High-dose tranexamic acid for patients with acute gastrointestinal hemorrhage

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Key Article

Roberts I, et al. Effects of a high-dose 24-h infusion of tranexamic acid on death and thromboembolic events in patients with acute gastrointestinal bleeding (HALT-IT): an international randomised, double-blind, placebo-controlled trial. The Lancet. 2020 Jun 20.

Background

- Acute gastrointestinal (GI) bleeding is a common cause of death worldwide, with morality rates approximately 10% for upper GI bleeds and 3% for lower GI bleeds
- Rebleeding is a common phenomenon and may increase mortality by up to 4-fold
- Current management for GI bleeds includes resuscitation with blood products, endoscopy and occasionally surgery
- Tranexamic acid (TXA) has been used to decrease blood loss across a variety of clinical encounters and in certain situations, may decrease mortality by inhibiting fibrinolysis
- To date, no large randomized trial has assessed the impact on mortality and rate of thromboembolic adverse events of TXA in acute GI hemorrhage with modern treatment strategies

Objective

- Quantify the effects of TXA on death and thromboembolic complications in patients with an acute gastrointestinal hemorrhage

Study

- International, randomized, multi-center, double-blind placebo-controlled pragmatic trial from July, 2013 to June, 2019
- 15 countries including 164 hospitals (UK, Pakistan, Nigeria, Egypt, Malaysia, Georgia, Romania, Nepal, Sudan, Saudi Arabia, Spain, Ireland, Albania, Papua New Guinea, and Australia)

- Inclusion criteria were *clinical*: adult (either 16 or 18 years, depending on country) and treating clinician was "substantially uncertain" whether to use TXA for patients with a significant GI bleed
- No exclusion criteria provided
- Significant GI bleed defined as: "risk of bleeding to death and included patients with hypotension, tachycardia, or signs of shock, or those likely to need transfusion or urgent endoscopy or surgery"
- Intervention
    - *Intervention group*: loading dose of 1 g TXA was added to a 100 mL infusion bag of 0·9% sodium chloride and infused by slow intravenous injection over 10 min, followed by a maintenance dose of 3 g tranexamic acid added to 1 L of any isotonic intravenous solution and infused at 125 mg/h for 24 h
    - *Control group*: 100 mL infusion bag of 0·9% sodium chloride and infused by slow intravenous injection over 10 min, followed by a maintenance dose of 1 L of any isotonic intravenous solution and infused at 125 mg/h for 24 h
- Outcomes
    - Primary: death due to bleeding within 5 days of randomization
    - Secondary:
        - Death due to bleeding with 24 hours and 28 days of randomization
        - All-cause and specific-cause mortality at 24 hours, 5 days, and 28 days of randomization
        - Rebleeding within 24 hours, 5 days, and 28 days of randomization[1]
        - Surgical or radiological intervention, blood product transfusion
        - Thromboembolic events (DVT, stroke, PE and MI)
        - Days in intensive care unit
        - Functional status[2]
        - Other complications (seizure, sepsis, pneumonia, respiratory failure, renal failure, hepatic failure, other significant cardiac event)
    - **Primary outcome was changed** from all-cause mortality at 5 days to death due to bleeding at 5 days of randomization on 11/2018 due to a high percentage of deaths from non-bleeding causes

Results

- 12,009 total patients were enrolled (10,190 prior to change in primary outcome) of which 5994 (49.9%) were randomized to TXA and 6015 (50.1%) were in placebo group
- Primary outcome: NO DIFFERENCE in death due to bleeding at 5 days (3.7% vs. 3.8%, RR 0.99) in TXA and placebo group, respectively
    - Prespecified subgroups: time to treatment, location of bleeding, Rockall score all not significantly different between TXA and placebo

[1] Made by the clinician based on established criteria
[2] Measured by the Katz Index of Independence in Activities of Daily Living at either hospital discharge or in-hospital at 28 days

    - Non-prespecified subgroups: anticoagulant use, country income level, or systolic BP all not significantly different between TXA and placebo
- Secondary Outcomes
    - No difference in death from bleeding at 24 hours and 28 days
    - No difference in all-cause mortality at 28 days
    - Similar proportion of patients with rebleeding, surgery, radiological intervention, and blood product transfusion
    - No change in ICU duration or Katz score
- Complications
    - Higher rates of venous thromboembolic events [0.8% vs. 0.4%, OR 1.85 (1.15 to 2.98)] and seizures [(0.6% vs. 0.4%, OR 1.73 (1.03 to 2.93)] in TXA group
    - No composite total for complications provided

Limitations

- Clinical diagnosis of GI bleed and inclusion of wide spectrum of bleeds
- Potential for misclassification of location and type of bleed by study teams
- Patients without equipoise for TXA were excluded
- Change in primary outcome near end of trial
- Higher dose of TXA (4 g over 24 hours) and duration of infusion longer than those with trauma (2 g over 8 hours) and post-partum hemorrhage (1 g bolus with additional 1 g as needed)
- Unable to determine if VTE due to TXA

Take Home Points:

- **TXA without benefit in management of acute GI bleeds**
- **Is there a role for TEG to help guide TXA in cirrhotics with GI bleeds?**
- **All-cause mortality is a more important outcome. It is the same at 28 days, but not reported at 5 days. If the lives saved from bleeding are lost due to thrombosis and seizures, is this better?**
- **Stick with TXA for patients with known benefit and favorable side-effect profile (e.g. trauma, post-partum hemorrhage)**
- **We need to restrain ourselves from feeling like since we have a medicine we must give it**