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SYSTEMATIC REVIEW

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

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Abstract

Purpose: With the publication of a large randomized-controlled trial (RCT) suggesting that tranexamic acid (TXA) may improve head-injury-related deaths, we aimed to determine the safety and efficacy of TXA in acute traumatic brain injury (TBI).

Methods: In this systematic review and meta-analysis, we searched MEDLINE, PubMed, EMBASE, CINHAL, ACPJC, Google Scholar, and unpublished sources from inception until June 24, 2020 for randomized-controlled trials comparing TXA and placebo in adults and adolescents (≥ 15 years of age) with acute TBI. We screened studies and extracted summary estimates independently and in duplicate. We assessed the quality of evidence using the grading of recommendations assessment, development, and evaluation approach. This study is registered with PROSPERO (CRD42020164232).

Results: Nine RCTs enrolled 14,747 patients. Compared to placebo, TXA had no effect on mortality (RR 0.95; 95% CI 0.88–1.02; RD 1.0% reduction; 95% CI 2.5% reduction to 0.4% increase, moderate certainty) or disability assessed by the Disability Rating Scale (MD, − 0.18 points; 95% CI − 0.43 to 0.08; moderate certainty). TXA may reduce hematoma expansion on subsequent imaging (RR 0.77; 95% CI 0.58–1.03, RD 3.6%, 95% CI 6.6% reduction to 0.5% increase, low certainty). Risks of adverse events (all moderate, low, or very low certainty) were similar between placebo and TXA.

Conclusions: In patients with acute TBI, TXA probably has no effect on mortality or disability. TXA may decrease hematoma expansion on subsequent imaging; however, this outcome is likely of less importance to patients. The use of TXA probably does not increase the risk of adverse events.

Keywords: Randomized, Clinical trial, Tranexamic acid, Traumatic, Brain injury

Introduction

Traumatic brain injury (TBI) is a leading cause of mortality and morbidity worldwide [1–3], with the vast majority of patients presenting with intracranial bleeding [4]. In particular, TBI is more common in low- and middle-income countries with youth and adolescents being

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disproportionately affected [5, 6]. Progressive hematoma expansion secondary to high levels of fibrinolysis and coagulopathy has been associated with worse prognosis and increased risk of intracranial hypertension, brain herniation, and death in patients with TBI [7]. Tranexamic acid (TXA) is an antifibrinolytic agent that reduces bleeding by inhibiting plasmin production and preventing fibrin degradation. Trauma guidelines have recommended the early administration of TXA in severely injured adult trauma patients with extracranial bleeding based on the results of the CRASH-2 trial which demonstrated survival benefit in bleeding trauma patients with no increase in adverse events [8–10]. Other large RCTs have further confirmed the safety of TXA administration in a number of heterogenous populations [8, 11, 12]; however, in a recently published RCT, TXA was associated with an increased rate of venous thromboembolic events in patients with gastrointestinal bleeding [13].

The role of TXA in patients with TBI or intracranial bleeding is controversial, with conflicting trial results [14]. Previously published meta-analyses examining the effect of TXA in TBI have suggested benefit of TXA in this population, but conclusions are limited by imprecision [15]. With the recent publication of the CRASH-3 trial [16], the largest examining this question, as well as the out-of-hospital TXA versus placebo trial [17], we conducted a systematic review and meta-analysis examining the efficacy and safety of TXA in acute TBI.

Take-home message

In patients with acute TBI, TXA probably has no effect on mortality or disability. The use of TXA probably does not increase the risk of adverse events.

Methods

The protocol for this systematic review was registered on PROSPERO (CRD42020164232) April 28, 2020. We last updated our search on June 24, 2020 to ensure that there were no new trials that would meet the inclusion criteria of our systematic review and meta-analysis. We have submitted an update to PROSPERO which reflects this search update. Any deviations from the published protocol are highlighted with an accompanying explanation.

Systematic search

We conducted a comprehensive search of MEDLINE, PubMed EMBASE, CINHAL, American College of Physicians Journal Club (ACPJC), Google Scholar, and unpublished sources including WHO ICTRP, PROSPERO, Clinicaltrials.gov, and the Cochrane trial registry from inception until June 24, 2020 for RCTs investigating the role of TXA in adult patients with TBI. We did not apply language restrictions. We developed the search strategy with the assistance of an expert medical librarian and included three search terms: 'Tranexamic acid', 'Traumatic Brain injury' and 'Randomized Controlled Trials' (see supplementary appendix for search strategy, appendix 1–7). We used the Medical Subject Headings database for identification of synonyms. We examined the reference list of full-text articles for additional relevant studies. We also searched conference proceedings within the last 2 years for the Society of Critical Care Medicine (SCCM), the European Society of Intensive Care and Emergency Medicine (ESICM), the American Association for the Surgery of Trauma (AAST), and the Eastern Association for the Surgery of Trauma (EAST).

Study selection

We included RCTs if they examined patients with TBI who were randomized to intravenous TXA administration as compared to placebo or usual care. We included studies of adolescent ($\geq$15 years of age) and adult patients with any type of intracranial hemorrhage secondary to TBI and who received TXA at any dose. We included studies which reported on the following outcomes: mortality, disability (as measured by the Glasgow Outcome Scale (GOS), the Glasgow Outcome Scale-Extended (GOS-E), or the Disability Rating Scale (DRS)), hematoma expansion on subsequent neuroimaging, need for neurosurgical intervention, hospital and intensive care unit (ICU) length of stay, and adverse events including pulmonary embolism (PE), deep vein thrombosis (DVT), stroke, and seizure. For outcomes reported at multiple timepoints, we used the longest reported follow-up timepoint.

After implementation of the search strategy, two reviewers screened all potentially relevant citations independently and in duplicate. Citations deemed potentially relevant by either screener were advanced to second-stage full-text review. Full texts were subsequently reviewed for eligibility, with disagreements resolved by consensus, and third-party adjudication if required. We captured reasons for exclusion at the full-text screening stage.

Data extraction and quality assessment

Reviewers extracted data independently and in duplicate using pre-piloted data abstraction forms. We extracted the following information from included studies: study title, first author, demographic data, details of the intervention, and control, outcome data, and risk of bias (RoB) for each study. We contacted study authors for clarification when the population characteristics, method of

follow-up, or outcome data were unclear or not reported. In particular, we acquired all-cause mortality data from the CRASH-3 authors. We assessed RoB independently and in duplicate using a modified Cochrane RoB tool [18] for which each domain is rated as "low", "probably low", "high", or "probably high". We examined the following RoB domains: sequence generation, allocation sequence concealment, blinding, selective outcome reporting, and other bias (such as stopping early and funding source). We rated the overall RoB for an individual study as the highest risk attributed to any domain.

We assessed the overall certainty of evidence for each outcome using the Grading Recommendations Assessment, Development and Evaluation (GRADE) approach [19]. We resolved disagreements for RoB or GRADE assessment by consensus. We used the Guideline Development Tool (https://www.gradepro.org) to formulate the Summary of Findings table.

Statistical analysis

We used DerSimonian and Laird random-effects models to conduct the meta-analysis [20] with RevMan 5.3 (Cochrane Collaboration, Oxford) software. We generated study weights using the inverse variance method. We present results as relative risks (RRs) and risk difference (RD) for dichotomous outcomes and as mean differences (MDs) for continuous outcomes, all with 95% confidence intervals (CIs). We calculated absolute effects using the pooled baseline prevalence from the control arm of included trials.

We assessed heterogeneity between trials using visual inspection of the forest plots, the Chi-squared test for homogeneity (where $p < 0.1$ indicates important heterogeneity), and the I^2 statistic (for which a value of 50% or greater was considered reflective of potentially important heterogeneity) [21]. Although planned, 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 [22]. We performed a predefined subgroup analysis comparing studies at high RoB compared to those at low RoB. We also performed two post hoc sensitivity analyses, one excluding the results of the largest trial (CRASH-3) [16] and another excluding studies enrolling adolescents [17, 23–25]. We performed this sensitivity analysis excluding the results of CRASH-3 as it was the largest trial and because they changed their primary outcome midway through the trial; of note, this was explained by the authors in their statistical plan as an effort to reduce the dilution of effect from non-head-injury-related deaths [26]. We also performed a post hoc subgroup analysis as requested by peer reviewers examining mortality in high-income versus low-to-middle-income countries as defined by the World Bank Classification.

We conducted trial sequential analysis (TSA) [27] using a random-effects model for mortality. For the TSA, we used a statistical significance level of 5%, a power of 80%, and a relative risk reduction of 10%. We used a model variance-based heterogeneity correction and did this analysis using Trial Sequential Analysis v.0.9.5.10 beta software (Copenhagen Trial Unit, Centre for Clinical Intervention Research, Rigshospitalet, Copenhagen, Denmark, https://www.ctu.dk/tsa).

Results

Of the 672 citations identified in the search (see Fig. 1), we excluded 200 duplicates and a further 446 citations after title and abstract screening. We assessed 26 full texts and included 9 RCTs in the review [16, 17, 23–25, 28–31]. There were 14,747 patients included in this study. One trial was initially not published in a peer-reviewed journal [17]; however, we extracted the data from ClinicalTrials.gov and then subsequently updated this data upon its publication [17]. Baseline characteristics of included trials are summarized in Table 1.

Description of included studies

Three RCTs were multicenter [16, 17, 30], while six were conducted at a single site [23–25, 28, 29, 31]. The mean age of participants ranged from 35 to 55 years. All trials included adults; however, four trials also included adolescents [17, 23–25]. One trial excluded severe TBI, defined as Glasgow Coma Scale (GCS) < 8 at presentation [25], while two trials excluded mild TBI (GCS > 12) [17, 24]. The other trials enrolled patients with any TBI severity; however, the majority of included patients had moderate-to-severe TBI (see Table 1 for more details regarding TBI severity from included trials). Although all included trials focused mainly on patients with TBI, three trials explicitly excluded patients with extracranial injuries [16, 23, 31], two trials excluded patients who required immediate surgery [24, 25], and two trials excluded patients who required either massive transfusions or transfusion of fresh frozen plasma [28, 29]. The timing of TXA administration varied among studies: within 2–3 h in 3 trials [16, 17, 25] and within 8 h in 5 trials [23, 24, 28–30]. One trial allowed for TXA administration up to 24 h from initial presentation [31]. The dosage of TXA was similar across included trials with the most common regimen being a loading dose of 1 g, followed by a maintenance dose of 1 g over 8 h. One trial compared two different TXA dosing regimens (1 g and 2 g loading dose) versus placebo, and we grouped both TXA arms together for the purposes of analyses [17]. Two of the included trials [23, 31] were judged to be at high RoB, four trials [17, 25, 28, 29]

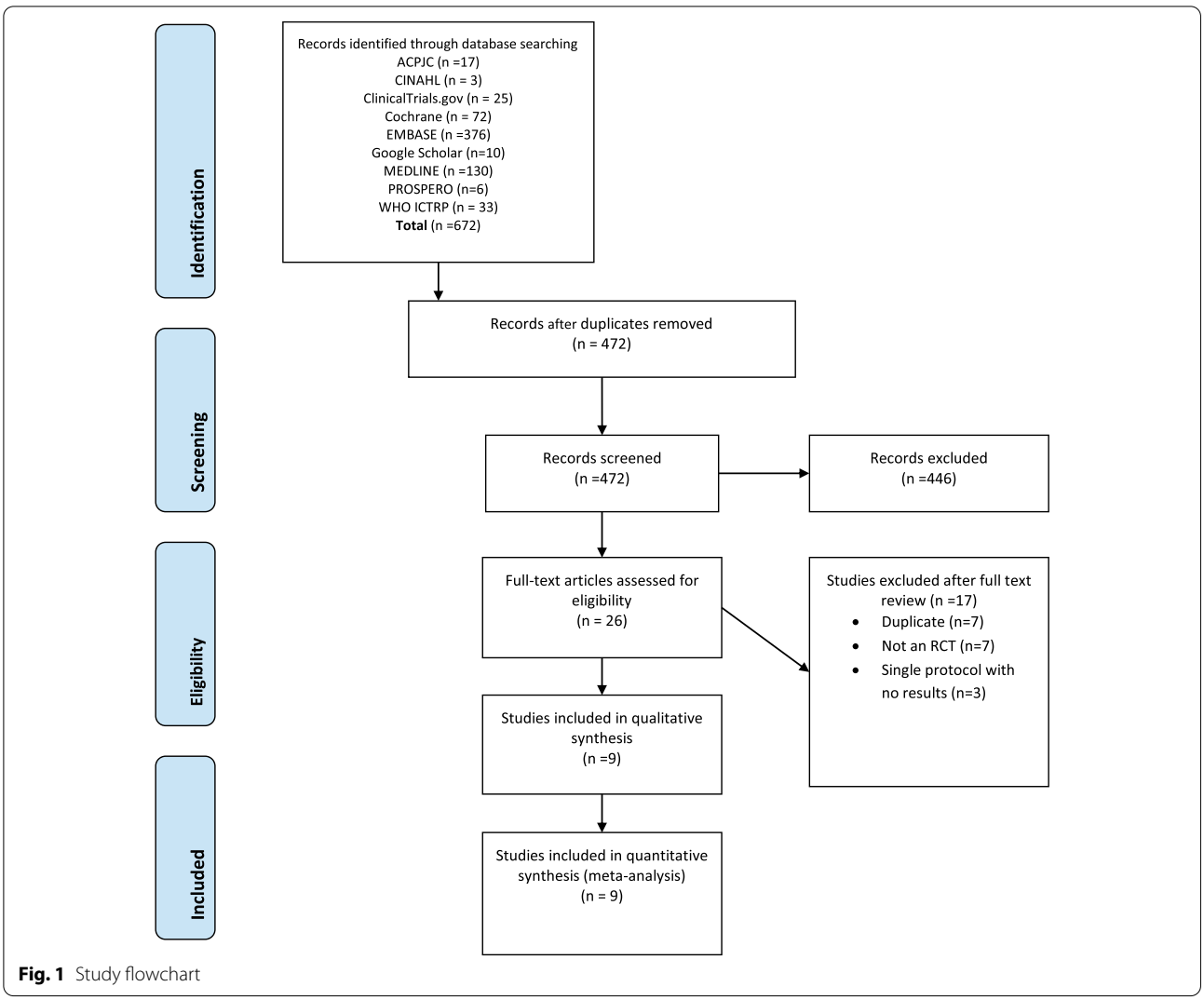

Fig. 1 Study flowchart

at probably high RoB, and one trial [16] at probably low RoB, while two trials [8, 24] were judged to be at low RoB (see Table 2 for all RoB judgements).

Efficacy outcomes

Table 3 shows the summary of findings for all outcomes including the certainty of evidence. Pooled analysis found that TXA likely had no effect on mortality [RR 0.95; 95% CI 0.88–1.02; risk difference (RD) 1.0% reduction; 95% CI 2.5% reduction to 0.4% increase; moderate certainty] (Fig. 2 and Table 3), or disability as assessed with the DRS (MD − 0.18 points; 95% CI − 0.43 to 0.08; moderate certainty), and an uncertain effect on disability based on the proportion of patients with a GOS score less than 4 or a GOS-E score less than or equal to 4 [RR 0.9; 95% CI 0.69–1.17; 0.3% risk difference (RD); 95% CI − 1.1% to 0.6%; very low certainty] (Figs. 3, 4). Of note, one of the studies did not report the standard deviation of the DRS in their published manuscript, but we were able to acquire these data from their results presented on ClinicalTrials.gov [17]. As per the TSA analysis, the optimal information size was not reached for mortality, contributing to the assessment of imprecision and overall moderate certainty (See supplementary appendix, appendix 9, supplement Fig. 12).

TXA administration may reduce hematoma expansion on subsequent neuroimaging (see supplementary appendix, appendix 8, supplement Fig. 4b) (RR 0.77; 95% CI 0.58–1.03; RD 3.6% reduction; 95% CI 6.6% reduction to 0.5% increase); however, this was based on low certainty evidence, limited by imprecision. Hematoma expansion as assessed by volume of blood in millilitres (mL) seen on subsequent neuroimaging may also be reduced in patients who received TXA (MD − 2.46 mL; 95% CI − 6.46 mL to 1.55 mL; moderate certainty), although the

Table 1 Baseline characteristics of included studies

Study author and year	Study design	No. of patients TXA/placebo	Mean or median age in years TXA/placebo	Enrollment time after trauma	Length of follow-up	Length of follow-up for mortality	TXA dose	Inclusion criteria	Exclusion criteria	Severity of TBI Mild 13–15 Moderate 9–12 Severe 3–8
Rowell et al., 2020	Multisite RCT	657/309	Bolus-Maintenance arm: 39 Bolus Only arm: 40 Placebo arm: 36	2 h	6 m	28d	Bolus-Maintenance arm: 1 g TXA bolus followed by 1 g TXA. Bolus only arm: 2 g TXA bolus followed by a placebo infusion	(1) GCS ≤ 12 (2) Prehospital SBP ≥ 90 (3) Age ≥ 15yrs (or weight ≥ 50 kg if age is unknown)	(1) GCS = 3 with unreactive pupil (2) CPR by EMS prior to randomization (3) Burns (4) Pregnancy	Mild (3.2%) Moderate (41.7%) Severe (55.1%)
Mousavinejad et al., 2020	Single site RCT	20/20	55 ± 19/55 ± 18	8 h	6 h after surgery	N/A	1 g TXA bolus followed by 1 g TXA maintenance	(1) ≥ 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)	Mild (7.5%) Moderate (20%) Severe (67.5%)
Roberts et al., 2019	Multisite RCT	6406/6331	42 (19)/42 (19)	Within 3 h and up to 8 h from injury	28 days or at hospital discharge or death	28d	1 g TXA bolus followed by 1 g TXA maintenance	(1) Adults with TBI within 3 h of injury (2) GCS ≤ 12 or any intracranial bleeding on CT scan	Major extracranial bleed	Mild: (TXA arm 27%), (Placebo arm 28%) Moderate: (TXA arm 33%), (placebo 33%) Severe: (TXA arm 40%), (Placebo arm 38%)
Ebrahimi et al., 2019	Single site RCT	40/40	SDH: 40 ± 18/40 ± 18 EDH: 24 ± 7/25 ± 7	8 h	7 days or at discharge	At hospital discharge	1 g TXA bolus followed by 1 g TXA maintenance	(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	N/A

Table 1 (continued)

Study author and year	Study design	No. of patients TXA/placebo	Mean or median age in years TXA/placebo	Enrollment time after trauma	Length of follow-up	Length of follow-up for mortality	TXA dose	Inclusion criteria	Exclusion criteria	Severity of TBI Mild 13–15 Moderate 9–12 Severe 3–8
Chakroun-Walha et al., 2018	Single site RCT	96/84	44 ± 20/39 ± 18	24 h	28 days	28d	1 g TXA bolus followed by 1 g TXA maintenance	(1) Age ≥ 18 years (2) TBI with intracranial bleeding on initial or second CT (3) Randomization and treatment within 24 h of injury	(1) Significant extracranial bleeding (2) History of VTE (3) Pregnancy (4) Coagulopathy	N/A
Fakharian et al., 2017	Single site RCT	78/78	42 ± 18/39 ± 18	8 h	3 m	3 m	1 g TXA bolus followed by 1 g TXA maintenance	(1) Age ≥ 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	N/A
Jokar et al., 2017	Single site RCT	40/40	35 ± 15/ 36 ± 145	2 h	48 h	N/A	1 g TXA bolus followed by 1 g TXA maintenance	(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	N/A

Table 1 (continued)

Study author and year	Study design	No. of patients TXA/placebo	Mean or median age in years TXA/ placebo	Enrollment time after trauma	Length of follow-up	Length of follow-up for mortality	TXA dose	Inclusion criteria	Exclusion criteria	Severity of TBI Mild 13–15 Moderate 9–12 Severe 3–8
Yutthakasemsunt et al., 2013	Single site RCT	120/118	35 (16)/ 34 (15)	8 h	Until second CT was done at 24 h ± 8 h	At hospital discharge	1 g TXA bolus followed by 1 g TXA maintenance	(1) Age ≥ 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	Mild: Excluded Moderate: (TXA arm 53%), (Placebo arm 47%) Severe: (TXA arm 49%), (Placebo arm 51%)
Perel et al., 2012	Multisite RCT	133/137	36.2 (14.0)/ 37.0 (13.7)	8 h	28 days	28d, hospital discharge, or death (which ever came first)	1 g TXA bolus followed by 1 g TXA maintenance	(1) Fulfils the inclusion criteria for the CRASH-2 trial (2) GCS ≤ 14 (3) Baseline clinical CT scan consistent with TBI	(1) Pregnancy and (2) Patients for whom a second brain CT scan was not possible	N/A

RCT randomized-controlled trial, *TXA* tranexamic acid, *GCS* Glasgow Coma Scale, *SBP* systolic blood pressure, CPR cardiopulmonary resuscitation, *EMS* emergency medical services, *TBI* traumatic brain injury, *CT* computed tomography, *SDH* subdural hemorrhage, *EDH* epidural hemorrhage, *VTE* venous thromboembolism, *ICH* intracranial hemorrhage, *N/A* not applicable

Table 2 Risk of bias assessment

Study (author, year)	Bias arising from the randomization process	Bias due to deviations from intended interventions	Bias due to missing outcome data	Bias in measurement of the outcome	Bias in selection of the reported result	Overall ROB
Rowell, 2020	Low	Low	Probably high	Low	Low	Probably high
Mousavinejad, 2020	Low	Low	Low	Probably high	Low	Probably high
Roberts I, 2019 (CRASH 3)	Low	Low	Low	Low	Probably low	Probably low
Ebrahimi, 2019	Low	Low	Low	Probably high	Low	Probably high
Chakroun-Walha, 2018	High	High	Low	High	Low	High
Fakharian, 2017	Low	Probably high	Low	Probably high	Low	High
Jokar, 2017	Low	Probably high	Low	Low	Low	Probably high
Yutthakasemsunt, 2013	Low	Low	Low	Low	Low	Low
P Perel,2012 (CRASH 2)	Low	Low	Low	Low	Low	Low

absolute difference was small (See supplementary appendix, appendix 8, supplement Fig. 4a).

TXA administration had an uncertain effect on hospital length of stay [MD 0.19 days (d); 95% CI − 1.11d to 1.49d; low certainty] and ICU length of stay (MD 1.33d; 95% CI − 0.99d to 3.65d; very low certainty) (supplementary Appendix, appendix 8, supplement Figs. 5–6). We found an uncertain effect on the need for neurosurgical intervention in those receiving as compared to those not receiving TXA (RR 1.11, 95% CI 0.89–1.39; RD 1.7% increase; 95% CI 1.7% reduction to 5.9% increase; low certainty) (supplementary Appendix, appendix 8, supplement Fig. 2). A post hoc subgroup analysis found that TXA administration had a similar effect in low-to-middle-income countries (RR 0.94, 95% CI 0.74–1.18) as it did in high-income countries (p value for subgroup effect > 0.10) (supplementary Appendix, appendix 8, supplement Fig. 11). CRASH-2 and CRASH-3 were not a part of this analysis, because these trials included patients from both high- and low-to-middle-income countries [8, 16].

Safety

We found similar rates of adverse events (a composite outcome variably defined by individual study authors) between those receiving and those not receiving TXA (RR 0.97, 95% CI 0.85–1.11, RD 0%, 95% CI 0.2% lower to 0.1% higher, moderate certainty). Pooled results demonstrated probably no increased risk of deep vein thrombosis (RR 0.94, 95% CI 0.57–1.55, low certainty), vascular occlusive events (RR 0.86, 0.62–1.2, moderate certainty), stroke (RR 0.83, 95% CI 0.53–1.29, moderate certainty), or seizure (RR 1.11, 95% CI 0.92–1.34, moderate certainty) 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 (Table 3). There was an uncertain effect of TXA on pulmonary embolism (RR 1.19, 95% CI 0.46–3.06, very low certainty). Of note, the studies which reported on deep vein thrombosis and pulmonary embolism did not comment whether patients were routinely screened for VTE (identifying asymptomatic events) or only imaged if symptomatic [17, 26, 31].

Sensitivity and subgroup analysis

Neither post hoc sensitivity analyses, one excluding the largest trial (CRASH-3) and the other excluding trials enrolling adolescents, showed differences in estimates or conclusions for any of the outcomes of interest (See supplementary appendix for forest plots, appendix 8, supplement Figs. 8–10).

A prespecified subgroup analysis comparing mortality on high RoB studies-to-low RoB studies did not find RoB to be an effect modifier (p value for subgroup interaction = 0.50) (see supplementary appendix, appendix 8, supplement Fig. 7). Although we planned additional subgroups based on severity of TBI and timing of TXA administration, the number of trials reporting separate outcome data for these subgroups of interest did not allow for this analysis.

Discussion

This systematic review and meta-analysis demonstrates that TXA probably does not have an important effect on mortality or disability, and an uncertain effect on need for neurosurgical intervention and length of stay when administered to patients with TBI. TXA probably does not increase the risk of adverse events.

Table 3 GRADE summary of findings

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TXA	PLACEBO	Relative (95% CI)	Absolute (95% CI)		
All-cause mortality at longest follow-up												
8	Randomized trials	Not serious	Not serious	Not serious	Serious[a]	None	1093/5623 (19.4%)	1074/5228 (20.5%)	RR 0.95 (0.88–1.02)	10 fewer per 1000 (from 25 fewer to 4 more)	⨁⨁⨁◯ MODERATE	CRITICAL
Glasgow Outcome Scale (GOS)- proportion of patients with a score of < 4 and Glasgow Outcome Scale-Extended (GOS-E) proportion of patients with a score of ≤ 4												
5	Randomized trials	Serious[b]	Serious[c]	Not serious	Serious[a,d]	None	329/978 (33.6%)	238/689 (34.5%)	RR 0.90 (0.69–1.17)	3 fewer per 100 (from 11 fewer to 6 more)	⨁◯◯◯ VERY LOW	CRITICAL
Disability Rating Scale (continuous outcome)												
2	Randomized trials	Not serious	Not serious	Not serious	Serious[a]	None	6954	6597	–	MD 0.18 lower (0.43 lower to 0.08 higher)	⨁⨁⨁◯ MODERATE	CRITICAL
Hematoma expansion (*n*) on subsequent imaging												
3	Randomized trials	Serious[e]	Not serious	Not serious	Serious[a,d]	None	89/855 (10.4%)	79/505 (15.6%)	RR 0.77 (0.58–1.03)	36 fewer per 1000 (from 66 fewer to 5 more)	⨁⨁◯◯ LOW	IMPORTANT
Hematoma expansion (mL) on subsequent imaging												
2	Randomized trials	Not serious	Not serious	Not serious	Serious[a]	None	173	177	–	Mean 2.46 ml lower (6.46 lower to 1.55 higher)	⨁⨁⨁◯ MODERATE	IMPORTANT
PE												
3	Randomized trials	Not serious	Not serious	Serious[f]	Very serious[a,d]	None	44/7112 (0.6%)	39/6673 (0.6%)	RR 1.19 (0.46–3.06)	1 more per 1000 (from 3 fewer to 12 more)	⨁◯◯◯ VERY LOW	IMPORTANT
DVT												
3	Randomized trials	Not serious	Not serious	Serious[f]	Serious[a,d]	None	35/7112 (0.5%)	28/6673 (0.4%)	RR 0.94 (0.57–1.55)	0 fewer per 1000 (from 2 fewer to 2 more)	⨁⨁◯◯ LOW	IMPORTANT
Vascular occlusive events												
2	Randomized trials	Not serious	Not serious	Not serious	Serious[a,d]	None	145/7016 (2.1%)	132/6589 (2.0%)	RR 0.86 (0.62–1.20)	3 fewer per 1000 (from 8 fewer to 4 more)	⨁⨁⨁◯ MODERATE	IMPORTANT
Stroke												
4	Randomized trials	Not serious	Not serious	Not serious	Serious[a,d]	None	68/7269 (0.9%)	67/6844 (1.0%)	RR 0.83 (0.53–1.29)	2 fewer per 1000 (from 5 fewer to 3 more)	⨁⨁⨁◯ MODERATE	IMPORTANT

Table 3 (continued)

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	TXA	PLACEBO	Relative (95% CI)	Absolute (95% CI)		
Seizure												
2	Randomized trials	Not serious	Not serious	Not serious	Serious[a,d]	None	228/7016 (3.2%)	193/6589 (2.9%)	RR 1.11 (0.92–1.34)	3 more per 1000 (from 2 fewer to 10 more)	⨁⨁⨁◯ MODERATE	IMPORTANT
Total adverse events												
5	Randomized trials	Not serious	Not serious	Not serious	Serious[a]	None	543/42,541 (1.3%)	480/39,957 (1.2%)	RR 0.97 (0.85–1.11)	0 fewer per 1000 (from 2 fewer to 1 more)	⨁⨁⨁◯ MODERATE	IMPORTANT
Need for neurosurgery for intervention												
5	Randomized trials	Serious[g]	Not serious	Not serious	Serious[a]	None	194/1084 (17.9%)	109/726 (15.0%)	RR 1.11 (0.89–1.39)	17 more per 1000 (from 17 fewer to 59 more)	⨁⨁◯◯ LOW	IMPORTANT
Hospital length of stay												
3	Randomized trials	Serious[h]	Not serious	Not serious	Serious[a]	None	831	471	–	MD 0.19 higher (1.11 lower to 1.49 higher)	⨁⨁◯◯ LOW	IMPORTANT
ICU length of stay												
3	Randomized trials	Serious[i]	Serious[j]	Not serious	Serious[a]	None	831	471	–	MD 1.33 higher (0.99 lower to 3.65 higher)	⨁◯◯◯ VERY LOW	IMPORTANT

CI confidence interval, *RR* risk ratio, *MD* mean difference

[a] Wide confidence intervals do not exclude important benefit or harm which lowers our certainty in effect

[b] 2 studies (Fakharian 2017; ChakrounWalha 2018) have high ROB and one study (Rowell, 2020) has probably high ROB and their contribution weight to this outcome is 5.8%, 11.6%, and 35.1 respectively, which lower our certainty in effect.

[c] High I^2 (58%) and non-overlapping confidence intervals suggests important inconsistency which lowers our certainty in effect

[d] Low number of events below optimal information size contributing to imprecision which lowers our certainty in effect

[e] One study (Fakharian 2017) has high ROB, and one study (Rowell 2020) has probably high ROB and their contribution weight to this outcome is 21.2% and 44.7% respectively, which lower our certainty in effect

[f] Three included studies reported on this outcome (CRASH-3, Chakroun et al and Rowell et al). In CRASH-3, DVT/PE was recorded only if a positive result was found on imaging or at a post-mortem examination; however, they do not mention whether imaging was done based on the presence of specific symptoms or signs. Unfortunately, Chakroun and Rowell do not mention how they identified DVT/PE

[g] 2 studies (Fakharian 2017; Chakroun Walha 2018) have high ROB and one study (Rowell, 2020) has probably high ROB, and their contribution weight to this outcome is 6.8%, 14.9, ad 59.2 %, respectively, which lower our certainty in effect

[h] 2 studies (Fakharian 2017; Chakroun Walha 2018) have high ROB and one study (Rowell, 2020) has probably high ROB, and their contribution weight to this outcome is 10.4%, 7.8 %, and 81.8% respectively, which lower our certainty in effect

[i] 2 studies (Fakharian 2017; Chakroun Walha 2018) have high ROB and one study (Rowell, 2020) has probably high ROB, and their contribution weight to this outcome is 24.8%, 19.5%, and 55.7%, respectively, which lower our certainty in effect

[j] High I^2 (44%) and non-overlapping confidence intervals suggest important inconsistency which lowers our certainty in effect

This review was prompted by the publication of the CRASH-3 trial, which concluded that TXA is safe in patients with TBI and that treatment within 3 h of injury reduces head-injury-related death. The primary outcome for CRASH-3 was revised mid-trial from all-cause mortality to head-injury-related mortality at 28 days following injury. In the published statistical analysis plan, the authors explain this change which was made to limit the analysis to causes of death that might be affected by TXA (i.e., head-injury-related death), thereby avoiding dilution of effect from non-head-injury-related deaths [26]. As there may be subjectivity in classifying the cause of death, misclassification is a concern with this approach and could introduce bias in an otherwise objective outcome [26]. We chose to analyze all-cause mortality, as opposed to head-injury-related death, due to the classification issues raised above, and because we anticipated this outcome would be more widely reported across the included trials. In fact, no other trial reported head-injury-related death. Using all-cause mortality, our pooled analysis demonstrates no effect of TXA on all-cause mortality. Given these concerns and because CRASH-3 provided the greatest weight to the pooled analysis, we performed a post hoc sensitivity analysis excluding this trial which did not change the results or conclusions for any of the outcomes of interest.

A previously published meta-analysis examining patients with TBI demonstrated a reduction in mortality with TXA [15]; however, it did not include the latest data, and analyzed all patients enrolled in the CRASH-2 trial, including those with TBI and extracranial traumatic injuries. To limit clinical heterogeneity, we only included the subset of CRASH-2 patients who also had a TBI [30]. Although beneficial in other populations, there are a number of possible explanations for TXA's lack of efficacy in patients with TBI. Mortality in TBI is best predicted by durations of hypotension, hypoxemia, and pyrexia insults [32–34]. As such, the emphasis of management in patients with TBI is limiting secondary brain injury. TXA does not physiologically or mechanistically address these features, which may explain the lack of benefit. In the absence of an effect on survival or disability, it is unclear how important the difference seen in hematoma expansion would be to patients and clinicians in the setting of TBI. The mean difference of -2.46 mL (95% CI − 6.46 to 1.55 mL) is likely of very limited clinical significance, especially without improvements in other more patient-important outcomes. However, even a small difference in hematoma size in a critical location may be relevant.

Although of limited efficacy, these results demonstrate no increased risk of adverse events with the administration of TXA. This finding is consistent with prior large RCTs examining TXA in postpartum hemorrhage, trauma, and intracerebral hemorrhage [8, 11, 12]. In addition to being safe, TXA has been shown to be cost-effective when given to heterogenous trauma patients in low-, middle-, and high-income settings [35]. Of note, our post-hoc subgroup analysis comparing high-income versus low-to-middle-income countries did not show a benefit with the use of TXA in either group. Although TXA is a cheap drug, given its uncertain effects and the subgroup findings, these results do not support the routine use of TXA in high-income or low-to-middle-income countries [35]. It is unlikely that another study as large as CRASH-3 or the out-of-hospital TXA study by Rowell et al. [17] will be conducted over the short term; and as such, these findings likely represent the best summary of evidence on which clinicians have to guide their practice. These results do not support strong directives (either for giving TXA or against giving TXA) to clinicians caring for patients with TBI. Some clinicians may rationalize not giving TXA to these patients given the costs and lack of clear benefit, while others may choose to administer TXA given the lack of demonstrable harm and potential reduction in hematoma size. The findings of this review will be of interest to future guidelines addressing the topic of TXA in TBI who will be able to more carefully consider these aspects of balancing benefits, harms, values, preferences, and costs [9, 36].

It is possible certain subgroups of patients may benefit more or less from TXA; unfortunately, we did not have sufficient trial-level data to perform a number of planned subgroup analyses. The TSA found that the information size was not enough to exclude an important effect with the intervention. It is possible that TXA could be more efficacious in those that receive the drug earlier (for example within 3 h of injury) or in those with differing severity of TBI; however, this analysis is not able to address these questions. Future studies need to focus on these specific populations, with a large enough sample size, including TBI patients with a concomitant hemorrhagic brain injury stratified by subtype of hemorrhage (i.e., subdural, epidural, subarachnoid, and intraparenchymal). Further data are also needed examining the role of TXA in TBI patients also taking oral anticoagulants and antiplatelet agents.

This systematic review and meta-analysis has several strengths including a pre-registered protocol, a comprehensive literature search including unpublished sources, duplicate and independent screening and data abstraction, and GRADE assessment of certainty of evidence. There are also limitations. First, we were unable to perform a number of pre-planned subgroup analyses due to lack of sufficient granularity in published data. Second, the included studies were heterogenous in regards to

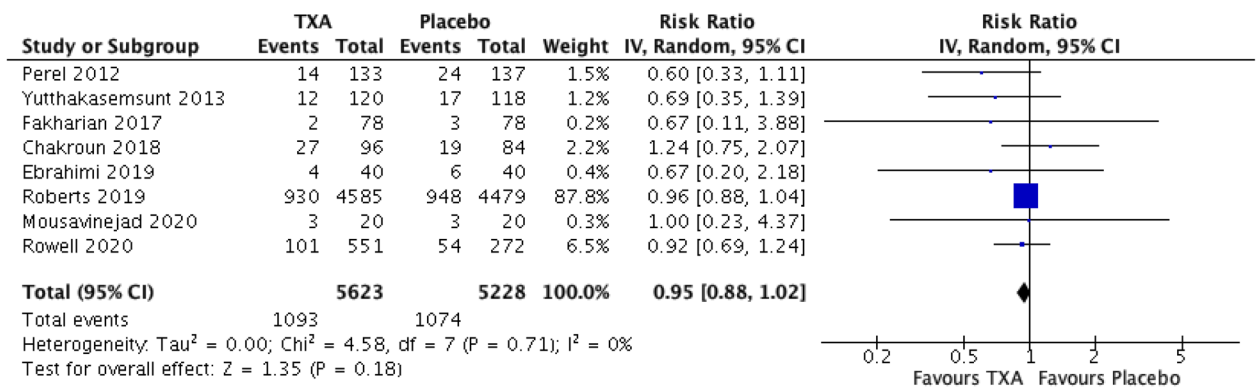

Fig. 2 Forest plot comparing TXA and placebo for the outcome of all-cause mortality at the longest point of follow-up

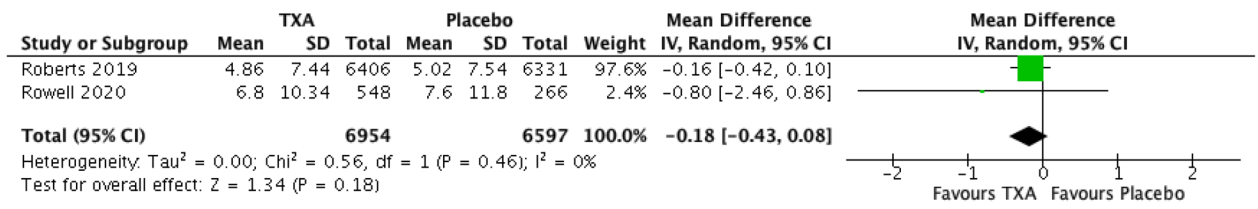

Fig. 3 Forest plot comparing TXA and placebo for the continuous outcome of disability using the Disability Rating Scale

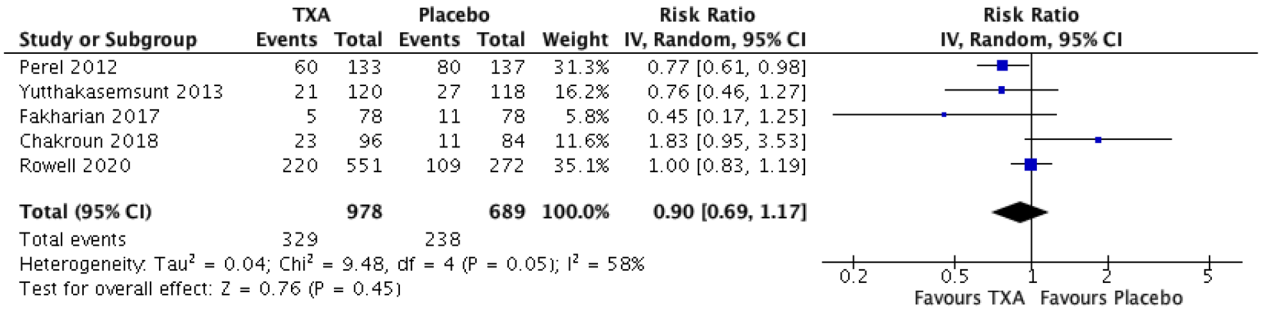

Fig. 4 Forest plot comparing TXA and placebo for the dichotomous outcome of disability using the Glasgow Outcome Scale with a score of < 4 indicating a poor outcome and the Glasgow outcome scale-extended ≤ 4 indicating a poor outcome

patients enrolled, specifically severity of TBI and presence of extracranial injuries. Fortunately, this clinical heterogeneity did not translate into important inconsistency (statistical heterogeneity) amongst any of the outcomes of interest. Although we tried to limit analysis to studies that enrolled patients with isolated TBI, some included a small number of patients with TBI and extracranial injuries; however, even if included, these extracranial injuries were not severe with clear exclusions for major injuries requiring massive transfusion.

Conclusion

In patients with acute TBI, TXA probably has no effect on mortality or disability. TXA may decrease hematoma expansion on subsequent imaging; however, this outcome is probably of less importance to patients. The use of TXA probably does not increase the risk of adverse events.

Electronic supplementary material

The online version of this article (https://doi.org/10.1007/s00134-020-06279-w) contains supplementary material, which is available to authorized users.

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Author contributions
KA, SS, and BR designed the study. SA and HA collected the data. KA, SS, BR, and WA analyzed and interpreted the data. KA, SS, BR, SA, HA, AP, EPB, SVS, JM, SMF, JJO, MZ, DQ, and WA contributed to the writing of the manuscript.

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