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Efficacy and safety of tranexamic acid in acute traumatic brain injury: A meta-analysis of randomized controlled trials

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ABSTRACT

Introduction: Tranexamic acid (TXA) holds a pivotal role in the therapeutic approach to traumatic conditions. Nevertheless, its precise influence on diminishing mortality and limiting the progression of intracranial hemorrhage (ICH) during the treatment of traumatic brain injury (TBI) remains indeterminate.
Methods: PubMed, EMBASE, Cochrane Library, and Web of Science were searched for randomized controlled trials that compared TXA and a placebo in adults with TBI up to September 31, 2023. Two authors independently abstracted the data and assessed the quality of evidence. Additionally, subgroup analyses were performed to assess outcomes with low heterogenety.
Results: Our search strategy yielded 11,299 patients from 11 studies. The result showed that TXA had no effect on mortality (RR 0.93 [0.86, 1.00], $p = 0.06$; I^2: 0%, $p = 0.79$), poor clinical outcomes (RR 0.92 [0.78, 1.09], $p = 0.34$; I^2: 0%, $p = 0.40$), adverse events (RR 0.94 [0.83, 1.07], p = 0.34; I^2: 48%, $p = 0.10$), vascular occlusive events (RR 0.85 [0.68, 1.06], $p = 0.16$; I^2: 32%, $p = 0.22$), pulmonary embolism (RR 0.76 [0.47, 1.22], $p = 0.26$; I^2: 0%, $p = 0.83$), seizure (RR 1.11 [0.92, 1.35], $p = 0.27$; I^2: 0%, $p = 0.49$) and hemorrhagic complications (RR 0.78 [0.55, 1.09], $p = 0.14$; I^2: 0%, $p = 0.42$). TXA might reduce the rate of hemorrhagic expansion (RR 0.83 [0.70, 0.99], $p = 0.03$; I^2: 18%, $p = 0.29$) and mean hemorrhage volume (SMD −0.39 [−0.60, −0.18], p <0.001; I^2: 44%, $p = 0.13$).When the time interval from symptom onset to treatment was <3 h, TXA reduced mean hemorrhage volume (SMD −0.51 [−0.81, −0.20], $p = 0.001$; I^2: 0%, $p = 0.94$).
Conclusions: TXA did not elevate the risk of adverse event, however, the lack of reduction in mortality and the poor clinical outcomes constrain the value of clinical application. Early administration of TXA (within 3 h) may significantly decrease the likelihood of ICH growth in patients with TBI.

1. Introduction

Traumatic brain injury (TBI) stands as the predominant contributor to mortality among young adults and constitutes a significant source of both death and disability across all age groups in all countries [1]. The global annual incidence of TBI is estimated to range between 50 million to 60 million cases [2]. The pathophysiology of TBI encompasses diffuse axonal injury with damage to white matter tracts, traumatic intracerebral hemorrhage, and extracerebral bleeding, often with or without concurrent mass effect. Secondary brain damage can ensue from the expansion of hemorrhagic lesions, brain swelling, hypotension, hypoxia, hyperglycemia, pyrexia, and the ensuing activation of multiple biochemical cascades [3]. Among lots of potential secondary processes, the expansion of hemorrhagic lesions is one of the most important and devastating factors [4], which elevates the complexity of surgical excision and contributes to elevated rates of mortality and disability [5].

Tranexamic acid (TXA) has the capacity to competitively bind to lysine residues on fibrin, thereby effectively inhibiting the interaction between fibrinolytic enzymes and fibrin, ultimately preventing the dissolution of fibrin clots [6]. In a sizable clinical trial involving patients with intracranial hemorrhage and no significant extracranial blood, early administration of TXA (within 3 h) after an accident demonstrated heightened survival rates compared to a placebo [7]. Other RCTs have subsequently confirmed the safety of TXA [8,9]. The effect of TXA on reducing mortality and progression of intracranial hemorrhage (ICH) in patients with TBI remains a matter of contention [10-13]. The objective

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of this meta-analysis is to synthesize the most recent data in order to assess the effectiveness and safety of TXA on TBI.

2. Methods

This systematic review and meta-analysis was conducted based on the Cochrane Handbook for Systematic Reviews of Interventions [14] and the "Preferred Reporting Items for Systematic Reviews and Meta-Analysis" recommendations [15].

2.1. Search strategy

A thorough and exhaustive search was carried out across the databases of PubMed, EMBASE, Cochrane Library, and Web of Science to identify RCTs comparing TXA and a placebo in the adult with TBI up to September 31, 2023. Collaborating with a proficient medical librarian, we devised a meticulous search strategy, encompassing three key search terms: "tranexamic acid," "traumatic brain injury," and "randomized controlled trial." (see supplementary Appendix A. for search strategy, Appendix 1–1).

2.2. Inclusion and exclusion criteria

The inclusion criteria were as follows: (1) patients with any form of ICH arising from TBI; (2) compared the effectiveness of TXA, irrespective of dosage and timing of administration, and a corresponding placebo; (3) initial administration of TXA or placebo within 24 h after injury; (4) the study was a clinical RCT. Furthermore, the criteria for exclusion encompassed the following: (1) studies lacking relevant prognostic data, including adverse events, good clinical outcome, or mortality; (2) non-randomized controlled trials (non-RCTs), such as retrospective studies, case reports, literature reviews, conference abstracts, and correspondence; (3) studies that were either ongoing or still in the preliminary design phase; (4) investigations involving animal subjects and publications not in the English language.

2.3. Study selection

Two independent investigators, denoted as MZ and TL, undertook the initial screening of study titles and abstracts. Subsequently, studies conforming to the inclusion criteria underwent a comprehensive evaluation through the examination of full-text versions. The extraction of data and the evaluation of the included studies were performed independently by the same two investigators. In cases where disagreement arose regarding the eligibility of specific studies, these were resolved through deliberation and consensus.

2.4. Data extraction

One of the researchers, MZ, employed a standardized data extraction form for the extraction process. Subsequently, a second researcher, TL, reviewed the extracted data to assess the risk of bias and the quality of evidence for each included study individually. The extracted data encompassed various parameters, such as authors, year of publication, study design, TXA patients/placebo patients, mean or median age in years TXA/placebo, initial hemorrhage volume, TXA dosed, time from symptom onset to treatment, length of TXA treatment, length of follow-up, key results. The primary outcome was mortality, poor clinical outcomes, hemorrhagic expansion and mean hemorrhage volume. The secondary endpoint pertained to adverse events (including vascular occlusive events, new hemorrhage and seizure), vascular occlusive events (including pulmonary embolism (PE), deep vein thrombosis (DVT), stroke and myocardial infarction (MI)), pulmonary embolism, seizure and hemorrhage complication (including gastrointestinal bleeding and new cerebral hemorrhage).

The Glasgow Outcome Scale (GOS) was dichotomized, categorizing death, persistent vegetative state, and severe disability as poor clinical outcomes (GOS < 4), whereas good clinical outcomes (GOS ≥ 4) included moderate disability and good recovery.

2.5. Statistical analysis

For the execution of the meta-analysis, we utilized RevMan version 5.3 software developed by the Cochrane Collaboration Network. The pooled measure for dichotomous data was expressed as the risk ratio (RR) with a corresponding 95% confidence interval (CI). In cases where certain studies exhibited inconsistent units for average blood loss compared to others, continuous variables were quantified using the standardized mean difference (SMD) and its associated 95% CI in this analysis. The examination of heterogeneity across studies was conducted employing the Inconsistency Index (I^2), which spans from 0 to 100%. A value exceeding 50% or a p-value < 0.10 indicated statistically significant heterogeneity. The fixed-effects model was used for the meta-analysis. The Mantel-Haenszel method was employed to calculate the risk ratios (RR). We did not construct funnel plots to assess publication bias, as their reliability diminishes when the study count is less than ten. Furthermore, subgroup analyses were conducted to evaluate outcomes characterized by low heterogeneity. All p-values were subjected to two-tailed testing, with statistical significance established at a threshold of 0.05 or below.

3. Results

3.1. Description of included studies

Following a comprehensive database search, a total of 359 studies were identified. Subsequent to the elimination of duplicate entries and review articles, 167 studies were excluded. The evaluation of abstracts and titles led to the exclusion of an additional 171 records. Ultimately, after a meticulous review of 21 full-text articles with respect to the predefined inclusion and exclusion criteria, 11 articles met the eligibility criteria and were included in the qualitative synthesis (Fig.1) [11-13,16-23]. A collective cohort of 11,299 patients participated across 11 RCTs, with random allocation to either TXA treatment ($n = 5876$) or placebo ($n = 5423$). The sample size within each group ranged from 20 to 4649 patients. Three of the RCTs adopted a multicenter approach [11,18,23], while the remaining eight were conducted at single sites [12,13,16,17,19-22]. Participants in these trials were aged 13 years or older, encompassing both adult and adolescent populations. Across the included trials, the TXA dosage regimen was mostly similar, with the prevailing approach being a loading dose of 1 g, succeeded by a maintenance dose of 1 g administered over an 8-h period [11-13,16,18,21-23]. However, one trial employed a loading dose of 2 g followed by a maintenance dose of 1 g over 8 h [18], while another trial implemented a loading dose of 1 g, followed by a maintenance dose of 1 g administered every 6 h over a 48-h span [17]. Time from symptom onset to treatment displayed variation among the selected studies. Specifically, this interval was within 8 h in six trials [16,19-23], within 3 h in 3 trials [11,12,17] and within 2 h in 2 trials [13,18]. Furthermore, the length of following-up exhibited considerable diversity, spanning from a mere 8 min to a comprehensive 48 h. The follow-up periods extended across a range from 16 h to 6 months. Detailed baseline characteristics of the included trials are consolidated within Table 1 for reference.

3.2. Primary outcomes

The results of the meta-analysis revealed no substantial disparity in mortality between the TXA and control groups (RR 0.93 [0.86, 1.00], $p = 0.06$; I^2: 0%, $p = 0.79$) (Fig. 2A). Likewise, there was no statistically

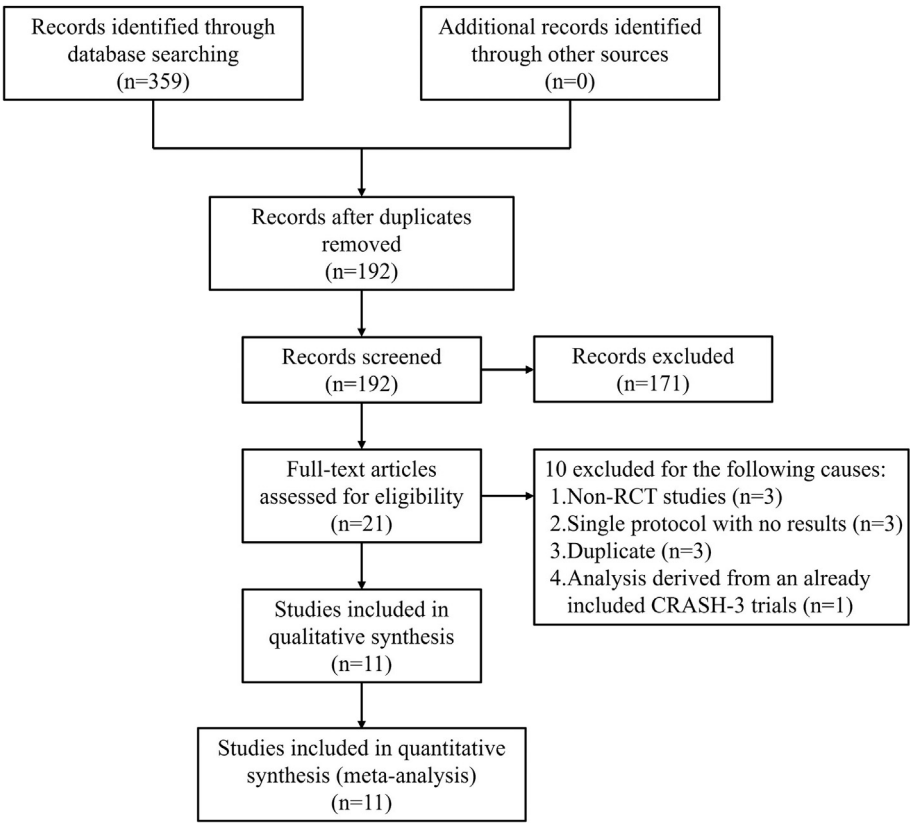

Fig. 1. Literature search and study selection strategy.

significant variation in the incidence of poor clinical outcomes between the TXA and placebo cohorts (RR 0.92 [0.78, 1.09], $p = 0.34$; I^2: 0%, $p = 0.40$) (Fig. 2B). However, it is notable that the rate of hemorrhagic expansion was notably lower in the TXA group (RR 0.83 [0.70, 0.99], $p = 0.03$; I^2: 18%, $p = 0.29$) (Fig. 2C). Furthermore, our meta-analysis suggests that the administration of TXA may potentially lead to a reduction in the mean hemorrhage volume observable in TBI patients, either in subsequent imaging or following surgical intervention (SMD −0.39 [−0.60, −0.18], p <0.001; I^2: 44%, $p = 0.13$) (Fig. 2D).

3.3. Secondary outcomes

The meta-analysis indicated that the use of TXA did not exhibit any association with adverse events (RR 0.94 [0.83, 1.07], $p = 0.34$; I^2: 48%, $p = 0.10$) (Fig. 3A), vascular occlusive events (RR 0.85 [0.68, 1.06], $p = 0.16$; I^2: 32%, $p = 0.22$) (Fig. 3B), pulmonary embolism (RR 0.76 [0.47, 1.22], $p = 0.26$; I^2: 0%, $p = 0.83$) (Fig. 3C), seizure (RR 1.11 [0.92, 1.35], $p = 0.27$; I^2: 0%, $p = 0.49$) (Fig. 3D) and hemorrhagic complications (RR 0.78 [0.55, 1.09], $p = 0.14$; I^2: 0%, $p = 0.42$) (Fig. 3E).

3.4. Subgroup analysis for RCTs with low heterogeneity

We performed a subgroup analysis based on two factors: the time from symptom onset to treatment (<3 h or >3 h) and the length of TXA treatment (<8 h or ≥8 h) (Appendix 1–2). When the time from symptom onset to treatment was <3 h, TXA did not demonstrate a significant impact on mortality (RR 0.94 [0.86, 1.02], $p = 0.12$; I^2: 0%, $p = 0.99$), poor clinical outcomes (RR 0.98 [0.82, 1.17], $p = 0.79$; I^2: 4%, $p = 0.31$) and adverse events (RR 0.93 [0.76, 1.15], $p = 0.51$; I^2: 51%, $p = 0.15$), however, it did show a reduction in mean hemorrhage volume (SMD −0.51 [−0.81, −0.20], $p = 0.001$; I^2: 0%, $p = 0.94$). In contrast, when the time from symptom onset to treatment exceeded 3 h, TXA exhibited no discernible effect on mortality (RR 0.75 [0.52, 1.09], $p = 0.14$; I^2: 0%, $p = 0.66$), poor clinical outcomes (RR 0.72 [0.47, 1.11], p = 0.14; I^2: 0%, $p = 0.68$), adverse events (RR 0.75 [0.36, 1.58], $p = 0.45$; I^2: 48%, $p = 0.09$) and mean hemorrhage volume (SMD −0.27 [−0.57, −0.02], $p = 0.07$; I^2: 66%, $p = 0.05$). Furthermore, different length of TXA treatment (<8 h or ≥8 h) were not associated with any statistically significant variation in mortality (RR 1.58 [0.61, 4.08], $p = 0.35$; I^2: 0%, p = 0.45; RR 0.92 [0.85, 1.00], p = 0.05; I^2: 0%, $p = 0.80$).

3.5. Risk of bias assessment

A detailed depiction of the risk of bias is provided in Fig. 4. The evaluation of risk of bias was carried out utilizing the Cochrane risk-of-bias tool designed for randomized trials. Notably, one of the articles (Mojallal et al.) exhibited a higher risk of bias, while the remaining ten articles displayed a lower risk of bias.

4. Discussion

This meta-analysis provides evidence that TXA effectively mitigated the progression of ICH in TBI patients. However, it did not yield a discernible effect on poor clinical outcomes or mortality. Additionally, the prevalence rates of adverse events did not demonstrate statistically significant distinctions.

Following a TBI, the hyperfibrinolysis state reaches its peak within 3 h, leading to hematoma expansion [24]. However, Moore et al. discovered that in the majority of traumatic injury cases, hyperfibrinolysis rapidly occurs post-injury, leading to a swift transition to fibrinolysis shutdown [25,26]. The fibrinolysis shutdown within one hour of severe injury is correlated with elevated mortality [27]. Theoretically, the use of TXA as an anti-fibrinolytic drug may enhance the likelihood of

Table 1
Characteristics of the included studies.

Reference	Study design	No. TXA/placebo	Age, years, TXA/placebo	Dose	Time interval*	Length of treatment	Length of follow-up	Key results
Rowell 2020	Multisite RCT	312/345/309	39(26–57)/40(26–56) /36(25–55)	1 g TXA followed by 1 g TXA maintenance,2 g TXA followed by 1 g TXA maintenance	<2 h	>8 h	6 months	TXA did not improve 6-month neurologic outcome.
Jokar 2017	Single site RCT	40/40	35.4(14.6)/ 36.2 (14.9)	1 g TXA followed by 1 g TXA maintenance	<2 h	>8 h	48 h	TXA reduced intracranial hemorrhage growth.
CRASH-32019	Multisite RCT	4649/4553	41.7 (19.0)/ 41.9 (19.0)	1 g TXA followed by 1 g TXA maintenance	<3 h	>8 h	28 days	TXA reduced the risk of head injury-related death in patients with mild-to-moderate head injury.
Fakharian 2022	Single site RCT	40/40	45.55(21.12)/40.30(18.24)	1 g TXA followed by 1 g TXA maintenance	<3 h	>8 h	3 months	TXA did not reduce the in-hospital post-TBI hemorrhage enlargement and improve the 3-months neurological outcome.
Safari 2021	Single site RCT	47/47	36.2(15.1)/36.4(14.1)	1 g TXA followed by 1 g every 6 h for 48 h	<3 h	48 h	48 h	TXA would reduce the amount of intracranial hematoma expansion.
CRASH-22012	Multisite RCT	133/137	36.0 (14.0) /37.0 (14.0)	1 g TXA followed by 1 g TXA maintenance	<8 h	>8 h	28 days	TXA did not increase the risk of hemorrhage.
Yutthakasemsunt 2013	Single site RCT	120/118	34.8 (16.0)/ 34.1 (15.3)	1 g TXA followed by 1 g TXA maintenance	<8 h	>8 h	24 h ± 8 h	TXA did not reduce intracranial hemorrhage, thromboembolic events and the risk of death.
Fakharian 2017	Single site RCT	74/75	42.3(18.3)/ 39.3(18.1)	1 g TXA followed by 1 g TXA maintenance	<8 h	8 h	3 months	TXA did not improve 3-month neurologic outcome and reduce intracranial hemorrhage.
Mousavinejad 2020	Single site RCT	20/20	54.89 (19.14)/ 55.16(18.15)	1 g TXA followed by 1 g TXA maintenance	<8 h	<8 min	6 h	TXA did not reduce intracranial hemorrhage.
Ebrahimi 2019	Single site RCT	40/40	32.22(15.90)/32.64(15.86)	1 g TXA followed by 1 g TXA maintenance	<8 h	>8 h	6 h	TXA did not reduce the epidural and subdural hemorrhage.
Mojallal 2020	Single site RCT	56/44	41.15(20.27)/37.40(19.6)	1 g TXA followed by 1 g TXA maintenance	<8 h	1 h	7d	TXA did not reduce the cerebral hemorrhage volume and mortality rate, but it decreased the ICU stay.

Time interval*: from symptom onset to treatment (hours).

fibrinolysis shutdown after injury. The observation that administering TXA late (3 h after injury) is linked to mortality [28] suggests that TXA should be administered early and may not be suitable for patients exhibiting evidence of fibrinolysis shutdown [29,30]. Prolonged fibrinolysis shutdown during resuscitation might pose a risk for persistent respiratory failure, potentially explaining the association between delayed TXA administration and increased mortality [26]. Our findings revealed that TXA exerted an inhibitory effect on hematoma growth, consistent with previous investigations [31-33]. In instances of substantial hematoma volumes, the potential for secondary brain damage intensifies, stemming from processes such as inflammation, oxidative stress, and cytotoxicity induced by erythrocyte lysates [34]. The release of thromboplastin after TBI is followed by the activation of both coagulation and fibrinolytic pathways [24]. The escalation of fibrinolysis represents a central contributor to coagulopathy in TBI, suggesting a potential avenue for TXA to mitigate traumatic intracerebral hemorrhage [35]. Nevertheless, certain studies have reported inconclusive findings regarding the efficacy of TXA in reducing intracranial hemorrhage [19,20,22]. This discrepancy in the results may be attributed to the fact that the time elapsed between symptom onset and treatment in these RCTs exceeded 3 h. Therefore, a subgroup analysis was conducted, revealing that when the time from symptom onset to treatment was <3 h, TXA demonstrated a reduction in mean hemorrhage volume. Therefore, our findings suggest that the timing of TXA administration is a pivotal determinant influencing its hemostatic effects, advocating for its prompt initiation, preferably within the first 3 h following symptom onset.

Our findings indicate that TXA administration did not yield a reduction in mortality. The CRASH-3 trial observed the most notable reductions in mortality following adjustments when TXA was administered within the first 3 h, particularly in cases of mild to moderate Glasgow Coma Scale (GCS) scores, while the effect on mortality appeared to be comparable in individuals with severe GCS scores [11]. Nonetheless, certain randomized controlled trials (RCTs) have reported findings in which TXA did not demonstrate a reduction in the mortality rate [16,20,36]. The CRASH-3 trial underwent a mid-trial revision of its primary outcome, shifting from all-cause mortality to mortality specifically related to head injury within the 28-day period following the initial injury. Other trial did not report head-injury-related death. Given the potential for subjectivity in determining the cause of death, which could introduce bias into an otherwise objective outcome. There remains controversy surrounding the mortality rates associated with TXA in patients with TBI. Early administration of TXA within <60 min has demonstrated the ability to attenuate endothelial apoptosis and necrosis in an in vitro trauma model [37]. In an animal model of TBI, the administration of TXA exhibited the capacity to ameliorate cellular inflammation and achieve notable immune modulation [38]. Nevertheless, the effects of TXA on poor clinical outcomes were not significantly improved, consistent with prior research findings [39,40]. Furthermore, our meta-analysis indicated that there was no heightened risk of adverse events associated with TXA administration, which aligns with the results of previous large-scale RCTs investigating the use of TXA in aneurysmal subarachnoid hemorrhage, trauma, and intracerebral hemorrhage [9,41,42]. However, the potential for bias should not be dismissed, as the pre-existing medical conditions of TBI patients were not comprehensively documented.

Chakroun et al. reported an elevated occurrence of pulmonary embolism associated with the application of TXA in individuals with TBI [36]. Beyond its plasmin-inhibiting effects, TXA competitively inhibits the activation of trypsinogen by enterokinase, exerts noncompetitive inhibition on trypsin, and demonstrates a weak inhibitory effect on thrombin [43]. TXA was observed to exhibit a dose-dependent increase in thrombus formation in animal models [44]. An extensive prospective analysis encompassing 17 trauma centers suggested that the risk of venous thromboembolism (VTE) remained elevated among trauma patients administered TXA. However, TXA was not definitively established

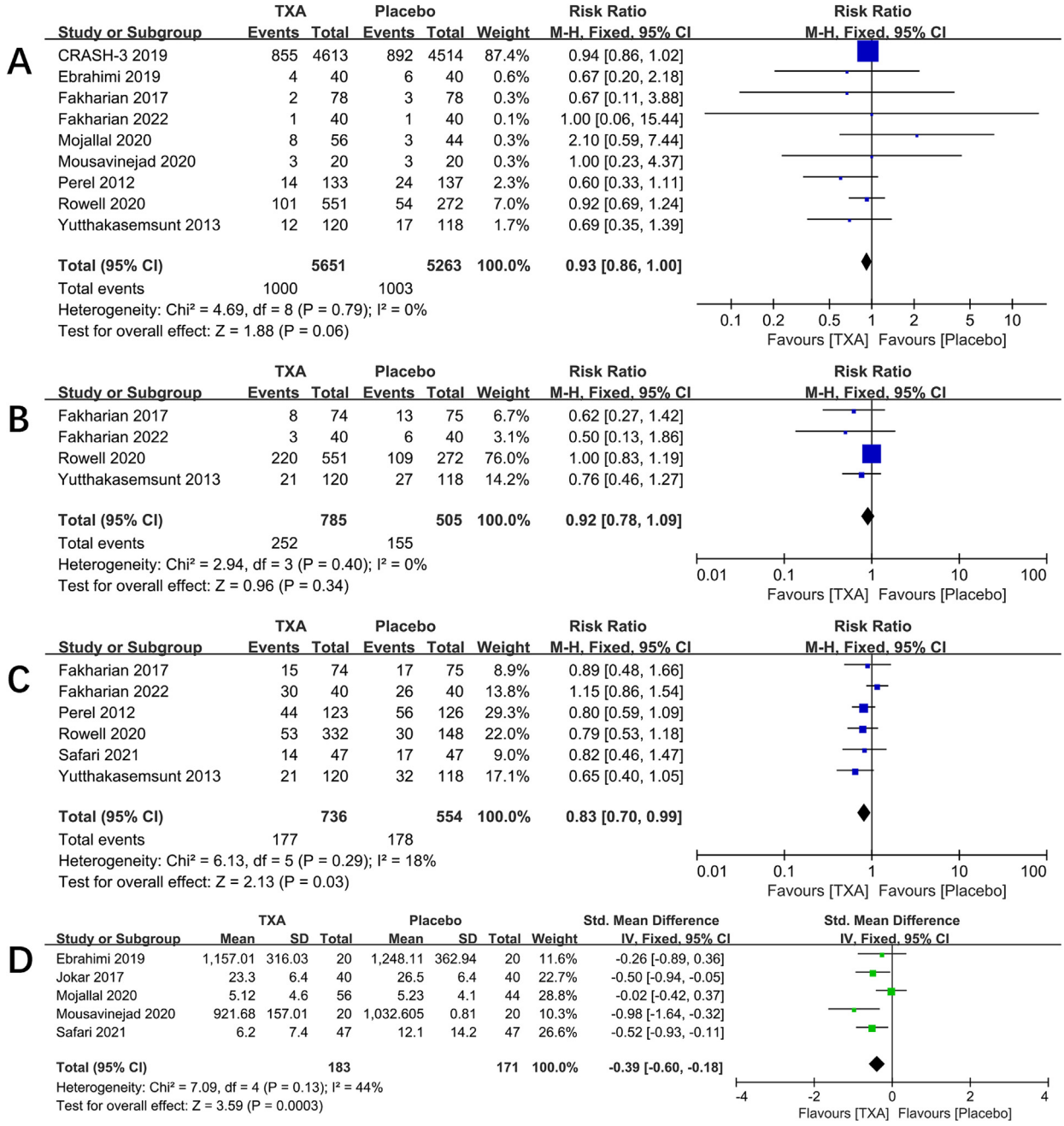

Fig. 2. Forest plot comparing the all-cause mortality (A), poor clinical outcomes (B), hemorrhagic expansion (C) and mean hemorrhage volume (D) between the TXA and placebo groups.

as an independent risk factor for VTE [45]. In another study conducted by Yutthakasemsunt et al., the use of TXA did not yield a reduction in thromboembolic events among patients with TBI [16]. Similarly, our analysis did not uncover evidence indicating that TXA heightened the risk of VTE, which suggests a certain level of safety associated with the use of TXA in TBI patients.

Seizures associated with the administration of TXA are most commonly observed in the immediate postoperative phase following cardiac surgery, although they can also manifest in patients undergoing noncardiac surgical procedures and other medical interventions [46]. The topical administration of TXA to the cerebral cortex has been demonstrated to induce seizures in cats [47]. The potential induction of hyperexcitability by TXA could be attributed to its interference with GABA-driven inhibition of the central nervous system (CNS) [48], and there might be a dose-dependent escalation in the risk of seizures associated with TXA [49]. In patients suffering from moderate to severe TBI, excepting those in a state of shock, there was an apparent threefold rise in the incidence of epilepsy in comparison to the placebo group. Nevertheless, this observed disparity did not attain statistical significance [18]. The potential risk of seizures associated with TXA was brought to attention in a systematic review conducted by Lin and Xiaoyi. Nevertheless, the majority of the subjects in this review underwent cardiac surgery and predominantly received higher doses of tranexamic acid, exceeding 50 mg/kg [50]. Within a comprehensive meta-analysis incorporating a total of 234 studies, no substantiated evidence emerged to suggest that TXA heightened the risk of seizures in patients with bleeding disorders [49]. Moreover, a prospective study identified lobar hematoma as the most influential independent predictor of early seizures following intracerebral hemorrhage, and it was determined that TXA did not introduce an elevated risk of post-intracerebral

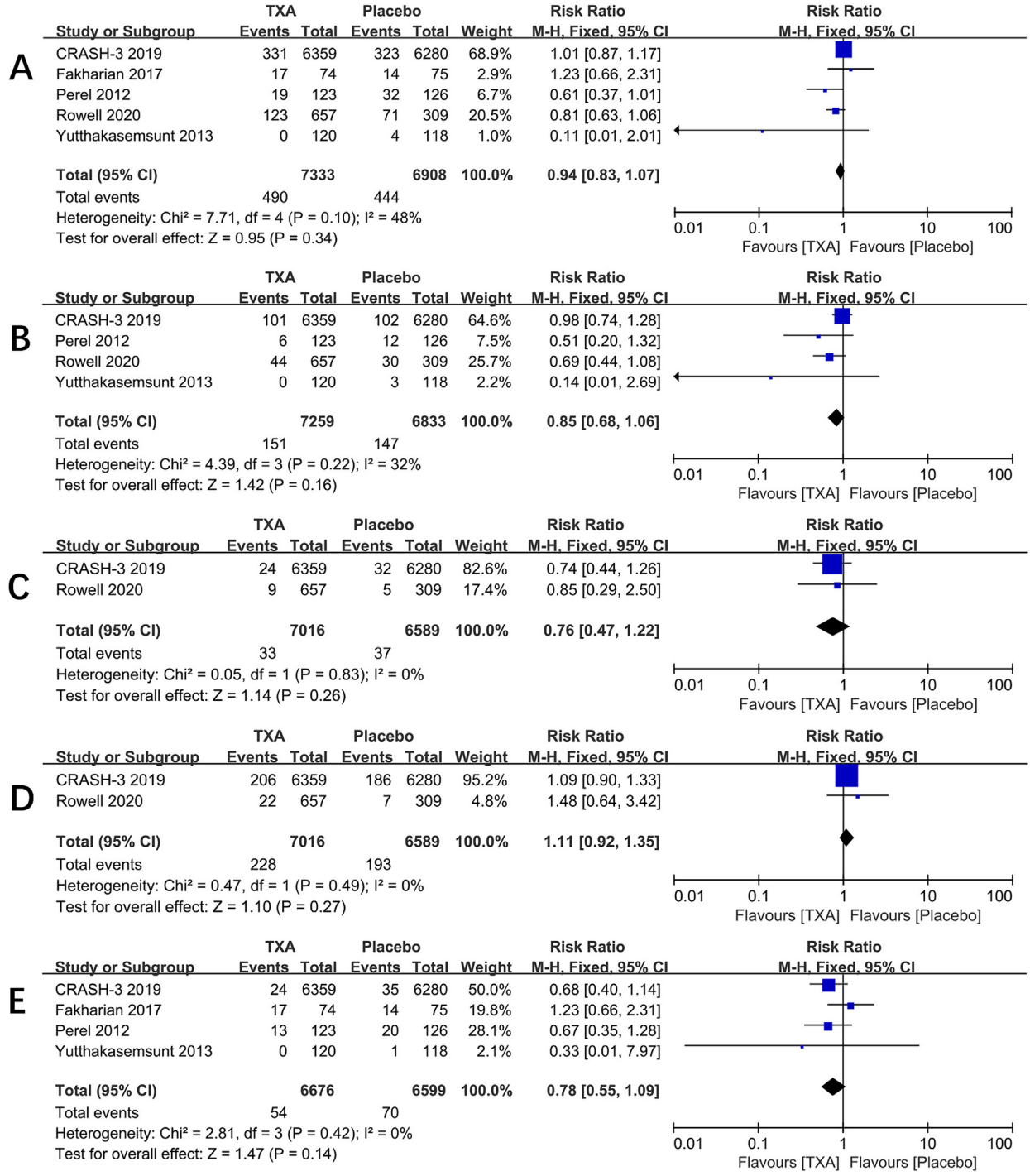

Fig. 3. Forest plot comparing the adverse events (A), vascular occlusive events (B), pulmonary embolism (C), seizure (D) and hemorrhagic complications (E) between the TXA and placebo groups.

hemorrhage seizures within the initial 90-day period [51]. Similarly, our own meta-analysis yielded results aligning with this observation, failing to identify any increased risk of seizures associated with TXA.

Several limitations must be acknowledged in our study. Firstly, we encountered constraints in executing various pre-planned subgroup analyses owing to the paucity of granular data within the published literature. Secondly, the included RCTs in our meta-analysis exhibited limitations in reporting complications, such as seizures and pulmonary embolism. Thirdly, due to the differences in factors such as the duration of TXA treatment, intervention dose, time from symptom onset to treatment and the severity of TBI, our broad inclusion criteria led to a certain degree of population heterogeneity.

5. Conclusion

Early TXA administration (within 3 h) confers a marked and statistically significant reduction in the likelihood of progressive intracranial hemorrhage in individuals suffering from TBI. Moreover, the absence of a discernible increase in the incidence of adverse events underscores the safety profile of TXA when administered to patients with TBI.

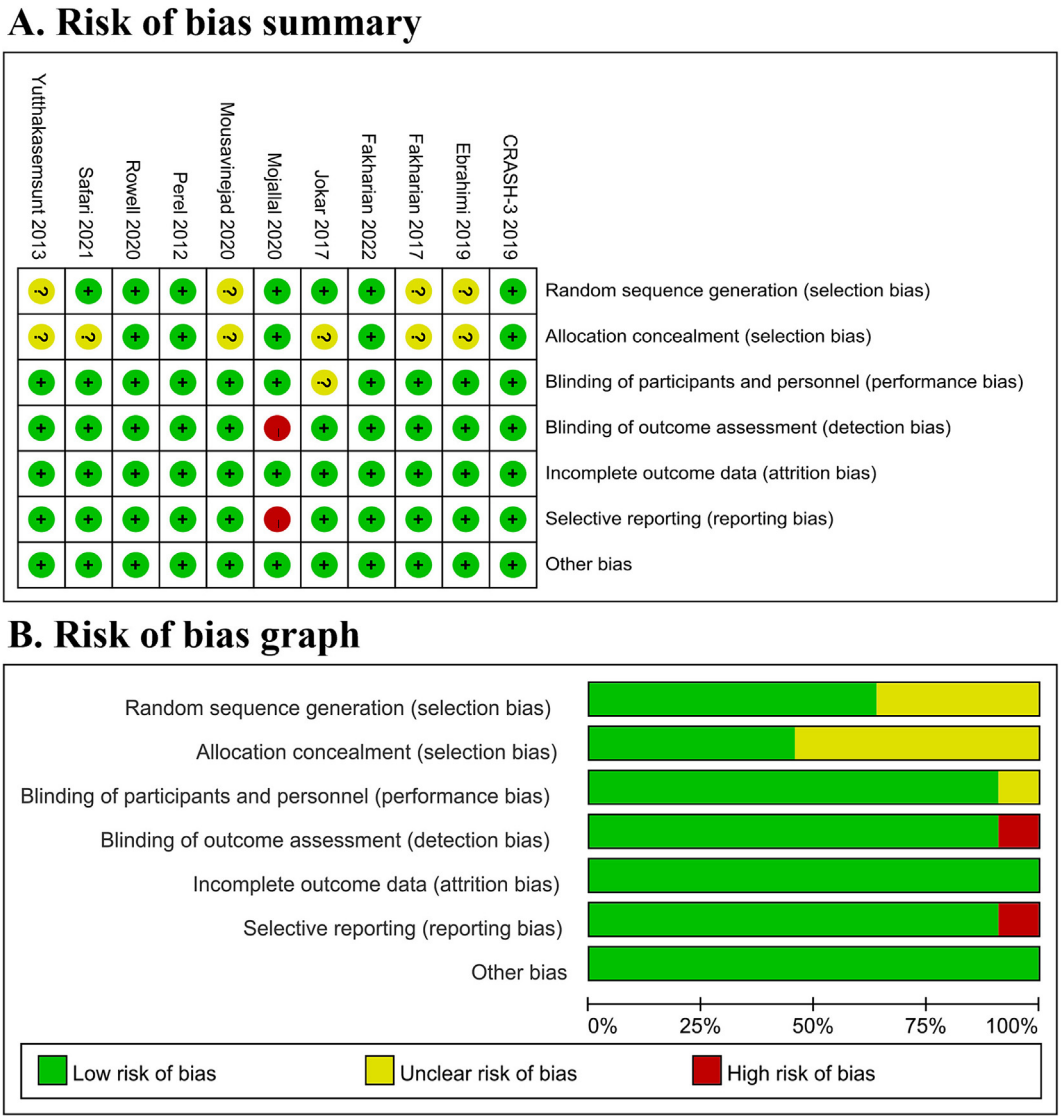

Fig. 4. Risk of bias assessment. A. Authors' judgments about each risk of bias item for each included study. B. Authors' judgments about each risk of bias item presented as percentages across all included studies.

Nevertheless, the absence of demonstrable ameliorations in mortality rates and the persistence of suboptimal clinical outcomes serve as constraining factors that curtail the utility of TXA in the clinical context.

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Authors' contributions

Minzhi Zhang collected information and wrote articles. Tao Liu designed the research and modified the article. The two authors read and approved the final manuscript.

CRediT authorship contribution statement

Minzhi Zhang: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Tao Liu:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no competing interests.

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Not applicable.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ajem.2024.03.005.

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