Haemorrhage alleviation with tranexamic acid - Intestinal system

PROTOCOL SUMMARY

FULL TITLE OF STUDY	Tranexamic acid for the treatment of gastrointestinal haemorrhage: an international randomised, double blind placebo controlled trial		
SHORT TITLE	**H**aemorrhage **AL**leviation with **T**ranexamic acid – **I**n**T**estinal system		
TRIAL ACRONYM	HALT-IT		
PROTOCOL NUMBER	ISRCTN11225767		
EUDRACT NUMBER	2012-003192-19	**CLINICAL TRIALS.GOV**	NCT01658124

BACKGROUND: Gastrointestinal (GI) bleeding is a common emergency that causes substantial mortality worldwide. The common causes of upper GI bleeding are peptic ulcer, oesophageal varices and erosive mucosal disease. Acute upper GI bleeding accounts for about 60,000 hospital admissions each year in the UK and causes the death of about 10% of these patients. Lower GI bleeding accounts for a further 15,000 admissions each year with a case fatality of about 15%. GI bleeding is also common in low and middle income countries, where patients are usually young and poor. The source of bleeding is often varices. Re-bleeding occurs in about 10% of patients with non-variceal bleeding and up to 25% of those with variceal bleeding. Mortality is four times higher in patients who re-bleed.

Fibrinolysis may play an important role in GI bleeding and re-bleeding, due to premature breakdown of blood clots at the bleeding site. Tranexamic acid (TXA) reduces clot breakdown by inhibiting the action of plasmin. A systematic review of the effect of TXA in surgical patients shows that it reduces the probability of blood transfusion by about a third (RR=0.62, 95% CI 0.58 to 0.65), with no evidence of any increase in risk of thromboembolic events. The CRASH-2 trial showed that early administration of TXA reduces deaths due to bleeding (RR=0.85, 95% CI 0.76 to 0.96), and all-cause mortality (RR=0.91, 95% CI 0.85 to 0.97) in trauma patients, without increasing thromboembolic events. A systematic review of clinical trials of TXA in upper GI bleeding shows a reduction in the risk of death with TXA (RR=0.61, 95% CI 0.42 to 0.89), but the quality of the trials was poor and the estimate is imprecise. All but one of the trials were conducted before the use of endoscopy and proton pump inhibitors and were too small to assess the effect of TXA on thromboembolic events. For these reasons, we believe that the effectiveness and safety of TXA in GI bleeding is uncertain and that a high quality randomised controlled trial is needed.

AIM: The HALT-IT trial will determine the effect of early administration of TXA on mortality, morbidity (re-bleeding, non-fatal vascular events), blood transfusion, surgical intervention and health status in patients with acute gastrointestinal bleeding.

PRIMARY OUTCOME: The primary outcome is death in hospital within 28 days of randomisation (cause-specific mortality will also be recorded). Cause specific mortality will be described as per section 3.1 of the outcome form (haemorrhage, myocardial infarction, stroke, pulmonary embolism, pneumonia, malignancy, other).

SECONDARY OUTCOMES:

a) Death from haemorrhage
b) Re-bleeding
c) Need for surgery or radiological intervention
d) Blood product transfusion
e) Thromboembolic events (deep vein thrombosis, pulmonary embolism, stroke, myocardial infarction)
f) Other complications (significant cardiac event, sepsis, pneumonia, respiratory failure, renal failure, liver failure, seizures)
g) Patient's self care capacity using the Katz Index of Independence in Activities of Daily Living
h) Days spent in intensive care unit or high dependency unit
i) Patient status (death, hospital readmission) at 12 months

TRIAL DESIGN:

A pragmatic, randomised, double blind, placebo controlled trial among 12,000 patients with significant gastrointestinal bleeding.

DIAGNOSIS AND INCLUSION/EXCLUSION CRITERIA:

Adults with significant acute upper or lower gastrointestinal bleeding. The diagnosis of significant bleeding is clinical but significant implies a risk of bleeding to death and may include patients with hypotension, tachycardia, signs of shock, or those needing urgent transfusion, endoscopy or surgery. The fundamental eligibility criterion is the responsible clinician's 'uncertainty' as to whether or not to use tranexamic acid in a particular patient with GI bleeding. If the clinician believes there is a clear indication for, or clear contraindication to, tranexamic acid use, the patient should not be randomised. There are no pre-specified exclusion criteria.

TEST PRODUCT, REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION:

A loading dose of tranexamic acid (1 gram by intravenous injection) or placebo (sodium chloride 0.9%) will be given as soon as possible after randomisation, followed by an intravenous infusion of 3 grams of TXA or placebo (sodium chloride 0.9%) over 24 hours.

SETTING:

This trial is coordinated from the London School of Hygiene & Tropical Medicine Clinical Trials Unit (University of London) and conducted in hospitals worldwide.

DURATION OF TREATMENT AND PARTICIPATION:

Eligible patients should be randomised as soon as possible. The loading dose will be given immediately after randomisation and the maintenance dose will be given immediately after the loading dose, over 24 hours. Participation will end at discharge from randomising hospital, death or at 28 days post randomisation, whichever occurs first.

CRITERIA FOR EVALUATION:

All patients randomly allocated to tranexamic acid will be compared with those allocated to placebo, irrespective of whether they received the allocated treatment or not ('intention to treat' analysis).

CLINICAL PHASE	3
PLANNED TRIAL START	2 January 2013
PLANNED DATE OF LAST PATIENT ENROLMENT	31 May 2019