

CRASH-2 (Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage) intracranial bleeding study: the effect of tranexamic acid in traumatic brain injury – a nested, randomised, placebo-controlled trial

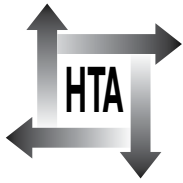
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Abstract

CRASH-2 (Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage) intracranial bleeding study: the effect of tranexamic acid in traumatic brain injury – a nested, randomised, placebo-controlled trial

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Background: Tranexamic acid (TXA) has been shown to reduce blood loss in surgical patients and the risk of death in patients with traumatic bleeding, with no apparent increase in vascular occlusive events. These findings raise the possibility that it might also be effective in traumatic brain injury (TBI).

Objective: The Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage Intracranial Bleeding Study (CRASH-2 IBS) was conducted to quantify the effect of an early short course of TXA on intracranial haemorrhage and new focal cerebral ischaemic lesions in patients with TBI.

Design: CRASH-2 IBS was a prospective randomised controlled trial nested within the CRASH-2 trial. Randomisation was balanced by centre, with an allocation sequence based on a block size of eight. We used a local pack system that selected the lowest numbered treatment pack from a box containing eight numbered packs. Apart from the pack number, the treatment packs were identical. The pack number was recorded on the entry form, which was sent to the international trial co-ordinating centre in London, UK. Once the treatment pack number was recorded, the patient was included in the trial whether or not the treatment pack was opened or the allocated treatment started. All site investigators and trial co-ordinating centre staff were masked to treatment allocation.

Setting: Ten hospitals: (India) Aditya Neuroscience Centre, Sanjivani Hospital, CARE Hospital, Christian Medical College, Medical Trust Hospital, Jeevan Jyoti Hospital and (Colombia) Hospital Universitario San Vicente de Paul, Hospital Pablo Tobón Uribe, Hospital Universitario San José de Popayán and Fundación Valle del Lili.

Participants: The trial was conducted in a subset of 270 CRASH-2 trial participants. Patients eligible for inclusion in the CRASH-2 IBS fulfilled the inclusion criteria for the CRASH-2 trial, and also had TBI [Glasgow Coma Scale score of ≤ 14 and a brain computerised tomography (CT) scan compatible with TBI]. Pregnant women and patients for whom a second brain CT scan was not possible were excluded.

Interventions: Participants were randomly allocated to receive either a loading dose of 1 g of TXA infused over 10 minutes followed by an intravenous infusion of 1 g over 8 hours or matching placebo.

Main outcome measure: The primary outcome was the increase in size of intracranial haemorrhage growth between a CT scan at hospital admission and a second scan 24–48 hours later.

Results: One hundred and thirty-three patients were allocated to TXA and 137 to placebo, of whom information on the primary (imaging) outcome was available for 123 (92%) and 126 (92%) respectively. The analysis suggested that TXA was likely to be associated with a reduction in haemorrhage growth [adjusted difference –3.8 ml, 95% credibility interval (CrI) –11.5 ml to 3.9 ml], fewer focal ischaemic lesions [adjusted odds ratio (OR) 0.54, 95% CrI 0.20 to 1.46] and fewer deaths (adjusted OR 0.49, 95% CrI 0.22 to 1.06).

Conclusions: This was the first randomised controlled study to evaluate the effect of TXA in TBI patients and it found that neither moderate benefits nor moderate harmful effects can be excluded. However, although uncertainty remains, our analyses suggest that TXA administration might improve outcome in TBI patients and provide grounds for evaluating this hypothesis in future research.

Trial registration: Current Controlled Trials ISRCTN86750102.

Source of funding: This project was funded by the NIHR Health Technology Assessment programme and will be published in full in *Health Technology Assessment*; Vol. 16, No. 13. See the HTA programme website for further project information.

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List of abbreviations

CI	confidence interval
CRASH-2	Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage
CRASH-2 IBS	CRASH-2 Intracranial Bleeding Study
CrI	credibility interval
CT	computerised tomography
GCS	Glasgow Coma Scale
mOHS	modified Oxford Handicap Scale
OR	odds ratio
RR	relative risk
SD	standard deviation
sSH	spontaneous subarachnoid haemorrhage
TBI	traumatic brain injury
TXA	tranexamic acid

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices, in which case the abbreviation is defined in the figure legend or in the notes at the end of the table.

Executive summary

Background

Traumatic brain injury (TBI) is a leading cause of death and disability worldwide.

Approximately one-third of patients with TBI have coagulopathy. Those with coagulopathy have an increased risk of haemorrhage growth and higher mortality. Increased fibrinolysis, as indicated by high levels of fibrinogen degradation products, is a common feature of the coagulopathy in TBI raising the possibility that antifibrinolytics agents, such as tranexamic acid (TXA) might reduce traumatic intracranial haemorrhage. To date, there have been no randomised controlled trials of TXA in TBI. The CRASH-2 (Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage) trial, conducted in 20,211 bleeding trauma patients evaluated the effect on mortality and transfusion requirements of TXA in trauma patients with significant bleeding. Although TBI was not an inclusion criterion, it is likely that a significant proportion of included patients would also have had TBI.

Objectives

The Intracranial Bleeding Study (CRASH-2 IBS) was conducted nested within the CRASH-2 trial, to quantify the effect of an early short course of TXA on intracranial haemorrhage and new focal cerebral ischaemic lesions in patients with TBI.

Methods

Trial design

A double-blind, randomised, placebo-controlled trial of the effects of TXA on intracranial haemorrhage and focal ischaemic brain lesions, in adult trauma patients with significant haemorrhage and TBI, was conducted.

Participants

The trial was conducted in a subset of CRASH-2 trial participants. Patients eligible for inclusion in the CRASH-2 IBS fulfilled the inclusion criteria for the CRASH-2 trial, but also had TBI [Glasgow Coma Scale (GCS) score of ≤ 14 and a brain computerised tomography (CT) scan compatible with TBI]. Pregnant women and patients for whom a second brain CT scan was not possible were excluded.

Study settings

Patients were recruited from 10 hospitals in India and Colombia.

Interventions

Participants were randomly allocated to receive a loading dose of 1 g of TXA infused over 10 minutes, followed by an intravenous infusion of 1 g over 8 hours or matching placebo (sodium chloride 0.9%).

Outcomes

We obtained two brain CT scans for each participant: the first before randomisation and the second 24–48 hours later.

The primary outcome was the occurrence of total haemorrhage growth. Secondary outcomes were (1) the occurrence of significant haemorrhage growth defined as an increase by 25% or more of total haemorrhage in relation to its initial volume; (2) new intracranial haemorrhage (apparent on the second scan, but not apparent on the first); (3) change in subarachnoid haemorrhage grade; (4) mass effect; and (5) the occurrence of new focal cerebral ischaemic lesions (apparent on the second scan, but not apparent on the first).

The clinical outcomes were death from any cause and the need for neurosurgical intervention. Clinical outcomes were recorded on discharge from hospital, at 28 days, or death, whichever occurred first. We also reported a combined 'poor outcome' defined as a patient who developed one or more of the following during the scheduled follow-up period: significant haemorrhage growth, new intracranial haemorrhage, new focal cerebral ischaemic lesions, the need for neurosurgery or death. Adverse events that were serious, unexpected, and suspected to be related to the study treatment, were reported separately.

Randomisation and blinding

Randomisation was balanced by centre, with an allocation sequence based on a block size of eight. All site investigators and trial co-ordinating centre staff were masked to treatment allocation. TXA and placebo ampoules were indistinguishable.

Statistical methods

We used a Bayesian statistical approach. Our primary analysis used non-informative priors to reflect the lack of previous knowledge. A sensitivity analysis using information from the systematic review of TXA in aneurysmal subarachnoid haemorrhage was conducted.

We used generalised linear-mixed models adjusted for baseline variables. Adjusted effects are considered in the primary analysis, but both adjusted and unadjusted effect measures are reported.

Haemorrhage growth was analysed using multiple linear regression (analysis of covariance), the main factor being the treatment group. Binary outcomes were analysed using logistic regression. All analyses were undertaken on an intention to treat basis. We used the statistical software package Stata (version SE/11.0) from StataCorp LP (College Station, TX, USA).

Results

We recruited 270 patients (133 allocated to TXA and 137 allocated to placebo) between August 2008 and January 2010. All patients received the loading and maintenance doses, except one placebo-allocated patient who did not receive the maintenance dose. All patients were followed up for clinical outcomes. A total of 256 patients (95%) had the first CT scan. A total of 211 patients (82%) had some form of intracranial haemorrhage (intra-parenchymal haematoma, haemorrhagic contusion, subdural haematoma or epidural haematoma). Five patients had a focal ischaemic lesion (two patients in the TXA group and three in the placebo group). Forty patients (20 TXA allocated and 20 placebo allocated) had neurosurgical evacuation on the basis of the first CT scan findings.

The mean total haemorrhage growth was 5.9 ml [standard deviation (SD) 26.8 ml] and 8.1 ml (SD 29.2 ml) in the TXA and placebo group respectively. The adjusted analysis showed a greater reduction in total haemorrhage growth in the TXA group than in the placebo group [−3.8 ml, 95% credibility interval (CI) −11.5 ml to 3.9 ml]. In patients who had neurosurgical evacuation before the second CT scan, the extent of this reduction was even larger (−15 ml, 95% CrI −45.7 ml to 15.5 ml).

A beneficial effect of TXA was highly probable (range 89% to 94%) for all of the binary CT scan outcomes. The sensitivity analysis for significant haemorrhage growth gave an adjusted odds ratio (OR) of 0.53 (95% CrI 0.41 to 0.68) with a very high probability (99%) of a clinical significant beneficial effect. The sensitivity analysis for new focal cerebral ischaemic lesions gave an adjusted OR of 1.18 (95% CrI 0.87 to 1.60). The probability of a clinically significant harmful effect was 35%.

There were 14 (10.5%) deaths in the TXA group and 24 (17.5%) in the placebo group (OR 0.57, 95% CrI 0.28 to 1.14). The adjusted OR for death was 0.49 (95% CrI 0.22 to 1.06). Twenty (15%) patients in the TXA group and 21 (15%) in the placebo group had neurosurgery other than those evacuations based on first CT scan findings (OR 0.98, 95% CrI 0.50 to 1.93). The adjusted OR for neurosurgery was 0.98 (95% CrI 0.50 to 1.91). The probability of a beneficial effect was 96% and 53% for mortality and neurosurgery respectively. Sixty (45%) patients in the TXA group and 80 (58%) in the placebo group had a poor outcome (OR 0.59, 95% CrI 0.37 to 0.96). The adjusted OR for poor outcome was 0.57 (95% CrI 0.33 to 0.98).

No emergency unblinding was needed, and there were no adverse events regarded as serious, unexpected, or suspected to be related to the study treatment.

Conclusions

This was the first randomised controlled study to evaluate the effect of TXA in TBI patients, and found that neither moderate benefits nor moderate harmful effects can be excluded. However, although uncertainty remains, our analyses suggest that TXA administration might improve outcome in TBI patients and provide grounds for evaluating this hypothesis in future research.

We found a reduction in new focal cerebral ischaemic lesions in TXA allocated patients. Overall, the incidence of these lesions was low and it is possible that the observed difference between the groups may have arisen by chance alone. The CRASH-2 trial has shown reliably that early administration of TXA in trauma patients with, or at risk of, significant bleeding reduces the risk of all-cause mortality. However, many patients with traumatic haemorrhage also have TBI and concerns about the risk of cerebral ischaemia may influence some doctors' decision to give TXA to these patients. The results presented here provide reassurance about the safety of TXA in bleeding trauma patients with TBI.

Our results have important research implications. If TXA reduces intracranial haemorrhage after TBI without increasing the risk of ischaemic lesions, it could substantially improve patient outcomes. Although an increased risk of cerebral ischaemia cannot be ruled out, there is a reasonable basis to expect that the benefits of TXA administration could outweigh the risks. However, the CRASH-2 IBS was conducted among TBI patients with significant (extra-cranial) haemorrhage and the effect of TXA might be different in patients with isolated TBI. Future research should be conducted to reliably assess the effectiveness and safety of the early administration of a short course of TXA in patients with isolated TBI.

Trial registration

This trial is registered as ISRCTN86750102.

Funding

This project was funded by the NIHR Health Technology Assessment programme and will be published in full in *Health Technology Assessment*; Vol. 16, No. 13. See the HTA programme website for further project information.

Chapter 1

Introduction

Traumatic brain injury (TBI), which can be defined as an alteration in brain function or other evidence of brain pathology caused by an external force, is a leading cause of death and disability worldwide.¹ It is estimated that each year more than 1.5 million people die and about 10 million people are hospitalised following a TBI.² TBI is commonly accompanied by intracranial bleeding. Its frequency varies according to TBI severity. In the CRASH-1 (Corticosteroid Randomisation after Significant Head Injury) trial, which included 10,008 patients with mild, moderate and severe TBI, 67% of participants had computerised tomography (CT) scan evidence of intracranial bleeding.³

Regardless of location, patients with large haematomas have a substantially higher mortality rate than patients with small haematomas. We conducted an analysis of 13,962 patients with TBI from the Trauma Audit & Research Network (TARN) and found that large intracranial bleeds were associated with an increased risk of mortality compared with small ones. The odds ratios (ORs) for mortality for large subdural, parenchymal and epidural bleeds, in comparison with small bleeds, were 3.41 [95% confidence interval (CI) 2.68 to 4.33], 3.47 (95% CI 2.26 to 5.33) and 2.86 (95% CI 1.86 to 4.38), respectively.⁴

In about half of TBI patients with intracranial bleeding, the haematomas enlarge after hospital admission. Studies involving repeated CT scanning have found that intracranial bleeds can develop or expand in the 24 hours after injury. Oertel *et al.*⁵ studied a group of patients in whom two CT scans were obtained within 24 hours of injury to determine the prevalence of progressive intracranial haemorrhage. Among patients who had their first CT scan within 2 hours of injury, 49% had radiological evidence of progressive haemorrhage. Yadav *et al.*⁶ conducted repeat CT scanning of TBI patients at hospital admission and 24 hours later and found that 16% of 262 parenchymal haematomas and contusions increased in size in the first 24 hours. Similarly, Sullivan *et al.*⁷ found that traumatic epidural haemorrhages enlarged in 23% of 160 TBI patients treated non-operatively. The mean enlargement was 7 mm, and the mean time to enlargement was 8 hours from injury and 5.3 hours from CT diagnosis. More recently, Narayan *et al.*⁸ reported a study in which they included patients with TBI and parenchymal intracranial bleeding confirmed by CT scan of ≥ 2 ml. They repeated the CT scan at 24 and 72 hours and found that in 51% of the included patients the lesions expanded.

In summary, traumatic intracranial bleeding appears to be a common complication after TBI, it is associated with a worse prognosis, larger bleeds have worse outcomes and the bleeding appears to continue after hospital admission. These observations raise the possibility that an intervention administered in the first hours after the injury may prevent the enlargement of intracranial bleeding and therefore might improve patients' outcomes.

In the haemostatic process, coagulation occurs rapidly at the site of a damaged vessel, building a tight net of fibrin, while at the same time the fibrinolytic system removes the fibrin deposits that could cause permanent vascular occlusion once vascular repair has taken place.⁹ The coagulation and fibrinolytic system are believed to be in a state of dynamic balance that maintains an intact vascular system. Tranexamic acid (TXA) is a potent antifibrinolytic agent that exerts its effect by blocking lysine binding sites on plasminogen molecules and has the potential to enhance the effectiveness of the patient's own haemostatic mechanisms. Consequently, clot breakdown

(fibrinolysis) is inhibited and excessive or recurrent bleeding is reduced. TXA is commonly used in surgery to reduce blood loss. A systematic review of randomised controlled trials of TXA in elective surgery showed that it reduces the need for transfusion by one-third, reduces donor exposure by one unit and halves the need for further surgery to control bleeding.¹⁰

It is biologically plausible that TXA reduces haemorrhage growth in TBI patients. About one-third of TBI patients have coagulopathy at hospital admission.¹¹ TBI patients with coagulopathy are more likely to have progressive haematomas and are more likely to die.¹¹ Increased fibrinolysis, as indicated by low levels of fibrinogen and high levels of fibrinogen degradation products and D-dimers, is a common feature of the coagulopathy seen in TBI patients, raising the possibility that an antifibrinolytic agent might reduce intracranial bleeding.¹² To date, there have been no randomised controlled trials of TXA in TBI.¹³

The possibility that TXA might reduce intracranial bleeding has, however, been evaluated in spontaneous subarachnoid haemorrhage (sSH). A systematic review of randomised controlled trials of TXA administration in patients with sSH found that TXA reduced the rate of rebleeding by approximately 40%.¹⁴ However, because of an increase in cerebral ischaemia there was no overall clinical benefit. This finding has resulted in scepticism about its potential for benefit in TBI.¹⁵ However, the effect of TXA from the sSH trials might not be directly generalisable to TBI patients. The characteristics and risk of ischaemia of patients with sSH are different from those of patients with TBI. Moreover, the duration of TXA treatment in the sSH trials was up to 6 weeks and this may account for the increase in cerebral ischaemia reported. It is possible that a shorter treatment might have prevented rebleeding while avoiding the risk of ischaemia.

The potential benefit of a simple and affordable intervention such as TXA for TBI patients could have important public health implications. The CRASH-2 (Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage) trial¹⁶ represented a unique opportunity to evaluate the effect of TXA in TBI patients, in order to reassess the existing belief of harm, and to generate a plausible prior of benefit, which could be informative to design future studies. The CRASH-2 trial recruited 20,211 trauma patients with significant (extracranial) haemorrhage.¹⁶ Although TBI was not an inclusion criterion, it was expected that a significant proportion of patients with multiple trauma would also have TBI. However, to keep data collection to a minimum, and to ensure recruitment to detect the main outcome (overall mortality), CT scan data were not routinely collected. Nevertheless, the CRASH-2 trial represented a unique opportunity to nest an exploratory study collecting CT scan data to evaluate the effect of TXA on imaging outcomes in TBI patients. Collection of evidence to inform future studies of TXA in this population, and specifically addressing the existing safety concerns about the increase of cerebral ischaemia in patients with TBI who receive TXA, also formed part of this study.¹³

The Intracranial Bleeding Study (CRASH-2 IBS) was a prospective randomised controlled trial nested within the CRASH-2 trial to quantify the effect of an early short course of TXA on intracranial haemorrhage and new focal cerebral ischaemic lesions in patients with TBI.

Chapter 2

Methods

Trial design

The CRASH-2 IBS is a double-blind randomised placebo-controlled trial nested in a cohort of CRASH-2 trial participants of the effects of TXA on intracranial bleeding and focal ischaemic brain lesions in adult trauma patients with significant haemorrhage and TBI (the trial protocol can be found in *Appendix 1*).

Participants

The CRASH-2 IBS was conducted in a subset of CRASH-2 trial participants. Eligible patients fulfil CRASH-2 trial inclusion criteria 'Adult trauma patients with significant haemorrhage (systolic blood pressure < 90 mmHg or heart rate > 110 beats per min, or both), or who were considered to be at risk of significant haemorrhage, and who were within 8 h of injury, were eligible for the trial. Entry was governed by the uncertainty principle¹⁷ and have a TBI [Glasgow Coma Scale (GCS) score of ≤ 14 and a CT scan compatible with TBI]. Pregnant women and patients for whom a second CT scan was not possible were excluded. Consent procedures at participating hospitals were established by local regulation and the appropriate ethics committees. Informed consent was obtained from patients if physical and mental capacity allowed. If patients could not give consent, proxy consent was obtained from a relative or representative. If a proxy was unavailable then, if permitted by local regulation, consent was deferred or waived. When consent was deferred or given by a proxy, the patient was informed about the trial as soon as possible and consent obtained for use of the data collected if required.

Study settings

Ten hospitals were selected based on level of interest by the principal investigator in the research question, recruitment rate in the CRASH-2 trial and ability of the hospital to collect and send the necessary CT scan data to the trial co-ordinating centre. The selected hospitals were (India) Aditya Neuroscience Centre, Sanjivani Hospital, CARE Hospital, Christian Medical College, Medical Trust Hospital, Jeevan Jyoti Hospital and (Colombia) Hospital Universitario San Vicente de Paul, Hospital Pablo Tobón Uribe, Hospital Universitario San José de Popayán and Fundación Valle del Lili.

Interventions

Patients were randomly allocated to receive either a loading dose of 1 g of TXA infused over 10 minutes followed by an intravenous infusion of 1 g over 8 hours or matching placebo (sodium chloride 0.9%). Each patient was assigned a uniquely numbered treatment pack that contained four ampoules of either TXA 500 mg or placebo, one 100-ml bag of 0.9% sodium chloride (for use with the loading dose), instructions for administration of trial treatment, a syringe and needle and stickers with the trial details and randomisation number (for attaching to infusion

bags, data forms and patient medical records). Information leaflets for patients and their representatives, consent forms and data collection forms were available in each box. The stickers, instructions, leaflets and forms were translated into local languages where needed.

Outcomes

Brain imaging outcomes

We obtained two brain CT studies for each participant, the first before randomisation and the second 24–48 hours later. A neuroradiologist (ZM), who was blind to treatment allocation, evaluated the pre-randomisation and 24- to 48-hour scans. She made the readings of the two scans twice (with the second reading blind to the results of the first reading), by central reading of the Digital Imaging and Communications in Medicine (DICOM) image files in Digital Jacket™ (DesAcc, Inc, Chicago, IL, USA) software. She measured the size of four types of intracranial haematomas (intraparenchymal, haemorrhagic contusion, subdural and epidural), subarachnoid haemorrhage, mass effect findings and the overall amount of tissue damage, using validated rating scales based on previous work. The individual ratings and measurements were combined into a rating form developed for the purposes of this study (see *Appendix 2*). She followed structured guidance to complete the CT scan form. This guidance provided definitions of the overall appearance of the scan, haemorrhagic findings, non-haemorrhagic findings and mass effect findings as detailed in the following section.

Computerised tomography scan guidance

Computerised tomography parameters

Slice thickness, interval, matrix and field of view should be recorded on CT 1 and 2 to allow comparison in case of differences in parameters between CT 1 and 2. For best comparison, parameters on CT 1 and 2 should be identical.

Angulation need not be identical but should allow direct comparison between CT 1 and 2 to be made (subjective assessment, based on planning scan and axial imaging).

Overall appearance of scan

Subjective assessment based on summation of all lesions present:¹⁸

- mild focal lesion (e.g. small contusion in one area of brain only, but rest of brain normal)
- medium focal lesion (e.g. several contusions in one or two immediately adjacent areas of brain, or small epidural haematoma or small subdural haematoma but rest of brain normal)
- mild or moderate diffuse injury (several small contusions or haematomas in several non-adjacent areas of brain, but normal appearance elsewhere)
- massive focal injury (e.g. large epidural haematoma or subdural haematoma or massive contusions or parenchymal haematoma in one area of the brain)
- massive diffuse injury (severe generalised swelling of the brain or many contusions or haematomas in multiple areas).

Haemorrhagic findings

Parenchymal haematoma

Definition: brain parenchymal blood collection secondary to local loss of vascular integrity.¹⁹

Volume measurement: $ABC/2$. A representative slice at the centre of the haematoma will be selected. The maximum linear length (A) in cm will be multiplied by the maximum width perpendicular to A (B) and the maximum depth (C) in cm. The depth (C) will be determined by multiplying the number of slices on which the haematoma is visible by the slice thickness listed on the CT scan. To obtain the volume in cm^3 the final product will be divided by 2.^{20,21}

If there is more than one haematoma, list all of them, specify the location and estimate the volume of each individual bleed and *give total by adding volumes*. Codes for location are: L = left, R = right, T = temporal, F = frontal, P = parietal, O = occipital, BG = basal ganglia, B = brainstem.

Subdural haematoma

Definition: haemorrhagic collection in subdural space.¹⁹

Volume measurement: adaptation of ABC/2 method. A representative slice near the centre of the haematoma will be selected. The linear distance in cm between each corner of the subdural crescent will be used to determine the length (A). The width (B) will be measured as the maximum thickness in cm of haematoma from the inner table of the skull perpendicular to the length. The depth (C) will be determined by multiplying the number of slices on which the haematoma is visible by the slice thickness listed on the CT scan. To obtain the volume in cm³ the final product will be divided by 2.²¹ *If there is more than one haematoma*, list all of them, specify the location and estimate the volume of each individual bleed and *give total by adding volumes*. Codes for location are: L = left R = right, T = temporal, F = frontal, P = parietal, O = occipital, BG = basal ganglia, B = brainstem.

Also, specify if there is tentorial subdural haematoma (TSH).

Epidural haematoma

Definition: blood collection within potential space between skull inner table and dura mater.¹⁹

Volume measurement: ABC/2, method as above.²²

If there is more than one haematoma, list all of them, specify the location and estimate the volume of each individual bleed and *give total by adding volumes*. Codes for location are: L = left, R = right, T = temporal, F = frontal, P = parietal, O = occipital, BG = basal ganglia, B = brainstem.

Subarachnoid haemorrhage

Definition: blood within subarachnoid spaces between pia and arachnoid membranes.

Subarachnoid haemorrhage score:²³ rates the thickness of subarachnoid haemorrhage within a representative sulcus: subarachnoid haemorrhage thickness ≤ 5 mm, subarachnoid haemorrhage thickness > 5 mm.

Specify whether subarachnoid haemorrhage is basal (B) or convexity (C).

Intraventricular haemorrhage

Definition: blood within ventricular system.

Intraventricular haemorrhage score:²⁴ the amount of intraventricular haemorrhage will be quantified in the lateral, third and fourth ventricles as follows: 0 indicates no blood; 1 – sedimentation (< 25% filled); 2 – moderately filled; 3 – completely filled, leading to an intraventricular haemorrhage score ranging from 0 to 12.

Haemorrhagic contusions

Definition (contusion): injury to brain surfaces involving superficial grey matter.¹⁹

Refinement of definition: injury to superficial parenchyma secondary to trauma against the skull or fixed dural fold, characterised by focal low attenuation with or without oedema. If haemorrhagic, haemorrhage is patchy and relatively ill-defined. The distinction between

contusion and parenchymal haemorrhage is blurred because both involve bleeding within the brain tissue; however, an arbitrary cut-off exists that the injury is a contusion if two-thirds or less of the tissue involved is blood, and a haemorrhage otherwise.

Volume measurement: $ABC/2$, method as above. Measure volume of entire contusion rather than just volume of haemorrhagic component.

If there is more than one contusion, list all of them, specify the location and estimate the volume of each individual bleed and *give total by adding volumes*. Codes for location are: L = left, R = right, T = temporal, F = frontal, P = parietal, O = occipital, BG = basal ganglia, B = brainstem.

Petechial haemorrhages

Definition: small punctuate haemorrhages measuring ≤ 15 mm in diameter indicative of diffuse axonal injury.

Non-haemorrhagic findings

Acute focal ischaemic lesion

Definition: focal low attenuation in distribution indicating arterial ischaemic cause rather than traumatic contusional injury.

Non-haemorrhagic contusion

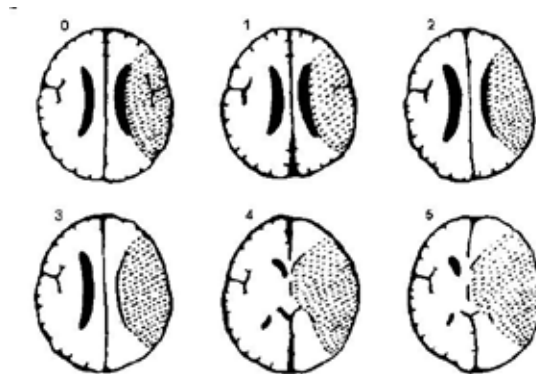
Definition: see *Haemorrhagic contusions*.

Volume measurement: $ABC/2$, method as above.

If there is more than one contusion, give total by adding volumes.

Mass effect findings

Scoring system based on Wardlaw and Sellar:²⁵



- 0 = no swelling
- 1 = effacement of the sulci overlying the infarct
- 2 = 1 + minor effacement of adjacent lateral ventricle
- 3 = 1 + complete effacement of lateral ventricle
- 4 = 1 + effacement of the lateral and third ventricles
- 5 = 4 + shift of the midline away from the side of the ventricle
- 6 = 5 + effacement of the basal cisterns/uncal herniation.

Measurement of midline shift



FIGURE 1 Computerised tomography scan image showing midline shift.

Method of measurement

1. Define the midline: straight line connecting the fixed anterior and posterior margins of the falx cerebri.
2. Degree of midline shift = longest distance to midline structures (interhemispheric fissure, septum pellucidum or third ventricle) measured perpendicular to the midline.

The primary outcome was the adjusted change in total haemorrhage growth from the first to the follow-up scan, defined as the difference in the combined volume (ml) of all intracranial haemorrhagic lesions (intraparenchymal haematoma + haemorrhagic contusion + subdural haematoma + epidural haematoma) from the first to the second scan. The secondary imaging outcomes were (1) the occurrence of significant haemorrhage growth (any haematoma that increased by 25% in relation to its initial volume), (2) new intracranial haemorrhage (apparent on the follow-up brain CT but not on the baseline brain CT), (3) change in subarachnoid haemorrhage grade, (4) the mass effect and (5) the occurrence of new focal cerebral ischaemic lesions (apparent on the follow-up brain CT, but not on the baseline brain CT).

Clinical outcomes

The clinical outcomes were death and the need for neurosurgical intervention. Dependency was measured using the five-point modified Oxford Handicap Scale (mOHS).²⁶ The scale was dichotomised into 'dependent' (fully dependent requiring attention day and night, or dependent but not requiring constant attention) or 'independent' (some restriction in lifestyle but independent, minor symptoms or no symptoms). Clinical outcomes were recorded at hospital discharge, 28 days or death, whichever occurred first. The corresponding form is shown in *Appendix 3*.

Combined outcome

We defined 'poor outcome' as a patient who developed one or more of the following during the scheduled follow-up period: significant haemorrhage growth, new intracranial haemorrhage, new focal cerebral ischaemic lesions, the need for neurosurgery or death.

Sample size

Assuming an initial intracranial haematoma volume of 20 ml, an average haemorrhage growth of 7 ml in the control group and a correlation of 0.6 between initial and follow-up volumes, we estimated that a trial with 300 patients would have 80% power ($\alpha = 0.05$) to detect a 35% reduction in haemorrhage growth. A trial with 200 patients would have the same power to detect a 40% reduction. We prespecified in the protocol that, as this study was nested within the main CRASH-2 trial, even if the planned sample size of 300 patients was not achieved, recruitment would stop at the same time as that for the main CRASH-2 trial.

Randomisation

Patients were randomised using a local pack system. Consecutively numbered treatment packs were taken from a box of eight packs (with a random allocation sequence based on a block size of eight). After eligibility had been confirmed and the locally approved consent procedures had been completed, patients were randomised by selecting the lowest numbered treatment pack from a box containing eight numbered packs.

Blinding

Blinding was achieved through the use of matching placebo. TXA and placebo ampoules were indistinguishable. The placebo was manufactured by St Mary's Pharmaceutical Unit, Cardiff, UK. TXA was manufactured by Pharmacia (Pfizer, UK). The treatment packs were prepared by an independent clinical trial supply company (Bilcare GCS Ltd, Crickhowell, UK). Correct blinding and coding of the ampoules was assured by independent random testing of each batch by high-performance liquid chromatography to confirm the contents. Emergency unblinding of treatment allocation was available by telephoning the Clinical Trials Service Unit at the University of Oxford.

Statistical methods

We assessed the intraobserver reliability of haemorrhage growth measurements on brain imaging using the intraclass correlation coefficient. We assessed the reliability of the measurement of binary outcomes using a kappa statistic. In all subsequent analyses, we used the average measurement of the two readings of continuous variables and considered binary outcomes to be positive when reported as positive on both of the radiologist's readings of a particular brain image for a patient.

We used a Bayesian statistical approach as it has several advantages in comparison with the traditional frequentist approach for the purposes of our study. A Bayesian approach can be defined as a mathematical method for combining the prior belief that we have about an effect size with the information observed in the actual study we conduct, to produce a 'posterior' belief of the effect size. This 'posterior belief' is presented in the form of a 95% credibility interval (CrI), that is, there is a 95% probability that the true effect lies within this interval.²⁷ Furthermore, a

Bayesian approach allows us to calculate probabilities for specific effect sizes. For example, the probability of an OR < 1 can be estimated. We used a Bayesian statistical approach because it fitted with the aims of this exploratory study. We were interested in obtaining a reliable 'degree of belief' about the effect of TXA in patients with TBI that could justify (or not) a future study in this population. At the time that the study was designed there was no evidence about the effect of TXA on TBI patients. The Bayesian approach allowed us to generate a probability distribution of the effect of TXA that could be used as a prior for future research. Unlike traditional frequentist analysis, in which you can only reject (or not) a null hypothesis, the Bayesian approach allows you to report how probable a specific effect will be (e.g. an OR < 0.8).

Because this was the first randomised controlled trial of TXA in TBI patients, we used non-informative priors for the primary analysis to reflect the lack of previous knowledge in this area. For the difference of continuous variables between groups the prior was a normal distribution mean = 0 and standard deviation (SD) = 100. For the relative risk (RR) the prior was defined in the log scale with a normal distribution $\ln(\text{RR}) \sim N(0, \text{SD} = 1.74)$. This is equivalent to having a 95% prior belief that the RR will be between 1/30 and 30, centred on 1. We conducted a sensitivity analysis using an enthusiastic prior for significant haemorrhage growth and a sceptical prior for new focal cerebral ischaemic lesions. These priors were provided by the systematic review of TXA in subarachnoid haemorrhage that reported an OR of 0.49 (95% CI 0.37 to 0.65) for rebleeding and an OR of 1.28 (95% CI 0.93 to 1.75) for confirmed cerebral ischaemia.¹⁴

For all the estimated effects we reported a posterior 95% CrI. We also reported the probability of a beneficial effect of TXA for all the outcomes, except for new focal cerebral ischaemic lesions, for which we reported the probability of a harmful effect. We defined the effect as beneficial if the effect size was < 0 (for differences) or < 1 (for ratios). For the sensitivity analysis we also reported the posterior probability of a 'clinical significant beneficial effect' (OR < 0.8) for significant haemorrhage growth and the posterior probability of a 'clinical significant harmful effect' (OR > 1.25) for new focal cerebral ischaemic lesions.

All analyses were undertaken on an intention-to-treat basis. We used generalised linear mixed models adjusted for baseline variables. The covariates included in the adjustment were GCS score and age because these variables are predictors of poor outcome.²⁸ In addition, for CT outcomes we adjusted for time from injury to first and second CT scan and for initial bleeding volume. In our analysis of mass effect we adjusted for initial mass effect. Adjusted effects are considered in the primary analysis, but both adjusted and unadjusted effect measures are reported.

We evaluated haemorrhage growth for four types of intracranial haematomas (intraparenchymal, haemorrhagic contusion, subdural and epidural) combined and separately. Haemorrhage growth was analysed using multiple linear regression (analysis of covariance, ANCOVA), the main factor being the treatment group. Outcomes are reported combined and separately for patients who did or did not undergo neurosurgery evacuation between the first and second CT scan. The binary outcomes, significant haemorrhage growth, new intracranial haemorrhage, new focal cerebral ischaemic lesion, mass effect, need for neurosurgery (other than the one indicated based on the pre-randomisation CT scan) and mortality, were analysed using logistic regression. Subarachnoid haemorrhage was measured on an ordinal scale ranging from 0 to 4 points. We compared the distribution of this outcome in the two groups using a non-parametric rank test (Kruskal–Wallis).

Neurosurgery was defined as initial (if decision of evacuation was based on the pre-randomisation CT scan), intermediate (if the evacuation was conducted after the pre-randomisation CT scan but before the follow-up CT scan) and late (if the evacuation was conducted after the follow-up CT scan).

To evaluate the clinical relevance of the primary surrogate outcome selected in this study we also analysed the clinical effect of haemorrhage growth. We conducted a logistic regression analysis with dependency (as defined by mOHS) as the outcome and haemorrhage growth as the main exposure variable, adjusting by the potential confounders initial volume, GCS score, age, time from injury to CT scan and treatment.

Funding

The funder of the study had no role in study design, data collection, data analysis, data interpretation or writing of the report. The Writing Committee had full access to all data in the study and had final responsibility for the decision to submit for publication.

This study is registered as ISRCTN86750102.

Chapter 3

Results

Summary of the trial

We recruited 270 patients between August 2008 and January 2010, when the main CRASH-2 trial reached its prespecified sample size. All patients (*Figure 2*) received the loading and maintenance doses except for one placebo-allocated patient who did not receive the maintenance dose. All patients were followed up for clinical outcomes. A total of 256 patients (95%) had an initial CT scan. In 14 patients (six TXA allocated, eight placebo allocated) the initial CT scan was unavailable for reading for technical reasons. Five patients died before the second CT scan (three TXA allocated, two placebo allocated). In terms of protocol deviations, nine (3%) patients were randomised before the initial CT scan (six TXA allocated, three placebo allocated). A total of 31 (11%) patients had a GCS score of 15 at baseline (17 TXA allocated, 14 placebo allocated). In 51 (19%) patients the second CT scan was conducted outside the 24- to 48-hour window (25 TXA allocated, 26 placebo allocated). We included all 270 patients in our analyses.

Baseline characteristics

Baseline characteristics of the included patients and their initial CT scan findings are shown in *Tables 1* and *2*, respectively. In total, 211 patients (82%) had an intraparenchymal haematoma, haemorrhagic contusion, subdural haematoma or epidural haematoma. A focal cerebral ischaemic lesion was present in three patients (2%) in the placebo group and two (2%) in the TXA group at the initial CT scan. A total of 40 patients (20 TXA allocated, 20 placebo allocated) had an initial neurosurgery evacuation.

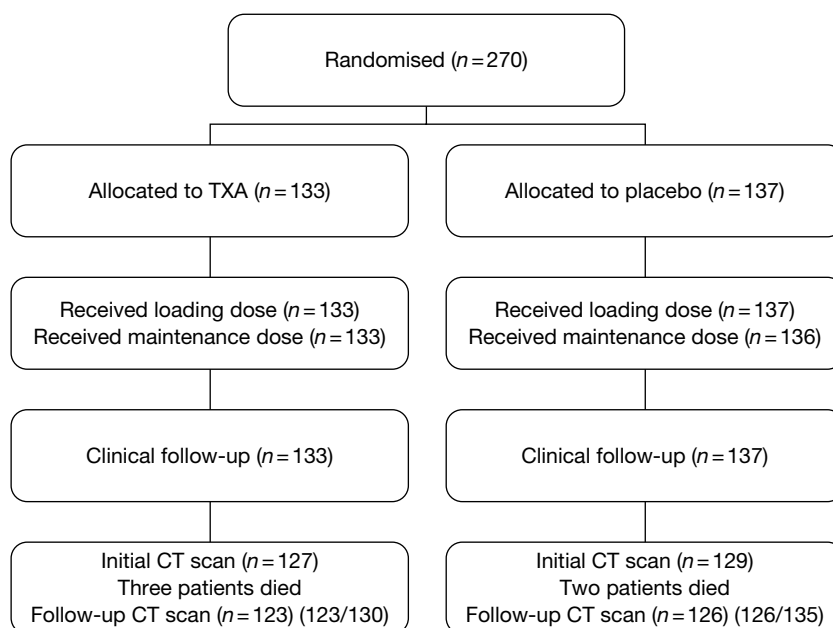


FIGURE 2 Summary of the trial.

TABLE 1 Baseline data of participants

	TXA (<i>n</i> =133)	Placebo (<i>n</i> =137)
Sex		
Male	111 (83.5%)	117 (85.4%)
Female	22 (16.5%)	20 (14.6%)
Injury type		
Blunt	132 (99.2%)	136 (99.3%)
Penetrating	1 (0.8%)	1 (0.7%)
Age (years), mean (SD)	36.2 (14.0)	37.0 (13.7)
Hours since injury, mean (SD)	4.4 (1.8)	4.2 (1.7)
Glasgow Coma Scale score, mean (SD)	10.5 (3.6)	10.5 (3.6)
Systolic blood pressure (mmHg), mean (SD)	116.4 (31.2)	113.5 (29.4)
Central capillary refill time (seconds), mean (SD)	3.4 (1.0)	3.5 (1.1)
Heart rate (beats per minute), mean (SD)	100.7 (25.7)	101.6 (23.5)

TABLE 2 Baseline CT scan characteristics

	TXA (<i>n</i> =127), <i>n</i> (%)	Placebo (<i>n</i> =129), <i>n</i> (%)	Total no. of patients (%)
CT scan baseline characteristics			
Normal	4 (3)	3 (2)	7 (3)
Mild focal injury	26 (20)	22 (17)	48 (19)
Medium focal injury	39 (31)	41 (32)	80 (31)
Mild/moderate diffuse injury	23 (18)	19 (15)	42 (16)
Massive focal (\pm diffuse)	17 (13)	23 (18)	40 (16)
Massive diffuse (\pm focal)	18 (14)	21 (16)	39 (15)
Types of bleeding			
Intracranial haemorrhage (intraparenchymal, haemorrhagic contusion, subdural and epidural)	106 (83)	105 (81)	211 (82)
Intraparenchymal haematoma	9 (7)	15 (12)	24 (9)
Haemorrhagic contusion	61 (48)	66 (51)	127 (50)
Subdural haematoma	38 (30)	45 (35)	83 (32)
Epidural haematoma	38 (30)	28 (22)	66 (26)
Subarachnoid haemorrhage	55 (43)	79 (61)	134 (52)
Mass effect findings			
Ventricular effacement	45 (35)	47 (36)	92 (36)
Uncal herniation	15 (12)	18 (14)	33 (13)
Cisterns compressed	12 (9)	19 (15)	31 (12)
Midline shift	28 (22)	29 (22)	57 (22)
Any mass effect	69 (54)	78 (60)	147 (57)

Imaging outcomes

Intraobserver agreement

The intraobserver agreement between the two CT scan readings by the radiologist was high for all outcomes except new intracranial haemorrhage. The intraclass correlation coefficient for total haemorrhage growth was 0.89 and the corresponding kappas for significant haemorrhage growth, new intracranial haemorrhage, any mass effect and new focal cerebral ischaemic lesions were 0.82, 0.32, 0.81 and 0.89, respectively. Imaging outcomes were available for 249 (99%) of the 251 patients who had an initial CT scan and were alive at 24 hours.

Effect on haemorrhage growth

The mean total haemorrhage growth was 5.9 ml (SD 26.8 ml) and 8.1 ml (SD 29.2 ml) in the TXA and placebo group, respectively. The adjusted analysis showed a reduction in total haemorrhage growth in the arm that received TXA in comparison with placebo (−3.8 ml, 95% CrI −11.5 to 3.9 ml). In patients who had neurosurgical evacuation before the second CT scan, the reduction in total haemorrhage growth in the TXA arm was larger (−12 ml, 95% CrI −45.7 to 15.5 ml). The posterior probability that TXA reduces haemorrhage growth was high for total haematoma and each type separately except for epidural haematoma (*Table 3*). The change in the subarachnoid haemorrhage scale was −0.11 for TXA-allocated patients and −0.12 for placebo-allocated patients ($p = 0.93$).

Computerised tomography scan binary outcomes

There were 44 (35.8%) patients with significant haemorrhage growth in the TXA group compared with 56 (44.4%) in the placebo group. In total, 13 (10.6%) patients had new haemorrhage area in the TXA group compared with 20 (15.9%) in the placebo group, and there were 58 (47.2%) patients with signs of mass effect in the TXA group compared with 76 (60.3%) in the placebo group. In *Table 4* the unadjusted and adjusted ORs are reported for all of the CT scan binary outcomes. A beneficial effect was highly probable for all of the binary CT scan outcomes considered (range 89–93%).

Sensitivity analysis for significant haemorrhage growth

The sensitivity analysis for significant haemorrhage growth with an enthusiastic prior gave an adjusted OR of 0.52 (95% CrI 0.41 to 0.68) with a very high posterior probability (99%) of a clinically significant beneficial effect. *Figure 3* displays the probability distributions of the effect of TXA on significant haemorrhage growth, assuming a non-informative prior and an enthusiastic prior.

New focal cerebral ischaemic lesions

There were six (4.9%) patients with new focal cerebral ischaemic lesions in the TXA group compared with 12 (9.5%) in the placebo group. The unadjusted and adjusted ORs were 0.51 (95% CrI 0.19 to 1.37) and 0.54 (95% CrI 0.20 to 1.46), respectively. The probability of a harmful effect of TXA was 10%. The sensitivity analysis with a sceptical prior gave an adjusted OR of 1.18 (95% CrI 0.87 to 1.60) and a posterior probability of a clinically significant harmful effect of 35%. *Figure 4* displays the probability distributions of the effect of TXA on new focal cerebral ischaemic lesions, assuming a non-informative prior and a sceptical prior.

TABLE 3 Effect of TXA on haemorrhage growth

	Total no. of patients	Haemorrhage growth (ml), unadjusted (95% CrI)	Haemorrhage growth (ml), adjusted (95% CrI)	Probability of benefit (%)
All haematomas combined				
All patients	206	-2.12 (-9.82 to 5.56)	-3.79 (-11.45 to 3.88)	84
Evacuated patients	46	-6.160 (-34.603 to 22.284)	-15.120 (-45.744 to 15.504)	84
Non-evacuated patients	160	-1.62 (-7.25 to 4.00)	-2.11 (-7.12 to 2.89)	80
Intraparenchymal haematoma				
All patients	24	-6.19 (-17.57 to 5.18)	-4.50 (-17.69 - 8.68)	76
Evacuated patients	4	-1.49 (-33.69 to 30.71)	NA	NA
Non-evacuated patients	20	-7.99 (-20.88 to 4.90)	-9.14 (-24.89 to 6.61)	89
Haemorrhagic contusions				
All patients	124	-5.69 (-15.15 to 3.77)	-1.57 (-9.08 to 5.92)	66
Evacuated patients	31	-17.52 (-46.87 to 11.82)	-14.34 (-40.78 to 12.09)	87
Non-evacuated patients	93	-0.61 (-8.50 to 7.27)	2.04 (-3.75 to 7.84)	24
Subdural haematoma				
All patients	78	1.50 (-9.85 to 12.86)	-2.80 (-8.68 to 3.06)	83
Evacuated patients	29	0.52 (-25.60 to 26.66)	-14.37 (-32.89 to 4.14)	95
Non-evacuated patients	49	-0.31 (-3.48 to 2.86)	0.26 (-1.76 to 2.29)	39
Epidural haematoma				
All patients	66	5.68 (-4.88 to 16.24)	3.86 (-1.85 to 9.58)	9
Evacuated patients	21	2.70 (-25.02 to 30.43)	-5.24 (-14.21 to 3.73)	89
Non-evacuated patients	45	2.12 (-1.77 to 6.01)	2.71 (-1.54 to 6.98)	10

NA, not applicable.

TABLE 4 Effect of TXA on CT scan binary outcomes

CT scan finding	Unadjusted OR (95% CrI) (n=249)	Adjusted OR (95% CrI) (n=249)	Probability of benefit (%)
New haemorrhage	0.64 (0.31 to 1.33)	0.63 (0.29 to 1.35)	88
Mass effect	0.59 (0.36 to 0.98)	0.55 (0.24 to 1.22)	93
Significant haemorrhage growth	0.70 (0.42 to 1.16)	0.68 (0.41 to 1.13)	93

Clinical outcomes

Clinical outcomes were available for all patients (*Table 5*). A total of 14 (10.5%) patients died in the TXA group compared with 24 (17.5%) in the placebo group. There were 12 (9.0%) deaths in the TXA group due to head injury compared with 20 (14.6%) in the placebo group. Intermediate or late neurosurgical evacuation was required in 20 (15.0%) patients in the TXA group compared with 21 (15.3%) in the placebo group. Except for the need for neurosurgical intervention, there was a high probability of a beneficial effect of TXA on all of the clinical outcomes (*Table 5*). Finally, a poor outcome was observed in 60 (45.1%) patients in the TXA group and 80 (58.4%) in the placebo group (adjusted OR 0.59, 95% CrI 0.37 to 0.96).

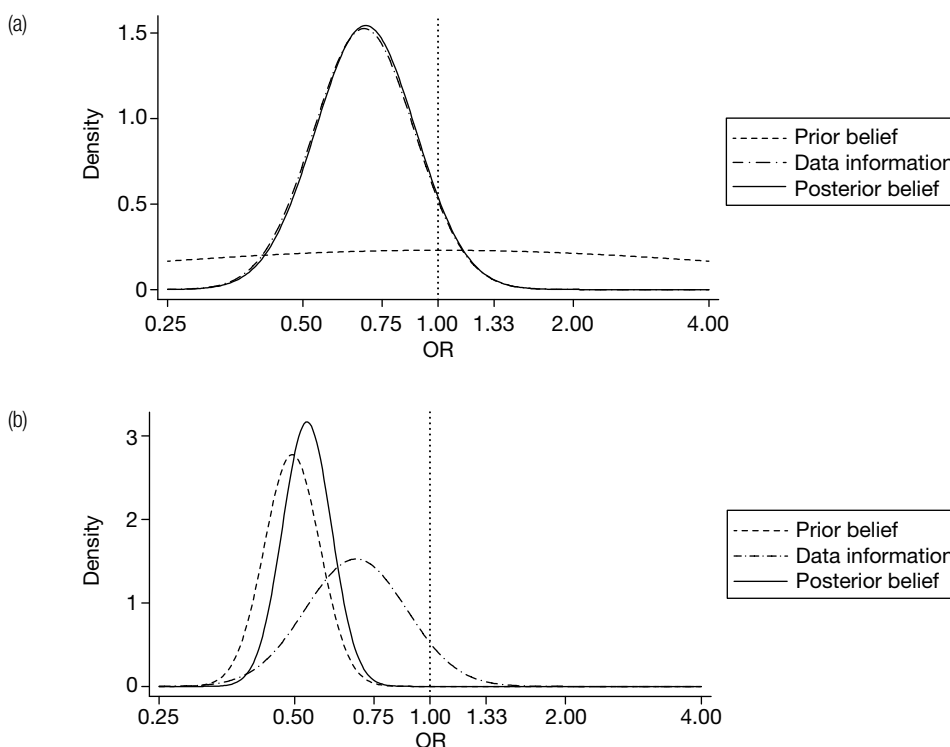


FIGURE 3 Probability distributions of the effect of TXA on significant haemorrhage growth using (a) a non-informative prior and (b) an enthusiastic prior.

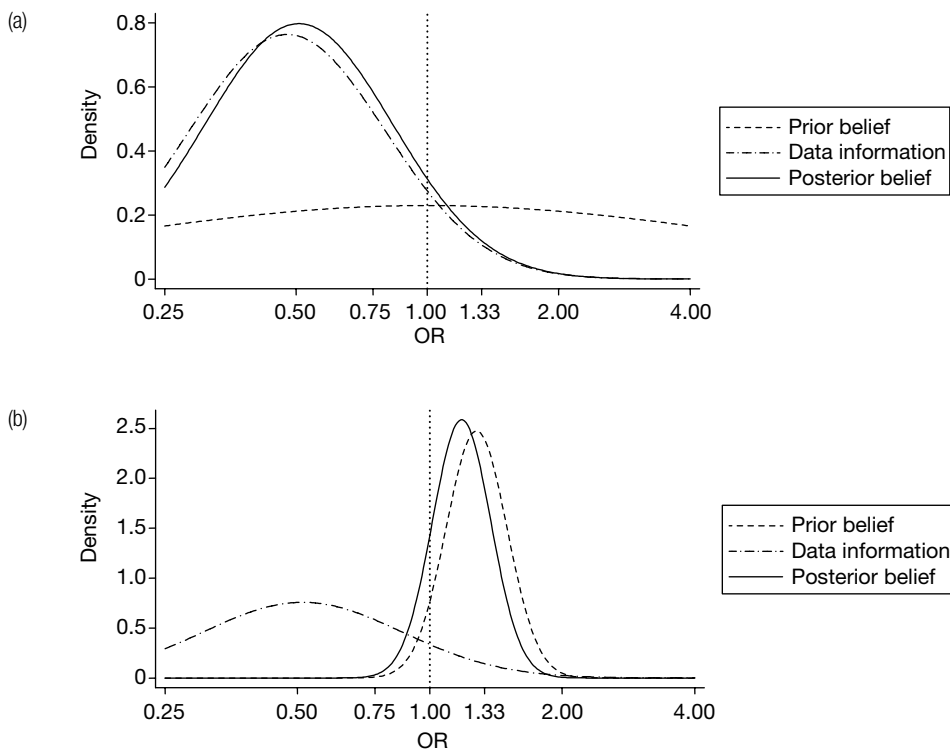


FIGURE 4 Probability distributions of the effect of TXA on new focal cerebral ischaemic lesions using (a) a non-informative prior and (b) a sceptical prior.

TABLE 5 Effect of TXA on clinical outcomes

	Unadjusted OR (95% CrI) (<i>n</i> =270)	Adjusted OR (95% CrI) (<i>n</i> =270)	Probability of benefit (%)
Mortality	0.57 (0.28 to 1.14)	0.49 (0.22 to 1.06)	96
Mortality due to head injury	0.59 (0.28 to 1.25)	0.54 (0.24 to 1.22)	93
Need for neurosurgery	0.98 (0.50 to 1.93)	0.98 (0.50 to 1.91)	53

Relationship between haemorrhage growth and dependency

We found that an increase of 10 ml in haematoma growth was strongly associated with dependency at hospital discharge (adjusted OR 1.32, 95% CI 1.08 to 1.62).

Adverse events

No emergency unblinding was needed and there were no adverse events regarded as serious, unexpected or suspected to be related to the study treatment.

Chapter 4

Discussion

This was the first randomised controlled study to evaluate the effect of TXA in TBI patients and it found that neither moderate benefits nor moderate harmful effects can be excluded. However, although uncertainty remains, our analyses suggest that TXA administration might improve outcome in TBI patients and provide grounds for evaluating this hypothesis in future research.

If we assume no prior knowledge of the effect of TXA on significant haemorrhage growth with a non-informative prior, the posterior probability of benefit provides reasonable grounds for therapeutic optimism. Using an enthusiastic prior, based on the effect of TXA on intracranial bleeding observed in trials in subarachnoid haemorrhage, it appears highly probable that TXA reduces total haemorrhage growth in TBI.

The reduction in haemorrhage growth observed in this study could be because of several different reasons. There is good evidence that a large proportion of TBI patients become coagulopathic early on after injury.¹¹ The exact mechanism of this coagulopathy is still disputed. Among the existing hypotheses it has been suggested that the release of thromboplastin after TBI is followed by the activation of the coagulation and fibrinolytic pathways. Pathak *et al.*²⁹ have recently reported an increase in activity of tissue thromboplastin among TBI patients. The fact that a larger effect was found in intraparenchymal haematoma, for which release of thromboplastin is more likely, is consistent with this hypothesis. Alternatively, it has been suggested that only TBI patients with hypotension activate the fibrinolytic response.³⁰ CRASH-2 IBS was conducted among TBI patients with significant (extracranial) haemorrhage and the effect of TXA might be different in patients with isolated TBI. It is possible that in our study population TXA reduced extracranial bleeding, and therefore patients in the TXA group were less hypotensive and less coagulopathic, and through this mechanism TXA reduced haemorrhage growth. However, only 7% of the included patients had systolic blood pressure < 90 mmHg and we did not find evidence of interaction according to blood pressure at admission (data not shown) that would support this hypothesis; however, we acknowledge that our study was not powered to detect this interaction. Additionally, a recent paper has challenged this hypothesis by reporting that coagulopathy is also found in TBI patients without hypotension.³¹ Antifibrinolytic agents have been shown to reduce blood loss in surgical patients.¹⁰ Therefore, the larger effect observed in surgical patients is consistent with the evidence of effectiveness of antifibrinolytic agents in elective surgery.

There are several potential explanations for the observed reduction in mortality. It could be because of the reduction in haemorrhage growth, mass effect and focal ischaemic lesions, or alternatively the observed effect on mortality could be related to the survival benefit observed in the main CRASH-2 study for trauma patients and significant (extracranial) bleeding. However, in the main CRASH-2 study the largest and most significant effect was observed in deaths because of bleeding, while in the CRASH-2 IBS 85% of the observed deaths were because of brain injury.

With regard to new focal cerebral ischaemic lesions, we found a reduction in TXA-allocated patients. The posterior probabilities were compatible with either a beneficial or a harmful effect, although a beneficial effect was more likely assuming a non-informative prior. Overall, the incidence of these lesions was low and it is possible that the observed difference between the groups may have arisen by chance alone. On the other hand, it is plausible that, if TXA reduces

haemorrhage growth and volume, this will reduce local pressure on arteries and also total intracranial pressure and any consequent ischaemia. Given that TXA has been shown to reduce mortality because of bleeding, it is also possible that TXA-allocated patients may have had a more stable circulation with higher blood pressure and that this may have accounted for the observed reduction in ischaemic lesions. Using a sceptical prior, based on the effect of TXA on ischaemic lesions in subarachnoid haemorrhage trials, a harmful effect of TXA appeared more probable, although the probability of a clinically significant harmful effect remains low.

Our study has several strengths. The randomisation methods ensured that participating clinicians did not have foreknowledge of treatment allocation, baseline clinical factors were well balanced, there was a high follow-up rate and all analyses were performed on an intention-to-treat basis. Although there were baseline differences between TXA- and placebo-allocated patients for some CT scan characteristics, we conducted adjusted analyses that should have accounted for any imbalance. We attempted to minimise measurement error through the use of central CT reading by a neuroradiologist following a strict protocol made up mostly of already validated methods (those that had not been validated were further tested in the present study). We found that intra-rater reliability was high for most imaging measurements.

The Bayesian analysis presented many advantages. We were able to report the 95% CrI, which is the intuitive interpretation that most readers (incorrectly) make of the traditional 95% CI.²⁵ It also allowed us to explicitly incorporate sceptical prior beliefs about the potential harms of TXA (from prior experience with a different disease, aneurysmal subarachnoid haemorrhage); thus, taking into account some clinicians' concerns about the potential for harm. Finally, the posterior probability about the effect size can be used very conveniently as a 'prior' belief for future trials.

Among the limitations is the fact that our study included only a relatively small sample of the CRASH-2 participants with TBI, and a larger sample size could have provided more precise results. The nature of a large pragmatic trial such as the CRASH-2 trial constrained our ability to collect CT scans in all TBI patients included in the CRASH-2 trial. Nevertheless, the relatively small sample size does not affect the internal validity of this study and, although imprecise, the results should be unbiased. Another important limitation is that for our sensitivity analysis we used information from a systematic review of the effect of TXA in a different clinical condition (aneurysmal subarachnoid haemorrhage). The doses of TXA used in these trials were larger and more prolonged than in our study and so the enthusiastic and sceptical priors could overestimate the reduction in significant haemorrhage growth and the risk of cerebral ischaemic lesions, respectively. A more recent trial of a short course of TXA in aneurysmal subarachnoid haemorrhage has shown that TXA reduces rebleeding without apparently increasing the risk of ischaemia.³² These data provide support for our findings that a short course of TXA could reduce intracranial haemorrhage after TBI without increasing the risk of cerebral ischaemia. A further limitation is that 19% of the patients had their second CT scan conducted outside the 24- to 48-hour window; however, the distribution was similar in both groups and because we adjusted for time from randomisation to first and second CT scan the results should be unbiased.

Chapter 5

Conclusion

Implications for health care

The CRASH-2 trial has shown reliably that early administration of TXA in trauma patients with, or at risk of, significant bleeding reduces the risk of all-cause mortality. However, many patients with traumatic haemorrhage also have TBI and concerns about the risk of cerebral ischaemia may influence the decision of some doctors to give TXA to these patients. The results presented here provide reassurance about the safety of TXA in bleeding trauma patients with TBI.

Implications for research

Our results also have implications for research. If TXA reduces intracranial bleeding after TBI without increasing the risk of ischaemic lesions, then TXA clearly has the potential to improve patient outcomes. The results of this trial provide a reasonable basis to expect such effects. Although an increased risk of cerebral ischaemia cannot be ruled out, our results provide a sound basis to believe that the benefits of TXA administration could outweigh the risks. If such an inexpensive and widely practicable treatment were found to improve patient outcomes after traumatic intracranial bleeding this would have major implications for clinical care. Future research should be conducted to reliably assess the effectiveness and safety of the early administration of a short course of TXA in patients with isolated TBI.

Acknowledgements

Writing Committee

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Collaborators by site

India: Aditya Neuroscience Centre and Sanjivani Hospital: Anil P Lal and Natasha Gohain; CARE Hospital: Pamidimukkala Venkataramana Ramana; Christian Medical College: Yashbir Dewan, Sarvpreet Singh Grewal and Pradipta Tripathy; Medical Trust Hospital: Ramalingam Ramanathan Ravi, Subbiah Raja and Anand Doshi; Jeevan Jyoti Hospital: Prakash Ketan.

Colombia: University of Antioquia, Hospital Universitario San Vicente de Paul: Carlos Morales and Santiago Naranjo; Hospital Pablo Tobón Uribe: Alfredo Constain and Edwin Vazquez Salazar; Hospital Universitario San José de Popayán: Jorge Herrera and Liliana Caicedo; Fundación Valle del Lili: Jorge Mejía-Mantilla and Ana Maria Varela.

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Contributions of authors

Pablo Perel, Rustam Al-Shahi Salman, Taemi Kawahara, Zoe Morris, Ian Roberts, Peter Sandercock, Haleema Shakur, and Joanna Wardlaw contributed to the study design including the study protocol and study data forms. David Prieto Merino provided expertise in statistics and undertook the statistical analysis. Joanna Wardlaw and Zoe Morris contributed with expertise on neuroradiology. Zoe Morris conducted the reading of all the CT scans. Peter Sandercock and Rustam Al-Shahi Salman contributed with expertise in neurology. Pablo Perel, Ian Roberts and Haleema Shakur provided expertise in clinical trials. Taemi Kawahara and Haleema Shakur provided expertise in trial management. Pablo Perel drafted the first version of the monograph and all the authors commented and contributed to the final version.

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Appendix 1

CRASH-2 IBS trial protocol



CRASH-2 substudy The effect of tranexamic acid on intracranial bleeding among CRASH-2 trial participants

1. Background

CRASH-2 is a large randomised controlled trial of the effect on mortality and transfusion requirements of tranexamic acid (TXA) in trauma patients with significant bleeding (www.crash2.lshtm.ac.uk). Over 9,000 patients have been enrolled so far and recruitment will continue until 20,000 patients have been randomised. Many of the patients included in the CRASH-2 trial have multiple injuries and in about 40% of patients this includes traumatic brain injury (TBI). The CRASH-2 trial will assess as sub-group analyses, the effect of TXA in patients who also have TBI. These analyses will examine the effect of TXA on mortality, on the need for a neurosurgical operation and on neurological impairment, using a modified version of the Oxford Handicap Score (our previous analyses have shown that this score is strongly correlated with outcome on the Glasgow Outcome Scale at six months).

Traumatic intracranial bleeding: TBI is commonly accompanied by intracranial bleeding, which can be epidural, subdural, subarachnoid or parenchymal. Of the 7,814 patients with TBI enrolled in the MRC CRASH trial who had a computerised tomography (CT) scan, 31% had subarachnoid haemorrhage and 40% had an intracranial haematoma. Overall 56% of TBI patients had some type of intracranial bleeding.¹

Prognostic studies show that intracranial bleeding is associated with increased mortality and disability six months after injury. In the MRC CRASH trial, the presence of subarachnoid haemorrhage, petechial haemorrhage or intracranial haematoma were independently associated with poor outcome at 2 weeks and 6 months.² Similarly, the IMPACT study found that after controlling for age, Glasgow Coma Score (GCS) motor score and pupil reactions, subarachnoid and subdural haemorrhages more than doubled the odds of poor outcome at six months.³ The larger the intracranial bleeding, wherever the location, the worse prognosis it is associated with. The Brain Trauma Foundation Guideline for Surgery takes into account the bleeding size to recommend surgical evacuation: 50 cm³ for parenchymal haematoma, 30 cm³ for epidural and 10 mm for subdural haematoma.⁵

In patients with TBI, intracranial bleeding can develop or worsen after hospital admission. Studies involving repeated CT scanning have found that intracranial bleeds can develop or expand in the 24 hours after injury. Ortel studied a group of patients in whom two CT scans were obtained within 24 hours of injury to determine the prevalence of progressive intracranial haemorrhage.⁴ Among patients who had their first CT scan within 2 hours of injury, 49% had radiological evidence of progressive haemorrhage. Yadav conducted repeat CT scanning of TBI patients at hospital admission and 24 hours later, and found that 16% of 262 parenchymal

haematomas and contusions increased in size in the first 24 hours.⁶ Similarly, Sullivan *et al.* found that traumatic epidural haemorrhages enlarged in 23% of 160 TBI patients treated non-operatively.⁷ The mean enlargement was 7 mm, and the mean time to enlargement was 8 hours from injury and 5.3 hours from CT diagnosis. Although these studies provide estimates of the occurrence of intracranial bleeding and expansion they all have limitations. All included patients who have an abnormal initial CT scan and there is little information on the proportion of patients that develop new intracranial bleeds in the first 24 hours who have the potential to benefit from early treatment.

Tranexamic acid and intracranial bleeding: Tranexamic acid is commonly used in surgery to reduce blood loss. A systematic review of randomised controlled trials of TXA in elective surgery showed that it reduces the need for transfusion by one third, reduces donor exposure by one unit, and halves the need for further surgery to control bleeding.⁸ A systematic review of randomised trials of TXA in patients with aneurysmal subarachnoid haemorrhage showed that TXA reduced the rate of rebleeding by approximately 40%, but because of an increase in cerebral ischaemia there was no overall benefit.⁹ However, the duration of TXA treatment in these trials was six weeks and it is possible that a shorter treatment might prevent rebleeding whilst avoiding the risk of ischaemia. The systematic review was conducted in 2003 but since then a randomised controlled trial of the early administration of a short course (3 days) of TXA in aneurysmal subarachnoid haemorrhage found that TXA reduced the occurrence of rebleeding from 10.8% to 2.4% with no evidence of increased side effects.¹⁰ Almost all of the effect on rebleeding was observed within the first few hours after hospital admission. Tranexamic acid could also improve outcome after TBI by reducing systemic blood loss. Hypotension is an established risk factor for poor outcome after TBI.

Hypothesis: Early administration of TXA can prevent the occurrence or increase of intracranial bleeding in patients with TBI and significant bleeding.

Aim: The aim of the proposed substudy is to quantify the effect on intracranial bleeding of the early administration of TXA, in CRASH-2 trial participants with traumatic brain injury.

Primary outcome:

1. Increase in volume of intracranial bleeding

Secondary outcomes:

1. Frequency of progressive haematomas
2. Frequency of delayed haematomas
3. New focal ischaemic lesions

Other relevant outcomes including mortality, disability, need of neurosurgical operation and non fatal thromboembolic events are collected in the CRASH-2 trial and will be reported for the TBI subgroup in the main analysis.

2. Study design

Methods

Participating hospitals: Participating hospitals have been selected based on level of interest by the principal investigator in the research question, the recruitment rate in the CRASH-2 trial and the ability of the hospital to collect and send the necessary CT scan data to the trial co-ordinating centre. This substudy will be conducted in the hospitals listed in *Appendix 1*.

Inclusion criteria: All patients meeting the following criteria will be eligible for inclusion in the substudy:

- Fulfils the inclusion criteria for the CRASH-2 trial
- GCS of 14 or less
- Baseline clinical CT scan shows intracranial abnormality consistent with TBI
- Non pregnant

Number of patients needed: Assuming a baseline intracranial bleeding volume of 20 ml, an average increase of 7 ml in the control group and a correlation of 0.6 between baseline and follow-up bleeding, we need to recruit 900 patients to have 80% power (with $\alpha = 0.05$) to detect a 20% reduction in the increase of intracranial bleeding volume in the control group. If 400 patients were recruited the trial could detect a 30% reduction in the primary outcome. A sample size of 200 patients could detect a 40% reduction in the primary outcome.

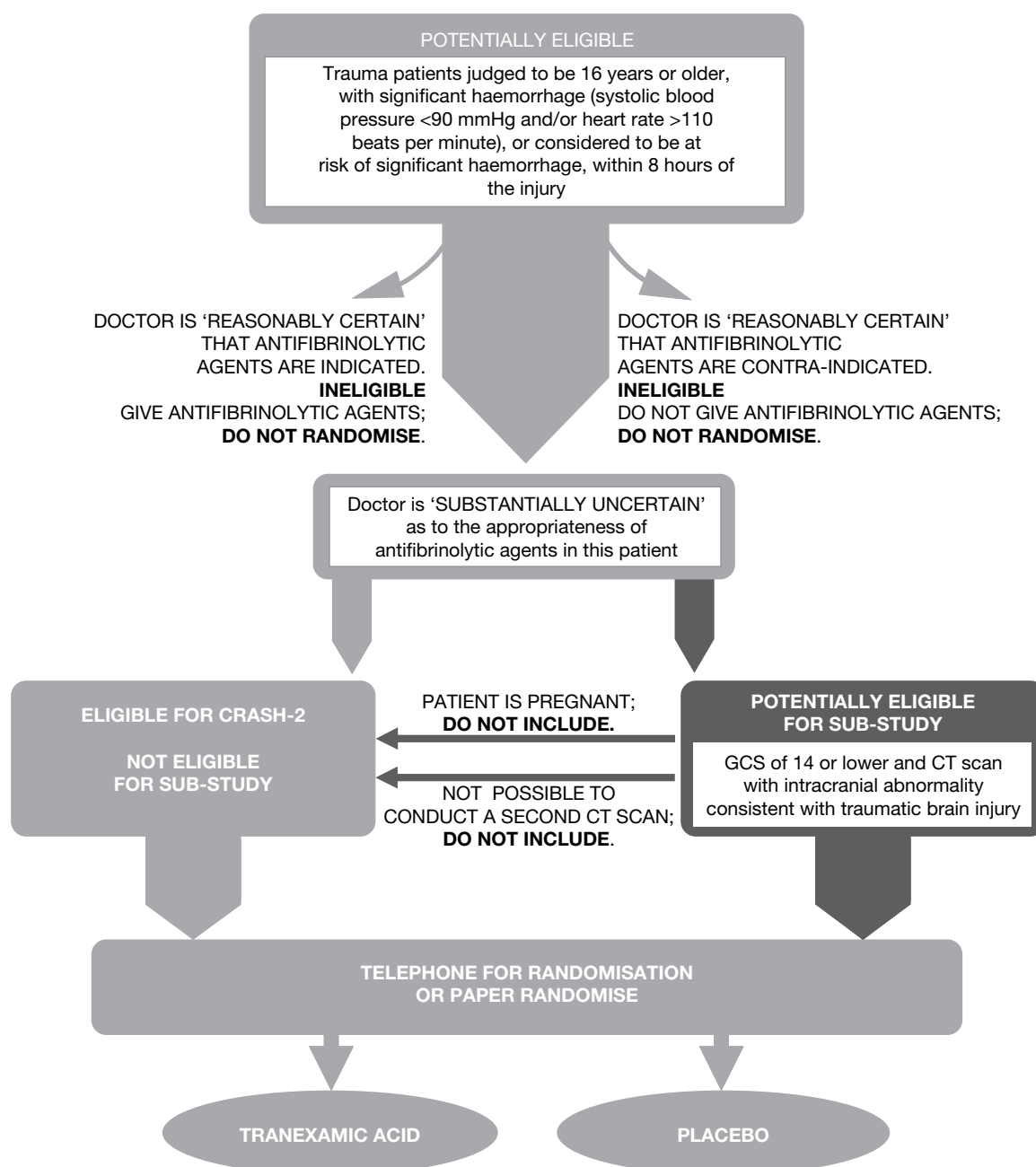


FIGURE 1 Eligibility.

Procedures: Patients will follow all procedures as per CRASH-2 protocol; Additional procedures for the substudy are as follows:

Patients enrolled in the substudy will be identified by the completion of one form that will collect data on time since injury, time of initial (pre-randomisation) and follow-up CT scans and the file identifiers of the respective CT scan images. This form will also collect information on whether or not a decision to undertake neurosurgery was taken based on the CT scan result (see *Appendix 2*). This form will be sent to the trial co-ordinating centre in the same way as the CRASH-2 trial data.

CT scan protocol:

CT scan data acquisition: Two CT scans will be obtained for each participant, a clinical pre-randomisation scan and second scan 24–48 hours later. CT scans will be sent to the co-ordinating centre by uploading them onto the CRASH-2 trial server. Scans will be checked by the trial data manager to ensure that they are of the head, from the correct patient, performed on the correct date and of sufficient quality to be read. All study sites will be required to provide documentation as to the standard parameters used for each CT scanner. The specific scan protocol/parameters of the initial CT evaluation will be limited by the emergent nature at the time of admission. However, after a patient is enrolled, the follow-up scan must match the baseline CT scan with regard to section thickness, section spacing (overlap or no gap), matrix, field of view, and scan angulations. Consistency in these parameters across all CT evaluations for a patient allow comparable measurements because of identical spatial resolution. All name identifiers will be removed before loading the scans onto the CT reading system. The CT scans will be allocated to an expert CT scan reader for evaluation who will be blind to the treatment allocation.

CT scan data analysis: In both CT scans we will measure: type of bleeding (subdural, epidural, subarachnoid haemorrhage, parenchymal haematoma), volume of bleeding, ischaemic lesions and indirect signs of intracranial pressure. Volume of intracranial bleeding will be measured using validated methods; further details are described in the statistical analysis plan.

Consent

Because patients included in this substudy will have significant TBI, relatives or legal representatives would be asked to sign the informed consent in line with local legal requirements. To minimise the need for multiple information sheets and consent forms, one form which combines the CRASH-2 and substudy information will be used (*Appendix 3*).

Randomisation

As per CRASH-2 protocol.

Treatment

As per CRASH-2 protocol.

Serious unexpected suspected adverse events

As per CRASH-2 protocol.

Expected side effects

As per CRASH-2 protocol.

Potential risks associated with this substudy

It is standard care for all patients with a history of TBI and associated clinical signs to have a CT scan. Therefore, the initial scan will form part of standard care. The substudy requires one additional CT Scan to be done 24 to 48 hours after the first, which in many cases is likely to be

clinically indicated. The effective radiation dose from a CT scan is about 2 mSv, which is about the amount received from background radiation in eight months.

Unblinding

As per CRASH-2 protocol.

Analysis

Haemorrhage volume from CT scans will be analysed with use of generalised linear mixed models. The baseline bleeding volume and the time from injury to CT will be included as covariates. Because patients who undergo a neurosurgery based on the pre-randomisation CT scan would not have a baseline haematoma they would be excluded of this analysis.

We will express the effect of TXA on the occurrence of secondary endpoints using relative risks and 95% confidence intervals. All analysis will be based on the intention to treat principle. We will conduct subgroup analysis according to type of bleeding. No interim analysis is planned for the sub-study; the analysis will be done at the end of the CRASH-2 Trial. Further details are described in the statistical analysis plan.

Definitions

Progressive haematoma will be defined as a growth of the haematoma larger than 25% from the initial to the follow-up CT scan.

Delayed haematoma will be defined as appearance of an haematoma in the follow-up CT scan where there was not one on the initial scan.

New focal ischaemic lesions will be defined as those ischaemic lesions which appear in the follow-up CT scan but not in the initial one.

3. Organisation

Data monitoring committee

The data monitoring committee members would be the same as CRASH-2.

Standard Operating Procedures: As per CRASH-2 protocol.

Steering committee

The steering committee members would be the same as CRASH-2 plus Professor Peter Sandercock.

Standard Operating Procedures: As per CRASH-2 protocol.

Substudy Protocol Committee

Rustam Al-Shahi Salman (UK), Yashbir Dewan (India), Anil P Lal (India), Carlos Morales (Colombia), Zoe Morris (UK), Pablo Perel (UK), P V Ramana (India), R R Ravi (India), Ian Roberts (UK), Peter Sandercock (UK), Haleema Shakur (UK), Joanna Wardlaw (UK).

Co-ordinating centre responsibilities

As per CRASH-2 protocol.

Publication

The results of the trial will be reported first to trial collaborators. Dissemination of results to patients will take place via the media, trial website (www.crash2@Lshtm.ac.uk) and relevant patient organisations.

Indemnity

As per CRASH-2 protocol.

Financial support

LSHTM.

4. IBS protocol references


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Appendix 1**Hospitals that will participate in the substudy**

1. Aditya Neuroscience Centre, Dibrugarh, India
2. Sanjivani Hospital, Dibrugarh, India
3. Care Hospital, Visakhapatnam, India
4. Christian Medical College, Ludhiana, India
5. Medical Trust Hospital, Kochi, India
6. Hospital Universitario San Vicente de Paul, Medellín, Colombia
7. Hospital Universitario San Jose De Popayan, Colombia
8. Hospital Pablo Tobon Uribe, Medellín, Colombia
9. Fundacion Clinica Valle del Lili, Colombia
10. Jeevan Jyoti Hospital & Research Centre, Allahabad, India.

Other hospitals may be added if recruitment falls below predicted.

Appendix 2
Investigator computerised tomography scan form

CRASH-2 Intracranial Bleeding Substudy INVESTIGATOR CT SCAN FORM	
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A. Section to be completed after the initial CT Scan

1. Hospital ID			
2. Patient initials	3. Patient hospital identification number	4. Box	
5. CT scan compatible with head injury <i>(circle the correct answer)</i>	6. Time and date of injury Time _____ : _____ (24 hours) Date ____/____/____ (dd/mm/yy)	7. Time and date of initial CT scan Time _____ : _____ (24 hours) Date ____/____/____ (dd/mm/yy)	Pack
Yes No			
8a. Haematoma evacuation decided based on initial CT results? <i>(circle the correct answer)</i>	8b. If yes, type of haematoma evacuated: <i>(tick all that apply)</i>		
Yes No	<input type="checkbox"/> Parenchymal <input type="checkbox"/> Epidural <input type="checkbox"/> Subdural		
9. CT scan Identifier: <small>(OFFICE USE ONLY)</small>	10. CT scan parameters		
	Section thickness:		
	Section spacing:		
	Matrix:		
	Field of view:		
	Scan angulations :		
11. Name of the person completing the form	12. Date		

B. Section to be completed after the follow-up CT Scan

13. Patient initials	14. Patient hospital identification number	15. Box	
16. Time and date of follow-up CT scan Time _____ : _____ (24 hours) Date ____/____/____ (dd/mm/yy)	17b. If yes, type of haematoma evacuated: <i>(tick all that apply)</i>		
17a. Haematoma evacuation decided based on follow-up CT results? <i>(circle the correct answer)</i>	<input type="checkbox"/> Parenchymal <input type="checkbox"/> Epidural <input type="checkbox"/> Subdural		
Yes No			
18. CT scan identifier: <small>(OFFICE USE ONLY)</small>	19. CT scan parameters		
	Section thickness:		
	Section spacing:		
	Matrix:		
	Field of view:		
	Scan angulations:		
20. Name of the person completing the form	21. Date		

Appendix 3a Information for relatives and representatives

INTRACRANIAL BLEEDING SUBSTUDY – LEGAL REPRESENTATIVE INFORMATION SHEET & CONSENT, (HOSPITAL NAME)

**PI & Hospital name
Address
Tel, Email**

INFORMATION FOR RELATIVES AND REPRESENTATIVES

INTERNATIONAL STUDY OF BLEEDING AFTER INJURY AND INTRACRANIAL BLEEDING SUBSTUDY

This hospital is taking part in a research study to find ways to reduce severe bleeding after serious injury. We would like to include (name of patient) in this study.

WHAT YOU SHOULD KNOW ABOUT RESEARCH STUDIES:

This form gives information about the study including the aims, risks and benefits of taking part.

In this hospital, patients with severe bleeding and injury to the head are given the usual emergency treatment. The aim of this research study is to find a better treatment. We hope that the study treatment (tranexamic acid) will help clotting and so lessen the amount of blood lost and reduce the need for a blood transfusion and bleeding into the brain. But the study treatment may cause clots where they are not needed. We hope to find that the treatment will do a little more good than harm but we don't yet know this. Please read the information below carefully and ask the responsible doctor for any questions you have.

1) Why is this research being done?

Severe bleeding is a common cause of death after injury and it is important to find better ways of reducing the amount of blood lost.

2) What is the purpose of this study?

Tranexamic acid is often used to reduce bleeding after major surgery such as heart operations. This study is being done to see if it can also reduce bleeding after major injury. Tranexamic acid is not a new drug and is an approved treatment for many common conditions that involve bleeding.

3) Who is doing the study?

Dr (name) is in charge of this study at this hospital. The study is co-ordinated by doctors at the University of London.

4) A patient cannot be in this study if:

- he/she is known not to be legally adult
- he/she was injured more than 8 hours before arriving in hospital
- the doctor thinks there is a particular reason why tranexamic acid definitely **should not** be given
- the doctor thinks there is a particular reason why tranexamic acid definitely **should** be given
- she is pregnant
- the brain scan is normal

INTRACRANIAL BLEEDING SUBSTUDY – LEGAL REPRESENTATIVE INFORMATION SHEET &
CONSENT, (HOSPITAL NAME)

5) What will happen to the patient after he/she is included in this study?

The patient will be given all the usual emergency treatments for bleeding, including fluids to replace the blood that he/she lost. The patient will also be given a dose of either the active tranexamic acid or an inactive dummy medicine called saline. The dose will be given over a period of eight hours. The choice of what to give (active treatment or dummy treatment) will be made randomly by a computer at the University of Oxford, UK. The doctors looking after (patient name) will not know whether he/she gets the active or the dummy medicine. This information is kept on a confidential list in another hospital. It is routine practice to do a CT scan after a traumatic brain injury; this study involves doing a second CT scan within 24-48 hours of the injury. Doctor (doctor's name) will send brief details about how the patient is doing to the Co-ordinating Centre in London. This information will be used in strict confidence by the people working on the study and will not be released under any circumstance.

6) What are the possible risks of being in the study?

Tranexamic acid is widely used and at the moment there is no conclusive evidence of serious side effects with short term use. Tranexamic acid is NOT a new drug. A patient would normally be exposed to at least one CT scan; during this study an extra CT scan (within 24-48 hours) would be done. Level of exposure to X-ray radiation is about the same as (patient name) would receive naturally from the environment over eight months.

7) What are the possible benefits of being in the study?

We hope that tranexamic acid may help reduce blood loss and bleeding into the brain. The knowledge that we gain from this study will help people with similar injuries in the future.

8) If you have any questions or problems, who can you call?

If you have any questions you can contact Dr (name) by telephoning (tel)

9) What information do we keep private?

All information about (patient name) and his/her injury will be kept private. The only people allowed to look at the information will be the doctors who are running the study, the staff at the Co-ordinating Centre and the regulatory authorities who check that the study is being carried out correctly. We will publish the results of the study in a medical journal so that other doctors can benefit from the knowledge, but (patient name)'s personal information will not be included and there will be no way that he/she can be identified.

10) Can the study end early for the participant?

We hope that you will let us use information about how the patient got on, but if you do not want us to use it then please tell the doctor who is looking after the patient.

11) What else do you need to know?

- The study is funded by the University of London and the World Health Organisation, not the makers of tranexamic acid.
- The London School of Hygiene & Tropical Medicine (University of London) as the Co-ordinating Centre for the study accepts responsibility attached to its sponsorship of the study and, as such, would be responsible for claims for any non-negligent harm suffered by anyone as a result of participating in this study.
- We will ask you to sign a separate consent form and give you a copy to keep.

STUDY CO-ORDINATING CENTRE:

International Study of Bleeding After Injury, Room 180
London School of Hygiene & Tropical Medicine, Keppel Street, London WC1E 7HT
Tel +44 20 7299 4684
WWW.CRASH2.LSHTM.AC.UK

INTRACRANIAL BLEEDING SUBSTUDY – LEGAL REPRESENTATIVE INFORMATION SHEET &
CONSENT, (HOSPITAL NAME)

**PI & Hospital name
Address
Tel, Email**

Hospital Name:	
Patient Hospital ID:	
Randomisation Number:	
Name of Principal Investigator:	

RELATIVE AND REPRESENTATIVE CONSENT FORM

INTERNATIONAL STUDY OF BLEEDING AFTER INJURY and Intracranial Injury Substudy

PLEASE INITIAL BOX

1. I confirm that I have read and understood the information sheet Version 1, dated 6 June 2008, for the above study and have had the opportunity to ask questions.
2. I understand that the patient participation is voluntary and that he/she is free to withdraw at any time, without giving any reason, without his/her medical care or legal rights being affected.
3. I understand that sections of any of the patient's medical notes may be looked at by responsible individuals from The London School of Hygiene & Tropical Medicine or from regulatory authorities where it is relevant to his/her taking part in research. I give permission for these individuals to have access to the patient records.
4. I agree for (patient name) to take part in the above study / for (patient name)'s information to be used in this trial.
5. I understand that I can withdraw my consent at any time and the patient's medical care will not be affected in anyway by my withdrawal.

Name of relative or representative Date Signature

Name of Person taking consent
(if different from researcher) Date Signature

Researcher Date Signature

Appendix 3b
Information for patients

INTRACRANIAL BLEEDING SUBSTUDY – PATIENT INFORMATION SHEET & CONSENT
(HOSPITAL NAME)

PI & Hospital name
Address
Tel, Email

INFORMATION FOR PATIENTS

INTERNATIONAL STUDY OF BLEEDING AFTER INJURY AND INTRACRANIAL INJURY SUBSTUDY

This hospital is taking part in a research study to find ways to reduce severe bleeding after serious injury. You have been included in this study.

WHAT YOU SHOULD KNOW ABOUT RESEARCH STUDIES:

This form gives information about the study including the aims, risks and benefits of taking part.

In this hospital, patients with severe bleeding and injury to the head are given the usual emergency treatment. The aim of this research study is to find a better treatment. We hope that the study treatment (tranexamic acid) will help clotting and so lessen the amount of blood lost and reduce the need for a blood transfusion and bleeding into the brain. But the study treatment may cause clots where they are not needed. We hope to find that the treatment will do a little more good than harm but we don't yet know this. Please read the information below carefully and ask the doctor looking after you any questions you have.

1) Why is this research being done?

Severe bleeding is a common cause of death after injury and it is important to find better ways of reducing the amount of blood lost.

2) What is the purpose of this study?

Tranexamic acid is often used to reduce bleeding after major surgery such as heart operations. This study is being done to see if it can also reduce bleeding after major injury. Tranexamic acid is not a new drug and is an approved treatment for many common conditions that involve bleeding.

3) Who is doing the study?

Dr (name) is in charge of this study at this hospital. The study is co-ordinated by doctors at the University of London.

4) A patient cannot be in this study if:

- he/she is known not to be legally adult
- he/she was injured more than 8 hours before arriving in hospital
- the doctor thinks there is a particular reason why tranexamic acid definitely **should not** be given
- the doctor thinks there is a particular reason why tranexamic acid definitely **should** be given
- she is pregnant
- the brain scan is normal

INTRACRANIAL BLEEDING SUBSTUDY – PATIENT INFORMATION SHEET & CONSENT
(HOSPITAL NAME)

5) What has happened to you after you were included in this study?

You were given all the usual emergency treatments for bleeding, including fluids to replace the blood that you lost. You were also given a dose of either the active tranexamic acid or an inactive dummy medicine called saline. The dose was given over a period of eight hours. The choice of what to give (active treatment or dummy treatment) was made randomly by a computer at the University of Oxford, UK. The doctors looking after you do not know whether you got the active or the dummy medicine. This information is kept on a confidential list in another hospital. It is routine practice to do a CT scan after a traumatic brain injury; this study involves doing a second CT scan within 24-48 hours of the injury. Your doctor will send brief details about how you have been to the Co-ordinating Centre in London. This information will be used in strict confidence by the people working on the study and will not be released under any circumstance.

6) What are the possible risks of being in the study?

Tranexamic acid is widely used and at the moment there is no conclusive evidence of serious side effects with short term use. Tranexamic acid is NOT a new drug. You would normally be exposed to at least one CT scan; during this study an extra CT scan (within 24-48 hours) would be done. Level of exposure to X-ray radiation is about the same as you would receive naturally from the environment over eight months.

7) What are the possible benefits of being in the study?

We hope that tranexamic acid may help reduce blood loss and bleeding into the brain. The knowledge that we gain from this study will help people with similar injuries in the future.

8) If you have any questions or problems, who can you call?

If you have any questions you can contact Dr (name) by telephoning (tel)

9) What information do we keep private?

All information about you and your injury will be kept private. The only people allowed to look at the information will be the doctors who are running the study, the staff at the Co-ordinating Centre and the regulatory authorities who check that the study is being carried out correctly. We will publish the results of the study in a medical journal so that other doctors can benefit from the knowledge, but your personal information will not be included and there will be no way that you can be identified.

10) Can the study end early for the participant?

The study treatment was given in the emergency situation. We hope that you will let us use information about how you got on, but if you do not want us to use it then please tell your doctor.

11) What else do you need to know?

- The study is funded by the University of London and the World Health Organisation, not the makers of tranexamic acid.
- The London School of Hygiene & Tropical Medicine (University of London) as the Co-ordinating Centre for the study accepts responsibility attached to its sponsorship of the study and, as such, would be responsible for claims for any non-negligent harm suffered by anyone as a result of participating in this study.
- We will ask you to sign a separate consent form and give you a copy to keep.

STUDY CO-ORDINATING CENTRE:

International Study of Bleeding After Injury, Room 180
London School of Hygiene & Tropical Medicine, Keppel Street, London WC1E 7HT
Tel +44 20 7299 4684
WWW.CRASH2.LSHTM.AC.UK

Appendix 2

Computerised tomography scan reader forms

CRASH-2 Intracranial Bleeding Substudy						1. a. <input type="checkbox"/> first reader b. <input type="checkbox"/> second reader
Radiologist CT Scan Form						
<i>Fill in the information and circle where appropriate, please do not leave blanks.</i>						
2. CT Identifier		3.	a.Box			4. Time and date of CT scan a. Time _____:_____ (24 hours) b. Date ____/____/____ (dd/mm/yy)
			b.Pack			

Section to be completed after the initial CT Scan
5. CT characteristics

Overall appearance of the CT Scan (<i>circle one option on each line</i>)		
a. Normal	YES	NO
b. Mild Focal Injury	YES	NO
c. Medium Focal Injury	YES	NO
d. Mild/Moderate diffuse injury	YES	NO
e. Massive focal (\pm diffuse)	YES	NO
f. Massive diffuse (\pm focal)	YES	NO

6. Haemorrhagic findings

a. Is there any intracranial haemorrhage? (<i>circle one option on each line</i>)				YES	NO	If NO go to Question 7
Please classify type of haemorrhage: (List location and volume of each individual bleed in notes fields)				If YES		
b. Parenchymal haematoma	YES	NO	bi. <i>total volume in ml</i>		Codes: L=Left R=Right, T=temporal, F=frontal, P=parietal, O=occipital, BG=basal ganglia, B=brainstem	
bii. Notes						
c. Subdural haematoma	YES	NO	ci. <i>total volume in ml</i>		Codes: L=Left R=Right, T=temporal, F=frontal, P=parietal, O=occipital, BG=basal ganglia, B=brainstem <i>Also specify if there is tentorial subdural haematoma (TSH)</i>	
cii. Notes						
d. Epidural haematoma	YES	NO	di. <i>total volume in ml</i>		Codes: L=Left R=Right, T=temporal, F=frontal, P=parietal, O=occipital, BG=basal ganglia, B=brainstem	
dii. Notes						
e. Subarachnoid haemorrhage	YES	NO	ei. <i>score</i>		Codes: L=Left R=Right, T=temporal, F=frontal, P=parietal,	
eii. Notes						

				O=occipital Also specify if there is convexity subarachnoid haemorrhage (CSH)
f. Intraventricular haemorrhage	YES	NO	fi. score	
g. Haemorrhagic contusions	YES	NO	gi. total volume in ml	
gii. Notes				Codes: L=Left R=Right, T=temporal, F=frontal, P=parietal, O=occipital, BG=basal ganglia, B=brainstem
h. Petechial haemorrhages	YES	NO		

7. Non-haemorrhagic findings (circle one option on each line)

a. Is there any sign of acute focal ischaemic lesion?	YES	NO		
b. Are there any non-haemorrhagic contusions?	YES	NO	bi. total volume in ml	

8. Mass effect findings (circle one option on each line)

Please specify if any of the following mass effect signs are present:				
a. Sulcal effacement	YES	NO		
b. Ventricular effacement	YES	NO		
c. Uncal herniation	YES	NO		
d. Cisterns compressed	YES	NO		
e. Cisterns absent	YES	NO		
f. Midline shift	YES	NO	fi. approximate shift in mm	
If yes to any of the above, is the mass effect caused by:				
g. Haemorrhage	YES	NO		
h. Oedema	YES	NO		
i. Both	YES	NO		

9. Details of reading

a. Name of the person completing the form		b. Date of reading	____/____/____ (dd/mm/yyyy)
---	--	--------------------	--------------------------------

CRASH-2 Intracranial Bleeding Substudy						1. a. <input type="checkbox"/> first reader
RADIOLOGIST CT SCAN FORM						b. <input type="checkbox"/> second reader
<i>Fill in the information and circle where appropriate, please do not leave blanks.</i>						
2. CT Identifier		3.	a.Box			4. Time and date of CT scan a. Time ____:____ (24 hours) b. Date ____/____/____ (dd/mm/yy)
			b.Pack			

Section to be completed after the follow-up CT Scan

5. CT characteristics

a. Follow-up CT scan parameters comparable with the initial CT scan	YES	NO
Overall appearance of the CT Scan (circle one option on each line)		
b. Normal	YES	NO
c. Mild Focal Injury	YES	NO
d. Medium Focal Injury	YES	NO
e. Mild/Moderate diffuse injury	YES	NO
f. Massive focal (\pm diffuse)	YES	NO
g. Massive diffuse (\pm focal)	YES	NO

6. Haemorrhagic findings

a. Is there any intracranial haemorrhage? (circle one option on each line)			YES	NO	If NO go to Question 7
Please classify type of haemorrhage: (List location and volume of each individual bleed in notes fields)				If YES	
b. Parenchymal haematoma	YES	NO	bi. total volume in ml		
bii. Notes				Codes: L=Left R=Right, T=temporal, F=frontal, P=parietal, O=occipital, BG=basal ganglia, B=brainstem	
c. Subdural haematoma	YES	NO	ci. total volume in ml		
cii. Notes				Codes: L=Left R=Right, T=temporal, F=frontal, P=parietal, O=occipital, BG=basal ganglia, B=brainstem <i>Also specify if there is tentorial subdural haematoma (TSH)</i>	
d. Epidural haematoma	YES	NO	di. total volume in ml		
dii. Notes				Codes: L=Left R=Right, T=temporal, F=frontal, P=parietal, O=occipital, BG=basal ganglia, B=brainstem	

e. Subarachnoid haemorrhage	YES	NO	ei. <i>score</i>	
eii. Notes				Codes: L=Left R=Right, T=temporal, F=frontal, P=parietal, O=occipital <i>Also specify if there is convexity subarachnoid haemorrhage (CSH)</i>
f. Intraventricular haemorrhage	YES	NO	fi. <i>score</i>	
g. Haemorrhagic contusions	YES	NO	gi. <i>total volume in ml</i>	
gii. Notes				Codes: L=Left R=Right, T=temporal, F=frontal, P=parietal, O=occipital, BG=basal ganglia, B=brainstem
h. Petechial haemorrhages	YES	NO		
Compared to the first CT scan, are there any new areas of haemorrhage?				YES NO
If yes please describe:				

7. Non-haemorrhagic findings (circle one option on each line)

a. Is there any new acute focal ischaemic lesion not present in the first CT scan	YES	NO		
b. Are there any non-haemorrhagic contusions?	YES	NO	bi. <i>total volume in ml</i>	

8. Mass effect findings (circle one option on each line)

Please specify if any of the following mass effect signs are present:				
a. Sulcal effacement	YES	NO		
b. Ventricular effacement	YES	NO		
c. Uncal herniation	YES	NO		
d. Cisterns compressed	YES	NO		
e. Cisterns absent	YES	NO		
f. Midline shift	YES	NO		
If yes to any of the above, is the mass effect caused by:				
g. Haemorrhage	YES	NO		
h. Oedema	YES	NO		
i. Both	YES	NO		

9. Details of reading

a. Name of the person completing the form		b. Date of reading	____/____/____ (dd/mm/yyyy)
---	--	--------------------	--------------------------------

Appendix 3

CRASH-2 outcome form

CRASH₂ OUTCOME FORM

Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage

COMPLETE AT DISCHARGE FROM THE RANDOMISING HOSPITAL,

DEATH IN HOSPITAL OR 28 DAYS AFTER INJURY, WHICHEVER OCCURS FIRST

Attach
treatment
pack sticker
here

1. HOSPITAL

2. PATIENT

Patient Initials	<input type="text"/>	Hospital ID Number	<input type="text"/>	Sex	<input type="checkbox"/> M	<input type="checkbox"/> F
Date of Birth	<input type="text" value="YEAR"/> / <input type="text" value="MONTH"/> / <input type="text" value="DAY"/>					

3. OUTCOME

<p>3.1 DEATH IN HOSPITAL</p> <p>Date of death <input type="text" value="YEAR"/> / <input type="text" value="MONTH"/> / <input type="text" value="DAY"/></p> <p>Cause of death</p> <p><input type="checkbox"/> Bleeding</p> <p><input type="checkbox"/> Head injury</p> <p><input type="checkbox"/> Myocardial Infarction</p> <p><input type="checkbox"/> Stroke</p> <p><input type="checkbox"/> Pulmonary Embolism</p> <p><input type="checkbox"/> Multi organ failure</p> <p><input type="checkbox"/> Other - describe</p> <input type="text"/>	<p>3.2 PATIENT ALIVE</p> <p><input type="checkbox"/> Discharged - Date of discharge <input type="text" value="YEAR"/> / <input type="text" value="MONTH"/> / <input type="text" value="DAY"/></p> <p><input type="checkbox"/> Still in this hospital now (28 days after injury) - Date <input type="text" value="YEAR"/> / <input type="text" value="MONTH"/> / <input type="text" value="DAY"/></p>
<p>3.3 IF ALIVE TICK ONE BOX THAT BEST DESCRIBES THE PATIENT'S CONDITION (at 28 days or prior discharge)</p> <p><input type="checkbox"/> No symptoms</p> <p><input type="checkbox"/> Minor symptoms</p> <p><input type="checkbox"/> Some restriction in lifestyle but independent</p> <p><input type="checkbox"/> Dependent, but not requiring constant attention</p> <p><input type="checkbox"/> Fully dependent, requiring attention day and night</p>	

4. MANAGEMENT

a) Days in Intensive Care Unit (if not admitted to ICU, write '0' here)	<input type="text"/>
b) Significant Head Injury	<input type="checkbox"/> YES <input type="checkbox"/> NO
c) Operation site - Tick one box on every line	
• Neurosurgical	<input type="checkbox"/> YES <input type="checkbox"/> NO
• Chest	<input type="checkbox"/> YES <input type="checkbox"/> NO
• Abdomen	<input type="checkbox"/> YES <input type="checkbox"/> NO
• Pelvis	<input type="checkbox"/> YES <input type="checkbox"/> NO

7. TRANSFUSION

a) Blood products transfusion	<input type="checkbox"/> YES	<input type="checkbox"/> NO
b) Units transfused in 28 days		
• Red cell products	<input type="text"/>	units
• Fresh frozen plasma	<input type="text"/>	units
• Platelets	<input type="text"/>	units
• Cryoprecipitate	<input type="text"/>	units
• Recombinant Factor VIIa	<input type="checkbox"/> YES	<input type="checkbox"/> NO

8. PERSON COMPLETING

5. COMPLICATIONS*Tick one box on every line*

• Pulmonary Embolism	YES	NO
• Deep Vein Thrombosis	YES	NO
• Stroke	YES	NO
• Operation for bleeding	YES	NO
• Myocardial Infarction	YES	NO
• Gastrointestinal bleeding	YES	NO

6. TRIAL TREATMENT

a) Complete loading dose given	YES	NO
b) Complete maintenance dose given	YES	NO

FORM

NAME	
POSITION	
DATE	

NOW SEND THIS FORM TO THE CO-ORDINATING CENTRE IN ONE OF THE FOLLOWING WAYS:

- SECURE WEBSITE
- ELECTRONIC DATA FORMS / EMAIL
- FAX +44 (0)20 7299 4663

SEE INSTRUCTIONS IN YOUR SITE FILE

ISRCTN86750102

Health Technology Assessment programme

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 Director, NIHR HTA programme,
 Professor of Clinical Pharmacology,
 University of Liverpool

Deputy Director,
Professor Hywel Williams,
 Professor of Dermato-Epidemiology,
 Centre of Evidence-Based Dermatology,
 University of Nottingham

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 and Screening Panel

Professor Scott Weich,
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 Sciences Research Institute,
 University of Warwick
 Chair – Psychological and
 Community Therapies Panel

Professor Hywel Williams,
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 Trials Unit, Centre of Evidence-
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 Chair – HTA Commissioning
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 Deputy HTA Programme Director

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 Biostatistics, Robertson Centre for
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 Lecturer in Medical Statistics,
 Department of Primary Health
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Diagnostic Technologies and Screening Panel

Members

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Disease Prevention Panel

Members

<p>Chair, Professor Margaret Thorogood, Professor of Epidemiology, University of Warwick Medical School, Coventry</p> <p>Dr Robert Cook, Clinical Programmes Director, Bazian Ltd, London</p> <p>Dr Colin Greaves, Senior Research Fellow, Peninsula Medical School (Primary Care)</p> <p>Mr Michael Head, Public contributor</p>	<p>Professor Cathy Jackson, Professor of Primary Care Medicine, Bute Medical School, University of St Andrews</p> <p>Dr Russell Jago, Senior Lecturer in Exercise, Nutrition and Health, Centre for Sport, Exercise and Health, University of Bristol</p> <p>Dr Julie Mytton, Consultant in Child Public Health, NHS Bristol</p>	<p>Professor Irwin Nazareth, Professor of Primary Care and Director, Department of Primary Care and Population Sciences, University College London</p> <p>Dr Richard Richards, Assistant Director of Public Health, Derbyshire County Primary Care Trust</p> <p>Professor Ian Roberts, Professor of Epidemiology and Public Health, London School of Hygiene & Tropical Medicine</p>	<p>Dr Kenneth Robertson, Consultant Paediatrician, Royal Hospital for Sick Children, Glasgow</p> <p>Dr Catherine Swann, Associate Director, Centre for Public Health Excellence, NICE</p> <p>Mrs Jean Thurston, Public contributor</p> <p>Professor David Weller, Head, School of Clinical Science and Community Health, University of Edinburgh</p>
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External Devices and Physical Therapies Panel

Members

<p>Chair, Dr John Pounsford, Consultant Physician North Bristol NHS Trust</p>	<p>Dr Dawn Carnes, Senior Research Fellow, Barts and the London School of Medicine and Dentistry</p>	<p>Dr Shaheen Hamdy, Clinical Senior Lecturer and Consultant Physician, University of Manchester</p>	<p>Mr Jim Reece, Public contributor</p>
<p>Deputy Chair, Professor E Andrea Nelson, Reader in Wound Healing and Director of Research, University of Leeds</p>	<p>Dr Emma Clark, Clinician Scientist Fellow & Cons. Rheumatologist, University of Bristol</p>	<p>Professor Christine Norton, Professor of Clinical Nursing Innovation, Bucks New University and Imperial College Healthcare NHS Trust</p>	<p>Professor Maria Stokes, Professor of Neuromusculoskeletal Rehabilitation, University of Southampton</p>
<p>Professor Bipin Bhakta, Charterhouse Professor in Rehabilitation Medicine, University of Leeds</p>	<p>Mrs Anthea De Barton-Watson, Public contributor</p>	<p>Dr Lorraine Pinnigton, Associate Professor in Rehabilitation, University of Nottingham</p>	<p>Dr Pippa Tyrrell, Senior Lecturer/Consultant, Salford Royal Foundation Hospitals' Trust and University of Manchester</p>
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Interventional Procedures Panel

Members

<p>Chair, Professor Jonathan Michaels, Professor of Vascular Surgery, University of Sheffield</p>	<p>Mr Seumas Eckford, Consultant in Obstetrics & Gynaecology, North Devon District Hospital</p>	<p>Dr Fiona Lecky, Senior Lecturer/Honorary Consultant in Emergency Medicine, University of Manchester/Salford Royal Hospitals NHS Foundation Trust</p>	<p>Professor Jon Moss, Consultant Interventional Radiologist, North Glasgow Hospitals University NHS Trust</p>
<p>Deputy Chair, Mr Michael Thomas, Consultant Colorectal Surgeon, Bristol Royal Infirmary</p>	<p>Professor Sam Eljamel, Consultant Neurosurgeon, Ninewells Hospital and Medical School, Dundee</p>	<p>Dr Nadim Malik, Consultant Cardiologist/Honorary Lecturer, University of Manchester</p>	<p>Dr Simon Padley, Consultant Radiologist, Chelsea & Westminster Hospital</p>
<p>Mrs Isabel Boyer, Public contributor</p>	<p>Dr Adele Fielding, Senior Lecturer and Honorary Consultant in Haematology, University College London Medical School</p>	<p>Mr Hisham Mehanna, Consultant & Honorary Associate Professor, University Hospitals Coventry & Warwickshire NHS Trust</p>	<p>Dr Ashish Paul, Medical Director, Bedfordshire PCT</p>
<p>Mr Sankaran Chandra Sekharan, Consultant Surgeon, Breast Surgery, Colchester Hospital University NHS Foundation Trust</p>	<p>Dr Matthew Hatton, Consultant in Clinical Oncology, Sheffield Teaching Hospital Foundation Trust</p>	<p>Dr Jane Montgomery, Consultant in Anaesthetics and Critical Care, South Devon Healthcare NHS Foundation Trust</p>	<p>Dr Sarah Purdy, Consultant Senior Lecturer, University of Bristol</p>
<p>Professor Nicholas Clarke, Consultant Orthopaedic Surgeon, Southampton University Hospitals NHS Trust</p>	<p>Dr John Holden, General Practitioner, Garswood Surgery, Wigan</p>		<p>Dr Matthew Wilson, Consultant Anaesthetist, Sheffield Teaching Hospitals NHS Foundation Trust</p>
<p>Ms Leonie Cooke, Public contributor</p>			<p>Professor Yit Chiun Yang, Consultant Ophthalmologist, Royal Wolverhampton Hospitals NHS Trust</p>

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Pharmaceuticals Panel

Members

Chair, Professor Imti Choonara, Professor in Child Health, University of Nottingham	Dr James Gray, Consultant Microbiologist, Department of Microbiology, Birmingham Children's Hospital NHS Foundation Trust	Dr Maria Kouimtzi, Pharmacy and Informatics Director, Global Clinical Solutions, Wiley-Blackwell	Mrs Katrina Simister, Assistant Director New Medicines, National Prescribing Centre, Liverpool
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Mr Simon Reeve, Head of Clinical and Cost- Effectiveness, Medicines, Pharmacy and Industry Group, Department of Health	Professor Tom Walley, CBE, Director, NIHR HTA programme, Professor of Clinical Pharmacology, University of Liverpool	

Psychological and Community Therapies Panel

Members

Chair, Professor Scott Weich, Professor of Psychiatry, University of Warwick, Coventry	Mrs Val Carlill, Public contributor	Dr Jeremy J Murphy, Consultant Physician and Cardiologist, County Durham and Darlington Foundation Trust	Dr Paul Ramchandani, Senior Research Fellow/Cons. Child Psychiatrist, University of Oxford
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Feedback

The HTA programme and the authors would like to know your views about this report.

The Correspondence Page on the HTA website (www.hta.ac.uk) is a convenient way to publish your comments. If you prefer, you can send your comments to the address below, telling us whether you would like us to transfer them to the website.

We look forward to hearing from you.