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Tranexamic acid and Seizures in Pediatric Trauma

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Tranexamic acid (TXA) is a synthetic analog of lysine that reversibly and competitively inhibits conversion of plasminogen into plasmin. In doing so, it slows fibrinolysis by decreasing the cleavage of fibrin into fibrin split products. This can prevent thrombus breakdown, slow hemorrhage, and potentially decrease blood product requirements. The only U.S. Food and Drug Administration (FDA)-approved indication for TXA is the treatment of heavy menstrual bleeding.(1) However, TXA is often used off-label during major surgical procedures and has been shown to reduce transfusion requirements during pediatric cardiac, orthopedic, and craniofacial surgery.(2)

Although TXA was discovered in 1962, its use has significantly increased in the last several years, largely because of exciting recent study results in trauma patients. The rationale is that TXA reverses some of the hyperfibrinolysis that underlies acute traumatic coagulopathy.(2) In a landmark 20,000 patient international trial(3) of TXA use within three hours of civilian injury causing bleeding, both hemorrhagic and all-cause mortality decreased. No increase in venous thromboembolism was seen. Two subsequent retrospective cohort studies of TXA use in military trauma(4, 5) also found that TXA use was associated with lower mortality. In an innovative use of a military trauma registry, TXA was associated with lower mortality among injured children cared for at a NATO field hospital in Afghanistan.(6) No significant increase in adverse events was seen. In combination, these studies led to widespread implementation of TXA in trauma protocols.

TXA has few contraindications (acute venous or arterial thrombosis, established risk of thrombosis, allergy to TXA)(1) and is generally considered to have few significant adverse effects (nausea, diarrhea, orthostasis, muscle spasms).(2) It is renally cleared and the dose is

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typically reduced in the setting of renal insufficiency. In addition, seizures have been associated with TXA use in adults(7) and children(8), most often after the higher TXA doses given during cardiopulmonary bypass. This is biologically plausible, as TXA crosses the blood-brain barrier and inhibits both GABA_A and glycine receptors in animal models.(7)

In this issue of *Pediatric Critical Care Medicine*(9), Maeda et al. sought to test for associations between TXA use and seizures, thromboembolism, and renal dysfunction. The study cohort included children (≤ 12 years old, to avoid changes in thromboembolism risk with puberty) who were hospitalized after trauma between July 1, 2010 and March 31, 2014 and also received a blood product transfusion. The authors used a national database in Japan covering more than 1,000 hospitals and 90% of the country's tertiary care centers. The primary comparison was between children who received TXA on the day of admission and those who did not. Of the three primary outcomes, seizures and thromboembolism were defined using sets of International Classification of Diseases, version 10 (ICD-10) diagnosis codes and renal dysfunction was captured using local renal replacement procedure codes. Mortality was a secondary outcome.

The authors used 1:1 propensity score matching to establish covariate balance between those who received TXA and those who did not. From nearly 62,000 eligible patients, 1,914 matched pairs were created. In the matched analysis, no difference was found in the rates of thromboembolism, renal dysfunction, or mortality. However, the authors did identify an association between TXA use and seizures (0/1,914 control versus 7/1,914 TXA, $p = 0.008$).

Strengths of the current manuscript include the biologic plausibility of the association found between TXA and seizures, previous reports of seizures after TXA in other patient populations, the large national data source analyzed, and the good covariate balance achieved using propensity matching. The most important limitations of the study are the small number of outcome events, the lack of information about when seizures occurred, and the absence from the analysis of known risk factors for the primary outcomes. Traumatic brain injury (TBI), for example, is well-known to cause seizures, particularly among young children, those with subdural hemorrhage (SDH), and those with inflicted injury.(10) Age and "head or neck" injury were included in the propensity model, but SDH and injury mechanism were not. Similarly important risk factors for thromboembolism (e.g. central venous catheters, immobilization) and renal dysfunction (e.g. cardiac arrest, direct renal injury, nephrotoxic medications) were not included in the analysis. The sets of codes used to identify the primary outcomes were not validated as computable phenotypes.(11) Although the propensity model was adjusted for hospital volume and teaching status, hospital care practices (e.g. continuous electroencephalography) that might affect outcome rates were not reported.

Now that TXA is in wider use, how do we detect uncommon adverse effects in countries, like the U.S., lacking national databases like the one used by Maeda et al.? One solution might be the FDA's Mini-Sentinel project, a national surveillance system for uncommon adverse events potentially caused by marketed drugs and devices.(12) The CRASH-3 trial(13) of early TXA in 13,000 adult patients with isolated head injury is nearing completion and will also likely be a rich source of information.

Broad implementation of protocolized early TXA use might lead to a small increase in seizures among children with trauma. On balance, would that be acceptable if hemorrhagic deaths were prevented? It may be, but pediatric studies to inform patient selection are needed. In addition, TXA use has been associated with higher mortality in adult trauma patients with physiologic fibrinolysis as measured by thromboelastography (TEG).⁽¹⁴⁾ TEG can be slow to result and may not be currently feasible in many trauma settings, but caution is appropriate when administering TXA empirically to broad populations of injured patients.

The evidence supporting TXA use in military and resource-poor areas is impressive. TXA is generic and inexpensive, making it accessible globally. Studies of TXA use in adult trauma resuscitation are now being extrapolated to pediatric populations worldwide. However, gaps remain in our knowledge of TXA effectiveness and adverse event rates in children (and adults) with trauma. In particular, questions remain about when to administer TXA in areas with mature trauma systems. Perhaps because of this uncertainty, the American Academy of Pediatrics has yet to publish recommendations for its use, and U.S. pediatric trauma centers vary in their local practices.

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References

1. Tengborn L, Blomback M, Berntorp E. Tranexamic acid--an old drug still going strong and making a revival. *Thromb Res* 2015;135(2):231–242. [PubMed: 25559460]
2. Beno S, Ackery AD, Callum J, et al. Tranexamic acid in pediatric trauma: why not? *Crit Care* 2014;18(4):313. [PubMed: 25043066]
3. Crash-2 trial collaborators, Shakur H, Roberts I, 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(9734):23–32. [PubMed: 20554319]
4. Morrison JJ, Dubose JJ, Rasmussen TE, et al. Military Application of Tranexamic Acid in Trauma Emergency Resuscitation (MATTERS) Study. *Arch Surg* 2012;147(2):113–119. [PubMed: 22006852]
5. Morrison JJ, Ross JD, Dubose JJ, et al. Association of cryoprecipitate and tranexamic acid with improved survival following wartime injury: findings from the MATTERS II Study. *JAMA Surg* 2013;148(3):218–225. [PubMed: 23670117]
6. Eckert MJ, Wertin TM, Tyner SD, et al. Tranexamic acid administration to pediatric trauma patients in a combat setting: the pediatric trauma and tranexamic acid study (PED-TRAX). *J Trauma Acute Care Surg* 2014;77(6):852–858; discussion 858. [PubMed: 25423534]
7. Lecker I, Wang DS, Whissell PD, et al. Tranexamic acid-associated seizures: Causes and treatment. *Ann Neurol* 2016;79(1):18–26. [PubMed: 26580862]
8. Gertler R, Wiesner G, Tassani-Prell P, et al. Measurement of tranexamic acid serum concentrations in a 7-month-old infant with clinical seizures after open heart surgery. *Pediatr Neurol* 2014;51(2):e1–2. [PubMed: 25079582]
9. Maeda T, Michihata N, Sasabuchi Y, et al. Safety of tranexamic acid during pediatric trauma: a nationwide database study. *Pediatr Crit Care Med*. 2018; in press
10. Bennett KS, DeWitt PE, Harlaar N, et al. Seizures in Children With Severe Traumatic Brain Injury. *Pediatr Crit Care Med* 2017;18(1):54–63. [PubMed: 27654815]

11. Richesson RL, Sun J, Pathak J, et al. Clinical phenotyping in selected national networks: demonstrating the need for high-throughput, portable, and computational methods. *Artif Intell Med* 2016;71:57–61. [PubMed: 27506131]
12. Psaty BM, Breckenridge AM. Mini-Sentinel and regulatory science--big data rendered fit and functional. *N Engl J Med* 2014;370(23):2165–2167. [PubMed: 24897081]
13. Clinical Randomisation of an Antifibrinolytic in Significant Head Injury (CRASH-3) Trial. [cited Available from: <http://crash3.lshtm.ac.uk/>. Accessed August 7, 2018.
14. Moore HB, Moore EE, Huebner BR, et al. Tranexamic acid is associated with increased mortality in patients with physiological fibrinolysis. *J Surg Res* 2017;220:438–443. [PubMed: 28755903]