Prehospital Pharmacotherapy in Moderate and Severe Traumatic Brain Injury: A Systematic Review

2LT William Coburn[1,2]; Zachary Trottier[1]; Ricardo Villareal, PhD[1,2]; 1LT Matthew Paulson[1,2,3]; MAJ (Ret.) Jerome McKay, PhD[1,4]; Col Vikhyat Bebarta, MD[1,2,5]; Brig Gen (Ret.) Kathleen Flarity, DNP, PhD[1,2,6]; COL (Ret.) Sean Keenan, MD[2,6,7]; LTC Steven Schauer, DO[6,8,9]

1. University of Colorado School of Medicine, Aurora, Colorado; 2. CU Anschutz Center for COMBAT Research, Department of Emergency Medicine, University of Colorado School of Medicine, Aurora, Colorado; 3. Colorado National Guard Medical Detachment, Buckley Space Force Base, Colorado; 4. Department of Biomedical Informatics, University of Colorado School of Medicine, Aurora, Colorado; 5. 59th Medical Wing, JBSA Lackland, Texas; 6. Uniformed Services University of the Health Sciences, Bethesda, Maryland; 7. Joint Trauma System, Defense Health Agency, JBSA Fort Sam Houston, Texas; 8. Department of Emergency Medicine, Brooke Army Medical Center, Fort Sam Houston, Texas; 9. United States Army Institute of Surgical Research, JBSA Fort Sam Houston, Texas.

BACKGROUND

- Traumatic brain injury (TBI) affects military populations with high morbidity and mortality and devastating sequelae.
- As the United States Department of Defense shifts its operational paradigm to prepare for future large-scale combat operations, the need for prolonged casualty care in austere environments is expected to intensify.
- Numerous pharmacotherapies—including beta blockers, calcium channel blockers, statins, progesterone, erythropoietin, and others—have demonstrated benefit in TBI in the inpatient setting.
- However, little is known about the employment and efficacy of these agents in the prehospital setting.
- We sought to identify any agent of potential therapeutic benefit in the prehospital management of moderate and severe TBI.

OBJECTIVES

We performed a systematic review to elucidate any agent of potential therapeutic benefit by any outcome metric in the prehospital management of moderate and severe TBI (Glasgow Coma Scale<12).

METHODS

Inclusion Criteria

Each study must:

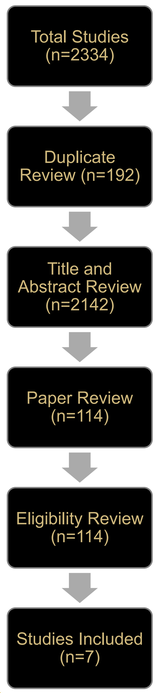
- Be a randomized controlled trial, meta-analysis, or cohort study;
- Assess a pharmacologic intervention within 3 hours from injury;
- Assess patients with GCS<12;
- Utilize any outcome metric.

Electronic Database Search

We searched PubMed, PubDefense, EMBASE, MEDLINE, Web of Science, and Cochrane without restriction using a variety of MeSH terms.

MeSH Terms

Terms were designed to capture any civilian or military study of prehospital TBI
(ex: “traumatic brain injury AND pharmacotherapy AND prehospital”).



RESULTS

Table 1. Summary of included studies.

Author	Country	Number of Patients	Pharmacologic Agent	Study Design	Primary Outcome Metric
Roberts (2021)	Multiple (29)	9127	TXA[1]	RCT	28-Day Mortality
Rowell (2020)	United States and Canada	966	TXA	RCT	6-Month Neurologic Outcome (GOS-E)
Jokar (2017)	Iran	80	TXA	RCT	Growth of ICH
Walker (2020)	United States and Canada	71	TXA	RCS	Neurologic Outcome (GCS, GOS)
Morte (2019)	Multiple[2]	174	TXA	RCS	In-Hospital Mortality, GCS on Discharge
Bossers (2020)	Netherlands	1827	TXA	PCS	30-Day Mortality
Raj (2016)	Multiple[3]	95,941	Ethanol	MA	In-hospital Mortality

1. Tranexamic acid
2. All NATO hospitals in Iraq and Afghanistan
3. 11 included studies

Table 2. Summary of included studies’ findings.

	Study Design	Key Findings
Roberts	Prehospital bolus of and subsequent infusion of either TXA or placebo.	Treated group with improved 28-day mortality* (RR=0.89). Treated moderate TBI group with improved 24- and 48-hour mortality (RR=0.81 and 0.89). Earlier time-to-treatment correlated with decreased mortality in treated moderate TBI group (p=0.005).
Rowell	Prehospital/in-hospital bolus/infusion of TXA/TXA, TXA/placebo, or placebo/placebo.	Bolus-only group with intracerebral hematoma expansion with decreased mortality (p=0.03) and improved disability ratings score (95% CI: -4.2 to -0.08).
Jokar	Treated patients with ICH with TXA or placebo.	Treated group with significantly smaller increase in ICH (p<0.001).
Walker	Compared outcomes of TBI patients who received TXA with those who did not.	Treated patients left with significant increases in GCS (p=0.008) and similar discharge GCS (p=0.58).
Morte	Matched cohort comparing trauma patients who received TXA to those who did not.	Treated group with significantly lower mortality (0% vs 10.1%; p=0.02) and improvement of GCS to 14 or 15 (100%; p=0.01).
Bossers	Prospectively enrolled patients with suspected severe TBI with one-year follow-up.	Higher 30-day mortality in treated patients (p<0.01). However, more severely injured patients were more likely to be treated.
Raj	Meta-analysis of 95,941 patients. Found significant protective effect of positive BAC (p<0.00001) that remained after controlling for heterogeneity.	Found significant protective effect of positive blood alcohol content (p<0.00001) that remained after controlling for study heterogeneity.

*when controlling for bilateral nonreactive pupils or GCS=3.

DISCUSSION

- The seven studies include tranexamic acid (TXA; n=6) and ethanol (EtOH; n=1). No agents with demonstrated inpatient efficacy have been studied in the prehospital arena.
- TXA is an antifibrinolytic agent likely efficacious in TBI due to modulation of the coagulopathic axis.
- Jokar and Walker found that TXA had a mortality benefit in patients with CT-confirmed ICH.
- With TXA, questions of optimal time-to-treatment and dosing remain.
- EtOH likely confers neuroprotection, possibly due to GABAergic modulation.
- Questions remain about utility in battlefield settings and post-exposure prophylaxis.

LIMITATIONS

- Lack of access to internal Department of Defense databases
- No non-English literature included
- Broad heterogeneity in studies, study designs, and outcome metrics

FUTURE DIRECTIONS

- Employ agents validated in the inpatient management of TBI in the prehospital management of TBI.
- Employ agents with GABAergic modulatory activity in the prehospital management of TBI.
- Characterize time-to-treatment and dose-response efficacies of TXA in moderate TBI in the prehospital setting.

CONCLUSIONS

- Despite strong evidence for the benefit of multiple agents in the inpatient management of TBI, none of these agents has been studied in the prehospital setting.
- TXA remains the most widely studied prehospital agent and likely confers some benefit in moderate TBI with or without ICH.
- EtOH confers some neuroprotection in TBI, obviating further study of GABAergic agents in moderate/severe TBI in pre- and in-hospital settings.
- Severe TBI has worse outcomes regardless of pharmaceutic agent.