Tranexamic acid to reduce head injury death in people with traumatic brain injury: the CRASH-3 international RCT

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Scientific summary

The CRASH-3 international RCT

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Scientific summary

Background

Traumatic brain injury is the leading cause of injury-related death and disability globally. Each year, worldwide, there are over 60 million new cases of traumatic brain injury. Tranexamic acid reduces deaths due to blood loss in trauma patients with significant extracranial bleeding. Intracranial bleeding is common after traumatic brain injury and can cause brain herniation and death. Tranexamic acid may improve outcomes in patients with intracranial bleeding by reducing the expansion of intracranial haemorrhages. This is supported by data from a meta-analysis of randomised controlled trials of tranexamic acid in traumatic brain injury, which showed a significant reduction in haemorrhage growth and mortality with tranexamic acid. An effective, widely practicable and affordable treatment for traumatic brain injury could save many thousands of lives and substantially reduce the burden of disability.

Objective

We assessed the effects and cost-effectiveness of tranexamic acid in traumatic brain injury patients on death, disability, vascular occlusive events, seizures, complications and adverse events.

Methods

The CRASH-3 (Clinical Randomisation of an Antifibrinolytic in Significant Head Injury-3) trial was an international, multicentre, randomised, placebo-controlled trial conducted in 175 hospitals in 29 countries. Adults with traumatic brain injury ($n = 12{,}737$) who were within 3 hours of injury and had a Glasgow Coma Scale score of ≤ 12 or any intracranial bleeding on computerised tomography scan, and no significant extracranial bleeding, were eligible. The time window for eligibility was originally within 8 hours of injury. However, in September 2016, in response to evidence external to the trial indicating that tranexamic acid is unlikely to be effective when initiated beyond 3 hours of injury, the Trial Steering Committee amended the protocol to limit recruitment to within 3 hours of injury.

Patients were randomly allocated to receive tranexamic acid (loading dose of 1 g over 10 minutes and then infusion of 1 g over 8 hours) or matched placebo. Patients were assigned to their treatment group by selecting a numbered treatment pack from a box containing eight packs that were identical apart from the pack number. Patients, caregivers and those assessing outcomes were masked to allocation.

The primary outcome was head injury death in hospital within 28 days of injury in patients randomised within 3 hours of injury. Secondary outcomes were early head injury death (within 24 and 48 hours after injury), all-cause and cause-specific mortality, disability, vascular occlusive events (myocardial infarction, stroke, deep-vein thrombosis, pulmonary embolism), seizures, complications, neurosurgery, days in an intensive care unit and adverse events within 28 days of randomisation. A diagnosis of deep-vein thrombosis or pulmonary embolism was recorded only if there was a positive result on imaging (e.g. ultrasound) or at post-mortem examination. We assessed the cost-effectiveness of tranexamic acid versus no treatment from a UK NHS perspective using a Markov model and data directly from the CRASH-3 trial. We estimated incremental cost-effectiveness ratios by dividing the incremental costs (in Great British pounds) by the incremental quality-adjusted life-years. We compared incremental cost-effectiveness ratios to the UK cost-effectiveness threshold of £20,000 per quality-adjusted life-year.

To minimise the risk of missing data, we developed simple data collection tools and kept data collection to a minimum. For the primary analysis, we conducted a complete-case analysis with no imputation for missing data. All analyses were by intention to treat. A subgroup analysis was conducted of the effect of tranexamic acid according to the time interval between injury and tranexamic acid treatment (≤ 1, > 1 to ≤ 3, > 3 hours). The effects of tranexamic acid on the primary outcome were also stratified by severity of head injury, blood pressure and age.

Results

Patients were allocated to tranexamic acid ($n = 6406$) or to placebo ($n = 6331$); 6359 and 6280 patients, respectively, were analysed. A total of 9202 patients were enrolled within 3 hours of injury, of whom 9127 had outcome data available for analysis (tranexamic acid group, $n = 4613$; placebo group, $n = 4514$).

Primary outcome

Among patients treated early, the risk of head injury death was 18.5% in the tranexamic acid group versus 19.8% in the placebo group (855 vs. 892 events, risk ratio 0.94, 95% confidence interval 0.86 to 1.02). In the prespecified sensitivity analysis that excluded patients with a Glasgow Coma Scale score of 3 or with bilateral unreactive pupils at baseline (tranexamic acid group, $n = 3880$; placebo group, $n = 3757$), the risk of head injury death was 12.5% in the tranexamic acid group and 14.0% in the placebo group (485 vs. 525 events; risk ratio 0.89, 95% confidence interval 0.80 to 1.00). There was a reduction in the risk of head injury death with tranexamic acid in those with mild to moderate head injury [5.8% (166/2846) vs. 7.5% (207/2769); risk ratio 0.78, 95% confidence interval 0.64 to 0.95], but in those with severe head injury [39.6% (689/1739) vs. 40.1% (685/1710); risk ratio 0.99, 95% confidence interval 0.91 to 1.07] there was no clear evidence of a reduction (p-value for heterogeneity = 0.030). Early treatment was more effective in mild and moderate head injury ($p = 0.005$), but there was no obvious impact of time to treatment in severe head injury ($p = 0.73$).

Secondary outcome

The risk of disability, vascular occlusive events and seizures was similar in both groups. There was no apparent benefit or harm among those randomised beyond 3 hours of injury.

The cost-effectiveness analysis showed that tranexamic acid is highly cost-effective for mild and moderate traumatic brain injury with an incremental cost-effectiveness ratio of £4288 per quality-adjusted life-year gained, and was also cost-effective for patients with both pupils reactive, with an incremental cost-effectiveness ratio of £6097 per quality-adjusted life-year gained. The results were highly robust in probabilistic sensitivity analyses, with treatment 99% likely to be cost-effective at the UK cost-effectiveness threshold of £20,000 per quality-adjusted life-year, in both of these populations.

Conclusion

Tranexamic acid is safe in traumatic brain injury patients, and treatment within 3 hours of injury reduces head injury deaths. Patients should be treated as soon as possible after injury. Treatment is highly likely to be cost-effective for those with mild or moderate traumatic brain injury, or those with both pupils reactive.

Implications for practice

On the basis of the CRASH-2 (Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage-2) trial results, tranexamic acid was included in guidelines for the pre-hospital care of patients with trauma. However, patients with isolated traumatic brain injury were specifically excluded. The CRASH-3 trial provides evidence that tranexamic acid is safe for use in patients with traumatic brain injury and that treatment within 3 hours of injury reduces head injury-related deaths. In the light of this evidence, the exclusion of patients with isolated traumatic brain injury from tranexamic acid treatment guidelines seems unnecessary. This is supported by economic evidence that shows that the treatment of patients with mild or moderate traumatic brain injury, or with both pupils reactive, is highly cost-effective.

Recommendations for future research

Based on the CRASH-3 trial results, patients with traumatic brain injury within 3 hours of injury, who have a Glasgow Coma Scale score of ≤ 12 or any intracranial bleeding on computerised tomography scan are likely to be treated with tranexamic acid, either at the scene of the injury or after arrival in hospital. However, most patients with mild traumatic brain injury will not receive pre-hospital tranexamic acid and, by the time they have been assessed in hospital, for many patients it will be either too late to give tranexamic acid or too late to experience the full benefits of early treatment. Even mild traumatic brain injury can have important consequences (death and disability), especially in older adults. Further research into the effects of the early (including pre-hospital) use of tranexamic acid in older adults with mild traumatic brain injury is needed.

Immediate tranexamic acid treatment improves survival, but the treatment benefit decreases by about 10% for every 15 minutes of treatment delay until 3 hours, after which there is no benefit. One of the main obstacles to further reducing treatment delay is the need for an intravenous injection. If tranexamic acid could be given by intramuscular injection, this might reduce the time to tranexamic acid treatment. To determine whether or not intramuscular tranexamic acid has the potential to improve the care of trauma patients, research is required to understand the pharmacokinetics of tranexamic acid following intramuscular use. If we find that intramuscular tranexamic acid is well absorbed, with therapeutic tranexamic acid levels achieved in a timely manner, intramuscular tranexamic acid would provide a rapid alternative to intravenous injection use when immediate intravenous injection administration is not possible.

Trial registration

This trial is registered as ISRCTN15088122 (19 July 2011), ClinicalTrials.gov number NCT01402882 (26 July 2011) and EudraCT 2011-003669-14 (12 June 2012) and in the Pan African Clinical Trial Registry as PACTR20121000441277 (30 October 2012).

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This report

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