DEM Journal Club

Article Appraisal

Article: Effects of tranexamic acid on death, disability, vascular occlusive events and other morbidities in patients with acute traumatic brain injury (CRASH-3): a randomised, placebo-controlled trial. The CRASH-3 trial collaborators.

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Resident Reviewer Name(s) and Residency Affiliation: Sean Nugent R2 FRCPC Kelowna Site, Holly Sherman R2 FRCPC Vancouver Site

Faculty Methodology/Bio -statistics Resource Person: Dr. John Tallon

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Background and Study Objective(s):

Traumatic brain injury (TBI) is common. Intracranial bleeding is a common complication of TBI and increases the risk of death and disability. The CRASH-2 trial showed that in patients with trauma with major extracranial bleeding, early administration (within 3 h of injury) of Tranexamic acid (TXA) reduces death due to bleeding. Isolated TBI in that study was an exclusion criteria. Prior small RCTs studying the benefit of TXA in TBI showed a reduction in death with TXA, but as these trials were small they were considered hypothesis generating. Therefore, it is proposed that early administration of tranexamic acid in patients with TBI may prevent or reduce intracranial haemorrhage expansion and thus avert brain herniation and death. The CRASH-3 trial aimed to quantify the effects of tranexamic acid on head injury-related death, disability, and adverse events in patients with TBI.

Study Design:

This was a pragmatic, double-blinded randomized controlled trial that included 175 Hospitals in 29 countries between July 20, 2012, and Jan 31, 2019. Inclusion criteria were adults with TBI who were within 3 h of injury, had a Glasgow Coma Scale (GCS) score of 12 or lower or any intracranial bleeding on CT scan, and no major extracranial bleeding. The time window for eligibility was originally 8 hours but, in 2016, the protocol was amended to limit recruitment to patients within 3 hours of injury. This change was made blind to the trial data, in response to external evidence suggesting that delayed treatment is unlikely to be effective. The investigators randomly assigned patients to receive TXA (loading dose 1 g over 10 min then infusion of 1 g over 8 h) or matching placebo. The primary outcome was head injury-related death in hospital within 28 days of injury in patients treated within 3 h of injury. There was a pre-specified sensitivity analysis of the primary outcome that excluded patients with a GCS score of 3 and those with bilateral unreactive pupils at baseline, as these patients would be thought to skew the results towards the null hypothesis. Pre-specified subgroup analysis of the primary outcome were performed, stratified by baseline GCS and pupillary reaction, time to treatment, and age. All analyses were done by intention to treat.

Results:

Investigators randomly allocated 12 737 patients with TBI to receive TXA (6406 [50·3%] or placebo [6331 [49·7%], of whom 9202 (72·2%) patients were treated within 3 h of injury. Among patients treated within 3 h of injury, the risk of head injury-related death within 28 days was 18.5% in the TXA group versus 19.8% in the placebo group (855 vs 892 events; risk ratio [RR] 0.94 [95% CI 0.86–1.02]). In the prespecified sensitivity analysis that excluded patients with a GCS score of 3 or bilateral unreactive pupils at baseline, the risk of head injury-related death was 12.5% in the TXA group versus 14.0% in the placebo group (485 vs 525 events; RR 0.89 [95% CI 0.80–1.00]).

Patients with mild to moderate TBI (GCS 9-15) were found to have a significantly reduced head injury related mortality of 5.8% in the TXA group compared to 7.5% in the placebo group (166 vs 207 events; RR 0.78 [95% CI 0.65-0.95]). All cause mortality was not different between groups (RR 0.96 [0.89-1.04]), as was non-head injury related deaths (RR 1.31 [0.93-1.85]). Disability, measured on the Disability Rating Scale was similar between groups, 4.99 in the TXA group and 5.03 in the placebo group. The risk of vascular occlusive events was similar in the TXA and placebo groups (RR 0.98 (0.74–1.28).

Validity of Results:

This was a large, well done trial with few methodological limitations. However, despite efforts to correct for their change in protocol, they did remain underpowered and there was ultimately a negative endpoint. There was no significant difference in head injury-related mortality between the TXA group and the placebo group who were treated within 3 hours of presentation even when accounting for GCS of 3 or bilateral unreactive pupils. There were no significant differences noted in the severely head injured patient in any subgroup analyses.

In the subgroup analysis, those with mild-moderate head injury did experience a significant reduction in mortality in the TXA group and this was more effective if treatment was given early. We noted that in this particular analysis, the authors chose to include those they enrolled in the initial 8-hour enrollment protocol, which skews our results towards early administration and limits the validity of this result.

Generalizability of Results:

One methodological limitation is the lack of information regarding if the groups were treated equally aside from the experimental intervention of TXA administration. No data was provided regarding availability of CT, neurosurgical care, intensive care or neurosurgical monitoring. This trial was done in many countries and hospitals that may not have the resources that our academic centers do. The majority of patients were from Pakistan, United Kingdom, Malaysia, and many other less resource rich nations. There was only one center in Canada. The authors did examine the effect of TXA in head injury related death stratified by country income, but this was not pre-planned and showed no significance. One must take these results with a grain of salt when applying it to our setting.

Another issue with generalizability of the results is how to practically apply this information to our isolated TBI patients with mild injury (GCS 15-13) with positive CT scans, who were shown to have benefit in this study. We think that it would likely be difficult logistically to get the patient assessed, CT scan performed and read, and then to get the patient TXA within 3 hours of injury.

The Bottom Line:

There was no benefit in the primary end-point (head injury-related death at 28 days) despite being a very large well-run study. The results of the subgroup analysis show improve survival in the mild-moderate head injured group, these findings were underpowered and should be interpreted as hypothesis generating for further investigation. Overall, there was no role for TXA in the severely head injured and there may be a role for TXA in the moderate group (9-12) if able to be given early.

The lack of adverse events and relative benefit in the mild-moderate also may confer that we are not harming patients with both extracranial and intracranial bleeding when we are giving TXA although not directly studied. Most importantly, TXA administration should not be prioritized over other standard management of the traumatic TBI patient. Our nursing staff included in the discussion wanted to highlight that TXA infusions in particular are non-

compatible with many medications. This needed to be considered in balance with other competing priorities during resuscitation of these patients.