ABSTRACT

INTRODUCTION: Traumatic brain injury (TBI) is a leading cause of death and disability. In many cases of TBI-related intracranial hemorrhage (ICH) is associated with a high risk of coagulopathy and may lead to an increased risk of hemorrhage growth. Therefore, tranexamic acid (TXA), which is known as an antifibrinolytic agent that reduces bleeding by inhibiting the breakdown of blood clots, might limit ICH expansion.

MATERIAL AND METHODS: We aimed to quantify the effects of TXA in brain injury and thus performed a literature search using PubMed, Web of Science, Scopus, EMBASE, and Cochrane Center Register of Controlled Trials (CENTRAL) for studies that were published between the respective database inception, and April 10, 2021.

RESULTS: A total of nine studies were identified; these included 5845 patients treated with, and 5380 treated without TXA. The 28-day or in-hospital mortality was 17.8% for the TXA group, compared with 19.3% for the no-TXA group (OR = 0.92; 95% CI: 0.83, 1.01; p = 0.08). At 6-months follow-up, mortality was 18.3% vs 19.9% (OR = 0.91; 95% CI: 0.63–1.31; p = 0.60), with and without TXA, respectively. A Glasgow Outcome Scale less than 4 points at 28-days follow-up was reported in 3 studies and was 29.8% vs 34.8% (OR = 0.91; 95% CI: 0.45, 1.82; p = 0.78), with and without TXA, respectively. No differences were found in adverse events between TXA and non-TXA groups.

CONCLUSIONS: Our analysis found showed no statistical significance between TXA and non-TXA treatment of TBI patients, however, in the TXA group a trend to decrease 28-day mortality compared to non-TXA.
INTRODUCTION

Traumatic brain injury (TBI), which is a form of acquired brain pathology, occurs when a sudden force inflicts damage to the brain [1]. According to the Centers for Disease Control and Prevention, around 2.5 million people in the U.S. report to the emergency departments seeking help regarding TBI [2]. While the classification of the TBI can be complicated, most systems consider physical abnormality and dysfunctional severity to assess the injury [4]. One of the most popular and widespread systems is the Glasgow Coma Scale (GCS). It stratifies injury on a 3–15 point scale; where 13–15 is considered mild, 9–12 moderate, and below 9 to be severe brain injury [5]. When discussing severity, one may also classify TBI depending on the length of unconsciousness, where mild, moderate, or severe injury results in the loss of consciousness in terms of seconds, minutes, or hours, respectively [6]. While the vast majority of TBI represents a mild concussion [7], in which the symptoms resolve within 1–2 weeks, around 15% of patients suffer long-term complications [8]. Although accounting for a minority of overall cases, severe TBI is a leading cause of morbidity and mortality worldwide [9]. Severe trauma causes may result in coagulopathy [10], with the consequence of bleeding and cerebral edema. Several procedures have been implemented in order to reduce damage caused by this cascade of events such as hyperventilation, diuretics, and CFS drainage [11]. In order to protect the brain, several drugs are used, e.g., barbiturates, [12] which reduce the brain metabolism; however, U.S. Food and Drug Administration (FDA) has not approved any drug therapy for the treatment of TBI. Tranexamic acid has been proposed as a candidate drug in the management of severe TBI due to its ability to decrease the conversion of plasminogen to plasmin, which reduces fibrinolysis and stabilizes the blood clot [13]. At present, whether it is effective in improving outcomes is unclear.

We thus conducted a systematic review of randomized-controlled trials (RCTs) to evaluate the safety and efficacy of tranexamic acid in acute brain injury, hypothesizing that we would find a clinically meaningful result.

MATERIAL AND METHODS

This systematic review and meta-analysis were performed under the preferred reporting items for systematic review and meta-analysis (PRISMA) guidelines [14]. This study represents a continuation of prior research on the use of TXA previously undertaken by the authors [15, 16].

Search strategy

Two independent reviewers (M.A-J, L.S.) performed a computerized search of EMBASE, PubMed, Scopus, Web of Science and Cochrane Center Register of Controlled Trials (CENTRAL) from database inception until April 10, 2021. We included only English-language publications. Following the strategy, which combined keywords was used: ‘tranexamic’ or ‘TXA’ or ‘tranexamic acid’ or ‘hemorrhage control’ and ‘injuries*’ or ‘trauma’ or ‘wounds’ or ‘head injury’ or ‘brain injury’ or ‘traumatic brain injury’ or ‘TBI’ and ‘prehospital’ or ‘military’ or ‘combat’ or ‘civil*’ or ‘emergency medicine’ or ‘ED’ or ‘ER’. Additionally, we manually searched references listed in reports and review articles to identify potentially missed trials.

Selection criteria

Studies that were included in this meta-analysis had to fulfill the following PICOS criteria: 1. Participants, patients with head injury 18 years old or older; 2. Intervention, tranexamic acid treatment; 3. Comparison, non-TXA treatment; 4. Outcomes, detailed information for survival or mortality; 5. Study design, randomized controlled trials comparing TXA and non-TXA care for their effects in patients with brain injury. Studies were excluded if they were reviews, observational studies, animal studies, case reports, letters, conference or poster abstracts, or articles not containing original data.

Treatment was observed. More high-quality studies are needed to show the significant benefit of using TXA, especially in moderate and severe TBI patient groups.

KEY WORDS: blood conservation, antifibrinolytic, tranexamic acid, hemostasis, head trauma, meta-analysis

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Data extraction
Two reviewers (M.A-J, and L.S.) independently extracted all important information from the full-text original publications and entered it into an electronic data sheet specifically designed for this trial. Any disagreements were discussed and resolved in a consensus meeting with the third reviewer (A.G.). Extracted information included: year of study, country, study design, patient demographics, and study outcomes. Data were extracted for the following outcomes: 28-day or in-hospital mortality, Glasgow Outcome Scale (GOS) less than 4 points in 28-days follow-up [17], length of stay in Intensive Care Unit (ICU), and in-hospital and adverse events including thrombotic events. We also extracted data for longer follow-up if available. Duplicate reports from the same study were excluded.

Risk of bias and quality assessment
Two investigators (M.A-J, and L.S.) independently evaluated studies for risk of bias and quality assessment. Any disagreements were discussed and resolved in a consensus meeting with the third reviewer (A.G.). The RoB 2 tool (revised tool for risk of bias in randomized trials) was used to assess the quality of randomized studies [18] and the ROBINS-I tool (tool to assess the risk of bias in non-randomized studies of interventions) was used to assess the quality of non-randomized trials [19]. The risk of bias assessments was visualized using the Robvis application [20]. The scale has seven main domains (confounding, participant selection, classification of interventions, deviation from interventions, missing data, outcome measurement, and selection of reported results) and assigns one point for each of the following four judgments: critical, serious, moderate, and low. The review authors’ judgments about each risk of bias item are provided in Figures 4–5 in Supplementary File 1.

To assess the quality of evidence we applied the Grading of recommendations Assessment, Development, and Evaluation (GRADE) approach [21] with GRADEpro software (version 3.6 for MacOS). Moreover, the quality of evidence was rated (presence or absence) on the following variables: inconsistency, indirectness, imprecision of the results, and publication bias. The quality of evidence for the main outcomes was graded as high, low, and very low.

Outcomes
The primary outcome of the current meta-analysis was 28-day or in-hospital mortality. The secondary outcomes were Glasgow Outcome Scale (GOS) less than 4 points in 28-days follow-up, length of stay in Intensive Care Unit (ICU) and in hospital, and adverse events including thrombotic events.

Statistical analysis
We performed statistical analysis using Review Manager (version 5.4., Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark). To calculate the pooled odds ratio (OR) and 95% confidence interval (CI) of binary outcomes trial data were combined using the Mantel-Haenszel estimator. For continuous outcomes, the pooled mean difference with 95% CI were calculated using inverse-variance estimator. When the continuous outcomes were reported in a study as median, range, and interquartile range, we estimated means and standard deviations using the formula described by Hozo et al. [22].

Statistical heterogeneity was assessed by the Cochrane Q statistic and I² statistic which indicates the percentage of variability due to heterogeneity rather than sampling error [23]. A p-value < 0.10, and I² > 50%, indicated heterogeneity. This helps avoid false-negative results and the inclusion of such results in the meta-analysis. We performed a sensitivity analysis using the Hartung–Knapp–Sidik–Jonkman method when the number of studies was less than 10 [24]. Moreover, the random-effects model was used for analyses [25]. A p-value < 0.05 was taken to indicate statistical significance [26]. Statistical testing was 2-tailed.

We planned a priori to investigate potential publication bias using a funnel plot if it included over 10 trials for an outcome. For continuous outcomes, the Egger test was used to detect funnel plot asymmetry [27]. For dichotomous outcomes, we used the arc sine test. We considered publication bias to be present when the p-value was < 0.1 in the asymmetry test.

RESULTS

Study selection and characteristics
We identified 547 articles using the predefined search strategy. Of these, 96 were excluded because of duplication. After an assessment of the titles and abstracts, 415 publications were excluded as not relevant to the analyses. After examination of the full text of the selected articles, we finally include 9 randomized controlled trials for this meta-anal-
ysis. We display the process of study selection in the flowchart (Fig. 1). We summarize the details of selected trials in Table 1.

Of the nine trials meeting the inclusion criteria, a total of 5845 patients were treated with, and 5380 without, TXA [17, 28–35]. Four studies were conducted in Iran [31–34], and one in each of the following countries: Tunisia [28] and Thailand [35]. One study was performed in cooperation between the USA and Canada [17], and there were 2 multi-country studies involving more than 2 countries [29, 34].

Outcomes
Twenty-eight-day or in-hospital mortality were reported in six studies [17, 28–35]. It was 17.8% with and 19.3% without TXA (OR = 0.92; 95% CI: 0.83–1.01; p = 0.08; I² = 0%; Fig 2). Mortality rate between TXA vs non-TXA group was not statistically different at 7-days (14.3% vs 6.8% respectively; OR = 2.28; 95% CI: 0.57–9.15; p = 0.25) and 6-months (18.3% vs 19.9%; OR = 0.91; 95% CI: 0.63–1.31; p = 0.60; SDF).

Glasgow Outcome Scale (GOS) less than 4 points at 28-days follow-up was reported in three studies [28, 34, 35] and was 29.8% with TXA compared to 34.8% in the non-TXA group (OR = 0.91; 95% CI: 0.45, 1.82; p = 0.78; I² = 73%; Fig. 3A). GOS less than 4 points at 6-months follow-up was reported in two studies and was 35.8% vs 34.3% (OR = 0.76; 95% CI:
0.35–1.67; p = 0.50; I² = 55%; Fig. 3B) with and without TXA, respectively.

Length of stay in ICU was reported in two studies [28, 30] and was 14.7 ± 15.7 for TXA, and 11.4 ± 12.1 days for the non-TXA group (MD = 2.85; 95% CI: -0.07, 5.76; p = 0.06; I² = 0%; Figure 4A). Two studies reported length of hospital stay for TXA and non-TXA cohorts [28, 30]. The average length of hospital stay was 14.3 ± 14.9 days, vs 14.4 ± 14.0 days (MD = -0.30; 95% CI: -3.39, 2.79; p = 0.85; I² = 0%; Fig. 4B), with and without TXA, respectively.

### Table 1. Patient characteristics of the included studies

| Trial                     | Country       | Study design                              | TXA group | Non-TXA group |
|---------------------------|---------------|-------------------------------------------|------------|---------------|
|                           |               |                                           | No         | Age: 44 ± 20  | Sex/male: NS  | ISS: 21.8 ± 23.2 | 23.5 ± 25.6 |
|                           |               |                                           | 96         |               |               |               |               |
| CRASH-3 2019              | Multi-country | Randomized, placebo-controlled trial      | 4649       | 41.7 ± 19.0   | (80.5%)       | 3,742 ± 19.0   | NS           |
|                           |               |                                           | 84         | 39 ± 18       |               | 4,553 ± 19.0   | NS           |
|                           |               |                                           | 74         | 42.3 ± 18.3   | (90.5%)       | 67 ± 18.1     | NS           |
|                           |               |                                           | 75         | 39.3 ± 18.1   |               | 66 ± 18.1     | NS           |
| Fakharian et al. 2017     | Iran          | Double-blind, randomized clinical trial   | 40         | 35.4 ± 14.6   | (40.0%)       | 32 ± 14.9     | NS           |
|                           |               |                                           | 40         | 36.2 ± 14.9   | (70.0%)       | 28 ± 14.9     | NS           |
| Jokar et al. 2017         | Iran          | Single-blinded, controlled, randomized trial | 56        | 41.15 ± 20.3  |               | 40 ± 20.3     | NS           |
|                           |               |                                           | 44         | 37.40 ± 19.6  | (90.9%)       | 40 ± 19.6     | NS           |
| Mojallal et al. 2020      | Iran          | Double-blind controlled clinical trial    | 20         | 54.89 ± 19.1  | (70.0%)       | 14 ± 19.1     | NS           |
|                           |               |                                           | 20         | 55.16 ± 18.1  | (60.0%)       | 12 ± 18.1     | NS           |
| Mousavinejad et al. 2020  | Iran          | A double-blind, randomized, and placebo-controlled trial | 133       | 36.2 ± 14     | (83.5%)       | 111 ± 13.7    | NS           |
|                           |               |                                           | 137       | 37 ± 13.7     | (85.4%)       | 117 ± 13.7    | NS           |
| Perel et al. 2012         | Multi-country | A prospective randomized controlled trial | 657       | 40.4 ± 5.1    | (73.4%)       | 482 ± 3.2     | 233 ± 17.5   |
|                           |               |                                           | 309       | 38 ± 5        | (75.4%)       | 17.3 ± 3.2    | 17.5 ± 3     |
| Rowell et al. 2020        | USA/Canada    | A randomized, double-blind, 3-group, multicenter phase II trial | 120       | 34.8 ± 16.0   | (85.8%)       | 103 ± 15.3    | 107 ± 15.3   |
|                           |               |                                           | 118       | 34.1 ± 15.3   | (90.7%)       | 118 ± 15.3    | 118 ± 15.3   |
| Yutthakasemsunt et al. 2013 | Thailand          | A double blinded, placebo controlled randomized trial | 5580      | 5120          | 100.0%        | 0.92 (0.83, 1.01) | 1.00 (0.90, 1.11) |

**FIGURE 2.** Forest plot of 28-day or in-hospital mortality in TXA vs non-TXA group. The center of each square represents the weighted odds ratio for individual trials, and the corresponding horizontal line stands for a 95% confidence interval. The diamonds represent pooled results.
In the case of the TXA group, the most frequently observed adverse event (in 28-day or in-hospital follow-up) was a seizure, which occurred in 3.2% of patients in TXA group compared to 2.9% in non-TXA group (OR = 1.12; 95% CI: 0.92, 1.36; p = 0.27; I² = 0%). In the case of other complications, no differences were observed between TXA and non-TXA groups (Tab. 2).

**DISCUSSION**

This meta-analysis was designed to evaluate the safety and efficacy of TXA in the management of TBI. We found no statistically significant differences in both short- and long-term mortality between patients who received TXA and those who did not. However, while those findings are not statistically significant we observed that TXA decreases mortality in a 28-days period compared to non-TXA treatment (17.5% vs 19.0%, respectively; p = 0.06). Interestingly the authors of the CRASH-3 trial, the largest trial to date on the use of TXA, reported that the early administration (within 3 hours following injury) reduces head injury-related mortality in patients with mild-to-moderate, but not in those with severe head injury [29]. Similarly, Sprigg et al. [36] reported improvement in short-term mortality with TXA, but that long-term status was the same as in the non-TXA administered group.

Others report no mortality effect, although a study by Jokar [31] demonstrated a potential TXA benefit by a reduced size of intracranial hemorrhage. While these findings are supported by Yuthhakasem-sunt [35] and Mousavinejad, [33] Fakharian [30]
found that administration of TXA did not change the size of intracranial hemorrhage nor provide beneficial effects on clinical outcomes.

The lack of clinical outcome benefit was also reflected in our secondary outcome analysis. We found Glasgow Outcome Scale scored below 4 was not significantly different in those receiving TXA or not. In fact, the number of patients who scored below 4 was higher in the TXA group. The study by Roberts [37] revealed that the timing of the TXA administration is crucial. The early administration (up to 3 hours) reduces mortality regardless of confounding factors, while the administration after the 3-hour mark increases the risk of death due to bleeding. The length of stay in the ICU and the overall length of stay, although not statistically significant was surprisingly shorter for the non-TXA group. This might indicate that the use of TXA does not improve outcomes measured by the time spent in the ICU nor shortens the overall hospitalization time in TBI patients. This stands in contrast to overall trauma patients who benefit from the administration of TXA [37].

The most frequently observed adverse event following TBI was seizures. Although not significantly different, the TXA group experienced a 1.12 increase in seizure occurrence. This finding stands in line with those studies that report increased risk of seizure with TXA administration in a dose-dependent manner [38]. Other complications which were not significant but occurred at a numerically higher rate were thrombotic in nature. TXA administration increased the risk of thrombotic events [39] and should be taken into account when treating with this agent. Although some authors [40] indicate that the neurological outcomes after TXA administration in trauma are better than in the control group, possibly due to reduced cytotoxicity in the TLR4/TNF axis [41], it is worth noting that several studies blatantly forbid the use of TXA due to increased risk of thrombosis without additional clinical benefit [42, 43].

The results of our study should be interpreted in the context of its limitations. Most studies were of small size and thus at risk of overestimating treatment effects and underreporting relevant adverse effects. Furthermore, the findings of the CRASH-3 trial due to the high number of patients may distort the results, which is a major limitation in the interpretation of the data. Substantial heterogeneity was observed and contributed to lowering the evidence grade from high to moderate, however, this value is still high enough to justify the conclusions.

**CONCLUSIONS**

In summary, our analysis found showed no statistical significance between TXA and non-TXA treatment of TBI.

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**Table 2. Adverse events in 28-days follow-up**

| Adverse event               | No of studies | Events/participants | Events | Heterogeneity between trials | p-value for differences across groups |
|-----------------------------|---------------|---------------------|--------|-----------------------------|--------------------------------------|
|                             |               | TXA group           | Non-TXA group | OR | 95% CI | I² statistic |                                  |
| All vascular occlusive event| 2             | 146/7 016 (2.1%)    | 132/6 589 (2.0%) | 0.90 | 0.70–1.14 | 0.21 | 37% | 0.38 |
| Stroke                     | 3             | 62/7 136 (0.9%)     | 55/6 707 (0.8%) | 0.95 | 0.66–1.37 | 0.31 | 15% | 0.78 |
| Pulmonary embolus          | 4             | 44/7 232 (0.6%)     | 39/6 791 (0.6%) | 1.22 | 0.45–3.27 | 0.06 | 65% | 0.70 |
| Deep vein thrombosis       | 4             | 35/7 232 (0.5%)     | 28/6 791 (0.4%) | 0.95 | 0.58–1.57 | 0.60 | 0%  | 0.84 |
| Gastrointestinal bleeding  | 2             | 24/6 479 (0.4%)     | 36/6 398 (0.6%) | 0.66 | 0.40–1.11 | 0.66 | 0%  | 0.11 |
| Myocardial infarction      | 2             | 23/7 016 (0.3%)     | 21/6 589 (0.3%) | 0.98 | 0.54–1.79 | 0.39 | 0%  | 0.95 |
| Renal failure              | 1             | 100/6 359 (1.6%)    | 84/6 280 (1.3%) | 1.18 | 0.88–1.58 | NA  | NA  | 0.27 |
| Seizure                    | 2             | 228/7 016 (3.2%)    | 193/6 589 (2.9%) | 1.12 | 0.92–1.36 | 0.49 | 0%  | 0.27 |
Conflict of interest
All authors declare no conflict of interest.

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