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World maternal antifibrinolytic trial-2

Submission date
23/11/2017

Recruitment status
No longer recruiting

Registration date
07/12/2017

Overall study status
Completed

Last Edited
28/10/2024

Condition category
Pregnancy and Childbirth

[X] Prospectively registered
[X] Protocol
[X] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims:
Postpartum haemorrhage (PPH) is characterised as a large amount of blood loss after giving birth. PPH is responsible for about 100,000 maternal deaths every year, almost all of which occur in low and middle income countries. When given within three hours of birth, tranexamic acid (a drug which helps in keeping blood clots firm) reduces deaths due to bleeding in women with PPH by almost one third. However, for many women, the use of tranexamic acid to treat PPH is too late to prevent death and severe health problems. Over one-third of pregnant women in the world are anaemic. The aim of this study is to progress the WOMAN-2 trial to see if giving tranexamic acid can prevent PPH and other severe outcomes in women with moderate and severe anaemia.

Who can participate?
Women with moderate or severe anaemia who are in the active stage of labour and plan to give birth vaginally are eligible (if their doctor believes there is no reason why the woman cannot receive the trial drug). Where a woman is less than 18 years old, unless she has an appropriate guardian available to witness the consent process, she cannot take part.

What does the study involve?
Women do not need to change their birth plans and they continue to receive all care and treatments which their doctor/midwife/nurse believe is required. Additionally, they are given a single injection of either tranexamic acid or a dummy drug (salty water) immediately the umbilical cord is cut or clamped and no later than 15 minutes after. Women are then be followed-up for a maximum 42 days. There is no special hospital visits required unless an adverse event occurs.

What are the possible benefits and risks of participating?
Women with anaemia have a higher risk of severe bleeding after childbirth and cannot afford to lose any blood. Tranexamic acid has been shown to reduce blood loss in surgery and can stop women dying from bleeding if they are treated as soon as possible. We do not know if giving tranexamic acid before bleeding develops will help reduce the risk of severe bleeding after childbirth and this trial will help us answer that question. Although there is a theoretical risk of forming clots where they are not wanted (e.g. deep vein thrombosis) with tranexamic acid, there is no evidence of this when available data is reviewed. Tranexamic acid can sometimes cause nausea, dizziness and diarrhoea.

Where is the study run from?
The trial will be coordinated by the Clinical Trials Unit at the London School of Hygiene and Tropical Medicine (UK) and supported by Regional Coordinating Centres in Pakistan (Rawalpindi Medical University), Nigeria (University College Hospital, Ibadan) and Tanzania (Muhimbili University of Health and Allied Sciences).

When is the study starting and how long is it expected to run for?
January 2018 to September 2023

Who is the main contact?
Ian Roberts, woman2@lshtm.ac.uk

Study website
woman2.lshtm.ac.uk

Contact information

Type(s)
Scientific

Contact name
Prof Haleema Shakur-Still

ORCID ID
http://orcid.org/0000-0002-6511-109X

Contact details
Clinical Trials Unit - Global Health Trials Group
London School of Hygiene & Tropical Medicine
Keppel Street
London
United Kingdom
WC1E 7HT
+44(0)20 7299 4684
woman2@lshtm.ac.uk

Type(s)
Public

Contact name
Ms Eni Balogun

ORCID ID
http://orcid.org/0009-0001-6066-3688

Contact details
Clinical Trials Unit - Global Health Trials Group
London School of Hygiene & Tropical Medicine
Keppel Street
London

United Kingdom
WC1E 7HT
-
woman2@lshtm.ac.uk

Additional identifiers

EudraCT/CTIS number

IRAS number

ClinicalTrials.gov number
NCT03475342

Secondary identifying numbers
WOMAN-2

Study information

Scientific Title
Tranexamic acid for the prevention of postpartum bleeding in Women with anaemia: an international, randomised, double-blind, placebo controlled trial

Acronym
WOMAN-2

Study objectives
Can tranexamic acid by intravenous injection prevent PPH and other severe outcomes in women with moderate and severe anaemia?

Ethics approval required
Old ethics approval format

Ethics approval(s)
1. Approved 10/05/2018, London School of Hygiene and Tropical Medicine Research Ethics Committee (Keppel Street, London, WC1E 7HT, United Kingdom; no phone number provided; ethics@lshtm.ac.uk), ref: 15194
2. Approved 29/09/2019, National Health Research Ethics Committee (Federal Ministry of Health, Federal Secretariat Complex Shehu Shagari Way, Garki, Abuja, Abuja, P.M.B. 083, Nigeria; no phone number provided; info@nhrec.net), ref: NHREC/01/01/2007-29/09/2019
3. Approved 27/11/2018, National Bioethics Committee (NIH (HRI), Shahrah-e-Jamhuriat, G-5/2 Islamabad, Pakistan, Islamabad, N/A, Pakistan; no phone number provided; nbcpakistan@nih.org.pk), ref: NBC-340
4. Approved 19/08/2021, National Institute of Medical Research (3 Barack Obama Drive, P.O. Box 9653, Dar-es-Salaam, 11101, Tanzania; no phone number provided; info@nimr.or.tz), ref: NIMR/HQ/R.8a/Vol.IX/3767
5. Approved 02/02/2019, University of Zambia Biomedical Research Ethics Committee (Ridgeway Campus, Lusaka, P.O. Box 50110, Zambia; no phone number provided; unzarec@unza.zm), ref: REF. 001-04-19

Study design
A multi centre randomised double blind placebo controlled trial

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Prevention

Participant information sheet
Not available in web format, please use the contact details below to request a patient information sheet

Health condition(s) or problem(s) studied
Prevention of postpartum haemorrhage in women with moderate or severe anaemia having given birth vaginally

Interventions
Current intervention as of 21/12/2023
Participants are randomly allocated to one of two groups. The randomisation list is generated by computer.

Active Comparator: Tranexamic acid, one intravenous injection of tranexamic acid. Total dose 1 g (10 mL).

Placebo Comparator: One Injection of 10 mL Sodium Chloride (0.9%).

Women receive clinically indicated care for the prevention and treatment of postpartum haemorrhage.

We will also conduct a pre-planned cohort analysis of data from the WOMAN-2 trial to assess the effect of pain control and episiotomy on the risk of post-partum haemorrhage. Adrenaline is a potent stimulus for fibrinolysis. Adrenaline causes the release of tissue plasminogen activator (TPA) from the endothelium. In trauma victims, high adrenaline levels are associated with increased fibrinolysis, decreased clot strength and increased deaths due to bleeding. Childbirth is intensely painful and maternal adrenaline levels are two to six times higher during labour. Maternal adrenaline concentrations peak in the second and third stages of labour but then rapidly return to normal after birth. Pain control can reduce the maternal catecholamine response. We hypothesize that painful procedures such as episiotomy will significantly increase the risk of postpartum haemorrhage and that pain control will reduce the risk of PPH.

The exposures of interest are the presence or absence of pain control during labour and delivery and whether episiotomy was conducted prior to birth. Pain control will be categorised as present or absent but the type of pain control administered during labour will also be described and examined. The types of pain control recorded in the study are epidural, opioids, ‘other’, or a

combination of opioids and other pain control. For the multivariable regression analysis, the pain control variable was converted into a binary variable indicating whether a participant received any pain control or not. Episiotomy will be categorised as present or absent according to the CRF. The main outcome variable will be a clinical diagnosis of PPH (binary: yes/no), defined as an estimated blood loss of more than 500 mL or any blood loss sufficient to compromise haemodynamic stability within 24 hours. Potential confounding factors will include maternal age, BMI, anaemia, history of PPH, antepartum hemorrhage, hypertensive disease, multiple gestation, parity, prophylactic uterotonics, duration of labor, induction and augmentation of labor, assisted delivery, gestational age, birth canal trauma, placental abruption, and macrosomia.

We will use multivariable logistic regression to examine the association between pain control and episiotomy and the risk of PPH after adjusting for confounding factors. We will describe our causal assumptions using a directed acyclic graph. We will examine the association between the exposures of interest and PPH with odds ratios and 95% confidence intervals. We will estimate odds ratios and 95% CI for the crude association between the exposures of interest and PPH and after controlling for confounding factors. We will check for collinearity using variance inflation factors. Finally, we will examine whether the effect of pain control and episiotomy on the risk of PPH is modified by tranexamic acid treatment. To do this we will conduct stratified analysis and calculate a p-value for heterogeneity using a likelihood ratio test.

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Previous intervention as of 08/08/2018:
Participants are randomly allocated to one of two groups. The randomisation list is generated by computer.

Active Comparator: Tranexamic acid, one intravenous injection of tranexamic acid. Total dose 1 gram (10mL).

Placebo Comparator: One Injection of 10 mL Sodium Chloride (0.9%).

Women receive clinically indicated care for the prevention and treatment of postpartum haemorrhage.

_____

Previous intervention:
Participants are randomly allocated to one of two groups. The randomisation list is generated by computer.

Active Comparator: Tranexamic acid, one intravenous injection of tranexamic acid. Total dose 1 gram (10mL).

Placebo Comparator: One Injection of 10 mL Sodium Chloride (0.9%).

Women receive clinically indicated care for the prevention of postpartum haemorrhage.

Intervention Type
Drug

Phase

Phase III

Drug/device/biological/vaccine name(s)
Tranexamic Acid

Primary outcome measure
Current primary outcome measure as of 08/08/2018:
Postpartum haemorrhage is measured using a clinical assessment (estimated blood loss of more than 500 mL or any blood loss sufficient to compromise haemodynamic stability) within 24 hours after administration of trial medication or discharge from hospital (whichever is earlier). The cause of postpartum haemorrhage will be described.

Previous primary outcome measure:
Postpartum haemorrhage is measured using a clinical assessment (estimated blood loss of more than 500 mL or any blood loss sufficient to compromise haemodynamic stability) within 24 hours after administration of trial medication or discharge from discharge hospital whichever is earlier.

Secondary outcome measures
Current secondary outcome measures as of 08/08/2018:
1. Postpartum blood loss is measured using a clinical assessment at 24 hours after administration of the trial medication or at discharge from hospital whichever is earlier
2. Haemoglobin is measured using Haemacue (Point of care test) at 24 hours after administration of the trial medication or at discharge from hospital whichever is earlier
3. Haemodynamic instability is measured based on clinical signs e.g. low blood pressure, tachycardia, reduced urine output requiring intervention e.g. intravenous fluid at 24 hours after administration of the trial medication or at discharge from hospital whichever is earlier
4. Shock index is measured using lowest recorded heart rate/systolic blood pressure at 24 hours after administration of the trial medication or at discharge from hospital whichever is earlier
5. Symptoms of anaemia is measured using a questionnaire developed specifically for this trial at 42 days or discharge from hospital whichever is earlier (please move this to number 5 if possible)
6. Quality of life, including overall wellbeing, ability to care for herself and her baby, breastfeeding (time to first feed, ability to sustain breastfeeding at discharge is measured using questionnaire at day 42 or discharge from hospital whichever is earlier (questionnaire specifically developed for this trial)
7. Expected side effects of trial medication is measured using patient self reports and medical records of nausea, vomiting, and diarrhoea at day 42 or discharge from hospital whichever is earlier
8. Exercise tolerance is measured using the 6 minute walk test at day 42 or discharge from hospital whichever is earlier (standardised test)
9. Interventions to control primary postpartum haemorrhage (including uterotonics, removal of placenta/placenta fragments, intrauterine balloon tamponade, bimanual uterine compression, external aortic compression, non-pneumatic anti-shock garments, uterine artery embolisation, uterine compression suture, hysterectomy and laparotomy to control bleeding) is measured using medical records at day 42 or discharge from hospital whichever is earlier
10. Vascular occlusive events including pulmonary embolism (PE), deep vein thrombosis (DVT), stroke and myocardial infarction (MI) are measured using from medical records at day 42 or discharge from hospital whichever is earlier
11. Organ dysfunction (cardiovascular, respiratory, renal, coagulation / haemotological, hepatic, neurological) is measured using medical records at day 42 or discharge from hospital whichever is earlier
12. Sepsis is measured using medical records at day 42 or discharge from hospital whichever is

earlier
13. In hospital death (with cause described) is measured using medical records at day 42 or discharge from hospital whichever is earlier
14. Length of hospital stay is measured using medical records at day 42 or discharge from hospital whichever is earlier
15. Admission to and time spent in higher level facility is measured using medical records at day 42 or discharge from hospital whichever is earlier
16. Status of baby/babies (alive/dead) is measured using medical records at day 42 or discharge from hospital whichever is earlier
17. Thromboembolic events in breastfed babies are measured using medical records at 42 days or discharge from hospital whichever is earlier
18. Adverse events are measured as any untoward medical occurrences from medical records, patient self-report or report by any treating clinician up to day 42
19. Receipt of blood transfusion

Previous secondary outcome measure:
1. Postpartum blood loss is measured using a clinical assessment at 24 hours after administration of the trial medication or at discharge from hospital whichever is earlier
2. Haemoglobin is measured using Haemacue (Point of care test) at 24 hours after administration of the trial medication or at discharge from hospital whichever is earlier
3. Haemodynamic instability is measured based on clinical signs e.g. low blood pressure, tachycardia, reduced urine output requiring intervention e.g. intravenous fluid at 24 hours after administration of the trial medication or at discharge from hospital whichever is earlier
4. Shock index is measured using lowest recorded heart rate/systolic blood pressure at 24 hours after administration of the trial medication or at discharge from hospital whichever is earlier
5. Symptoms of anaemia is measured using a questionnaire developed specifically for this trial at 42 days or discharge from hospital whichever is earlier (please move this to number 5 if possible)
6. Quality of life, including overall wellbeing, ability to care for herself and her baby, breastfeeding (time to first feed, ability to sustain breastfeeding at discharge is measured using questionnaire at day 42 or discharge from hospital whichever is earlier (questionnaire specifically developed for this trial)
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11. Organ dysfunction (cardiovascular, respiratory, renal, coagulation / haemotological, hepatic, neurological) is measured using medical records at day 42 or discharge from hospital whichever is earlier
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14. Length of hospital stay is measured using medical records at day 42 or discharge from

hospital whichever is earlier
15. Admission to and time spent in higher level facility is measured using medical records at day 42 or discharge from hospital whichever is earlier
16. Status of baby/babies is measured using medical records definition at day 42 or discharge from hospital whichever is earlier
17. Thromboembolic events in breastfed babies are measured using medical records at 42 days or discharge from hospital whichever is earlier
18. Adverse events are measured as any untoward medical occurrences from medical records, patient self-report or report by any treating clinician up to day 42

Overall study start date
01/11/2017

Completion date
20/09/2023

Eligibility

Key inclusion criteria
Women with moderate or severe anaemia (haemoglobin level <100 g/ L or packed cell volume <30%) after giving birth vaginally where the responsible clinician is substantially uncertain whether to use tranexamic acid.

Participant type(s)
Patient

Age group
Adult

Sex
Female

Target number of participants
15,000

Total final enrolment
15068

Key exclusion criteria
1. Women who are not legally adult (<18 years) and not accompanied by a guardian
2. Women with a known allergy to tranexamic acid or its excipients
3. Women who develop postpartum haemorrhage before randomisation

Date of first enrolment
01/10/2018

Date of final enrolment
19/09/2023

Locations

Countries of recruitment
Nigeria

Pakistan

Tanzania

Zambia

Study participating centre
Mother & Child Hospital
-
Akure
Nigeria
-

Study participating centre
University of Medical Sciences Teaching Hospital
-
Akure
Nigeria
-

Study participating centre
Adeoyo Maternity Hospital
-
Ibadan
Nigeria
-

Study participating centre
Ilorin General Hospital
-
Ilorin
Nigeria
-

Study participating centre
Muhammad Abdullahi Wase Specialist Hospital
-
Kano

Nigeria
-

Study participating centre
Ladoke Akintola University of Technology Teaching Hospital
-
Ogbomoso
Nigeria
-

Study participating centre
Oyo State Hospital
-
Oyo
Nigeria
-

Study participating centre
Ayub Teaching Hospital
-
Abbottabad
Pakistan
-

Study participating centre
Bahawalpur Victoria Hospital
-
Bahawalpur
Pakistan
-

Study participating centre
MCH PIMS
-
Islamabad
Pakistan
-

Study participating centre

Islamabad Military Hospital
-
Islamabad
Pakistan
-

Study participating centre
Karachi Civil Hospital
-
Karachi
Pakistan
-

Study participating centre
Jinnah Postgraduate Medical Centre
-
Karachi
Pakistan
-

Study participating centre
Koohi Goth Hospital
-
Karachi
Pakistan
-

Study participating centre
Jinnah Hospital
-
Lahore
Pakistan
-

Study participating centre
Lahore Services Hospital
-
Lahore
Pakistan
-

Study participating centre
Sir Ganga Ram Hospital
-
Lahore
Pakistan
-

Study participating centre
Chandka SMBBMU Sheikh Zaid Woman Hospital
-
Larkana
Pakistan
-

Study participating centre
Nishtar Hospital
-
Multan
Pakistan
-

Study participating centre
Bolan Medical Centre
-
Quetta
Pakistan
-

Study participating centre
Benazir Bhutto Shaheed Hospital
-
Rawalpindi
Pakistan
-

Study participating centre
Federal Government Polyclinic
-
Rawalpindi

Pakistan
-

Study participating centre
Holy Family Hospital
-
Rawalpindi
Pakistan
-

Study participating centre
Mount Meru Regional Referral Hospital
-
Arusha
Tanzania
-

Study participating centre
Muhimbili National Hospital
-
Dar Es Salaam
Tanzania
-

Study participating centre
Amana Regional Referral Hospital
-
Dar Es Salaam
Tanzania
-

Study participating centre
Temeke Regional Referral Hospital
-
Dar Es Salaam
Tanzania
-

Study participating centre

Dodoma Regional Referral Hospital
-
Dodoma
Tanzania
-

Study participating centre
Tumbi Regional Referral Hospital
-
Kibaha
Tanzania
-

Study participating centre
Mwananyamala Regional Referral Hospital
-
Kinondoni
Tanzania
-

Study participating centre
Mbeya Zonal Referral Hospital
-
Mbeya
Tanzania
-

Study participating centre
Women and Newborn Hospital
-
Lusaka
Zambia
-

Sponsor information

Organisation
London School of Hygiene and Tropical Medicine

Sponsor details
Keppel Street
London
England
United Kingdom
WC1E 7HT

Sponsor type
University/education

ROR
https://ror.org/00a0jsq62

Funder(s)

Funder type
Charity

Funder Name
Wellcome

Alternative Name(s)
Wellcome, WT

Funding Body Type
Private sector organisation

Funding Body Subtype
Trusts, charities, foundations (both public and private)

Location
United Kingdom

Funder Name
Bill & Melinda Gates Foundation

Results and Publications

Publication and dissemination plan
Planned publication in a high-impact peer reviewed journal.

Intention to publish date
31/10/2024

Individual participant data (IPD) sharing plan

The data sharing plans for the current study are unknown and will be made available at a later date.

IPD sharing plan summary

Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article	protocol	29/12/2018		Yes	No
Statistical Analysis Plan		03/08/2023	04/09/2023	No	No
Other publications	Cohort analysis of association between pre-birth anaemia and postpartum haemorrhage	01/08/2023	21/12/2023	Yes	No
Results article		26/10/2024	28/10/2024	Yes	No