Tranexamic acid for postpartum haemorrhage – WOMAN-2

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PPH Community of Practice Annual Meeting
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Conflicts of interest:
I have no financial conflicts of interest
I am a co-lead investigator for the WOMAN & WOMAN-2 trials
The WOMAN-2 programme

- Tranexamic acid (TXA) in PPH – importance of time to treatment
- Woman-2 programme:
  - Alternative routes to intravenous TXA to allow nurses and other healthcare professionals to be able to treat women earlier
  - Can we prevent PPH with TXA?
TXA reduces death from PPH

TRANEXAMIC ACID
A drug that reduces bleeding

Results from the WOMAN trial

The drug could save 1/3 of women who would otherwise bleed to death after childbirth. An estimated 100,000 women die from severe bleeding after giving birth every year.

- The drug reduced the number of women bleeding to death after childbirth by more than 30%.
- The drug reduced the need for urgent surgery to control bleeding by more than 35%.
- £2 ($2.5) — The cost of tranexamic acid in most countries.

Source: The WOMAN trial (2017)
Credit: Rebecca Robinson/LSHTM

Find out more at womantrial.lshtm.ac.uk
Analysis of 40,000 bleeding patients (PPH and trauma)

Impact of treatment delay for severe bleeding:
- Immediate treatment: 70% improvement in survival
- For every 15 minute delay: 10% decrease in survival benefit
- After 3 hours: No benefit

Source: The Lancet (2017). Analysis of data for 40,000 trauma patients and women with severe bleeding after childbirth.
Credit: Rebecca Robinson, CRASH2
Find out more at TXAcentral.org
### Death by hours since randomisation

<table>
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<th>Hours since randomisation</th>
<th>Number of deaths</th>
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**Graph:**

- **Y-axis:** Number of deaths
- **X-axis:** Hours since randomisation
- **Legend:**
  - Red: Bleeding
  - Black: Other
WOMAN-2: Programme of studies to identify alternative routes to IV TXA

1. What concentration of tranexamic acid is needed to inhibit fibrinolysis?
2. Simulation & Modelling – optimum dose and route
3. Healthy volunteer study – Pharmaco-TXA
4. Repeat Simulation & Modelling to inform optimal dose and route selection in postpartum women
5. Study of different routes in postpartum women – WOMAN-PharmacoTXA study
What concentration of tranexamic acid is needed to inhibit fibrinolysis?

Systematic review:

• 457 papers identified through database searching.

• 21 included in the review.

• TXA concentrations between 10 and 15 mg/L resulted in substantial inhibition of fibrinolysis.

• Concentrations between 5 and 10 mg/L were partly inhibitory.
Modelling and Simulation – optimal dose selection

• To evaluate the bioavailability of TXA to allow optimal dose selection for each route (IV, oral solution, IM and SC).
• Using published data, developed a physiologically based pharmacokinetics model that can predict plasma concentration-time profiles for TXA.
Simulation & Modelling – oral

**Red** – using highest permeability and stomach transit time
**Green** – using lowest permeability and stomach transit time

- Plasma levels are predicted to exceed 15 µg/mL in ≤ 30 min
- Concentrations are maintained above this level out to at least 5.5 hrs
Simulation & Modelling – intramuscular

\[ Q = \text{muscle blood flow at the site of injection} \]
\[ K_p = \text{muscle partition coefficient (solubility in tissue)} \]

- Even the slowest absorption rate - plasma levels likely to exceed 15 µg/mL in \( \leq 15 \text{min.} \)
- Concentrations are predicted to be maintained above the target level for between 2.5-3hrs
Pharmaco-TXA trial

Clinicaltrials.gov identifier: NCT03777488

Primary objective
• To determine the PK of TXA in healthy volunteers after oral solution, intramuscular or intravenous administration

Secondary objectives
• To evaluate the local and systemic tolerance with the different routes of administration
Pharmaco-TXA trial

Intramuscular

![Graph showing concentration over time for various timepoints.](image-url)
Trauma-INTACT trial: absorption of IM TXA in shocked patients

Therapeutic concentrations reached after 1 gram TXA:
- 5 mg/L $\approx 4$ minutes
- 10 mg/L $\approx 11$ minutes

TRAUMA-INTACT Trial: ClinicalTrials.gov Identifier: NCT03875937
Can TXA prevent PPH in women at high risk?
Aim
To determine the effect of TXA on postpartum bleeding in women with moderate or severe anaemia

Trial design
• Randomised, double-blind, placebo-controlled trial
• 10 000 women with moderate or severe anaemia
• Randomised to receive 1 g of TXA or matching placebo (sodium chloride 0.9%) intravenously immediately and no later than 15 minutes after the umbilical cord is cut or clamped

Inclusion criteria
• Women with moderate or severe anaemia (Hb level <100 g/L or PCV <30%), who have given birth vaginally and for who the responsible clinician is substantially uncertain whether to use TXA

Exclusion criteria
• Women who are not legally adult (<18 years) and permission not provided by a guardian
• Women with a known allergy to TXA or its excipients
• Women who develop PPH before umbilical cord is clamped/cut

Protocol published @ https://trialsjournal.biomedcentral.com/articles/10.1186/s13063-018-3081-x
Recruitment
## Baseline haemoglobin

<table>
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<tr>
<th>Haemoglobin (g/dL)</th>
<th>N (%) Participants (n=2062)</th>
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<tbody>
<tr>
<td>&lt;6</td>
<td>160 (8)</td>
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<tr>
<td>6 - &lt;7</td>
<td>310 (15)</td>
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<tr>
<td>7 - &lt;8</td>
<td>394 (19)</td>
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<tr>
<td>8 - &lt;9</td>
<td>550 (27)</td>
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<tr>
<td>9 - 10</td>
<td>648 (31)</td>
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