CRASH-2 intracranial bleeding study

CRASH-2 (Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage) intracranial bleeding study: the effect of tranexamic acid in traumatic brain injury – a nested, randomised, placebo-controlled trial

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Executive summary

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Executive summary

Background

Traumatic brain injury (TBI) is a leading cause of death and disability worldwide.

Approximately one-third of patients with TBI have coagulopathy. Those with coagulopathy have an increased risk of haemorrhage growth and higher mortality. Increased fibrinolysis, as indicated by high levels of fibrinogen degradation products, is a common feature of the coagulopathy in TBI raising the possibility that antifibrinolytics agents, such as tranexamic acid (TXA) might reduce traumatic intracranial haemorrhage. To date, there have been no randomised controlled trials of TXA in TBI. The CRASH-2 (Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage) trial, conducted in 20,211 bleeding trauma patients evaluated the effect on mortality and transfusion requirements of TXA in trauma patients with significant bleeding. Although TBI was not an inclusion criterion, it is likely that a significant proportion of included patients would also have had TBI.

Objectives

The Intracranial Bleeding Study (CRASH-2 IBS) was conducted nested within the CRASH-2 trial, to quantify the effect of an early short course of TXA on intracranial haemorrhage and new focal cerebral ischaemic lesions in patients with TBI.

Methods

Trial design

A double-blind, randomised, placebo-controlled trial of the effects of TXA on intracranial haemorrhage and focal ischaemic brain lesions, in adult trauma patients with significant haemorrhage and TBI, was conducted.

Participants

The trial was conducted in a subset of CRASH-2 trial participants. Patients eligible for inclusion in the CRASH-2 IBS fulfilled the inclusion criteria for the CRASH-2 trial, but also had TBI [Glasgow Coma Scale (GCS) score of ≤14 and a brain computerised tomography (CT) scan compatible with TBI]. Pregnant women and patients for whom a second brain CT scan was not possible were excluded.

Study settings

Patients were recruited from 10 hospitals in India and Colombia.

Interventions

Participants were randomly allocated to receive a loading dose of 1 g of TXA infused over 10 minutes, followed by an intravenous infusion of 1 g over 8 hours or matching placebo (sodium chloride 0.9%).

Outcomes

We obtained two brain CT scans for each participant: the first before randomisation and the second 24–48 hours later.

The primary outcome was the occurrence of total haemorrhage growth. Secondary outcomes were (1) the occurrence of significant haemorrhage growth defined as an increase by 25% or more of total haemorrhage in relation to its initial volume; (2) new intracranial haemorrhage (apparent on the second scan, but not apparent on the first); (3) change in subarachnoid haemorrhage grade; (4) mass effect; and (5) the occurrence of new focal cerebral ischaemic lesions (apparent on the second scan, but not apparent on the first).

The clinical outcomes were death from any cause and the need for neurosurgical intervention. Clinical outcomes were recorded on discharge from hospital, at 28 days, or death, whichever occurred first. We also reported a combined 'poor outcome' defined as a patient who developed one or more of the following during the scheduled follow-up period: significant haemorrhage growth, new intracranial haemorrhage, new focal cerebral ischaemic lesions, the need for neurosurgery or death. Adverse events that were serious, unexpected, and suspected to be related to the study treatment, were reported separately.

Randomisation and blinding

Randomisation was balanced by centre, with an allocation sequence based on a block size of eight. All site investigators and trial co-ordinating centre staff were masked to treatment allocation. TXA and placebo ampoules were indistinguishable.

Statistical methods

We used a Bayesian statistical approach. Our primary analysis used non-informative priors to reflect the lack of previous knowledge. A sensitivity analysis using information from the systematic review of TXA in aneurysmal subarachnoid haemorrhage was conducted.

We used generalised linear-mixed models adjusted for baseline variables. Adjusted effects are considered in the primary analysis, but both adjusted and unadjusted effect measures are reported.

Haemorrhage growth was analysed using multiple linear regression (analysis of covariance), the main factor being the treatment group. Binary outcomes were analysed using logistic regression. All analyses were undertaken on an intention to treat basis. We used the statistical software package Stata (version SE/11·0) from StataCorp LP (College Station, TX, USA).

Results

We recruited 270 patients (133 allocated to TXA and 137 allocated to placebo) between August 2008 and January 2010. All patients received the loading and maintenance doses, except one placebo-allocated patient who did not receive the maintenance dose. All patients were followed up for clinical outcomes. A total of 256 patients (95%) had the first CT scan. A total of 211 patients (82%) had some form of intracranial haemorrhage (intra-parenchymal haematoma, haemorrhagic contusion, subdural haematoma or epidural haematoma). Five patients had a focal ischaemic lesion (two patients in the TXA group and three in the placebo group). Forty patients (20 TXA allocated and 20 placebo allocated) had neurosurgical evacuation on the basis of the first CT scan findings.

The mean total haemorrhage growth was 5.9 ml [standard deviation (SD) 26.8 ml] and 8.1 ml (SD 29.2 ml) in the TXA and placebo group respectively. The adjusted analysis showed a greater reduction in total haemorrhage growth in the TXA group than in the placebo group [–3.8 ml, 95% credibility interval (CI) –11·5 ml to 3.9 ml]. In patients who had neurosurgical evacuation before the second CT scan, the extent of this reduction was even larger (–15 ml, 95% CrI –45.7 ml to 15.5 ml).

A beneficial effect of TXA was highly probable (range 89% to 94%) for all of the binary CT scan outcomes. The sensitivity analysis for significant haemorrhage growth gave an adjusted odds ratio (OR) of 0·53 (95% CrI 0.41 to 0.68) with a very high probability (99%) of a clinical significant beneficial effect. The sensitivity analysis for new focal cerebral ischaemic lesions gave an adjusted OR of 1.18 (95% CrI 0.87 to 1.60). The probability of a clinically significant harmful effect was 35%.

There were 14 (10.5%) deaths in the TXA group and 24 (17.5%) in the placebo group (OR 0·57, 95% CrI 0.28 to 1.14). The adjusted OR for death was 0.49 (95% CrI 0.22 to 1.06). Twenty (15%) patients in the TXA group and 21 (15%) in the placebo group had neurosurgery other than those evacuations based on first CT scan findings (OR 0.98, 95% CrI 0.50 to 1.93). The adjusted OR for neurosurgery was 0.98 (95% CrI 0.50 to 1.91). The probability of a beneficial effect was 96% and 53% for mortality and neurosurgery respectively. Sixty (45%) patients in the TXA group and 80 (58%) in the placebo group had a poor outcome (OR 0·59, 95% CrI 0.37 to 0.96). The adjusted OR for poor outcome was 0·57 (95% CrI 0.33 to 0.98).

No emergency unblinding was needed, and there were no adverse events regarded as serious, unexpected, or suspected to be related to the study treatment.

Conclusions

This was the first randomised controlled study to evaluate the effect of TXA in TBI patients, and found that neither moderate benefits nor moderate harmful effects can be excluded. However, although uncertainty remains, our analyses suggest that TXA administration might improve outcome in TBI patients and provide grounds for evaluating this hypothesis in future research.

We found a reduction in new focal cerebral ischaemic lesions in TXA allocated patients. Overall, the incidence of these lesions was low and it is possible that the observed difference between the groups may have arisen by chance alone. The CRASH-2 trial has shown reliably that early administration of TXA in trauma patients with, or at risk of, significant bleeding reduces the risk of all-cause mortality. However, many patients with traumatic haemorrhage also have TBI and concerns about the risk of cerebral ischaemia may influence some doctors' decision to give TXA to these patients. The results presented here provide reassurance about the safety of TXA in bleeding trauma patients with TBI.

Our results have important research implications. If TXA reduces intracranial haemorrhage after TBI without increasing the risk of ischaemic lesions, it could substantially improve patient outcomes. Although an increased risk of cerebral ischaemia cannot be ruled out, there is a reasonable basis to expect that the benefits of TXA administration could outweigh the risks. However, the CRASH-2 IBS was conducted among TBI patients with significant (extra-cranial) haemorrhage and the effect of TXA might be different in patients with isolated TBI. Future research should be conducted to reliably assess the effectiveness and safety of the early administration of a short course of TXA in patients with isolated TBI.

Trial registration

This trial is registered as ISRCTN86750102.

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Publication

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NIHR Health Technology Assessment programme

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