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RANDOMISED CONTROLLED TRIAL

Alternative routes for tranexamic acid treatment in obstetric bleeding (WOMAN-PharmacoTXA trial): a randomised trial and pharmacological study in caesarean section births

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Abstract

Objective: To examine the safety, efficacy and pharmacology of intravenous (IV), intramuscular (IM) and oral tranexamic acid (TXA) use in pregnant women.

Design: Randomised, open-label trial.

Setting: Hospitals in Pakistan and Zambia.

Population: Women giving birth by caesarean section.

Methods: Women were randomised to receive 1 g IV, 1 g IM, 4 g oral TXA or no TXA. Adverse events in women and neonates were recorded. TXA concentration in whole blood was measured and the concentrations over time were examined with population pharmacokinetics. The relationship between drug exposure and D-dimer was explored. The trial registration is NCT04274335.

Main outcome measures: Concentration of TXA in maternal blood.

Results: Of the 120 women included in the randomised safety study, there were no serious maternal or neonatal adverse events. TXA concentrations in 755 maternal blood and 87 cord blood samples were described by a two-compartment model with one effect compartment linked by rate transfer constants. Maximum maternal concentrations were 46.9, 21.6 and 18.1 mg/L for IV, IM and oral administration, respectively, and 9.5, 7.9 and 9.1 mg/L in the neonates. The TXA response was modelled as an inhibitory effect on the D-dimer production rate. The half-maximal inhibitory concentration (IC_{50}) was 7.5 mg/L and was achieved after 2.6, 6.4 and 47 minutes with IV, IM and oral administration of TXA, respectively.

Conclusions: Both IM and oral TXA are well tolerated. Oral TXA took about 1 hour to reach minimum therapeutic concentrations and would not be suitable for emergency treatment. Intramuscular TXA inhibits fibrinolysis within 10 minutes and may be a suitable alternative to IV.

KEYWORDS
caesarean section, clinical trial, intramuscular, oral, pharmacodynamics, pharmacokinetics, postpartum haemorrhage, tranexamic acid

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1 | INTRODUCTION

Severe bleeding after childbirth is a leading cause of maternal death.[1] Most of these deaths are in low- and middle-income countries.[1] Tranexamic acid (TXA) reduces bleeding by inhibiting blood clot breakdown. The WOMAN-PharmacoTXA trial found that intravenous TXA given within 3 hours of birth reduced postpartum haemorrhage (PPH) deaths by about one-third with no adverse effects.[2] In 2017, the World Health Organization (WHO) strongly recommended early treatment with intravenous (IV) TXA (within 3 hours of birth) in addition to standard care for women with PPH after vaginal birth or caesarean section, regardless of the cause of bleeding.[3] The WHO advised that TXA must be available wherever emergency obstetric care is provided.

The need for an IV injection is an important barrier to timely TXA treatment. Health workers able to give IV drugs are unavailable in some rural health centres for many home births. Even when available, IV cannulation can be difficult in shocked patients with collapsed veins. TXA tablets are available, but dissolution and absorption take time and are incomplete, limiting oral bioavailability. Intramuscular (IM) injection or oral administration of the intravenous solution might achieve therapeutic TXA blood concentrations more rapidly.[4]

Although there have been studies of different routes of TXA administration in healthy volunteers and trauma patients, pregnancy can have important effects on the pharmacokinetics (PK) and pharmacodynamics (PD) of drugs, including a larger volume of distribution and increased renal elimination.[5]

Our primary objective was to assess the population PK and PD of IV, IM and oral TXA solution in women at increased risk of PPH giving birth by caesarean section (CS). Our secondary objectives were to assess: (1) the safety of the three routes of TXA administration (adverse events and postpartum bleeding); (2) the concentration of TXA that crosses the placenta into the neonate and clearance of any TXA via the three routes of administration; and (3) the effect of the three routes of TXA administration on D-dimer concentration in blood samples.

2 | METHODS

2.1 | Patients and public contribution to trial concept and design

Prior to protocol development, we carried out a focus group discussion at one hospital in Pakistan to collect views on the acceptability of administering TXA by intramuscular injection, the willingness of women to be randomised, and what information should be given about the trial and when. Information is provided in the GRIPP2-SF checklist (Data S1).

2.2 | Study design

We conducted a phase-2, randomised, open-label, parallel-group trial (Woman-PharmacoTXA) in two hospitals in Pakistan and one hospital in Zambia. The trial was approved by the following ethics committees and regulatory authorities: National Bioethics Committee Pakistan (ref. 4-87/NBC-532/20/409), Drug Regulatory Authority of Pakistan (ref. 16/2020 DD [PS]), Ethical Review Board of MCH Centre – Pakistan Institute of Medical Sciences Hospital (ref. F1-1/2015/ERB/SZABMU/583), Ethics Committee of the Federal Government Polyclinic Hospital (ref. FGPC.1/12/2020/Ethical Committee), University of Zambia Biomedical Research Ethics Committee (ref. 933–2020), Zambia Medicines Regulatory Authority (ref. DMS/7/9/22/CT/102), Zambia National Health Research Authority (NHREB) and the London School of Hygiene & Tropical Medicine's Ethics Committee (ref. 21255). We published the study protocol at https://wellcomeopenresearch.org/articles/6-157.

2.3 | Participants

We included women aged 18 years or older giving birth by CS who had one or more risk factors for PPH. We excluded women giving birth vaginally, women known to be allergic to TXA or its excipients, women with antepartum bleeding, women who had received TXA in the previous 48 hours and women with renal or clotting problems. We obtained written consent from all women. If a woman could not read, we read the information sheet to her and obtained verbal consent in the presence of a witness who confirmed this in writing.

2.4 | Randomisation and masking

To assess the safety outcomes, we randomly allocated women to receive one of the following about 1 hour (±30 minutes) before caesarean section: 1 g IV TXA; 1 g IM TXA; 4 g oral TXA solution; or no TXA. The allocation ratio was 1:1:1:1. An independent statistician and IT expert prepared the allocation sequence using computer-generated random numbers with blocking to ensure balance in the allocation of participants to the different arms. We used an online database for random allocation. Participants and study staff were blind to allocation until

after randomisation. The study procedures are described in full in the protocol.[6] Briefly, after obtaining consent, we collected baseline data on demographics, anthropometrics, medical and pregnancy history, bleeding risk factors, reason for caesarean, vital signs and fetal abnormalities or distress.

As participants from the safety study could refuse blood sampling or there were valid reasons why samples could not be taken in line with the protocol, such as the need for urgent clinical care, additional participants were included for the PK and D-dimer analysis to achieve a sample size of 120 participants. The protocol detailed the following circumstances in which participants could be replaced because they would adversely affect the PK analysis: (1) if consent procedures were completed but the TXA dose was not given in full; (2) when oral TXA was given and the participant vomited within the first hour of receiving the intervention; (3) where the CS was delayed and took place more than 2 hours after the administration of the intervention; and (4) when a participant received the TXA dose but there were fewer than six post-treatment evaluable PK samples obtained after TXA administration.

2.5 | Intervention

Intravenous TXA was given by slow IV injection over a period of 10 minutes. Intramuscular TXA was given as two 5-mL (0.5 g each) injections into the rectus femoris, vastus lateralis or gluteal muscles, depending on muscle mass, using the Z-track method. Oral TXA was given as 40 mL of TXA solution. Participants randomised to receiving no TXA were included to acts as the control group for D-dimer and safety parameters. TXA brands with local regulatory approval were used in Pakistan (Transamin; Hilton Pharma, Karachi City, Sindh, Pakistan) and in Zambia (Pause; Emcure Pharmaceuticals, Hinjewadi, Pune, India). We used the same IV TXA solution for IV, IM and oral administration.

2.6 | Safety outcomes

The following core outcomes for the prevention of PPH were included in this study: blood loss; maternal death; use of additional uterotonics; and adverse events.[7] Maternal blood was taken before and 24 hours after randomisation for a full blood count and renal function tests. Samples were analysed at a central laboratory in each country. Vital signs were recorded and IM injection sites were assessed for local reactions. Neonatal Apgar scores were recorded at 1 and 5 minutes after birth. Any nausea, vomiting, dizziness, seizures or vascular occlusive events were recorded. Adverse events were recorded up to 7 days. We measured maternal blood loss for 2 hours after incision. We estimated surgical blood loss by weighing the sponges and drapes used in the surgery and measuring blood loss from suctioning (excluding amniotic fluid). At the end of the surgery, a calibrated obstetric drape (Owens & Minor Halyard UK Limited, Manchester, UK) was used to measure blood loss for 2 hours. A diagnosis of PPH was recorded if the blood loss exceeded 1 L, caused haemodynamic instability or needed further treatment.[8] While the trial was continuing, an independent Data Monitoring Committee reviewed the data on adverse events in mothers or neonates and any injection site reactions. The trial is registered at https://clinicaltrials.gov/ct2/show/NCT04274335.

2.7 | Pharmacokinetics and pharmacodynamics

We recruited additional women for our PK and PD studies to ensure that there were sufficient women with usable blood samples for the analyses. The main outcome was TXA concentration over time after IV, IM and oral solution administration. Secondary outcomes were maternal D-dimer concentrations and TXA concentrations in umbilical cord blood and neonate blood. Maternal blood for PK analysis was obtained using a Mitra® cartridge (Neoteryx LLC, Torrance, CA, USA) from a finger prick (2 × 10 µl) blood sample and using both sampling tips. Samples were taken at baseline and at the following time points after TXA administration: 15 ± 5 minutes; 30 ± 15 minutes; 1 hour ± 30 minutes; 2 ± 1 hour; 4 ± 1 hour; 8 ± 1 hour; 12 ± 2 hours; 24 ± 2 hours. We did not take post-randomisation PK blood samples from women in the no-TXA group. As clinical care took priority, we did not always sample blood at the scheduled times but the samples were collected as soon as possible and the time was recorded.

Cord blood was collected from the umbilical vein immediately after cord clamping using a syringe and needle. The blood was then transferred to the Mitra® cartridge. Neonatal blood (2 × 10 µl) was collected using the Mitra® cartridge during routine heel prick blood testing, but no later than 24 hours after maternal TXA administration. Treatments that might affect the TXA concentration (e.g. blood transfusion, IV fluids and TXA) were collected from the time of TXA administration until the last PK sample.

The PK samples were sent to a central laboratory at UFR Simone Veil – Santé, University Versailles Saint Quentin, France, for analysis. TXA concentrations in whole blood were measured using a validated liquid chromatography–mass spectrometry method.[9,10] The lower limit of quantification is 0.1 mg/L with a linearity range of 0.1–1000.0 mg/L, a precision of <12.6% and an accuracy of 85.2%–112.8%.

The PD blood samples (3 ml of venous blood in tubes with 3.2% sodium citrate) were taken for D-dimer measurement at baseline and at the following times after randomisation (4 ± 1, 8 ± 1, 12 ± 2 and 24 ± 2 hours). Blood samples for D-dimer analysis were taken for all patient groups. The D-dimer measurement was performed within 3 hours of sampling by immunoassay at a central laboratory in each country.

2.8 | Statistical analysis

A sample size of 120 participants for the PK study was determined using PFIM 3.2.1 (www.pfim.biostat.fr), based on the population PK parameters previously described and data for a trial of the IV route in trauma patients.[10,11] We anticipated that this will allow estimates (with relative standard errors of <30%) of the PK parameters of the IV, IM and oral administration of TXA. Evaluable participants must receive the full dose, not vomit the oral dose within 1 hour of administration and have at least six post-randomisation PK blood samples.

Statistical analyses were conducted using STATA 17.0 (StataCorp LLC, College Station, TX, USA). We show baseline characteristics by treatment group. For continuous variables, we present the mean, standard deviation, interquartile range, median, minimum and maximum values. We present frequencies and percentages for categorical variables. We present changes from baseline and shift tables for laboratory parameters and vital signs. For compartmental population PK analysis, we used the nonlinear mixed-effect modelling program Monolix 2021R1 (Lixoft, Antony, France). The Rsmlx package in R (https://CRAN.R-project.org/package=Rsmlx) was used to compute confidence intervals for the population parameters with log-likelihood profiling. Simulations were performed in Simulx 2021R1 (Lixoft). For the maternal PK, the equations, model building and validation procedures were as previously described.[12] The two-compartment model was parameterised with the first-order absorption constant for the intramuscular (Ka_{IM}) and oral (Ka_{PO}) routes, intramuscular (F_{IM}) and oral (F_{PO}) bioavailability, the lag time before oral absorption (T_{lag}), elimination clearance (CL), intercompartmental clearance (Q), volume of the central compartment (V_C) and volume of the peripheral compartment (V_p). For transplacental transfer, cord blood samples were linked to maternal samples using an effect compartment with first-order mother-to-fetus (K_{MF}) and fetus-to-mother (K_{FM}) rate constants. The effect on the PK of the following covariates was investigated: age, height, body weight, body mass index, body surface area, country of investigation centre, anaemia (haemoglobin concentration of <110 g/L), haematocrit, serum creatinine, estimated glomerular filtration rate (eGFR), and intra-, postoperative and total blood loss.

The PD response was modelled considering a delay between drug exposure and response, according to indirect PD response models.[13] A mechanism-based turnover model was used that included the physiological production of D-dimers during pregnancy, with a further induction of D-dimer production at the time of incision. We modelled the inhibitory effect of TXA administration on D-dimer production (R) with the following differential equation:

$$\frac{dR}{dt} = \left(K_{in}^{0} + Stim\right) \cdot A(\mathrm{Cc}) - K_{out} \cdot R,$$

with K_{in}^{0} the apparent zero-order rate constant for the physiological production of D-dimers during pregnancy, K_{out} the first-order rate constant for the elimination of D-dimers Stim the term representing the stimulation of D-dimer production at CS ($Stim = 0$ for $t < t_{incision}$; $Stim = K_{STIM}$·STIM for $t > t_{incision}$) and A the function modelling the effect of TXA in the central compartment (Cc).

The model was parameterised with the initial values of R (R_0) and $Stim$ ($Stim_0$) and the parameter K_{out}. K_{in} was derived as $K_{in} = R_0 \cdot K_{out}$. For the effect of TXA, the function takes the concentration of TXA in the central compartment (Cc) as an input and is parameterised with I_{max} 00B7($0 < I_{max} < 1$ for partial inhibition; $I_{max} = 1$ for total inhibition), IC_{50} and γ (Hill coefficient, representing the sigmoidicity of the response) using the following equation:

$$A(\mathrm{Cc}) = 1 - \frac{I_{max} \cdot \mathrm{Cc}^{\gamma}}{\mathrm{Cc}^{\gamma} + IC_{50}^{\gamma}}.$$

Placental transfer was measured as the ratio between the fetal TXA area under the curve (AUC) and the maternal TXA AUC.[14]

3 | RESULTS

3.1 | Safety

A total of 120 women were randomised into the safety study between 18 December 2020 and 15 June 2021 (Figure 1). The baseline characteristics were similar between treatment groups (Table 1). All women received uterotonics for PPH prophylaxis. There were no serious maternal or neonate adverse events associated with the trial intervention. No vascular occlusive events or seizures were reported (Table 2). Eight women had a PPH: five women in the oral TXA group and three women in the no-TXA group. There were no occurrences of PPH in the IV or IM TXA groups. Of the 29 women that received IM TXA, six had erythema, two had induration or subcutaneous nodules and one had injection site bruising. None had erythema, induration or subcutaneous nodules beyond the day of injection. Eight women reported injection pain. The median and maximum pain score was 3/10 and 4/10, respectively.

3.2 | Pharmacokinetics and pharmacodynamics

Ninety-four participants from the safety study and a further 26 participants were enrolled for the PK and PD study, 114 of whom provided useable data (Table S2). Some PK samples were excluded at the laboratory analysis stage as the Mitra® blood sample collection was inadequate. A total 755 maternal blood samples and 87 cord blood samples were available for TXA measurement. The measured TXA concentrations for each route are shown in Figure S1. The final PK model was a two-compartment open model with first-order absorption and elimination, with a lag-time for oral absorption. Among the covariates of interest, the effect of allometrically scaled body

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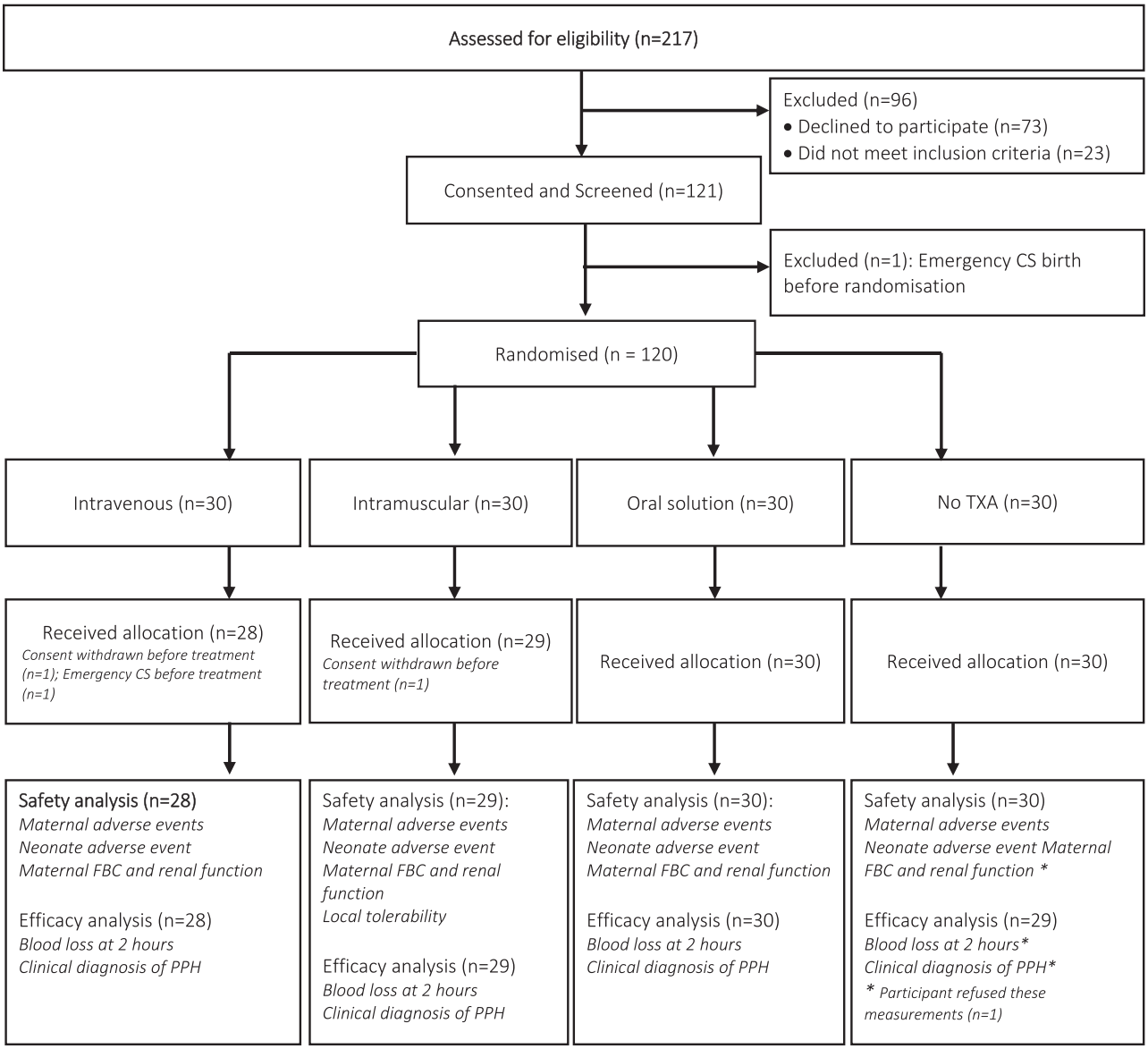

FIGURE 1 CONSORT flow diagram showing participant flow (for the safety analysis) through the trial (enrolment, intervention allocation, follow-up and data analysis).

weight on *CL*, *Q*, V_C and V_p improved the model, whereas age, height, body mass index, body surface area, country, anaemia, haematocrit, eGFR and blood loss had no apparent effect on the PK. Simulated PK profiles by route of administration are shown in Figure 2 and were used to determine the maximum blood concentration (C_{max}) and time to C_{max} (T_{max}). The maximum blood concentrations were 46.9 ± 23.3, 21.6 ± 8.3 and 18.1 ± 7.4 mg/L for IV, IM and oral administration, respectively, and were reached after 26 ± 47 minutes, 49 ± 52 minutes and 3.8 ± 2.6 hours, respectively.

Neonatal PK was described by an effect compartment linked by rate transfer constants. The simulated PK profiles in neonates are shown in Figure 2. The C_{max} in neonates was 9.5 ± 4.5, 7.9 ± 3.6 and 9.1 ± 4.7 mg/L after IV, IM and oral administration, respectively. The population PK estimates and diagnostic plots for the model are shown in Figures S2 and S3 and Table S1.

Placental transfer, measured as the ratio between fetal TXA AUC and maternal TXA AUC for 24 hours, was estimated at 52%. Neonate observed serum TXA concentrations versus population and individual predictions and the visual predictive checks for neonate serum TXA concentrations are presented in Figures S6 and S7.

The PK/PD analysis was performed with the PK data set and with D-dimer concentrations measured in 567 plasma samples from 114 women. The measured D-dimer concentration versus time curves are shown in Figure S4. The response to TXA was modelled as an inhibitory effect on the D-dimer production rate. Estimates of I_{max}, the maximal effect, and γ, the Hill coefficient, did not significantly differ from 1.0, and were therefore fixed at 1.0, meaning that TXA exerted a full inhibitory effect, without sigmoidicity. The estimate of the IC_{50}, defined as the TXA concentration providing half-maximal inhibitory effect, was 7.5 mg/L.

TABLE 1 Baseline characteristics of randomised participants.

	Intramuscular TXA ($n=30$)	Intravenous TXA ($n=30$)	Oral solution TXA ($n=30$)	No TXA ($n=30$)
Age (years)	31 (5)	32 (5)	31 (4)	32 (5)
Body mass index (kg/m^2)	32 (5)	30 (4)	30 (6)	32 (6)
Body surface area (m^2)	2 (0.2)	2 (0.1)	2 (0.2)	2 (0.2)
Gravida*	4 (3–5)	4 (3–5)	4 (3–5)	4 (2–5)
Parity*	4 (3–5)	4 (3–5)	4 (3–5)	4 (2–4)
Gestational age (weeks)*	38 (37–39)	38 (37–39)	38 (37–39)	38 (37–39)
Singleton pregnancy	29 (97%)	27 (90%)	30 (100%)	29 (97%)
Haemoglobin (g/dl)	11 (2)	12 (1)	12 (2)	11 (2
Serum creatinine (μmol/L)	1 (0.2)	1 (0.2)	1 (0.1)	1 (0.2)
Serum UREA (mmol/L)	18 (8)	19 (8)	17 (5)	16 (6)
eGFR (ml/minute/1.73 m^2)	146 (41)	151 (60)	131 (36)	132 (37)
Haematocrit/packed cell volume (%)	34 (4)	34 (3)	35 (4)	34 (4)
Risk factors for PPH				
Anaemia (Hb < 110 g/L)	4 (13%)	2 (7%)	5 (17%)	5 (17%)
Intrauterine fetal death	0 (0%)	0 (0%)	1 (3%)	0 (0%)
Grand multipara (>3)	21 (70%)	18 (60%)	16 (53%)	16 (53%)
Previous CS	26 (87%)	26 (87%)	25 (83%)	25 (83%)
Previous PPH	2 (7%)	1 (3%)	0 (0%)	2 (7%)
Gestational diabetes	0 (0%)	1 (3%)	1 (3%)	3 (10%)
Gestational hypertension	4 (13%)	3 (10%)	5 (17%)	6 (20%)
Intra-amniotic infection	1 (3%)	0 (0%)	0 (0%)	0 (0%)
Macrosomia	2 (7%)	0 (0%)	1 (3%)	4 (13%)
Placental abruption	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Placenta praevia	1 (3%)	0 (0%)	6 (20%)	1 (3%)
Polyhydramnios	1 (3%)	1 (3%)	0 (0%)	0 (0%)
Pre-eclampsia with thrombocytopaenia	0 (0%)	0 (0%)	0 (0%)	1 (3%)
Uterine anomaly	1 (3%)	0 (0%)	0 (0%)	0 (0%)
Uterine fibroids	0 (0%)	1 (3%)	3 (10%)	2 (7%)

Note: data are *n* (%), mean (SD) and *median (range).

Among the different covariates, only the country of the investigation centre had an impact on the estimates of the PD model: patients included in Zambia had higher baseline and CS-induced D-dimer production. The estimates are shown in Table S2 and diagnostics plots for model validation are presented in Figure S5. Maternal simulated D-dimer concentrations by route of administration are shown in Figure 3. For the sake of extrapolation to values reported in other studies with different PD outcomes, it may be useful to have the correspondence between whole blood and serum concentrations for the IC_{50}. This relationship was previously described,[10] and varies with haematocrit. Therefore, an IC_{50} of 7.5 mg/L in whole blood is equivalent to 9.4–13.6 mg/L in serum for haematocrit values between 20% and 45%.

The time to reach IC_{50} and the duration above this concentration were also calculated from the PK model. The median time (25th–75th centile) to reach the IC_{50} was 2.6 minutes (1.6–4.2 minutes) for the IV route, 6.4 minutes (4.0–10.3 minutes) for the IM route and 47 minutes (26–85 minutes) for the oral route. The concentration remained above the IC_{50} for 4.7 hours (2.9–6.7 hours) with IV TXA, 4.7 hours (3.0–6.7 hours) with IM TXA and 9.6 hours (6.7–13.9 hours) with oral TXA.

4 | DISCUSSION

4.1 | Main findings

Intramuscular TXA is well tolerated and rapidly absorbed in pregnant women. Intramuscular administration of 1 g TXA achieves a therapeutic blood concentration within 10 minutes of injection and remains above this concentration for over 4 hours. Oral administration of 4 g TXA solution was

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TABLE 2 Maternal and neonatal safety and efficacy outcomes.

	Intramuscular TXA ($n=29$)	Intravenous TXA ($n=28$)	Oral solution TXA ($n=30$)	No TXA ($n=29$)
Maternal blood loss				
Clinically diagnosed PPH	0 (0%)	0 (0%)	5 (17%)	3 (10%)
Total estimated blood loss at time of PPH diagnosis (ml)	–	–	2100 (1169)	1200 (500)
Intraoperative blood loss (ml)	467 (174)	462 (191)	742 (755)	569 (301)
2-h postoperative blood loss (ml)	110 (89)	140 (101)	136 (130)	115 (89)
Total blood loss (ml)	577 (181)	602 (205)	878 (784)	684 (328)
Interventions				
Uterotonics (prophylactic)	29 (100%)	28 (100%)	30 (100%)	29 (100%)
Additional uterotonics (after third stage)	6 (21%)	6 (21%)	10 (33%)	3 (10%)
Hysterectomy	0 (0%)	0 (0%)	3 (10%)	2 (7%)
Maternal adverse events				
Nausea	0 (0%)	2 (7%)	2 (7%)	1 (3%)$^{+}$
Vomiting	0 (0%)	2 (7%)	0 (0%)	0 (0%)$^{+}$
Diarrhoea	0 (0%)	0 (0%)	0 (0%)	0 (0%)$^{+}$
Dizziness	0 (0%)	2 (7%)	0 (0%)	0 (0%)$^{+}$
Seizures	0 (0%)	0 (0%)	0 (0%)	0 (0%)$^{+}$
Any vascular occlusive event	0 (0%)	0 (0%)	0 (0%)	0 (0%)$^{+}$
Maternal status				
Discharged alive	29 (100%)	28 (100%)	30 (100%)	29 (100%)
Length of hospital stay (days)*	2 (1–2)	1 (1–2)	2 (1–2)	2 (1–2)
Neonatal outcomes				
Baby 1				
Status at birth – alive	29 (100%)	28 (100%)	29 (97%)	29 (100%)
Status at discharge – alive	29 (100%)	28 (100%)	29 (97%)	28 (97%)
Birthweight (g)	2958 (537)	3162 (493)	3047 (545)	3009 (609)
APGAR score at 1 minute*	8 (7–9)	8 (7–9)	8 (7–9)	8 (7–9)
APGAR score at 5 minutes*	9 (8–9)	9 (9–9)	9 (8–9)	9 (9–9)
Neonate with medical issues at birth	1 (3%)	1 (4%)	2 (7%)	2 (7%)
Neonate adverse events				
Moaning, grunting, nasal flaring	0 (0%)	1 (4%)***	0 (0%)	0 (0%)
Transitory tachypnoea of newborn	0 (0%)	0 (0%)	1 (3%)	1 (3%)
Anorectal fistula	0 (0%)	0 (0%)	1 (3%)	0 (0%)
Birth asphyxia, low set ears, choanal atresia, symbrachydactyly, pulmonary hypoplasia	0 (0%)	0 (0%)	0 (0%)	1 (3%)**, ****
Baby 2				
Status at birth – alive	1 (100%)	1 (100%)	–	1 (100%)
Status at discharge – alive	1 (100%)	1 (100%)	–	1 (100%)
Birthweight (g)	2300	2500	–	2000
APGAR score at 1 minute*	9 (9–9)	9 (9–9)	–	9 (9–9)
APGAR score at 5 minutes*	9 (9–9)	9 (9–9)	–	10 (10–10)
Medical issues at birth	0 (0%)	0 (0%)	–	0 (0%)

Note: data are *n* (%), mean (SD) and *median (range); $^{+}n=30$; *stillbirth; **multiple congenital abnormalities (not identified prior to randomisation); ***; ****events present in the same neonate.

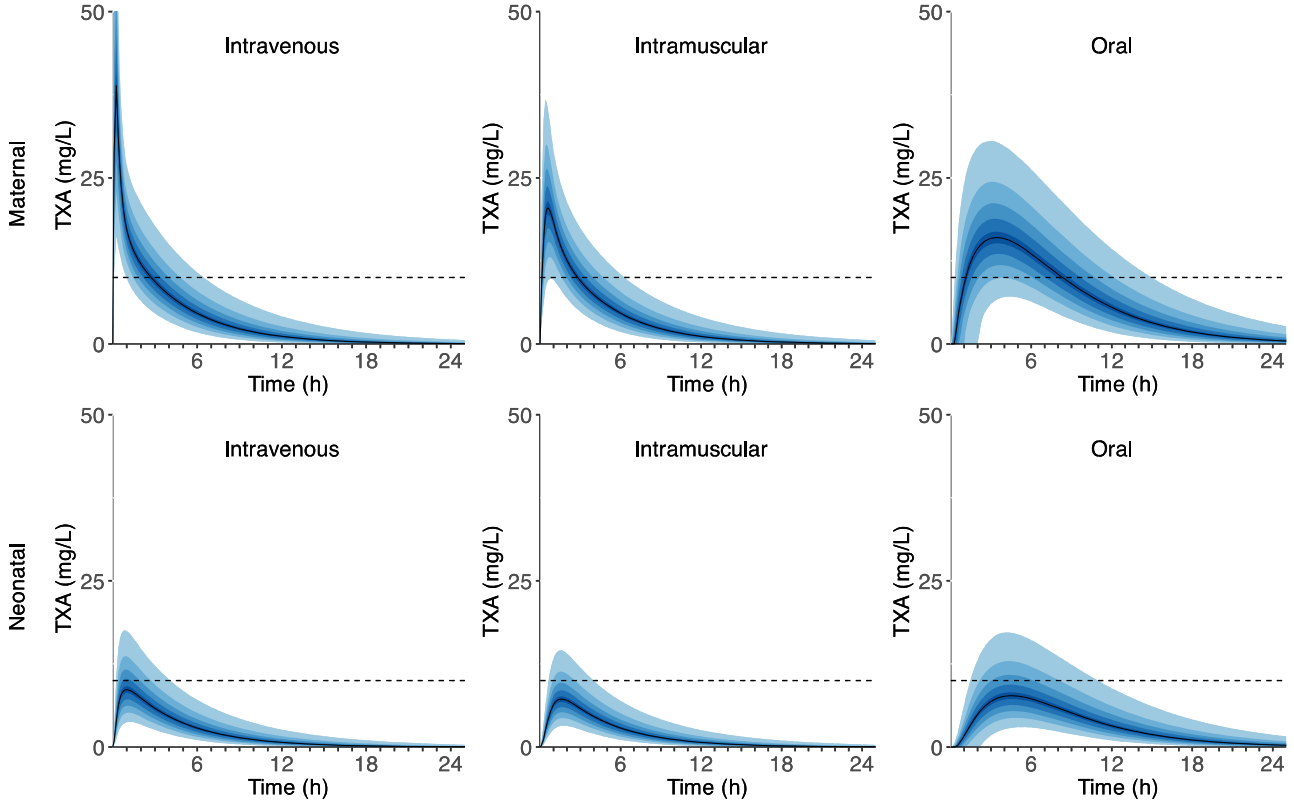

FIGURE 2 Simulated maternal and neonatal TXA concentrations versus time plots for each route of administration (500 simulations, 200 patients). The centre line is the median. The shaded blue area is a 90% confidence interval. Horizontal dotted line is at 10 mg/L

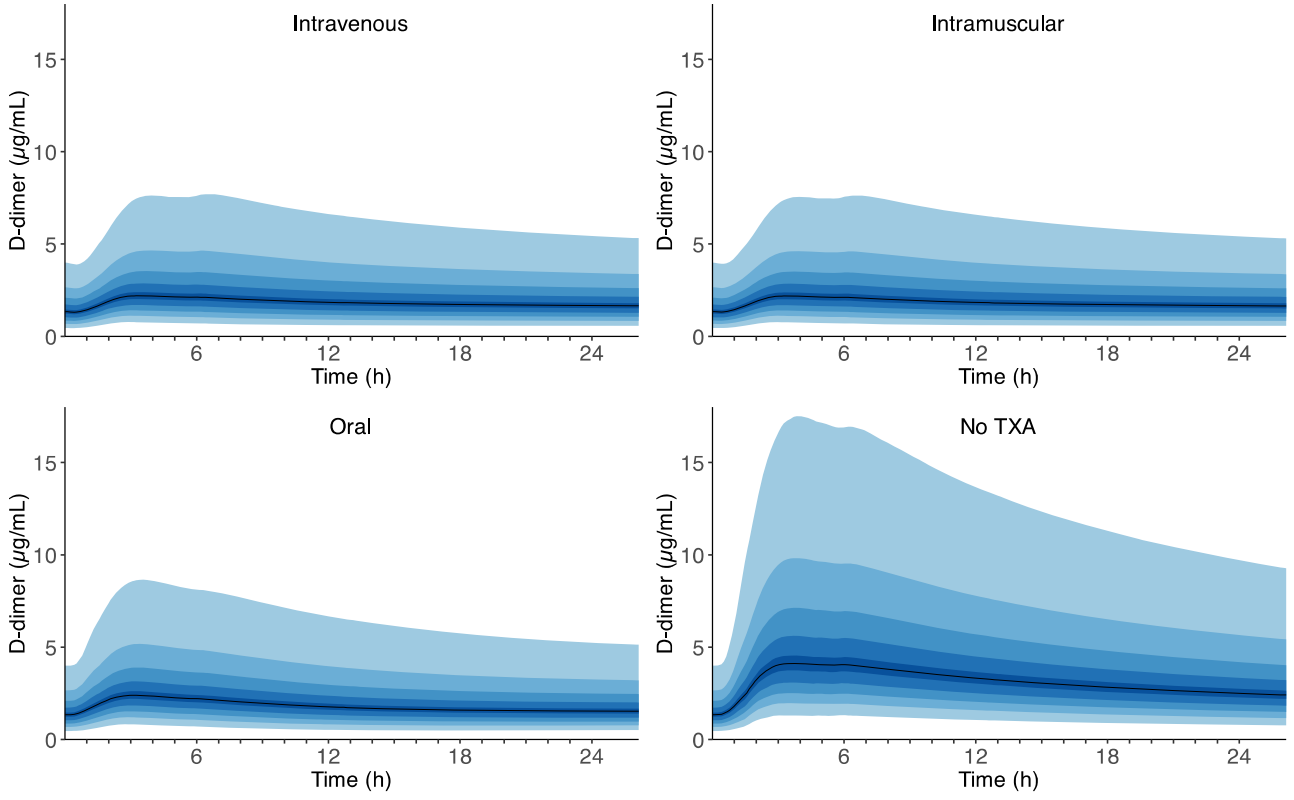

FIGURE 3 Simulated maternal D-dimer concentrations versus time plots for each route of administration and for the placebo (500 simulations, 200 patients). The centre line is the median. The shaded blue area is the 90% confidence interval.

well tolerated but it took close to 1 hour to achieve therapeutic concentrations. As women with severe obstetric bleeding can die within hours of bleeding onset,[2] the intramuscular route is a potential alternative to intravenous administration, but the oral route is not suitable for emergency treatment.

4.2 | Strength and limitations

Our study has strengths but also limitations. Our conclusions about safety are based on randomised comparisons of alternative routes of administration. The allocation was well concealed and the baseline characteristics were similar between groups. However, the route of administration was not masked, raising the possibility of outcome assessment bias. Although this is the largest comparative study of alternative routes, the sample size was limited and so we cannot exclude modest differences in safety outcomes. The within-patient PK and PD analyses are based on a large sample of women with 755 maternal samples and 87 cord blood samples available for TXA measurement. We used a well-validated, high-sensitivity liquid chromatography tandem mass spectrometry (LC-MS/MS) method for the quantification of TXA concentrations.[9,10] We measured TXA in whole blood collected using the Mitra® volumetric absorptive microsampling device, having previously demonstrated that concentrations obtained from the use of such samples correspond closely with those measured in liquid blood samples collected by venepuncture.[12] However, because of limited data, the neonatal PK model described is driven by the effect compartment of the maternal model. Ours is the largest PK and PD study of TXA in pregnant women and the first to assess neonatal PK after placental transfer.

4.3 | Interpretation

Our in vivo PD results confirm the conclusions from in vitro PD studies that plasma concentrations over 10 mg/L are sufficient to inhibit fibrinolysis.[15] As a result of physiological changes in pregnancy, pregnant women have a greater volume of distribution and elimination clearance than non-pregnant women. Nevertheless, a 1 g IM injection of TXA achieved a therapeutic blood concentration within 10 min, which is less than the time it takes to give the slow intravenous dose. TXA crosses the placenta with an estimated fetal-to-maternal exposure ratio of 52%. However, TXA is a drug with a short half-life and is rapidly eliminated.

4.4 | Conclusion

Intravenous TXA reduces PPH deaths but in some situations this route is not feasible. Pharmacokinetics studies in healthy volunteers, bleeding trauma patients and now pregnant women show that IM administration rapidly achieves therapeutic TXA concentrations.[12,16] We might reasonably expect IM and IV TXA to be similarly effective, whereas oral treatment takes about 1 hour to reach therapeutic concentration and would not be suitable for emergency treatment. Our results provide sufficient information for the conduct of a phase 3 trial to test whether the IM route of administration is as efficacious (within limits) as the IV route to reduce postpartum bleeding.[17]

AUTHOR CONTRIBUTIONS

HSS and IR are the co-lead investigators with responsibility for the original idea and obtaining funding. HSS and IR can both claim lead authorship as they contributed equally to this trial. HSS, IR and SGD designed the trial and drafted the article. SGD and EL carried out the laboratory PK analysis. RC was lead coordinating investigator in Pakistan. AG and DP managed the data collection. MKL, NI and SBM were lead site investigators. MA managed the trial. KJ and AK managed the trial in Pakistan. SGD, SU and NB carried out the PK/PD modelling, and FF contributed to the PK aspects of study design. RM contributed to the safety and efficacy analysis. LC, CB, JGO and EB provided regulatory and administrative support. All authors contributed to reviewing the article and approved the final version for publication.

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CONFLICT OF INTERESTS

None declared. Completed disclosure of interests form available to view online as supporting information.

ETHICS APPROVAL

The trial was approved by the following ethics committees and regulatory authorities: National Bioethics Committee Pakistan (ref. 4-87/NBC-532/20/409), Drug Regulatory Authority of Pakistan (ref. 16/2020 DD [PS]), Ethical Review Board of MCH Centre – Pakistan Institute of Medical Sciences Hospital (ref. F1-1/2015/ERB/SZABMU/583), Ethics Committee of the Federal Government Polyclinic Hospital (ref. FGPC.1/12/2020/Ethical Committee), University of Zambia Biomedical Research Ethics Committee (ref. 933–2020), Zambia Medicines Regulatory Authority (ref.

DMS/7/9/22/CT/102), Zambia National Health Research Authority (NHREB) and the London School of Hygiene & Tropical Medicine's Ethics Committee (ref. 21255). We published the study protocol at https://wellcomeopenresearch.org/articles/6-157.

DATA AVAILABILITY STATEMENT

The anonymised dataset, protocol, published manuscript, data dictionary and other relevant trial documents will be made freely available on https://freebird.lshtm.ac.uk/home/

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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