Maine Medical Center
Department of Emergency Medicine
Journal Club Summary Template

Date: March 20201	**Presenter Name: Tamar Stokelman**

Article Citation: Association Between Prehospital TXA Administration and Outcomes of Severe Traumatic Brain Injury. Published in JAMA Neurology Dec 7 2020.
Country(ies): Netherlands
Funding Source(s): Not Stated

Purpose
Research Question(s): To assess whether prehospital administration of TXA is associated with mortality and functional outcomes in a patients with severe TBI
Study Purpose: TBI associated with bleeding, poor outcomes. TXA has shows advantage in certain severe hemorrhage situations by preventing exsanguination. There had been prior trials that that looked at TXA when initiated in hospital settings in trauma patients who had severe TBI's they found no advantage, and trials looking at prehospital administration of TXA and found no neurologic or mortality benefits. Non of the trials could comment on the **advantage** or **disadvantage** of TXA on patients with a severe (isolated) TBI injury, which is what this paper could do. So severe isolated TBI is ones who had no severe extracranial damage, or if they did it was very mild based on a grading scale.

Methods
Study Design: Cohort study, performed retrospective analysis of protectively collected observation data from the BRAIN-PROJECT.
Outcome(s) ***[or Dependent Variable]:*** Primary outcome was 30 day morality. Secondary outcomes looked at included 1-year functional neurological outcome based on GCS score and also length of hospital stay.
Intervention ***[or Independent Variable]:*** TXA administration in the prehospital setting
Ethics Review: The ethics board of the Amsterdam University Medical Center and Erasmus MC Rotterdam reviewed the study protocol and included that the research did not fall under the Dutch Medical Research Involving Human Subject Act, so study approval and informed consent were waved.
Research Setting: The BRAIN-PROJECT was a Multicenter observational study or prehospital treatment of patients with severe TBI (Brain Injury: Prehospital Registry of Outcome, Treatment and Epidemiology of Cerebral Trauma)

Study Subjects: BRAIN PROJECT had 2589 patients transported to 9 trauma centers (8 level 1's and one level 2). Of them 290 were excluded. Ultimately 1827 were used for analysis. 70% were male. 30% were female. Of those 1375 had confirmed TBI and 719 had **isolated TBI cohort.** A total of 693 patients received prehospital TXA.

Inclusion Criteria: Patients with suspected severe TBI (based on the mechanism of trauma or clinical findings of severe TBI and a prehospital GCS score of 8 or lower) who were treated by the Dutch Physician-staffed Helicopter Emergency Medical Services (HEMS) from 2012- 2017

Exclusion Criteria: Excluded 290 patients that that had cardiopulmonary arrest on the way to the hospital (these patients inherently had a high mortality despite the intervention) and patients who were not transported to the trauma center (because they couldn't followed those up)

Study Interventions: Prehospital TXA was given to 693 patients. Of those 90% received 1gm and then 4 patients received more than 2grams of TXA.

Study Groups:

They tested the hypothesis of the associated between TXA and mortality in 3 groups:
Full cohort, patient with **confirmed TBI,** and patients with **isolated TBI**

Confirmed TBI: Head abbreviated injury score (AIS) was 3 or higher
Isolated TBI: Head AIS score 3 or higher, with neck/spine/thorax/abdomen/ extremities and external IS of 2 or lower. They allowed for some wiggle room of other injuries but not major

AIS is an anatomic based coding system of injury graded on a scale of 1-6, 6 is max points and max injury (you get points for the region of your body injured, the type of injury and level of involvement (artery, vein, bone)

Instruments/Measures Used: The associated between TXA and mortality was evaluated using **logistical** regression analysis.

Data Analysis:

***A priori* sample size calculation?** Published a priori calculations were done and showed that sample size of 2000 patients provided 80% power to detect an absolute 5.6% mortality reduction, a sample size of 1500 patients has an 80% power to detect a 6.4% decreased in mortality and a sample size of 1000 has a 80% power to detect a 7.8% decreased in mortality

Statistical analyses used:
Continuous data was analyzed using quantile -quantile plots and Shaprio Wilks tests. They also used 2-tailed t-tests, Mann-Whitney tests and chai squared test . Data was presented as mean, median and percentages.

To look at the associated between TXA and mortality at 30 days they used **logistic regression**.

In the **unadjusted logistical regression analysis,** a **multivariate model** was built in to account for **confounders**. Control variables were also added into the model (there were multiple control variables including things like patient age, sex, pre-injury medications, initial GCS score) . They used **cox proportional hazard regression model** to analyze survival times .

Results

Brief answers to research questions *[key findings]:*

What they found was that of the three cohorts (full cohort, confirmed TBI cohorta and isolated TBI) after they adjusted for potential confounders

- There was **no evidence of increased mortality** in the **full cohort** and in patients with **confirmed TBI cohort** who received prehospital TXA
- However, in patients with **isolated TBI**, there was a substantially increased odd of mortality, OR 4.45 and subsequent estimated survival analysis showed a consistently increased mortality in patients only in the severe isolated TBI cohort who received prehospital TXA

Additional findings:

For the secondary outcome at 12 months mortality they found a statistically significant increase in 12 month mortality only in the Isolated TBI group (Odds ratio 2.21, p=0.02)

They did a post hoc analysis to check if there was an association between TXA with mortality and anticoagulation use before injury and they found no evidence of interaction.

Limitations: They commented on several limitations include that it's a observational study, they could be missing data. Potential for section bias or information bias. They also used the standard Dutch protocol and accepted international protocol of 1gm of TXA, and didn't study other doses which could have different outcomes.

Clinical Implications

This study can't be feasible replicated exactly in a prehospital setting because it's as retrospective and they used AIS scores to create the cohorts of suspected vs confirmed TBI and to identify isolated TBI patients. However, the findings are very **clinically relevant** because it has influenced prehospital EMS protocal.

There were 2 prior studies looking at the role of TXA in **hemorrhagic** shock, CRASH-2 trial and Matters trial. CRASH-2 showed that TXA decreased mortality when given within 3 hours of from injury and a further mortality benefit intros who received it within 1 hour of injury. The Matters trial showed that TXA use decreased the number of blood transfusion required. Up until this point, TXA administration was studied in multi trauma patients but not **isolated TBI alone.** Then CRASH-3 trial came out, which administered TXA in the hospital setting (not prehospital) and it did not find an advantage or disadvantage to giving TXA in patients in their subgroup analysis that had isolated TBI. The study we just reviewed is one of the first that showed that specifically in the the **isolated TBI cohort,** the survival showed that there is a marked increase in mortality. EMS protocols now have **isolated head injury** as a contraindication to giving TXA.

Level of evidence generated from this study

Ia: evidence obtained from meta-analysis of randomized controlled trials
Ib: evidence obtained from at least one randomized controlled trial
IIa: evidence obtained from at least one well-designed, controlled study without randomization
IIb: evidence obtained from at least one other type of well-designed quasi-experimental study
III: evidence obtained from a well-designed, non-experimental study
IV: expert committee reports; expert opinion; case study; case report