Results of the CRASH-3 trial

Tranexamic Acid (TXA) in Traumatic Brain Injury (TBI)

Implications for practice

Key findings

- **TXA treatment within three hours of injury reduces deaths in patients with mild and moderate head injury**
- **Give TXA as soon as possible after significant head injury**
- **TXA is safe in TBI patients**
- **TXA is cheap**

Suggested treatment algorithm

Pre-hospital

- Has the patient had a head injury?
- Has the injury occurred within the last 3 hours?
- Is the GCS 12 or less?

If the answer to all three questions is yes, administer 1g TXA IV ASAP

Audit standard: Administer TXA when indicated within 1 hour of arrival on scene

Emergency Department

For self-presenters and to ambulance patients who have not had TXA pre-hospital for head injury:

- Has the patient had a head injury?
- Has the injury occurred within the last 3 hours?
- Is the GCS 12 or less?

If the answer to all three questions is yes, administer 1g TXA IV ASAP

There is then a second patient group with GCS 13-15:

- Does the CT scan show a TBI?
- Is it less than 3 hours since injury?

If the answer to both questions is yes, administer 1g TXA IV ASAP

- TXA infusion (1g over 8 hours) should be commenced for all patients who have had TXA administered for head injury and have any TBI on CT scan
- TXA infusion should not be given (or can be stopped) in those who have a CT scan that does not demonstrate TBI

Audit standard 1: *Administer TXA when clinically indicated within 1 hour of arrival at hospital*

Audit standard 2: *Administer TXA within 3 hours of injury to patients who have a TBI demonstrated on CT scan*

The algorithm above follows the CRASH-3 criteria and so has an evidence base. It is for individual clinicians to decide on their approach for children. The Royal College for Child Health published guidance following CRASH-2 and I hope they will do the same following CRASH-3

This algorithm and the CRASH-3 published results raises a number of key clinical questions, including:

- Should TXA be administered to patients with head injury who have a GCS of > 12 either pre-hospital or at hospital (before CT)?
- If a patient meets the NICE criteria for a CT head but has a GCS>12, should they have TXA whist awaiting the scan?

The current CRASH-3 published analysis does not answer these questions but the investigators are undertaking further analysis, including a health economics analysis, and hope to provide answers soon.

Summary of the CRASH-3 Study

Study design

The CRASH-3 trial was an international randomized placebo-controlled trial of tranexamic acid (TXA) in adult patients with acute traumatic brain injury (TBI). [1]

The initial inclusion criteria were adults with TBI, within 8 hours of injury, with a GCS ≤12 or any intracranial bleeding on CT scan, and no significant extra-cranial bleeding (which would warrant administration of TXA as per the findings of the CRASH-2 trial[2]). The time frame for administration of IV TXA changed to 'within 3 hours of injury' half way through the trial. Patients received a loading dose of 1g intravenous TXA over 10 minutes followed by a maintenance infusion of 1g TXA over 8 hours, or matching placebo. 12,737 patients were recruited to the trial (9202 within three hours of injury) and the groups were well matched at baseline.

In patients treated within 3 hours of injury, the risk of head injury death was 18.5% in the TXA group versus 19.8% in the placebo group (RR=0.94, 95% CI 0.86-1.02). When patients with a GCS score of 3 and those with bilateral unreactive pupils were excluded from analysis, the risk of head injury death was 12.5% in the TXA group versus 14% in the placebo group (RR=0.89, 95% CI 0.80-1.00). This gives a Number Needed to Treat of 67.

TXA within 3 hours for patients with mild to moderate head injury reduces TBI deaths

Patients with mild-moderate head injury were recruited as GCS 13-15 with a positive CT scan, or GCS ≤12 on presentation. 27.9% of the patients randomized within three hours had a GCS score of 13-15 and 33.5% had a GCS score of 9-12. Patients with mild-moderate head injury are likely to have smaller and slower intracranial bleeds, which may be responsive to TXA treatment. These patients have less irreversible brain tissue damage than those with severe head injury.

When stratified for baseline GCS, there was a significant reduction in the risk of head injury death with TXA in mild-moderate TBI (RR=0.78, 95%CI 0.64-0.95) but in severe head injury there was no clear evidence of a reduction (RR=0·99, 95% CI 0·91–1·07). In patients with severe head injury, TXA should still be administered as there is unlikely to be an abrupt cutoff of effectiveness at GCS 9, so at present TXA treatment is recommended in this patient group for simplicity of implementation and due to the low risk of harm.

Give TXA as soon as possible after injury

Early treatment was more effective in patients with mild and moderate head injury, but there was no impact of time to treatment in severe head injury. TXA should be administered as soon as possible after head injury and ideally within one hour. In the mild-moderate head injured patients there is a 10% reduction in the effectiveness of TXA for every 20-minute delay from the time of injury.

TXA is safe in TBI patients

The risk of vascular occlusive events and other complications were similar in the TXA and placebo groups. Unlike the results of CRASH-2 (in traumatic extra-cranial bleeding) there was no evidence that administration of TXA beyond 3 hours, and up to 8 hours, increased the risk of head injury death or complications. There was also no difference in the prevalence of disability in survivors between the two groups.

TXA is cheap

The current cost of 1g intravenous TXA is £1.20.

TXA should be considered for paediatric patients with TBI

The trial did not include patients aged <16 years and therefore cannot provide any evidence of a treatment benefit in children. The findings of the CRASH-2 trial in adult patients were adapted for clinical practice in children by the Royal College of Paediatrics and Child Health using a pragmatic dosage schedule of 15mg/kg loading dose (max 1g) followed by maintenance infusion of 2mg/kg/hour (max 1g) for a maximum of eight hours.[3]

References

1. CRASH-3 Published Online October 14, 2019 https://doi.org/10.1016/ S0140-6736(19)32233-0
2. The CRASH-2 collaborators. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomized, placebo-controlled trial. Lancet 2010;376:23-32.
3. https://www.rcem.ac.uk/docs/External%20Guidance/10k.%20Major%20trauma%20and%20the%20use%20of%20tranexamic%20acid%20in%20children%20Evidence%20statement%20(RCPCH,%20Nov%202012).pdf