Effects of tranexamic acid on death, disability, vascular occlusive events and other morbidities in patients with acute traumatic brain injury (CRASH 3)

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Intracranial bleeding is a common in traumatic brain injury (TBI) and is a strong risk factor for death and disability from TBI. Intracranial bleeding can start at the time of injury, though often continues for several hours after, leading to such associated sequelae as elevated ICP and potential herniation. Prior to this trial, the CRASH 2 study showed that early administration of tranexamic acid (TXA) reduced the risk of bleeding-related deaths in trauma patients with extracranial bleeding, though patients with TBI were excluded. However, given that increased fibrinolysis had also been suggested in TBI, smaller trials had studied TXA in terms of bleeding-related deaths in TBI, and such trials had shown a mortality benefit. For this reason, CRASH 3 was undertaken to determine the effect of TXA on longer term outcomes (death, adverse events, disability) in patients with TBI.

Experimental design and statistics: This was an international, multi-center, randomized, placebo-controlled trial. Adults presenting with a TBI within 3hrs of injury[1], a GCS of $\leq$12, or any intracranial bleeding evident on CT head, but no extracranial bleeding, were eligible for enrollment. Eligible patients were randomly assigned to receive either IV tranexamic acid (loading dose of 1g over 10min, then 1g q8hr) or a matching IV placebo (sodium chloride); treatment packs were blinded and both participants and study staff were masked to group allocation. Outcome data were collected 28 days after randomization. The primary outcome was head injury-related death in the hospital within 28 days of injury; this was limited to those randomized to treatment within 3hrs of presentation (patients presenting outside of 3hrs were analyzed separately). The primary outcome was analyzed with and without patients who had a GCS <3 and unreactive pupils on presentation, given an expected, poor prognosis in this subgroup regardless of treatment. Secondary outcomes included early (w/in 24hr) head-injury related deaths, all-cause mortality, disability, vascular occlusive events (MI, stroke, DVT, PE), seizures, days in the ICU, need for surgery, and adverse events. Data were analyzed via the use of relative risks/confidence intervals, as well as regression analyses for continuous variables.

Results: A total of 12,737 patients from 29 different countries were enrolled from July 2012 to January of 2019, with 6406 allocated to TXA and 6331 to placebo; 98.6% of these patients received their allocated treatment and 72% were enrolled within 3hrs of injury. Baseline patient characteristics were similar (**Table 1**). In terms of the primary outcome, head-injury related deaths occurred in 18.5% of the TXA vs. 19.8% of the placebo group (RR: 0.94, CI of 0.86 – 1.02), or 12.5% vs. 14.0% (TXA v. placebo, RR: 0.89, CI of 0.80 – 1.00) when excluding patients with a GCS <3 and unreactive pupils on presentation[2]. When stratifying by TBI severity, the benefit of TXA was present only in those with mild to moderate injuries (RR: 0.78, CI of 0.64 -

[1] At the start of the trial, the time point restriction was originally set to 8hrs, though the study authors eventually changed this restriction to 3hrs following evidence showing a lack of efficacy of TXA if given after 3hrs of injury. This led to a change in enrollment eligibility criteria

[2] The effect of TXA was also notable within 24hrs of injury, with an RR of 0.81 (CI: 0.69 – 0.95) for all patients

0.95) and not in those with severe injuries (**Fig 3**). In those with mild to moderate injuries (but not with severe injuries), early treatment (<3hr) was more effective than later treatment (p = 0.005, regression analysis, **Fig 4**). Finally, the risk of all-cause mortality and the prevalence of disability in survivors were similar among the two treatment groups, as were the risks for vascular occlusive events, stroke, seizure, or other adverse events (**Table 3**).

Conclusion: Overall, this trial showed that TXA reduced head-injury related deaths in patients with mild to moderate TBI, though it did not confer an overall mortality benefit for all cases of TBI. Nonetheless, the trial data did suggest that TXA appears to be safe to use at the time of injury and does not increase the risk for longer term disability. Given that TXA was most effective when given early, and reduced mortality within 24hrs of injury in mild/moderate cases, TXA may work by reducing intracranial hemorrhage expansion (which occurs hours after injury) and, consequently, head-injury related deaths from bleeding (which occur in the first few days after injury). The authors note several strengths of the study related to trial design, though they also note that a main limitation was the potential for variability between clinicians in terms of the consistency with which deaths were attributed to head-injury related deaths (the primary outcome). Regardless, this study suggested that early use of TXA for mild or moderate TBI may be considered, if clinically appropriate.

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