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 *vs* 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 *vs* 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.

Funding UK National Institute for Health Research Health Technology Assessment Programme.

Lancet 2020; 395: 1927–36

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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

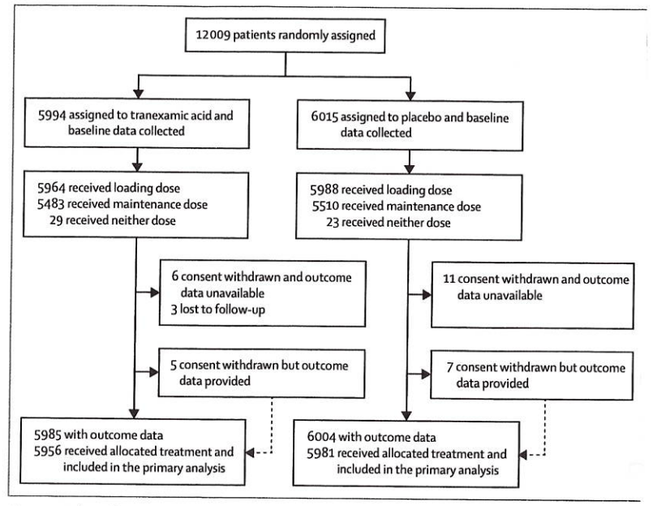

Figure 1: Trial profile

	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