Need to Know: CJEM *Journal Club*

Does tranexamic acid reduce traumatic brain injury-related death?

Pierre-Gilles Blanchard, MD, MSc, PhD, MBA*; David Paré, MD*; Jennifer Truchot, MD†; Eric Mercier, MD*

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Article type: Randomized controlled trial (RCT).
Ratings: Methods – 4/5 Usefulness – 3/5

INTRODUCTION

Background

Previous reports suggest that tranexamic acid (TXA) reduces bleeding death in patients with extracranial hemorrhage and led to its adoption in trauma protocols. The role of TXA in traumatic brain injury (TBI) remains unclear.

Objectives

The CRASH-3 trial aimed to test whether TXA reduces head injury-related death and disability in patients following a TBI.

METHODS

Design

International, multicentre, randomized, placebo-controlled trial.

Setting

175 hospitals across 29 countries, 1 North American site.

Eligibility criteria

Adult patients presenting within 3 hours of injury (initially 8 hours before a protocol amendment) with a Glasgow Coma Score (GCS) of 12 or lower or a computed tomography (CT) scan with evidence of intracranial bleeding, and no extracranial bleeding. The treating clinician had to be uncertain about the appropriateness of TXA treatment.

Intervention

Loading dose of 1 g of TXA followed by an intravenous infusion of 1 g over 8 hours versus matching placebo.

Outcomes

The primary outcome was head injury-related death in hospital within 28 days of injury.

MAIN RESULTS

A total of 9,202 patients with TBI treated within 3 hours of injury were randomly allocated to receive TXA or placebo. There was no statistically significant difference in the risk of head injury-related death between the TXA group (18.5%) and the placebo group (19.8%; risk ratio [RR] 0.94, 95% CI 0.86-1.02). If the patients presenting with a GCS of 3 or with bilateral unreactive pupils were excluded, the risk of head injury-related death was significantly reduced to 12.5% in the TXA group versus 14.0% in the placebo group (RR 0.78, 95% CI 0.64-0.95, number needed to treat [NNT] 67; prespecified analysis). A

From the *Faculté de médicine, Département de médicine familiale et de médicine d'urgence, Université Laval, Québec, QC; and the †Université Paris Diderot – APHP Hôpital Lariboisière, Paris, France.

Correspondence to: Dr. Pierre-Gilles Blanchard, 1401, 18e Rue, Bureau H-504, Québec, QC G1J 1Z4; Email: pierre-gilles.blanchard.1@ulaval.ca

reduction in head injury-related death was significant in patients with a GCS of 9-15 (RR 0.78, 95% CI 0.64-0.95, NNT 59) but not in those with a severe TBI (0.99, 95% CI 0.91-1.07). The RR for all-cause mortality was 0.96 (95% CI 0.89-1.04) and 1.31 (95% CI 0.93-1.85) for non-head, injury-related deaths. TXA had no significant impact on disability or adverse effects.

APPRAISAL

Strengths

- Largest randomized controlled trial on the subject
- Minimal loss to follow-up
- Similar baseline characteristics between treatment groups
- All analyses done by intention to treat
- Evaluation of uncommon adverse events
- Patient-centred outcomes (disability)

Limitations

- With the specified eligibility criteria, patients with a GCS of 12 or lower with no evidence of intracranial bleed would be included into the study.
- The eligibility criteria regarding the appropriateness of TXA treatment as evaluated by the treating clinician increase the risk of selection bias.
- External validity: only 0.05% of recruited patients were from North America compared with 36% from Pakistan.
- Between the protocol submission (ClinicalTrials.gov identifier NCT01402882) and publication, the primary outcome was changed from death in hospital to head injury-related death.
- The time window for eligibility was changed from 8 hours to 3 hours post-injury during the study.
- Wide confidence intervals resulted, despite the large sample size.
- Positive findings from unplanned subgroup analysis should be viewed as exploratory.
- The fact that TXA reduces head injury-related death only for mild to moderate TBI but not for severe TBI challenges biological plausibility.

CONTEXT

CRASH-2 study showed a modest absolute risk reduction in all-cause mortality in patients with traumatic extracranial bleeding after early administration of TXA.[1] To date, the effects of TXA on head injury-related death, disability, and vascular occlusive events in patients with TBI are unknown. Although meta-analysis of previous trials of TXA in TBI suggested a potential reduction in death, this hypothesis has yet to be tested in a large scale, randomized trial.[2,3]

BOTTOM LINE

CRASH-3 trial collaborators conclude that TXA is safe in patients with TBI and reduces head injury-related death.[4,5] However, this interpretation is misleading because the primary outcome is negative, and only one subgroup analysis supports this conclusion. Despite no statistical difference in the rate of adverse events, the RR of TXA administration was 1.31 for non-head injury-related death, calling for caution in the interpretation of results. The CRASH-3 trial is a robust study underlining the need for further research to identify the subgroup of patients, if any, that could benefit from TXA after traumatic intracranial bleeding in our population.

Keywords: Neurosurgery, tranexamic acid, trauma, traumatic brain injury

Competing interests: None declared.

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