Canadian Journal of Emergency Medicine (2021) 23:164–165
https://doi.org/10.1007/s43678-020-00053-z

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Does tranexamic acid reduce 5-day death due to bleeding in acute gastrointestinal bleed?

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Received: 16 October 2020 / Accepted: 24 November 2020 / Published online: 4 January 2021

Full Citation: Roberts, Ian, 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 395.10241 (2020): 1927–1936.

Abstract Link: https://www.sciencedirect.com/science/article/pii/S0140673620308485

Article Type: randomized, double-blind, placebo-controlled study

Ratings: *Methods—4/5, Usefulness—4.5/5*

Introduction

Background

As an antifibrinolytic agent, tranexamic acid (TXA) has been used in trauma, intracranial and post-partum hemorrhage; however, a large RCT was lacking to support its use in gastrointestinal bleeding (GIB).

Objectives

To determine if TXA reduces 5-day death due to bleeding in acute GIB compared to placebo.

Methods

Design

International, multicenter, randomized placebo control trial.

Eligibility criteria

Adult patients > 16 years old with acute GIB, and clinical uncertainty surrounding TXA use.

Intervention

TXA 1 g IV over 10 min, followed by 3 g infused over 24 h.

Control

Placebo.

Outcomes

Primary outcome: Death at 5-days due to bleeding. Subgroup analysis included onset time, bleed location, variceal bleeding and Rockall score. Secondary outcomes: death due to bleeding within 24 h and 28 days of randomization, all-cause mortality, rebleeding rates, rates of surgery/radiologic intervention, transfusion need, arterial/venous thromboembolic events, seizure, systemic complications, days in ICU, and functional status.

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Main results

164 hospitals in 15 countries were included in the trial, with a total of 12,009 patients. There was no significant difference in death due to bleeding within 5 days of randomization, with 3.7% in the TXA group and 3.8% in the placebo group (RR 0.99, [95% CI: 0.82–1.18]). There were no differences in any of the subgroup analyses for the primary outcome (onset time, bleed location, variceal bleeding, or Rockall score).

There were no statistically significant differences in the secondary outcomes of death due to bleeding within 24 h (TXA 2.1% vs. placebo 2.0%, RR 1.04 [95% CI 0.81–1.33]), need for surgical, endoscopic, or radiologic intervention (87.6% vs. 87.5%, RR 1.00 [95% CI 0.99–1.01]), or need for transfusion (68.5% vs. 69.1%, RR 0.99 [95% CI 0.97–1.02]). A significantly increased risk of venous thromboembolic (VTE) events were observed in the TXA group compared to placebo, (0.8% vs 0.4%, RR 1.85 [95% CI 1.15–2.98]).

Appraisal

Strengths

- Largest randomized controlled clinical trial interrogating TXA in GIB
- Execution of blinded randomization and robust endpoint evaluation
- Included high, medium, and low-income countries to enhance generalizability [1]
- Included a variety of GIB presentations
- Only 3 patients lost to follow-up out of 12,009 patients

Limitations

- Primary outcome changed during the trial. The initial primary outcome, all-cause mortality, was patient-centred and objective. The new primary outcome, death due to bleeding, measured disease specific mortality, which may be fraught with bias, inaccuracy and subjectivity.
- Sample size calculation adjusted mid-trial to power for death due to bleeding within 5 days compared to all-cause mortality as > 50% of deaths were not related to bleeding.
- Majority of patients had variceal bleeding; categorized as the most severe type of GIB, which may not be generalizable across other centres, demographics and patient populations
- First study to show an increased rate of VTE as a consequence of TXA, however these were only in patients with concomitant liver disease.

Context

Unlike the findings of 'HALT-IT, previous evidence for the use of TXA in GIB was based on a systematic review demonstrating a reduction in all-cause mortality [2]. Compared to other clinical presentations which benefit from the use of TXA (ex. trauma and post-partum hemorrhage [1]), determining the time of onset of a GIB may be difficult, and the window of potential treatment benefit may be missed. This is the first study to find a statistically significant increased risk of VTE with the use of TXA [3], which may be explored in future research. Local Gastroenterology experts support the primary findings of this study, with current practice not routinely utilizing TXA for UGIB.

Bottom line

HALT-IT is a high quality randomized controlled trial that showed no significant benefit from TXA in GIB, either for the primary or important secondary endpoints. Rather, a small increased risk of venous thromboembolism was observed. TXA should not be routinely used for GIB.

References

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