CRASH-3 Trial Coordinating Centre
Clinical Trials Unit
London School of Hygiene & Tropical Medicine
Room 180, Keppel Street, London WC1E 7HT, UK

Tel +44(0)20 7299 4684 | Fax +44(0)20 7299 4663
crash@Lshtm.ac.uk
crash3.Lshtm.ac.uk

CRASH-3
Clinical Randomisation of an Antifibrinolytic in Significant Head Injury

ISRCTN15088122

SUMMARY OF CHANGES BETWEEN PROTOCOL VERSIONS 1.0 AND 2.0

ELIGIBILITY:

Although there is no change to the original eligibility criteria, for the remainder of the trial we will limit recruitment to patients who are within 3 hours of injury.

PRIMARY OUTCOME:

The primary outcome will include only patients randomised within 3 hours of injury. The primary outcome is death in hospital within 28 days of injury among patients randomised within 3 hours of injury (cause-specific mortality will also be recorded).

SAMPLE SIZE

A study with 10,000 traumatic brain injury (TBI) patients randomised within 3 hours of injury would have about 90% power (two sided alpha=1%) to detect a 15% relative reduction (from 20% to 17%) in all-cause mortality. About three thousand patients have been recruited beyond three hours of injury already, therefore the total sample size would be approximately 13,000 patients.

STATISTICAL ANALYSIS:

We expect tranexamic acid (TXA) to be most effective when given soon after injury, when tissue plasminogen activator levels are highest, and less effective when given several hours after injury when the risk of thrombotic DIC may be increased. We will examine this hypothesis by conducting a sub-group analysis of the effect of TXA according to the time interval between injury and TXA treatment (≤1, > 1 to ≤ 3, > 3 h). The outcome measure for this subgroup analysis will be death due to head injury.

RATIONALE FOR CHANGES: New research highlights the importance of treatment in the first few hours after injury:

Since the start of the CRASH-3 trial, new research suggests that TXA is likely to be most effective in the first few hours after injury and less effective when given later. Trauma triggers the early release of tissue plasminogen activator (TPA), the enzyme that converts plasminogen to the fibrinolytic enzyme plasmin, resulting in increased clot breakdown and bleeding.[1,2] TPA levels peak about 30 minutes after injury and plasmin peaks at one hour.[2] By inhibiting early fibrinolysis, TXA prevents coagulopathic bleeding.[3] However, the effects appear to be short lived. Around 2 hours after injury, plasminogen activator inhibitor (PAI-1) levels increase, reaching a peak at 3 hours.[2] PAI-1 inhibits fibrinolysis resulting in "fibrinolytic shutdown."[4] This might explain why the benefits of TXA in poly-trauma patients appear to be limited to the first three hours.[5] Because recent research shows that the coagulopathy after TBI is similar to that in poly-trauma, a similar time dependent effect might be expected after TBI.[6,7] To ensure that the CRASH-3 trial is large enough to reliably confirm or refute an early (<3 hours) treatment benefit, the sample size has been increased from 10,000 to 13,000 patients with the aim to enrol 10,000 patients within 3 hours of injury. In addition, the primary outcome has been amended to deaths among patients treated within 3 hours of injury. If the pathophysiological mechanisms affected by TXA are most relevant in the early hours after injury, the effect of TXA in this early period is the outcome of greatest importance. Nevertheless, intracranial bleeding can continue for up to 24 hours after injury and so examination of the effects of TXA within and beyond three hours remains an important scientific objective that will be addressed in pre-planned sub-group analyses.

CRASH-3 Trial Coordinating Centre
Clinical Trials Unit
London School of Hygiene & Tropical Medicine
Room 180, Keppel Street, London WC1E 7HT, UK

Tel +44(0)20 7299 4684 | Fax +44(0)20 7299 4663
crash@Lshtm.ac.uk
crash3.Lshtm.ac.uk

References

1. Chapman MP, Moore EE, Moore HB, Gonzalez E, Gamboni F, Chandler JG, Mitra S, Ghasabyan A, Chin TL, Sauaia A, Banerjee A, Silliman CC. Overwhelming tPA release, not PAI-1 degradation, is responsible for hyperfibrinolysis in severely injured trauma patients. J Trauma Acute Care Surg. 2016; 80:16-25.
2. Wu X, Darlington DN, Cap AP. Procoagulant and Fibrinolytic Activity after Polytrauma in Rat. Am J Physiol Regul Integr Comp Physiol. 2015: doi: 10.1152/ajpregu.00401.2015. Epub 2015 Dec 2.
3. Roberts I, Prieto-Merino D, Manno D. Mechanism of action of tranexamic acid in bleeding trauma patients: an exploratory analysis of data from the CRASH-2 trial. *Critical Care* 2014,**18**:685 doi:10.1186/s13054-014-0685-8
4. Moore E, Moore H, Gonzalez E, Chapman M, Hansen K, Sauaia A, Silliman C, Banerjee A. Postinjury fibrinolysis shutdown: Rationale for selective tranexamic acid. J Trauma Acute Care Surg 2015; 78, Supplement 1 S65-69.
5. CRASH-2 collaborators, Roberts I, Shakur H, Afolabi A, Brohi K, Coats T, et al. The importance of early treatment with tranexamic acid in bleeding trauma patients: an exploratory analysis of the CRASH-2 randomised controlled trial. Lancet. 2011;377(9771):1096-101, 101 e1-2. Epub 2011/03/29.
6. Epstein DS, Mitra B, O'Reilly G, Rosenfeld JV, Cameron PA. Acute traumatic coagulopathy in the setting of isolated traumatic brain injury: a systematic review and meta-analysis. Injury. 2014 May;45(5):819-24. doi: 10.1016/j.injury.2014.01.011. Epub 2014 Jan 19.
7. Abdelmalik PA, Boorman DW, Tracy J, Jallo J, Rincon F. Acute Traumatic Coagulopathy Accompanying Isolated Traumatic Brain Injury is Associated with Worse Long-Term Functional and Cognitive Outcomes. Neurocrit Care. 2015 Aug 21. [Epub ahead of print]

NON-SUBSTANTIAL CHANGES:

Membership of the trial Steering Committee has been updated: Dr Manjul Joshipura has left the World Health organisation and resigned from the TSC. He will not be replaced.

Funding: The following has been added to the protocol in Section 3.11: Full funding for the main trial is provided through a grant provided by the UK Department for International Development/Medical research Council /Wellcome Trust through the Joint Global Health Trials Scheme in low-middle income countries and by the National Institute for Health Research, Health Technology Assessment programme for the UK. Funding for recruitment in the European Union and North America is provided by the LSHTM.