EVMS EM Journal Club/Critical Review Form

THERAPY ARTICLE

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Citation: PATCH-Trauma Investigators and the ANZICS Clinical Trials Group; Gruen RL, et al Prehospital Tranexamic Acid for Severe Trauma. N Engl J Med. 2023 Jul 13;389(2):127-136. Epub 2023 Jun 14. PMID: 37314244.

Background:

TXA has been around since the 1950s developed by a Japanese husband and wife team trying to address high mortality rates in Japan from postpartum hemorrhage.

TXA is an OTC medicine in countries like Europe and Asia for heavy menstrual bleeding.

It is currently listed in the WHO list of essential medicines.

Tranexamic Acid (TXA) is an anti-fibrinolytic medicine, which works by binding to plasminogen, decreasing the conversion of plasminogen to plasmin, thus preventing the degradation of fibrin. This preserves the fibrin matrix with the goal of treating or preventing excessive blood loss. This stabilizes the clot and prevents bleeding.

Trauma is the leading cause of death among young people. The thought is that TXA might be an effective treatment for the trauma-induced coagulopathy caused by tissue injury and hemorrhagic shock.

The CRASH-2 and CRASH-3 trials looked at administration of TXA within 3 hours of injury and mortality. But this involved countries that had less advanced region-wide systems of trauma care. Subsequent trials in advanced systems did not show benefit of pre-hospital TXA administration, and possibly increased risk for thromboembolism. Also, the patients were only followed 28 days after the trauma, so long term outcomes were not determined, bringing quality of long-term survival into question.

Study Objective:

Evaluate the efficacy and safety of TXA therapy in patients with severe trauma who were at risk for trauma-induced coagulopathy.

Primary outcome was survival with a favorable functional outcome at 6 months assessed using the Glasgow Outcome Scale- Extended (GOS-E).

GOS-E is a standardized questionnaire to assess functional outcomes in major trauma patients.

Scoring: (1-8)

- 1 = death
- 8 - upper good recovery (or no injury related problems)
- Categories broke down into two categories
- Group 1 - scores from 1 to 4 (death, unfavorable functional outcomes, vegetative, severe disability)
- Group 2 - scores 5 to 8 (favorable functional outcomes, lower moderate disability)

Secondary outcome was death within 24 hours, 28 days, and 6 months following injury.

The cause of death had to include death from bleeding, vascular occlusion, multiorgan failure, TBI, or other.

Study Methodology:

International (Australia, New Zealand and Germany), double-blind, randomized, placebo-controlled trial

Approved by the human research ethics committee responsible for each participating site. Informed consent waivered as TXA commonly used in the study municipalities.

Patients (or legal representative) were asked to consent to participate regarding data collection.

Inclusion criteria

- Adults 18 or older with suspected severe traumatic injuries being treated in the prehospital setting and transported to a trauma center
- Had to be deemed high risk for trauma-induced coagulopathy AND the first dose of TXA or placebo could be given within 3 hours after injury and before hospital admission.
- Risk assessment done via Coagulopathy of Severe Trauma (COAST) score.
    - Range 0 to 7
    - 1 point for each of the following:
        - Entrapment in a vehicle
        - SBP < 100mmHg
        - Body Temperature <35 C
        - Suspected PTX
        - Suspected intra abdominal or pelvic injury
    - Additional points given for the following
        - SBP < 90 mm Hg
        - Body temperature <32 C
    - **COAST score ≥3 --> high risk**
- Exclusion criteria
    - Suspected to be pregnant
    - Reside in a facility for older persons
- **Pre-specified sub-groups**
    - Age (<50 y/o or ≥ 50 y/o)
    - Initial Glasgow Coma Scale (<9 or ≥9)
    - Initial SBP
    - Mechanism of injury
    - Time from injury to first dose of TXA or placebo
- Randomization
    - 1:1 ratio of TXA or placebo
    - Randomization was computer-generated
        - Packaging was tamper-proof
        - Each package with 2 identical 10ml ampules with either 1g TXA or NS
    - Blinded was all-personnel (participants, clinicians, follow-up accessors)
- Procedure
    - As soon as practical (at scene/en route), with first ampule, one dose given as bolus of TXA or placebo
    - At hospital, other ampule in pack given with 1L NS infused over 8 hours
    - Screening for DVT in legs was performed with US on or around Day 7 of hospitalization

With these inclusion and exclusion criteria, the study enrolled 1310 patients between July 2024 and September 2021. This included treatment by 15 EMS services at 21 hospitals in Australia, New Zealand, and Germany.

Three of the trial packs were lost in the field, so the assignments were unknown.

661 of the patients received TXA, with 4 withdrawing consent, for a total of 657.

646 of the patients received the placebo, with 3 withdrawing consent, for a total of 643.

50 of the patients declined to participate in the follow-up and 119 of the patients could not be contacted, for a total of 1131 patients available for the primary outcome data. (572 TXA and 559 placebo)

GUIDE	COMMENTS
I. Are the results valid?	
A. Did experimental and control groups begin the study with a similar prognosis	Yes, patients included were deemed to have a COAST score of 3 or greater, meaning high risk.
1. Were patients randomized?	Yes. 1:1 ratio of TXA or placebo Randomization was computer-generated
2. Was randomization concealed (blinded)? In other words, was it possible to subvert the randomization process to ensure that a patient would be "randomized" to a particular group?	Yes. Packaging was tamper-proof (Each package with 2 identical 10ml ampules with either 1g TXA or NS)
3. Were patients analyzed in the groups to which they were randomized?	Yes, this was an intention-to-treat analysis although authors also provided per protocol findings
4. Were patients in the treatment and control groups similar with respect to known prognostic factors?	Mostly. (See table 1) Patients in the TXA group were 15.7% more likely to get the intervention within the first hour and those in the control group were 11% more likely to receive the intervention in the 1-2 hour time period. No difference at >2 hours. Authors did not report whether this was statistically significant.
5. Were patients aware of group allocation?	No. **"All trial personnel — including the participants, treating clinicians, and follow-up assessors — were unaware of the trial-group assignments."**
6. Were clinicians aware of group allocation?	No.
7. Were outcome assessors aware of group allocation?	No.
8. Was follow-up complete?	No, there were 13% of the patients lost to follow-up

What are the results ?	**Primary outcome:** GOS-E level ≥5 (favorable functional outcome at 6-months) ITT Group • TXA group had 307/572 (53.7%) with favorable functional outcome vs. Placebo group had 299/559 (53.5%) with favorable functional outcome • Absolute Risk Reduction 0.2 (95% CI -5.6-6.0) which is **not statistically significant.** There was no sig. difference noted in per protocol group as well. **Secondary outcome**: **Mortality** **24 hours after injury** (risk ratio, 0.69; 95% CI, 0.51 to 0.94) s**tatistically significant** TXA group had 64/657 (9.7%) vs. 90/640 (14.1%) placebo ARR=4.4% NNT= 1/ARR= 22.7 **Day 28 after injury** (risk ratio 0.79; 95% CI, 0.63 to 0.99) **statistically significant** o TXA group had 113/653 (17.3%) deaths o Placebo had 139/637 (21.8%) deaths o Risk ratio 0.79 **6 months after injury** (risk ratio, 0.83; 95% CI, 0.67 to 1.03) **not statistically significant** o TXA group had 123/648 (19%) deaths o Placebo had 144/629 (22.9%) deaths **Vascular occlusive events** (risk ratio, 1.20; 95% CI, 0.97 to 1.48) **not statistically significant** in TXA group occurred 155/657 and placebo 126/641
1. How large was the treatment effect?	See above
2. How precise was the estimate of the treatment effect? (CI's?)	CI's were fairly narrow
III **How can I apply the results to patient care?**	
1. Were the study patients similar to my patient?	Yes and no. European Study. European Trauma systems. New Zealand and Australia use paramedics. Germany staffs critical EMS calls with scene MD's. A minority of the patients were penetrating (approx. 7%) We have plenty of severely injured patients with GSWs, MVCs with entrapment, unstable patients that are at high risk of exsanguination within the first 24 hours.

2. Were all clinically important outcomes considered?	No, the long-term (beyond 6-mos.) and quality of survival is still yet to be determined. Trauma patients oftentimes have extended recovery times (i.e. TBI's). Is a long-term disability preferred over death in a younger trauma cohort?
3. Are the likely treatment benefits worth the potential harm and costs?	**Thoughts?** The greatest effect of TXA was on reducing deaths within 24 hours after injury without **any** increase in harms. This is when the threat of severe bleeding is the greatest. But there was no difference in favorable functional outcome at 6 months between TXA and placebo. Is a disability outcome worse than death? So, there is early survival benefit from TXA, but no benefit when it comes to functional outcome at 6 months. More patients in the TXA group survived but had more severe disabilities at 6 months as well (more patients in the lower severe disability group).

Limitations:

Loss to follow-up (13% of patients in the primary outcome data). Some patients did not receive the intended doses. Given the loss to follow up, this can bias the observed treatment effects toward the null.

Protocol violations occurred in 35% of the patients (17% of the patients assigned to receive placebo received tranexamic acid, and 21% assigned to receive tranexamic acid did not receive the second dose.

This studied one standard dose of TXA prehospital and in hospital (1g bolus + 1g infusion), whereas there are other studies looking at giving 2g initially, would this change results/outcomes? (so that the 2g is given within the 3 hour window and not delayed?)

This study was considered international, studying in Australia, New Zealand, and Germany. Is this representative of the practice in the United States or other countries?

Small number of penetrating injuries to draw any conclusions.

Clinical Bottom Line:

More studies need to be done to draw conclusions on the quality of survival due to TXA. More patients will survive the first 24 hours (and 28 days), but more research needs to be done about long-term survival, what is quality of life in the long term does it continue to improve beyond 6 months?