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

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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.

<table>
<thead>
<tr>
<th>Author</th>
<th>Country</th>
<th>Number of Patients</th>
<th>Pharmacologic Agent</th>
<th>Study Design</th>
<th>Primary Outcome Metric</th>
</tr>
</thead>
<tbody>
<tr>
<td>Roberts</td>
<td>Multiple (29)</td>
<td>9127</td>
<td>TXA1</td>
<td>RCT</td>
<td>28-Day Mortality</td>
</tr>
<tr>
<td>Rowell</td>
<td>United States and Canada</td>
<td>966</td>
<td>TXA</td>
<td>RCT</td>
<td>6-Month Neurologic Outcome (GOS-E)</td>
</tr>
<tr>
<td>Jokar</td>
<td>Iran</td>
<td>80</td>
<td>TXA</td>
<td>RCT</td>
<td>Growth of ICH</td>
</tr>
<tr>
<td>Walker</td>
<td>United States and Canada</td>
<td>71</td>
<td>TXA</td>
<td>RCS</td>
<td>Neurologic Outcome (GCS, GOS)</td>
</tr>
<tr>
<td>Moro</td>
<td>Multiple2</td>
<td>174</td>
<td>TXA</td>
<td>RCS</td>
<td>In-Hospital Mortality, GCS on Discharge</td>
</tr>
<tr>
<td>Bossers</td>
<td>Netherlands</td>
<td>1827</td>
<td>TXA</td>
<td>PCS</td>
<td>30-Day Mortality</td>
</tr>
<tr>
<td>Raj</td>
<td>Multiple3</td>
<td>95,941</td>
<td>Ethanol</td>
<td>MA</td>
<td>In-hospital Mortality</td>
</tr>
</tbody>
</table>

Table 2. Summary of included studies’ findings.

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Key Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Roberts</td>
<td>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&lt;0.005).</td>
</tr>
<tr>
<td>Rowell</td>
<td>Bolus-only group with intracerebral hematoma expansion with decreased mortality (p&lt;0.03) and improved disability ratings score (95% CI: 4.2 to -0.08).</td>
</tr>
<tr>
<td>Jokar</td>
<td>Treated group with significantly smaller increase in ICH (p&lt;0.01).</td>
</tr>
<tr>
<td>Walker</td>
<td>Treated patients left with significant increases in GCS (p&lt;0.008) and similar discharge GCS (p=0.58).</td>
</tr>
<tr>
<td>Moro</td>
<td>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).</td>
</tr>
<tr>
<td>Bossers</td>
<td>Higher 30-day mortality in treated patients (p=0.01). However, more severely injured patients were more likely to be treated.</td>
</tr>
<tr>
<td>Raj</td>
<td>Meta-analysis of 95,941 patients. Found significant protective effect of positive blood alcohol content (p=0.00001) that remained after controlling for heterogeneity.</td>
</tr>
</tbody>
</table>

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 pharmacologic agent.