The efficacy of tranexamic acid treatment with different time and doses for traumatic brain injury: a systematic review and meta-analysis

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Abstract

Objective: Tranexamic acid (TXA) has been shown to play a significant role in the treatment of trauma diseases. However, its effectiveness in patients with traumatic brain injury (TBI) seems to be contradictory according to the recent publication of several meta-analyses. We aim to determine the efficacy of TXA treatment with different time and doses for TBI.

Methods: PubMed, MEDLINE, EMBASE, Cochrane library and Google scholar were searched for randomized (RCT) that compared TXA and placebo in adults and adolescents (≥ 15 years of age) with TBI, up to January 31, 2022. Two authors independently abstracted data and assessed the quality of evidence.

Results: Of the identified 673 studies, 13 trials involving 18,675 patients met our inclusion criteria. TXA had no effect on mortality (RR 0.99; 95% CI 0.92–1.06), adverse events (RR 0.93, 95% CI 0.76–1.14), severe TBI (Glasgow Coma Scale score from 3 to 8) (RR 0.99, 95% CI 0.94–1.05), unfavorable Glasgow Outcome Scale (GOS <4) (RR 0.96, 95% CI 0.82–1.11), neurosurgical intervention (RR 1.11, 95% CI 0.89–1.38), or new bleeding (RR 0.97, 95% CI 0.82–1.16). TXA might reduce mean hemorrhage volume on subsequent imaging (SMD -0.35; 95% CI [-0.62, -0.08]).

Conclusion: TXA at different times and doses was associated with reduced mean bleeding, but not with mortality, adverse events, neurosurgical intervention and new bleeding. We need more research data on different detection indexes and levels of TXA in patients with TBI, as compared to those not receiving TXA although the prognostic outcome for all harm outcomes was no effect, did not rule out the potential for harm.

Trial registration

The review protocol was registered in the PROSPERO International Prospective Register of Systematic Reviews (CRD42022300484).

1 Introduction

Traumatic brain injury (TBI) is an organic injury of brain tissue caused by outside violence^[1]. The global incidence rate of TBI is estimated as 50%, leading to more than 2.5 million disabilities or death per year^[2]. The high mortality in TBI may be closely related to its complex pathophysiology. TBI includes an initial head trauma via an external force that results in mechanical damage to brain tissue, and the subsequent biochemical cascades such as apoptosis, mitochondrial dysfunction, cortical spreading depression (CSD), and microvascular thrombosis^[3]. As a result, a series of nerve damage in differing proportions inevitably happens with various resultant clinical courses occurring during this process, including the intracranial hematoma, brain tissue contusion, cerebral ischemia^[4]. In particular, the intracranial hematoma in half of the patients enlarges after hospital admission, which increased the difficulty of surgical removal and leads to high mortality and disability^[5]. Currently, the treatment of TBI mainly involves hyperosmolar therapy, seizure prophylaxis, medically induced comatose state, invasive intracranial monitoring, and as a last resort to radical decompressive surgical interventions^[6]. These methods, except the surgical interventions, may achieve symptom relief in a short time but do not address the prognosis of TBI. Therefore, research on the treatment of this disease is still required, especially regarding the hemostatic drug designed to protect TBI.

Recently, tranexamic acid (TXA), a synthetic lysine derivative has been shown to play important roles in the treatment of trauma diseases^[7]. TXA exerts its hemostatic function by competitively occupying the lysine binding site of plasminogen, thereby blocking interaction with fibrin and subsequent clot breakdown^[8]. The extensive trial in severe trauma with massive bleedings using TXA have demonstrated that the survival was increased when TXA was given early after the accident compared to placebo^[9]. However, the role of TXA in patients with TBI or intracranial bleeding is controversial^[10]. With the recent publication of the TXA versus placebo trial, we performed this meta-analysis of all related articles to examine the prognostic of TXA in TBI patient.

2 Methods

This systematic review and meta-analysis were conducted based on the Cochrane Handbook for Systematic Reviews of Interventions^[11] and the “Preferred Reporting Items for Systematic Reviews and Meta-Analysis” recommendation^[12]. Two investigators have independently searched articles, extracted data, and assessed the quality of included studies.

2.1 Search Strategy

PubMed, MEDLINE, EMBASE, Cochrane library and Google scholar were searched for randomized (RCT) that compared TXA and placebo in adults and adolescents (≥ 15 years of age) with TBI, up to January 31, 2022. With the assistance of an expert medical librarian, we developed a search strategy, including three search terms: “tranexamic acid”, “traumatic brain injury” and “randomized controlled trial” (appendix 1–1). We also searched the proceedings of emergency medicine, hematology, trauma, neurology, and neurosurgery conferences to look for relevant presented abstracts.

2.2 Study Selection

We included all English literature on RCT in the treatment of TBI with TXA and performed meta-analysis. Our inclusion criteria were as follows: 1) studies conducted in TBI patients receiving any dose of TXA. 2) Patients with any type of intracranial hemorrhage secondary to TBI. The exclusion criteria were as follows: 1) preclinical study; 2) The research type is repeated report or published study is case report, review, or literature without control, focusing on surgical methods, surgical techniques and imported instruments; 3) study with nonclinical patients such as animals, corpses, or specimens; 4) non-English-language publications; and 5) study with repetitive.

2.3 Data extraction and quality assessment

Two authors independently abstracted data and assessed the quality of evidence. We extracted the following information from included studies^[13–25]: study author and years, study design, demographic data, ages and sexes of participants, details of the intervention, and risk of bias. We extracted the results of the included study as follow: mortality, severe TBI (Glasgow Coma Scale from 3 to 8), unfavorable Glasgow Outcome Scale (GOS < 4), neurosurgical intervention, mean hemorrhage volume, the number people of new bleeding, adverse events including vascular occlusive events, pulmonary embolism (PE), deep vein thrombosis (DVT), neurological complications (including stroke and seizure), gastrointestinal bleeding, myocardial infarction, infectious complications, renal failure. We used Cochrane Risk of Bias Assessment tool (Cochrane Collaboration) to assess the quality of the included trial and rate the level of evidence.

2.4 Statistical analysis

We used RevMan 5.3 software provided by Cochrane Collaboration Network for meta-analysis, and Stata 16.0 software to Harbord's test and Egger's test. Dichotomous data was measured by the risk ratio (RR) and a 95% CI. In this analysis, because the average blood loss unit in some literatures is inconsistent with that in other literatures, continuous variables were measured by Standardized Mean Difference (SMD) and a 95% CI. Heterogeneity among included studies was examined the chi-square and I^2 tests. When there was statistical homogeneity among the results ($P \geq 0.1$, $I^2 < 50\%$), the fixed effect model was used to continue the meta-analysis. If there is statistical heterogeneity among the research results ($P < 0.1$, $I^2 > 50\%$), the random effect model is used for meta-analysis. we did not construct funnel plots to assess for publication bias as these are inaccurate when less than ten trials are included in the analysis. The publication bias of the included studies was analyzed by Harbord's test and Egger's test.

3 Result

3.1 Literature search

According to the search strategy results, 1782 relevant articles were screened. After excluding duplications and other reasons, 673 articles remained. By reading the title and abstract, 547 articles were excluded, yielding 126 studies. Of these, full text was assessed, leading to the exclusion of another 113 studies, resulting in 13 studies that were included in the analysis^[13–25]. Studies were conducted in patients undergoing TBI patients. 18675 patients were included in our study. The baseline characteristics of the included literature are summarized in Table 1. The flowchart of the literature search strategy of studies was presented in Fig. 1.

Table 1
Baseline characteristics of included studies

study autor and years	study design	patients TXA/placebo	TXA dose	male(%)	Mean or median age in years TXA/placebo	Enrollment time after trauma	inclusion criterial	exclusion criterial
Roberts et al.2019	Multisite RCT	6406/6331	1g TXA bolus followed by 1g TXA maintenance	TXA: 3742 (80%) placebo: 3660 (80%)	TXA:41.7(19) placebo:41.9(19)	2h	(1) Adults with TBI within 3 h of injury (2) GCS $\leq$ 12 or any intracranial bleeding on CT scan	Major extracranial bleed
Rowell et al.2020	Multisite RCT	657/309	Bolus-Maintenance arm: 1g TXA bolus followed by 1g TXA. Bolus only arm: 2g TXA bolus followed by a placebo infusion	Bolus-Maintenance: 227(73%) Bolus-Only: 255(74%) placebo: 233(75%)	Bolus-Maintenance arm: 39(26–57) Bolus Only arm: 40(26–56) Placebo arm: 36(25–55)	2h	(1) GCS $\leq$ 12 (2) Prehospital SBP $\geq$ 90 (3) Age $\geq$ 15yrs (or weight $\geq$ 50 kg if age is unknown)	(1) GCS = 3 with unreactive pupil (2) CPR by EMS prior to randomization (3) Burns (4) Pregnancy
Mahmood et al.2021	Multisite RCT	884/883	1g TXA bolus followed by 1g TXA maintenance	TXA: 701(79%) placebo: 712(81%)	TXA:45(29–64) placebo: 45(29–63)	3h	(1) Adults with head injury who were within 3 hours of injury; (2) Glasgow Coma Score (GCS) of $\leq$ 12; (3) any intracranial bleeding on CT, and no significant extracranial bleeding	significant extracranial bleeding
van Wessem et al.2021	Single site RCT	120/114	1g TXA bolus followed by 1g TXA maintenance	TXA: 80(67%) placebo: 77(68%)	TXA:42 (23–59) placebo: 53 (33–65)	1h	TBI (AIS head $\geq$ 3) who were admitted to the adult ICU	AIS head scores based on isolated C-spine injuries
Mojallal et al.2020	Single site RCT	56/44	1g TXA bolus followed by 1g TXA maintenance	TXA: 40(71.4%) placebo: 40(90.9%)	N/A	8h	(1)age > 18. (2)detection of cerebral hemorrhage in brain CT scan (3)passage of less than 8 hours after trauma incidence (4)negative history of taking anticoagulants (5)negative history of blood coagulation system impairments	patients who underwent craniotomy less than 24 hours
Mousavinejad et al.2020	Single site RCT	20/20	1g TXA bolus followed by 1g TXA maintenance	TXA: 6(30%) placebo: 8(40%)	55 $\pm$ 19/55 $\pm$ 18	8h	(1) $\geq$ 18 years within 8 h of injury (2) TBI on brain CT with no significant epidural hemorrhage (3) The need for surgery	(1) Pregnancy (2) Coagulopathy (3) Massive transfusion and/or fresh frozen plasma (FFP)

RCT randomized-controlled trial, TXA tranexamic acid, GCS Glasgow Coma Scale, GOS Glasgow Outcome Scale, TBI traumatic brain injury, SDH subdural hemorrhage, EDH epidural hemorrhage, ICH intracranial hemorrhage, N/A not applicable

study autor and years	study design	patients TXA/placebo	TXA dose	male(%)	Mean or median age in years TXA/placebo	Enrollment time after trauma	inclusion criterial	exclusion criterial
Yutthakasemsunt et al.2013	Single site RCT	120/118	1g TXA bolus followed by 1g TXA maintenance	TXA: 103(86%) placebo: 107(91%)	35 (16)/ 34 (15)	8h	(1) Age $\geq$ 16 years (2) Moderate to severe TBI (GCS) 4 to 12 (3) Had a CT brain within 8 h (4) No immediate indication for surgery	(1) Immediate need for surgery (2) Coagulopathy (3) Known to be receiving a medication that affects hemostasis (4) Pregnancy
Fakharian et al.2017	Single site RCT	78/78	1g TXA bolus followed by 1g TXA maintenance	TXA: 67(90.5) placebo: 66(88)	42 $\pm$ 18/39 $\pm$ 18	8h	(1) Age $\geq$ 15 years (2) Non-penetrating injury and any kind of Traumatic ICH (3) Arrived at the hospital within 8 h 4) No need for brain surgery during the first 8 h	(1) Major organ damage (2) Pregnancy (3) Receiving any medication that disturbs homeostasis (4) Coagulopathy
Jokar et al.2017	Single site RCT	40/40	1g TXA bolus followed by 1g TXA maintenance	TXA: 32(40.0%) placebo: 28(35.0%)	35 $\pm$ 15/ 36 $\pm$ 145	2h	(1) TBI patients aged 15 years and more (2) Within 2 h of injury onset (3) Acute ICH (volume of less than 30 ml) based on CT scan findings	(1) GCS < 8 (2) Need for surgery (3) Cerebral edema with midline shift (4) Coagulation disorders (5) Pregnancy (6) History or current VTE
Ebrahimi et al.2019	Single site RCT	40/40	1g TXA bolus followed by 1g TXA maintenance	SDH-TXA: 17(85%) SDH-placebo: 17(85%) EDH-TXA: 16(80%) EDH-placebo: 18(90%)	SDH: 40 $\pm$ 18/40 $\pm$ 18 EDH: 24 $\pm$ 7/25 $\pm$ 7	8h	(1) Adults within 8 h of injury (2) Isolated SDH or EDH requiring surgery	(1). Major extracranial bleeding (2) Massive transfusion (3) Coagulopathy (4) Pregnancy

RCT randomized-controlled trial, TXA tranexamic acid, GCS Glasgow Coma Scale, GOS Glasgow Outcome Scale, TBI traumatic brain injury, SDH subdural hemorrhage, EDH epidural hemorrhage, ICH intracranial hemorrhage, N/A not applicable

study autor and years	study design	patients TXA/placebo	TXA dose	male(%)	Mean or median age in years TXA/placebo	Enrollment time after trauma	inclusion criterial	exclusion criterial
Perel et al.2012	Multisite RCT	133/137	1 g TXA bolus followed by 1 g TXA maintenance	TXA: 111(84.0) placebo: 117(85.0)	36.2 (14.0)/37.0 (13.7)	8h	1) Fulfils the inclusion criteria for the CRASH-2 trial (2) GCS $\leq$ 14 (3) Baseline clinical CT scan consistent with TBI	(1) Pregnancy and (2) Patients for whom a second brain CT scan was not possible
Bossers et al.2021	Multisite RCT	693/1134	1g TXA bolus followed by 1g TXA maintenance: 615 > 2g TXA bolus: 4	TXA: 486 (70%) placebo: 797 (70%)	47 (25–66)/45 (22–65)	N/A	1)severe TBI, GCS $\leq$ 8 2)suspected rather than confirmed TBI because prehospital treatment, including administration of tranexamic acid	1)BRAIN-PROTECT database who were not transported to a participating trauma center (no follow-up data were available) 2)undergoing prehospital traumatic cardiopulmonary resuscitation (inherently very high mortality, regardless of treatment)
chakroun et al.2018	Single site RCT	96/84	1g TXA bolus followed by 1g TXA maintenance	TXA: 88 (91.7%) placebo: 797 (70%)	44 $\pm$ 20/39 $\pm$ 18	8h	(1)age > 18. (2)intracranial bleeding in the first or the second brain CT-scan (3)a delay of management in the study centre under 24 h after trauma	1)significant extra cranial bleeding 2)TXA can improve outcome
RCT randomized-controlled trial, TXA tranexamic acid, GCS Glasgow Coma Scale, GOS Glasgow Outcome Scale, TBI traumatic brain injury, SDH subdural hemorrhage, EDH epidural hemorrhage, ICH intracranial hemorrhage, N/A not applicable								

3.2 Description of included studies

A total of 13 articles were included, including 8 single-site RCTs^[16–22, 25] and 5 multisite RCTs^[13–15, 23–24]. The minimum age of participants was greater than 15 years, which included adults and adolescents. The timing of TXA administration varied among studies: There were 5 trials whose post-traumatic registration time was less than 3h^[13–14, 16, 18, 21], 7 trials whose post-traumatic registration time was more than 3h^[15, 17, 19–20, 22, 23, 25], and 1 article did not clearly explain the registration time. In the included trials, the TXA dose was mostly similar, and the most common regimen was a loading dose of 1 g, followed by a maintenance dose of 1 g over 8 h^[13–25]. However, one trial was a loading dose of 2 g, followed by a maintenance dose of 2 g over 8 h^[14]. The risk of bias was lower in 8 articles and higher in 5 articles. the risk of bias of studies was presented in Fig. 2. Regression-based Harbord's test and Egger's test were not statistically significant for all outcomes (Table 2). Since the mean hemorrhage volume is continuous data, Harbord's test cannot be detected by us. Gastrointestinal bleeding (n = 2), myocardial infarction (n = 2), infection complications (n = 2) and renal failure (n = 1) were included in less relevant articles, so they were not tested.

Table 2
The risk of bias of studies

Outcomes	Heterogeneity (I^2), P-value	Harbord's test	Egger's test	number of studies
Mortality	48%, 0.04	0.4865	0.4832	10
severe TBI (GCS 3 to 8)	0%, 0.79	0.3983	0.3346	4
GOS $\leq$ 4	71%, 0.004	0.5533	0.5925	6
Neurosurgical Intervention	0%, 0.73	0.3403	0.3356	5
New bleeding	0%, 0.73	0.5421	0.5066	4
adverse event ^a	50%, 0.08	0.1543	0.2468	6
Vascular occlusive events	0%, 0.37	0.8878	0.9214	3
Pulmonary embolism	64%, 0.06	0.2980	0.7334	4
Deep vein thrombosis	0%, 0.60	0.6228	0.8206	4
Neurological complications	27%, 0.25	0.0328	0.0682	4
TBI Traumatic Brain Injury, GCS Glasgow Coma Scale, GOS Glasgow Outcome Scale				
^a indicates Vascular occlusive events + Pulmonary embolism + Deep vein thrombosis + Neurological complications				

3.3 Prognostic outcome

Ten articles^[13–14,16–20,22–24] reported the mortality of patients with traumatic brain injury treated with TXA and placebo. Meta-analysis showed that TXA was associated with reduced mortality (RR 0.99; 95% CI 0.92–1.06, Fig. 3), adverse events (RR 0.93, 95% CI 0.76–1.14, Fig. 4), severe TBI (Glasgow Coma Scale score from 3 to 8) (RR 0.99, 95% CI 0.94–1.05, Fig. 5), the unfavorable Glasgow Outcome Scale (GOS < 4) (RR 0.96, 95% CI 0.82–1.11, Fig. 6), neurosurgical intervention (RR 1.11, 95%CI 0.89–1.38, Fig. 7), or the number people of new bleeding (RR 0.97, 95%CI 0.82–1.16, Fig. 8). TXA may reduce mean hemorrhage volume on subsequent imaging (SMD – 0.35; 95% CI [-0.62, -0.08], Fig. 9).

3.4 Safety

We found similar rates of adverse events^[13–14, 16, 19, 23, 25] between those receiving and those not receiving TXA (RR 0.93, 95% CI 0.76–1.14). In order to understand the impact of TXA on different adverse events, we conducted an in-depth analysis of adverse events (Fig. 10). Pooled results demonstrated probably no increased risk of vascular occlusive events (RR 1.05, 95% CI 0.83–1.33), pulmonary embolism (RR 1.19, 0.46–3.10), deep vein thrombosis (RR 0.94, 95% CI 0.57–1.55), neurological complication (RR 0.97, 95% CI 0.70–1.30), gastrointestinal bleeding (0.66, 95% CI 0.40–1.11), myocardial infarction (RR 0.96 95% CI 0.52–1.77), infectious complication (RR 0.98, 95% CI 0.87–1.11), or renal failure (RR 1.18, 95% CI 0.88–1.57) in patients receiving, as compared to those not receiving TXA although confidence intervals for all harm outcomes were wide, and did not rule out the potential for harm.

3.5 Sensitivity and subgroup analysis

We performed a subgroup analysis of study design (multisite RCT or single site RCT), Enrollment time after trauma (< 3h or > 3h), and TXA dose (2g TXA bolus followed by a placebo infusion or 1g TXA bolus followed by 1g TXA maintenance). The analysis results are shown in Table 3. All subgroup analyses did not show differences in estimates or conclusions for any of the outcomes of interest appendix 1–2).

Table 3
Subgroup Analysis of TXA and placebo

	Mortality		Adverse Events		Neurosurgical Intervention		New bleeding		Mean hemorrhage volume	
	RR, 95%	P- Value	RR, 95%	P- Value	RR, 95%	P- Value	RR, 95%	P- Value	RR, 95%	P- Value
Study design										
Multisite RCT	0.99	0.90	0.91	0.38	1.01	0.96	0.81	0.17	-0.08	0.52
	[0.79– 1.24]		[0.73– 1.13]		[0.61– 1.55]		[0.59– 1.10]		[-0.32, 0.16]	
Single site RCT	1.03	0.88	1.07	0.90	1.15	0.29	1.65	0.88	-0.46	0.0005
	[0.73– 1.43]		[0.39– 2.88]		[0.89– 1.48]		[0.94– 2.89]		[-0.72, -0.20]	
Enrollment time after trauma										
< 3h	0.94	0.15	0.91	0.28	1.18	0.24	0.91	0.34	-0.50	0.03
	[0.87– 1.02]		[0.77– 1.08]		[0.89– 1.55]		[0.75– 1.10]		[-0.94, -0.05]	
> 3h	0.76	0.15	2.45	0.07	1.00	0.99	1.14	0.64	-0.33	0.05
	[0.51– 1.11]		[0.92– 6.52]		[0.70– 1.44]		[0.65– 2.02]		[-0.65, 0.00]	
TXA dose										
2g TXA bolus followed by a placebo infusion	0.80	0.22	1.22	0.28	N/A	N/A	1.24	0.17	N/A	N/A
	[0.56– 1.15]		[0.85– 1.74]				[0.91– 1.70]			
1g TXA bolus followed by 1g TXA maintenance	1.01	0.95	1.00	0.97	N/A	N/A	1.00	1	N/A	N/A
	[0.82– 1.24]		[0.92– 1.08]				[0.71– 1.41]			
N/A not applicable										

We divided the study design into single site RCT^[16–22, 25] and multisite RCT^[13–15, 23–24]. TXA had no effect on mortality (RR 0.99, 95% CI 0.79–1.24, P 0.90), adverse event (RR 0.91, 95% CI 0.73–1.13, P 0.38), neurosurgical Intervention (RR 1.01, 95% CI 0.61–1.55, P 0.96), new bleeding (RR 0.81, 95% CI 0.59–1.10, P 0.17), or mean hemorrhage volume (RR -0.08, 95% CI [-0.32, 0.16], P 0.52) in multisite RCT, respectively. TXA had no effect on mortality (RR 1.03, 95% CI 0.73–1.43, P 0.88), adverse event (RR 1.07, 95% CI 0.39–2.88, P 0.90), neurosurgical Intervention (RR 1.15, 95% CI 0.89–1.48, P 0.29), new bleeding (RR 1.65, 95% CI 0.94–2.89, P 0.88), or mean hemorrhage volume (RR -0.46, 95% CI [-0.72, 0.20], P 0.0005) in single site RCT, respectively.

We observed the effect of TXA on prognostic according to enrollment time after trauma. When enrollment time after trauma is less than 3h^[13–14, 16, 18, 21], TXA had no effect on mortality (RR 0.94, 95% CI 0.87–1.02, P 0.15), adverse event (RR 0.91, 95% CI 0.77–1.08, P 0.28), neurosurgical Intervention (RR 1.18, 95% CI 0.89–1.55, P 0.24), new bleeding (RR 0.91, 95% CI 0.75–1.10, P 0.34), or mean hemorrhage volume (RR -0.50, 95% CI [-0.94, 0.05], P 0.03), respectively. When enrollment time after trauma is greater than 3h^[15, 17, 19–20, 22, 23, 25], TXA had no effect on mortality (RR 0.76, 95% CI 0.51–1.11, P 0.15), adverse event (RR 2.45, 95% CI 0.92–6.52, P 0.07), neurosurgical Intervention (RR 1.00, 95% CI 0.70–1.44, P 0.99), new bleeding (RR 1.14, 95% CI 0.65–2.20, P 0.34), mean hemorrhage volume (RR -0.33, 95% CI [-0.65, 0.00], P 0.05), respectively.

Different doses of TXA had no effect on adverse events. TXA^[14] had no effect on mortality (RR 0.80, 95% CI 0.56–1.15, P 0.22), adverse event (RR 1.22, 95% CI 0.85–1.74, P 0.28), or new bleeding (RR 1.24, 95% CI 0.91–1.70, P 0.17) in 2g TXA bolus followed by a placebo infusion, respectively. TXA^[13–25] had no effect on mortality (RR 1.01, 95% CI 0.82–1.24, P 0.95), adverse event (RR 1.00, 95% CI 0.92–1.08, P 0.97), or new bleeding (RR 1.00, 95% CI 0.71–1.41, P 1) in 1g TXA bolus followed by 1g TXA maintenance, respectively.

4 Discussion

TBI is a serious threat to human health and have attracted much research interest due to the high mortality rate^[26]. However, due to the complex pathophysiology, the treatment of TBI has posed a problem for clinicians and researchers^[27]. Recently, TXA, a new hemostatic drug, have been shown to play an important role in the treatment of TBI. However, the efficacy of TXA at different times and doses is still unclear. We will discuss hemostatic effect, mortality, and adverse events in TBI patients treated with TXA compared with placebo in different time and doses.

4.1 Hemostatic effect of TXA with respect to time and dose

Post-TBI coagulation disorders can be affected by progressive hemorrhagic injury (PHI) and intracranial hemorrhage (ICH), especially in patients with brain parenchyma contusion^[28]. Laboratory manifestations of fibrinolysis are associated with PHI, poorer outcomes, and the need for neurosurgical intervention. Furthermore, secondary infection after hemorrhage is also one of the factors promoting the death of patients^[29]. The effect of TXA with antifibrinolytic and somehow anti-inflammatory properties on avoiding the progression of hemorrhage volume and controlling its associated inflammation in traumatized patients.

This meta-analysis demonstrated that TXA had no effect on new bleeding, but reduce mean hemorrhage volume on subsequent imaging. This result is different from some previous researches, which indicated that TXA can inhibit rebleeding after TBI, and the possible benefits of TXA appear in specific populations^[30, 31]. For example, patients with moderate and severe hypertension might achieve a better inhibit effect on rebleeding using TXA. Due to the lack of data related to blood pressure, we cannot analyze it in depth.

Our subgroup analysis showed that the timing and dose of TXA did not become a risk factor for new bleeding. The result of mean hemorrhage volume was consistent with CRASH-2 trial^[32]. This is different from other study conclusions, which believe that TXA is easy to cause rebleeding due to massive activation of fibrinogen^[33]. Our subgroup analysis showed that the timing of TXA administration within 3 hours after injury could reduce mean hemorrhage volume, but had no effect beyond 3 hours after injury. Therefore, the timing of TXA administration is one of the factors affecting the hemostatic effect.

4.2 Mortality after the treatment of TXA with respect to time and dose

This meta-analysis demonstrated that TXA had no obvious effect on mortality. This is in discordance with other meta-analysis performed at an earlier stage. Some studies have demonstrated a reduction in mortality with TXA^[34]. However, the latest study believed that they did not include the latest data, and analyzed all patients enrolled in the CRASH-2 trial, including those with TBI and extracranial traumatic injuries^[35]. Our conclusions are consistent with the latest study results. Current perspectives performed that the efficacy of TXA may depend on the severity of TBI, the timing of TXA administration, and the severity of extracranial hemorrhage, of which the advantages on extracranial bleeding might be offset by side effects of TXA^[36]. In addition, patients with both impeding exsanguination and associated severe TBI are likely to be deceased prior to arrival in emergency department (ED), which can lead to selection bias in the process of data collection. Therefore, mortality may be affected by multiple factors.

In this study, we performed a subgroup analysis including the timing of TXA administration which did not change the results or conclusions for any of the outcomes of interest. Our conclusion showed that TXA had no effect on mortality. This is consistent with some research results^[15–16, 18–20]. However, this is different from the findings of a previous CRASH-3 trial, which claimed that TXA was safe in patients with TBI and that treatment within 3 h of injury reduced head-injury-related death^[37]. This conflicting result does not mean that administration within 3h is ineffective for TBI patients due to the confounding effect of hemorrhage growth and TBI severity. Although the mortality of patients with TBI treated with TXA may be affected by multiple factors, the result of many large-scale RCT trials such as CRASH-3 indicated that absolute mortality reduction by TXA was low.

4.3 Adverse event after the treatment of TXA with respect to time and dose

Thrombotic and neurological complications are the most common adverse events surrounding TXA administration, because of its antifibrinolytic activity and a competitive antagonist of γ -aminobutyric acid (GABA) ^[8]. The coagulation disorders after TBI are associated with the complex interplay between coagulopathy, fibrinolysis, and hypercoagulability. Hypercoagulable state can promote the occurrence of different coagulation complications, such as cerebral intravascular microthrombi or systemic disseminated intravascular coagulation. TXA which blocks non-competitive plasmin, inhibiting the dissolution and degradation of fibrin clots can alter the delicate balance between coagulation and fibrinolysis, and theoretically have detrimental implications for outcomes, which obtained vascular occlusive events, pulmonary embolism, deep vein thrombosis, and gastrointestinal bleeding^[38]. Neurological complications, such as neurodegeneration and convulsion, are also frequently reported during the treatment. An increased risk for neurodegeneration after TBI were associated with the impairment of neural signal transduction caused by the release of various signals and inflammatory molecules by nerve, glial and immune cells. TXA can inhibiting competitively glycine receptors in cortical and spinal cord neurons, as well as GABA receptors in cortical and medullary neurons. Both inhibitory pathways of TXA cause an increased excitatory synaptic stimulus, which is theoretically prone to convulsion and stroke^[39, 40].

In this meta-analysis, we analyzed various reported adverse events after treatment, including vascular occlusive events, deep vein thrombosis, neurological complication, gastrointestinal bleeding, myocardial infarction, infectious complication, or renal failure. No obvious adverse events were demonstrated to be related to the TXA administration. The incidence of these events might be too low to demonstrate any significant effect. Nevertheless, the possibility of bias should not be ruled out because the pre-injury underlying diseases of TBI patients were not fully recorded.

Our subgroup analysis showed that the timing of TXA administration were not factors affecting the result of adverse event. Notably, some opinions is that early use of TXA can effectively prevent adverse events^[16, 23]. However, the latest study believed that they did not include the latest data^[35]. Our conclusions are consistent with the latest study results. Study design were not factors affecting the result of adverse event. This shows that the experiment has low heterogeneity in different regions. TXA dose were not factors affecting the result of adverse event. This indicates that different doses of TXA may have the same effect. However, there are few articles contained in TXA dose. Therefore, there is a risk of publication bias with regard to TXA dose. In conclusion, using TXA to treat TBI patients should not be given up in clinical practice, only on account of the possibility of adverse events.

5 Limitation

This paper is the first study to investigate the efficacy of different time and dose of TXA in the treatment of TBI. We collected the latest study and drew reliable conclusions. TXA at different times and doses was associated with reduced mean bleeding, but not with mortality, adverse events, neurosurgical intervention and new bleeding. However, our analysis also has several limitations. The risk of publication bias cannot be excluded even though Harbord's test and Egger's

test showed $P > 0.05$. Only a few studies reported the average time from injury to TXA administration and stratify them, hence, the result will be affected by covariates in the studies.

6 Conclusion

TXA at different times and doses was associated with reduced mean bleeding, but not with mortality, adverse events, neurosurgical intervention and new bleeding. We need more research data on different detection indexes and levels of TXA in patients with TBI, as compared to those not receiving TXA although the prognostic outcome for all harm outcomes was no effect, did not rule out the potential for harm.

Abbreviations

- TXA: Tranexamic acid
- TBI: Traumatic brain injury
- PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
- CSD: Cortical spreading depression
- PE: Pulmonary embolism
- DVT: Deep vein thrombosis
- RR: Risk ratio
- SMD: Standardized Mean Difference
- PHI: Progressive hemorrhagic injury
- ICH: Intracranial hemorrhage
- ED: Emergency department
- GABA: γ -aminobutyric acid

Declarations

Availability of supporting data

All data generated or analysed during this study are included in this published article and its supplementary information files.

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Not applicable.

Conflict of interest

None

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Author contributions

Honghao Huang contributed substantially to the conception, design, acquisition, analysis, and interpretation of data for the work; and drafted and revised the work. Mei Xin contributed substantially to the acquisition, analysis, interpretation of data, and revising the intellectual content. Xiqiang Wu made substantial contributions to the interpretation of data and revising the intellectual content. Jian Liu made substantial contributions to the interpretation of data and revising the intellectual content. Wenxin Zhang made substantial contributions to the interpretation of data and revising the intellectual content. Ke Yang and Jinbao Zhang contributed substantially to the conception, design, acquisition, analysis, and interpretation of data for the work; and drafted and revised the work.

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References

1. Najem D, Rennie K, Ribecco-Lutkiewicz M, et al. Traumatic brain injury: classification, models, and markers[J]. *Biochem Cell Biol*, 2018,96(4):391–406.DOI:10.1139/bcb-2016-0160.
2. Capizzi A, Woo J, Verduzco-Gutierrez M. Traumatic Brain Injury: An Overview of Epidemiology, Pathophysiology, and Medical Management[J]. *Med Clin North Am*, 2020,104(2):213–238.DOI:10.1016/j.mcna.2019.11.001.
3. Khellaf A, Khan D Z, Helmy A. Recent advances in traumatic brain injury[J]. *J Neurol*, 2019,266(11):2878–2889.DOI:10.1007/s00415-019-09541-4.
4. McGinn M J, Povlishock J T. Pathophysiology of Traumatic Brain Injury[J]. *Neurosurg Clin N Am*, 2016,27(4):397–407.DOI:10.1016/j.nec.2016.06.002.
5. Anderson T N, Hwang J, Munar M, et al. Blood-based biomarkers for prediction of intracranial hemorrhage and outcome in patients with moderate or severe traumatic brain injury[J]. *J Trauma Acute Care Surg*, 2020,89(1):80–86.DOI:10.1097/TA.0000000000002706.
6. Galgano M, Toshkezi G, Qiu X, et al. Traumatic Brain Injury: Current Treatment Strategies and Future Endeavors[J]. *Cell Transplant*, 2017,26(7):1118–1130.DOI:10.1177/0963689717714102.
7. Maegele M. Prehospital Tranexamic Acid (TXA) in Patients with Traumatic Brain Injury (TBI)[J]. *Transfus Med Rev*, 2021,35(4):87–90.DOI:10.1016/j.tmr.2021.08.003.
8. Henry D A, Carless P A, Moxey A J, et al. Anti-fibrinolytic use for minimising perioperative allogeneic blood transfusion[J]. *Cochrane Database Syst Rev*, 2011(1):D1886.DOI:10.1002/14651858.CD001886.pub3.
9. Brenner A, Belli A, Chaudhri R, et al. Understanding the neuroprotective effect of tranexamic acid: an exploratory analysis of the CRASH-3 randomised trial[J]. *Crit Care*, 2020,24(1):560.DOI:10.1186/s13054-020-03243-4.
10. de Faria J L, Da S B J, Costa E S L, et al. Tranexamic acid in Neurosurgery: a controversy indication-review[J]. *Neurosurg Rev*, 2021,44(3):1287–1298.DOI:10.1007/s10143-020-01324-0.
11. Cumpston M, Li T, Page M J, et al. Updated guidance for trusted systematic reviews: a new edition of the Cochrane Handbook for Systematic Reviews of Interventions[J]. *Cochrane Database Syst Rev*, 2019,10:D142.DOI:10.1002/14651858.ED000142.
12. Parums D V. Editorial: Review Articles, Systematic Reviews, Meta-Analysis, and the Updated Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 Guidelines[J]. *Med Sci Monit*, 2021,27:e934475.DOI:10.12659/MSM.934475.
13. Roberts I, Shakur-Still H, Aeron-Thomas A, et al. Tranexamic acid to reduce head injury death in people with traumatic brain injury: the CRASH-3 international RCT[J]. *Health Technol Assess*, 2021,25(26):1–76.DOI:10.3310/hta25260.
14. Rowell S E, Meier E N, McKnight B, et al. Effect of Out-of-Hospital Tranexamic Acid vs Placebo on 6-Month Functional Neurologic Outcomes in Patients With Moderate or Severe Traumatic Brain Injury[J]. *JAMA*, 2020,324(10):961–974.DOI:10.1001/jama.2020.8958.
15. Mahmood A, Needham K, Shakur-Still H, et al. Effect of tranexamic acid on intracranial haemorrhage and infarction in patients with traumatic brain injury: a pre-planned substudy in a sample of CRASH-3 trial patients[J]. *Emerg Med J*, 2021,38(4):270–278.DOI:10.1136/emered-2020-210424.
16. van Wessem K, Jochems D, Leenen L. The effect of prehospital tranexamic acid on outcome in polytrauma patients with associated severe brain injury[J]. *Eur J Trauma Emerg Surg*, 2021.DOI:10.1007/s00068-021-01827-5.
17. Mojjallal F, Nikoie M, Hajimaghsoudi M, et al. The effect of intravenous tranexamic acid on preventing the progress of cerebral hemorrhage in patients with brain traumatic injuries compared to placebo: A randomized clinical trial[J]. *Med J Islam Repub Iran*, 2020,34:107.DOI:10.34171/mjiri.34.107.
18. Mousavinejad M, Mozafari J, Ilkhchi R B, et al. Intravenous Tranexamic Acid for Brain Contusion with Intraparenchymal Hemorrhage: Randomized, Double-Blind, Placebo-Controlled Trial[J]. *Rev Recent Clin Trials*, 2020,15(1):70–75.DOI:10.2174/157488711466619111811826.
19. Yutthakasemsunt S, Kittiwatanagul W, Piyavechvirat P, et al. Tranexamic acid for patients with traumatic brain injury: a randomized, double-blinded, placebo-controlled trial[J]. *BMC Emerg Med*, 2013,13:20.DOI:10.1186/1471-227X-13-20.
20. Fakharian E, Abedzadeh-Kalahroudi M, Atoof F. Effect of Tranexamic Acid on Prevention of Hemorrhagic Mass Growth in Patients with Traumatic Brain Injury[J]. *World Neurosurg*, 2018,109:e748-e753.DOI:10.1016/j.wneu.2017.10.075.
21. Jokar A, Ahmadi K, Salehi T, et al. The effect of tranexamic acid in traumatic brain injury: A randomized controlled trial[J]. *Chin J Traumatol*, 2017,20(1):49–51.DOI:10.1016/j.cjtee.2016.02.005.
22. Ebrahimi P, Mozafari J, Ilkhchi R B, et al. Intravenous Tranexamic Acid for Subdural and Epidural Intracranial Hemorrhage: Randomized, Double-Blind, Placebo-Controlled Trial[J]. *Rev Recent Clin Trials*, 2019,14(4):286–291.DOI:10.2174/1574887114666190620112829.
23. Perel P, Al-Shahi S R, Kawahara T, et al. CRASH-2 (Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage) intracranial bleeding study: the effect of tranexamic acid in traumatic brain injury—a nested randomised, placebo-controlled trial[J]. *Health Technol Assess*, 2012,16(13):1–54.DOI:10.3310/hta16130.
24. Bossers S M, Loer S A, Bloemers F W, et al. Association Between Prehospital Tranexamic Acid Administration and Outcomes of Severe Traumatic Brain Injury[J]. *JAMA Neurol*, 2021,78(3):338–345.DOI:10.1001/jamaneurol.2020.4596.
25. Chakroun-Walha O, Samet A, Jerbi M, et al. Benefits of the tranexamic acid in head trauma with no extracranial bleeding: a prospective follow-up of 180 patients[J]. *Eur J Trauma Emerg Surg*, 2019,45(4):719–726.DOI:10.1007/s00068-018-0974-z.
26. Kaur P, Sharma S. Recent Advances in Pathophysiology of Traumatic Brain Injury[J]. *Curr Neuropharmacol*, 2018,16(8):1224–1238.DOI:10.2174/1570159X15666170613083606.

27. Jha R M, Kochanek P M, Simard J M. Pathophysiology and treatment of cerebral edema in traumatic brain injury[J]. *Neuropharmacology*, 2019,145(Pt B):230–246.DOI:10.1016/j.neuropharm.2018.08.004.
28. Moore E E, Moore H B, Kornblith L Z, et al. Trauma-induced coagulopathy[J]. *Nat Rev Dis Primers*, 2021,7(1):30.DOI:10.1038/s41572-021-00264-3.
29. Lighvani S, Baik N, Diggs J E, et al. Regulation of macrophage migration by a novel plasminogen receptor Plg-R KT[J]. *Blood*, 2011,118(20):5622–5630.DOI:10.1182/blood-2011-03-344242.
30. Currie S, Saleem N, Straiton J A, et al. Imaging assessment of traumatic brain injury[J]. *Postgrad Med J*, 2016,92(1083):41–50.DOI:10.1136/postgradmedj-2014-133211.
31. Suri M F, Suarez J I, Rodrigue T C, et al. Effect of treatment of elevated blood pressure on neurological deterioration in patients with acute intracerebral hemorrhage[J]. *Neurocrit Care*, 2008,9(2):177–182.DOI:10.1007/s12028-008-9106-7.
32. Roberts I, Shakur H, Coats T, et al. 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[J]. *Health Technol Assess*, 2013,17(10):1–79.DOI:10.3310/hta17100.
33. Cerny V, Maegele M, Agostini V, et al. Variations and obstacles in the use of coagulation factor concentrates for major trauma bleeding across Europe: outcomes from a European expert meeting[J]. *Eur J Trauma Emerg Surg*, 2021.DOI:10.1007/s00068-020-01563-2.
34. July J, Pranata R. Tranexamic acid is associated with reduced mortality, hemorrhagic expansion, and vascular occlusive events in traumatic brain injury - meta-analysis of randomized controlled trials[J]. *BMC Neurol*, 2020,20(1):119.DOI:10.1186/s12883-020-01694-4.
35. Lawati K A, Sharif S, Maqbali S A, et al. Efficacy and safety of tranexamic acid in acute traumatic brain injury: a systematic review and meta-analysis of randomized-controlled trials[J]. *Intensive Care Med*, 2021,47(1):14–27.DOI:10.1007/s00134-020-06279-w.
36. Sprigg N, Flaherty K, Appleton J P, et al. Tranexamic acid for hyperacute primary IntraCerebral Haemorrhage (TICH-2): an international randomised, placebo-controlled, phase 3 superiority trial[J]. *Lancet*, 2018,391(10135):2107–2115.DOI:10.1016/S0140-6736(18)31033-X.
37. 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[J]. *Lancet*, 2019,394(10210):1713–1723.DOI:10.1016/S0140-6736(19)32233-0.
38. Moore E E, Moore H B, Kornblith L Z, et al. Trauma-induced coagulopathy[J]. *Nat Rev Dis Primers*, 2021,7(1):30.DOI:10.1038/s41572-021-00264-3.
39. de Faria J L, Da S B J, Costa E S L, et al. Tranexamic acid in Neurosurgery: a controversy indication-review[J]. *Neurosurg Rev*, 2021,44(3):1287–1298.DOI:10.1007/s10143-020-01324-0.
40. Brenner A, Belli A, Chaudhri R, et al. Understanding the neuroprotective effect of tranexamic acid: an exploratory analysis of the CRASH-3 randomised trial[J]. *Crit Care*, 2020,24(1):560.DOI:10.1186/s13054-020-03243-4.

Figures

Figure 1

Flow diagram of study selection process for systematic review.

A Risk of bias summary

Figure 2
Risk of bias assessment. A Authors' judgments about each risk of bias item for each included study. B Authors' judgments about each risk of bias item presented as percentages across all included studies.

Figure 3
Forest plot comparing TXA and placebo for the outcome of all-cause mortality

Figure 4

Forest plot comparing TXA and placebo for all adverse events

Figure 5

Forest plot comparing TXA and placebo for severe TBI (Glasgow Coma Scale score from 3 to 8)

Figure 6

Forest plot comparing TXA and placebo for the unfavorable Glasgow Outcome Scale (GOS < 4)

Figure 7

Forest plot comparing TXA and placebo for the need of neurosurgical intervention

Figure 8

Forest plot comparing TXA and placebo for the number people of new bleeding

Figure 9

Forest plot comparing TXA and placebo for mean hemorrhage volume.

Figure 10

Forest plot comparing TXA and placebo for adverse events of various causes

Supplementary Files

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