A high-dose 24-hour tranexamic acid infusion for the treatment of significant gastrointestinal bleeding: HALT-IT RCT

Ian Roberts,[1*] Haleema Shakur-Still,[1] Adefemi Afolabi,[2] Adegboyega Akere,[3] Monica Arribas,[1] Emma Austin,[1] Kiran Bal,[1] Nuha Bazeer,[4,5] Danielle Beaumont,[1] Amy Brenner,[1] Laura Carrington,[1] Rizwana Chaudhri,[6] Timothy Coats,[7] Ian Gilmore,[8] Kenneth Halligan,[9] Irshad Hussain,[10] Vipul Jairath,[11] Kiran Javaid,[12] Aasia Kayani,[12] Ton Lisman,[13] Raoul Mansukhani,[1] Alec Miners,[14] Muttiullah Mutti,[15] Muhammad Arif Nadeem,[16] Richard Pollok,[17] Danielle Prowse,[1] Jonathan Simmons,[18] Simon Stanworth,[19,20,21] Andrew Veitch[22] and Jack Williams[14]

[1]Clinical Trials Unit, London School of Hygiene & Tropical Medicine, London, UK
[2]Department of Surgery, University College Hospital Ibadan, Ibadan, Nigeria
[3]Department of Medicine, University College Hospital Ibadan, Ibadan, Nigeria
[4]Department of Health Services Research and Policy, London School of Hygiene & Tropical Medicine, London, UK
[5]Department of Health Policy, London School of Economics and Political Science, London, UK
[6]Department of Obstetrics and Gynaecology, Rawalpindi Medical University, Rawalpindi, Pakistan
[7]Emergency Department, Leicester Royal Infirmary, Leicester, UK
[8]Liverpool Centre for Alcohol Research, University of Liverpool, Liverpool, UK
[9]Patient representative, UK
[10]Department of Medicine, King Edward Medical University, Mayo Hospital, Lahore, Pakistan
[11]Division of Gastroenterology, Western University and London Health Sciences Centre, London, ON, Canada
[12]Rawalpindi Medical University – Pakistan National Coordinating Centre (RMU-PNCC), Rawalpindi, Pakistan
[13]Department of Surgery, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands

[14]Department of Health Services Research and Policy, London School of Hygiene & Tropical Medicine, London, UK
[15]Department of Medicine, Rawalpindi Medical University, Rawalpindi, Pakistan
[16]Medical Unit III, Services Institute of Medical Sciences, Services Hospital Gastrointestinal, Lahore, Pakistan
[17]Gastroenterology and Hepatology Department, St George's Hospital, London, UK
[18]Gastroenterology Department, Royal Berkshire Hospital, Reading, UK
[19]Transfusion Medicine, NHS Blood and Transplant (NHSBT), John Radcliffe Hospital, Oxford, UK
[20]Department of Haematology, Oxford University Hospitals NHS Foundation Trust, Churchill Hospital, Oxford, UK
[21]Radcliffe Department of Medicine, University of Oxford, John Radcliffe Hospital, Oxford, UK
[22]Gastroenterology Department, New Cross Hospital, Wolverhampton, UK

*Corresponding author Ian.Roberts@lshtm.ac.uk

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Scientific summary

HALT-IT RCT

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Scientific summary

Background

Tranexamic acid reduces blood loss in surgery and death in trauma patients. Meta-analyses of small trials show that tranexamic acid may decrease the number of deaths from gastrointestinal bleeding. However, meta-analyses of small trials are prone to selection bias and have a low positive predictive value compared with results from large trials.

Objectives

We assessed the effects of tranexamic acid on the occurence of death, rebleeding and complications in acute gastrointestinal bleeding.

Methods

In an international, multicentre, randomised, placebo-controlled trial, adults with significant upper or lower gastrointestinal bleeding were randomly assigned to receive tranexamic acid (1-g loading dose followed by a 3-g maintenance dose over 24 hours) or a matching placebo. Patients were assigned by selecting a numbered treatment pack from a box containing eight packs that were identical apart from the pack number. Patients, caregivers and those assessing outcomes were masked to allocation. The primary outcome was death due to bleeding within 5 days of randomisation. Secondary outcomes were cause-specific and all-cause mortality; rebleeding; surgical or radiological intervention; blood transfusion; thromboembolic events (deep-vein thrombosis, pulmonary embolism, stroke, myocardial infarction); seizures; and other complications.

Results

Between July 2013 and June 2019, we randomly allocated 12,009 patients from 164 hospitals in 15 countries to receive tranexamic acid ($n = 5994$; 49.9%) or matching placebo ($n = 6015$; 50.1%), of whom 11,952 (99.5%) received the first dose of the allocated treatment.

Primary outcome

Death due to bleeding within 5 days of randomisation occurred in 222 out of 5956 patients (4%) in the tranexamic acid group and in 226 out of 5981 patients (4%) in the placebo group (risk ratio 0.99, 95% confidence interval 0.82 to 1.18).

Secondary outcomes

Fatal or non-fatal thromboembolic events occurred in 86 (1.4%) patients in the tranexamic acid group and 72 (1.2%) patients in the placebo group (risk ratio 1.20, 95% confidence interval 0.88 to 1.64). The risk of arterial thromboembolic events (myocardial infarction or stroke) was similar in tranexamic acid- and placebo-treated patients (0.7% vs. 0.8%; risk ratio 0.92, 95% confidence interval 0.60 to 1.39), but the risk of venous thromboembolic events (deep-vein thrombosis or pulmonary embolism) was

higher in tranexamic acid-treated patients than in placebo-treated patients (0.8% vs. 0.4%; risk ratio 1.85, 95% confidence interval 1.15 to 2.98). Seizures occurred in 38 patients who received tranexamic acid and in 22 patients who received placebo (0.6% vs. 0.4%; risk ratio 1.73, 95% confidence interval 1.03 to 2.93).

The effect of tranexamic acid on death due to bleeding within 5 days of randomisation did not appear to vary when stratified by country income, anticoagulant use or systolic blood pressure in an analysis that was not prespecified.

Death due to bleeding within 24 hours of randomisation occurred in 124 (2.1%) patients in the tranexamic acid group and in 120 (2.0%) patients in the placebo group (risk ratio 1.04, 95% confidence interval 0.81 to 1.33). Death due to bleeding within 28 days of randomisation occurred in 253 (4.2%) patients in the tranexamic acid group and in 262 (4.4%) patients in the placebo group (risk ratio 0.97, 95% confidence interval 0.82 to 1.15). Death from all causes within 28 days of randomisation occurred in 564 patients (9.5%) in the tranexamic acid group and in 548 patients (9.2%) in the placebo group (risk ratio 1.03, 95% confidence interval 0.92 to 1.16).

The proportion of patients with rebleeding was similar in both groups at 24 hours, 5 days and 28 days after randomisation.

The proportion of patients who had surgery, radiological intervention and blood product transfusion was also similar in both groups.

The results from the economic analysis suggest that the costs and outcomes of treating people with acute gastrointestinal bleeding with and without tranexamic acid are very similar, with no tranexamic acid being more likely to be the most cost-effective option.

Conclusion

In this trial, tranexamic acid did not reduce death from gastrointestinal bleeding but was associated with an increased risk of venous thromboembolic events and seizures. Therefore, although it is inexpensive, tranexamic acid does not represent value for money in adults with acute gastrointestinal bleeding.

Implications for practice

Many emergency physicians and surgeons believe that tranexamic acid improves outcomes in patients with acute severe gastrointestinal bleeding. The promotion of 'major haemorrhage protocols' in UK hospitals encourages the notion that all bleeding is fundamentally the same and can be treated in a similar way. Furthermore, the Cochrane systematic review and meta-analysis of previous trials of tranexamic acid in gastrointestinal bleeding shows a large reduction in mortality with tranexamic acid (pooled risk ratio 0.61, 95% confidence interval 0.42 to 0.89; $p = 0.01$) (Gluud LL, Klingenberg SL, Langholz E. Tranexamic acid for upper gastrointestinal bleeding. *Cochrane Database Syst Rev* 2012;**1**:CD006640).

The results from the HALT-IT (Haemorrhage ALleviation with Tranexamic acid – Intestinal system) trial caution against a 'one size fits all' approach to the management of patients with major haemorrhage, and highlight the need for randomised trials targeted at specific pathophysiological processes. Based on the HALT-IT trial results, tranexamic acid should not be used for the treatment of gastrointestinal bleeding outside the context of a randomised trial.

Because gastrointestinal bleeding is a licensed indication for tranexamic acid, our results could have regulatory implications.

Recommendations for future research

Although we cannot rule out a modest increase or decrease in death due to bleeding with tranexamic acid, we can rule out the large mortality reduction suggested by the Cochrane systematic review and meta-analysis of previous small trials (Gluud, *et al.* 2012). In this respect, the HALT-IT trial highlights the dangers of overinterpreting results from systematic reviews of small trials.

The large discrepancy between the results of the Cochrane review (Gluud, *et al.* 2012) and the results of the HALT-IT trial should encourage a reconsideration of the role of systematic reviews of small trials in informing health care and health research. In most cases, the results of such reviews should be considered hypothesis generating, requiring confirmation in adequately powered randomised trials.

Because tranexamic acid reduces bleeding deaths in patients with traumatic and post-partum haemorrhage, individual patient data meta-analyses should assess the strength of the evidence that the effectiveness and safety of tranexamic acid varies by the site and cause of bleeding. Basic research could also inform this question by examining the role of fibrinolysis in patients with gastrointestinal bleeding and whether or not this varies depending on the aetiology of the bleeding.

A large proportion of patients in this trial had liver disease (40%), so future research could also assess the effect of tranexamic acid on bleeding from peptic ulcers in patients without liver disease.

Trial registration

This trial is registered as ISRCTN11225767, ClinicalTrials.gov NCT01658124 and EudraCT 2012-003192-19.

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