Clinical trial results:
Tranexamic Acid for the treatment of significant traumatic brain injury: an international, randomised, double blind, placebo controlled trial.

Summary

EudraCT number	2011-003669-14
Trial protocol	ES GB IT IE SI
Global end of trial date	28 February 2019

Results information

Result version number	v1 (current)
This version publication date	02 July 2020
First version publication date	02 July 2020
Summary attachment (see zip file)	CRASH-3_The Lancet (CRASH-3 publication.pdf) CRASH-3_The Lancet figures (CRASH-3 figures.ppt) CRASH-3_The Lancet supplementary files (CRASH-3_The Lancet_Supplementary files.pdf)

Trial information

Trial identification

Sponsor protocol code	ISRCTN15088122

Additional study identifiers

ISRCTN number	ISRCTN15088122
ClinicalTrials.gov id (NCT number)	NCT01402882
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	London School Of Hygiene and Tropical Medicine
Sponsor organisation address	Keppel Street, London, United Kingdom, WC1E 7HT
Public contact	Haleema Shakur-Still, London School Of Hygiene and Tropical Medicine, +44 2079588113, haleema.shakur-still@lshtm.ac.uk
Scientific contact	Ian Roberts, London School Of Hygiene and Tropical Medicine, +44 2079588128, haleema.shakur-still@lshtm.ac.uk

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	30 May 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	28 February 2019
Global end of trial reached?	Yes
Global end of trial date	28 February 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The CRASH-3 trial will see if a drug called tranexamic acid will improve outcomes for people who have suffered a traumatic head injury. The main outcome is its effect on death within 28 days of the head injury among patients randomised within 3 hours of injury. We will also assess the cause of death.

Protection of trial subjects:

The trial was done in accordance with the good clinical practice guidelines by the International Conference on Harmonisation. The procedure at each site was approved by the relevant ethics committee and regulatory agencies. Consent was obtained from participants if their physical and mental capacity allowed (as judged by the treating clinician). If a participant was unable to give consent, proxy consent was obtained from a relative or representative. If a proxy was unavailable, then if permitted by local regulation, consent was waived. When consent was waived or given by a proxy, the participant was informed about the trial as soon as possible, and consent was obtained for ongoing data collection, if needed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	20 July 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Romania: 35
Country: Number of subjects enrolled	Slovenia: 15
Country: Number of subjects enrolled	Spain: 425
Country: Number of subjects enrolled	United Kingdom: 3143
Country: Number of subjects enrolled	Ireland: 12
Country: Number of subjects enrolled	Italy: 72
Country: Number of subjects enrolled	Afghanistan: 87
Country: Number of subjects enrolled	Albania: 214
Country: Number of subjects enrolled	Cambodia: 45
Country: Number of subjects enrolled	Cameroon: 116
Country: Number of subjects enrolled	Canada: 7
Country: Number of subjects enrolled	Colombia: 335
Country: Number of subjects enrolled	Egypt: 20
Country: Number of subjects enrolled	El Salvador: 28
Country: Number of subjects enrolled	Indonesia: 6
Country: Number of subjects enrolled	Iraq: 55

Country: Number of subjects enrolled	Jamaica: 7
Country: Number of subjects enrolled	Japan: 165
Country: Number of subjects enrolled	Kenya: 1
Country: Number of subjects enrolled	Mexico: 79
Country: Number of subjects enrolled	Myanmar: 121
Country: Number of subjects enrolled	Nepal: 255
Country: Number of subjects enrolled	Nigeria: 409
Country: Number of subjects enrolled	Papua New Guinea: 10
Country: Number of subjects enrolled	United Arab Emirates: 126
Country: Number of subjects enrolled	Zambia: 44
Country: Number of subjects enrolled	Pakistan: 4567
Country: Number of subjects enrolled	Malaysia: 1567
Country: Number of subjects enrolled	Georgia: 771
Worldwide total number of subjects	12737
EEA total number of subjects	3702

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	3
Adolescents (12-17 years)	55
Adults (18-64 years)	10417
From 65 to 84 years	1895
85 years and over	367

Subject disposition

Recruitment

Recruitment details:

The CRASH-3 trial randomised patients aged 16 and older with a traumatic brain injury in 175 hospitals in 29 countries.
The first patient was randomised on 20/07/2012 and the final patient on 31/01/2019.

Pre-assignment

Screening details:

All adult patients with TBI, within 3 hours of injury, with a GCS score of 12 or lower or any intracranial bleeding on CT scan, and no major extracranial bleeding were eligible. The fundamental eligibility criterion is the responsible clinician's 'uncertainty' as to whether or not to use an antifibrinolytic agent in a particular patient with TBI.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer, Assessor

Blinding implementation details:

Ampoules and packaging for tranexamic acid (TXA) and placebo were identical in appearance. The masking involved the removal of the original manufacturer's label and replacement with the clinical trial label bearing the randomisation number, which was used as the pack identification. Patients were randomly allocated to receive TXA or placebo. The randomisation codes were generated and held by an independent statistical consultant.

Arms

Are arms mutually exclusive?	Yes
Arm title	Tranexamic acid

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Cyklokapron
Investigational medicinal product code	B02AA02
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravascular use

Dosage and administration details:

Patients were randomly allocated to receive a loading dose of 1 g of tranexamic acid or matching placebo infused over 10 min, started immediately after randomisation, followed by an intravenous infusion of 1 g over 8 h.

Arm title	Placebo

Arm description: -

Arm type	Placebo
Investigational medicinal product name	Sodium chloride 0.9%
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Patients were randomly allocated to receive a loading dose of 1 g of tranexamic acid or matching placebo infused over 10 min, started immediately after randomisation, followed by an intravenous infusion of 1 g over 8 h.

Number of subjects in period 1[1]	Tranexamic acid	Placebo
Started	4649	4553
Completed	4613	4514
Not completed	36	39
Consent withdrawn so outcome data unavailable	7	14
Lost to follow-up	29	25

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: During the trial, new research suggested that TXA was likely to only be effective within 3 hours of injury. From this point onwards, only patients within 3 hours of their injury were randomised and the primary outcome was amended to deaths among patients treated within 3 hours of injury. The total number of patients randomised worldwide is 12,737 (including all patients). The total number of patients included in the primary analysis is 9,202 (including only patients treated within 3 hours).

Baseline characteristics

Reporting groups	
Reporting group title	Tranexamic acid
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Reporting group values	Tranexamic acid	Placebo	Total
Number of subjects	4649	4553	9202
Age categorical Units: Subjects			
< 25 years	1042	996	2038
25 - 44 years	1716	1672	3388
45 - 64 years	1169	1184	2353
65 years and over	722	701	1423
Gender categorical Units: Subjects			
Female	906	893	1799
Male	3742	3660	7402
Other	1	0	1
Time since injury Units: Subjects			
< 1 hour	877	869	1746
1 - 2 hours	2003	1889	3892
2 - 3 hours	1769	1795	3564
Systolic blood pressure Units: Subjects			
< 90 mm Hg	89	85	174
90 - 119 mm Hg	1508	1490	2998
120 - 139 mm Hg	1461	1504	2965
140 or over mm Hg	1576	1466	3042
Unknown	15	8	23
Glasgow Coma Scale score Units: Subjects			
GCS 3	495	506	1001
GCS 4	213	213	426
GCS 5	163	172	335
GCS 6	221	232	453
GCS 7	311	294	605
GCS 8	354	315	669
GCS 9	335	292	627
GCS 10	371	364	735
GCS 11	375	390	765
GCS 12	476	478	954
GCS 13	297	312	609
GCS 14	526	458	984
GCS 15	484	492	976
Unknown	28	35	63

Pupil Reaction Units: Subjects			
None reacted	425	440	865
One reacted	374	353	727
Both reacted	3706	3636	7342
Unable to assess or unknown	144	124	268

End points

End points reporting groups	
Reporting group title	Tranexamic acid
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Primary: Effect of tranexamic acid on head injury-related death in patients randomly assigned within 3 h of injury	
End point title	Effect of tranexamic acid on head injury-related death in patients randomly assigned within 3 h of injury
End point description:	
End point type	Primary
End point timeframe: Within 28 days of randomisation	

End point values	Tranexamic acid	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	4613	4514		
Units: Dead or alive	855	892		

Attachments (see zip file)	CRASH-3 primary analysis/CRASH-3 primary analysis.pptx

Statistical analyses

Statistical analysis title	Primary analysis
Comparison groups	Tranexamic acid v Placebo
Number of subjects included in analysis	9127
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Risk ratio (RR)
Point estimate	0.94
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.86
upper limit	1.02

Other pre-specified: Effect of tranexamic acid on head injury-related death in patients randomly assigned within 3 h of injury excluding patients with GCS score of 3 or bilateral unreactive pupils

End point title	Effect of tranexamic acid on head injury-related death in patients randomly assigned within 3 h of injury excluding patients with GCS score of 3 or bilateral unreactive pupils

End point description:

End point type	Other pre-specified

End point timeframe:

Within 28 days of randomisation

End point values	Tranexamic acid	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	3880	3757		
Units: Dead or alive	485	525		

Statistical analyses

Statistical analysis title	Primary outcome: prespecified sensitivity analysis
Comparison groups	Tranexamic acid v Placebo
Number of subjects included in analysis	7637
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Risk ratio (RR)
Point estimate	0.89
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.8
upper limit	1

Adverse events

Adverse events information

Timeframe for reporting adverse events:

A written report must be submitted within 24 hours to the Trial Coordinating Centre if any SAE, SAR or SUSAR that occurs during hospitalisation or any untoward medical occurrence after discharge and up to 28 days after the trial treatment.

Adverse event reporting additional description:

Prior to discharge, all randomised patients will be given a (supplied) alert card, so either the patient or their family can present the card to any healthcare provider they see after they are discharged.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	13.0

Reporting groups

Reporting group title	Tranexamic acid
Reporting group description: -	
Reporting group title	Placebo

Reporting group description: -

Serious adverse events	Tranexamic acid	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	76 / 6359 (1.20%)	68 / 6280 (1.08%)	
number of deaths (all causes)	855	892	
number of deaths resulting from adverse events	28	18	
Vascular disorders			
Haematoma			
subjects affected / exposed	1 / 6359 (0.02%)	0 / 6280 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	1 / 6359 (0.02%)	0 / 6280 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
General disorders and administration site conditions			
Hypothermia			
subjects affected / exposed	0 / 6359 (0.00%)	1 / 6280 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Immune system disorders			

Allergic reaction			
subjects affected / exposed	0 / 6359 (0.00%)	1 / 6280 (0.02%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pneumothorax			
subjects affected / exposed	3 / 6359 (0.05%)	1 / 6280 (0.02%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Haemothorax			
subjects affected / exposed	0 / 6359 (0.00%)	2 / 6280 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	3 / 6359 (0.05%)	0 / 6280 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	0 / 6359 (0.00%)	3 / 6280 (0.05%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory distress syndrome			
subjects affected / exposed	1 / 6359 (0.02%)	0 / 6280 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory arrest			
subjects affected / exposed	1 / 6359 (0.02%)	1 / 6280 (0.02%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pulmonary haemorrhage			
subjects affected / exposed	1 / 6359 (0.02%)	0 / 6280 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pulmonary oedema			
subjects affected / exposed	0 / 6359 (0.00%)	1 / 6280 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Psychotic episode			
subjects affected / exposed	1 / 6359 (0.02%)	0 / 6280 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Abnormal liver function tests			
subjects affected / exposed	2 / 6359 (0.03%)	1 / 6280 (0.02%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 2	0 / 0	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	4 / 6359 (0.06%)	3 / 6280 (0.05%)	
occurrences causally related to treatment / all	0 / 6	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 1	
Traumatic brain injury			
subjects affected / exposed	1 / 6359 (0.02%)	1 / 6280 (0.02%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Unintended unilateral bronchial intubation			
subjects affected / exposed	1 / 6359 (0.02%)	1 / 6280 (0.02%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute alcoholic intoxication			
subjects affected / exposed	1 / 6359 (0.02%)	0 / 6280 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye injury			

subjects affected / exposed	1 / 6359 (0.02%)	0 / 6280 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip dislocation			
subjects affected / exposed	0 / 6359 (0.00%)	1 / 6280 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Overdose			
subjects affected / exposed	0 / 6359 (0.00%)	1 / 6280 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	2 / 6359 (0.03%)	1 / 6280 (0.02%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	1 / 6359 (0.02%)	0 / 6280 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	3 / 6359 (0.05%)	0 / 6280 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Heart block			
subjects affected / exposed	0 / 6359 (0.00%)	2 / 6280 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial flutter			
subjects affected / exposed	1 / 6359 (0.02%)	0 / 6280 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			

subjects affected / exposed	0 / 6359 (0.00%)	1 / 6280 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular fibrillation			
subjects affected / exposed	0 / 6359 (0.00%)	1 / 6280 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Ventricular tachycardia			
subjects affected / exposed	0 / 6359 (0.00%)	1 / 6280 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebral haemorrhage			
subjects affected / exposed	1 / 6359 (0.02%)	3 / 6280 (0.05%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 1	
Cerebral haematoma			
subjects affected / exposed	2 / 6359 (0.03%)	0 / 6280 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			
subjects affected / exposed	0 / 6359 (0.00%)	1 / 6280 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	2 / 6359 (0.03%)	0 / 6280 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	1 / 2	0 / 0	
Seizure			
subjects affected / exposed	0 / 6359 (0.00%)	1 / 6280 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cerebrospinal fluid leakage			

subjects affected / exposed	0 / 6359 (0.00%)	1 / 6280 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cranial nerve paralysis			
subjects affected / exposed	1 / 6359 (0.02%)	0 / 6280 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial palsy			
subjects affected / exposed	0 / 6359 (0.00%)	1 / 6280 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydrocephalus			
subjects affected / exposed	0 / 6359 (0.00%)	1 / 6280 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stroke			
subjects affected / exposed	1 / 6359 (0.02%)	0 / 6280 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vasovagal reaction			
subjects affected / exposed	0 / 6359 (0.00%)	1 / 6280 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventriculitis			
subjects affected / exposed	1 / 6359 (0.02%)	0 / 6280 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Vocal cord paresis			
subjects affected / exposed	1 / 6359 (0.02%)	0 / 6280 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Ileus			

subjects affected / exposed	1 / 6359 (0.02%)	1 / 6280 (0.02%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	1 / 6359 (0.02%)	0 / 6280 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	1 / 6359 (0.02%)	0 / 6280 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	1 / 6359 (0.02%)	1 / 6280 (0.02%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal compartment syndrome			
subjects affected / exposed	1 / 6359 (0.02%)	0 / 6280 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Bowel obstruction			
subjects affected / exposed	1 / 6359 (0.02%)	0 / 6280 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hepatobiliary disorders			
Liver failure			
subjects affected / exposed	0 / 6359 (0.00%)	1 / 6280 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Renal and urinary disorders			
Urinary retention			
subjects affected / exposed	1 / 6359 (0.02%)	1 / 6280 (0.02%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			

Thyroid haemorrhage			
subjects affected / exposed	1 / 6359 (0.02%)	0 / 6280 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	28 / 6359 (0.44%)	29 / 6280 (0.46%)	
occurrences causally related to treatment / all	0 / 30	0 / 30	
deaths causally related to treatment / all	0 / 7	0 / 7	
Respiratory infection			
subjects affected / exposed	6 / 6359 (0.09%)	3 / 6280 (0.05%)	
occurrences causally related to treatment / all	0 / 6	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 6359 (0.02%)	1 / 6280 (0.02%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	1 / 6359 (0.02%)	0 / 6280 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
subjects affected / exposed	0 / 6359 (0.00%)	1 / 6280 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection MRSA			
subjects affected / exposed	0 / 6359 (0.00%)	1 / 6280 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis			
subjects affected / exposed	0 / 6359 (0.00%)	2 / 6280 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile infection			

subjects affected / exposed	2 / 6359 (0.03%)	0 / 6280 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gangrene			
subjects affected / exposed	1 / 6359 (0.02%)	0 / 6280 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 6359 (0.02%)	0 / 6280 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrospinal infection			
subjects affected / exposed	1 / 6359 (0.02%)	0 / 6280 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemophilus influenza pneumonia			
subjects affected / exposed	0 / 6359 (0.00%)	1 / 6280 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Necrotising fasciitis			
subjects affected / exposed	0 / 6359 (0.00%)	1 / 6280 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural infection			
subjects affected / exposed	0 / 6359 (0.00%)	1 / 6280 (0.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shunt infection			
subjects affected / exposed	1 / 6359 (0.02%)	0 / 6280 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hypokalaemia			

subjects affected / exposed	1 / 6359 (0.02%)	1 / 6280 (0.02%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	1 / 6359 (0.02%)	0 / 6280 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Tranexamic acid	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	84 / 6359 (1.32%)	72 / 6280 (1.15%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 6359 (0.00%)	2 / 6280 (0.03%)	
occurrences (all)	0	2	
Surgical and medical procedures			
Fractured zygomatic arch reduction			
subjects affected / exposed	0 / 6359 (0.00%)	1 / 6280 (0.02%)	
occurrences (all)	0	1	
Tracheostomy			
subjects affected / exposed	0 / 6359 (0.00%)	1 / 6280 (0.02%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	3 / 6359 (0.05%)	0 / 6280 (0.00%)	
occurrences (all)	3	0	
Pyrexia			
subjects affected / exposed	2 / 6359 (0.03%)	2 / 6280 (0.03%)	
occurrences (all)	2	2	
Immune system disorders			
Allergic reaction			
subjects affected / exposed	4 / 6359 (0.06%)	4 / 6280 (0.06%)	
occurrences (all)	4	4	
Respiratory, thoracic and mediastinal			

disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	0 / 6359 (0.00%)	1 / 6280 (0.02%)	
occurrences (all)	0	1	
Atelectasis			
subjects affected / exposed	0 / 6359 (0.00%)	1 / 6280 (0.02%)	
occurrences (all)	0	1	
Haemothorax			
subjects affected / exposed	1 / 6359 (0.02%)	0 / 6280 (0.00%)	
occurrences (all)	1	0	
Pleural effusion			
subjects affected / exposed	0 / 6359 (0.00%)	1 / 6280 (0.02%)	
occurrences (all)	0	1	
Pneumothorax			
subjects affected / exposed	1 / 6359 (0.02%)	1 / 6280 (0.02%)	
occurrences (all)	1	1	
Psychiatric disorders			
Agitation			
subjects affected / exposed	1 / 6359 (0.02%)	0 / 6280 (0.00%)	
occurrences (all)	1	0	
Depression			
subjects affected / exposed	1 / 6359 (0.02%)	0 / 6280 (0.00%)	
occurrences (all)	1	0	
Investigations			
Abnormal liver function tests			
subjects affected / exposed	4 / 6359 (0.06%)	5 / 6280 (0.08%)	
occurrences (all)	4	5	
ECG signs of myocardial ischaemia			
subjects affected / exposed	0 / 6359 (0.00%)	1 / 6280 (0.02%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	5 / 6359 (0.08%)	2 / 6280 (0.03%)	
occurrences (all)	5	2	
Humerus fracture			

subjects affected / exposed	1 / 6359 (0.02%)	0 / 6280 (0.00%)	
occurrences (all)	1	0	
Laceration of head			
subjects affected / exposed	1 / 6359 (0.02%)	0 / 6280 (0.00%)	
occurrences (all)	1	0	
Tracheostomy complication			
subjects affected / exposed	0 / 6359 (0.00%)	1 / 6280 (0.02%)	
occurrences (all)	0	1	
Cardiac disorders			
Atrial flutter			
subjects affected / exposed	3 / 6359 (0.05%)	1 / 6280 (0.02%)	
occurrences (all)	3	1	
Heart block			
subjects affected / exposed	1 / 6359 (0.02%)	0 / 6280 (0.00%)	
occurrences (all)	1	0	
Sinus pause			
subjects affected / exposed	1 / 6359 (0.02%)	0 / 6280 (0.00%)	
occurrences (all)	1	0	
Supraventricular tachycardia			
subjects affected / exposed	2 / 6359 (0.03%)	2 / 6280 (0.03%)	
occurrences (all)	2	2	
Nervous system disorders			
Cranial nerve palsies multiple			
subjects affected / exposed	0 / 6359 (0.00%)	1 / 6280 (0.02%)	
occurrences (all)	0	1	
Epilepsy			
subjects affected / exposed	0 / 6359 (0.00%)	1 / 6280 (0.02%)	
occurrences (all)	0	1	
Foot drop			
subjects affected / exposed	0 / 6359 (0.00%)	1 / 6280 (0.02%)	
occurrences (all)	0	1	
Headache			
subjects affected / exposed	5 / 6359 (0.08%)	1 / 6280 (0.02%)	
occurrences (all)	5	1	
Intracranial venous sinus thrombosis			

subjects affected / exposed	1 / 6359 (0.02%)	2 / 6280 (0.03%)	
occurrences (all)	1	2	
Metabolic encephalopathy			
subjects affected / exposed	1 / 6359 (0.02%)	0 / 6280 (0.00%)	
occurrences (all)	1	0	
Neuroleptic malignant syndrome			
subjects affected / exposed	0 / 6359 (0.00%)	1 / 6280 (0.02%)	
occurrences (all)	0	1	
Paraesthesia			
subjects affected / exposed	1 / 6359 (0.02%)	0 / 6280 (0.00%)	
occurrences (all)	1	0	
Seizure			
subjects affected / exposed	1 / 6359 (0.02%)	0 / 6280 (0.00%)	
occurrences (all)	1	0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 6359 (0.00%)	2 / 6280 (0.03%)	
occurrences (all)	0	2	
Neutropenia			
subjects affected / exposed	1 / 6359 (0.02%)	0 / 6280 (0.00%)	
occurrences (all)	2	0	
Thrombocytopenia			
subjects affected / exposed	2 / 6359 (0.03%)	0 / 6280 (0.00%)	
occurrences (all)	2	0	
Thrombocythaemia			
subjects affected / exposed	0 / 6359 (0.00%)	1 / 6280 (0.02%)	
occurrences (all)	0	1	
Thrombocytosis			
subjects affected / exposed	1 / 6359 (0.02%)	1 / 6280 (0.02%)	
occurrences (all)	1	1	
Eye disorders			
Corneal ulcer			
subjects affected / exposed	1 / 6359 (0.02%)	0 / 6280 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			

Abdominal distension			
subjects affected / exposed	0 / 6359 (0.00%)	1 / 6280 (0.02%)	
occurrences (all)	0	1	
Constipation			
subjects affected / exposed	0 / 6359 (0.00%)	2 / 6280 (0.03%)	
occurrences (all)	0	2	
Diarrhoea			
subjects affected / exposed	1 / 6359 (0.02%)	0 / 6280 (0.00%)	
occurrences (all)	1	0	
Ileus			
subjects affected / exposed	0 / 6359 (0.00%)	2 / 6280 (0.03%)	
occurrences (all)	0	2	
Intestinal pseudo-obstruction			
subjects affected / exposed	1 / 6359 (0.02%)	1 / 6280 (0.02%)	
occurrences (all)	1	1	
Rectal bleeding			
subjects affected / exposed	1 / 6359 (0.02%)	0 / 6280 (0.00%)	
occurrences (all)	1	0	
Toothache			
subjects affected / exposed	0 / 6359 (0.00%)	1 / 6280 (0.02%)	
occurrences (all)	0	1	
Hepatobiliary disorders			
Hyperbilirubinaemia			
subjects affected / exposed	1 / 6359 (0.02%)	0 / 6280 (0.00%)	
occurrences (all)	1	0	
Obstructive jaundice			
subjects affected / exposed	0 / 6359 (0.00%)	1 / 6280 (0.02%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	1 / 6359 (0.02%)	1 / 6280 (0.02%)	
occurrences (all)	1	1	
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	0 / 6359 (0.00%)	1 / 6280 (0.02%)	
occurrences (all)	0	1	
Painful urination			

subjects affected / exposed	0 / 6359 (0.00%)	1 / 6280 (0.02%)	
occurrences (all)	0	1	
Urinary retention			
subjects affected / exposed	2 / 6359 (0.03%)	1 / 6280 (0.02%)	
occurrences (all)	2	1	
Musculoskeletal and connective tissue disorders			
Cervical pain			
subjects affected / exposed	0 / 6359 (0.00%)	1 / 6280 (0.02%)	
occurrences (all)	0	1	
Jaw pain			
subjects affected / exposed	1 / 6359 (0.02%)	0 / 6280 (0.00%)	
occurrences (all)	1	0	
Leg pain			
subjects affected / exposed	0 / 6359 (0.00%)	1 / 6280 (0.02%)	
occurrences (all)	0	1	
Infections and infestations			
Bacteraemia			
subjects affected / exposed	0 / 6359 (0.00%)	1 / 6280 (0.02%)	
occurrences (all)	0	1	
Cellulitis			
subjects affected / exposed	3 / 6359 (0.05%)	4 / 6280 (0.06%)	
occurrences (all)	3	4	
Central line infection			
subjects affected / exposed	1 / 6359 (0.02%)	0 / 6280 (0.00%)	
occurrences (all)	1	0	
Herpes zoster			
subjects affected / exposed	1 / 6359 (0.02%)	0 / 6280 (0.00%)	
occurrences (all)	1	0	
Infection MRSA			
subjects affected / exposed	1 / 6359 (0.02%)	1 / 6280 (0.02%)	
occurrences (all)	1	1	
Laryngopharyngitis			
subjects affected / exposed	1 / 6359 (0.02%)	0 / 6280 (0.00%)	
occurrences (all)	1	0	
Meningitis			

subjects affected / exposed	1 / 6359 (0.02%)	0 / 6280 (0.00%)	
occurrences (all)	1	0	
Pneumonia			
subjects affected / exposed	20 / 6359 (0.31%)	20 / 6280 (0.32%)	
occurrences (all)	21	20	
Respiratory infection			
subjects affected / exposed	4 / 6359 (0.06%)	4 / 6280 (0.06%)	
occurrences (all)	4	4	
Sepsis			
subjects affected / exposed	0 / 6359 (0.00%)	1 / 6280 (0.02%)	
occurrences (all)	0	1	
Tracheostomy infection			
subjects affected / exposed	1 / 6359 (0.02%)	0 / 6280 (0.00%)	
occurrences (all)	1	0	
Urinary tract infection			
subjects affected / exposed	8 / 6359 (0.13%)	4 / 6280 (0.06%)	
occurrences (all)	8	4	
Wound dehiscence			
subjects affected / exposed	0 / 6359 (0.00%)	2 / 6280 (0.03%)	
occurrences (all)	0	2	
Wound infection			
subjects affected / exposed	4 / 6359 (0.06%)	2 / 6280 (0.03%)	
occurrences (all)	4	2	
Metabolism and nutrition disorders			
Diabetic ketoacidosis			
subjects affected / exposed	1 / 6359 (0.02%)	0 / 6280 (0.00%)	
occurrences (all)	1	0	
Hypernatraemia			
subjects affected / exposed	1 / 6359 (0.02%)	0 / 6280 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 September 2016	ELIGIBILITY: Although there was no change to the original eligibility criteria, for the remainder of the trial we limited recruitment to patients who were within 3 hours of injury. PRIMARY OUTCOME: The primary outcome included only patients randomised within 3 hours of injury. The primary outcome is death in hospital within 28 days of injury among patients randomised within 3 hours of injury (cause-specific mortality was also recorded). SAMPLE SIZE A study with 10,000 traumatic brain injury (TBI) patients randomised within 3 hours of injury would have about 90% power (two sided alpha=1%) to detect a 15% relative reduction (from 20% to 17%) in allcause mortality. About three thousand patients had been recruited beyond three hours of injury already, therefore the total sample size was increased to approximately 13,000 patients. STATISTICAL ANALYSIS: We expected tranexamic acid (TXA) to be most effective when given soon after injury, when tissue plasminogen activator (TPA) levels are highest, and less effective when given several hours after injury when the risk of thrombotic DIC may be increased. We planned to examine this hypothesis by conducting a subgroup analysis of the effect of TXA according to the time interval between injury and TXA treatment (≤1, > 1 to ≤ 3, > 3 h). The outcome measure for this subgroup analysis was death due to head injury. RATIONALE: After the CRASH3 trial had started, new research suggested that TXA was likely to be most effective in the first few hours after injury and less effective when given later. To ensure that the CRASH3 trial was large enough to reliably confirm or refute an early (<3 hours) treatment benefit, the sample size was increased from 10,000 to 13,000 patients with the aim to enrol 10,000 patients within 3 hours of injury. In addition, the primary outcome was been amended to deaths among patients treated within 3 hours of injury.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported