

Article Appraisal

**Article:**  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

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**Background and Study Objective(s):**

Tranexamic acid (TXA) is an antifibrinolytic therapy that prevents conversion of plasminogen to plasmin. It is used as a treatment for surgical bleeding and bleeding associated with major trauma, epistaxis, and heavy menstruation. Many recent studies have investigated its use in trauma (CRASH 2), head injury (CRASH 3), post-partum haemorrhage (WOMAN), intracerebral haemorrhage (TICH-2), post-tonsillectomy, and more.

Acute gastrointestinal bleeds are a common presentation to the emergency department and associated with a mortality of up to 10%. A 2012 Cochrane systemic review and meta-analysis of 1654 patient showed a reduction in all-cause mortality with the use of tranexamic acid (risk ration 0.6, 95% CI 0.42-0.87).1 However, the studies included in this analysis had a high attrition rate, small sample sizes, and were at high risk of bias. Thus, the authors sought to quantify the effects of TXA on acute gastrointestinal bleeding.

**Study Design:**

This is an international, multi-centre, randomized, and placebo-controlled trial of 12,009 patients in 164 hospitals in fifteen countries. Over 2/3 of study participants were recruited from the United Kingdom and Pakistan. Inclusion criteria included adults (>16 or >18 years old depending on the age of majority in their country) who presented with significant gastrointestinal bleeding. Significant bleeding was defined as that which posed a risk of death (hypotension, tachycardia, signs of shock, requiring urgent transfusion, endoscopy or surgery). Patients were enrolled only if the responsible clinician was “substantially uncertain” if TXA would be appropriate for the particular patient. Exclusion criteria were not stated. Patients, caregivers, outcome assessors were blinded to allocation.

The primary outcome was death due to bleeding within 5 days of randomization. There were many secondary outcomes including rebleeding, surgery or radiology intervention, blood product transfusion, thromboembolic events, seizures, etc.

The intervention (TXA) group received 1g of TXA in 100mL of 0.9% normal saline slow IV over 10 minutes followed by a maintenance of 3g of TXA added to 1L of isotonic fluids and transfused over 24 hours. The placebo group received only normal saline. The study arms were otherwise treated the same.

**Results:**

The mean age of the patients was 58 and 65% of patients were male. The mean time of randomization was 22 hours. The baseline patient characteristics were similar between groups.

The primary outcome, death due to bleeding at 5 days following randomisation, occurred in 4.2% of patients who received TXA and 4.4% of patients who received placebo; this was not statistically significant (95% CI 0.82-1.15). There was no statistically significant difference between groups in death due to thromboembolic events, sepsis, organ failure, or all cause mortality at 24 hours or 28 days. Sub-group analysis demonstrated no difference between groups when stratified for time since onset of bleed, suspected bleeding location (upper or lower), variceal/liver bleed, and rockall score.

There was no difference in the secondary outcomes that looked at other therapeutic interventions (need for endoscopy, surgery, transfusion, etc). There was a statistically significant higher number of venous events (DVT, PE) and seizures in the TXA group (0.8% vs 0.4% and 0.6% vs 0.4%, respectively), although absolute numbers were very small and the study was not powered for this outcome.

**Validity of Results:**

This study addresses a clearly defined clinical question and mostly adhered to accepted methodologic principles. It was a large multi-national RCT and was appropriately powered. Intention-to-treat analysis was used. Very few of the patients randomized were lost to follow-up or excluded for other reasons.

Notably, the primary outcome was changed after >80% of study participants were recruited. The initial sample size calculation was based on the primary outcome of all cause mortality at 28 days following randomization. However, the authors realized over half of all deaths were due to non-bleeding causes (~57%), rather than an anticipated death due to bleeding rate of ~60%. Additionally, the authors considered data from two additional trials (CRASH-2 and WOMAN) that were not initially published at the time of initial study design. In articles published in 2018 and 2019, prior to the publication of the HALT-IT trial data and analysis, the authors argue that using all cause mortality as the primary outcome has low power, lacks generalizability, and can obscure harmful effects of the intervention.2,3 However, changing the primary outcome does bring into question the validity of the results. Regardless, there was no difference in mortality rates between groups regardless of the cause or timing of death.

Additionally, eligibility criteria included physician “substantial uncertainty” regarding the utility of TXA for the specific patient. This inclusion criteria is pragmatic. However, it alters the reproducibility of the study given the study results will alter physician judgement of the utility of TXA for future patients presenting with gastrointestinal bleeds.

**Generalizability of Results:**

This study has strong external validity. Overall, this trial addresses a clearly focused question which is relevant to the emergency department setting. A large number of patients were recruited from acute care settings. Although no specific Canadian epidemiology data was found, the baseline patient characteristics are generally similar to those who present with gastrointestinal bleeds to British Columbia emergency departments. Baseline characteristics of patients studied were similar between groups; most (~89%) of bleeding were characterized as upper GI bleeds, ~45% of bleeding was suspected variceal, and ~8-9% of patients were taking oral anticoagulants. The large number of secondary outcomes for which data was collected are clinically important (i.e. need for endoscopy, transfusion, surgical intervention, etc).

**The Bottom Line:**

The ‘HALT-IT trial’ is a large, multi-centre, randomized, placebo controlled trial which demonstrated no benefit from tranexamic acid in GI bleeds. The results are especially significant given a previously published meta-analysis that suggested that TXA may have a positive effect on all-cause mortality. Although the study authors change the primary outcome part-way through recruitment, the results were neutral regardless of cause of mortality. The study has good external validity. Overall, the results suggest that TXA does not have a benefit in GI bleeds and should not be used specifically for this indication.

**References:**

1. Gluud LL, Klingenberg SL, Langholz E. Tranexamic acid for upper gastrointestinal bleeding. Cochrane Database Syst Rev 2012; **1:** CD006640. https://doi.org/10.1002/14651858.CD006640.pub3
2. Brenner, A., Arribas, M., Cuzick, J. *et al.* Outcome measures in clinical trials of treatments for acute severe haemorrhage. *Trials* **19,**533 (2018). https://doi.org/10.1186/s13063-018-2900-4
3. Brenner A, Afolabi A, Ahmad SM, et al. Tranexamic acid for acute gastrointestinal bleeding (the HALT-IT trial): statistical analysis plan for an international, randomised, double-blind, placebo-controlled trial. *Trials* 2019; **20:** 467