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Washington University Emergency Medicine Journal Club
The Use of Tranexamic Acid in the Treatment of Traumatic Hemorrhage

Vignette

As you are sitting in a break room at the NATO Role 3 Hospital at Kandahar Air Field (KAF) eating your 7th bag of beef jerky and waiting 45 minutes for a 2 minute you tube video to download you hear on the radio that a 9-line MEDEVAC flight is inbound with a severely wounded soldier. The pt arrives and the flight medic relays the history of a 24 y/o active duty army soldier that was on patrol in Southern Afghanistan when a dismounted improvised explosive device (IED) detonated. He had no obvious head injury and a GCS of 15 but suffered significant extremity injuries, blood loss, and multiple traumatic amputations; tourniquets were applied to all 4 extremities. Primary and secondary survey reveals the following injuries: traumatic BKA bilateral LE's; fragment wounds right buttock; fingers 3-5 traumatic amputation with open metacarpal fracture left hand; fragment wounds left forearm with transection of the ulnar artery and nerve; traumatic AEA amputation right UE; fragment wounds right axillary artery; fragment wounds to neck; and bilateral ruptured TM's. CT H/C/A/P was negative and C/T/L spine were radiographically normal.

You initiate Damage Control Resuscitation (DCR) and Massive Transfusion (MT) guidelines and the patient received 38 units PRBC's; 33 units FFP; 4 units of platelets; 30 units of cryoprecipitate; and Tranexamic acid (TXA) 1 g IV in 100 ml NS over 10 min followed by 1 g IV in NS over 8 hr in the ED and OR. In the OR the pt underwent D&I of his wounds with conversion of his LUE injury to a mid-forearm amputation and BLE injuries to AKA's. Post–op H/H 9.9/26.5 and INR 1.2. Pt was airlifted by a Critical Care Air Transport Team (CCATT) to Bagram Air Field (BAF) for further stabilization. At BAF pt was taken to OR for further wound management and received 10 units PRBC's, 4 units FFP, 1 unit of platelets, and 10 units Cryoprecipitate. Post-op H/H 11.2/31.8 , platelet count 105, INR 1.2. A chest CT revealed a PE and pt was started on Heparin. His Bun/Cr and K^+ began to increase and he was started on continuous renal replacement therapy (CRRT). The patient was then validated for air movement to Landsthul Army Medical Center (LRMC), Germany via CCATT. Prior to flight CRRT was discharged and H/H was 7.2/21, pt was given 2 units PRBC's and loaded onto the aircraft with follow-up H/H 8.5/25. During the flight, his H/H decreased to 6.8/20 and 1 unit PRBC's and 1 unit FFP were transfused with increase in H/H to 7.5/22. The pt was safely delivered to the ICU at LRMC.

Total time from point of injury (POI) to LRMC ~ 48 hrs. and 51 units PRBC's, 38 units FFP, 5 units of platelets, and 40 units cryoprecipitate were transfused. You begin to wonder what affect the TXA really had, and what evidence there is to support its use in military and civilian settings. You sit down to begin your literature search...

PICO Question
Population: Civilian trauma patients presenting to the ED with hemorrhage requiring massive transfusions.
Intervention: Administration of TXA in the ED.
Comparison: Standard resuscitative measures.
Outcome: Overall mortality, death due to bleeding, thromboembolic events, coagulopathy, transfusion requirements.

Search Strategy

MEDLINE was searched via PubMed using the strategy "tranexamic acid trauma" resulting in 299 articles (http://tinyurl.com/qxn4c45). The 4 most relevant articles were then chosen.

Article 1: CRASH-2 trial collaborators. 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 Jul 3;376(9734):23-32. Answer Key.

Article 2: CRASH-2 collaborators. The importance of early treatment with tranexamic acid in bleeding trauma patients: an exploratory analysis of the CRASH-2 randomised controlled trial. Lancet. 2011 Mar 26;377(9771):1096-101, 1101.e1-2. Answer Key.

Article 3: Morrison JJ, Dubose JJ, Rasmussen TE, Midwinter MJ. Military Application of Tranexamic Acid in Trauma Emergency Resuscitation (MATTERs) Study. Arch Surg. 2012 Feb;147(2):113-9. Answer Key.

Article 4: Valle EJ, Allen CJ, Van Haren RM, Jouria JM, Li H, Livingstone AS, Namias N, Schulman CI, Proctor KG. Do all trauma patients benefit from tranexamic acid? J Trauma Acute Care Surg. 2014 Jun;76(6):1373-8. Answer Key.

Bottom Line

Traumatic injuries represent a significant source of morbidity and mortality worldwide, with hemorrhage responsible for 30% of in-hospital trauma deaths each year. Tranexamic acid (TXA) has been used for decades to reduce bleeding in a variety of situations, including cardiopulmonary bypass, menorrhagia, and upper GI bleeding. TXA is a lysine analog that binds the lysine-binding site on plasminogen and prevents its conversion to plasmin, which would lead to fibrin degradation (Okamoto 1997). This antifibrinolytic property theoretically leads to decreased hemorrhage and blood loss, and would potentially benefit those at risk of bleeding due to significant trauma.

CRASH-2

The CRASH-2 (Clinical Randomization of an Antifibrinolytic in Significant Haemorrhage) trial, published in 2010, was an international, multicenter study that sought to evaluate the benefit of TXA in trauma from a global health perspective. Patients were enrolled primarily in low and middle-income countries, where 90% of trauma deaths occur worldwide. Over 20,000 trauma patients from 274 hospital in 40 countries were enrolled and randomized to receive either TXA of placebo. A small but significant reduction in mortality was observed in those patients receiving TXA (absolute risk reduction [ARR] 1.5%, 95% CI 0.49 to 2.47), with a number needed to treat (NNT) of 68. There was no observed increase in the number of vascular occlusive events (PE, DVT, MI, CVA), the most dreaded potential complication of TXA. Critics of the study point mainly to the subjective nature of the inclusion criteria (patients at risk of "significant hemorrhage") and exclusion criteria (those with clear indications or contraindications to TXA), the low risk of hemorrhage in the study (only half of the patients required transfusion), and differences in transport time and trauma care between the included countries and the United States. Despite these critiques, this study led to the inclusion of TXA in the World Health Organizations list of essential medicines.

A subgroup analysis of data from the CRASH-2 trial attempted to further clarify situations in which TXA would be beneficial in trauma. In this analysis, a reduction in death due to bleeding was noted in those who received TXA less than 1 hour from the time of injury (RR 0·68, 95% CI 0·57–0·82) and those who received TXA between 1 and 3 hours from the time of injury (RR 0·79, 95% 0·64–0·97). Interestingly, a paradoxical increase in the risk of death due to bleeding was observed in those who received TXA more than 3 hours from the time of injury (RR 1·44, 95% CI 1·12–1·84). The authors also evaluated the effect of TXA on death due to bleeding based on initial SBP, GCS, and type of injury, but did not find homogeneity in the results of these subgroup analyses.

MATTERs

A retrospective analysis of 896 patients treated in the military was undertaken using a cohort of patients treat at Camp Bastion Hospital in Afghanistan, of whom 293 (32.7%) received TXA. Both NATO personnel (US and UK military) and Afghan national military personnel were included in the study. Given the observational nature of this study, it is not surprising that patients who received TXA were much sicker than those who did not receive TXA, based on Injury Severity Score (ISS), Abbreviated Injury Scale (AIS), Revised Trauma Score (RTS), initial Glasgow Coma Score (GCS), and systolic blood pressure. Despite have worse baseline prognosis, patients who received TXA had decreased mortality compared to those who did not, with an unadjusted RR for in-hospital mortality of 0.73 (95% CI 0.54 to 0.98). In a subset of patients who met criteria for massive transfusion (requiring 10 or more units of blood within 24 hours), a similar reduction in in-hospital mortality was observed with the use of TXA (RR 0.51, 95% CI 0.32 to 0.83). Multivariate logistic regression analysis revealed that the use of TXA was independently associated with reduced mortality in the massive transfusion subgroup of patients, with an odds ratio for survival of 7.23 (95% CI 3.02 to 17.32).

As in the CRASH-2 trial, differences between patients enrolled in the MATTERs study and those cared for in a civilian US level 1 trauma center make it difficult to apply the results to our patient population. Patients in MATTERs were quite young, with a mean age of 23, and were almost entirely male. Additionally, the mechanism of injury was predominantly explosion, accounting for three-fourths of the patients receiving TXA and over 60% of those not receiving TXA. The remainder of the injuries were due to gunshot wounds, presumably mostly from large caliber, military weapons. The injury patterns involved likely resulted in significantly more hemorrhage than would typically be observed in motor vehicle crashes and smaller caliber gunshot wounds, and the effect of TXA potentially magnified.

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To evaluate the effect of TXA on a civilian US population, a retrospective analysis of outcomes was conducted at Ryder Trauma Center in Miami, FL over a 3-year period from August, 2009 to January, 2013. A cohort of 150 patients who were given TXA during that time period (at the discretion of the treating physician) was matched to a similar cohort using propensity matching. Patients were matched based on age, sex, presence of traumatic brain injury, mechanism of injury, systolic blood pressure, need for blood transfusion, and injury severity score (ISS). They found that patients who received TXA had *increased* mortality (31% v 23%), though this difference was not statistically significant (RR 1.31, 95% CI 0.90 to 1.92). By excluding groups of patients (those that died within 2 hours of arrival, those with TBI, those that received less than 2 liters of blood, and those with a systolic blood pressure over 120 mmHg), the authors were able to find statistically significant increases in mortality with the use of TXA.

While this study would seem to suggest significant harm from the use of TXA in a civilian US trauma center, this seems unlikely. Given that patients who received TXA in this study were taken to the OR more rapidly than their counterparts (median 24 minutes vs. 35 minutes) and required significantly more blood products over the first 24 hours (2,250 vs. 1,999 mLs), it seems likely that this was a baseline sicker cohort of patients who began their course with a more sinister prognosis. Additionally, the observed mortality increase was not statistically significant due to the underpowered nature of the study; while statistical significance was achieved by excluding certain groups of patients, these were subgroup analyses and must be validated prospectively before changing practice. Unfortunately, the authors do not report the incidence of thrombotic events; aside from thrombosis, no reasonable mechanism for the observed increase in mortality can be attributed to TXA

Conclusions

The bulk of the existing evidence suggests that TXA reduces mortality in trauma patients with hemorrhage. This includes data from a cohort of patients with less significant hemorrhage (CRASH-2) as well as a military cohort of patients with significant hemorrhage and those requiring massive transfusion (MATTERs). While the single study

performed on US patients revealed a non-statistically significant increase in mortality with the use of TXA, the methodological limitations of this case control trial, and the large disparity of its results compared to other existing studies, bring these results under scrutiny. For now, the evidence suggests that TXA, when given within 3 hours of injury, likely reduces mortality in patients at risk of significant traumatic hemorrhage, and should at least be considered in those requiring massive transfusion protocol initiation.