Effects of a high-dose 24-h infusion of tranexamic acid on death and thromboembolic events in patients with acute randomised, double-blind, placebo-controlled trial

TheHALT-ITCollaborators*  

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 identified International Multicentre Randomised Placebo-controlled Trials in 164 hospitals in 35 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 for England and Japan, 18 years and older in France, and if not identified as a patient in the emergency department), and had significant defined gastrointestinal bleeding (loose stools). Upper or lower gastrointestinal bleeding. Patients were randomly assigned by selection of numbered treatment packs from a box, containing eight packs that were identical apart from the code number. Patients received either in a loading dose of 12 g of tranexamic acid, which was added to 100 mL of infusate (solution, 9% sodium chloride and in some cases 10% dextrose, slow intravenous injection over 10 min). Followed by 14 maintenance dose was 8 g of tranexamic acid added to 250 mL of a 3% saline solution and infused at 24 h, control placebo, or sodium chloride 9%. Patients, caregivers, and those assessing outcomes were masked to the allocation. The primary outcome was either death due to bleeding within 5 days of randomisation; analysis was excluded patients who received the other dose of the allocated treatment and those for whom outcome data were not available. This trial was registered with Current Controlled Trials, ISRCTN12257677, and Clinical Trials.gov, NCT01658124.

Findings Between July 3, 2013, and June 21, 2017, we randomly allocated 2,009 patients to receive tranexamic acid (594; 29.5%) or matching placebo (580; 29.5%). Of whom 1,052 (52.0%) were the first dose, the allocated treatment. Death due to bleeding within 5 days of randomisation occurred in 222 (4%; 95% CI 1956) patients in the tranexamic acid group and 272 (6%; 95% CI 2098) in the placebo group (risk ratio 0.99; 95% CI 0.82-1.18). Arterial thromboembolic events (myocardial infarction or stroke) occurred in Similar numbers in the tranexamic acid group and the placebo group (42; 0.7%; 95% CI 0.3-0.8% vs 77; 0.9%; 95% CI 0.6-2.0%); 39 venous thromboembolic events (deep vein thrombosis or pulmonary embolism) occurred in Similar numbers in the two groups (18; 0.8%; 95% CI 0.41-0.8% vs 30; 0.7%; 95% CI 0.49-0.98).

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. Bleeding can occur from the upper or lower gastrointestinal tract, but upper gastrointestinal bleeding is more common. The leading causes are peptic ulcer, esophageal varices, and malignancy. The case fatality rate of approximately 30% for upper gastrointestinal bleeding and 3% for lower gastrointestinal bleeding. Many patients are blooded and initial haemostasis and those who lose have it four-times increased risk of death. These patients with acute severe gastrointestinal bleeding are usually present with haematemesis or melena. Patients are often haemodynamically unstable and in need of urgent resuscitation. Acute management of gastrointestinal bleeding includes blood products transfusion, medical and endoscopic therapy, and surgery. Tranexamic Acid reduces gastrointestinal bleeding by inhibiting blood clot breakdown (thrombolysis). Tranexamic Acid decreases surgical bleeding and decreases death due to bleeding in patients with traumatic and postpartum haemorrhage. A systematic review and meta-analysis of randomised trials of tranexamic Acid for upper gastrointestinal bleeding included seven trials with a total of 1,654 patients. These was a larger reduction in all-cause mortality with tranexamic Acid.

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Evidence before this study

Before this study, a Cochrane systematic review and meta-analysis of randomised trials of tranexamic acid (low or upper gastrointestinal bleeding included) showed that 1654 patients with a large reduction in mortality with tranexamic acid pooled trial 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 66.5–24).

Added value of this study

The HALT-IT trial included 2109 patients from 164 hospitals in 31 countries. Adult patients with significant upper or lower gastrointestinal bleeding were randomly assigned to receive tranexamic acid (1 g loading dose followed by 1 g maintenance dose/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 (2.73, 1.03–2.93).

Implications of all the available evidence

The latest update of the Cochrane review included eight small randomised trials with 3701 participants and showed no reduction in mortality with tranexamic acid (RR 0.60, 95% CI 0.42–0.87). Although we cannot entirely rule out a modest increase in death due to bleeding with tranexamic acid, we can rule out a large reduction in mortality. Reduction suggested by the Cochrane review. Furthermore, tranexamic acid appeared to increase the risk of venous thromboembolic events in patients with gastrointestinal bleeding. On the basis of the results, tranexamic acid should not be used for the treatment of gastrointestinal bleeding outside the context of randomised trials. Our results highlight the unreliability of meta-analyses in small trials.

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 31 countries (UK, US, Pakistan, Philippines, Egypt, Malaysia, Germany, Switzerland, Korea, China, Japan, Sri Lanka, Italy, Germany, Belgium, Greece, China, Mexico, Denmark, Canada, the Netherlands, Norway, Turkey, Portugal, Belgium, and Denmark). Patients were enrolled if they were 50 years of age or older, had a minimum age consideration of 16 years, and were in their country of residence. Patients who had received previous treatment with tranexamic acid, had a known or suspected bleeding disorder, or had a severe acute gastrointestinal bleeding were excluded.

Severe gastrointestinal bleeding is defined as a frightening experience and blood loss that impairs patients' mental and emotional state, impairing their decision making—the consensus procedures considered this as well as the need for transfusion urgently. Of the patients who were fully competent, 42% were consented. The consent rate was 48% (20% of patients who were fully consented were included in the study. The trial was approved by the UK National Research Ethics Committee East, the National Research Ethics Committee London, and the National Research Ethics Committee South East.

The trial was carried out in accordance with the Local Ethics Committees in all participating non-UK countries.
Randomisation and masking

An independent statistician from the United Kingdom, who was blind to the study design, randomised all patients to either the tranexamic acid or placebo groups. The randomisation was performed centrally using a computer-generated randomisation sequence, which was stratified by study centre and type of surgery. The randomisation list was not made available to any of the study centres until all data had been collected and the study was completed. The randomisation list was stored securely at the Clinical Trials and Evaluation Unit, University of Oxford, until the final analysis was conducted.

Articles

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Procedures

Eligible patients were randomly assigned to get tranexamic acid or placebo. The randomisation was stratified by site and primary surgery type. The randomisation list was not made available to any of the study centres until all data had been collected and the study was completed. The randomisation list was stored securely at the Clinical Trials and Evaluation Unit, University of Oxford, until the final analysis was conducted.

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and Torbay and South Devon NHS Foundation Trust (MIA/ 071MP/ 3079). Manufactured by Gedeon Richter Ltd, Hungary. 0–9% placebo. We provided information for patients and representatives, consent forms, and data collection forms. Stickers, instructions, and 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 three times: discharge from the randomising hospital on day 1; 28 days after randomisation, whichever occurred first; or trial investigators and their institutions provided direct access to their sources of data. Trial-related monitoring, audits, and regulatory inspections were monitored on the sponsor’s standard operating procedure and the trial protocol. Formal inspections were carried out by the relevant regulatory agencies, including the EU Medicines and Healthcare products Regulatory Agency, and the Irish Health Products Regulatory Authority, and the Nigerian State National Agency for Food and Drug Administration and Control. Adherence to allocation sequence was monitored throughout the trial and any deviation identified and tracked. The database and the investigators were retrained.

Outcomes

The primary outcome was death due to bleeding within 28 days of randomisation. Cause of death was assigned by the local principal investigator who provided the narrative of the events leading to death. These were reviewed by the chief investigator (masked for 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 mortality at 28 days, rebleeding within 28 days, and time to death from randomisation to 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), and any death attributable to the intervention. Details of death and causes are shown in Table 2.

Statistical analysis

The sample size calculation was initially based on all-cause mortality in the primary outcome since it was expected that most deaths would be due to bleeding. However, while the trial was underway, we observed that overall mortality in all deaths were due to non-bleeding causes. A cumulative evidence from other large trials with tranexamic acid showed no apparent effect on non-bleeding deaths. Furthermore, patients received tranexamic acid (or placebo) only if their initial bleed and because tranexamic acid has a short half-life (approximately 20 h), it will be largely eliminated within 24 h. A Dutch observational study 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 28 days of randomisation on Nov 21, 2018. Based on the extended primary outcome, assuming a 15% difference in death due to bleeding, 8% power (two-sided, 95% CI) detected a clinically important 25% relative reduction in death due to bleeding from 4% to 3%.

We published the statistical analysis plan before unblinding. The plan gave due 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 and

<table>
<thead>
<tr>
<th>Tramexamic Acid (n=5956)</th>
<th>Placebo (n=5981)</th>
<th>Risk ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death due to bleeding within 24 h</td>
<td>124(2.1%)</td>
<td>120(2.0%)</td>
</tr>
<tr>
<td>Death due to bleeding within 3 days</td>
<td>222(3.7%)</td>
<td>226(3.8%)</td>
</tr>
<tr>
<td>Death due to bleeding within 5 days</td>
<td>253(4.2%)</td>
<td>262(4.4%)</td>
</tr>
<tr>
<td>Rebleeding within 24 h</td>
<td>41(0.7%)</td>
<td>41(0.7%)</td>
</tr>
<tr>
<td>Rebleeding within 5 days</td>
<td>28(4.8%)</td>
<td>31(5.3%)</td>
</tr>
<tr>
<td>Rebleeding within 28 days</td>
<td>24(4.1%)</td>
<td>44(7.5%)</td>
</tr>
</tbody>
</table>

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

Figure 2: Mortality by days from randomisation