TXA Should be Urgently and Broadly Adopted for Brain Bleeds

The bottom line: Tranexamic acid keeps patients with mild and moderate bleeds from dying

By Matt Bivens, MD

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Let's travel through space and time to Paris during the French Revolution to conduct a medical trial. It is the dawn of the Reign of Terror. More than 17,000 people will be beheaded over the next two short years.

What an opportunity for science!

Our team, armed with computer tablets and clipboards, halts each new victim of the Committee of Public Safety entering the Place de la Révolution for study enrollment and to start an IV. The "patient" is then placed into the guillotine, the blade whisks down, the head flies off, and our hard-working researchers leap into action, pushing either tranexamic acid (TXA) or placebo intravenous.

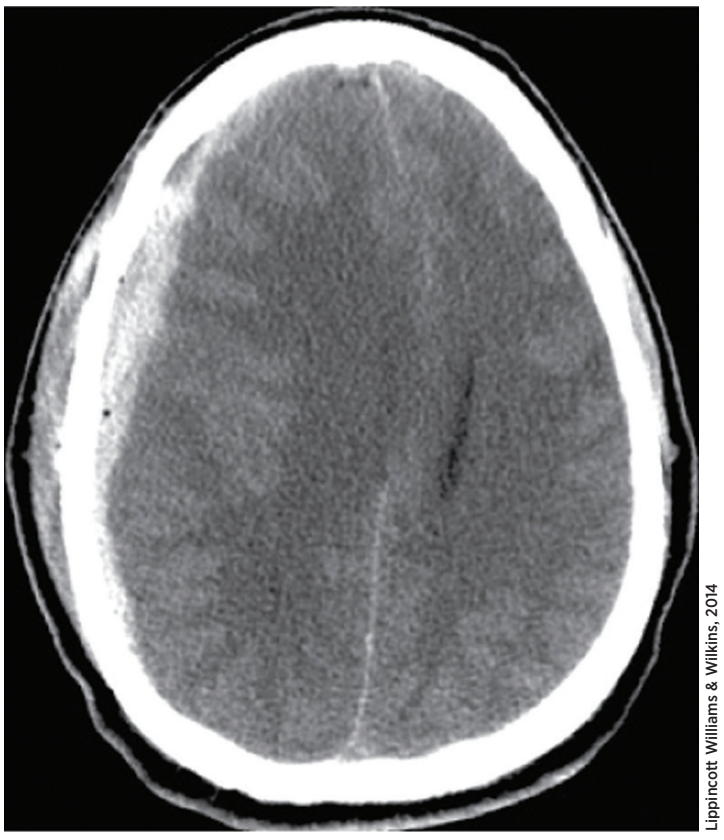
Once we get enough cases, we'll find out whether TXA works. Isn't this exciting?

Hmm. You don't seem impressed. Perhaps you think decapitation might preclude a good neurological outcome?

Well, I like where your head is at. (See what I did there?) Bring along that skepticism as we explore what the studies say about treating traumatic intracranial hemorrhage with TXA. Spoiler alert: It seems clear, despite the real challenges in designing a perfect investigation, that TXA saves the lives of patients with head bleeds and ought to be urgently and broadly adopted.

No Pulmonary Embolus

The landmark investigation remains CRASH-3. (*Lancet*. 2019;394[10210]:1713; https://bit.ly/36xP2sn.) This study randomized 9202 patients within three hours of a traumatic intracranial hemorrhage to TXA or placebo. It built on the network of the better-known CRASH-2, which studied TXA in undifferentiated trauma.



Lippincott Williams & Wilkins, 2014

Death rates in a CRASH-3 subgroup of 5615 patients were 5.7% in the TXA group and 7.5% in the placebo group, a p value of 0.007

Side note: CRASH-3 actually randomized a whopping 12,737 to TXA or saline over seven years, but only 9202 were treated inside the three-hour window. All 12,737 patients, however, were included in assessing safety events, and there was no signal whatsoever of TXA causing any pathological clotting, just as seen among the 20,127 trauma patients of CRASH-2 and the 20,070 post-partum hemorrhage patients of the WOMAN trial. (*Lancet*. 2010;376[9734]:23; https://bit.ly/2CoZJB4; *Lancet.* 2017;389[10084]:2105; https://bit.ly/2skflDp.)

That's right: The dreaded pulmonary embolus never surfaced in more than 50,000 patients in three large, well-done randomized trials. Nor was it seen in smaller RCTs, including TICH-2, which looked at 2325 hemorrhagic stroke patients, and STAAMP, which studied 903 U.S. trauma patients. (*Lancet*. 2018;391[10135]:2107; https://bit.ly/44dXU3V; *JAMA Surg*. 2020;156[1]:11; https://bit.ly/42WKpVo.)

In fact, the only major randomized trial to detect an uptick in PE or deep vein thrombosis was HALT-IT, where patients with gastrointestinal bleeds who were randomized to TXA saw a 0.4 percent increased risk of PE or deep vein thrombosis. (*Lancet*. 2020;395[10241]:1927; https://bit.ly/3iM28sg.) The HALT-IT authors hypothesized that GI bleeding is different from, say, trauma or post-partum hemorrhage because it can be indolent, often going on for days or weeks before being noticed, and because patients so often have cirrhosis with an associated brittle coagulopathy.

So, why do we associate clots with TXA if they are not as a rule seen in randomized trials? Mostly because they are seen in observational studies, such as the military's MATTERs, where the sickest patients were observed to be receiving TXA at a higher rate and to be developing PE and DVT, the known complications of major trauma, at a higher rate. (*Arch Surg*. 2012;147[2]:113; https://bit.ly/3Jny7hK.) It is a failure of the house of medicine that we are giving weight to observational studies at all when we have robust RCTs at hand.

Sitting on Our Hands

Let's return to CRASH-3. Head injury-related death among all comers was 18.5 percent with TXA and 19.8 percent with placebo. This 1.3 percent advantage for TXA was not statistically significant, but the study included some patients with devastating injuries. So, CRASH-3 tried to weed out the functionally guillotined, to coin a phrase, with a (prespecified) subgroup analysis, and removed patients with a Glasgow Coma Scale score of 3 or bilateral unreactive pupils.

The resulting "subgroup" was still massive, 7637 patients, far larger than many other entire studies! Death rates were 12.5 percent in the TXA group and 14 percent in the placebo group. That 1.5 percentage survival advantage equals a number needed to treat to save one life of 67—if we believe it.

We insist, by convention, however, that the p be less than 0.05, corresponding to a 95 percent likelihood we're seeing a real treatment effect. The p in this subgroup, however, is "only" 0.059, corresponding to only a 94.1 percent chance that we are seeing a real treatment effect. (This drug is safe and cheap, and we might use it if there were a 95 percent chance it was saving lives among all but the most guillotine-devastated head bleeds. But there's only a 94.1 percent chance it is saving those lives, so we won't. Got it?)

The CRASH-3 team distilled their population further, creating a new subgroup of 5615 patients with "mild to moderate" traumatic brain bleeds, defined as a GCS of 9 to 15. Death rates were 5.7 percent in the TXA group and 7.5 percent in the placebo group. This now is statistically significant (p=0.007!). That's a 1.8 percent survival benefit after TXA for an NNT of 59.

Consider it: More than 5000 mild-to-moderate brain bleeds and TXA saved one life in 59 with no downsides. Yet we're still sitting on our hands.

Disdain for Subgroups

A trial a few years ago tried to provide more clarity. This was a double-blind, placebo-controlled study at 20 U.S. and Canadian trauma centers. (*JAMA*. 2020; 324[10]:961; https://bit.ly/3XllfP3.) Paramedics randomized 966 patients within two hours of a major head injury (judged clinically without brain imaging) to TXA or placebo. About half of the patients were intubated in the field, but only about 58 percent even had a head bleed! (Mimic diagnoses included intoxication.)

It's a small study, barely a tenth the size of CRASH-3. More than 15 percent were lost to follow-up, and an outsized number of those who walked out and were never heard from again got TXA, not placebo. (If all of the patients are healed by your drug and elope, wouldn't your study underestimate how well the drug works?)

The short version of the study: Everything looked better with TXA, and none of it was statistically significant. True, in a subgroup analysis of patients who actually had a head bleed on imaging—which, gee whiz, seems like an important subgroup!—28-day mortality was 27 percent for those who got placebo but 18 percent for those who got a large TXA bolus of 2 g. The p=0.03, so this is statistically significant, suggesting we could save the life of one in 11 head bleeds.

But we serious doctors disdain subgroups. The authors only mention this finding in the fine print. Their abstract one-liner? Prehospital TXA "did not significantly improve 6-month neurologic outcome."

Sorry, why aren't we giving TXA to patients with head bleeds again? It prevents mild and moderate brain bleeds from worsening and keeps those people from dying. It does this without increased adverse events, including no increase in survival to a neurologically devastated state. But we're waiting for the day it actually resurrects people from the dead before we'll commit? **EMN**

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