# Pharmacokinetics and safety of IM, IV and oral tranexamic acid in women giving birth by C-Section

*Woman-PharmacoTXA Trial Collaborators*


LONDON SCHOOL of HYGIENE &TROPICAL MEDICINE

SHIFA TAMEER-E-MILLAT UNIVERSITY STMU

F.G. POLYCLINIC POST GRADUATE MEDICAL INSTITUTE

PAKISTAN INSTITUTE OF MEDICAL SCIENCES ISLAMABAD

THE UNIVERSITY OF ZAMBIA SERVICE AND EXCELLENCE

Département de Biotechnologie de la Santé

UNIVERSITÉ DE VERSAILLES ST-QUENTIN-EN-YVELINES

UFR SIMONE VEIL - SANTÉ

université PARIS-SACLAY

# TXA is life saving

- Early administration TXA reduces the risk of death from bleeding by 1/3
- No increase on adverse effects


**TIME IS CRITICAL:**

- Every fifteen minutes treatment delay reduces the survival benefit by about 10%
- After 3 h from onset of bleeding there is no benefit
- Based on this evidence, the WHO recommends the early use of IV TXA (within 3 hours of birth) in women with PPH.

The WHO also states that "*research on other routes of TXA administration is a priority*".

# WHY alternative routes needed

- Many women die within few hours of bleeding onset, not treated or not treated soon enough .
- Administration of IV injection is a main barrier for rapid treatment.
- Medical personnel trained to insert intravenous lines not available in areas far from a clinical setting, or in understaffed hospitals.
- If TXA can be given orally or intramuscularly more women are likely to receive the treatment sooner.
- Relevant in LMICs where many of the PPH deaths happen before the women reach hospital.

If administration of the TXA solution orally and intramuscularly is shown to be safe and can achieve therapeutic levels, this will allow the rapid treatment of women with PPH at the hospitals and in the community

WOMAN PHARMACO TXA

# TXA Pharmacokinetics (PK)

*"What the body does to the drug"* Concentration of TXA in blood over time

- TXA reduces bleeding by inhibiting the breakdown of the blood clot (fibrinolysis).

- Concentration at which TXA inhibits the breakdown of the blood clot: *"TXA concentrations between **10 and 15 mg/L** provide substantial inhibition of fibrinolysis"* [1]

- Investigate if TXA given by the oral and IM routes:
- Reaches therapeutic concentration needed to inhibit fibrinolysis
- Time taken to reach therapeutic (must be early enough to be useful for women with PPH).

Compared Oral and IM to the IV route (standard).

1.-Picetti R, Shakur-Still H, Medcalf RL, Standing JF, Roberts I. What concentration of tranexamic acid is needed to inhibit fibrinolysis? A systematic review of pharmacodynamics studies

# Alternative routes of TXA administration

**Previous PK studies:**

**Bleeding trauma patients (Trauma-INTACT trial, 30 patients UK)**

- IM TXA: well tolerated and rapidly absorbed.
- Therapeutic concentrations (>10 mg/L) reached within 15 min.

**Healthy volunteers (PharmacoTXA trial, 15 HV France)**

- IV, IM and Oral TXA
- Oral TXA is absorbed too slowly, taking hours (1h plus) to reach therapeutic concentrations.
- IM: Therapeutic concentrations reached within 5 min after IM injection.
- All routes well tolerated. No SAE.

**WHY a trial on TXA PK in pregnant women?**

- Safety (woman and neonate)
- Higher fibrinolytic potential in pregnant women
- Higher circulatory plasma volume
- Faster renal clearance

WOMAN PHARMACO TXA

# Woman-PTXA Trial design

- Randomised, open-label trial to assess the pharmacokinetics (PK), safety and efficacy of different routes TXA.
- 120 adult women giving birth by C-section with at least one risk factor for PPH recruited in Zambia and Pakistan (safety and efficacy cohort).
  - Recruitment continued to include around 120 participants with at least 6 evaluable PK samples
- Randomised to receive either:
  - 1 gram of TXA IV (over 10 min injection)
  - 1 gram of TXA IM (2x5 mL injections)
  - 4 grams of TXA oral solution (40 mL to drink)
  - No TXA.

# Outcomes measures

**PRIMARY**

- Blood TXA concentrations over time

**SECONDARY**

- Adverse events (maternal and neonate)
- Local reactions at IM injection sites
- Blood concentrations of D-dimer over time
- TXA concentration in umbilical cord and neonate after birth
- Neonate status Apgar score
- Measured blood loss from start of CS to 2 hours after
- Clinical diagnosis of PPH

# Participants

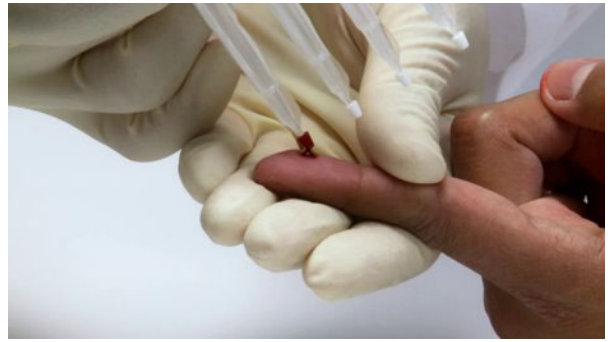
| | IM (N=30) | IV (N=30) | Oral (N=30) | No TXA (N=30) |
|---|---|---|---|---|
| **Age(years)** Mean (SD) | 31 (5) | 32 (5) | 31 (4) | 32 (5) |
| **BMI** ($kg/m^2$) | 32 (5) | 30 (4) | 30 (6) | 32 (6) |
| **Gravida** Median (IQR) | 4 (3-5) | 4 (3-5) | 4 (3-5) | 4 (2-5) |
| **Parity** Median (IQR) | 4 (3-5) | 4 (3-5) | 4 (3-5) | 4 (2-4) |
| **Grand multipara** (>3) | 21 (70%) | 18 (60%) | 16 (53%) | 16 (53%) |
| **Gestational age** (weeks) Median (IQR) | 38 (37-39) | 38 (37-39) | 38 (37-39) | 38 (37-39) |
| **Previous caesarean section** | 26 (87%) | 26 (87%) | 25 (83%) | 25 (83%) |

WOMAN PHARMACO TXA

# Methods

- Women received TXA about 1h before CS

- PK samples taken using Mitra® device from a finger prick.
  - Maternal samples taken at baseline and at 8 timepoints after TXA 15 min → 24 hours.
    (15 min; 30 min; 1h; 2h; 4h; 8h; 12h; 24h).
  - Umbilical cord samples taken at cord clamping; neonatal samples shortly after birth.



- TXA concentrations in the blood measured by liquid chromatography–mass spectrometry method.

- Maternal blood samples taken for safety at baseline and 24h (renal function and FBC).

WOMAN PHARMACO TXA

# Maternal Safety

- No serious adverse events

| Maternal adverse events | IM (N=29) | IV (N=28) | Oral (N=30) | No TXA (N=29) |
|---|---|---|---|---|
| **Nausea** | 0 | 2 | 2 | 1 |
| **Vomiting** | 0 | 2 | 0 | 0 |
| **Diarrhoea** | 0 | 0 | 0 | 0 |
| **Dizziness** | 0 | 2 | 0 | 0 |
| **Seizures** | 0 | 0 | 0 | 0 |
| **Any vascular occlusive event** | 0 | 0 | 0 | 0 |
| **Other adverse events** | 0 | 0 | 0 | 0 |

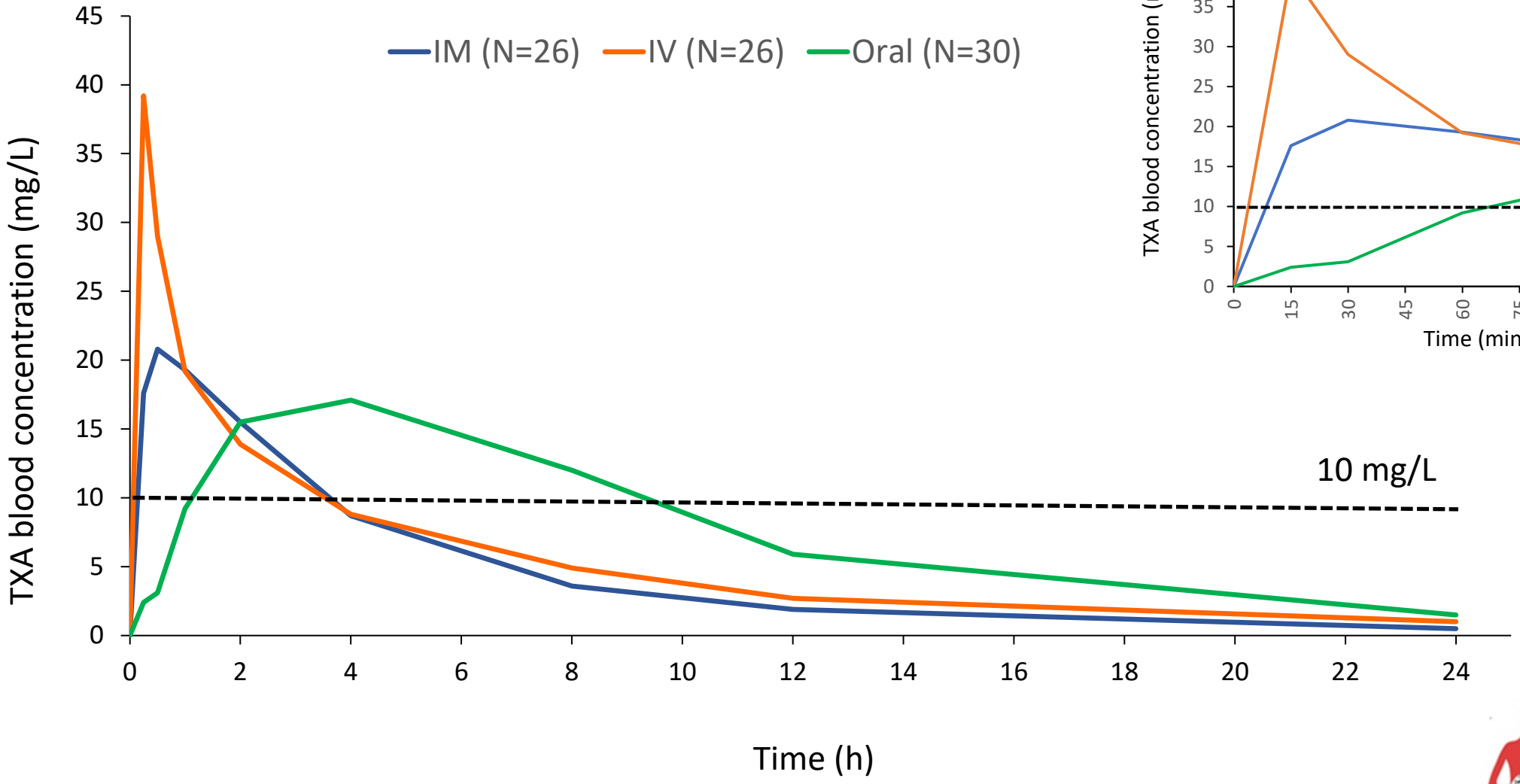
# Maternal Safety

Reactions at the site of injection - IM participants (N=29)

- **Pain**: 8 participants.
  Pain Score (scale 1-10) – Median (Min, Max) : **3** (1,4) *Mild and transient*
  Duration – Median (Min, Max): 1 h (15 min, 2hrs)

- **Skin reaction at site of injection**: Redness (6 participants- *Mild)*
  Induration (2 participants- *Mild)*, Bruising (1 participant)

# TXA acid blood levels (mean)



# Maternal blood loss

| | IM (n=29) | IV (n=28) | Oral (n=30) | No TXA (n=29) |
|---|---|---|---|---|
| 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) |
| Intra-operative blood loss (ml) | 467 (174) | 462 (191) | 742 (755) | 569 (301) |
| 2-hour post-operative blood loss (ml) | 110 (89) | 140 (101) | 136 (130) | 115 (89) |
| **Total blood loss (ml)** | 577 (181) | 602 (205) | 878 (784) | 684 (328) |

WOMAN PHARMACO TXA

# Neonate safety

- No serious adverse events

| | IM (n=29) | IV (n=28) | Oral (n=30) | No TXA (n=29) |
|---|---|---|---|---|
| **Status at birth** | | | | |
| **Alive** | 29 (100%) | 28 (100%) | 29 (97%) | 29 (100%) |
| **Died** | 0 (0%) | 0 (0%) | 1 (3%) * | 0 (0%) |
| **Status at discharge** | | | | |
| **Alive** | 29 (100%) | 28 (100%) | 29 (97%) | 28 (97%) |
| **Died** | 0 (0%) | 0 (0%) | 1 (3%) * Still birth | 1 (3%) * Multiple congenital abnormalities |
| **Birth weight (g)** | 2958 (537) | 3162 (493) | 3047 (545) | 3009 (609) |
| **APGAR Score 1 min** | 8 (7-9) | 8 (7-9) | 8 (7-9) | 8 (7-9) |
| **APGAR Score 5 min** | 9 (8-9) | 9 (9-9) | 9 (8-9) | 9 (9-9) |
| **Medical issues at birth** | 1 (3%) | 1 (4%) | 2 (7%) | 2 (7%) |

*Not associated with trial intervention. Present before entering the trial.

# Alternatives to IV TXA for PPH

- Intramuscular (1g): rapid absorption, target level reached in about 10 minutes. Safe for the mother and the neonate. Fast administration.
- Oral solution (4g): slow absorption, target level reached about 1 hour – may be too late to treat PPH.
- In an emergency situation, it can take time to place an IV line, plus the 10 minutes of slow injection time.
- PK profile of IM route is a favourable alternative to IV administration.
- Large randomised clinical trial planned to learn more about the clinical efficacy of the IM route (I'M WOMAN trial)

# Thank you

*Funded by*

BILL & MELINDA GATES foundation

wellcome

*Woman-PharmacoTXA Trial Collaborators*

**PAKISTAN**
Rizwana Chaudhri
Kiran Javaid
Aasia Kayani
Syeda Batool Mazhar
Naila Israr

**FRANCE**
Stanislas Grassin-Delyle
Elodie Lamy
Saïk Urien
Naïm Bouazza
Frantz Foissac

**ZAMBIA**
Mwansa Ketty Lubeya

**LSHTM**
Monica Arribas
Amber Geer
Raoul Mansukhani
Danielle Prowse
Laura Carrington
Collette Barrow
Eni Balogun
Ian Roberts
Haleema Shakur-Still

# Neonate Adverse Events

## Medical issues at birth

| | IM (1/29) | IV (1/28) | Oral (2/30) | No TXA (2/29) |
|---|---|---|---|---|
| **Neonate Adverse Events** | Birth asphyxia<br>1 (3%) | Moaning<br>Grunting<br>Nasal flaring<br>1 (4%) | Anorectal fistula<br>1 (3%) | Birth asphyxia<br>Multiple congenital abnormalities<br>1 (3%) |
| | | | Transitory tachypnea<br>1 (3%) | Transitory tachypnea<br>1 (3%) |