PLACE OF TRANEXAMIC ACID IN TRAUMATIC BRAIN INJURY. A SYSTEMATIC REVIEW AND META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS

SUPPLEMENTARY DIGITAL FILE

Table 1. Methodology characteristics of included trials

Trial	Inclusion criteria	Exclusion criteria	TXA treatment	Primary outcome(s)	Findings
Chakroun-Walha et al. 2019	Patients aged 18 years or over, admitted in the ER for TBI, and who satisfied all of the following criteria: intracranial bleeding in the first or the second brain CT-scan, and with a delay of management in the study center under 24 h after trauma	Patients with significant extracranial bleeding (that is, not in need of immediate blood transfusion) or with evidence that TXA improves outcome	TXA was administered as soon as possible after randomization, with the first dose of 1 g in 100 mL of normal saline in 10 min and then with a maintenance dose of 1 g per 500 mL of normal saline for 8 h	The benefits of TXA in reducing the need for surgery or transfusion and the mortality rate up to 28 days after trauma	TXA is an interesting treatment for hemorrhagic shock. Its efficiency in head trauma is still debated and controversial. Its impact on mortality and the need for transfusion or surgery were not demonstrated in this study
CRASH-3 2019	Adults with TBI who were within 3 h of injury; GCS ≤ 12; Any intracranial bleeding on CT scan; Responsible clinician was substantially uncertain as to the appropriateness of tranexamic acid therapy	Major extracranial bleeding	Patients receive a loading dose of 1 g of tranexamic acid infused over 10 min, started immediately after randomization, followed by an intravenous infusion of 1 g over 8 h, or matching placebo. Every patient was assigned a uniquely numbered treatment pack, which contained four ampoules of either tranexamic acid (500 mg)	Head injuryrelated death in hospital within 28 days of injury in patients randomly assigned within 3 h of injury	Results show that tranexamic acid is safe in patients with TBI and that treatment within 3 h of injury reduces head injury-related death. Patients should be treated as soon as possible after injury
Fakharian et al. 2017	Patients with isolated TBI or multiple trauma patients, with TBI as the main problem, who arrived at the hospital within 8 hours of trauma, aged 15 and older, with nonpenetrating injury and any kind of traumatic intracranial bleedings (subdural hemorrhage, subarachnoid hemorrhage, contusion, intraventricular hemorrhage, and epidural hematoma) in admission CT scans, no need for brain surgery during the first 8 hours, no coagulation disorder, serum creatinine < 2 mg, and nonpregnancy	Major organ damage requiring surgical intervention within the first 8 hours, receiving any medication that disturbs homeostasis, those who do not have a secondary CT scan, and those who missed follow-up	Intravenous TXA was administered with the first dose of 1 g in 100 mL of normal saline for 10 minutes and then with a maintenance dose of 1 gram per 1000 mL of normal saline for 8 hours	An assessment of any increase in the volume of hemorrhagic lesion in comparison with the initial size	Administration of a short dose of TXA does not lead to significant prevention of growth of posttraumatic hemorrhagic lesion or improvement of clin- ical outcomes

Jokar et al. 2017	The TBI patients aged 15 years and more, within 2 h of injury onset, and with acute ICH (volume of less than 30 ml) based on CT scan findings	1. Glasgow coma scale (GCS) total score < 8; 2. unknown onset time; 3. ICH volume more than 30 ml as measured by CT scan; 4. need for surgery; 5. presence of focal neurologic deficits; 6. subarachnoid hemorrhage; 7. the cerebral edema with midline shift; 8. use of TA within the previous 14 d; 9. hereditary or acquired hemorrhagic diathesis or coagulation factor deficiency; 10. creatinine > 20 mg/L; 11. pregnancy (women of childbearing potential must be tested); 12. history or current evidence suggestive of venous or arterial thrombotic events, including deep vein thrombosis, pulmonary emboli, cerebral vein thrombosis, cerebrovascular accident; 13. history of hypersensitivity to TA; and 14. history of acquired color blindness or visual vascular problems	Intravenous a bolus of 1 g in 100 ml 0.9% NaCl over 10 min followed by a continuous infusion of 1 g in 500 ml 0.9% NaCl over 8 h	The extent of ICH growth at 48 h after admission	It has been established that TA, as an effective hospital-based treatment for acute TBI, could reduce ICH growth
Mojallal et al. 2020	Age older than 18 years; detection of a cerebral hemorrhage in brain CT scan, including subdural hematoma, epidural hematoma, intracerebral hemorrhage, and intraventricular hemorrhage; absence of subarachnoid hemorrhage along with the hemorrhages mentioned above; passage of less than 8 hours after trauma incidence; negative history of taking anticoagulants; and negative history of blood coagulation system impairments, such as hemophilia or idiopathic thrombocytopenic purpura	The patients who underwent craniotomy less than 24 hours after entry into the study	Tranexamic acid (Tranexipm®, from Caspian Tamin Company, Iran) was purchased as 500 mg 5 cc boluses. Seeing the hypotension induced by rapid injection of tranexamic acid, this drug was infused intravenously during 1 h as 1 gr dose diluted in 500 cc NaCL	Patient characteristic	Tranexamic acid has no effect on reducing cerebral hemorrhage volume in patients. Although this drug was not effective in reducing mortality rate in patients, it decreased their ICU stay

Mousavinejad et al. 2020	Age 18 years referred to hospital within 8 h after the accident, diagnosed with brain contusion with intraparenchymal hemorrhage by brain CT scan, having no significant extradural hemorrhage such abdominal bleeding, no fracture and/or deformity in membranes, no hematuria and coagulation disorders, and the need for surgery depending on clinical condition and neurosurgeons' opinion	pregnant women, the patients taking anticoagulant drugs such as warfarin, heparin as well as aspirin, patients with intracranial hemorrhage (in addition to contusion and intraparenchymal) along with the need for massive transfusion and/or fresh frozen plasma (FFP) injection	1 g TAX with 500 ml of 0.09% normal saline and intravenous Infusion within 10 min) and maintenance dose (combination of 1 g TXA with 500 ml of 0.09% NaCL Intravenous Infusion within 8 min.	The severity of TBI	Using TXA may reduce the hemorrhage in patients with TBI, but this effect, as in this study, was not statistically significant
Perel et al. 2012	All trauma patients with ongoing significant hemorrhage (systolic blood pressure less than 90 mm Hg and/or heart rate more than 110 beats per minute), or who are considered to be at risk of significant hemorrhage, and are within 8 hours of the injury, are eligible for trial entry if they appear to be at least 16 years old. Although entry is allowed up to 8 hours from injury, the earlier that patients can be treated the better, and TBI (GCS) score of ≤ 14 and a brain computerized tomography (CT) scan compatible with TBI	Pregnant women and patients for whom a second brain CT scan was not possible	Loading dose of 1 g of TXA infused over 10 minutes, followed by an intravenous infusion of 1 g over 8 hours or matching placebo (sodium chloride 0.9%)	The increase in the size of intracranial hemorrhage growth between a CT scan at hospital admission and a second scan 24–48 hours later	Found that neither moderate benefits nor moderate harmful effects can be excluded. However, although uncertainty remains, our analyses suggest that TXA administration might improve outcomes in TBI patients

Rowell et al. 2020	Blunt and penetrating traumatic mechanism consistent with TBI with prehospital GCS ≤ 12 prior to administration of sedative and/or paralytic agents, prehospital SBP ≥ 90 mm Hg, prehospital intravenous (IV) access, age ≥ 15 years (or weight ≥ 50 kg if age is unknown), EMS transport destination based on standard local practices determined to be a participating trauma center	Prehospital GCS = 3 with no reactive pupil, estimated time from injury to start of study drug bolus dose > 2 hours, unknown time of injury, clinical suspicion by EMS of seizure activity, acute MI or stroke or known history, to the extent possible, of seizures, thromboembolic disorders or renal dialysis, CPR by EMS prior to randomization, burns > 20% TBSA, suspected or known prisoners, suspected or known pregnancy, prehospital TXA or other pro-coagulant drug given prior to randomization, subjects who have activated the 'opt-out' process when required by the local regulatory board	1 g IV TXA bolus in the prehospital setting followed by a 1 g IV maintenance infusion initiated upon hospital arrival and infused over 8 hours or 2 g IV TXA bolus in the prehospital setting followed by a placebo maintenance infusion initiated upon hospital arrival and infused over 8 hours	To determine the efficacy of two dosing regimens of TXA initiated in the prehospital setting in patients with moderate to severe TBI (GCS score ≤ 12)	Among patients with moderate to severe TBI, out-of-hospital tranexamic acid administration within 2 hours of injury compared with placebo did not significantly improve 6-month neurologic outcome as measured by the Glasgow Outcome Scale-Extended
Yutthakasemsunt et al. 2013	All patients, older than 16 years, with moderate to severe TBI (post-resuscitation Glasgow Coma Scale (GCS) 4 to 12) who had a computerized tomography (CT) brain scan performed within eight hours of injury, and whom there was no immediate indication for surgery	Pregnant, had evidence of coagulopathy, known to be receiving a medication that affects hemostasis, or had a serum creatinine over 2 mg/dL	TXA loading dose of 1 g over 30 minutes followed by a maintenance dose of 1 g infused over eight hours	Progressive intracranial hemorrhage. It would have more association to the therapeutic effect of given tranexamic acid than other outcomes in this study	TXA may reduce PIH in patients with TBI; however, the difference was not statistically significant in this trial

Table 2. Head CT scan findings

Parameter	No of studies	Events/participants		Events		Heterogeneity between trials		P-value for differences across groups
		TXA	Non-TXA	OR	95% CI	P-value	I^2 statistic	
Subarachnoid hemorrhage	4	176/353 (49.9%)	173/332 (52.1%)	1.03	0.54–1.98	0.009	74%	0.92
Extradural hematoma	5	97/393 (24.7%)	104/372 (28.0%)	0.73	0.33–1.62	< 0.001	81%	0.44
Subdural hematoma	4	109/337 (32.3%)	103/328 (31.4%)	1.03	0.74–1.43	0.43	0%	0.86
Intracerebral hemorrhage	2	60/152 (39.5%)	43/128 (33.6%)	1.47	0.84–2.56	0.68	0%	0.18
Intraparenchymal hemorrhage	1	9/127 (7.1%)	15/129 (11.6%)	0.58	0.24–1.38	NA	NA	0.22
Petechial hemorrhage	1	20/96 (20.8%)	14/84 (16.7%)	1.32	0.62–2.80	NA	NA	0.48
Diffuse axonal injury	1	8/96 (8.3%)	5/84 (6.0%)	1.44	0.45–4.57	NA	NA	0.54
Brain herniation	1	10/96 (10.4%)	12/84 (14.3%)	0.70	0.28–1.71	NA	NA	0.43
Cerebral oedema	2	41/136 (30.1%)	40/124 (32.3%)	0.96	0.52–1.78	0.46	0%	0.90

CI — confidence interval; NA — not applicable; OR — odds ratio

Table 3. Mortality in included trials

Parameter	No of studies	Events/participants		Events		Heterogeneity between trials		P-value for differences across groups
		TXA	Non-TXA	OR	95% CI	P-value	I^2 statistic	
Mortality at 7 days period	1	8/56 (14.3%)	3/44 (6.8%)	2.28	0.57–9.15	NA	NA	0.25
Mortality at 28-days period	6	993/5580 (17.9%)	987/5120 (19.3%)	0.92	0.83–1.01	0.78	0%	0.08
Mortality at 6-months period	1	101/551 (18.3%)	54/272 (19.9%)	0.91	0.63–1.31	NA	NA	0.60

CI — confidence interval; NA — not applicable; OR — odds ratio

Table 4. The Grading of Recommendations Assessment, Development and Evolution (GRADE) approach. TXA compared to non-TXA for Traumatic brain injury

Certainty assessment							Summary of findings				
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With non-TXA	With TXA		Risk with non-TXA	Risk difference with TXA
Survival rate (follow up: mean 28 days)											
10700 (6 RCTs)	not serious	not serious	not serious	not serious	none	HIGH	4133/5120 (80.7%)	4587/5580 (82.2%)	OR 1.09 (0.99 to 1.20)	807 per 1000	13 more per 1000 (from 2 fewer to 27 more)

CI — confidence interval; OR — odds ratio

Table 5. PRISMA checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review	1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist	1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge	2
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses	2
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses	2
Information sources	6	Specify all databases, registers, websites, organizations, reference lists, and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted	2,3
Search strategy	7	Present the full search strategies for all databases, registers, and websites, including any filters and limits used	2,3
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process	2,3
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process	2,3
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect	2,3
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information	2,3
Study risk of bias assessment	11	Specify the methods used to assess the risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process	2,3
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results	2,3
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5))	2,3
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions	2,3
	13c	Describe any methods used to tabulate or visually display the results of individual studies and syntheses	2,3
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used	2,3
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression)	2,3
	13f	Describe any sensitivity analyses conducted to assess the robustness of the synthesized results	2,3

Reporting bias assessment	14	Describe any methods used to assess the risk of bias due to missing results in a synthesis (arising from reporting biases)	2,3
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome	2,3
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram	4-8
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded	4,5
Study characteristics	17	Cite each included study and present its characteristics	4,5
Risk of bias in studies	18	Present assessments of risk of bias for each included study	4
Results of individual studies	19	For all outcomes, present, for each study: a) summary statistics for each group (where appropriate) and b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots	4–8
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies	4–8
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect	4–8
	20c	Present results of all investigations of possible causes of heterogeneity among study results	4–8
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results	4–8
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed	4–8
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed	4–8
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence	8, 9
	23b	Discuss any limitations of the evidence included in the review	8, 9
	23c	Discuss any limitations of the review processes used	8, 9
	23d	Discuss implications of the results for practice, policy, and future research	8, 9
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered	-
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared	-
	24c	Describe and explain any amendments to the information provided at registration or in the protocol	—
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review	9
Competing interests	26	Declare any competing interests of review authors	9
Availability of data, code, and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review	9

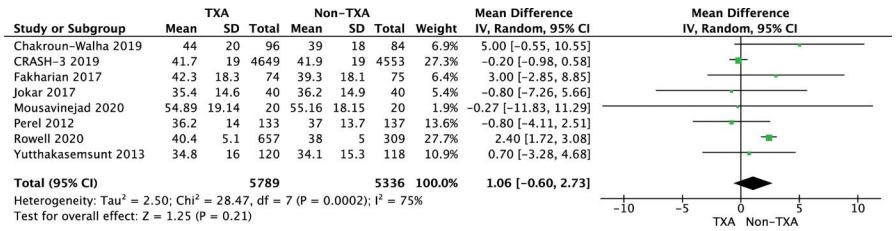

FIGURE 1. Forest plot of patients' age in TXA vs. non-TXA group. The center of each square represents the weighted mean differences for individual trials, and the corresponding horizontal line stands for a 95% confidence interval. The diamonds represent pooled results

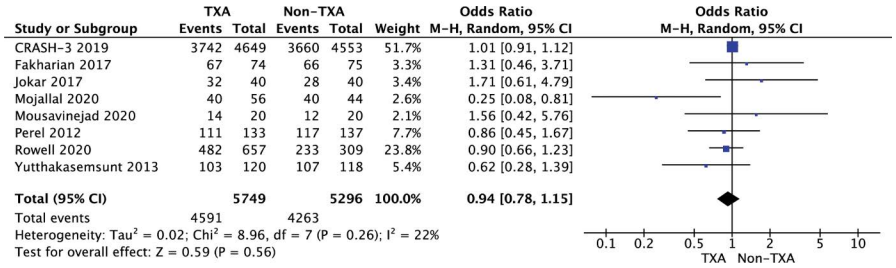

FIGURE 2. Forest plot of patients' sex (male) in TXA vs. non-TXA group. The center of each square represents the weighted odds ratios for individual trials, and the corresponding horizontal line stands for a 95% confidence interval. The diamonds represent pooled results

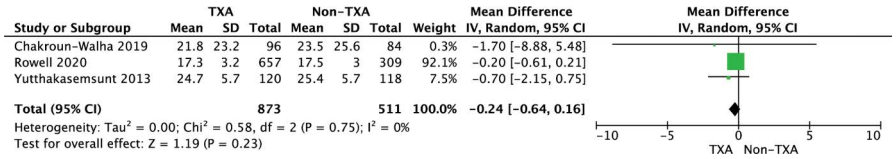

FIGURE 3. Forest plot of injury severity score in TXA vs. non-TXA group. The center of each square represents the weighted mean differences for individual trials, and the corresponding horizontal line stands for a 95% confidence interval. The diamonds represent pooled results

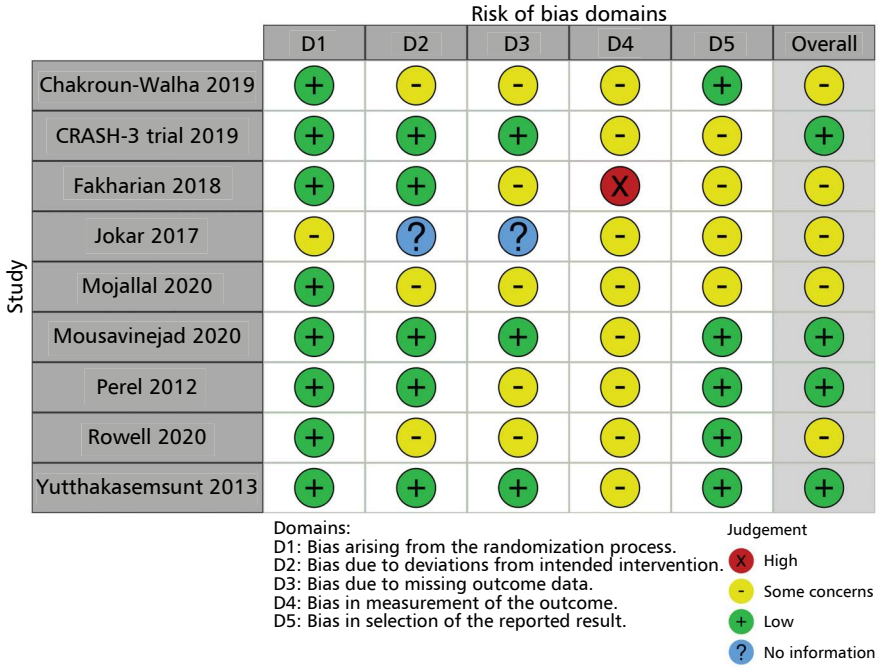

FIGURE 4. A summary table of review authors' judgments for each risk of bias item for each randomized study

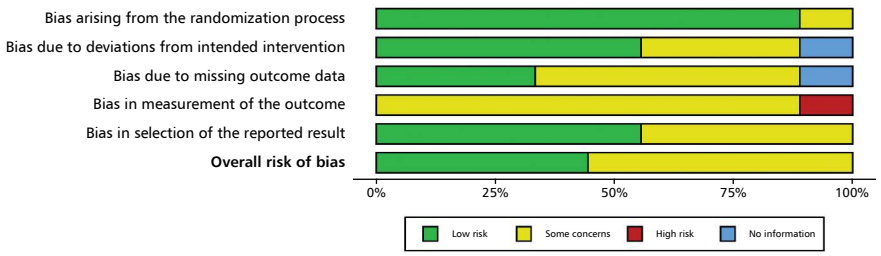

FIGURE 5. A plot of the distribution of review authors' judgments across randomized studies for each risk of bias item