Intracranial bleeding is common after traumatic brain injury, and the larger the bleed the greater the risk of death and disability. Bleeding continues after hospital admission in 84% of patients with moderate or severe injuries, and can continue for up to 24 hours. About one third of patients have laboratory evidence of abnormal coagulation. High levels of fibrin degradation products are seen within the first three hours. Such patients have a higher risk of intracranial haemorrhage and mortality.

Worldwide at least 200 per 100 000 people are killed or admitted to hospital each year after traumatic brain injury. This results in more than 10 million deaths or hospital admissions. In the UK, around one million people attend emergency departments every year with a traumatic brain injury.

Tranexamic acid reduces bleeding by inhibiting the enzymatic breakdown of fibrin blood clots (fig 1). Tranexamic acid is used routinely in some cases of trauma and in surgery. For example, it reduces the need for blood transfusion in surgical patients. In trauma patients with extracranial haemorrhage:

- Tranexamic acid treatment within an hour of injury reduces the risk of death caused by bleeding by about one third
- Treatment between one and three hours reduces the risk by about one fifth
- There is no apparent benefit after three hours, and tranexamic acid might even be harmful
- If tranexamic acid is effective after traumatic brain injury, it should also be most effective when given soon after injury, when intracranial bleeding is ongoing
- The potential for harm also exists however
- Tranexamic acid may increase the risk of ischaemia and cerebral thrombosis because it inhibits fibrinolysis. Cerebral ischaemia is already a known risk after traumatic brain injury, which worsens neurological outcome and increases mortality. For example, raised intracranial pressure can lead to

**WHAT YOU NEED TO KNOW**

- The effectiveness and safety of tranexamic acid in traumatic brain injury are uncertain, although randomised trials are under way to investigate the problem
- Tranexamic acid could reduce intracranial bleeding but might increase the risk of cerebral thrombosis and ischaemia
- We believe that tranexamic acid should not be used in routine clinical practice unless these trials show benefit

**HOW PATIENTS WERE INVOLVED IN THE CREATION OF THIS ARTICLE**

No patients were involved in the writing of this article.

Patients are involved in the design and conduct of CRASH-3 and these were reflected in the trial procedures. Organisations advised the investigators on outcome measures that matter most to patients, such as fatigue. Organisations also represent patients on the trial steering committee and are involved in the ongoing supervision of the trial.

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**UNCERTAINTIES**

**Does tranexamic acid improve outcomes in traumatic brain injury?**

Abda Mahmood, Ian Roberts, Haleema Shakur, Tim Harris, Antonio Belli

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cerebral hypoperfusion.18–20 Thrombotic disseminated intravascular coagulation might increase the risk of cerebral microthrombi, which are often seen in the brains of patients with traumatic brain injury who have died.21

- Seizures are also a risk because tranexamic acid is known to cross the blood-brain barrier.22 Although there was no evidence of any increase in seizures in the CRASH-2 trial of tranexamic acid in extracranial bleeding, seizure activity remains a concern because the blood-brain barrier is impaired after traumatic brain injury.23

What is the evidence of uncertainty?

A 2015 systematic review identified two relevant completed randomised trials (table 1).24,25 We judged that both trials were at low risk of bias; however, neither was large enough to answer the question definitively—the confidence intervals were wide and the P values statistically insignificant. The first trial (n=249) examined the effect of tranexamic acid in patients with extracranial bleeding but who also had traumatic brain injury.24 The second trial (n=229) examined the effect of tranexamic acid in patients with polytrauma and traumatic brain injury, or isolated traumatic brain injury.25 Both trials recruited patients who were within eight hours of injury but the numbers were not large enough to determine the balance of risks and benefits from tranexamic acid and whether this varies by time to treatment. Furthermore, the patients in one of the trials had extracranial bleeding in addition to intracranial bleeding.24 Because tranexamic acid reduces mortality in extracranial bleeding (CRASH-2), the mortality reduction seen in this trial could be from the extracranial injury rather than any effect on the brain injury itself.

When the two randomised trials are combined in a meta-analysis (fig 2), there is a statistically significant reduction in intracranial haemorrhage, but because the confidence intervals are wide, the quality of this evidence is low.

- Intracranial haemorrhage—relative risk 0.75 (95% confidence interval 0.58 to 0.98); 
P=0.03;
- Mortality—relative risk 0.63 (95% confidence interval 0.40 to 0.99); 
P=0.05.

The effect of tranexamic acid on disability and thrombotic adverse effects including stroke remains uncertain.

Is ongoing research likely to provide relevant evidence?

We identified three ongoing randomised trials of tranexamic acid versus placebo in patients with isolated traumatic brain injury (table 2). These will evaluate the

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Table 1 | Patients with intracranial haemorrhage, cerebral ischaemia, and mortality outcomes in two randomised trials of tranexamic acid in patients with traumatic brain injury. Values are numbers (percentages) unless stated otherwise

<table>
<thead>
<tr>
<th>Outcome</th>
<th>CRASH-2 intracranial bleeding substudy 2012</th>
<th>Yuthahkasemsunt et al 2013</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TXA</td>
<td>Placebo</td>
</tr>
<tr>
<td></td>
<td>Relative risk (95% CI)</td>
<td>Relative risk (95% CI)</td>
</tr>
<tr>
<td>Intracranial haemorrhage</td>
<td>44 (36)</td>
<td>56 (44)</td>
</tr>
<tr>
<td>Focal ischaemic lesion/stroke</td>
<td>6 (5)</td>
<td>12 (9)</td>
</tr>
<tr>
<td>Deaths</td>
<td>14 (11)</td>
<td>24 (18)</td>
</tr>
</tbody>
</table>

Table 2 | Ongoing randomised trials of tranexamic acid use for traumatic brain injury

<table>
<thead>
<tr>
<th>Trial</th>
<th>Trial type</th>
<th>Status</th>
<th>Proposed sample size</th>
<th>No of arms</th>
<th>Intervention</th>
<th>Comparison</th>
<th>Primary outcome</th>
<th>Secondary outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prehospital tranexamic acid use for moderate and severe traumatic brain injury (NCT02645552)</td>
<td>Double blind, randomised trial</td>
<td>Pending recruitment</td>
<td>400 patients with moderate to severe traumatic brain injury (Glasgow coma scale ≤12)</td>
<td>2</td>
<td>Arm 1: 1 g intravenous bolus of tranexamic acid over 10 minutes</td>
<td>Placebo (sodium chloride, 0.9%)</td>
<td>Neurological outcome (based on extended Glasgow outcome scale score at six months post-injury)</td>
<td>Vascular occlusive events, cerebral ischaemia, vascular occlusive events, alterations in fibrinolysis</td>
</tr>
<tr>
<td>Prehospital tranexamic acid use for traumatic brain injury (NCT01990768)</td>
<td>Double blind, randomised trial</td>
<td>Currently recruiting</td>
<td>1002 patients with moderate to severe traumatic brain injury (Glasgow coma scale ≤12)</td>
<td>3</td>
<td>Arm 1: 1 g intravenous bolus of tranexamic acid followed by 1 g intravenous infusion of tranexamic acid over eight hours. Arm 2: 2 g intravenous bolus of tranexamic acid followed by placebo infused over eight hours. Arm 3: placebo intravenous bolus followed by placebo infused over eight hours*</td>
<td>Placebo (sodium chloride, 0.9%)</td>
<td>Neurological outcome (based on extended Glasgow outcome scale score at six months after injury)</td>
<td>-</td>
</tr>
<tr>
<td>Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage (CRASH-3) (NCT01602882)</td>
<td>Double blind, randomised trial</td>
<td>Currently recruiting</td>
<td>13 000 patients with major traumatic brain injury (Glasgow coma scale score ≤12 or intracranial bleeding on computed tomography scan)</td>
<td>2</td>
<td>Arm 1: 1 g of intravenous bolus of tranexamic acid over 10 minutes followed by 1 g intravenous infusion of tranexamic acid over eight hours. Arm 2: placebo intravenous bolus followed by placebo infused over eight hours.</td>
<td>Placebo (sodium chloride, 0.9%)</td>
<td>Death in hospital within 28 days of randomisation</td>
<td>Vascular occlusive events, disability (based on disability rating scale and patient oriented outcome measures), seizures, neurosurgery, days in intensive care, other adverse events</td>
</tr>
</tbody>
</table>

*Intravenous bolus administered in prehospital setting, and maintenance infusion initiated on arrival at hospital.
Box 3 | Guidelines for general management of traumatic brain injury

The National Institute for Health and Care Excellence recommends to:28

• First treat the greatest threat to life and avoid further harm by assessing Airway, Breathing, and Circulation
• Maintain cervical spine immobilisation until a full risk assessment indicates it is safe to remove the immobilisation device
• Ascribe depressed consciousness level to intoxication only after a major brain injury has been excluded
• Effectively manage pain, because it can lead to a rise in intracranial pressure
• Immediately manage patients who present to the emergency department with a Glasgow coma scale score of 8 or less
• Immediately manage patients who return to the emergency department within 48 hours of injury if a relevant risk factor is identified—eg, suspicion of non-accidental injury, history of bleeding or clotting disorders, danger of mechanism of injury. Perform a CT scan done several hours after injury. This substudy will use computed tomography scans to examine the effect of tranexamic acid on intracranial haemorrhage and ischaemia and whether this varies by time to treatment.

Further research

Randomised trials looking at the effect of tranexamic acid in patients with isolated traumatic brain injury are currently ongoing. These trials will address the uncertainty of whether tranexamic acid improves outcomes in patients with traumatic brain injury. At this stage we do not make recommendations for further research in this area.

What should we do in light of the uncertainty?

The authors recommend that patients with isolated traumatic brain injury should not receive tranexamic acid outside the context of a randomised trial, and clinicians should consider enrolling their patients in one of the relevant trials wherever possible.

Box 3 signposts other aspects of management of traumatic brain injury.

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