Study protocol version 3.0 Pilot and RCT August 2023

Title

A pilot study and randomized controlled trial on the timing, dose and prophylactic effect of oral Tranexamic acid (TA) compared to placebo on postpartum haemorrhage after vaginal delivery

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Primary objectives

Phase 1

1. To assess how serum concentration varies over time between the different forms of orally administered TA and how they compare to intravenous uptake
2. To assess if 2 g of orally administered TA is enough to achieve therapeutic serum concentration immediately after the delivery of the child
3. To assess the timing of the administration of TA to achieve maximum effect when the risk of PPH is the highest (third stage of labour).

Phase 2

To evaluate the effect of orally administered TA compared to placebo postpartum hemorrhage (>=500ml) assessed by weight in vaginal deliveries.

Secondary objectives

Phase 2

- To evaluate the effect of orally administered TA compared to placebo on mean blood loss, pre-postpartal Hb difference ≥10 units, severe PPH (>=1000ml), and the need of blood transfusion
- To evaluate feasibility, i.e. adherence to administration of oral TA compared to placebo.
- To evaluate the acceptability of orally administered TA compared to placebo among women giving birth and providers
- To evaluate the safety of administration of oral TA compared to placebo
- To assess the effect of the intervention on PPH among the subgroup of women with anemia
- To assess the effect of the intervention on PPH according to time of administration in relation to delivery of the child.

Survey of the field

Severe postpartum hemorrhage (PPH) is the leading cause of maternal death worldwide especially in developing countries (1). The uterus and placenta are highly vascularized organs during pregnancy and labor which means that once bleeding starts it is often difficult to control. PPH increases the risk of emergency interventions such removal of the placenta, suturing of cervical or vaginal tears, embolization of uterine arteries, and hysterectomy as well as PPH-related complications such as postpartum endometritis, venous thrombosis, and transfusion-related complications (2, 3) Preventing PPH before onset is therefore of key importance.

Uterotonics such as Oxytocin, Ergometrine and Misoprostol are often used to improve uterine contraction during PPH (4). TA is an anti-fibrinolytic agent which blocks plasminogen from binding to fibrin and in doing so inhibits the break-down of blood clots. This means that hemorrhage is theoretically decreased regardless of its cause.

Intravenous TA reduces the rate of maternal deaths during diagnosed PPH and reduces the rate of PPH when used prophylactically (5, 6). The effect of oral treatment in vaginal deliveries has however not been studied and is a stated research priority by the WHO (7). Oral administration is low-cost, stable at room temperature and easy to administer which makes it applicable to all types of delivery settings including home-births.

In order to prevent PPH, a therapeutic serum concentration of TA should coincide with the period immediately after delivery of the child, when the risk of PPH is greatest.
After peroral administration to non-pregnant individuals, maximum serum concentration of TA is attained after 120 minutes, uptake and clearance is linear and a serum-concentration of 10-15mg/l is required to attain substantial effect on fibrinolysis in vitro (8, 9).

Prophylactic obstetric treatment is however complicated by the fact that gastric emptying and gastrointestinal motility is markedly decreased during labor (10), and duration of labor is unpredictable. The pharmacokinetics of TA during active labor is not known.

Project plan

Phase 1: Sequential 2-armed RCT on the optimal timing and dose of per oral Tranexamic acid in vaginal deliveries

Objectives

1. To assess how serum concentration varies over time between the different forms of orally administered TA and how they compare to intravenous uptake
2. To assess if 2 g of orally administered TA is enough to achieve therapeutic serum concentration immediately after the delivery of the child
3. To assess the timing of the administration of TA to achieve maximum effect when the risk of PPH is the highest (third stage of labour).

Study period: Aug 2022 – Nov 2022

Study population:
The study population will be women planned for vaginal delivery at Södersjukhuset, Stockholm (n=40).

Inclusion criteria: Women eligible for the study will be women with an uncomplicated pregnancy who are planned for vaginal delivery and are ≥18 years old.

Exclusion criteria: The following criteria make a woman ineligible for the study and are grounds for exclusion from the study: kidney or cardiovascular disease, preeclampsia, suspected or intrauterine growth retardation, intrauterine fetal death, ongoing treatment for venous thrombosis, threatening preterm labor, known bleeding disorder, or known hypersensitivity towards TA, or inability to understand spoken and written English or Swedish or the contents of the written information about the study.

Recruitment: We will recruit women during a routine or planned antenatal visit after 35 gestational weeks. Women will be included to the study after a private written informed consent procedure. During this process women will be informed of the risks and benefits of the study and their rights as participants.

Randomization:
Randomization will occur after a woman has been admitted to the labor ward with spontaneous onset of labor. Should a pregnancy complication have ensued between recruitment and time of admittance the woman will not be randomized. We plan to randomize 40 women into four different groups:
Group 1) will receive 2 g of TA oral solution at full cervical dilatation
Group 2) will receive 2 g of TA tablets at full cervical dilatation
Group 3) will receive 2 g of TA effervescent tablets at full cervical dilatation
Group 4) will receive 1 g of TA intravenously effervescent tablets at full cervical dilatation

Randomization to each group will occur upon admission to the delivery ward in a computer-generated sequence using the data collection system RedCap.

Study procedures:

Upon admission we will take a blood sample from the participant to measure Hemoglobin, hematocrit, MVC, MCH, MCHC as well as INR and APTT. At this time the midwife will insert a venous peripheral line to be used for future blood sampling. Blood samples for measurement of serum concentration of TA will be taken at 30 minutes after TA administration and then at 1, 2, 4, 6 and 8 hours after TA administration, or until 0 serum concentration of TA. 24 hours after delivery or before discharge if discharge occurs sooner, we will take another blood sample measuring hemoglobin and the related measures listed above.

Tranexamic acid analysis:

Samples will be stored at -70C and sent in bulk to the research laboratorium at the National Veterinary Institute (statens veterinärmedicinsak anstalt), Uppsala, who have developed a de novo protocol to measure serum Tranexamic acid using High Performance Mass Spectometry. Samples will be stored anonymized for a maximum of three months and will then discarded. According to the biobank law amendment these samples will therefore not require a biobank application approval.

Outcomes:

Our outcome will be comparison of the serum concentration of TA over time after administration between groups. This time period will correlate to the time when women are at highest risk of postpartum hemorrhage.

Sample size: We assume average therapeutic concentration (10mg/L) of po TA will be attained two hours after administration, but as therapeutic effect often can be seen at concentrations above 5 mg/L the effect is thus estimated to last about six hours after administration. This means that even with a relatively high variance (+/- 5mg/L) we should be able to see an adequate concentration curve with 10 people in each arm which is in accordance with previous studies. Concentration levels will be possible to follow even if the woman has a caesarean delivery.

Mean concentrations of TA will be compared using Students T-test. Optimal timing of administration will be estimated using serum concentration curves, comparing Area Under the

Curve representing therapeutic concentration in the 2 hours immediately postpartum, for each group.

Phase II RCT: A randomized placebo-controlled trial on the effect of oral Tranexamic acid (TA) on postpartum blood loss after vaginal delivery

Primary objective

1. To evaluate the effect of orally administered TA compared to placebo on postpartum hemorrhage (>500ml) assessed by weight in vaginal deliveries.

Secondary objectives

- To evaluate the effect of orally administered TA compared to placebo on mean blood loss, pre-postpartal Hb difference ≥10 units, severe PPH (>=1000ml), and the need of blood transfusion
- To evaluate feasibility, i.e. adherence to administration of oral TA compared to placebo.
- To evaluate the acceptability of orally administered TA compared to placebo among women giving birth and providers
- To evaluate the safety of administration of oral TA compared to placebo
- To assess the effect of the intervention on PPH among the subgroup of women with anemia
- To assess the effect of the intervention on PPH according to time of administration in relation to delivery of the child.

Study period: Sep 2023-Dec 2025

Study design: A multicentre 2-armed double-blinded randomized controlled trial on the effect of orally administered Tranexamic acid on the rate of postpartum hemorrhage and median blood loss.

Study population:

The study population will be women planned for vaginal delivery at Södersjukhuset, Stockholm, Hudiksvall hospital, Hudiksvall, Skånes Universitetssjukhus Lund, Mowbray

Maternity Hospital, Cape Town and Khayelitsha District Hospital, Cape Town, South Africa in the period Sep 2023 to Dec 2025 (n=1000).

Inclusion criteria: Women eligible for the study will be women who are planned for vaginal delivery and are ≥18 years old.

Exclusion criteria: The following criteria make a woman ineligible for the study and are grounds for exclusion from the study: ongoing treatment for venous thrombosis, known bleeding disorder or known hypersensitivity towards TA, threatening preterm labor before gestational week 36+0, or inability to understand spoken and written English, Swedish, Xhosa or Afrikaans (depending on the study site), or the contents of the written information about the study.

Recruitment: We will recruit women during a routine or planned antenatal visit. Women will be included to the study after a private written informed consent procedure. During this process women will be informed of the risks and benefits of the study and their rights as participants.

Randomization:
Randomization will occur after a woman has been admitted to the labor ward with spontaneous onset of labor. We plan to randomize 1000 women in total from five study sites. Randomization to each group will occur upon admission to the delivery ward by allocating the next numbered bottle of IP/placebo which have been numbered in a computer-generated randomization sequence 1:1 in permuted blocks of ten. Women will be randomized into one of two groups receiving either Tranexamic acid (n=500) or a non-distinguishable placebo (n=500), at the time-point when she is dilated 6 cm for multipara or 8 cm for nullipara.

Study procedures: Haemoglobin will be measured in a blood sample taken at arrival to the delivery ward, Haemoglobin level will be controlled 24 hours postpartum or directly before discharge if this occurs sooner. Blood loss during delivery and directly postpartum will be measured by weighing and recorded by the midwife in the delivery unit. Subsequent bleeding within 24 hours of delivery will be weighed and recorded by the midwife at the postpartum care ward. Time of TA administration in relation to labor/delivery, suspected side-effects of the tablets, as well as any difficulty taking the tablets will be recorded by the midwife on study case report forms. Pregnancy and delivery- related variables such as age, ethnicity, smoking,

reproductive history, gestational age, fetal weight, and placental weight will be retrospectively extracted from patient electronic records.

Outcomes:

Primary endpoints will be

1. Rate of postpartum hemorrhage (>500ml) based on weight-assessed blood loss

Secondary endpoints

1. Blood loss >500ml presumed based on a pre-postpartal hemoglobin (g/L) difference ≥10 units
2. Rate of severe postpartum hemorrhage (>1000ml)
3. Rate of blood transfusion within 48 hours.
4. Mean weight-assessed blood loss (ml)
5. Mean pre-postpartal hemoglobin difference(g/L)
6. Safety of oral TA administration (rate of thrombosis up to 6 weeks postpartum, rate of severe allergic or other adverse reactions)
7. Feasibility of oral TA administration (rate of women successfully taking TA as planned in the study protocol)
8. Rate of no to minor disruption caused by administration (acceptability)among participants
9. Rate of no to minor discomfort upon administration (acceptability) experienced by providers

Sample size:

The baseline incidence of PPH≥ 500ml at the main recruiting site is 39%. We assess that the smallest difference in treatment effect between TA and placebo groups would be an absolute decrease in PPH≥ 500ml of 9% (from 39% to 30%, relative treatment effect 23%). Using a 2-group Chi^2 test and 2-sided significance level we would require a sample size of 437 in each group to have 80% power to detect this decrease, or an equivalent decrease in rate of pre-postpartum hemoglobin difference ≥ 10 units, with 95% confidence (from 39% to 30%). Based on baseline rates we assume that 8% of participants will be discontinued after randomization due to emergency caesarean section, and 1% of women will discontinue participation for other reasons. Our main outcomes are collected within 24 hours which will minimize loss to follow up. Accounting for this, we plan to randomize 500 women in each group, 1000 women in total.

This sample size will give us 80% power to detect an absolute decrease in severe PPH (≥ 1000ml) of 5% assuming a baseline rate of 10.2%, and a 4% decrease in blood transfusion assuming baseline rate of 7%, using a 2-group Chi^2 test and 2-sided significance level, and a 3 unit difference pre-postpartum Hb (assuming a background Hb-difference of -8.9 gr/L and a standard deviation [SD] of 17gr/L) (11) using Student's *t*-test.

Analysis: Background, pregnancy and delivery variables will be compared to demonstrate successful randomization using Fischer exact or Chi-sqare tests. The rates of our primary and secondary outcomes will be compared group-wise in an intention to treat (ITT) and a per protocol (PP) analysis. Binary outcome data will be compared by Fischer exact or Chi-sqare tests, median blood loss will be compared using the Mann-Whitney-U test. A p-value <0.05 will be considered significant. A subanalysis of treatment effect will be performed according to study site, country, among women with prior anemia, women with prior PPH and according to timing of administration of TXA.

Significance:

The long-term aim of this project is to optimize intrapartum management of PPH in an effort to reduce morbidity. Reducing complications to PPH will reduce the need of hysterectomy, blood transfusion, and medication, length of hospital stay, sick leave, psychological sequelae and medical costs. It would also benefit the newborn, reducing acute morbidity at birth and separation from the mother, and increasing immediate uptake of breastfeeding.

Should prophylactic peroral TA prove to be effective in preventing postpartum hemorrhage it could be a critical treatment in both high and low resource settings due to its low cost, stability and easy administration. If TA given orally proves to be equally efficient in reducing blood loss postpartum as intravenous TA this should be considered for inclusion in routine delivery care. By including low resource settings in other countries in the larger RCT we hope to help increase optimal management of vaginal birth in these and other countries. In low income countries many women are anemic even before pregnancy due to malnutrition and concurrent diseases such as malaria, HIV and tuberculosis, it is therefore of utmost importance to prevent unnecessary bleeding during delivery. Oral TA compared to intravenous TA is widely available, easy to administer even by the woman herself, cheap, and stable at room temperature.

Ethical considerations

Participant safety

Participation in the study will involve venous blood sampling (phase 1 and 2) and the introduction of a peripheral line (in Phase 1). The blood sampling can be experienced as painful by some women, but for most this is a minor and transient discomfort. The placement of the peripheral line is one of the most common procedures in healthcare and is performed on most in-hospital patients. Occasionally, a small amount of bleeding occurs at the injection site, which can result in a bruise on the arm. Unusual complications are local or generalized infection, and in rare cases thrombophlebitis. After the first sampling, the following blood samples will be drawn from the peripheral line, which usually does not cause any pain or significant discomfort.

The medicine studied, Tranexamic acid, can sometimes cause side effects in the form of nausea, vomiting, diarrhea, abdominal pain, headaches and dizziness and in unusual and rare cases respectively, transient allergic skin reactions and effects on color perception. The risk of side effects is less with tablet intake than with intravenous administration.

TA is well-tested and is used both prophylactically and therapeutically in both pregnancy and postpartum with very low to unknown frequency of serious side effects. All research to date has shown that it is not associated with an increased risk of thrombosis and has no negative impact on the fetus.

All participants will be included in the study after an informed consent process. Informed consent will take place in-person with a well-informed doctor or midwife in a private space. Women will be recruited to the study at an antenatal check-up visit prior to the onset of labor, to ensure that the informed consent takes place at a time when the stress of labor does not interfere with the woman´s ability to understand the information conveyed or her decision to participate in the study. Participants will be informed about study procedures, rationale, the potential risks in taking the active medication, as well as the risks and potential benefits of participating in the study procedures such at the drawing of venous blood. Women will be informed of their rights as study participants and how their personal information will be safe-guarded. Women will have the opportunity to ask questions and it will be ascertained that all participants understand the information given them.

Adverse and severe adverse events will be continuously monitored during the trial. The trial will employ a clinical trial research monitor that will assess whether any unexpected rate of adverse events or discrepancy between treatment effects are grounds for an early closure of the study.

Data safety

When women are randomized to the study they will be automatically assigned a study ID by the Redcap data system. No identifying characteristics such as their name, address, telephone or unique personal identification number (personnummer) will be entered into the research database. All data from the study forms and patient records collected during the study will be registered in an anonymised form where participants are identified only by their study identification number. After data is entered into the database, any paper forms will be destroyed. The participant log where the personal identification number is linked to the study ID will be protected with a code key and stored as a computer file dedicated to the study which only the co-investigators will have access to.

Study team:

The principal investigator Margit Endler has previously led two RCTs, both in South Africa. She has an established network of collaborators and field workers in this setting. She has a PhD on the epidemiology and pathophysiology of retained placenta and postpartum hemorrhage and a strong background in register-based research.

Co-investigator **Gita Strindfors, M.D**, is a senior consultant in obstetrics at Södersjukhuset and a doctoral student. She is a member of the IS-PAS (International Society of Placenta Accreta Spectrum) and has worked clinically with this group of patients for the past five years. The co-investigator and associate professor **Pelle Lindqvist** is a senior consultant and researcher at Södersjukhuset and is part of the collaborative Nordic Obstetric Surveillance Study Group (NOSS) on placenta accreta spectrum disorders, which recently published results on placenta accreta among over 600 000 births in the period 2009-2012. Pelle Lindqvist therefore has well-established and tested research collaborations around Sweden. He also has an existing network at the Swedish study sites.

Co-investigator **Lars Thurn, MD PhD** is a senior consultant and researcher at Lund´s University Hospital with a PhD on the topic of placenta accreta and postpartum hemorrhage. He will lead and coordinate the Lund study site.

Co-investigator **Zoltan Zavczki, MD PhD** is head of the department of obstetrics at Hudiksvall hospital and twenty years of clinical experience. He will lead and coordinate the Hudiksvall study site.

Co-investigator **Chantal Stewart MD** is head of department at Mowbray Maternity Hospital (MMH)l in Cape Town Department and a specialist in high-risk pregnancy. She will lead and coordinate Mowbray study sites, MMH has approximately 12 000 deliveries per year.

Co-investigator **Christine Els MD** is head of the obstetric department at Khayelitsha District Hospital. The hospital has 3000 deliveries per year.

Co-investigator Professor **Justus Hofmeyr, MD PhD** is a consultant gynecologist and obstetrician at the East London Hospital Complex, East London and a highly recognized expert in obstetrics. He has published 50 Cochrane systematic reviews and is an experienced lead researcher in the field of postpartum hemorrhage and other high risk obstetric disorders. He will act as consultant to the trial as a whole.

Co-investigator **Lucia Knight** is Head of the Division of Social and Behavioural Sciences in the School of Public Health at the University of Cape Town, South Africa and an experience researcher foremost in qualitative methodology.

All research collaborators as well as research assistants will be GCP certified and receive GCP refresher courses if necessary.

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