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Title: Tranexamic acid has a role in polytrauma, but is it beneficial in traumatic brain injury?

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TXA has a role in polytrauma, but is it beneficial in prehospital management of TBI?

Clinical Scenario

Paramedics respond to an unconscious 22-year-old male at 1am in Surfers Paradise, who reportedly endured a sudden head strike from behind, from an intoxicated male. The patient is GCS9 (E2V2M5) and exhibits a pronounced occipital haematoma, periorbital ecchymosis, and bony crepitus upon palpation of the occiput. No other injuries are detected. Paramedics suspect traumatic brain injury (TBI) and manage $O2$ saturations, Et$CO2$ and mean arterial pressure accordingly.

PICO

In TBI, does prehospital tranexamic acid (TXA) reduce expansion of intracranial haemorrhage (ICH) and improve patient outcomes, without adverse effects?

Research Rationale

Approximately 69 million cases of TBI occur yearly worldwide (Roberts et al., 2019). ICH is a common complication, and increases mortality and morbidity rates. TXA is an antifibrinolytic agent which prevents fibrin degradation through competitive inhibition of plasminogen activation. The CRASH-2 and WOMAN trials demonstrated that TXA improves outcomes in haemorrhaging patients. The Australian PATCH study currently underway, will determine the applicability of these findings to paramedicine. TBI often causes a coagulopathic state, where increased fibrinolysis precipitates ICH expansion, brain herniation and death (Roberts et al., 2019). Given TXA's applicability in other domains, this appraisal aims to assess the safety and efficacy of prehospital TXA in TBI, to guide future research and clinical practice guidelines.

Search Strategy

Medline, Embase, Cochrane and CINAHL were searched from January 2015 to September 2020, using the keywords: (TXA OR "tranexamic acid") AND (TBI OR

"traumatic brain injury" OR "intracerebral haemorrhage" OR "head injury") AND (prehospital OR pre-hospital OR ambulance OR paramed* OR emergency*). Included articles discussed TXA for TBI in a prehospital, emergency or intensive care setting. Articles were excluded if they were not randomised controlled trials specific to TXA for TBI.

Search Results

The search identified 524 articles. 40 satisfied inclusion criteria and five were deemed suitable for appraisal following full-text evaluation. Figure 1 outlines the article selection process.

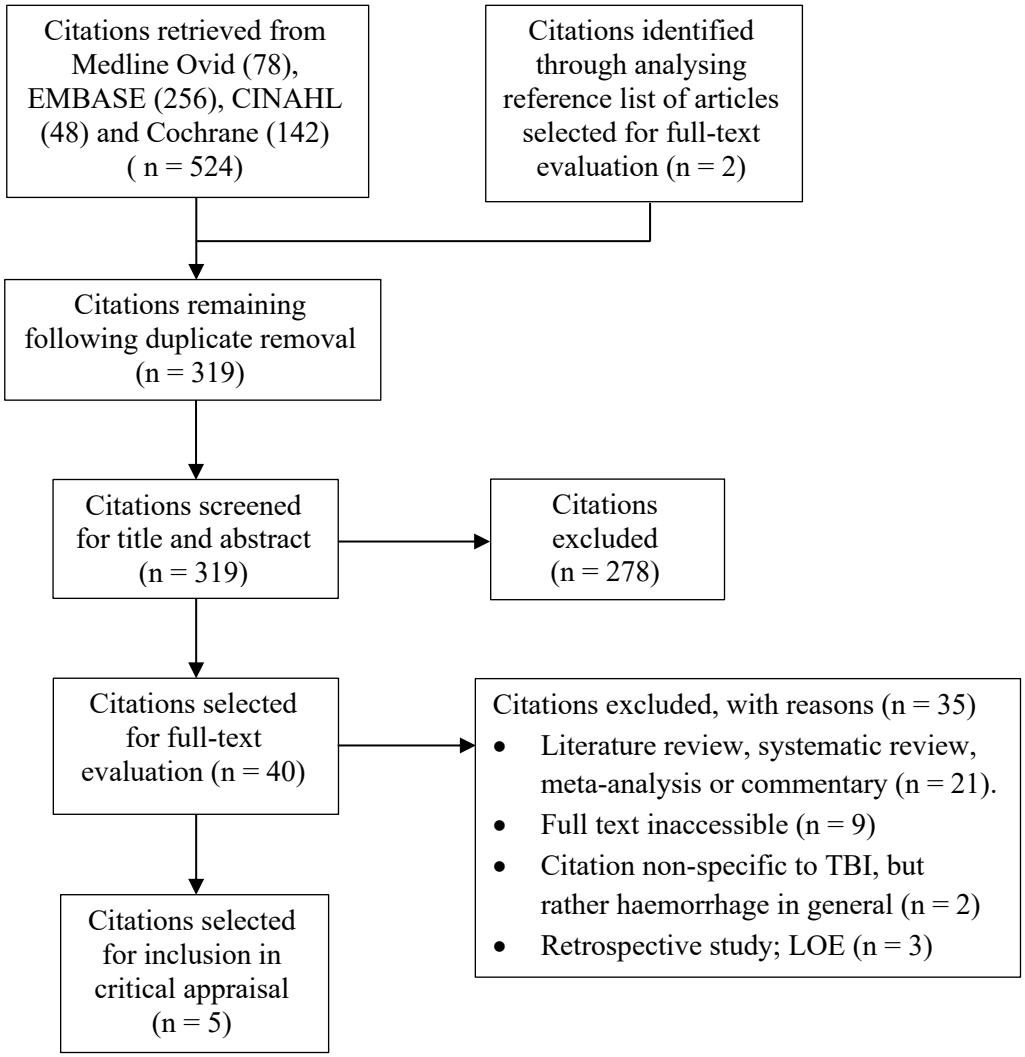

Figure 1. PRISMA diagram demonstrating article selection process.
Abbreviations: LOE; Level of Evidence.

Study Analysis

Author, Year.	Population	Study Design	Key Findings	Strengths & Limitations	Oxford LOE, IF.
(Roberts et al., 2019)	Adult TBI patients presenting to ED within 3hrs, without extracranial bleeding, in addition to a GCS≤12 or alternatively ICH on CT. Original eligibility window was 8hrs, but was reduced in light of pertinent evidence in 2016.	CRASH-3. Double-blind randomised controlled trial with 12737 subjects. Patients received either a 10min 1g TXA IV infusion followed by an 8hr 1g TXA infusion (n=6406), or placebo 0.9% NaCl with the same infusion regimen (n=6441).	• TXA group exhibited a lower value in 28-day head injury-related death (HIRD) compared to control; 18% vs. 19.8% respectively (non-statistically significant). • HIRD following TXA in mild/moderate TBI (GCS9-15) was 5.8%, compared to 7.5% in placebo, whereas no comparative benefit was observed in severe TBI (GCS≤8) (p=0.03). • Subgroup analysis revealed early TXA had higher mortality benefit than later administration, in mild/moderate TBI (p=0.005). • No difference in incidence of adverse effects.	<u>Strengths</u> • An exceptionally large sample across 175 centres, increasing the power of the study's conclusions regarding TXA's benefits and safety profile. • Double-blinding, randomisation–high internal validity. • Limited to 3hrs post-injury, increasing generalisabiltiy to paramedicine. • Performed sub-group analyses of TBI severity and timing of TXA administration on outcomes. <u>Limitations</u> • No account for death post 28 days. • In-hospital study, limiting generalisability. • No control for varied prehospital TBI treatment (fluids, O2 therapy, ventilation.)	1b, 60.392
(Schreiber, 2019)	Adult suspected TBI patients, with baseline	Double-blind randomised control trial with 967	• Among patients with ICH after TBI, mortality was significantly lower in the prehospital C group compared to	<u>Strengths</u> • Multicentre study (utilising 39 EMS systems) with a large sample, increasing power of results.	1b, 3.048.

	GCS3–12 and systolic BP≥90mmHg.	subjects. Patients, received either: (1) A–Prehospital saline bolus and 8hr in-hospital saline infusion. (n=309) (2) B–1g prehospital TXA bolus and 8hr 1g TXA hospital infusion. (n=312) (3) C–2g prehospital bolus and 8hr placebo infusion. (n=346)	B and A. Mortality values were 17%, 25% and 27% respectively. Accumulatively, this was 20.8% and 27% mortality for those who received TXA (B&C) and no TXA respectively. • Nil difference in the disability Glasgow Outcome Score (GOS) (Figure 2) after six months. • Non-statistically significant increase in seizure incidence in C.	• Prehospital study where median time of TXA was 40 minutes (75% within 1 hour) – high external validity and generalisability to paramedicine. • Double-blinded and randomised. • Observed disability 6 months post-injury and treatment. <u>Limitations</u> • No subgroup analysis of TBI severity on TXA benefit, meaning results may be skewed toward a null relationship. • Despite exclusion of SBP<90mHg, nil exclusion of polytrauma. • Exclusion of mild TBI.	
(Fakharian et al., 2018)	TBI patients ≥15 admitted to ED within 8hrs, with ICH on CT scan. Enrolled patients either exhibited isolated TBI or polytrauma with TBI as the	Double-blind randomised control trial with 149 subjects. Identical TXA dosaging and placebo regime to Roberts et al. (2019). TXA group (n=74)	• The TXA group exhibited a non-statistically significant lower incidence of ICH growth compared to placebo; 20.5% and 22.7% respectively. • Increases in ICH volume were significantly smaller following TXA (p=0.03). • TXA group exhibited statistically insignificant lower mortality and	<u>Strengths</u> • Double blinding and randomisation – high internal validity. • Disability reassessed three months post treatment. <u>Limitations</u> • In-hospital and treatment administered within 8hrs, decreasing generalisability paramedicine. • Small sample. • Assessment of adverse effects was incomprehensive; no account for pulmonary	1b, 1.723

	primary injury.	and placebo (n=75).	adverse outcomes at discharge and three months. • No evidence of any adverse effect following TXA.	embolism (PE), stroke or seizure. • Polytrauma not excluded – potentially skewing data toward mortality benefit. • No sub-group analyses of time of TBI severity of time of TXA administration on TXA's impact on outcomes. • Time of second CT scan was inconsistent, between 24-48 hours.	
(Jokar et al., 2017)	TBI patients ≥15 years admitted to ED within two hours, were GCS≥8 and exhibited an ICH of ≤30mL.	Single-blind randomised control trial with 80 subjects. Identical TXA dosaging and placebo regime to Roberts et al. (2019). TXA group (n=40) and placebo group (n=40).	• ICH expansion occurred in both groups, however a substantially lesser expansion of 7.87% following TXA was observed, compared to 19.37% after placebo ($p<0.001$).	<u>Strengths</u> • Randomisation and single blinding. • The physician who assessed CT scans was blinded, despite only single-blinding, to mitigate confirmation bias. • Treatment administered within 2 hours of incident – increasing generalisability to paramedicine. <u>Limitations</u> • Small sample. • In-hospital study, compromising generalisability. • Only single-blinded • No assessment of mortality, disability or adverse effects between the TXA and placebo. • No exclusion of polytrauma. • No specification that results are specific to mild/moderate TBI.	1b, 0.62

(Chakroun-Walha et al., 2019)	Patients ≥18 years presenting to the ED with TBI, no extracranial bleeding and ICH either on admission or 6 hours after. Patients were included if treated within 24 hours of injury.	Unblinded randomised control trial with 180 subjects. Identical TXA dosaging and placebo regime to Roberts et al. (2019). TXA group (n=96) and placebo group (n=84).	• No difference between TXA and placebo in mortality or disability after 28 days. • PE detected in 11.5% and 2.4% in the TXA and control group respectively (p=0.02). • No observed correlation between time of TXA administration and thrombotic events.	<u>Strengths</u> • Randomisation protocols followed. • Exclusion of polytrauma patients. <u>Limitations</u> • Unblinded nature may have increased clinician's tendency to diagnose PE in the TXA group, compromising the internal validity. • Inhospital study, impairing generalisability to paramedicine. • Small sample. • Limit for inclusion was 24 hours post-injury. Median treatment delay of 8hrs and 10% of subjects received treatment within 3hrs, meaning poor generalisabiltiy to paramedicine.	1b, 2.319

Abbreviations: IF; Impact Factor; CT; computed tomography.

Comments

The literature suggests TXA decreases volume expansion of ICH following TBI (Fakharian et al., 2018; Jokar et al., 2017) and decreases mortality. Evidence indicates TXA's mortality benefit is contingent on two primary factors: TBI severity and time of TXA administration after insult. Roberts et al. (2019) concluded prompt TXA administration within three hours decreases mortality in mild-to-moderate TBI, without mortality benefit in severe TBI. Mortality benefit increases with decreased time to treatment in mild-to-moderate TBI (GCS9–15). However, regardless of how soon TXA is administered to severe TBI patients (GCS≤8), mortality remains constant and is indifferent to placebo (Roberts et al., 2019). TXA administered within 8 hours incurred no mortality benefit, as TXA prevents further ICH expansion as opposed to reversing it (Chakroun-Wahla et al., 2019). All but one study reported no increase in adverse effects following TXA. That single study found TXA increased incidence of PE, however its findings lacked internal validity.

Considerations

At present, prehospital TBI management guidelines involve reducing secondary brain injury through reversing hypoxaemia, abnormal carbon dioxide levels and hypotension. Current research suggests TXA is safe and beneficial in treating mild-to-moderate TBI if delivered within three hours. However, current literature is predominately emergency department based. Additional prehospital double-blind randomised controlled trials would assist in solidifying TXA's benefit and safety profile in prehospital TBI management. Trials investigating the most effective TXA dosaging regimen would also assist in integrating TXA into prehospital TBI clinical practice guidelines.

Clinical Bottom Line

Early prehospital TXA administration likely reduces ICH expansion and improves mortality in mild-to-moderate TBI, without adverse effect.

References

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Appendix

Category	Name	Definition
5	Good recovery	Resumption of normal life (minor neurological or psychological deficit)
4	Moderate disability	Disabled but independent for daily life; work capacity reduced
3	Severe disability	Conscious but dependent for daily life; unable to travel or go shopping without assistance
2	Persistent vegetative state	Unresponsive and speechless
1	Death	Deceased.

Figure 2. Glasgow Outcome Scale Extended (GOS-E).