Clinical trial results:
Tranexamic acid for the treatment of postpartum haemorrhage: An international randomised, double blind, placebo controlled trial

Summary

EudraCT number	2008-008441-38
Trial protocol	GB
Global end of trial date	16 April 2016

Results information

Result version number	v1 (current)
This version publication date	03 November 2018
First version publication date	03 November 2018
Summary attachment (see zip file)	Final Results publication (PIIS0140673617306384.pdf)

Trial information

Trial identification

Sponsor protocol code	ISRCTN76912190

Additional study identifiers

ISRCTN number	ISRCTN76912190
ClinicalTrials.gov id (NCT number)	NCT00872469
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	London School of Hygiene & Tropical Medicine
Sponsor organisation address	Keppel Street, London, United Kingdom, WC1E 7HT
Public contact	Haleema Shakur, Clinical Trials Unit, London School of Hygiene & Tropical Medicine, London, UK, 0207 9588113, thewomantrial@LSHTM.AC.UK
Scientific contact	Haleema Shakur, Clinical Trials Unit, London School of Hygiene & Tropical Medicine, London, UK, 0207 9588113, thewomantrial@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	16 April 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	16 April 2016
Global end of trial reached?	Yes
Global end of trial date	16 April 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The WOMAN Trial aims to determine the effect of the early administration of tranexamic acid (TXA) on death and hysterectomy in women with a clinical diagnosis of postpartum haemorrhage.

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 women if their physical and mental capacity allowed (as judged by the treating clinician). If a woman 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 deferred or waived. When consent was deferred or given by a proxy, the woman 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	22 March 2010
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	United Kingdom: 569
Country: Number of subjects enrolled	Albania: 485
Country: Number of subjects enrolled	Bangladesh: 325
Country: Number of subjects enrolled	Burkina Faso: 142
Country: Number of subjects enrolled	Cameroon: 893
Country: Number of subjects enrolled	Colombia: 8
Country: Number of subjects enrolled	Côte d'Ivoire: 8
Country: Number of subjects enrolled	Congo, The Democratic Republic of the: 457
Country: Number of subjects enrolled	Egypt: 33
Country: Number of subjects enrolled	Ethiopia: 302
Country: Number of subjects enrolled	Ghana: 41
Country: Number of subjects enrolled	Jamaica: 73
Country: Number of subjects enrolled	Kenya: 1031
Country: Number of subjects enrolled	Nepal: 533
Country: Number of subjects enrolled	Nigeria: 5711
Country: Number of subjects enrolled	Pakistan: 5282
Country: Number of subjects enrolled	Papua New Guinea: 38

Country: Number of subjects enrolled	Sudan: 860
Country: Number of subjects enrolled	Tanzania, United Republic of: 538
Country: Number of subjects enrolled	Uganda: 2235
Country: Number of subjects enrolled	Zambia: 496
Worldwide total number of subjects	20060
EEA total number of subjects	569

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)	0
Adolescents (12-17 years)	54
Adults (18-64 years)	20006
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The WOMAN trial randomisedwomen aged 16 years and older with a clinical diagnosis of post-partum haemorrhage after a vaginal birth or caesarean section done in 193 hospitals in 21 countries. The first patient was randomised on 22/03/2010 and the final patient on 16/04/2016.

Pre-assignment

Screening details:

All legally adult women with clinically diagnosed of postpartum haemorrhage (PPH) following vaginal delivery or caesarean section are considered eligible for the trial. The fundamental eligibility criterion is the responsible clinician's 'uncertainty' as to whether or not to use an antifibrinolytic agent in a particular woman with PPH.

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	BO2AA02
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Patients were randomly allocated to receive 1 g tranexamic acid or placebo by slow intravenous injection. Investigators were advised to give 1 g (10 mg/mL) of tranexamic acid intravenously at an approximate rate of 1 mL per min. If bleeding continued after 30 min or stopped and restarted within 24 h of the first dose, a second dose of 1 g of tranexamic acid or placebo could be given.

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 1 g tranexamic acid or placebo by slow intravenous injection. Investigators were advised to give 1 g (10 mg/mL) of tranexamic acid intravenously at an approximate rate of 1 mL per min. If bleeding continued after 30 min or stopped and restarted within 24 h of the first dose, a second dose of 1 g of tranexamic acid or placebo could be given.

Number of subjects in period 1	Tranexamic Acid	Placebo
Started	10051	10009
Completed	10036	9985
Not completed	15	24
Consent withdrawn by subject	4	3
Lost to follow-up	11	21

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	10051	10009	20060
Age categorical Units: Subjects			
<16	1	3	4
16-25	3445	3407	6852
26-33	4580	4608	9188
>=34	2022	1987	4009
Unknown	3	4	7
Gender categorical			
All participants in this study were women			
Units: Subjects			
Female	10051	10009	20060
Baby delivered in the randomising hospital Units: Subjects			
Yes	8869	8756	17625
No	1181	1251	2432
Unknown	1	2	3
Type of delivery Units: Subjects			
Vaginal	7093	7126	14219
Caesarean section	2957	2879	5836
Unknown	1	4	5
Time between delivery and randomisation (h) Units: Subjects			
≤1	4852	4733	9585
>1 to ≤3	2678	2691	5369
>3	2517	2574	5091
Unknown	4	11	15
Primary cause of haemorrhage Units: Subjects			
Uterine atony	6437	6347	12784
Placenta praevia or accreta	943	935	1878
Surgical trauma or tears	1834	1857	3691
Other	720	737	1457
Unknown	117	133	250
Systolic blood pressure (mm Hg) Units: Subjects			
≥90	8138	8065	16203

<90	1908	1929	3837
Unknown	5	15	20
Estimated volume of blood lost (mL) Units: Subjects			
≤500	295	313	608
>500 to ≤1000	4949	4861	9810
>1000 to ≤1500	2832	2882	5714
>1500	1973	1953	3926
Unknown	2	0	2
Uterotonic prophylaxis given Units: Subjects			
Yes	9687	9618	19305
No	131	139	270
Unknown	233	252	485

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 maternal death	
End point title	Effect of tranexamic acid on maternal death
End point description:	
End point type	Primary
End point timeframe:	
x	

End point values	Tranexamic Acid	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10036	9985		
Units: Dead or alive				
Bleeding	155	191		
Pulmonary embolism	10	11		
Organ failure	25	18		
Sepsis	15	8		
Eclampsia	2	8		
Other	20	20		
Any cause of death	227	256		

Attachments (see zip file)	Effect of tranexmaic acid on maternal death/Effect of Death from bleeding by subgroup/Death from bleeding by

Statistical analyses

Statistical analysis title	WOMAN Trial
Comparison groups	Tranexamic Acid v Placebo
Number of subjects included in analysis	20021
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.05
Method	Chi-squared
Parameter estimate	Risk ratio (RR)

Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Any suspected unexpected serious adverse reaction that occurs during hospitalisation or any untoward medical occurrence after discharge and up to 42 days after the trial treatment has been given must be logged with the Coordinating Centre 24 hours.

Adverse event reporting additional description:

Prior to discharge, all randomised women will be given a (supplied) alert card, so either a woman or her family can present the card to any healthcare provider she sees after she is discharged. Also, a post discharge form which gives details of the woman and the contact details of the WOMAN trial PI were kept in the women's records.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	27

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	15 / 10029 (0.15%)	11 / 9979 (0.11%)	
number of deaths (all causes)	227	256	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Transfusion reaction			
subjects affected / exposed	3 / 10029 (0.03%)	0 / 9979 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Bleeding from caesarian section site			
subjects affected / exposed	0 / 10029 (0.00%)	1 / 9979 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac arrest			

subjects affected / exposed	1 / 10029 (0.01%)	0 / 9979 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
Eclampsia			
subjects affected / exposed	0 / 10029 (0.00%)	1 / 9979 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	0 / 10029 (0.00%)	1 / 9979 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incontinence			
subjects affected / exposed	1 / 10029 (0.01%)	0 / 9979 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Papilloedema	Additional description: Secondary to pre-eclampsia		
subjects affected / exposed	0 / 10029 (0.00%)	1 / 9979 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retained products of conception			
subjects affected / exposed	0 / 10029 (0.00%)	1 / 9979 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Secondary postpartum haemorrhage			
subjects affected / exposed	3 / 10029 (0.03%)	2 / 9979 (0.02%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vaginal bleeding			
subjects affected / exposed	1 / 10029 (0.01%)	1 / 9979 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			

Headache			
subjects affected / exposed	1 / 10029 (0.01%)	0 / 9979 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia	Additional description: Postpartum		
subjects affected / exposed	1 / 10029 (0.01%)	0 / 9979 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombotic thrombocytopenic purpura			
subjects affected / exposed	1 / 10029 (0.01%)	0 / 9979 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Jaundice			
subjects affected / exposed	0 / 10029 (0.00%)	1 / 9979 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain	Additional description: due to psammocarcinoma		
subjects affected / exposed	1 / 10029 (0.01%)	0 / 9979 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Vesicovaginal fistula			
subjects affected / exposed	1 / 10029 (0.01%)	0 / 9979 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pulmonary thrombosis			
subjects affected / exposed	1 / 10029 (0.01%)	1 / 9979 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			

Anxiety	Additional description: Palpatations and fainting		
subjects affected / exposed	0 / 10029 (0.00%)	1 / 9979 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Urinary retention	Additional description: Due to psammocarcinoma		
subjects affected / exposed	1 / 10029 (0.01%)	0 / 9979 (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			
Endometritis			
subjects affected / exposed	1 / 10029 (0.01%)	1 / 9979 (0.01%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	0 / 10029 (0.00%)	1 / 9979 (0.01%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound sepsis			
subjects affected / exposed	1 / 10029 (0.01%)	0 / 9979 (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	12 / 10029 (0.12%)	14 / 9979 (0.14%)	
Vascular disorders			
Bleeding			
subjects affected / exposed	1 / 10029 (0.01%)	1 / 9979 (0.01%)	
occurrences (all)	1	1	
Haematoma			
subjects affected / exposed	1 / 10029 (0.01%)	0 / 9979 (0.00%)	
occurrences (all)	1	0	

Blood and lymphatic system disorders			
Anaemia, postpartum			
subjects affected / exposed	1 / 10029 (0.01%)	2 / 9979 (0.02%)	
occurrences (all)	1	2	
Transfusion reaction			
subjects affected / exposed	0 / 10029 (0.00%)	1 / 9979 (0.01%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Swelling			
subjects affected / exposed	0 / 10029 (0.00%)	1 / 9979 (0.01%)	
occurrences (all)	0	1	
Immune system disorders			
Allergic reaction			
subjects affected / exposed	0 / 10029 (0.00%)	1 / 9979 (0.01%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	1 / 10029 (0.01%)	0 / 9979 (0.00%)	
occurrences (all)	1	0	
Reproductive system and breast disorders			
Dysfunctional uterine bleeding			
subjects affected / exposed	0 / 10029 (0.00%)	1 / 9979 (0.01%)	
occurrences (all)	0	1	
Vaginal Bleeding			
subjects affected / exposed	0 / 10029 (0.00%)	1 / 9979 (0.01%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Allergy rash			
subjects affected / exposed	1 / 10029 (0.01%)	0 / 9979 (0.00%)	
occurrences (all)	1	0	
Urticaria rash			
subjects affected / exposed	0 / 10029 (0.00%)	1 / 9979 (0.01%)	
occurrences (all)	0	1	
Renal and urinary disorders			
Urinary Retention			
subjects affected / exposed	1 / 10029 (0.01%)	1 / 9979 (0.01%)	
occurrences (all)	1	1	

Musculoskeletal and connective tissue disorders			
Muscular-skeletal pain			
subjects affected / exposed	1 / 10029 (0.01%)	0 / 9979 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Malaria			
subjects affected / exposed	0 / 10029 (0.00%)	1 / 9979 (0.01%)	
occurrences (all)	0	1	
Perineal infection			
subjects affected / exposed	0 / 10029 (0.00%)	1 / 9979 (0.01%)	
occurrences (all)	0	1	
Urinary Tract Infection			
subjects affected / exposed	2 / 10029 (0.02%)	2 / 9979 (0.02%)	
occurrences (all)	2	2	
Vaginal infection			
subjects affected / exposed	1 / 10029 (0.01%)	0 / 9979 (0.00%)	
occurrences (all)	1	0	
Wound infection			
subjects affected / exposed	1 / 10029 (0.01%)	1 / 9979 (0.01%)	
occurrences (all)	1	1	
Metabolism and nutrition disorders			
Hypoglycaemic event			
subjects affected / exposed	1 / 10029 (0.01%)	0 / 9979 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
31 January 2014	As of December 2013, the trial had recruited 10,014 women, 261 of whom died. Because the effect of tranexamic acid on maternal mortality is of considerable public health importance, the sample size was increased from 15,000 to 20,000 so that the trial has enough power to detect an effect on this important secondary outcome. This involved an additional 15 months of recruitment. On this basis, the Trial Protocol Version 1.0, dated 11 May 2009, was modified as follows: • Increase the sample size from 15,000 to 20,000 • Date of last patient recruitment: changes from 31 December 2014 to 31 March 2016 • Date of last patient follow up: changes from 11 February 2015 to 12 May 2016

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/28456509