Tranexamic acid for the treatment of significant traumatic brain injury: an international randomised, double blind placebo controlled trial

RATIONALE AND OVERVIEW
Traumatic brain injury

- 10 million killed or hospitalised every year
- 90% in low and middle income countries
- Mostly young adults and long lasting disability
- The incidence of TBI is predicted to rise

Tranexamic acid and bleeding

TXA reduces bleeding in surgery

**Transfusion**

- TXA better
- TXA worse

RR (95% CI) - 0.62 (0.58-0.65)

- 95 trials

**Mortality**

- TXA better
- TXA worse

RR (95% CI) - 0.61 (0.38-0.98)

- 72 trials

Ker et al. BMC Emergency Medicine 2012, 12:3
Bleeding is a common complication of traumatic brain injury

- It is associated with poor outcome
- It can develop or worsen after hospital admission
- Early intervention may prevent enlargement


Why TXA and intracranial bleeding?

- Coagulopathy affects about one third of patients with TBI
- Increased fibrinolysis is a common feature of coagulopathy
- Two randomised controlled trials of TXA in TBI

## CRASH-2 Intracranial Bleeding Study (IBS)

<table>
<thead>
<tr>
<th>Event</th>
<th>TXA n (%)</th>
<th>Placebo n (%)</th>
<th>OR (95% CI) n=249</th>
</tr>
</thead>
<tbody>
<tr>
<td>Significant haemorrhage growth (n 123/126)</td>
<td>44 (36)</td>
<td>56 (44)</td>
<td>0.70 (0.42–1.16)</td>
</tr>
<tr>
<td>New focal ischaemic regions (n 123/126)</td>
<td>6 (5)</td>
<td>12 (9)</td>
<td>0.49 (0.18–1.35)</td>
</tr>
<tr>
<td>Death (n 133/137)</td>
<td>14 (10.5)</td>
<td>24 (17.5)</td>
<td>0.55 (0.27–1.22)</td>
</tr>
</tbody>
</table>

Thai Study of TXA in TBI

240 patients with isolated TBI

<table>
<thead>
<tr>
<th></th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemorrhage growth</td>
<td>0.56 (0.32–0.96)</td>
</tr>
<tr>
<td>Mortality</td>
<td>0.67 (0.34–1.32)</td>
</tr>
</tbody>
</table>

Meta-analysis

**Significant Haemorrhage growth**

- CRASH-2 IBS: Odds ratio 0.70 (95% CI: 0.42, 1.16) with 58.8% weight
- Thai study: Odds ratio 0.48 (95% CI: 0.25, 0.95) with 41.2% weight
- Overall (95% CI): Odds ratio 0.61 (95% CI: 0.41, 0.91)
CRASH-2 IBS

Thai study

Overall (95% CI)

Meta-analysis

Mortality

<table>
<thead>
<tr>
<th>Study</th>
<th>Odds ratio (95% CI)</th>
<th>% Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRASH-2 IBS</td>
<td>0.55 (0.27,1.12)</td>
<td>56.6</td>
</tr>
<tr>
<td>Thai study</td>
<td>0.63 (0.29,1.37)</td>
<td>43.4</td>
</tr>
<tr>
<td>Overall (95% CI)</td>
<td>0.59 (0.35,0.99)</td>
<td></td>
</tr>
</tbody>
</table>
The CRASH-3 trial will provide reliable evidence about the effect of tranexamic acid on mortality and disability in patients with TBI.

The effect of TXA on the risk of vascular occlusive events and seizures will also be assessed.
Sample size

13,000 TBI patients

➢ 90% power (two sided alpha=1%)
➢ 15% relative reduction in all-cause mortality
Before the trial starts

- A completed Hospital & Principal Investigator CV Form
- GCP training certificate(s)
- Approval of your hospital (if required)
- Ethics Approval (local and/or national)
- Ministry of Public Health approval (if applicable)
- A signed Principal Investigator Agreement
- A copy of the approved Patient Information Sheet & Consent form (if different from the protocol sent to you)
Good Clinical Practice (GCP): is an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects.

➢ Free online training via our website

➢ All staff should complete prior to the study starting at your hospital
Create a trial team

- Nominate someone to be responsible in your absence
- Provide information and training to all team members
- Identify people to be responsible for specific trial processes – they must be interested in the trial
- Every specialty should be represented:
  - neurosurgeons
  - traumatologists
  - nurses
  - intensivists
  - general surgeons
  - clerical staff
  - pharmacy
  - managers
  - administrators

Roles may include:
- Principal Investigator
- Sub-investigator
- Data collection
- Study coordinator
Overview

**ELIGIBILITY**
- adult
- with traumatic brain injury
- within 8 hours of injury (for the remainder of the trial we will limit recruitment to patients who are within 3 hours of injury)
- any intracranial bleeding on CT scan OR GCS ≤12
- no significant extracranial haemorrhage (requiring immediate transfusion)
- where the responsible clinician is substantially uncertain as to the appropriateness of antifibrinolytic agents in a patient

All clinically indicated treatment is given in addition to trial enrolment.

Adverse events are reported up to day 28.

If prior consent waiver used, consent from patient or relative required after emergency is over.

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Appropriate **CONSENT PROCESS** for patient eg prior representative agreement or waiver

**RANDOMISE** (tranexamic acid or placebo)

**Entry form** completed

Give **loading dose** over 10 minutes

Give **maintenance dose** over 8 hours

Complete **outcome form** at prior discharge, death, or day 28
Consent – at trial entry

- **If representative is available:** Bear in mind the distressing nature of the situation and lack of time. Provide them with brief information and if agreement, continue to randomise. Full consent to be obtained after emergency situation is over.

- **If no representative:** Two clinicians (one independent of the trial) will consider the eligibility criteria and any known views of the patient about trial participation. Together they will decide whether or not to enrol the patient into the trial (i.e. a waiver)
Consent – after emergency is over

Full informed written consent for continuation to be obtained from either:

➢ patient (if capacity returns)
➢ relative (if they become known and patient unable)
➢ other representative (if patient unable and if no relative)
**Entry Form**

**One page only**

- Complete questions 1–14 to assess eligibility
- If eligible, follow appropriate consent process – complete 15–16
- **RANDOMISE**: Use next lowest available pack number – STRICT NUMERICAL ORDER

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### ABOUT YOUR HOSPITAL

- Please complete 1–16 before randomising the patient.

#### 1. Country

#### 2. Hospital code (in your Study Files)

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### ABOUT THE PATIENT

- **Patient’s initials (first name/last name)**
- **Patient hospital ID**
- **Age**: years – approximate (if unknown)
- **Sex**: (circle) MALE/FEMALE

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### ABOUT THE INJURY AND PATIENT’S CONDITION

- **Time since injury (insert hours)**: Best estimate from history
- **Systolic Blood Pressure**: mmHg (most recent measurement prior to randomisation)
- **Glasgow Coma Score (GCS)** (circle one response for each category)
  - 1. Eye opening
  - 2. Motor response
  - 3. Verbal response
- **First measurement in hospital of GCS** (if unknown give value at randomisation)
  - 1. Eye
  - 2. Motor
  - 3. Verbal
  - 4. Total

- **This GCS is**: (circle one)
  - Before
  - After
- **Intubation/Extrication**

- **Any significant extracranial bleeding?**
  - YES
  - NO

- **Any intracranial bleeding on CT scan (before randomisation)?**
  - YES
  - NO

- **Location of intracranial haemorrhage on CT Scan** (circle one response for each site)
  - a) Epidural
  - b) Subdural
  - c) Subarachnoid
  - d) Parenchymal
  - e) Intraventricular

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Randomisation

- Use next lowest available pack number
- Record on Randomisation log
- Record pack used on Drug Accountability Log
Entry form and Randomisation

RANDOMISATION INFORMATION
Eligible if adult, with TBI, no significant extracranial bleeding, within 8h of injury (GCS=12 or less, or any intracranial haemorrhage on CT scan)

<table>
<thead>
<tr>
<th></th>
<th>Eligible? (circle)</th>
<th>YES</th>
<th>Get the lowest available number treatment pack and follow instructions</th>
<th>NO</th>
<th>Do not randomise, record on screening log</th>
</tr>
</thead>
<tbody>
<tr>
<td>15.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>16. Consent process for entry used? (circle)</td>
<td>WAIVER</td>
<td>OTHER REPRESENTATIVE</td>
<td>RELATIVE</td>
<td></td>
<td></td>
</tr>
<tr>
<td>17. Insert treatment pack number here</td>
<td>BOX</td>
<td></td>
<td>PACK</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18. Date of randomisation</td>
<td>day</td>
<td>month</td>
<td>year</td>
<td>19. Time of randomisation (24-hour clock)</td>
<td>hours</td>
</tr>
<tr>
<td>20. Name of person randomising</td>
<td></td>
<td></td>
<td>21. Signature</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Dose

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Dose TXA or placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loading</td>
<td>1 gram / 10 minutes (IV infusion)</td>
</tr>
<tr>
<td>Maintenance</td>
<td>1 gram / 8 hours (IV infusion)</td>
</tr>
</tbody>
</table>
How to give the trial treatment

ALL AMPOULES ARE IDENTICAL AND CONTAIN 500mg OF EITHER TRANEXAMIC ACID OR PLACEBO

LOADING DOSE
2 ampoules over 10 minutes
Give immediately after randomisation
PRESCRIBE: “CRASH-3 Trial (1 gram of tranexamic acid/placebo) over 10 minutes”
Draw up 10mL (2 ampoules of tranexamic acid / placebo) and add to 100mL bag of Sodium Chloride 0.9% (provided) and infuse over 10 minutes.

MAINTENANCE DOSE
2 ampoules over 8 hours
Start immediately after completion of loading dose
PRESCRIBE: “CRASH-3 Trial (1 gram of tranexamic acid / placebo). Infuse at 60 mL/hour”
Draw up 10mL (2 ampoules of tranexamic acid / placebo) and add to 500mL bag of any isotonic intravenous solution and infuse over about 8 hours.
Outcomes

Primary outcome
- Death in hospital within four weeks of injury among patients randomised within 3 hours of injury
- Cause-specific mortality will also be recorded

Secondary outcomes
- Vascular occlusive events
- Disability
- Seizures
- Neurosurgical intervention
- Days in intensive care
- Other adverse events will be described
No extra tests required – a short single page Outcome form completed 4 weeks (28 days) after randomisation, at discharge, or at death (whichever occurs first)

Outcome to be collected even if the trial treatment is interrupted or is not actually given

Form to be sent to the TCC as soon as possible
Death, life-threatening complications and prolonged hospital stay are pre-specified outcomes.

Adverse events will be limited to serious events that are NOT already listed as primary or secondary outcomes, yet, which might reasonably occur as a consequence of the study drug.

Events that are part of the natural history of the primary event, or expected complications of critical medical events, should not be reported as serious adverse events e.g. low blood pressure, increased intracranial pressure and reduced urine output associated with TBI.

After discharge and up to Day 28 all untoward medical occurrences should be reported
Sending your data

**Internet:** Primary data collection is to be done via internet

A username and password to use this site will be sent to you by email before you start the trial.

**Email:** as scanned documents
Trial Materials

**BEFORE YOU START THE TRIAL YOU WILL RECEIVE:**

- a study file compiled specifically for your hospital, containing contact details, further information, guidance, spare forms and filing space for completed data forms
- training CD with PowerPoint presentations
- training DVD of the trial procedures and a protocol presentation
- randomisation posters with step by step guidance
- brief information leaflets and wall posters for the families

**TREATMENT PACKS**

- Initially one box of 8 patient packs
- Stock level is monitored by patient entries received at the TCC
- We will send new boxes when you reach your minimum stock level, which is dependent on your randomisation rate
- With each box you will receive a document pack containing your hospital specific patient information sheets, consent forms, alert cards and brief information leaflets

**TRAINING AND PRESENTATIONS**

Please contact the TCC if

- you need more training materials for staff sessions
- you are presenting the trial at meetings or conferences

**PROTOCOLS**

- protocol summaries
- pocket cards
Trial Materials
If a simple and widely practicable treatment was shown to improve outcomes in patients with TBI, it could save many thousands of lives

Join us now at crash3.Lshtm.ac.uk

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