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Efficacy and Safety of Tranexamic Acid Administration in Patients with Acute Traumatic Brain Injury: A Review of Current Literature

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Abstract

Hypothesis: Early administration of tranexamic acid (TXA) reduces mortality in patients suffering from acute traumatic brain injury (TBI).

Methods: A structured search of PubMed and CENTRAL from inception until July 1st, 2022 was carried out seeking RCTs comparing effects of TXA administration to placebo in patients suffering from TBI. Primary outcome tested was 28-day all-cause mortality. Secondary outcomes included intracranial hemorrhage growth and thromboembolic events.

Results: Eight RCTs involving a total of 14,714 patients met the inclusion criteria; 7573 patients received TXA while 7141 patients received placebo. There were 1415 patient deaths (18.7%) in the TXA group and 1410 patient deaths (19.7%) in the placebo group. None of the included studies reported a significant reduction in 28-day all-cause mortality, however they all shared positive trends towards superior outcomes in the intervention arms. Two of the included studies reported significant reductions in intracranial hemorrhage expansion in those patients treated with TXA, with four more studies reporting trends towards superior outcomes in the TXA groups. There was no evidence of increased incidence of thromboembolic events in the TXA groups in four of the five studies that reported relevant data, with one study representing 1.2% of total patients reporting increased incidence of pulmonary emboli in the intervention group.

Conclusions: In patients suffering from acute TBI, early administration of TXA reduces intracranial hemorrhage growth and may have positive effects on mortality with no corresponding increase in thromboembolic events. Given these results, early administration of TXA in patients experiencing TBI is recommended in initial care.

Keywords: Tranexamic acid, Traumatic brain injury, Intracranial hemorrhage, Mortality, Disability

Introduction

Traumatic brain injury (TBI) is a leading cause of mortality and morbidity across the world, with nearly 70 million individuals worldwide believed to experience a TBI each year [1]. The burden of TBI is felt disproportionality among low and middle income countries, who suffer from three times more cases proportionally in comparison to high-income countries [1]. A large proportion of people who suffer from TBI experience further mortality and morbidity following their primary brain injury, often days to weeks after the event [2]. This decline in health outcomes is thought to be due to some form of secondary injury such as free radical overload, excitotoxicity secondary to excessive glutamate release from damaged neurons, or damage to the blood-brain barrier (BBB) [2]. Systemic coagulopathy is frequently observed secondary to TBI and can be distinguished from the more commonly seen coagulopathies induced by hemorrhagic shock or extracranial trauma in that TBI-induced coagulopathy is missing key causal risk factors such as significant blood loss, hypothermia, or hemodilution secondary to fluid resuscitation [3].

The main mechanism behind TBI-induced coagulopathy is thought to be the disruption of the BBB leading to the release of brain-derived molecules and tissue factors into systemic circulation that initiate first a hypercoagulable state followed quickly by hyperfibrinolysis and a consumptive coagulopathy [3]. This hyperfibrinolytic state peaks roughly three hours post injury, highlighting the need for prompt intervention when attempting to reduce the morbidity and mortality associated with TBI [4]. This TBI-associated coagulopathy contributes to the incidence of intracranial hemorrhage (ICH), which includes epidural hematomas, subdural hematomas, intraparenchymal hemorrhages, hemorrhagic brain contusions, and subarachnoid hemorrhages, one of the most common complications following TBI [5]. Intracranial hemorrhages represent a serious complication with greater risk of increased intracranial pressure (ICP), cerebral edema, brain herniation, and death. The greatest risk of ICH is within 48 hours of TBI when it is most likely to develop or expand, with the greatest increases in size seen early on, and larger ICHs lending themselves to worse overall prognoses [5].

Tranexamic acid (TXA) is a synthetic derivative of the amino acid lysine that functions as an antifibrinolytic by inhibiting the lysine binding sites on plasminogen, leading to decreased conversion of plasminogen to plasmin thereby preventing the degradation of fibrin clots [6]. Extensive clinical trials have demonstrated the efficacy of

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TXA administration in reducing blood loss and improving mortality in a variety of heterogenous populations including trauma patients with significant hemorrhage [7], patients suffering from upper gastrointestinal bleeds [8], surgical patients [9], and pregnant patients at risk for obstetric hemorrhage [10]. Despite the high incidence of TBI worldwide and the significant morbidity and mortality associated with it, there remains a paucity of effective pharmacologic interventions in treating the immediate effects of TBI and in preventing the progressive nature of many TBIs [11]. The efficacy of TXA administration in those patients suffering from TBI is less clear, with the potential to reduce the hyperfibrinolysis that commonly occurs following TBI and thereby reduce ICH expansion and secondary brain injury. As TXA functions as an antifibrinolytic, potential complications are centered around the possibility of overcorrecting the body's hemostatic mechanisms leading to an increase in thrombotic adverse events. Several large RCTs investigating the efficacy of early TXA administration in patients suffering from TBIs have been published in recent years [12, 13], and the primary purpose of this paper is to perform a structured literature review to determine whether early administration of TXA in patients suffering from TBI reduces mortality. The effects of TXA administration on various secondary outcomes including ICH expansion, need for neurosurgical intervention, and thromboembolic events will also be reviewed.

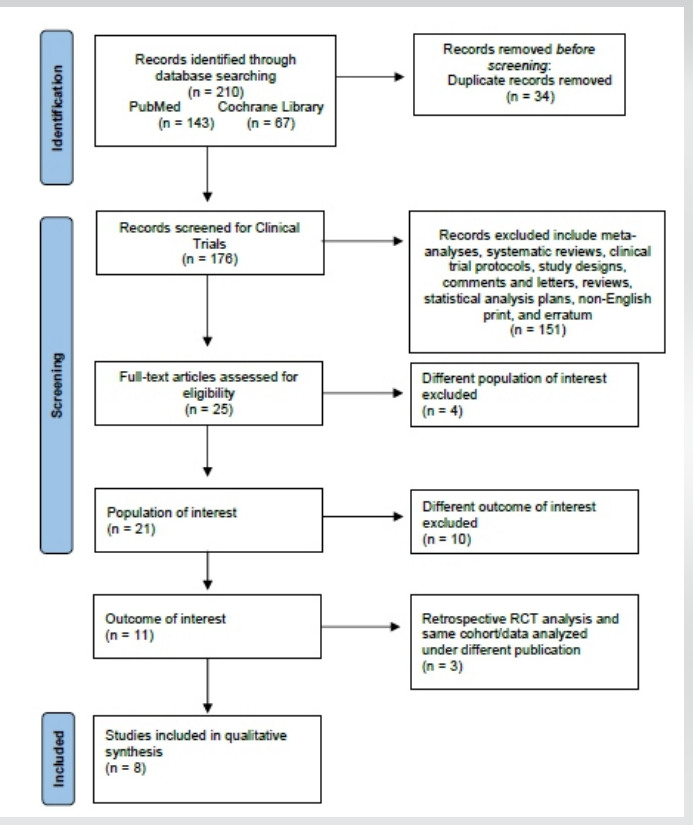
Methods

Databases searched include PubMed and Cochrane CENTRAL utilizing the search terms "tranexamic acid" AND "traumatic brain injury" as well as the MeSH terms Glasgow Coma Scale, Cerebral hemorrhage traumatic, Brain injuries traumatic, and Tranexamic acid.

Inclusion criteria were as follows 1) Population: patients suffering from TBI 2) Intervention: administration of TXA via any route w/in 24 hours of injury 3) Comparison: placebo or standard care 4) Outcome: mortality or ICH expansion 5) Study design: RCTs 6) Timeframe: any studies published before November 2020. Exclusion criteria includes meta-analyses, systematic reviews, clinical trial protocols, study designs, comments and letters, reviews, statistical analysis plans, non-English print, cohort studies, and erratum electronic supplementary materials.

In PubMed the initial search terms and MeSH terms yielded 143 unique results while the Cochrane Library CENTRAL search terms and MeSH terms yielded 67 unique results. Figure 1 demonstrates the flow chart for the selection process and detailed identification of the studies included in this review. The combination of the PubMed and Cochrane Library CENTRAL searches resulted in 176 unique records, after duplicates were excluded. These records were then screened to include only RCTs published in English, with 151 records excluded. The remaining 25 full-text articles were assessed based on the inclusion criteria listed above.

A total of four articles were excluded based on different study populations; two studies were assessing all-cause trauma patients, one study was assessing otolaryngologic patients, and one study was assessing spontaneous intracerebral hemorrhage patients. Out of the remaining 21 articles assessing patients suffering from TBI, ten more were excluded for investigating different outcomes; two studies were



investigating TXA efficacy in reducing hemorrhage in those patients requiring neurosurgery following TBI, two studies were investigating the cost-effectiveness of TXA administration in TBI patients, one study was investigating the utility of blood-based biomarkers in predicting patient outcome following TBI, one study was investigating the pharmacokinetics of TXA in patients with TBI, one study was investigating the mechanism of TXA benefits in TBI, one study was evaluating the effects of time to treat on TXA administration for TBI, one studies was investigating the effect of TXA administration on circulating markers of endotheliopathy following TBI, and the last study was investigating the impact of TXA administration on markers of coagulation and fibrinolysis. The remaining 11 studies were investigating mortality and ICH expansion in TBI patients who receive early TXA with two more studies excluded for analyzing the same nested cohort and data with identical results as an included study, but under different publications and one final study excluded for being a retrospective analysis of RCTs. The remaining eight studies were included for review below, all of which were available on both PubMed and Cochrane Library.

Results

The baseline characteristics of the included studies including demographics, time to treat, and dosing regimens are summarized in Table 1. These eight studies evaluated a total of 14714 TBI patients, with 7573 patients receiving TXA dosing while 7141 patients received placebos. Various outcome results of the reviewed studies including our primary outcome of 28-day mortality as well as other important outcomes including ICH growth, disability among survivors, and thromboembolic events are outlined in Table 2. Values for the 28-day non-head-injury related deaths for the CRASH-3 trial were obtained

Table 1. Baseline characteristics of included studies

First Author (year)	Study Design	No. Patients, TXA/Control	Females (%), TXA/Control	Dosing Regimen	Mean or Median Age (years), TXA/Control	Time to Treatment Post Trauma	Follow-up Window Post Trauma	GCS severity, Mild 15-13, Moderate 12-9, Severe 8-3, %, (SD), TXA/control	Systolic BP, TXA/Control
CRASH-2 (2011)	Multisite, nested, double-blind RCT	133/137	22 (16%)/20 (15%)	1g TXA bolus over 10 min then 1g TXA maintenance over 8 hours. Matching placebo of 0.9% NaCl	36/37	≤ 8 hours	28 days or hospital discharge	Mild: 47/42, Moderate: 19/25, Severe: 34/33	Patients <90 mmHg: 7%/7%
Yutthakasemsunt (2013)	Single site, double-blind, RCT	120/118	17 (14%)/11 (9%)	1g TXA bolus over 30 min then 1g TXA maintenance over 8 hours. Matching placebo of sterile water	34.8/34.1	≤ 7 hours	16-32 hours or hospital discharge	Moderate: 43/40, Severe: 57/60	N/A
Jokar (2017)	Single site, single blind, RCT	40/40	8 (20%)/12 (30%)	1g TXA bolus over 10 min then 1g TXA maintenance over 8 hours. Matching placebo of 0.9% NaCl	35.4/36.2	≤ 2 hours	48 hours	GCS <8 were exluded	160 mmHg/162 mmHg
Fakharen (2018)	Single site, double-blind, RCT	74/75	7 (10%)/9 (12%)	1g TXA bolus over 10 min then 1g TXA maintenance over 8 hours. Matching placebo of 0.9% NaCl	42.3/39.3	≤ 8 hours	3 months	12.7 (2.83)/11.65 (3.71)	118 mmHg/120 mmHg
Chakroun-Walha (2019)	Single site, open label, RCT	96/84	8 (8%)/10 (12%)	1g TXA bolus over 10 min then 1g TXA maintenance over 8 hours. Matching placebo of 0.9% NaCl	44/39	≤ 24 hours	28 days	10 (5) vs 9 (5)	87 mmHg/89 mmHg
CRASH-3 (2019)	Multisite, double-blind, RCT	6406/6331 (4649/4553 w/in 3 hours of injury)	1301 (20%)/1318 (21%)	1g TXA bolus over 10 min then 1g TXA maintenance over 8 hours. Matching placebo of 0.9% NaCl	41.7/41.9	≤ 3 hours	28 days	Mild: 28/28, Moderate: 33/33, Severe: 38/38	Patients <90 mmHg: 2%/2%
Rowell (2020)	Multisite, double-blind RCT	657/309	175 (27%)/76 (25%)	1g TXA bolus OoH then 1g TXA maintenance IH over 8 hours. 2g TXA bolus OoH then 1g placebo maintenance IH over 8 hours. 1g placebo bolus OoH then 1g placebo maintenance IH over 8 hours.	39.5/36	≤ 2 hours	6 months	Mild: 4/3, Moderate: 44/37, Severe: 52/61	Patients <90 mmHg excluded
Safari (2021)	Single site, double-blind, RCT	47/47	7 (15%)/9 (19%)	1g TXA bolus over 10 min followed by 1g every 6 hours for 48 hours. Matching placebo of 0.9% NaCl was administered at initiation of injections, and then at 6, 24, and 48 hours.	36.2/36.4	≤ 3 hors	Hospital discharge	11.1 (2.9) vs 11.1 (3.0)	N/A

from their Supplementary Appendix and combined with the 28-day head-injury related deaths to determine the 28-day all-cause mortality rates.

Primary Outcome

All-cause mortality at 28 days was evaluated in six of the included RCTs representing 7486 intervention patients and 7054 controls. 1415 (18.9%) patients in the intervention groups and 1410 (20%) of patients in the control groups suffered mortality from any cause within 28 days. The CRASH-2 collaborators (2011) analyzed a nested cohort of patients for expansion of ICH secondary to TBI within the much larger CRASH-2 study and reported 14/133 patient deaths (11%) in the TXA group and 24/137 patient deaths (18%) in the placebo group (OR 0.47, 95% CI 0.21 to 1.04, p= 0.06)14. Yutthakasemsunt et al. (2013) investigated the occurrence of progressive intracranial hemorrhage in patients with TBI who received early administration of TXA and reported 12 patient deaths (10%) in the TXA group and 17 patient deaths (14%) in the placebo group (RR 0.69, 95% CI 0.35 to 1.39)15. Fakharen et al. (2018) examined the effect of TXA in prevention of increased bleeding volume in TBI patients and recorded two patient deaths (3%) in the TXA group and three patient deaths (4%) in the placebo group [16]. Chakroun-Walha et al. (2018) studied the effects of early TXA administration on mortality in patients with TBI and detailed 27 patient deaths (28%) and 19 patient deaths (23%) at 28 days post trauma in the TXA and placebo groups respectively (p=0.4) [17]. The CRASH-3 collaborators (2019), building off the earlier CRASH-2 Intracranial Bleed Study cohort, investigated the effects of TXA on death and disability in TBI patients. They performed the largest RCT and documented 855 TXA group (19%) and 892 placebo group (20%) head-injury related deaths after 28 days (RR 0.94, 95% CI 0.86 – 1.02), with all-cause mortalities of 1266 patients (19.7%) and 1294 patients (20.4%) at 28 days post injury [12]. Rowell et al. (2020) examined the efficacy of TXA on improving functional neurologic outcome 6-months post-trauma and reported 94 patient deaths (14%) and 53 patient deaths (17%) at 28 days (AD -2.9%, 95% CI -7.9% to 2.1%, p= 0.26) for the TXA group and placebo group respectively [13].

Secondary Outcomes

The presence of ICH growth was an important outcome reported as the primary outcome in five studies in addition to Rowell et al. (2020) recording relevant data as a secondary outcome [13-16, 18, 19]. The CRASH-2 collaborators (2011) recorded a change in mean total hemorrhage growth of 5.9 mL (SD 26.8) for the TXA group and 8.1 mL (SD 29.2) among controls (95% CI -11.5 to 3.9, p= 0.33) [14]. Yutthakasemsunt et al. (2013) detailed progressive intracranial hemorrhage in 21 patients (18%) allocated to receive TXA and in 32 patients (27%) allocated to receive placebo (RR 0.65, 95% CI 0.40 to 1.05) [15]. Jokar et al. (2017) examined the extent of ICH growth following TXA administration in patients with TBI, documenting significant ICH growth of 1.7 mL (SD 9.7) and 4.3 mL (SD 12.9) in the TXA and placebo groups respectively (p= <0.001), with significantly less increased ICH volume after 48 hours seen in the TXA group, 23.3 mL (SD 6.4), versus the placebo group, 26.5 mL (SD 6.4; p=0.04) [18]. Fakharen et al. (2018) reported an increased volume of ICH in 15

Table 2: Data incorporated into this table was obtained from the included studies, with primary outcomes tested in bold. Numbers of patients counted for each outcome are listed, with percent of total study population in parentheses. The TXA groups are lis

First Author	*28-day All-cause Mortality*	*ICH Growth*	*Need for Neurosurgery*	*Thromboembolic Events*	*Disability Among Survivors*
CRASH-2 (2011)	14 (11%)/24 (18%)	**44 (36%)/56 (44%)**	20 (15%)/21 (15%)	N/A	26 (22%)/29 (26%) dependent upon discharge, mOHS
Yutthakasemsunt (2013)	12 (10%)/17 (14%)	**21 (18%)/32 (27%)**	3 (3%)/ N/A	0 (0%)/3 (3%)	21 (18%)/27 (23%) unfavourable outcome upon discharge, GOS
Jokar (2017)	N/A	**1.7 mL (SD 9.7)/4.3 mL (SD 12.9)**	N/A	N/A	N/A
Fakharen (2018)	2 (3%)/3 (4%)	**15 (21%)/17 (23%)**	8 (11%)/12 (16%)	No difference between groups	5 (7%)/11 (15%) unfavourable outcome upon discharge, GOS
Chakroun-Walha (2019)	**27 (28%)/19 (23%)**	N/A	23 (24%)/16 (19%)	14 (15%)/5 (6%)	23 (24%)/11 (13%) unfavourable outcome 28 days post trauma, GOS
CRASH-3 (2019)	1266 (19.7%)/1294 (20.4%)**{855 {19%}/892 {20%} head-injury deaths w/in 3 hours of injury)**	N/A	N/A	101 (2%)/102 (2%)	775 (12%)/811 (13%) unable to wash or dress 28 days post trauma, patient derived disability scale
Rowell (2020)	94 (14%)/53 (17%)	53/332 (16%) / 30/148 (20%)	137 (21%)/54 (17%)	44 (7%)/30 (10%)	**232 (35%)/117 (38%) unfavourable outcome 6 months post trauma, GOSE**
Safari (2021)	N/A	**1.17 mL (SD 2.53)/6.85 mL (SD 11.77)**	1 (2%)/4 (9%)	N/A	14.1 (SD 1.6) vs 13.9 (SD 1.9) GCS scale upon discharge

patients (21%) of the TXA group and in 17 patients (23%) of the placebo group (RR 0.89, 95% CI 0.55 - 1.74, p = 0.87) [16]. Rowell et al. (2020) documented 53 TXA patients (16%) and 30 placebo patients (20%) with progressive ICH (-5.4%, 95% CI -12.8% to 2.1%, p=0.16) [13]. Safari et al. (2021) documented significantly reduced hematoma volume after 48 hours in the TXA group, 6.2 mL (SD 7.4), as compared to the placebo group, 12.1 mL (SD 14.2) (p = 0.01), and significantly reduced hematoma growth rates in the intervention arm, 1.17 mL (SD2.53), as compared to the control arm, 6.85 mL (SD11.77) (p = 0.002) [19]. The incidence of thromboembolic events was measured in five of the studies, including both Rowell et al. (2020) and the CRASH-3 collaborators (2019), and was found to be non-significant in all of the studies [12, 13, 15, 16], with the exception of Chakroun-Walha et al. (2018) [17]. The requirement for neurosurgical intervention was reported on in six studies, with no evidence of heterogeneity recorded [13-17, 19]. Disability among patients as measured utilizing various disability scores including the Glasgow Outcome Scale (GOS) and Patient Derived Disability Scale (PDDS) was documented among seven of eight studies included, and as the primary outcome of Rowell et al. (2020), with no evidence of heterogeneity discovered [12-17, 19].

Discussion

The objective of this review paper was to determine the efficacy of early TXA administration in reducing mortality in TBI patients. Despite none of the six studies reporting data on 28-day mortality documenting statistically significant effects [12-17], there is reason to be optimistic about the potential for TXA administration to help fill the current void of pharmaceutical interventions at clinicians disposal for the treatment of secondary brain injury following TBI [20]. All six studies displayed a positive trend towards superior outcomes in the TXA treated groups [12-17], with several possible explanations for the failure to reach statistical significance. The time to administration of TXA varied in the studies with two of six studies administering TXA ≤3 hours post-injury [12, 13], one study dosing ≤7 hours post-injury [15], two studies ≤8 hours [14, 16], and one study within the first 24 hours post injury [17]. Multiple large clinical trials have demonstrated that early administration of TXA within 3 hours of insult yields the greatest benefits, both in trauma patients [7, 21] and among post-partum hemorrhage patients10. These results were supported by Gayet-Ageron et al. (2018) in their meta-analyses of individual patient level data from 40000 patients suffering from acute hemorrhage which demonstrated that immediate treatment of TXA produced the strongest survival benefit, with every 15 minutes of delay reducing benefit by 10% [22]. The importance of prompt administration in TBI patients specifically is further highlighted by recent data illustrating that the hyperfibrinolysis stage of hemostatic disruptions following TBI, a primary driving force behind intracranial bleed progression, occurs within hours of injury [23]. This is consistent with the suspected mechanism of action of TXA, a synthetic derivative of the amino acid lysine that functions as an antifibrinolytic by inhibiting the lysine binding sites on plasminogen and thereby reducing fibrinolysis, on reducing ICH and thereby reducing mortality in TBI patients.

The only study to stratify 28-day mortality based upon GCS score upon presentation as a marker for severity of TBI were the CRASH-3 collaborators who prespecified sensitivity analysis of patient deaths that excluded patients with GCS score of 3 or those with bilaterally unreactive pupils [12]. Patients with these presentations have a very poor prognosis regardless of treatment due to the severity of their primary brain injuries and presence of existing large ICH and brain herniations [24, 25], and so it was reasoned their inclusion might bias treatment effect towards the null [12]. Indeed, as expected by the authors, when these patients were removed early TXA treatment had a significant effect on reducing head-injury related 28-day mortality [12], therefore the inclusion of these patients across the six studies reporting mortality provides another reason the positive trend falling short of significance. A recent meta-analysis utilized all-cause 28-day mortality data from the CRASH-3 trial in their pooled analyses of

mortality following TXA administration and reached the conclusion that TXA probably has no effect on mortality in acute TBI [26]. While the CRASH-3 authors reasoned that all-cause mortality combined those causes of death that might be ameliorated by TXA administration (eg ICH causing head injury-related death) with other causes of death (eg pre-existing comorbidities, sepsis), thereby biasing the treatment effect towards the null [12, 27, 28], the remaining studies included in the analyses reported on all-cause mortality so analyzing similar data is at least desirable from a homogeneity perspective. However, the meta-analysis had insufficient data to address the differences in effect of TXA based on either time to administration or based on severity of TBI [26]. A post-hoc analyses of the CRASH-3 trial evaluating the 7637 patients remaining after the exclusion of patients with GCS 3 or bilaterally unreactive pupils sought to determine the efficacy of TXA on early (<24 hours post injury) versus late deaths. Their results were consistent with the reasoning above, finding that early TXA administration led to a statistically significant reduction in the risk of early all-cause mortality in patients with both mild to moderate and severe TBI [28]. The reduction was even greater when the analyses was restricted to head injury-related deaths, and smaller, although still significant, when patients with GCS 3 or bilaterally unreactive pupils were included [28].

The effect of TXA administration on ICH expansion was another widely reported outcome, with six of the eight studies including relevant data [13-16, 18, 19]. Given the proposed mechanism for TXA action in TBI patients this is a pertinent outcome. While only two of the included studies reported significant reduction in ICH growth in the intervention group [18, 19], a common positive trend toward superior outcomes was shared between the remaining studies [13-16]. This trend was supported by recent meta-analyses findings that TXA administration likely decreased hematoma expansion [26 29], with one recent meta-analyses finding a statistically significant reduction in ICH when analyzing their pooled results [30]. ICH and expansion in TBI patients were further investigated in an explanatory study analyzing the CT scans collected during the course of the CRASH-3 study. The results indicated that the median volume of intracranial bleeds upon baseline CT scans were greater in those patients with bilaterally unreactive pupils when compared to unilaterally unreactive pupils and lowest among those with bilaterally reactive pupils [31]. Similar trends were seen with greater volumes in those patients with severe GCS scores as compared to moderate GCS scores and lowest among those with mild GCS scores. Interestingly, the median volume of patients with even a unilaterally unreactive pupil was higher than those with a severe GCS score [31]. A statistically significant association between an increase in volume of ICH and an increase in midline shift was reported, as was a significant association between an increase in midline shift and the risk of having one or more unreactive pupils [31]. These findings would seem to support the prespecified analyses of the CRASH-3 study removing those patients with bilaterally unreactive pupils or GCS 3 based on reasoning that existing ICH volumes were past intervention and support the mechanistic action of TXA whereby reducing ICH leads to reduced secondary brain injury.

Disability upon discharge or latest follow-up was not found to be significant in any of the reviewed studies, a finding mirrored by recent meta-analyses [12-17, 19, 26, 29, 30]. Of the five studies reporting on incidence of thromboembolic events, only Chakroun-Walha et al. found a significant difference, with increased incidence of pulmonary emboli in the intervention arm [12, 13, 15-17]. This study was the only open-label trial included in this review while also utilizing weak simple randomization techniques to assign patients to their respective treatment arms, raising concerns over increased risk of bias and poor matching of baseline patient characteristics. Indeed, when comparing the TXA and placebo groups it was found that the TXA group had significantly larger numbers of patients with abdominal trauma ($P < 0.001$) as well as significantly higher mean scores on the Simplified Acute Physiologic Score II ($p= 0.05$), indicating a more severe patient presentation among the TXA group [17]. The recent meta-analyses examining TXA use in TBI patients were consistent with other trials investigating the use of TXA in all trauma, surgery, and post-partum hemorrhage patients in finding no increased risk of thromboembolic events [7, 10, 26, 29, 30, 32].

Given the evidence towards trends in reduced ICH and all-cause 28 day mortality with no increased risk of thromboembolic events, paired with the cost effectiveness of TXA administration [33, 34], TXA should be administered to all adult TBI patients within three hours of injury. These recommendations are supported by recent meta-analyses of TXA administration in TBI pateints [29, 30].

Declaration of patient consent : The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given his/her consent for his/her images and other clinical information to be reported in the Journal. The patient understands that his/her name and initials will not be published, and due efforts will be made to conceal his/her identity, but anonymity cannot be guaranteed.

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