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The CRASH3 study: Prehospital TXA for every injured patient?

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The CRASH3 results are out, but do we know what to do? The study enrolled 9202 head injured patients within 3 hours of injury with a Glasgow Coma Scale (GCS) of 12 or less, or any intracranial bleeding on CT scan and randomised them to Tranexamic Acid (TXA) or placebo. The relative risk (RR) of all-cause mortality (RR 0.96, 95% CI 0.89-1.04) and head injury death (RR 0.94, 95% CI 086-1.02) among those receiving TXA were not significant. However there were significant differences in subgroups who were less severely injured (RR 0.89 95%CI 0.80-1.00 if those with GCS=3 or bilateral fixed pupils were excluded, and RR 0.78, 95% CI 0.64 to 0.95, in the GCS 9 to 15 subgroup) or treated earlier (p=0.005 for time effect)[1].

The results need to be considered in the context of earlier CRASH2[2] results, which showed a reduction in all-cause mortality (RR 0.91, 0.85 to 0.97) and death due to bleeding (RR 0.85, 0.76-0.96) if trauma patients who were bleeding or at risk of bleeding were given TXA. In both CRASH2 and CRASH3 the TXA was given in the emergency department.

Interpretation

Both the CRASH2 and CRASH3 studies are on the borderline for power to detect important differences, despite being among the largest ever conducted in trauma care. However, there are unlikely to be better powered studies ever undertaken, so the current information has to be the basis for clinical decision making. A rigid evidence-based medicine approach ('this was a negative study – don't use TXA') risks a lost opportunity to improve care. However, the opposite view ('TXA is harmless give it to all head injuries') also risks a lost opportunity to improve care. Looking at confidence intervals rather than just thinking about the result as significant / non-significant is helpful, but translation of the CRASH3 trial results into clinical practice will ultimately be a matter of clinical judgement, which will undoubtedly lead to variation in clinical practice as there is no 'right' answer.

Setting of administration – hospital or prehospital?.

The first open question is about the setting of administration. None of the CRASH studies have given TXA in the prehospital phase, but across TXA studies there is a strong time effect, with earlier treatment linked to better outcomes[3]. The strong time effect was used as a justification for extrapolating from the CRASH2 results to recommend prehospital TXA treatment[4]. Prespecified analysis in CRASH3 showed a similar time effect, so it seems logical to assume that prehospital treatment would give better outcomes than delaying treatment until after a CT scan in the Emergency Department (although this has not been tested).

Which patients should get prehospital treatment?

As a prehospital GCS of 12 or less is associated with a 25% or more chance of having an abnormal CT scan,[5] it seems reasonable to recommend prehospital TXA treatment for these patients. This recommendation may be stronger in high income countries as post hoc analysis in the CRASH 3 paper suggested a greater reduction in head injury deaths with TXA (RR 0.76 for all severities) in high income countries.

It is more difficult to make a recommendation for head injury patients with a prehospital GCS 13-15, as they are much less likely to have a bleed, so earlier treatment would mean unnecessarily giving TXA to much larger numbers of patients. There are three potential ways

of implementing the CRASH3 findings in patients with a prehospital GCS of 13 to 15 (Table 1):

1) No prehospital treatment – await ED CT scan result

Treatment after CT (as per the CRASH3 trial method) would be expected to give the same effect as the trial. Unfortunately, the effect in the GCS 13-15 group is not reported separately in the CRASH3 paper. In a deviation from the statistical analysis plan[6], these patients were reported in a combined GCS 9 – 15 group, with a 22% reduction in head injury death RR 0.·78 (0.64–0.95)**.**

2) Prehospital treatment with TXA according to the local 'Head Injury CT Rules'

Early identification of intracerebral bleed is difficult[5], but minor head injury is routinely risk stratified according to 'Head Injury CT Rules', achieving a positive CT rate of about 5% (between 2% and 8% depending on the population) but <1% for neurosurgical abnormality[7-9]. There seems to be a logic (but no evidence) in thinking that if a patient with a minor head injury is at sufficient risk from intracranial bleeding to justify a CT scan (with associated radiation adverse effects) they also are at sufficient risk to warrant early TXA treatment. There would be simplicity in aligning the indications for TXA therapy with the local CT head scanning guidance. However, the CT head rules are often falsely positive (most minor head injury CTs are normal), so many patients would have unnecessary TXA treatment.

3) Prehospital treatment using a new risk stratification tool

The developers of the clinical decision rules for CT in minor head injury chose to maximise sensitivity (to detect all patients with traumatic brain injury) accepting low specificity. However, it would be possible to use the same information to create a 'rule' with increased specificity for intra-cranial haemorrhage (the trade-off being reduced sensitivity). A more specific rule would allow prehospital TXA therapy to be focussed to a higher risk group. Large prospective TBI studies supported by the International Initiative for Traumatic Brain Injury Research[10] suggest that blood based biomarkers of brain injury may improve the specificity of the head CT clinical decision rules, and – if developed as point of care tests – could potentially better target early (prehospital) TXA in patients with GCS 13 -15 head injury.

What is the Number Needed to Treat (NNT) for each prehospital strategy?

There is no NNT calculated in the CRASH3 paper, and separate relative risks were not provided for moderate and mild GCS scores (GCS 9 to 15 was considered as one group). This is unfortunate as the strong relationship between the incidence of intra-cranial haematoma and GCS means that the NNT is crucially dependent on the initial GCS.

In the GCS 9-15 group in the CRASH3 study the Absolute Risk Reduction was 1.7%, so the NNT to prevent one head injury death in this group of patients (who all have an intra-cranial bleed) can be calculated as 59 (Table 2). If the CT head scan indications were used to move TXA treatment earlier (either prehospital or before CT scan in hospital) the estimated NNT is between 294 and 1111 (Table 2). If TXA treatment was given to all head injuries the NNT would be several thousands. These are imprecise estimates which assume that the treatment effect (Risk Ratio) is constant across the GCS 9 to 15 range, but these calculations do give an indication of NNT.

As the NNT for a treatment increases, the key clinical decision is estimating where the accumulated harm (adverse effects) in patients who do not need the treatment outweighs the benefits. So, an estimation of the harm of TXA treatment is crucial. None of the prospective TXA trauma trials has shown an increase in venous thrombo-embolic or other complications (retrospective studies show an increase, but this is inevitable as only the most severely injured are treated with TXA). There is no drug without adverse effects, but the rate with TXA must be very low if it does not register in such large studies.[11]. However, if a NNT of thousands is being considered, even a very low adverse event rate might be significant.

In current use of CT head scanning for minor head injury management there is a precedent for a NNT in the thousands. There is no controlled trial evidence that defines the effect of early CT scanning on mortality, but it is likely that thousands of CT scans need to be performed in the GCS 13 – 15 group in order to prevent one death, as <1% of CT scans in this group have a neurosurgical abnormality[12] and most patients survive neurosurgery. CT scanning a large number of low risk patients is accepted emergency care practice, so we should not necessarily dismiss a TXA implementation that also involves treatment of a very large number of patients for each additional survivor.

Children.
There is unlikely ever to be a study similar to CRASH3 performed in children. As the coagulation system in children is very similar to the adult it is likely that, as with previous TXA trauma implementation, children will be treated with a weight adjusted dose using the same local guideline as adults.

Conclusions.
Decisions about the implementation of the CRASH3 results are complex, and it seems as if we should think about stratifying patients. The key implementation choices for the GCS <13 group (who probably have a NNT in the hundreds) are whether to move treatment into the prehospital phase, and whether the patients with the most severe injuries should be treated. Overall, in high income settings it seems reasonable to suggest prehospital intravenous TXA should be given for all injured patients with a prehospital GCS of 12 or less.

The situation for the GCS13-15 patients (who may have a NNT in the thousands) is more complex, particularly as the current CRASH3 publication does not give all the data needed to estimate a NNT for this group. The three approaches in GCS 13-15 patients are either; to only give TXA in the emergency department after a positive CT showing an intra-cranial bleed; or to give early (prehospital) treatment to all those at risk according to the local CT head scan criteria; or to develop a new method of prehospital risk stratification that emphasises specificity over sensitivity. In the GCS 13-15 group the current best recommendation seems to be to treat patients in the ED after a bleed is found on CT scan, but the future is likely to be the development of a clinical decision rule for TXA use with higher specificity for cerebral bleeding than the current CT scanning rules.

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Prehospital GCS 3-12

(>25% risk of intracranial injury)

(i) No prehospital administration (pre alert ED).

(ii) Give prehospital TXA to all.

(iii) Give prehospital TXA, excluding patients with GCS =3 or bilateral fixed pupils.

Prehospital GCS 13-15

(<1% risk of intra-cranial injury: 2-8% risk if indication for CT)

- No prehospital administration (pre alert ED to enable early CT).
- Give prehospital TXA if there is an indication for CT.
- Future high specificity rule (? including near patient blood biomarkers).

Table 1
Options for Prehospital TXA implementation in suspected isolated TBI

Implementation Strategy	Prevalence of cerebral bleed	Mortality	Risk Ratio	ARR	Estimated NNT	Notes
TXA in ED after CT (CRASH3 method)	100%	19.5%	0.78	1.7%	59	ARR assumed to be the same as the GCS 9-15 group in the CRASH3 paper.
Prehospital TXA if CT indicated (estimated)	2% to 8%	0.39% to 1.56%	0.78	0.09 to 0.34%	294 to 1111	This NNT will be smaller if early treatment is more effective
Prehospital TXA to all “head injured” (estimated)	<1%	<0.195	0.78	<0.04%	> 2500	Prevalence of cerebral bleed may be lower depending on definition of ‘head injured’.

Table 2
Impact of different implementation strategies on NNT in GCS 13-15 group
Note: ARR = Mortality – (Mortality * Risk Ratio)