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TXA: The future for stop the bleed?

What the CRASH-2 and CRASH-3 studies tell us about TXA bleeding control methods for rural EMS

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Editor's Note:

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EMS MEd Editor: Alicia Buck, MD

Articles:

The CRASH-2 Collaborators, Shakur H, et al. (2010). Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant hemorrhage (CRASH-2): a randomized, placebo-controlled trial. *Lancet, Vol 376* (Issue 9734), 23-32. doi: 10.1016/S0140-6736(10)60835-5

While trauma care in EMS has vastly improved in the United States, there is still room for improvement. (AP Photo/Michael Balsamo,File)

The CRASH-2 Collaborators, Roberts I, Shakur H, et al. (2011). The importance of early treatment with tranexamic acid in bleeding trauma patients: an exploratory analysis of the CRASH-2 randomized control trial. *Lancet*, Vol 277 (Issue 9771), 1096-101. doi: 10.1016/S0140-6726(11)60278-X.

The CRASH-3 Collaborators. (2019). Effects of tranexamic acid on death, disability, vascular occlusive events and other morbidities in patients with acute traumatic brain injury (CRASH-3): A randomized, placebo-controlled trial. *Lancet*. *Vol 394* (Issue 10210), 1713-1723. doi: 10.1016/S0140-6736(19)32233-0.

Background. If you recall the clotting cascade, the end of the process involves the breakdown of clots (also known as fibrinolysis), through the activation of plasminogen to plasmin. Tranexamic acid (TXA) is a synthetic form of lysine, an amino acid. TXA is used to block fibrinolysis by attaching to plasminogen and blocking the fibrin binding site, preventing the formation of plasmin. Historically, TXA has been used in the operating room to stabilize already formed clots to prevent worsening bleeding.

Naturally, the next step is to see whether the drug can prevent bleeding in other settings besides the O.R. In this article bite, we will discuss CRASH-2 and CRASH-3, two large studies on the efficacy of TXA in trauma.

CRASH-2 METHODS

CRASH-2 was a randomized double-blinded control study involving 20,211 patients across 274 hospitals in 40 countries. The study group had the following inclusion criteria:

- Adult trauma patients
- Significant hemorrhage
    - Hypotension with systolic blood pressure < 90 mmHg and/or
    - Tachycardia with heart rate > 110

- *At risk* for significant hemorrhage
- Within 8 hours of injury

In addition, the study *excluded* cases where giving TXA was the obvious clinical choice. This exclusion allowed the researchers to focus on patient care guided by the uncertainty principle (i.e., when the risk/benefit was less clear). Patients were randomized to either receive normal saline or TXA 1g infused over 10 minutes, then infusion of 1g over 8 hours.

The *primary outcome was death in hospital within 4 weeks* (28 days) of injury. This was then broken down by cause of death:

- All cause mortality
- Bleeding
- Vascular occlusion (myocardial infarction, stroke, PE)
- Multiorgan failure
- Head injury
- Other

Primary outcomes were further stratified by time since injury, systolic BP, GCS and type of injury in subgroup analysis.

Secondary outcomes included:

- Vascular occlusive events (myocardial infarction, stroke, PE, and DVT)
- Need for surgical intervention (neurosurgical, thoracic, abdominal and pelvic)
- Receipt of blood transfusion
- Units of blood products transfused
- Level of disability (measured with the 5-point Modified Oxford Handicap Scale)

CRASH-2 key results

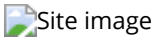
A total of 10,060 patients were analyzed in the TXA group and 10,067 patients were analyzed in the placebo group. The primary outcomes are illustrated in the following table (Table 2 in Crash-2).

CRASH-2 Primary Outcomes

Essentially, there was:

- *A decrease* in *any cause of death* in TXA (14.5%) versus placebo (16.0%)
- *A decrease* in *death by bleeding* in TXA (4.9%) versus placebo (5.7%)
- No noted difference in deaths from multiorgan failure, head injury, or other causes.

To put this into perspective, the number needed to treat (NNT) is 68, meaning in order to save one life from any cause of death, you need to treat 68 patients with TXA. In order to save one life from death by bleeding, you need to treat 119 patients.



Importantly, in a secondary analysis of the data, they found that *early administration* reduced mortality even more!

- Within 1 hour: 5.3% (TXA) vs. 7.7% (placebo)
- Between 1-3 hours: 4.8% (TXA) vs. 6.1% (placebo)

As for the *secondary outcomes*, there was:

- No difference in vascular occlusive events
- No difference in need for transfusion or surgery
- Statistically significant increase in patients discharged with *no symptoms* in the TXA group

Now before we dive into the takeaways, let's quickly talk about CRASH-3

CRASH-3 METHODS

CRASH-3 likewise was a multicenter double-blinded, randomized, placebo-controlled trial involving 12,737 patients with the following inclusion criteria:

- Adults age $\geq$ 18 years
- Within 3 hours of injury
- No major extracranial bleeding

- GCS ≤ 12 or evidence of intracranial bleeding on CT scan

Likewise, primary outcome was death at 28 days, with secondary outcomes of complications, need for surgical intervention, disability, etc.

CRASH-3 KEY RESULTS

CRASH-3 was able to show mortality benefit only in patients with mild to moderate head injury (GCS 9-15) with mortality of 5.8% in the TXA group versus 7.5% in the placebo group. To put it more practically, you would need to give 61 patients TXA with mild to moderate head injury in order to save 1 patient (NNT = 61). However, CRASH-3 was unfortunately not able to show a statistically significant reduction in mortality in all patient or a difference in disability. What is important, though, is that CRASH-3, like CRASH-2, was unable to show any increase in complications, therefore *highlighting the safety of TXA*.

TOP TAKEAWAYS ON TXA FOR EMS

In these two incredibly large studies in a very heterogeneous population group, TXA has been shown to improve overall patient survival in trauma and, in a specific patient group, isolated head trauma. However, it's important to remember that these improvements are modest at best. For all trauma, we are looking at a number needed to treat of 68 and for head trauma specifically, you are looking at a number needed to treat of 61, but only in mild to moderate head trauma.

So is it worth it? It probably depends! TXA in general is relatively inexpensive and *very* safe. Given that for our very sick trauma patients, there aren't a lot of options other than to take them to the operating room faster or to drive the ambulance faster, it is incredibly reasonable to incorporate TXA into your practice.

What this means for EMS. While trauma care in EMS has vastly improved in the United States, there is still room for improvement. As CRASH-2 and CRASH-3 have demonstrated, TXA is not only both efficacious and safe in trauma patients, but leads to even better outcomes when given as soon a possible after time of injury. As the first point of medical contact for our trauma patients, incorporation of TXA to EMS protocols can shorten the time to administration of TXA, *especially in rural communities with long transport times,* therefore improving patient survival.

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About the author

The National Association of EMS Physicians (NAEMSP) is an organization of physicians and other professionals partnering to provide leadership and foster excellence in the subspecialty of EMS medicine. The NAEMSP promotes meetings, publications and products that connect, serve and educate its members, and acts as an advocate of EMS-related decisions in cooperation with organizations throughout the country.

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