SNACC

SOCIETY FOR NEUROSCIENCE IN ANESTHESIOLOGY AND CRITICAL CARE

# ARTICLE OF THE MONTH

## Effect of Out-of-Hospital Tranexamic Acid vs Placebo on 6-Month Functional Neurologic Outcomes in Patients With Moderate or Severe Traumatic Brain Injury

*Rowell SE, Meier EN, McKnight B, Kannas D, May S, Sheehan K, et al. JAMA. 2020;324(10):961-74.*

Welcome to the final SNACC AOTM for the 2020 year. Personally, I've always enjoyed the works of Charles Dickens, but his statement "It was the best of times, it was the worst of times, it was the age of wisdom, it was the age of foolishness, it was the epoch of belief, it was the epoch of incredulity, it was the season of light, it was the season of darkness, it was the spring of hope, it was the winter of despair" rings incredibly true this year. We hope you enjoy the final AOTM for 2020 which further explores the role of TXA in TBI. Our commentary this month is courtesy of Dr. Alana Flexman.

Alana Flexman, MD, FRCPC is a Clinical Associate Professor and the past Head of the Division of Neuroanesthesia at the University of British Columbia (UBC) and Vancouver General Hospital in Vancouver, Canada. Dr. Flexman completed her medical school training at the University of Toronto followed by residency training at UBC and a two-year Neuroanesthesia and Research Fellowship at the University of California San Francisco. She has a research focus on clinical outcomes after neurosurgical and spine procedures as well as perioperative stroke. Dr. Flexman is the Past-Chair of the Neuroanesthesia Section of the Canadian Anesthesiologists' Society and serves as the Vice President for Education for the Society for Neuroscience in Anesthesiology and Critical Care (SNACC). She also serves as an associate editor for the Canadian Journal of Anesthesia and on the editorial board of the Journal of Neurosurgical Anesthesiology.

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

- Amie Hoefnagel, MD, Shilpa Rao, MD, Oana Maties, MD, and Nina Schloemerkemper, MD

# Commentary

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This study was a 3-armed, randomized, controlled trial examining the effect of pre-hospital tranexamic acid on outcomes after traumatic brain injury (TBI). Traumatic intracranial bleeding is a significant cause of morbidity and mortality after TBI, and the use of an antifibrinolytic such as tranexamic acid (TXA) may be beneficial. Prior to this study, the CRASH-2 trial (1) in 2010 reported overall improved survival in trauma patients who received TXA. The subsequent multicenter CRASH-3 (2) found no difference in the primary endpoint (all-cause mortality at 28 days) between TBI patients who received TXA vs not, although a secondary analysis found that TBI patients given TXA within 3 hours of injury had lower rates of head-injury related death, with a more pronounced effect with early administration and in the subgroup of mild to moderate TBI. The current trial was designed to specifically examine the effect TXA administered within 2 hours of moderate to severe TBI.

In this study, Rowell et al included 966 TBI patients over 15 years of age with moderate or severe TBI (GCS 3-12, at least one reactive pupil) who were not in shock (SBP >90mmHg) from 20 trauma centers. Patients were randomized to three treatment arms within 2 hours of injury: 1) TXA 1g (out of hospital) + 1g over 8 hours (in-hospital) n=312; 2) TXA 2g (out of hospital) + placebo infusion (in-hospital) n=345; 3) Placebo bolus (out of hospital) + placebo infusion (in-hospital) n=309. The primary outcome was favorable neurologic function at 6 months as measured by a Glasgow Outcome Scale-Extended score >4, or those categorized as moderate disability or good recovery. The authors also included several secondary outcomes including mortality, Disability Rating Scale score, progression of intracranial hemorrhage, and adverse events such as seizures and thromboembolic events. The planned primary analysis combined the two TXA arms. The study was well-blinded and an appropriate sample size calculation performed.

The majority of the study participants were male (74%) with a mean GCS of 8. The incidence of good neurologic outcome was similar between the groups, 65% in the TXA groups vs 62% in the placebo group (difference 3.5% [90% 1-sided confidence limit for benefit, −0.9%]; P = .16; [97.5% 1-sided confidence limit for harm, 10.2%]; P = .84). There was no difference in 28-day mortality (TXA 14% vs Placebo 17%, p=0.26), disability score, or progression of intracranial hemorrhage. The patients receiving the 2g TXA bolus only had a higher rate of seizures (5%) than the other two groups (2%), and thromboembolic events were observed more frequently in the bolus only (9%) and placebo (10%) groups compared to the bolus maintenance group (4%).

Overall, this well-conducted RCT adds to our understanding of the role of TXA in TBI and builds on the CRASH-3 results. These results confirm a lack of overall mortality benefit seen in CRASH-3, and lack of impact on neurologic outcome at 6 months. Reassuringly, there does not appear to be evidence of adverse neurologic impact from TXA, although the data raise the possibility of an increased risk of seizures with the 2g bolus of TXA (overall numbers are too low to draw definite conclusions). An important study limitation was seen in protocol deviations in recruitment due difficulty distinguishing TBI from intoxication in the out-of-hospital setting, as well as accurately assessing GCS: 23% (n=221) of study participants had no brain injury. Other limitations include the potential for survivor bias, loss to follow-up, a mix of blunt (97%) and penetrating trauma (3%).

Overall, this study does not support the routine administration of TXA to patients with moderate to severe TBI, although the results must be interpreted cautiously in light of the limitations. As the authors point out, further research is likely warranted to examine alternate dosing regimens of TXA and the effect in patients with less severe TBI or intracranial hemorrhage.

**References:**

(1) CRASH-2 trial collaborators, Shakur H, Roberts I, Bautista R, Caballero J, Coats T, Dewan Y, El-Sayed H, Gogichaishvili T, Gupta S, Herrera J, Hunt B, Iribhogbe P, Izurieta M, Khamis H, Komolafe E, Marrero MA, Mejía-Mantilla J, Miranda J, Morales C, Olaomi O, Olldashi F, Perel P, Peto R, Ramana PV, Ravi RR, Yutthakasemsunt S. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial. *Lancet*. 2010 Jul 3;376(9734):23-32.

(2) CRASH-3 trial collaborators. 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. *Lancet*. 2019 Nov 9;394(10210):1713-1723.