma settings[18]. Schöchl et al reported that depletion of intrinsic coagulation factor had the best predictive value for mortality in TBI patients[19]. Therefore, administration of TXA to improve the intrinsic coagulation system might be a promising treatment option in improving clinical outcomes of patients with severe TBI.

In this study, ROTEM and TEG revealed that intrinsic coagulations systems, but not extrinsic pathways, were improved by TXA administration. These findings have not been reported previously. Therefore, the most important mechanism in clot formation is difficult to identify. Thus, we focused on the results of T-TAS because T-TAS is a clot formation analysis device that incorporates artificial blood vessels in its system, as mentioned above. It can evaluate hemostasis ability itself by using whole-blood samples, regardless of any related mechanisms involved. Most importantly, although further studies of the mechanism by which TXA administration induces thrombus formation are warranted, T-TAS clearly showed a significant improvement in clot formation ability after TXA treatment in a patient with TBI.

Conclusions

The present report showed improvements in intrinsic coagulation functions and clot formation ability after TXA administration in a TBI patient with coagulopathy, as confirmed by multiple point-of-care testing devices.

Conflict of Interest: The authers declare no conflict of interest.

References

1. Brohi K, Singh J, Heron M, Coats T. Acute traumatic coagulopathy. J Trauma. 2003;54:1127–30.
2. Harhangi BS, Kompanje EJ, Leebeek FW, Maas AI. Coagulation disorders after traumatic brain injury. Acta Neurochir (Wien). 2008;150:165–75.
3. Allard CB, Scarpelini S, Rhind SG, et al. Abnormal coagulation tests are associated with progression of traumatic intracranial hemorrhage. J Trauma. 2009;67:959–67.
4. CRASH-2 trial collaborators. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial. Lancet. 2010;376: 23–32.
5. CRASH-3 trial collaborators. Effects of tranexamic acid on death, disability, vascular occlusive events and other morbidities in patients with acute traumatic brain injury (CRASH-3): a randomised, placebo-controlled trial. Lancet. 2019;394:1713–23.
6. Henry DA, Carless PA, Fergusson D, Laupacis A. The safety of aprotinin and lysine-derived antifibrinolytic drugs in cardiac surgery: a metaanalysis. CMAJ. 2009;180: 183–93.
7. Kagoma YK, Crowther MA, Douketis J, Bhandari M, Eikelboom J, Lim W. Use of antifibrinolytic therapy to reduce transfusion in patients undergoing orthopedic surgery: a systematic review of randomized trials. Thromb Res. 2009;123:687–96.
8. Schouten ES, van de Pol AC, Schouten AN, Turner NM, Jansen NJ, Bollen CW. The effect of aprotinin, tranexamic acid, and aminocaproic acid on blood loss and use of blood products in major pediatric surgery: a meta-analysis. Pediatr Crit Care Med. 2009;10:182–90.
9. Ferrer P, Roberts I, Sydenham E, Blackhall K, Shakur H. Anti-fibrinolytic agents in post partum haemorrhage: a systematic review. BMC Pregnancy Childbirth. 2009;9:29.
10. Boudreau RM, Johnson M, Veile R, et al. Impact of tranexamic acid on coagulation and inflammation in murine models of traumatic brain injury and hemorrhage. J Surg Res. 2017;215:47–54.
11. Koami H, Sakamoto Y, Miyasho T, et al. Haptoglobin reduces inflammatory cytokine INF-γ and facilitates clot formation in acute severe burn rat model. J Nippon Med

Sch. 2017;84:64–72.
12. Hoffman M, Monroe DM. Tissue factor in brain is not saturated with factor VIIa: implications for factor VIIa dosing in intracerebral hemorrhage. Stroke. 2009;40:2882–4.
13. Castellino FJ, Chapman MP, Donahue DL, et al. Traumatic brain injury causes platelet adenosine diphosphate and arachidonic acid receptor inhibition independent of hemorrhagic shock in humans and rats. J Trauma Acute Care Surg. 2014;76:1169–76.
14. Zhang D, Gong S, Jin H, et al. Coagulation parameters and risk of progressive hemorrhagic injury after traumatic brain injury: A systematic review and meta-analysis. BioMed Research Int. 2015;2015:261825.
15. Shore-Lesserson L, Reich DL, Vela-Cantos F, Ammar T, Ergin MA. Tranexamic acid reduces transfusions and mediastinal drainage in repeat cardiac surgery. Anesth Analg. 1996;83:18–26.
16. Yamasaki H, Tsuji H, Kitamura M. [Anti-inflammatory effect of the antiplasmin agents, epsilon-aminocaproic acid (EACA) and trans-4-aminomethylcyclohexanecarboxylic acid (AMCHA) in rats]. Nihon Yakurigaku Zasshi. 1967; 63:560–71. Japanese.
17. Kuriyama S, Nakayama M, Tomonari H, Kawaguchi Y, Hosoya T. Tranexamic acid increases peritoneal ultrafiltration volume in patients on CAPD. Peritoneal Dialysis International. 1999;19:38–44.
18. Tauber H, Innerhofer P, Breitkopf R, et al. Prevalence and impact of abnormal ROTEM(R) assays in severe blunt trauma: results of the 'Diagnosis and Treatment of Trauma-Induced Coagulopathy (DIA-TRE-TIC) study'. J Anaesth. 2011;107:378–87.
19. Schöchl H, Solomon C, Traintinger S, et al. Thromboelastometric (ROTEM) findings in patients suffering from isolated severe traumatic brain injury. J Neurotrauma. 2011; 28:2033–41.

(Received, December 3, 2019)
(Accepted, March 26, 2020)
(J-STAGE Advance Publication, April 30, 2020)