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SOCIETY FOR NEUROSCIENCE IN ANESTHESIOLOGY AND CRITICAL CARE

ARTICLE OF THE MONTH

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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Welcome to the December 2019 installment of SNACC's article of the month. The commentary this month addresses the important CRASH-3 trial, a study on the effects of tranexamic acid in patients with acute traumatic brain injury.

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As always, readers are welcome to join us for further discussion on the **Twitter** feed or on **Facebook**.

~ Oana Maties, MD; Nina Schloemerkemper, MD; Amie Hoefnagel, MD and Shilpa Rao, MD

Commentary

By Annie Zhu, MBBS; Jason Chui, MBChB, MSc, FANZCA, FHKCA, FHKAM

Traumatic brain injury (TBI) is one of the most serious and feared diagnoses. The mortality rates of TBI range from 20% in isolation to above 50% with concomitant hemorrhagic shock.[1,2] Over the past few decades, there has been minimal progress in developing new and effective interventions that could alter the devastating course of TBI. Because of this, the outcomes of TBI remain relatively unchanged. In recent years, the early administration of tranexamic acid (TXA) has been shown to reduce death in polytrauma patients (CRASH-2 study)[3], as well as in women with post-partum haemorrhage (WOMEN study).[4] These promising results inspired the hypothesis of the CRASH-3 trial[5] that early administration of TXA might reduce intracranial hemorrhage, thereby reducing disability and death in patients with TBI.

The CRASH-3 trial[5] represents a tremendous effort to assess the benefit and safety of early administration of TXA in TBI patients. The CRASH-3 trial is a multicentre, double-blinded, parallel design, prospective matched randomized controlled clinical trial, conducted at 175 hospitals in 29 countries over a 6.5-year study period. This massive trial randomized 12,737 adult patients with TBI (who were within three hours of injury, had an intracranial bleed on CT (or GCS score ≤ 12 if no CT available), and no major extra-cranial bleed) to either receiving TXA (1g loading dose over ten min, followed by an infusion of 1g over 8hr) or saline placebo. The primary outcome was head injury related-death in hospital within 28 days. The overall head injury-related mortality showed no difference between the two groups (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]). However, in the pre-specified sensitivity analysis that excluded patients with a GCS score of three or bilateral unreactive pupils at baseline, the early administration of TXA reduced head injury-related mortality from 14% in the placebo group to 12·5% in the TXA group (485 vs 525 events; RR 0·89 [95% CI 0·80–1·00]). Further, in the subgroup analysis, the early administration of TXA was shown to have a differential treatment benefit to reduce head injury-related mortality in patients with mild-to-moderate head injury (RR 0·78 [95% CI 0·64–0·95]), but not in patients with severe head injury (0·99 [95% CI 0·91–1·07]; p value for heterogeneity 0·030). The risks of vascular occlusive events (including myocardial infarction, stroke, deep vein thrombosis, and pulmonary embolism) and seizures were comparable between the two groups.

The design of the CRASH-3 trial is an excellent example of robust research methodology and superior trial management. The study was carefully designed with appropriate randomization and masking methods. The study protocol and statistical analysis plan were published prior to the trial to ensure credibility and transparency of the study.[6,7] The trial was appropriately monitored onsite and remotely; approximately 19% of records were reviewed and source verified to ensure data integrity. Primary outcome data could not be obtained in only 75 (0.8% of 9202) study participants; protocol violations were only seen in 98 study participants. Given the scale of the CRASH-3 trial and the expected challenges of conducting a multicentre clinical trial in 29 countries over a 6.5-year study period, the quality of the CRASH-3 trial is very impressive.

The eligibility criteria were modified to narrow the recruitment window from within eight hours to three hours following brain injury. This decision was made based on new external evidence that TXA is unlikely to be effective

when initiated beyond three hours after the index injury.[8-10] The primary outcome and sample size were also modified accordingly. Since no unblinded trial data was referenced regarding this decision, these changes to the study design were unlikely to bias the results.

A pre-specified sensitivity analysis was performed to exclude patients with GSC score of three or bilateral unreactive pupils at presentation.[6,7] The rationale of this sensitivity analysis is that these profoundly injured patients were unlikely to survive regardless of any intervention applied, but the inclusion of these patients might dilute the true treatment effect of TXA. After excluding 1,490 patients, a total of 7,637 patients were included in the final analysis, providing sufficient power to demonstrate the benefit of TXA on mortality related to head injury. Overall, despite several study design modifications that were made during the conduct of the trial, the study design remains robust and the results of CRASH-3 trial are still valid and credible.

There are several factors that support the universal implementation of early administration of TXA as part of head trauma protocols/guidelines. First, the CRASH-3 trial clearly demonstrated the efficacy and safety profile of TXA. The number-needed-to treat of early administration of TXA was 66, suggesting a moderate treatment effect. The same regimen has been demonstrated to be safe without increasing the risks of complications in CRASH-2 and WOMEN trials.[3,4] Second, the administration of TXA is easily implemented clinically in an acute setting. The CRASH-3 trial involves centres from both low-income and high-income countries, in which Pakistan and Malaysia contributed 4,567 and 1,567 patients respectively, suggesting a high likelihood of real-life implementation of early administration of TXA worldwide within a diverse clinical setting. Third, the cost of 2 gram of TXA is relatively low, which is likely to be cost effective in many settings and is unlikely to have financial barriers that would impact routine implementation.

In summary, the CRASH-3 trial is a remarkable study in the history of TBI research. TXA is the first pharmacological intervention used in the acute setting that is found to be lifesaving in patients with TBI. Our routine practice is very likely to change in the near future because of this trial. In addition, the CRASH-3 trial also represents a successful collaboration of efforts to overcome the scientific challenges of investigating TBI. It’s a true win for the patients, physicians and researchers.

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