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PRACTICE

UNCERTAINTIES

Does tranexamic acid improve outcomes in traumatic brain injury?

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Worldwide at least 200 per 100 000 people are killed or admitted to hospital each year after traumatic brain injury.[1] This results in more than 10 million deaths or hospital admissions.[2] In the UK, around one million people attend emergency departments every year with a traumatic brain injury.[3]

Intracranial bleeding is common after traumatic brain injury, and the larger the bleed the greater the risk of death and disability.[4 5] Bleeding continues after hospital admission in 84% of patients with moderate or severe injuries,[6 7] and can continue for up to 24 hours.[8] About one third of patients have laboratory evidence of abnormal coagulation.[9] High levels of fibrin degradation products are seen within the first three hours.[10] Such patients have a higher risk of intracranial haemorrhage and mortality.

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.[11 12] In trauma patients with extracranial haemorrhage:[13]

- Tranexamic acid treatment within an hour of injury reduces the risk of death caused by bleeding by about one third (5.3% tranexamic acid *v* 7.7% placebo relative risk 0.68, 95% confidence interval 0.57 to 0.82; P<0.001);
- treatment between one and three hours reduces the risk by about one fifth (4.8% *v* 6.1%; 0.79, 0.64 to 0.97; P=0.03);
- there is no apparent benefit after three hours, and tranexamic acid might even be harmful (4.4% *v* 3.1%; 1.44, 1.12 to 1.84; P=0.004).[14]

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.[8]

The potential for harm also exists however.

- Tranexamic acid may increase the risk of ischaemia and cerebral thrombosis because it inhibits fibrinolysis.[15] Cerebral ischaemia is already a known risk after after traumatic brain injury, which worsens neurological outcome and increases mortality.[16 17] For example, raised intracranial pressure can lead to 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

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What you need to know

- The effectiveness and safety of tranexamic acid in traumatic brain injury is 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

Box 1: Literature search

A 2015 systematic review of randomised trials of antifibrinolytic agents (including tranexamic acid) after acute traumatic injury, searched: the Cochrane Injuries Group's specialised register, Cochrane Library, Ovid Medline(R), Ovid Medline(R) In-process and other non-indexed citations, Ovid Medline(R) Daily and Ovid Medline(R), Embase Classic+Embase (OvidSP), PubMed and clinical trials registries.[30]

The review authors rated the quality of the evidence according to the GRADE approach and considered: impact of the risk of bias of individual trials; precision of the pooled estimate; inconsistency or heterogeneity; indirectness of evidence; and impact of selective reporting and publication bias on effect estimate. Risk of bias was assessed using the Cochrane Collaboration's "risk of bias" tool.

As the last update was published in May 2015, we reran the search to identify no new completed trials and one new pending trial (NCT02645552).

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 effect of tranexamic acid on death, disability, vascular occlusive events, and other adverse events in traumatic brain injury. The ongoing trials inform whether tranexamic acid can be given to those with traumatic brain injury.

In two of the ongoing trials (n=1402) patients are randomised within two hours of injury in the prehospital setting (NCT02645552, NCT01990768).

In the largest trial, the CRASH-3 trial (n=13 000), patients will be randomised in hospital and within eight hours of injury (NCT01402882).[26] The size of this trial should ensure that tranexamic acid and placebo groups are similar for known and unknown confounders, such as the concomitant degree of coagulopathy.[27] Therefore, it is unnecessary to standardise tranexamic acid and placebo groups for clinical management factors that may influence the extent of bleeding.

The results from the three ongoing trials should provide clinicians with information about whether the effect of tranexamic acid varies by time to treatment. Information on the effect of tranexamic acid administered within one hour, between one and three hours, and after three hours of injury may be more useful than the average effect of the treatment. Prespecified subgroup analyses in the CRASH-3 trial will provide information about the effect of tranexamic acid by time to treatment.

A substudy conducted within the CRASH-3 trial will use computed tomography scans to examine the effect of tranexamic acid on intracranial bleeding and thrombosis. These scans can detect traumatic haemorrhage (high attenuation) in the acute stage of traumatic brain injury. Ischaemic lesions (low attenuation) are visible on a computed tomography scan done several hours after injury. This substudy will provide information on 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.

We thank Deirdre Beecher (information specialist, Cochrane Injuries Group) for updating the systematic searches.

Contributors: AM drafted and revised the manuscript. IR revised and critically read the manuscript;. HS, TH, and AB critically read the manuscript. All authors approved the final version. AM is the guarantor.

Competing interests: We have read and understood BMJ policy on declaration of interests and declare the following: none.

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Box 2: Clinical registries used in search

Clinicaltrials.gov (https://clinicaltrials.gov/)

WHO International Clinical Trials Registry Platform (http://apps.who.int/trialsearch/—for ongoing trials

Box 3: Guidelines for general management of traumatic brain injury

The National Institute for Health and Care Excellence provides guidance on the assessment and early management of adults and children with traumatic brain injury.[28] The key recommendations are to:

- 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 less than 15
- Immediately manage patients who return to the emergency department within 48 hours of transfer to the community with any persistent problem relating to the initial head injury; these patients should be seen by or discussed with a senior clinician experienced in head injuries, and considered for a computed tomography scan
- Immediately intubate and ventilate patients in a coma (Glasgow coma scale score ≤8), or patients who cannot protect their airway or have abnormal respirations
- Transfer patients with a Glasgow coma scale score of 8 or less to a neuroscience unit irrespective of the need for neurosurgery
- Perform a computed tomography scan within one hour of injury if patients present with certain risk factors—for example, Glasgow coma scale score of less than 13 on initial assessment; suspected skull fracture; post-traumatic seizure; focal neurological deficit; more than one episode of vomiting. Perform a computed tomography scan within eight hours of injury if patients have experienced loss of consciousness or amnesia since the injury and show certain risk factors (eg, age ≥65, history of bleeding or clotting disorders, dangerous mechanism of injury). Perform a CT scan within eight hours of injury if patients are receiving warfarin treatment
- Monitor children closely and perform a computed tomography scan within an hour of injury if a relevant risk factor is identified—eg, suspicion of non-accidental injury, post-traumatic seizure without history of epilepsy
- Provide patients, family members, and carers with information about the nature and severity of the injury, risk factors that mean the patient should return to the emergency department—eg, loss of consciousness, amnesia for events before or after injury, headaches, vomiting episodes—details about what to expect during recovery, contact details of community and hospital services and support organisations, on discharge

The Centers for Disease Control and Prevention and the American College of Emergency Physicians provide guidance on the management of adults with mild traumatic brain injury.[29] The guidelines focus on determining whether patients with known or suspected mild traumatic brain injury require a computed tomography scan of the brain or may be safely discharged.

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. Focus groups were conducted with young men at a boxing club who were at risk of traumatic brain injury, to seek their views on consent procedures; and these were reflected in the trial procedures. Organisations such as the European Federation of Road Traffic Victims, and RoadPeace, the UK national charity for road crash victims, 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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Tables

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

Outcome	CRASH-2 intracranial bleeding substudy 2012[24]			Yutthakasemsunt et al 2013[25]		
	TXA	Placebo	Relative risk (95% CI)	TXA	Placebo	Relative risk (95% CI)
Intracranial haemorrhage	44 (36)	56 (44)	0.80 (0.59 to 1.09)	21 (18)	32 (27)	0.65 (0.40 to 1.05)
Focal ischaemic lesion/stroke	6 (5)	12 (9)	0.51 (0.20 to 1.32)	0 -	3 (3)	-
Deaths	14 (11)	24 (18)	0.60 (0.33 to 1.11)	12 (10)	17 (14)	0.69 (0.35 to 1.39)

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

Trial	Trial type	Status	Proposed sample size	No of arms	Intervention	Comparison	Primary outcome	Secondary outcomes
Prehospital tranexamic acid use for moderate and severe traumatic brain injury (NCT02645552)	Double blind, randomised trial	Pending recruitment	400 patients with moderate to severe traumatic brain injury (Glasgow coma scale score ≤12)	2	Arm 1: 1 g intravenous bolus of tranexamic acid over 10 minutes Arm 2: placebo intravenous bolus over 10 minutes	Placebo (sodium chloride, 0.9%)	Neurological outcome (based on extended Glasgow outcome scale score) at six months post-injury	Vascular occlusive events (myocardial infarction, stroke, pulmonary embolism, and deep vein thrombosis)
Prehospital tranexamic acid use for traumatic brain injury (NCT01990768)	Double blind, randomised trial	Currently recruiting	1002 patients with moderate to severe traumatic brain injury (Glasgow coma scale score ≤12)	3	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*	Placebo (sodium chloride, 0.9%)	Neurological outcome (based on extended Glasgow outcome scale score) at six months after injury	Volume of intracranial haemorrhage, disability rating scale score, 28 day survival, neurosurgery, ventilator-free days, seizures, cerebral ischaemia, vascular occlusive events, alterations in fibrinolysis
Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage (CRASH-3) (NCT01402882)	Double blind, randomised trial	Currently recruiting	13 000 patients with major traumatic brain injury (Glasgow coma scale score ≤12 or intracranial bleeding on computed tomography scan)	2	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	Placebo (sodium chloride, 0.9%)	Death in hospital within 28 days of randomisation	Vascular occlusive events, disability (based on disability rating scale and patient oriented outcome measures), seizures, neurosurgery, days in intensive care, other adverse events

*Intravenous bolus administered in prehospital setting, and maintenance infusion initiated on arrival at hospital.

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Figures

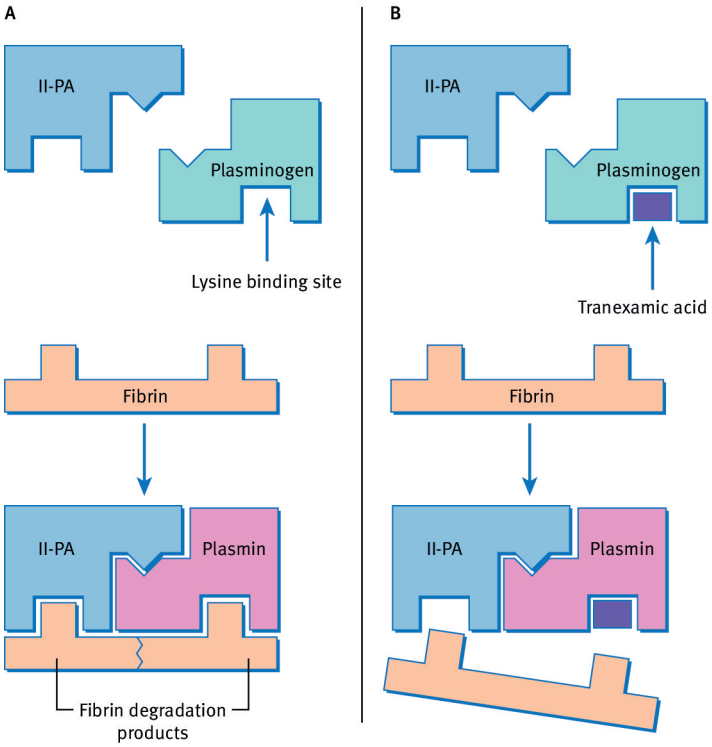

Fig 1 A Normal fibrinolysis. B: Fibrinolysis inhibited by tranexamic acid. Plasmin binds to fibrin via lysine binding sites and then splits fibrin into fibrin degradation products. Tranexamic acid is a molecular analogue of lysine that inhibits fibrinolysis by reducing the binding of plasmin to fibrin

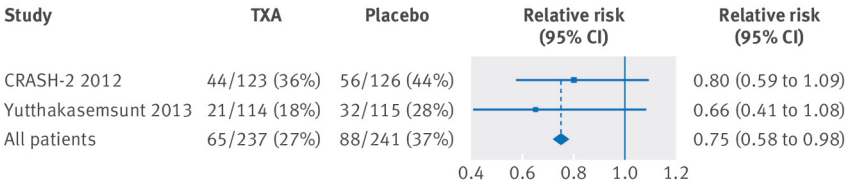

Fig 2 Meta-analysis of effect of tranexamic acid (TXA) versus placebo on intracranial bleeding in patients with traumatic brain injury

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