CRASH-2

Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage

A LARGE RANDOMISED PLACEBO CONTROLLED TRIAL AMONG TRAUMA PATIENTS WITH OR AT RISK OF SIGNIFICANT HAEMORRHAGE, OF THE EFFECTS OF ANTIFIBRINOLYTIC TREATMENT ON DEATH AND TRANSFUSION REQUIREMENT

BACKGROUND: For people at ages 5 to 45 years, trauma is second only to HIV/AIDS as a cause of death. Each year, worldwide, about three million people die as a result of trauma, many after reaching hospital. Among trauma patients who do survive to reach hospital, exsanguination is a common cause of death, accounting for nearly half of in-hospital trauma deaths. Central nervous system injury and multi-organ failure account for most of the remainder, both of which can be exacerbated by severe bleeding. Antifibrinolytic agents are widely used in major surgery to prevent fibrinolysis and reduce surgical blood loss, however, its effect in adult trauma patients with significant haemorrhage, or who are considered to be at risk of significant haemorrhage is unknown.

AIM: CRASH-2 aims to determine the effect of the early administration of the antifibrinolytic agent tranexamic acid (TXA) on death and transfusion requirement in adult trauma patients with ongoing significant haemorrhage, or who are considered to be at risk of significant haemorrhage. In addition, the effect on the risk of non-fatal vascular events (either haemorrhagic or occlusive) will be assessed.

METHOD: CRASH-2 is planned to be a large (approximately 20,000 patients), randomised, placebo controlled trial of the effects of tranexamic acid administration on death, vascular events and transfusion requirements. Adult trauma patients with ongoing significant haemorrhage or at risk of significant haemorrhage, within 8 hours of injury, except those for whom antifibrinolytic agents are thought to be clearly indicated or clearly contra-indicated, are eligible. Numbered drug or placebo packs will be available in participating emergency departments and randomised in one of two ways: Hospitals with reliable telephone access will use a central telephone randomisation service or where the doctors feel that central randomisation is not feasible a local pack system (next consecutively numbered treatment pack taken from a box of eight packs, with a random allocation sequence) will be used.

TREATMENT: The dosing regimen will entail intravenous administration of a loading dose of 1 gram of TXA or placebo in a 100mL intravenous infusion over 10 minutes followed by a maintenance infusion of 120 mg/hour for 8 hours.

OUTCOME: The primary outcome measure is death in hospital within four weeks of injury (causes of death will be classified). Secondary outcome measures will be receipt of a blood transfusion, volume of blood transfused, surgical intervention and the occurrence of vascular events (haemorrhagic stroke, occlusive stroke, myocardial infarction, pulmonary embolism, clinically diagnosed deep vein thrombosis). Data will be recorded on a single sided outcome form which can be completed entirely from the hospital notes. There will be no additional tests.

IF A WIDELY PRACTICABLE TREATMENT SUCH AS TXA COULD REDUCE BLOOD LOSS FOLLOWING TRAUMA THEN THIS MIGHT PREVENT THOUSANDS OF PREMATURE TRAUMA DEATHS EACH YEAR AND SECONDLY COULD REDUCE EXPOSURE TO THE RISKS OF BLOOD TRANSFUSION. BLOOD IS A SCARCE AND EXPENSIVE RESOURCE AND MAJOR CONCERNS REMAIN ABOUT THE RISK OF TRANSFUSION-TRANSMITTED INFECTION.

TRAUMA AND SIGNIFICANT HAEMORRHAGE

CONSIDER FOR CRASH 2 TRIAL OF ANTIFIBRINOLYTIC TREATMENT OF HAEMORRHAGE AFTER TRAUMA

CRASH2

ELIGIBILITY

- All adult trauma patients (appearing to be at least 16 years old) with ongoing significant haemorrhage (systolic blood pressure less than 90 mmHg and/or heart rate more than 110 beats per minute), or considered to be at risk of significant haemorrhage, within 8 hours of the injury
- No clear indication for, or contraindication to antifibrinolytic agents, in view of clinician

RANDOMISATION

TELEPHONE CENTRES

Telephone freecall randomisation service and give:

- patient initials and sex
- birth date (if known) or approximate age
- hours since injury and type of injury
- GCS, SBP, respiratory rate, central capillary refill time, heart rate

Treatment pack number will be allocated – get treatment pack and follow instructions on it

NON-TELEPHONE CENTRES

Complete patient entry form with:

- patient initials and sex
- birth date (if known) or approximate age
- hours since injury and type of injury
- GCS, SBP, respiratory rate, central capillary refill time, heart rate

Get lowest available number treatment pack and follow instructions on it

TREATMENT

- 10-minute loading infusion of 100mL (1g tranexamic acid or placebo)
- 8-hour infusion of 60mL/hr (120mg/hour tranexamic acid or placebo for about 8 hours)

DATA COLLECTION

One single-sided outcome form completed from hospital notes at discharge, death in hospital or four weeks from injury, whichever occurs first

FOR 24-HOUR RANDOMISATION

TELEPHONE CENTRES

FREECALL

(see number in your site file)

NON-TELEPHONE CENTRES

SECURE WEBSITE, ELECTRONIC DATA FORMS, EMAIL OR FAX

(see instructions in your site file)

INFORMATION AND STUDY MATERIALS:
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ISRCTN86750102