ONLINE EXCLUSIVE

Trauma care—don't delay with TXA

Tranexamic acid can significantly reduce the risk of death due to bleeding if it is administered early on in trauma treatment.

Jack C. Wells, MD, MHA; James J. Stevermer, MD, MSPH
Department of Family and Community Medicine, University of Missouri-Columbia

PURLs EDITOR
Anne Mounsey, MD
University of North Carolina at Chapel Hill

PRACTICE CHANGER

Ensure that patients who incur serious trauma receive tranexamic acid (TXA) within 3 hours of the injury.[1]

STRENGTH OF RECOMMENDATION

B: An analysis of a large randomized controlled trial (RCT).

CRASH-2 collaborators; Roberts I, Shakur H, Afolabi A, et al. The importance of early treatment with tranexamic acid in bleeding trauma patients: an exploratory analysis of the CRASH-2 randomised controlled trial. *Lancet*. 2011;377:1096-1101.

ILLUSTRATIVE CASE

You are working in the emergency department (ED) of a rural hospital when a 26-year-old man is brought in with multiple injuries sustained in a high-speed collision and motor vehicle rollover. The nearest trauma center is more than an hour away. Should you administer TXA to the patient before transferring him?

Trauma is a leading cause of death among those younger than 40 years, and in 30% of such fatalities, hemorrhage is the cause.[2] Tranexamic acid (TXA) minimizes blood loss by inhibiting lysine binding sites on plasminogen, thereby preventing the conversion of plasminogen to plasmin. This inhibits fibrinolysis and reduces clot breakdown, resulting in a reduction in bleeding.[3]

TXA has a proven track record

TXA is not new. It has been used to minimize blood loss associated with surgery for decades.[4] A retrospective cohort study involving recent military engagements in Afghanistan showed a reduction in both coagulopathy and mortality in trauma patients who were given TXA.[5] The CRASH-2 randomized controlled trial (RCT), initially published in 2010[6] and further analyzed in the study detailed below,[1] was the first extensive multicenter trial to evaluate the use of TXA in civilian trauma care.

STUDY SUMMARY

TXA saves lives—within a 3-hour window

CRASH-2 studied the early administration of TXA in adult trauma patients in 274 hospitals in 40 countries.[1,6] Patients (N=20,211) were enrolled if the treating physician judged them to have or be at risk for significant hemorrhage and were randomized to either TXA or placebo, administered in identical-looking packs. Within 8 hours of injury, participants received a 1-g intravenous (IV) loading dose of either TXA or placebo over 10 minutes; a 1-g infusion over 8 hours followed. Patients and study staff were blinded to the treatment groups.

The primary outcome was overall mortality in the 4 weeks after injury. Secondary outcomes included vascular occlusive events (myocardial infarction, stroke, pulmonary embolism, and deep venous thrombosis), major surgical intervention, quantity of blood transfusion (if any), and cause of death (bleeding, vascular occlusion, multi-organ failure, head injury, or other cause). In this

analysis, the researchers considered the effect of TXA on mortality based on time to administration of treatment after injury, severity of blood loss as assessed by systolic blood pressure, Glasgow coma scale score, and type of injury. All analyses were intention to treat, and follow-up was 99.6%.

TXA reduced all-cause mortality in the first month after trauma (relative risk [RR]=0.91; 95% confidence interval [CI], 0.85-0.97; *P*=.0035; number needed to treat [NNT]=68). There were 3076 deaths from all causes in both groups, 35% of which were the result of bleeding. Among patients who received TXA, the overall risk of death due to bleeding was 4.9%, vs 5.4% in the placebo group (RR=0.85; 95% CI, 0.76-0.96; *P*=.0077; NNT=119).

TXA is included in US Army trauma protocols, but has yet to be added to the American College of Surgeons' Advanced Trauma Life Support manual.

After 3 hours, TXA may do more harm than good

For those treated with TXA within the first hour of injury, the risk of death due to bleeding was 5.3%, vs 7.7% for the placebo group (RR=0.68; 95% CI, 0.57-0.82; *P*<.0001; NNT=41). Giving TXA between one and 3 hours of injury also reduced the risk of death due to bleeding, to 4.8% vs 6.1% for the placebo group (RR=0.79; 95% CI, 0.64-0.97; *P*=.03; NNT=77).

TXA administered more than 3 hours after injury, however, appeared to increase the risk of death due to bleeding, to 4.4% compared with 3.1% for the placebo group (RR=1.44; 95% CI, 1.12-1.84; *P*=.004; number needed to harm=77). The researchers found no evidence that TXA's effect on death due to bleeding varied on the basis of systolic pressure, Glasgow coma score, or type of injury.

The rate of occlusive vascular events over the 4-week study period was similar in both groups (RR=0.84; 95% CI, 0.68-1.02; *P*=.08). Of note, the rate of myocardial infarction was reduced by TXA (RR=0.64; 95% CI, 0.42-0.97; *P*=.035; NNT=504).

WHAT'S NEW

Greater emphasis on TXA timing

Current practice for the treatment of traumatic hemorrhage includes fluid resuscitation and the administration of blood products. This analysis of the CRASH-2 refines our understanding of TXA, revealing that the earlier it is given after injury, the better the outcome. A 2011 Cochrane review found only one other small RCT (N=240), which had findings consistent with the CRASH-2 results.[7]

TXA is easy to administer and to store and does not require refrigeration or reconstitution prior to administration. TXA has been included in both the US and British Army trauma protocols.[8] In addition, TXA is used by National Health Service ambulances in the United Kingdom, and given to all adults and teenagers who incur major traumatic injury.[8]

CAVEATS

Potential for thromboembolic events, need for high time sensitivity

Because the enrollment criteria for the study were based entirely on clinical findings, there may have been some participants who were not actively bleeding. However, this would have been true for both the treatment and placebo groups and, if anything, would have diluted the effects of TXA.

There was no increase in vaso-occlusive events in the CRASH-2 study. However, some studies of TXA have found an increase in instances of pulmonary embolism, deep vein thrombosis, and ureteral obstruction in patients with genitourinary bleeding.[3]

This analysis showed that early administration of TXA is the key to its success—and highlighted the importance of avoiding giving it more than 3 hours after traumatic injury. Although most of the 40 countries in which the CRASH-2 study was conducted have less well developed trauma systems than those in the United States, a subgroup analysis of patients in Europe, North America, and Australia (n=1960) still showed a mortality benefit (RR=0.63; 95% CI, 0.42-0.94).[8]

CHALLENGES TO IMPLEMENTATION

Bringing TXA into the mainstream

The acceptance of TXA in trauma care guidelines may be one of the biggest barriers to its use. Currently, the American College of Sur-

geons does not include the use of TXA in its Advanced Trauma Life Support manual.[9]

Given the short time window for its benefit, TXA may be most appropriate in the prehospital setting. However, there are no studies of its use in this setting. Lack of knowledge and access are also barriers in the emergency setting, as many ED clinicians, particularly in rural settings, may not yet have access to TXA. Physicians in the United Kingdom have tried a variety of methods, including the unorthodox use of comic books targeted to health care providers,[10] in an effort to get the word out. JFP

ACKNOWLEDGEMENT

The PURLs Surveillance System was supported in part by Grant Number UL1RR024999 from the National Center for Research Resources, a Clinical Translational Science Award to the University of Chicago. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Center for Research Resources or the National Institutes of Health.

References

1. CRASH-2 collaborators; Roberts I, Shakur H, Afolabi A, et al. The importance of early treatment with tranexamic acid in bleeding trauma patients: an exploratory analysis of the CRASH-2 randomised controlled trial. *Lancet*. 2011;377:1096-1101.
2. Kauvar DS, Lefering R, Wade CE. Impact of hemorrhage on trauma outcome: an overview of epidemiology, clinical presentations, and therapeutic considerations. *J Trauma*. 2006;60(suppl):S3-S11.
3. Cap AP, Baer DG, Orman JA, et al. Tranexamic acid for trauma patients: a critical review of the literature. *J Trauma*. 2011;71(suppl):S9-S14.
4. Ker K, Edwards P, Perel P, et al. Effect of tranexamic acid on surgical bleeding: systematic review and cumulative meta-analysis. *BMJ*. 2012;344:e3054.
5. Morrison JJ, Dubose JJ, Rasmussen TE, et al. Military Application of Tranexamic Acid in Trauma Emergency Resuscitation (MATTERs) Study. *Arch Surg*. 2012;147:113-119.
6. Shakur H, Roberts I, Bautista R, et al. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial. *Lancet*. 2010;376:23-32.
7. Roberts I, Shakur H, Ker K, et al. Antifibrinolytic drugs for acute traumatic injury. *Cochrane Database Syst Rev*. 2011;(1):CD004896.
8. Ker K, Kiriya J, Perel P, et al. Avoidable mortality from giving tranexamic acid to bleeding trauma patients: an estimation based on WHO mortality data, a systematic literature review and data from the CRASH-2 trial. *BMC Emerg Med*. 2012;12:3.
9. American College of Surgeons, Committee on Trauma. *Advanced Trauma Life Support (ATLS) Student Course Manual*. 9th ed. Chicago, IL: American College of Surgeons; 2012.
10. Roberts I, Vieceli E, Duffield P. *TXA*. London, UK: London School of Hygiene & Tropical Medicine; 2012. Available at: http://download.thelancet.com/flatcontentassets/pdfs/TXA-manga.pdf. Accessed April 23, 2013.