The CRASH-2 trial: a randomised controlled trial and economic evaluation of the effects of tranexamic acid on death, vascular occlusive events and transfusion requirement in bleeding trauma patients

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Executive summary

A RCT and economic evaluation of the effects of tranexamic acid on death

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Executive summary

Background

Each year, worldwide, about 3 million people die as a result of trauma, many after reaching hospital. Among trauma patients who do survive to reach hospital, bleeding is a common cause of death, accounting for about one-third of in-hospital deaths. The antifibrinolytic tranexamic acid (TXA) has been shown to reduce blood loss in surgical patients without apparently increasing the risk of postoperative complications. Surgery and trauma trigger similar haemostatic responses. If TXA reduces deaths due to bleeding in trauma patients, this would be an important discovery.

Objective

We sought to quantify the effects of early administration of TXA on death, vascular occlusive events and the receipt of blood transfusion in trauma patients.

Methods

The Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage-2 (CRASH-2) trial was a randomised controlled trial carried out in 274 hospitals in 40 countries. A total of 20,211 adult trauma patients with, or at risk of, significant bleeding were randomly assigned within 8 hours of injury to either TXA (loading dose 1 g over 10 minutes then infusion of 1 g over 8 hours) or matching placebo. Randomisation was balanced by centre, with an allocation sequence based on a block size of eight, generated with a computer random number generator. Both participants and study staff (site investigators and trial co-ordinating centre staff) were masked to treatment allocation. The primary outcome was death in hospital within 4 weeks of injury, and was described with the following categories: bleeding, vascular occlusion (myocardial infarction, stroke and pulmonary embolism), multiorgan failure, head injury and other. All analyses were by intention to treat.

Results

A total of 10,096 patients were allocated to TXA and 10,115 to placebo, of whom 10,060 and 10,067 patients, respectively, were analysed. All-cause mortality was significantly reduced with TXA [1463 patients (14.5%) in the TXA group vs 1613 patients (16.0%) in the placebo group; relative risk (RR) 0.91; 95% confidence interval (CI) 0.85 to 0.97; $p = 0.0035$]. The risk of death due to bleeding was significantly reduced [489 patients (4.9%) died in the TXA group vs 574 patients (5.7%) in the placebo group; RR 0.85; 95% CI 0.76 to 0.96; $p = 0.0077$]. We recorded strong evidence that the effect of TXA on death due to bleeding varied according to the time from injury to treatment (test for interaction $p < 0.0001$). Early treatment (≤1 hour from injury) significantly reduced the risk of death due to bleeding [198 out of 3747 (5.3%) patients died in the TXA group vs 286 out of 3704 patients (7.7%) in the placebo group; RR 0.68; 95% CI 0.57 to 0.82; $p < 0.0001$]. Treatment given between 1 and 3 hours also reduced the risk of death due to bleeding [147 out of 3037 patients (4.8%) died in the TXA group vs 184 out of 2996 patients (6.1%) in the placebo group; RR 0.79; 95% CI 0.64 to 0.97; $p = 0.03$]. Treatment given after 3 hours seemed to increase the risk of death due to bleeding [144 out of 3272 patients (4.4%) died in the TXA group vs 103 out of 3362 patients (3.1%) in the placebo group; RR 1.44; 95% CI 1.12 to 1.84; $p = 0.004$]. We recorded no evidence that the effect of TXA on death due to bleeding varied by systolic blood pressure, Glasgow Coma Scale score or type of injury.

The cost-effectiveness of the early administration of TXA was evaluated in high-, middle- and low-income settings. Administering TXA to bleeding trauma patients within 3 hours of injury saved an estimated 372, 315 and 755 life-years (LYs) per 1000 trauma patients in Tanzania, India and the UK, respectively. The cost of giving TXA to 1000 patients was (in international dollars) $17,483 in Tanzania, $19,550 in India and $30,830 in the UK. The incremental cost of giving TXA compared with not giving TXA was $18,025 in Tanzania, $20,670 in India and $48,002 in the UK. The estimated incremental cost per LY gained of administering TXA is $48, $66 and $64 in Tanzania, India and the UK, respectively.

Conclusions

Tranexamic acid safely reduced the risk of death in bleeding trauma patients in this study. TXA appears most effective when given early after the trauma and should be given only within approximately 3 hours. Treatment beyond 3 hours of injury is unlikely to be effective. TXA administration is highly cost-effective in high-, middle- and low-income countries. Future work [the Clinical Randomisation of an Antifibrinolytic in Significant Head injury-3 (CRASH-3) trial] will evaluate the effectiveness and safety of TXA in the treatments of isolated traumatic brain injury (http://crash3.lshtm.ac.uk/).

Trial registration

This trial is registered as ISRCTN86750102, ClinicalTrials.gov NCT00375258 and South African Clinical Trial Register DOH-27–0607–1919.

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