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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Summary

Background Tranexamic acid reduces surgical bleeding and reduces death due to bleeding in patients with trauma. Meta-analyses of small trials show that tranexamic acid might decrease deaths from gastrointestinal bleeding. We aimed to assess the effects of tranexamic acid in patients with gastrointestinal bleeding.

Methods We did an international, multicentre, randomised, placebo-controlled trial in 164 hospitals in 15 countries. Patients were enrolled if the responsible clinician was uncertain whether to use tranexamic acid, were aged above the minimum age considered an adult in their country (either aged 16 years and older or aged 18 years and older), and had significant (defined as at risk of bleeding to death) upper or lower gastrointestinal bleeding. Patients were randomly assigned by selection of a numbered treatment pack from a box containing eight packs that were identical apart from the pack number. Patients received either a loading dose of 1 g tranexamic acid, which was added to 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, or placebo (sodium chloride 0·9%). Patients, caregivers, and those assessing outcomes were masked to allocation. The primary outcome was death due to bleeding within 5 days of randomisation; analysis excluded patients who received neither dose of the allocated treatment and those for whom outcome data on death were unavailable. This trial was registered with Current Controlled Trials, ISRCTN11225767, and ClinicalTrials.gov, NCT01658124.

Findings Between July 4, 2013, and June 21, 2019, we randomly allocated 12 009 patients to receive tranexamic acid (5994, 49·9%) or matching placebo (6015, 50·1%), of whom 11 952 (99·5%) received the first dose of the allocated treatment. Death due to bleeding within 5 days of randomisation occurred in 222 (4%) of 5956 patients in the tranexamic acid group and in 226 (4%) of 5981 patients in the placebo group (risk ratio [RR] 0·99, 95% CI 0·82–1·18). Arterial thromboembolic events (myocardial infarction or stroke) were similar in the tranexamic acid group and placebo group (42 [0·7%] of 5952 *v* 46 [0·8%] of 5977; 0·92; 0·60 to 1·39). Venous thromboembolic events (deep vein thrombosis or pulmonary embolism) were higher in tranexamic acid group than in the placebo group (48 [0·8%] of 5952 *v* 26 [0·4%] of 5977; RR 1·85; 95% CI 1·15 to 2·98).

Interpretation We found that tranexamic acid did not reduce death from gastrointestinal bleeding. On the basis of our results, tranexamic acid should not be used for the treatment of gastrointestinal bleeding outside the context of a randomised trial.

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Introduction

Acute severe gastrointestinal bleeding is a common cause of death worldwide.[1] Bleeding can occur from the upper or lower gastrointestinal tract, but upper gastrointestinal bleeding is more common. The leading causes are peptic ulcer, oesophageal varices, and malignancy. The case fatality rate is approximately 10% for upper gastrointestinal bleeding and 3% for lower gastrointestinal bleeding.[2,3] Many patients re-bleed after initial haemostasis and those that do have a four-times increased risk of death.[4] Patients with acute severe gastrointestinal bleeding usually present with haematemesis or melaena. Patients are often haemodynamically unstable and in need of urgent resuscitation. Acute management of gastrointestinal bleeding includes blood product transfusion, medical or endoscopic therapy, and surgery.

Tranexamic acid reduces bleeding by inhibiting blood clot breakdown (fibrinolysis). Tranexamic acid decreases surgical bleeding and reduces death due to bleeding in patients with traumatic and postpartum haemorrhage.[5–8] A systematic review and meta-analysis of randomised trials of tranexamic acid for upper gastrointestinal bleeding included seven trials with a total of 1654 patients.[9] There was a large reduction in all-cause mortality with tranexamic

Research in context

Evidence before this study

Before this study a Cochrane systematic review and meta-analysis of randomised trials of tranexamic acid for upper gastrointestinal bleeding included seven trials with a total of 1654 patients. There was a large reduction in mortality with tranexamic acid (pooled risk ratio [RR] 0·61, 95% CI 0·42–0·89; p=0·01). However, given the small size of the included trials and the potential for selection and other biases, we considered this evidence to be hypothesis generating, requiring confirmation in larger trials. Furthermore, there was substantial uncertainty about the risk of thromboembolic events with tranexamic acid (pooled RR 1·86, 95% CI 0·66–5·24).

Added value of this study

The HALT-IT trial included 12 009 patients from 164 hospitals in 15 countries. Adult patients with significant upper or lower gastrointestinal bleeding were randomly assigned to receive tranexamic acid (1 g loading dose followed by 3 g maintenance dose over 24 h) or matching placebo. Tranexamic acid did not reduce death from gastrointestinal bleeding (RR 0·99, 95% CI 0·82–1·18) but was associated with an increased risk of venous thromboembolic events (1·85, 1·15–2·98) and seizures (1·73, 1·03–2·93).

Implications of all the available evidence

The most recent update of the Cochrane review included eight small randomised trials with 1701 participants and showed a reduction in mortality with tranexamic acid (RR 0·60, 95% CI 0·42–0·87). Although we cannot entirely 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 review. Furthermore, tranexamic acid appears to increase the risk of venous thromboembolic events in patients with gastrointestinal bleeding. On the basis of our results, tranexamic acid should not be used for the treatment of gastrointestinal bleeding outside the context of a randomised trial. Our results highlight the unreliability of meta-analyses of small trials.

acid (risk ratio [RR] 0·61, 95% CI 0·42–0·89; p=0·01). However, meta-analyses of small trials are prone to publication and other selection biases, and have a low positive predictive value when compared with results from large multicentre trials.[10] Furthermore, even in aggregate, the trials included in the meta-analysis were too small to assess the effect of tranexamic acid on thromboembolic adverse events.[9] Our objective was to quantify the effects of tranexamic acid on death and thromboembolic events in acute gastrointestinal bleeding.

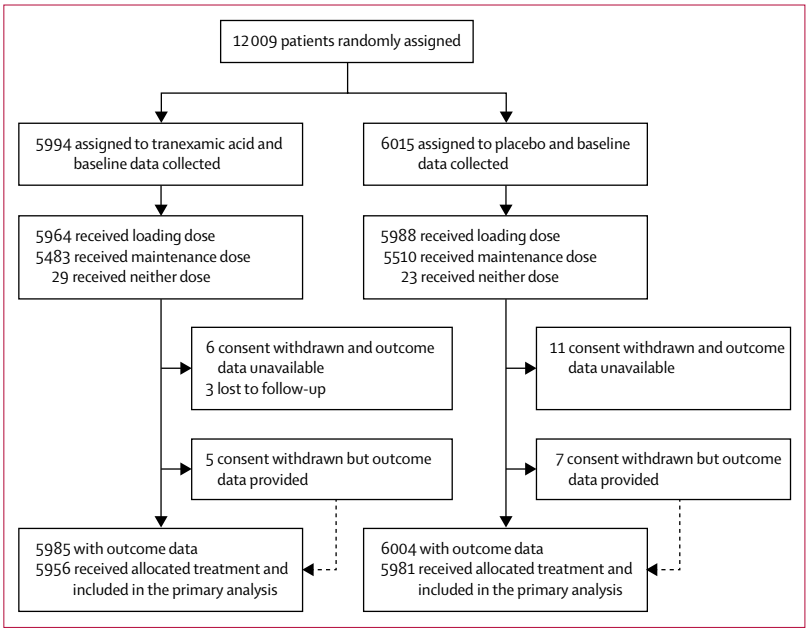

Figure 1: **Trial profile**

Methods

Study design and participants

The HALT-IT trial is an international, randomised, double blind (participants and trial staff), placebo-controlled trial done in 164 hospitals in 15 countries (UK, Pakistan, Nigeria, Egypt, Malaysia, Georgia, Romania, Nepal, Sudan, Saudi Arabia, Spain, Ireland, Albania, Papua New Guinea, and Australia).[11] Patients were enrolled if they were aged above the minimum age considered an adult in their country (either aged 16 years and older or aged 18 years and older) and if the responsible clinician was substantially uncertain whether to use tranexamic acid. The diagnosis of significant bleeding was clinical and significant was defined as a 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.

Severe gastrointestinal bleeding is a frightening experience and blood loss can impact on a patient's mental and emotional state, impairing their decision making—the consent procedures considered this, as well as the need to treat urgently. If the patient was fully competent, written consent was sought. If capacity was impaired and a personal or professional representative was available, consent was sought from the representative. If neither were able to provide consent, it was waived and the patient was informed about the trial and consented for ongoing data collection as soon as possible afterwards. The trial was approved by the UK NRES Committee East of England (reference number 12/EE/0038), and by the national and local research ethics committees in all participating non-UK countries.

	Tranexamic acid (n=5994)	Placebo (n=6015)
Age at randomisation, years		
Mean (SD)	58·1 (17·0)	58·1 (17·0)
<40	791 (13%)	779 (13%)
40–59	2356 (39%)	2333 (39%)
60–79	2078 (35%)	2130 (35%)
≥80	769 (13%)	773 (13%)
Sex		
Female	2142 (36%)	2124 (35%)
Male	3852 (64%)	3891 (65%)
Time from onset to randomisation, h		
Mean (SD)	21·4 (36·4)	22·5 (37·8)
≤3	960 (16%)	975 (16%)
>3–≤8	1607 (27%)	1551 (26%)
>8	3427 (57%)	3488 (58%)
Missing	0	1 (<1%)
Suspected location of bleeding		
Lower	674 (11%)	654 (11%)
Upper	5320 (89%)	5361 (89%)
Haematemesis		
Yes	4285 (72%)	4240 (71%)
No	1709 (29%)	1775 (30%)
Melaena or fresh blood per rectum		
Yes	4573 (76%)	4626 (77%)
No	1421 (24%)	1389 (23%)
Suspected variceal bleeding		
Yes	2694 (45%)	2739 (46%)
No	3300 (55%)	3276 (54%)
Suspected active bleeding		
Yes	5247 (88%)	5226 (87%)
No	747 (12%)	789 (13%)
Systolic blood pressure, mm Hg		
≥90	5222 (87%)	5216 (87%)
76–89	577 (10%)	577 (10%)
≤75	181 (3%)	201 (3%)
Missing	14 (<1%)	21 (<1%)
(Table 1 continues in next column)		

	Tranexamic acid (n=5994)	Placebo (n=6015)
(Continued from previous column)		
Heart rate, beats per min		
<77	812 (14%)	756 (13%)
77–91	1546 (26%)	1644 (27%)
92–107	1760 (29%)	1720 (29%)
>107	1864 (31%)	1885 (31%)
Missing	12 (<1%)	10 (<1%)
Signs of shock		
Yes	2574 (43%)	2648 (44%)
No	3420 (57%)	3367 (56%)
Rockall score		
1–2	1419 (24%)	1395 (23%)
3–4	2306 (38%)	2332 (39%)
5–7	2269 (38%)	2288 (38%)
Taking anticoagulants		
Yes	528 (9%)	500 (8%)
No	5422 (90%)	5466 (91%)
Unknown	44 (1%)	49 (1%)
Emergency admission		
Yes	5673 (95%)	5687 (94%)
No	321 (5%)	328 (6%)
Major comorbidities		
Cardiovascular	1108 (18%)	1132 (19%)
Respiratory	337 (6%)	324 (5%)
Liver	2432 (41%)	2532 (42%)
Renal	325 (5%)	310 (5%)
Malignancy	417 (7%)	382 (6%)
Other	999 (17%)	968 (16%)
Any comorbidity	4308 (72%)	4329 (72%)

Data are n (%) or mean (SD).

Table 1: **Baseline characteristics**

Randomisation and masking

An independent statistician from Sealed Envelope (London, UK) generated randomisation numbers and these were given to Sharp Clinical Services UK (Crickhowell, UK), a Good Manufacturing Practice certified clinical trial service provider, to make treatment packs. When a patient was enrolled, the lowest numbered treatment pack was taken from a box of eight packs. Sharp Clinical Services was responsible for masking, which involved removing the manufacturer's label and replacing it with the clinical trial label and randomisation number. Apart from the randomisation number, the pack label text was identical for tranexamic acid and placebo. Patients, caregivers, and those assessing outcomes were masked to allocation. We checked the coding by testing each batch of ampoules with high-performance liquid chromatography to determine the contents. Block randomisation was used but randomisation was not stratified.

Procedures

Eligible patients were randomly assigned to get tranexamic acid or placebo as soon as possible and treatment was started immediately. A loading dose of 1 g tranexamic acid or placebo (sodium chloride 0·9%) 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 or placebo added to 1 L of any isotonic intravenous solution and infused at 125 mg/h for 24 h. Every patient was assigned a uniquely numbered treatment pack, which contained eight ampoules of tranexamic acid 500 mg or placebo, one 100 mL bag of 0·9% sodium chloride (to use with the loading dose), two sterile 10 mL syringes and needles, stickers with the trial details and randomisation number (for attaching to infusion bags, forms, and the medical records), and instructions. Pfizer, Sandwich, UK (PL 00057/0952) manufactured the tranexamic acid

and Torbay and South Devon NHS Foundation Trust (MIA [IMP] 13079) manufactured the sodium chloride 0·9% placebo. We provided information for patients and representatives, consent forms, and data collection forms. Stickers, instructions, leaflets, and forms were in local languages.

Once randomly assigned, we collected outcome data even if the treatment was not given. Outcome data were collected at death, discharge from the randomising hospital, or 28 days after randomisation, whichever occurred first. Trial investigators and their institutions provided direct access to the source data for trial-related monitoring, audits, and regulatory inspections. Monitoring was done according to the Sponsor's Standard Operating Procedure and the trial protocol. Formal inspections were carried out by the relevant Regulatory Agencies including the UK Medicines and Healthcare products Regulatory Agency, Irish Health Products Regulatory Authority, and Nigeria's National Agency for Food and Drug Administration and Control. Adherence to allocation sequence was monitored throughout the trial and any out of sequence pack use was automatically flagged in the trial database and the investigators were retrained.

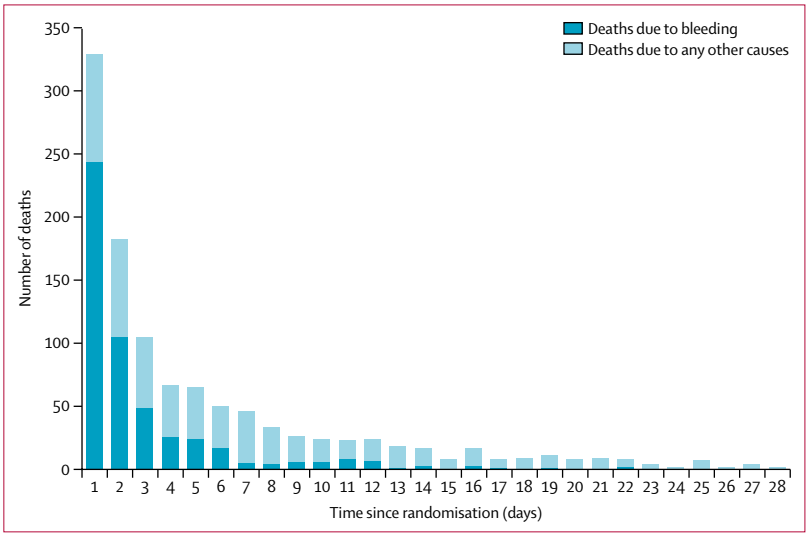

Figure 2: **Mortality by days from randomisation**

	Tranexamic acid (n=5956)	Placebo (n=5981)	Risk ratio (95% CI)
Death due to bleeding within 24 h	124 (2·1%)	120 (2·0%)	1·04 (0·81–1·33)
Death due to bleeding within 5 days	222 (3·7%)	226 (3·8%)	0·99 (0·82–1·18)
Death due to bleeding within 28 days	253 (4·2%)	262 (4·4%)	0·97 (0·82–1·15)
Rebleeding within 24 h*	41 (0·7%)	41 (0·7%)	1·00 (0·65–1·55)
Rebleeding within 5 days*	287 (4·8%)	315 (5·3%)	0·91 (0·78–1·07)
Rebleeding within 28 days*	410 (6·8%)	448 (7·5%)	0·92 (0·81–1·05)

Data are n (%) and risk ratio (95% CI). Death or rebleeding in hospital during follow-up. *Excludes 13 patients missing data on rebleed status or rebleed date.

Table 2: **Effect of tranexamic acid on death due to bleeding and rebleeding**

Outcomes

The primary outcome was death due to bleeding within 5 days of randomisation. Cause of death was assigned by local principal investigators who provided a narrative of events leading to death. These were reviewed by the chief investigator (masked to treatment allocation) and queried if more information was needed to confirm whether death was due to bleeding or another cause. Secondary outcomes were death due to bleeding within 24 h and within 28 days of randomisation, all-cause and cause-specific mortality at 28 days, rebleeding within 24 h, within 5 days, and within 28 days of randomisation, surgery or radiological intervention, blood product transfusion, thromboembolic events (deep vein thrombosis, pulmonary embolism, stroke, and myocardial infarction), seizures, other complications (including other significant cardiac event, sepsis, pneumonia, respiratory failure, renal failure, liver failure), days in an intensive care unit, and functional status. The diagnosis of rebleeding was made by the clinician based on established criteria. A diagnosis of thromboembolic events was made using strict definitions and diagnostic criteria, including a clinical assessment, diagnostic imaging, biomarker tests, and post-mortem examination. Seizures were diagnosed by clinical assessment. Functional status was measured with the Katz Index of Independence in Activities of Daily Living either at hospital discharge or in-hospital at 28 days.

Statistical analysis

The sample size calculation was initially based on all-cause mortality as the primary outcome since we expected that most deaths would be due to bleeding.[11] However, while the trial was underway, we observed that over half of all deaths were due to non-bleeding causes. Accumulating evidence from other large trials of tranexamic acid showed no apparent effect on non-bleeding deaths.[12] Furthermore, patients received tranexamic acid (or placebo) only for their initial bleed and because tranexamic acid has a short half-life (approximately 2 h), it will be largely eliminated within 2 days. As such, we did not expect tranexamic acid to reduce deaths from rebleeding episodes many weeks after randomisation. The primary outcome was therefore changed to death due to bleeding within 5 days of randomisation on Nov 21, 2018. Based on the amended primary outcome, assuming a risk of death due to bleeding of 4%, a study with 12 000 patients has about 85% power (two-sided α of 5%) to detect a clinically important 25% relative reduction in death due to bleeding from 4% to 3%.

We published the statistical analysis plan before unblinding.[13] The plan gave our reasons for amending the primary outcome measure and for increasing the sample size. The main analyses compared those allocated tranexamic acid with those allocated to placebo