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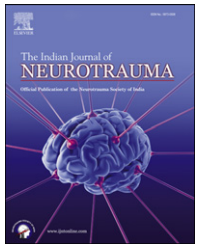

Editorial

Improving outcomes for patients with traumatic brain injury: The CRASH-3 trial in India

Worldwide, over 10 million people are killed or hospitalised because of traumatic brain injury (TBI) each year.[1] Approximately 90% of deaths from TBI occur in low and middle income countries.[2] TBI predominantly affects young adults and many patients experience long lasting or permanent disability. The social and economic burden of TBI is considerable. With rapidly increasing motorisation, the incidence of TBI is predicted to rise in low and middle income countries.[3]

Road traffic injuries resulted in an estimated 110, 000 deaths, 2.5 million hospitalisations and economic losses of about 3% of the gross domestic product in India in 2005. It is estimated that India will experience the deaths of 200,000 people and more than 3.5 million hospitalizations annually by 2015.[4] Effective preventative strategies need to be implemented urgently to reduce this burden to the Indian population. In addition, doctors who have to deal with victims of road traffic crashes need to have available to them effective treatments. An effective, widely practicable and affordable treatment for TBI could save many thousands of lives and substantially reduce the burden of disability.

Tranexamic acid (TXA) is commonly given to surgical patients to reduce bleeding and the need for blood transfusion. A systematic review of randomised trials of TXA in elective surgical patients shows that TXA reduces the number of patients receiving a blood transfusion by about a third, reduces the volume of blood transfused by about one unit, and halves the need for further surgery to control bleeding.[5]

TXA has been shown to reduce mortality in trauma patients with significant extra cranial bleeding. The CRASH-2 trial showed that the administration of TXA within 8 hours of injury significantly reduces deaths due to bleeding (RR = 0.85, 95% CI 0.76–0.96; $p = 0.008$), and all-cause mortality (RR = 0.91, 95% CI 0.85–0.97; $p = 0.0035$) compared to placebo, with no apparent increase in vascular occlusive events.[6] Among patients treated very soon after injury, the reduction in mortality with TXA is even greater.[7] Cost-effectiveness analysis has shown that the administration of TXA to bleeding trauma patients is highly cost effective in low, middle and high income settings.[8] As a consequence of the CRASH-2 trial results, TXA has been incorporated into trauma treatment protocols worldwide and has been included on the WHO List of Essential Medicines.

The knowledge that TXA reduces blood loss in surgery and reduces mortality in traumatic bleeding raises the possibility that it might also be effective in TBI. Intracranial haemorrhage is common after TBI and is associated with increased mortality and disability.

Two studies have evaluated the effect of TXA in traumatic brain injury. The CRASH-2 Intracranial Bleeding Study was a nested randomised trial conducted in 270 trauma patients who had evidence of TBI on a pre-randomisation CT scan. A second scan was conducted 24–48 hours after randomisation. There was a reduction in intracranial haemorrhage growth (RR = 0.80; 95% CI 0.59–1.09), fewer ischaemic lesions and lower all-cause mortality (RR = 0.60; 95% CI 0.32–1.11) in TXA allocated patients, but these results were not statistically significant.[9] A second randomised trial conducted in 240 patients with isolated TBI also found reductions in haemorrhage growth (RR = 0.56; 95% CI 0.32–0.97) and mortality (RR = 0.67; 95% CI 0.34–1.32) with TXA but this trial did not collect data on ischaemic lesions.[10] Meta-analysis of the two trials shows a significant reduction in haemorrhage growth (RR = 0.72; 95% CI 0.55 – 0.94) and mortality (RR = 0.63; 95% CI 0.40–0.99) with TXA.

Although the results from these trials are promising, the estimates are imprecise and there are no data on the effect of TXA on disability. Furthermore, because patients in the CRASH-2 Intracranial Bleeding Study also had significant extra cranial bleeding, the extent to which the results can be generalised to patients with isolated TBI is open to question. The CRASH-3 trial which aims to provide reliable evidence about the effect of TXA on mortality and disability in patients with TBI is planned. In addition, the trial will assess the effect of TXA on the risk of vascular occlusive events and seizures.

CRASH-3 is a pragmatic, randomised, double-blind, placebo-controlled trial in adults with traumatic brain injury. Inclusion criteria

- within 8 h of TBI
- with any intracranial bleeding on CT scan or who have a Glasgow coma scale of 12 or less, and
- no significant extra-cranial bleeding (needing immediate blood transfusion)
- The fundamental eligibility criterion is the responsible clinician's uncertainty as to whether or not to use tranexamic acid in a particular patient with traumatic brain injury.

1. Intervention

A loading dose of 1 g of tranexamic acid or placebo will be given as soon as possible after randomisation followed by a maintenance dose of tranexamic acid 1 g or placebo by intravenous injection over 8 hours.

2. Sample size

A study with 10,000 patients with traumatic brain injury would have about 90% power (two sided alpha = 1%) to detect a 15% relative reduction (from 20% to 17%) in all-cause mortality and also have more than 90% power to detect a difference in mean Disability Rating Scale score of 1·0 (assuming a SD of 9·0). Patients will be recruited from about 40 countries.

3. Endpoints

The primary outcome is death in hospital within 28 days of injury (cause-specific mortality will also be recorded). Secondary outcomes include: vascular occlusive events (myocardial infarction, pulmonary embolism, clinical evidence of deep vein thrombosis); stroke; disability assessed using the Disability Rating Scale and Patient Orientated Outcome measures; seizures; days in intensive care; and other adverse events.

4. Statistical analysis plan

The main analyses will compare all those allocated tranexamic acid versus those allocated placebo, on an intention to treat basis, irrespective of whether they received the allocated treatment or not. Results will be presented as effect estimates (relative risks and absolute risks) with 95% confidence intervals. Subgroup analyses for the primary outcome will be based on time from injury to randomisation, the severity of traumatic brain injury, location of intracranial bleeding, and baseline risk.

The trial protocol is registered at clinicaltrials.gov/ (Identifier NCT01402882) and on the ISRCTN Register (number 15088122). In addition the Protocol has been reviewed by the Lancet (see www.thelancet.com/protocol-reviews/11PRT-8142#).

As the burden on injuries grow in India, if a simple and widely practicable treatment such as TXA was shown to improve outcomes in patients with TBI, then it could be used in high, middle and low income countries, saving many thousands of lives and reducing the burden of disability.

Doctors across India are invited to join this global effort. Additional information is available from the CRASH-3 trial website at crash3.lshtm.ac.uk/.

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