Tranexamic acid for acute gastrointestinal bleeding (The HALT-IT trial): Statistical analysis plan for an international, randomised, double blind, placebo-controlled trial

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Abstract

Background: Acute gastrointestinal (GI) bleeding is an important cause of mortality worldwide. Bleeding can occur from the upper or lower GI tract, with upper GI bleeding accounting for most cases. The main causes include peptic ulcer / erosive mucosal disease, oesophageal varices and malignancy. The case fatality rate is around 10% for upper GI bleeding and 3% for lower GI bleeding. Rebleeding affects 5-40% of patients and is associated with a four-fold increased risk of death. Tranexamic acid (TXA) decreases bleeding and the need for blood transfusion in surgery and reduces death due to bleeding in patients with trauma and postpartum haemorrhage. It reduces bleeding by inhibiting the breakdown of fibrin clots by plasmin. Due to the methodological weaknesses and small size of the existing trials, the effectiveness and safety of TXA in GI bleeding is uncertain. The HALT-IT trial aims to provide reliable evidence about the effects of TXA in acute upper and lower GI bleeding.

Methods: The HALT-IT trial is an international, randomised, double blind (participant and trial staff), placebo-controlled trial of tranexamic acid in 12,000 adults (increased from 8,000) with acute upper or lower GI bleeding. Eligible patients are randomly allocated to receive tranexamic acid (1g loading dose followed by 3g maintenance dose over 24 hours) or matching placebo. The main analysis will compare those randomised to tranexamic acid with those randomised to placebo on an intention-to-treat basis, presenting the results as effect estimates (relative and absolute risks) and confidence intervals. The primary outcome is death due to bleeding within 5 days of randomisation and secondary outcomes are rebleeding, all-cause and cause-specific mortality, thromboembolic events, complications, endoscopic, radiological and surgical interventions, blood transfusion requirements, disability (defined by a measure of patient’s self-care capacity) and number of days spent in intensive care or high dependency units. Subgroup analyses for the primary outcome will consider time to treatment, location of bleeding, cause of bleed and clinical Rockall score.

Discussion: We present the statistical analysis of the HALT-IT trial. This plan was published before the treatment allocation was un-blinded.

Background

Acute gastrointestinal (GI) bleeding is a common medical emergency and an important cause of

mortality worldwide. Bleeding can occur from the upper or lower GI tract, with upper GI bleeding accounting for most cases. The incidence varies widely depending on the population prevalence of risk factors, with a reported incidence of upper GI bleeding of 50-140 per 100,000 across the US, Europe and Scandinavia [1–9]. The case fatality rate is around 10% for upper GI bleeding [1,10] and 3% for lower GI bleeding [11]. Despite evidence suggesting improvements in survival in recent decades, the case fatality rate for upper GI bleeding varies from 3-15%, with the highest risk of death in patients with upper GI malignancies and varices [1,3,4,8,10,12–16]. In addition to cause of bleeding, other factors associated with mortality include older age, signs of shock, severe bleeding, active bleeding, rebleeding and extent of comorbid disease [16–20].

The main causes of GI bleeding are peptic ulcer disease, erosive mucosal disease, oesophageal varices and malignancy [10]. Peptic ulcer disease and erosions due to *Helicobacter pylori* infection and NSAID use are common causes of GI bleeding worldwide [1,6,10,12,18,21–25]. Bleeding from gastro-oesophageal varices due to liver cirrhosis is an increasing cause of bleeding in the West, but is also a major cause in parts of South America, Asia, Africa and the Middle East where there is high prevalence of hepatitis or schistosomiasis [26–33]. Symptoms of GI bleeding include hematemesis and coffee grounds vomitus, melaena and the passage of fresh red blood in the stool, and clinical signs of shock such as hypotension and tachycardia.

Some patients with GI bleeding initially stop bleeding and have a brief period of haemodynamic stability before starting to bleed again. This phenomenon, known as rebleeding, is common and can affect between 5% and 40% of patients with acute GI bleeding. Rebleeding is associated with a four-fold increased risk of death [10,11,16,17,34]. Some of the variation in rebleeding rates may be explained by the use of different definitions, including fresh haematemesis or melaena and recurrent hypotension or tachycardia within varying timeframes of the index bleed [18]. The risk of rebleeding is highest in the days immediately after the index bleed and declines rapidly with time [35–37]. The risk factors for rebleeding are related to the lesion responsible for bleeding, but also influenced by age, comorbidity and concomitant medications. [16,17].

Tranexamic acid reduces clot breakdown by inhibiting the breakdown of fibrin clots by plasmin. It

decreases bleeding and the need for blood transfusion in surgery and reduces death due to bleeding in patients with traumatic and postpartum haemorrhage [38–40]. A systematic review and meta-analysis of tranexamic acid in patients with upper GI bleeding included eight randomised trials with a total of 1,702 patients [41]. Although there was a statistically significant reduction in mortality with TXA (RR 0.60, 95% CI 0.42-0.87; p=0.007) and a non-significant reduction in rebleeding (RR 0.72, 95% CI 0.50-1.03), because of methodological weaknesses in the included trials and the imprecise effect estimates from meta-analyses, the effectiveness and safety of tranexamic acid in GI bleeding remains uncertain [41]. Moreover, the included trials were too small to assess the effect of tranexamic acid on thromboembolic events. The HALT-IT trial aims to provide reliable evidence about the effects of TXA in acute GI bleeding [42].

Methods

Trial design

The HALT-IT trial is an international, randomised, double blind (participants and trial staff), placebo-controlled trial to quantify the effects of TXA on morbidity and mortality in adults with significant upper or lower GI bleeding.

Blinding and randomisation

Pfizer Manufacturing, marketing authorisation number PL 00057 /0952, manufactures the tranexamic acid. Torbay and South Devon NHS Foundation Trust, manufacturing authorisation number MIA (IMP) 13079, manufactures the placebo (sodium chloride 0.9%). Sharp Clinical Services (UK) Ltd., manufacturing authorisation number MIA (IMP) 10284, manufactures the study drug treatment packs containing either the active drug tranexamic acid or placebo. The Marketing Authorisation guarantees that the product is manufactured and released in accordance with the UK’s Good Manufacturing Practice (GMP) regulations. Ampoules and packaging are identical in appearance.

An independent statistician from Sealed Envelope Ltd (UK) generates randomisation codes to be sent to Sharp Clinical Services UK Limited, a GMP certified clinical trial supplies company who prepare trial treatment packs in accordance with the randomisation list. Sharp Clinical Services conduct the blinding process and first stage Qualified Person (QP) release, which involves complete removal of the

original manufacturer’s label and replacement with the clinical trial label bearing the randomisation number for use as the pack identification. Other pack label text are identical for tranexamic acid and placebo treatments and in compliance with requirements for investigational medicinal products. Sharp Clinical Services UK are also responsible for maintaining the Product Specification File (PSF) until final database lock and unblinding of the trial data. Quality control checks to assure the blinding process are performed on a random samples of final QP released drug packs. High Performance Liquid Chromatography (HPLC) separation of known TXA is assessed against blinded samples to confirm which ampoule contains the placebo and active treatment. The tested samples are unblinded to assure accuracy of blinding.

The Trial Coordinating Centre (TCC) is responsible for assuring all relevant approvals are available at the TCC before release of the trial treatment to a site. A separate Manual of Operating Procedures details the drug accountability system. The Investigator’s Brochure details labelling of the trial treatment and other processes for assuring adherence to Good Manufacturing Practice.

Eligible patients are randomised to receive either tranexamic acid or placebo as soon as possible and the study treatment started immediately. The next consecutively numbered treatment pack is taken from a box of eight packs. A fixed loading dosage of 1 g tranexamic acid or placebo (sodium chloride 0.9%) is administered, followed by a maintenance dose of 3 g tranexamic acid orf placebo (sodium chloride 0.9%) infused over 24 hours.

Ethics approval and consent

The trial was approved by the UK NRES Committee East of England (reference number 12/EE/0038), as well as national and local research ethics committees of participating countries outside of the UK. Acute severe GI bleeding can be a frightening condition for the patient and the ensuing blood loss may have adverse impact on the patient’s mental and emotional state, impairing their decision-making ability. The consent procedures consider this together with the need to randomise and treat urgently. If the patient is fully competent, written consent is sought. If the patient’s capacity is impaired and a personal or professional representative is available, consent is sought from the representative. If neither are able to provide informed consent, consent is waived and the patient is

informed about the trial as soon as it is possible.

Data collection

The entry form (Appendix 1) is used to assess eligibility and collect baseline information. Once a patient has been randomised, the outcome in hospital is collected even if the trial treatment is interrupted or is not actually given. No extra tests are required but a short outcome form (Appendix 2) is completed from the medical records 28 days after randomisation or on discharge from the randomising hospital or on death (whichever occurs first). Any adverse events that become known to the investigator are reported up to 28 days after randomisation.

Change in primary outcome

We originally specified all-cause mortality as the primary outcome because we believed that most deaths would be due to bleeding. However, as the trial was underway we observed that over half of all deaths were due to non-bleeding causes such as cancer and sepsis (see Figure 1). Tranexamic acid reduces bleeding by inhibiting fibrinolysis. Based on this mechanism of action, we do not expect any substantial reduction in non-bleeding deaths. This hypothesis is supported by evidence from trials of tranexamic acid in trauma and postpartum haemorrhage [39,40,43]. As such, the treatment effect on all-cause mortality will be diluted by non-bleeding causes of death, reducing statistical power [43]. Death due to bleeding is the relevant endpoint for the HALT-IT trial because it has the potential to be reduced by the trial treatment. Fibrinolysis may play an important role in GI bleeding: gastric vein blood samples from patients with peptic ulcers contain high concentrations of plasmin and many patients with acute upper GI bleeding have elevated levels of fibrin degradation products (a biomarker for fibrinolysis) which is associated with worse outcomes [44–46].

Cause of death is assigned by local investigators and a narrative of the events leading to death is reviewed by the principal investigator (who is blind to treatment allocation) and queried as necessary to verify cause of death. Due to double-blind nature of the trial, the coding of the cause of death cannot be affected by the patients' randomised group.

We also originally specified that the primary outcome would be measured up to 28 days after randomisation. However, patients receive tranexamic acid (or placebo) for their initial bleed but not

for rebleeding episodes. Tranexamic acid has a half-life of 2-3 hours so 99% will be eliminated within about 2 days of randomisation [47,48]. We do not expect tranexamic acid to reduce deaths from a rebleeding episode several weeks after the drug has been fully eliminated, therefore the primary outcome will consider early deaths due to bleeding only, defined as those that occur within 5 days of randomisation.

The rationale for changing the primary outcome from all-cause mortality to death due to bleeding was published in October 2018 [43]. The decision was supported by the Trial Steering Committee and was made prior to the end of the trial and prior to un-blinding and so was not a data-dependent change.

Sample size

We originally specified all-cause mortality as the primary outcome because we believed that most deaths would be due to bleeding. However, as the trial was underway we observed that over half of all deaths were due to non-bleeding causes such as cancer and sepsis (see Figure 1). Tranexamic acid reduces bleeding by inhibiting fibrinolysis. Based on this mechanism of action, we do not expect any substantial reduction in non-bleeding deaths. This hypothesis is supported by evidence from trials of tranexamic acid in trauma and postpartum haemorrhage [39,40,43]. As such, the treatment effect on all-cause mortality will be diluted by non-bleeding causes of death, reducing statistical power [43]. Death due to bleeding is the relevant endpoint for the HALT-IT trial because it has the potential to be reduced by the trial treatment. Fibrinolysis may play an important role in GI bleeding: gastric vein blood samples from patients with peptic ulcers contain high concentrations of plasmin and many patients with acute upper GI bleeding have elevated levels of fibrin degradation products (a biomarker for fibrinolysis) which is associated with worse outcomes [44–46]. The rationale for changing the primary outcome from all-cause mortality to death due to bleeding was published in October 2018 [43]. The decision was supported by the Trial Steering Committee and was made prior to the end of the trial and prior to un-blinding and so was not a data-dependent change.

Assuming a cumulative incidence of death due to bleeding of 4%, a study with 12,000 patients will have over 805% power (two sided alpha = 5%) to detect a clinically important 25% relative reduction in death due to bleeding from 4% to 3%. Loss to follow-up is expected to be less than 1% (it was

0.16% in the WOMAN trial). This power calculation is based on the primary analysis and refers to the unadjusted Chi-squared test.

Trial population

Eligibility

Patients with significant GI bleeding to whom the uncertainty principle applies are eligible. Specifically, a patient can be enrolled if the responsible clinician is substantially uncertain as to whether the trial treatment is appropriate for that particular patient. Significant bleeding is diagnosed clinically and implies a risk of bleeding to death. Patients with significant bleeding may include those with hypotension, tachycardia, signs of shock, or those needing urgent transfusion, endoscopy or surgery. Patients with a clear indication (e.g. traumatic haemorrhage) or contraindication (e.g. history of convulsions, thromboembolic disease) for tranexamic acid are excluded.

Recruitment, withdrawal and loss to follow-up

We will display the flow of study participants using a Consolidated Standards of Reporting Trials (CONSORT) diagram (see Appendix Figure 1). For each trial arm, we will present the total number randomised, the number with baseline data, the number lost to follow up, the number who withdrew consent, and the number of participants with outcome data.

Baseline patient characteristics

We collect data on the following baseline characteristics: age, biological sex, time from onset of GI bleeding symptoms to randomisation, suspected location of bleeding, clinical symptoms (e.g. haematemesis, melaena), suspected variceal bleeding, systolic blood pressure, heart rate, signs of shock, suspected active bleeding, major comorbidities, anticoagulation therapy and type of admission. We will present the distribution of baseline characteristics (n and %) in the treatment and placebo groups to check that randomisation was successful in producing similar groups (see Appendix Table 1).

Analysis

Primary analysis

The main analysis will compare death due to bleeding in those allocated tranexamic acid with those

allocated placebo on an intention-to-treat basis. We will present the results as effect estimates (relative risks) with a measure of precision (95% confidence intervals) and p-value from Pearson's chi-squared testan unadjusted modified Poisson regression model (see Appendix Table 2). Additionally, we will present results of the primary analysis adjusted for all baseline covariates to improve power and adjust for chance imbalances. We will also present risk differences to allow interpretation of the results on both the additive and ratio scales. The effect of tranexamic acid will also be examined graphically using cumulative incidence curves (see Appendix Figure 2) [49]. The effects of TXA tranexamic acid on death due to bleeding in the HALT-IT trial will be set in the context of other trials of tranexamic acid TXA in for acute severe haemorrhage (tThe CRASH-2 and Woman WOMAN trials).

Primary outcome

Death due to bleeding within five days of randomisation is the primary outcome. Patients receive tranexamic acid (or placebo) for their initial bleed but not for rebleeding episodes. Tranexamic acid has a half-life of 2-3 hours so 99% will be eliminated within about 2 days of randomisation ADDIN CSL_CITATION {"citationItems":[{"id":"ITEM-1","itemData":{"ISSN":"0031-6970","PMID":"7308275","abstract":"Tranexamic acid 1 g was given intravenously to three healthy volunteers. Plasma concentrations decayed in three monoexponential phases. Most elimination took place during the first eight hours, giving an apparent elimination half-life of approximately two hours. Plasma clearance ranged between 110-116 ml/min. The urinary recovery of tranexamic acid exceeded 95% of the dose. Ten healthy volunteers were given tranexamic acid 2 g orally on an empty stomach, and together with a meal. Food had no influence on the absorption of tranexamic acid, as judged by comparison of the peak plasma concentration, the time required to reach the peak, the AUC from zero to six hours, and the urinary excretion data. The oral bioavailability of tranexamic acid, calculated from 24 h urinary excretion after oral and intravenous administration, was 34% of the dose.","author":[{"dropping-particle":"","family":"Pilbrant","given":"A","non-dropping-particle":"","parse-names":false,"suffix":""},{"dropping-particle":"","family":"Schannong","given":"M","non-dropping-particle":"","parse-names":false,"suffix":""},{"dropping-particle":"","family":"Vessman","given":"J","non-dropping-particle":"","parse-

names":false,"suffix":""}],"container-title":"European journal of clinical pharmacology","id":"ITEM-1","issue":"1","issued":{"date-parts":[["1981"]]},"page":"65-72","title":"Pharmacokinetics and bioavailability of tranexamic acid.","type":"article-journal","volume":"20"},"uris":["http://www.mendeley.com/documents/?uuid=27d4f659-f852-333b-a644-15e068c9a066"]},{"id":"ITEM-2","itemData":{"ISBN":"9780781750097","author":[{"dropping-particle":"","family":"Rowland","given":"Malcolm","non-dropping-particle":"","parse-names":false,"suffix":""},{"dropping-particle":"","family":"Tozer","given":"Thomas N","non-dropping-particle":"","parse-names":false,"suffix":""},{"dropping-particle":"","family":"Derendorf","given":"Hartmut","non-dropping-particle":"","parse-names":false,"suffix":""},{"dropping-particle":"","family":"Hochhaus","given":"Guenther","non-dropping-particle":"","parse-names":false,"suffix":""}],"id":"ITEM-2","issued":{"date-parts":[["2011"]]},"title":"Clinical Pharmacokinetics and Pharmacodynamics","type":"book"},"uris":["http://www.mendeley.com/documents/?uuid=d0bf611a-5964-3897-a2ea-84ac689c5822"]}],"mendeley":{"formattedCitation":"[48,49]","plainTextFormattedCitation":"[48,49]","previouslyFormattedCitation":"[48,49]"},"properties":{"noteIndex":0},"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"}[48,49]. We do not expect tranexamic acid to reduce deaths from a rebleeding episode several weeks after the drug has been fully eliminated, therefore the primary outcome will consider early deaths due to bleeding only. Cause of death is assigned by local investigators who provide a narrative of the events leading to death. The cause of death narratives are reviewed by the principal investigator (who is blind to treatment allocation) and queried if more information is needed to confirm whether death is due to bleeding or another cause. Furthermore, due to double-blind nature of the trial, the coding of the cause of death cannot be affected by the patients' randomised group. For more details, please see accompanying information in the section ‘Change of primary outcome’.

Secondary outcomes

We will assess the effect of tranexamic acid on the following secondary outcomes. Unadjusted analyses will be presented in the main text and although we do not expect any baseline imbalances,

to complement the unadjusted analyses and increase statistical power we will present results of the analyses adjusted for all baseline covariates in an appendix.

Rebleeding

Rebleeding occurs in approximately 10-25% of patients with acute GI haemorrhage and is associated with an increased risk of death due to bleeding [50]. A clinical diagnosis of rebleeding is made by the treating clinician based on the presence of any of the following criteria, as defined in a data collection guide. These criteria for rebleeding were recommended by a methodological framework for trials in GI bleeding following an international consensus conference [51].

· Haematemesis or bloody NG aspirate > 6 hours after endoscopy.

· Melaena after normalisation of stool colour.

· Haematochezia after normalisation of stool colour or after melaena.

· Development of tachycardia (HR>110 beats per min) or hypotension (SBP<=≤90mmHg) after ≥1 hour of haemodynamic stability (i.e. no tachycardia or hypotension) in the absence of an alternative explanation for haemodynamic instability, such as sepsis, cardiogenic shock, or medication

· Haemoglobin drop of >2g/dl after two consecutive stable values(<0.5g/dl decrease) ≥3hours apart

· Tachycardia or hypotension that does not resolve within 8 hours after index endoscopy despite appropriate resuscitation (in the absence of an alternative explanation) associated with persistent melaena or haematochezia.

· Persistently dropping haemoglobin of >3g/dl in 24 hours associated with persistent melaena or haematochezia

It should be noted that patients may continue to have haemodynamic instability, falling haemoglobin levels or persistent melaena or rectal bleeding for hours and even days after bleeding has stopped, making these patients difficult to categorise; however, these criteria are more likely to indicate rebleeding than equilibration [51].

Rebleeding within 5 days

Most rebleeding tends to occur within 5 days of the index bleed [35–37]. We believe tranexamic acid will be most effective at reducing the risk of rebleeding soon after the index bleed when blood plasma

concentrations of the drug are above the level needed to inhibit fibrinolysis [52]. To determine whether tranexamic acid reduces rebleeding, we will analyse the effect on early rebleeding within 5 days of randomisation (see Appendix Table 2).

Rebleeding within 28 days

Rebleeding that occurs more than 5 days after randomisation will be defined as late rebleeding. We hypothesise that tranexamic acid will be much less effective for late rebleeding occurring days or weeks after the drug has been eliminated. To investigate this we will assess the effect of tranexamic acid on rebleeding within 28 days (see Appendix Table 2). If our hypothesis is correct, the inclusion of late rebleeding events will dilute the treatment effect.

Death due to bleeding within 28 days

As with late rebleeding, we do not expect tranexamic acid to have an effect on late deaths due to bleeding that occur several days after randomisation. To assess this we will analyse the effect of tranexamic acid on death due to bleeding within 28 days of randomisation (see Appendix Table 2). We expect to observe a smaller treatment effect when including late deaths due to bleeding.

Mortality

We will analyse the effect of tranexamic acid on all-cause and cause-specific mortality at 28 days. Specific causes of death to be analysed include death due to bleeding, thrombosis, organ failure, pneumonia, sepsis, malignancy and other causes (see Appendix Table 3). We will also examine the temporal distribution of causes of death by days since randomisation using a frequency bar chart (see Appendix Figure 3). Based on its mechanism of action and data from large randomised trials, we do not expect tranexamic acid to reduce deaths from non-bleeding causes like cancer or sepsis or to reduce late deaths from bleeding.

Endoscopic, radiological and surgical procedures for GI bleeding

It remains unclear whether tranexamic acid reduces the need for surgery in GI bleeding [41]. In large trials of tranexamic acid for postpartum and traumatic haemorrhage, there was no evidence of an effect on surgical interventions except for laparotomy for bleeding [39,40]. If tranexamic acid reduces GI bleeding, it has the potential to reduce the need for some surgical, endoscopic, and radiological

and surgical procedures. While we do not expect tranexamic acid to influence diagnostic endoscopic and radiological procedures planned around the time of hospital admission and randomisation, there is potential to reduce the need for diagnostic procedures planned after resuscitation, and therefore after randomisation [43]. Similarly, therapeutic procedures and surgical interventions planned and undertaken after diagnosis also have the potential to be influenced by tranexamic acid. We will assess the effect of tranexamic acid on diagnostic and therapeutic endoscopic and radiological procedures and surgical interventions (see Appendix Table 5). It is not possible to look at procedures by time as this information was not recorded.

Blood transfusion

Since blood transfusion is mostly determined by blood loss prior to randomisation, we do not expect to see a marked reduction in the need for blood transfusion with use of tranexamic acid [43]. Major haemorrhage protocols dictate the type and volume of blood components patients receive based on presenting clinical signs such as blood pressure and estimated blood loss. Furthermore, survivor bias could lead to higher transfusion rates in the tranexamic acid group. In keeping with this, a systematic review of tranexamic acid for GI bleeding found no reduction in transfusion [41]. Although tranexamic acid has the potential to reduce transfusion for blood lost after randomisation e.g. after rebleeding, we did not collect data on date and time of transfusion. Any effect on late transfusions is likely to be obscured by early transfusions for blood lost pre-randomisation. We will assess the effect of tranexamic acid on the use of whole blood or packed red cells, frozen plasma and platelets comparing the frequency of transfusion and the mean number of (adult-equivalent) units transfused (see Appendix Table 5).

Thromboembolic events

An individual patient data meta-analysis of the WOMAN and CRASH-2 trials found noevidence of increased risk of vascular occlusive events with tranexamic acida reduction in myocardial infarction with tranexamic acid (OR=0·64, 95% CI 0·43–0·97; p=0·0371) and no evidence of an increased risk of fatal vascular occlusive events (OR 0·73, 95% CI 0·49–1·09; p=0·1204) or other non-fatal events [53]. While this finding is reassuring, we cannot exclude the possibility of some increased risk with TXA,

particularly as patients with GI bleeding are older than those with traumatic or postpartum haemorrhage and many have multiple co-morbidities. Older age is associated with a pro-coagulation haemostatic profile including elevated fibrinogen and plasminogen activator inhibitor 1 and reduced clotting time [54–56]. A systematic review of tranexamic acid for the treatment of upper GI bleeding found no evidence for a difference in the risk of thromboembolic events but lacked power [41]. We will examine the effect of tranexamic acid on fatal and non-fatal pulmonary embolism, deep vein thrombosis, stroke and myocardial infarction (see Appendix Table 6).

Complications

We will analyse the effect of tranexamic acid on renal, hepatic and respiratory failure, cardiac events, sepsis, pneumonia and seizures (see Appendix Table 6). If tranexamic acid reduces death due to bleeding, patients in the tranexamic group will survive for longer on average and may therefore be at greater risk of complications such as sepsis, pneumonia and organ failure. Generally, death due to bleeding tends to occur soon after bleeding onset whereas infections and organ failure take several days to occur. On the other hand, if tranexamic acid reduces bleeding it may reduce liver failure because bleeding can lead to the deterioration of liver function. Although there is evidence that high-dose tranexamic acid can cause seizures, we do not expect to see an increase in seizures with the low dose given in the trial.

Self-care capacity

Patients self-care capacity will be measured using the Katz Index of Independence in Activities of Daily Living (Katz ADL) [57]. Participants' performance in six functions (bathing, dressing, toileting, transferring, continence and feeding) is assessed at the time of discharge from the randomising hospital or in-hospital 28 days after randomisation. A score of 1 is assigned to each function the individual can perform independently and they are summed to produce a total score. A score of 6 suggests full function, 4 suggests moderate impairment, and 2 or less suggests severe functional impairment. We expect that reduced blood loss in patients who receive tranexamic acid will result in less functional impairment. That said, it is possible that patients in the treatment group will be discharged faster which could mask improvements in self-care capacity at the time of discharge. . To

assess this hypothesis we will compare the difference in mean Katz ADL score in the tranexamic acid and placebo groups as well as the proportion of patients with no impairment (6), mild to moderate impairment (3-5) or severe impairment (0-2), (see Appendix Table 6).

Days spent in intensive care or high dependency unit

We will analyse the effect of tranexamic acid on number of days spent in the intensive care unit (ICU) or high dependency unit (HDU). We will compare the difference in mean number of days spentd in the ICU or HDU in the tranexamic acid and placebo groups (see Appendix Table 6). Because beds in these units can be limited, we may not see an effect on this outcome measure.

Adverse events

Data on the number of adverse events (AEs), serious adverse events (SAEs) and suspected unexpected serious adverse reactions (SUSARs) reported up to 28 days after randomisation will be presented. We will present a summary table in an appendix to describe the type of AE, Medical Dictionary for Regulatory Activities (MedDRA) preferred term (PT), MedDRA system organ class (SOC) and the number of occurrences and outcomes (completely recovered, recovered with sequelae, or died) in the tranexamic acid and placebo groups. With events grouped by MedDRA SOC, we will compare the frequency of events between trial arms using a chi-squared test or Fisher’s exact test an unadjusted modified Poisson regression model (see Appendix Table 7). AEs with evidence that they may be increased by tranexamic acid (i.e. seizures and thromboembolic events), will be analysed on an individual basis as well as recurrent episodes of gastrointestinal bleeding reported as Aes.

Subgroup analyses

We will conduct the following subgroup analyses for the primary outcome of death due to bleeding: time to treatment, location of bleeding, cause of bleeding and clinical Rockall score. We will fit interaction terms with randomised group in a Poisson regression model with robust error variance from the sandwich estimator [58]. Interaction tests (the Wald test) will be used to explore whether the effect of treatment (if any) differs across these subgroups. Results will be presented as crude unadjusted and adjusted effect estimates with a measure of precision (95% confidence intervals) and p-value (see Appendix Table 4). SExcept for time to treatment, statistically significant heterogeneity

between subgroups is required, as determined by the test for interaction p-value, and not just statistical significance of a result in a specific subgroup [59]. Selection of potential confounders is based upon review of unblinded data within the trial to date.

Although treatment group is randomised within subgroups, the factors defining subgroups are not randomised. Several baseline characteristics are associated with the subgroup variables. For example, early treatment is correlated with bleed characteristics and patient characteristics (see *Figure 2*), some of which confer a higher clinical Rockall score suggesting patients with more severe bleeding are treated earlier. Since these factors are also associated with mortality, they could confound the interaction between time to treatment and the treatment effect.

If tranexamic acid is shown to be effective and the treatment effect varies by time to treatment, there is potential to intervene on time to treatment in order to increase the treatment effect. Although we cannot intervene on location of bleeding, cause of bleeding or clinical Rockall score, we are interested in ascertaining causal interaction of these factors with the treatment effect rather than simply assessing effect heterogeneity. As such, Wwe will adjust all subgroup analyses for potential confounders [60]. Selection of potential confounders is based upon review of unblinded data within the trial to date in order to identify prognostic baseline characteristics that are associated with the subgroup variables. Specifically, we will adjust for including age, time to treatment, systolic blood pressure, heart rate, signs of shock, location of bleeding, suspected active bleeding, comorbid liver disease and suspected variceal bleeding. For example, early treatment is correlated with certain bleed characteristics and patient characteristics (see *Figure 2*). Some of these characteristics confer a higher clinical Rockall score suggesting patients with more severe bleeding are treated earlier. Since these factors are also associated with mortality, they could confound the interaction between time to treatment and the treatment effect. Signs of shock may be collinear with heart rate or blood pressure, and suspected variceal bleeding may be collinear with comorbid liver disease – if so, signs of shock and suspected variceal bleeding will not be included in the models.

Time to treatment (≤<=3h, >3h)

Trials of tranexamic acid in traumatic and postpartum haemorrhage provide evidence that early

treatment (within 3 hours of bleeding onset) confers the most benefit, while late treatment is ineffective [39,53,61]. As such, we plan to conduct a subgroup analysis of the treatment effect stratified by time to treatment. Patients with GI bleeding may not experience symptoms immediately so time of symptom onset may not accurately reflect time of bleeding onset. Time to treatment may therefore be underestimated. Because few patients are treated early (within 3 hours), there may be low power to detect an interaction if one exists. As such, we will analyse time to treatment as both a categorical (≤<=3h, >3h) and continuous variable because the latter will preserve more information so should have more power. However, a limitation of modelling time to treatment as a continuous variable is the need to specify the form of the association. A goodness of fit test will be used to assess non-linearities. Any differences between the two approaches will be noted.

Because tThere is strong prior evidence to expect a time to treatment interaction, with early treatment conferring a greater benefit and late treatment being ineffective and possible even harmful [53,61]., As such, for the subgroup analysis of time to treatment we do not require as strong evidence against the null hypothesis of homogeneity as we might usually require. Most trials lack power to detect heterogeneity in treatment effects and the lack of a statistically significant interaction does not mean that the overall treatment effect applies to all patients. Due to prior evidence that early treatment is more effective, we will consider the time to treatment subgroup analysis in the context of the existing data (in particular data from the CRASH-2 and WOMAN trials) on the time to treatment interaction and will rely more on scientific judgment than on statistical tests.

Location of bleeding (upper GI, lower GI)

We will examine the effect of tranexamic acid on death due to bleeding stratified by location (upper versus lower GI). Evidence suggests the rates of rebleeding and mortality after upper and lower GI bleeding are similar [34], and there is no reason to expect the effect of tranexamic acid to vary substantially by location of bleeding in the GI tract. Unless there is strong evidence against the null hypothesis of homogeneity of effects (i.e. $p<0.001$), the overall relative risk will be considered the most reliable guide to the approximate treatment effect in all patients.

Suspected variceal bleeding and comorbid liver disease (yes, no/unknown)

Outcomes in acute GI bleeding vary by cause of haemorrhage. Variceal bleeding is associated with the highest risk of rebleeding and death. Oesophageal varices are dilated submucosal veins that usually develop because of portal hypertension, often due to cirrhosis. Haemostasis is disturbed in patients with liver disease because many of the pro- and anti-coagulation factors and components of the fibrinolytic system are produced by hepatic parenchymal cells in the liver, although the overall sum of effects are debated [62–64]. Any resulting imbalance in coagulation or fibrinolysis may alter the antifibrinolytic activity of tranexamic acid; however, the direction of this potential effect remains to be determined. We will examine the effects of tranexamic acid on death due to bleeding in patients with suspected variceal bleeding and comorbid liver disease compared to other or unknown causes of bleeding. Unless there is strong evidence against the null hypothesis of homogeneity of effects (i.e. $p<0.001$), the overall relative risk will be considered the most appropriate measure of effect.

Clinical Rockall score (1-2, 3-4, 5-7)

We will assess the effect of tranexamic acid stratified by the clinical (pre-endoscopy) Rockall score, a widely used risk scoring system for GI bleeding. The score is derived from age, comorbidities, signs of shock, heart rate and systolic blood pressure, all of which are independent predictors of mortality. Although originally developed for upper GI bleeding [17], the Rockall score has also been shown to be predictive of mortality in lower GI bleeding [34]. We do not expect the treatment effect to vary by Rockall score. Unless there is strong evidence of an interaction ($p<0.001$), we will present to overall relative risk as the most appropriate measure of effect.

Per protocol analysis

We will conduct a per protocol analysis of the effect of tranexamic acid on death due to bleeding and thromboembolic events excluding patients who received neither the loading nor maintenance dose or received off-label TXA during the trial. We expect to observe a slightly larger treatment effect in the per-protocol analysis. If some patients allocated tranexamic acid did not actually receive it then the treatment group will be more similar to the placebo group, thereby diluting the treatment effect. Similarly, if some patients in the placebo group receive off-label TXA, this will also dilute the treatment effect.

Missing data

Based on the data collected to date, we expect loss to follow-up to be minimal (i.e. less than 1% missing data on the primary outcome). Any missing values will be reported but not imputed.

Other analyses to be reported in separate publications

Survival analysis to investigate the timing and duration of the treatment effect

We will conduct a survival analysis to explore the effect of tranexamic acid on rebleeding and death due to bleeding in more detail. In large trials of tranexamic acid for traumatic (CRASH-2) and postpartum haemorrhage (WOMAN), there were few late bleeding-related events. The precise timing and duration of tranexamic acid's antifibrinolytic effect remain to be determined. For example, it is unclear whether the treatment effect persists after the drug has been eliminated. Bleeding-related events occur later in acute GI bleeding, partly due to rebleeding, so the HALT-IT trial presents a unique opportunity to investigate this question.

We will report the median survival time and the cumulative incidence in the treatment and placebo groups, and model the treatment effect. Cox proportional hazards modelling assumes the hazards in the treatment and placebo groups are proportional over time. This assumption may be invalid if the antifibrinolytic effect of tranexamic acid declines over time as the drug is metabolised. We will formally assess this using the Royston-Palmer test for proportional hazards - a combined test with increased power when an early treatment effect is present [65]. If the treatment effect on death due to bleeding and rebleeding appears to change with time (non-proportional hazards), we will examine this in detail using various methods, firstly by including a time by treatment interaction term in the model. We will also estimate average cumulative hazard ratios for increasingly longer periods of follow-up. This method is preferred to period-specific hazard ratios, which can be susceptible to selection bias [66]. Nevertheless, we will also use Llexis expansion to calculate period-specific hazard ratios and test for interactions between treatment group and period. If we are able to identify the average duration of the treatment effect, we will examine whether this varies by baseline characteristics including time to treatment, bleeding severity, cause of bleeding and age. We will also assess how the treatment effect changes with time by including a time by treatment interaction term

in the model. Residual methods will be used to test the assumption of linear time (first order trend) by plotting Martinguale residuals against continuous covariates.

Death due to bleeding is a competing risk for non-bleeding causes of death and vice versa. Death is also a competing risk for rebleeding. We will estimate the treatment effect using a proportional cause-specific hazards model in which competing events are censored. The proportional cause-specific hazards model is preferred for aetiological research; however, both the cause-specific hazard and cumulative incidence can provide insights into a treatment's effects [67,68]. As such, a subdistribution hazards model and Gray's test for comparing cumulative incidence functions will be presented as a supplementary analysis [69,70]. Risk of rebleeding is highest immediately after the index bleed, death is a competing risk for rebleeding and some patients may experience more than one episode during the follow-up period. A survival analysis of the effect of tranexamic acid on rebleeding will take into account timing of events, and competing risks and dependence among repeated events.

Cost effectiveness analysis

If the trial demonstrates that tranexamic acid is an effective treatment for GI bleeding, we will conduct an economic evaluation to determine cost-effectiveness. Broadly speaking the methods will mirror those used by Li et al. who assessed the cost-effectiveness of tranexamic acid for the treatment of women with post-partum haemorrhage [71].

The analysis will compare tranexamic acid against clinical practice without tranexamic acid. A cost-utility analysis will be performed from a health services cost perspective with outcomes expressed as Quality-Adjusted Life-Years (QALYs). The analyses will be performed separately for a set of different countries, depending on where the majority of people have been recruited, but is likely to include at least the UK and Pakistan. A decision model will be used to extrapolate results from the trial into the longer term. Resource data, such as drugs and length of inpatient stay, are collected as part of the trial and will be analysed accordingly. Both deterministic and probabilistic sensitivity analysis will be undertaken. Results will also be presented by subgroups if considered appropriate.

Impact of baseline risk on treatment effectiveness

To assess whether the effect of tranexamic acid on death due to bleeding varies by baseline risk we will build a prognostic model using baseline characteristics identified as important predictors of death due to bleeding. Prognostic factors include age, systolic blood pressure, heart rate, suspected location of bleeding, haemetamesis/coffee ground vomitus, suspected variceal bleeding, suspected active bleeding, comorbidities and country. The prognostic model will then be used to stratify patients by risk of mortality and stratum-specific effect estimates (relative risk) and 95% confidence intervals will be calculated. We do not expect the treatment effect to vary by baseline risk. Unless there is strong evidence against the null hypothesis of homogeneity of effects ($P<0.001$), the overall relative risk will be considered the most reliable guide to the approximate treatment effect in all patients.

Adjustment for baseline risk

Due to the large size of the HALT-IT trial, baseline characteristics should be well balanced between the treatment and placebo groups so that any differences in outcomes is due to the treatment. There is still a small possibility, however, that some imbalance in baseline risk may have arisen by chance. If prognostic factors are distributed differently across the treatment and placebo groups, this could bias the treatment effect. To investigate this hypothesis, we will conduct an analysis of the treatment effect on death due to bleeding adjusted for baseline risk. Patients will be stratified by risk deciles based on the predicted probability of death due to bleeding and a pooled effect estimate (relative risk) will be calculated using inverse variance weighting. This will provide an estimate of the treatment effect where both groups have equal baseline risksun-confounded by baseline risk.

Centre and country effects

Centre and country-level characteristics can influence patient outcomes. Differences in outcome may be related to resource availability or clinical practice. To explore between-country differences we will present a graph showing the number of patients and bleeding deaths by country and will use multivariable regression modelling to examine the treatment effect by country, including an interaction term between county and treatment. We will not adjust for clustering as we expect the effects of clustering to be small. Because we aim to understand any between-country differences in the treatment effect, wWe will adjust for potential confounders including age, systolic blood pressure,

heart rate, comorbidities, location of bleeding, suspected variceal bleeding, suspected active bleeding and time to treatment. A comparison between low, middle and high-income countries will be included using the World Bank country groupings by income. We do not expect the effect of tranexamic acid on the risk of death due to bleeding to vary by country, even though the absolute risk will vary due to between-country differences in patient populations. Countries recruiting less fewer than 100 patients will be omitted from the analysis as necessary.

Between-centre differences in outcome may also influence the estimation of the treatment effect. We will first use a random effects regression model using restricted maximum likelihood estimation to examine whether there are differences in death due to bleeding between centres. Results will be presented in the form of a forest plot. Prognostic patient characteristics (age, systolic blood pressure, heart rate, comorbidities, location of bleeding, suspected variceal bleeding, suspected active bleeding), treatment group and time to treatment will be adjusted for. To take into account country-level effects we will also consider between-centre differences in outcome adjusted for country. We will then use fixed and random effects regression to estimate the treatment effect before and after accounting for between-centre differences, assuming a constant treatment effect across centres. To assess whether the treatment effect differs by centre, we will fit a model with an interaction term between centre and treatment.

Data monitoring

The progress of the HALT-IT trial, including recruitment, data quality, outcomes and safety data, are reviewed by an independent Data Monitoring Committee, which can decide to reveal unblinded results to the Trial Steering Committee. To date, four interim analyses have been conducted.

Data sharing

To maximise data utilisation and improve patient care, the trial data will be made available via our online data-sharing portal - The Free Bank of Injury and emergency Research Data (freeBIRD) (http://freebird.Lshtm.ac.uk) - once primary and secondary analyses have been published.

Trial status

The study has been actively recruiting since July 2013. End of recruitment is planned for 31 May 2019,

with end of follow-up expected on 30 June 2019. Further information is available at http://haltit.Lshtm.ac.uk/.

Discussion

We present our plan for the statistical analysis of the HALT-IT trial prior to the end of recruitment, database lock and un-blinding in order to avoid data-dependent analyses. We set out a priori hypotheses and propose ways to test these. We also provide the rationale for changing the primary outcome from all-cause mortality to death due to bleeding within 5 days of randomisation.

Abbreviations

AE = adverse event; CRASH-2 = Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage; GI = gastrointestinal; GMP = Good Manufacturing Practice; HALT-IT = Haemorrhage alleviation with tranexamic acid – Intestinal system; HDU = High Dependency Unit; HPLC = High Performance Liquid Chromatography; HR = heart rate; ICU = Intensive Care Unit; Katz ADL = Katz Index of Independence in Activities of Daily Living; MedDRA = Medical Dictionary for Regulatory Activities ; MedDRA PT = Medical Dictionary for Regulatory Activities Preferred Term; MedDRA SOC = Medical Dictionary for Regulatory Activities system organ class; PSF = product specification file; QALYs = Quality-Adjusted Life-Years; QP = qualified person; SAE = serious adverse event; SBP = systolic blood pressure; SUSAR = suspected unexpected serious adverse reaction; TCC = Trial Coordinating Centre; UK = United Kingdom; US = United States; WOMAN = World Maternal Antifibrinolytic.

Declarations

Ethics approval and consent to participate

The trial was approved by the UK NRES Committee East of England (reference number 12/EE/0038), as well as national and local research ethics committees of participating countries outside of the UK. Informed consent will be obtained from all study participants.

Consent for publication

Not applicable.

Availability of data and material

The datasets generated and/or analysed during the current study are not yet publicly available

because the trial is ongoing. Once recruitment has stopped and after publication of the planned primary and secondary analyses, the trial data will be made available via our data-sharing portal, The Free Bank of Injury and Emergency Research Data (freeBIRD) website at https://ctu-app.lshtm.ac.uk/freebird/.

Competing interests

The authors have no competing interests.

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Authors' contributions

HS and IR conceived and designed the HALT-IT trial. AB conducted the analyses. MA is the HALT-IT Trial Manager. AB and IR drafted the manuscript. AA, SMA, MA, RC, TC, JC, IG, CH, DH, VJ, KJ, AK, MM, MAN, HSS, SS and AV provided important feedback and contributed to the final version of the manuscript.

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Figures

Figure 1

Causes of death in the HALT-IT trial during recruitment (Nov 2018).

Figure 2

Potential confounding factors in the subgroup analysis of time to treatment.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

HALT-IT_SAP_Appendix_Shell_Tables_Mar19.doc