Tranexamic acid versus no tranexamic acid for the prevention of postpartum haemorrhage among women undergoing elective caesarean section at two hospitals in Harare, Zimbabwe: a randomised controlled trial

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INTRODUCTION

Postpartum haemorrhage (PPH) is a significant cause of maternal mortality and is responsible for 25% of all maternal deaths globally(1). Virtually all of these deaths (99%) occur in developing countries, with 66% occurring within Sub-Saharan Africa(2,3) .

Uterotonics after birth are the only intervention that have been shown to be effective for PPH prevention, having demonstrated a 50% reduction in the incidence of PPH (3). Tranexamic acid (TXA) has been explored as a possible additional agent in PPH prevention (4).

During an acute haemorrhage, both clot formation and clot breakdown (fibrinolysis) are necessary to achieve haemostasis. Fibrinolysis is the process by which tissue plasminogen activator enables plasmin to breakdown fibrin into fibrin degradation products. Antifibrinolytic agents, such as TXA, competitively inhibit lysine binding sites of the plasminogen molecule to stabilize fibrin levels and prevent fibrinolysis, thereby resulting in reduced blood loss (5). Similarly, during placental separation, fibrinogen and fibrin are rapidly degraded, while, due to activation of the fibrinolytic system, plasminogen activators and fibrin degradation products increase. This activation can last six to ten hours postpartum, resulting in more bleeding (6).

The use of TXA in obstetrics is gaining worldwide recognition, but its full potential is limited due to poor understanding on how to dose the drug, timing of administration, indications for use, and potential adverse effects profile (4). To date there is no definitive recommendation regarding the efficacy and safety of routine prophylactic TXA administration at delivery vaginal or caesarean delivery (4).

STATEMENT OF THE PROBLEM

PPH is a major cause of maternal mortality in Zimbabwe. PPH is the leading cause of maternal death, contributing 21 – 43% of maternal deaths within the provinces of Zimbabwe in 2018 based on the Maternal and Perinatal Death Surveillance and Response Report (7). According to the Zimbabwe Demographic Health Survey published in 2015, the MMR for Zimbabwe is estimated at 651 deaths per 100,000 births which is among the highest in the world (8) This makes fulfilling the third Sustainable Development Goal

(SDG3) a monumental task. Target 3.1 of SDG3 aims to decrease the worldwide MMR to less than 70 per 100,000 by 2030 by ending preventable maternal mortality (9).

Caesarean birth rates have increased in developing countries to as high as 25 – 30% with an accompanying upward trend in the incidence of PPH (4). In a local unpublished thesis in 2017, virtually all of the peripartum hysterectomies were due to PPH, with the majority (67%) of the deliveries in these cases having occurred by caesarean section.

The causes of PPH are related to abnormalities in one or more of four basic processes commonly described as the four T's (tone, trauma, tissue and thrombin) (10). The most common reason for primary PPH is uterine atony (tone) accounting for about 80% of cases (10,11). Uterotonics are able to address problems with tone, but an adjunct would be required to address the other causes of PPH particularly trauma.

Currently the public health sector is underfunded. The majority, 72%, of Zimbabweans are below the poverty datum line making them unable to bear the cost of their healthcare and blood products (12).

At present, there is no clear consensus around the use of TXA for prevention of PPH. In 2017, an updated World Health Organisation (WHO) guideline recommended the use of TXA for the treatment of PPH regardless of the cause of bleeding (13).

There is no similar guideline for the use of TXA in prevention of PPH and evidence is needed to inform such a recommendation for either or both vaginal and caesarean delivery. Unlike for treatment, to date there is no definitive recommendation regarding the efficacy and safety of routine prophylactic TXA administration for prevention of PPH(4).

LITERATURE REVIEW

Literature search strategy

We updated the literature search of the review that was done between April 2017 and August 2020 for the pilot study. The initial literature search was directed at the quoted trials and references in the Cochrane review 'Tranexamic acid for the prevention of postpartum haemorrhage' by Sentilhes et. al. (1) Subsequently further articles were accessed after searching Google and PubMed in April 2017 using the

search words ‘Tranexamic acid’ and ‘Tranexamic acid for prevention of PPH’, with a further search in August 2020. I identified articles on the use of Tranexamic acid, and its use in obstetrics.

Literature review

There is a significant interest among obstetricians in finding effective tools for managing blood loss during caesarean delivery, including the use of TXA prophylactically(4).

Caesarean birth increases the risk of postpartum haemorrhage

Caesarean section in itself increases the risk for PPH with an adjusted odds ratio of 7.54 (95% CI 4.11 – 13.81), and it also increases the risk of uterine atony which is a leading cause of PPH (14).

Current WHO recommendations

WHO currently recommends the use of TXA for the treatment of PPH where oxytocin and other uterotonics fail to stop bleeding or if it is thought that the bleeding may be partly due to trauma, although WHO cautions that this is a weak recommendation supported by moderate-quality evidence(3) .

Use of tranexamic acid as treatment for PPH

The WOMAN Trial collaborators found that TXA reduces mortality due to bleeding in women with PPH after caesarean and vaginal births with no adverse effects or an increase in the incidence of thromboembolic events. In this trial, the effects of TXA as treatment of PPH on death, hysterectomy, and other relevant outcomes were reviewed. The WOMAN Trial completed in 2016 was one of the first trials to be performed that was adequately powered given the 20,060 participants. The participants received either 1g of TXA or placebo in addition to the usual care for PPH. The results showed a significant reduction in bleeding and laparotomy to control bleeding particularly when TXA was administered soon after the onset of PPH. However, TXA was not shown to prevent hysterectomy, as the decision to perform a hysterectomy is usually made after the onset of primary PPH (15)

Use of tranexamic acid in preventing PPH at vaginal delivery

The TRAAP (Tranexamic Acid for Preventing Postpartum haemorrhage after vaginal delivery), a multicentre randomized placebo-controlled trial, involved 4,079 women in labour with a planned vaginal delivery of a live baby at 35 weeks and greater. In this double-blind trial, in France, participants received

1g intravenously of TXA or placebo 2 minutes after delivery, after the initial routine intravenous dose of oxytocin. The use of TXA did not result in a significantly lower incidence of PPH compared to the use of placebo. The limitations of this trial were that the prenatal blood tests for measurement of the haemoglobin and haematocrit were mostly done in out-of-hospital laboratories without standardized timing, and the trial was underpowered to assess the effect on severe PPH of TXA (16). Also, in the context of this research, the trial looked at vaginal births as opposed to caesarean births.

Use of tranexamic acid in preventing PPH at caesarean delivery

Three recent large meta-analyses demonstrate that prophylactic TXA at the time of caesarean birth may be helpful in reducing blood loss and conferring secondary advantages(6,17,18).

Table 1: Summary of recent meta-analyses on the use of TXA for the prevention of PPH during caesarean and vaginal delivery.

STUDY	#	MOD	BLOOOD LOSS > 1000ML	TRANSFUSION	VTE
NOVIKOVA ET. AL. (2015) (17)	12	VD CD	RR, 0.28 (95% CI, 0.06–1.36) RR, 0.43 (95% CI, 0.23–0.78)*	RR, 0.33 (95% CI, 0.03–3.17) RR, 0.23 (95% CI, 0.10–0.54)*	RR, 0.98 (95%CI, 0.14–6.78)
SIMONAZZI ET. AL. (2016) (18)	9	CD	RR, 0.42 (95% CI, 0.19–0.92)*	RR, 0.33 (95% CI, 0.19–0.58)*	RR, 0.98 (95%CI, 0.13–7.09
WANG ET AL (2015)(6)	11	CD	RR, 0.43 (95% CI, 0.20–0.92)*	RR, 0.23 (95% CI, 0.10–0.57)*	

*Found to be significant, #-Number of trials, MOD-Mode of delivery, VD-Vaginal delivery, CD-caesarean delivery

Simonazzi et. al. analysed 2345 caesarean deliveries. Compared with patients who did not receive TXA, the study group had significantly less blood loss, (−160.27; 95% CI, −224.63 to−95.92), a lower drop in haemoglobin (−0.61 g/dL; 95% CI, −1.04 to −0.18), and a lower incidence of PPH and severe PPH. They also had less need for additional uterotonics (4.2% vs 7.3%; RR, 0.54; 95% CI, 0.36–0.81). The percentage of patients requiring blood transfusion during or after caesarean delivery was significantly lower in the TXA group (1.9% vs 5.7%; RR,0.33; 95% CI, 0.19–0.58). The adverse outcomes showed no significant difference: 2 patients in the intervention group and 2 in the placebo group experienced thromboembolic events (Table 1). This study was unique in that it had broader inclusion criteria, including multiple gestation pregnancies, as well as both labouring and planned caesarean deliveries. However, clinical heterogeneity

may have conflicted the results due to differences in TXA dosing, timing of intervention, and methods for measuring blood loss among the included studies (18).

A widely referenced study by Wang et al is a large meta-analysis of 11 RCTs where TXA was administered before the start of scheduled caesarean deliveries. This study also showed that TXA intervention significantly reduced intraoperative blood loss during and after caesarean delivery without an increase in thromboembolic events; this reduction was similar for both 1 g dosing and weight-based TXA dosing regimens. Similar to the meta-analysis by Simonazzi et al, prophylactic TXA was associated with a lower incidence of PPH, a smaller drop in postpartum haemoglobin, and a reduced requirement for blood transfusion (6).

A third large meta-analysis of prophylactic TXA use at the time of caesarean delivery, published as a Cochrane Review, produced similar outcomes to other large meta-analyses. For scheduled elective caesarean deliveries, TXA use was effective in reducing the incidence of PPH and blood transfusion requirements. As in other studies, gastrointestinal adverse effects, such as nausea and vomiting, were the most common adverse outcomes. Of note, the authors concluded that the studies were too small and underpowered to detect the effect of TXA on risk of maternal death or thromboembolism (17).

Similar outcomes are described among small RCTs of TXA use before caesarean delivery (19–23).

Currently ongoing is the TRAAP 2 trial which started on March 3, 2018, and is expected to be completed in 2020. The targeted sample size is 4,524, in a multicentre double-blind randomized placebo-controlled trial. One gram of TXA or placebo is administered intravenously, slowly over 30 – 60 seconds, after administration of uterotonic, after the cord is clamped, within 3 minutes after birth. The investigators will assess the incidence of PPH (blood loss exceeding 1,000ml) following caesarean delivery (24).

In a local unpublished study conducted at Parirenyatwa and Sally Mugabe Central Hospitals, the pilot to this proposed study, the incidence of PPH was significantly lower in the TXA group compared to the control group in the per protocol analysis. The primary outcome occurred in 37(22.6%) of 164 women who received tranexamic acid and in 90 (31.4%) of the participants who did not receive tranexamic acid ($p = 0.021$).

There was no significant difference in the intention-to-treat analysis. The results showed a trend towards efficacy of tranexamic acid in preventing postpartum haemorrhage (25).

The available evidence suggests that routine TXA use before caesarean delivery may be a promising drug for the prevention of PPH, decreasing blood loss, and reducing the need for additional uterotonics and product transfusion with very mild adverse effects. However, the safest and most effective dosing, infusion rate, and timing of administration have yet to be determined (4).

JUSTIFICATION

TXA is already widely used in surgery to prevent clot breakdown to reduce blood loss (1). In the third stage of labour to prevent excessive bleeding, there are strong myometrial contractions that are potentiated by oxytocin; increased platelet action; as well as a massive release of coagulation factors with a concurrent increase in fibrinolysis. TXA can counter the fibrinolytic activity thereby facilitating coagulation (17). Its actions would therefore potentiate the effect of uterotonics already in use in reducing blood loss at caesarean section.

Early activation of fibrinolysis is common after trauma and is associated with increased mortality (26). Trauma triggers the release of tissue plasminogen activator, the enzyme that converts plasminogen to the fibrinolytic enzyme plasmin (27,28). Early activation of fibrinolysis is also recorded after childbirth. Within one hour of giving birth, the serum concentration of tissue plasminogen activator doubles, possibly because of tissue damage during childbirth; thereafter, the concentration falls (29). On the basis of results of clinical trials of PPH occurring during childbirth, tranexamic acid is recommended for the treatment of primary post-partum haemorrhage if uterotonics fail to control the bleeding or if the bleeding is thought to be due to trauma(15)

TXA is cheap, already readily available, easily administered, easily stored (does not require refrigeration), and would be easy to add to routine protocols(30). It has the potential to reduce the number of deaths of mothers due to bleeding related to delivery and the undocumented consequences of the deaths on all the children who survive without a mother, husbands without their wives, and dependents without their breadwinners.

Use of TXA for PPH prevention may also contribute to a reduction in blood product use, which is associated with multiple risks such as transfusion reactions, and transmission of blood-borne microorganisms that are not routinely screened for. Blood products are also expensive. While in Zimbabwe at present obstetric patients are receiving blood products at no cost, the cost is borne by the government. The majority of patients could not afford blood transfusion if charged, as only 30% of Zimbabweans are in formal employment and the majority (72.3%) are below the poverty datum line (31). A decrease in cost of blood transfusion would result in a cost saving of $125 per unit of packed red cells. Any savings would have important implications for the underfunded health system (11,32).

PPH contributes to near-miss cases in addition to actual deaths, due to the serious complications that can occur as a consequence of serious PPH. These include adult respiratory distress syndrome, coagulopathy, shock, loss of fertility, and pituitary necrosis (Sheehan syndrome) (4). If PPH is prevented this could contribute towards reduced hospital stay, avoidance of expensive interventions for intractable PPH (such as hysterectomies and the need for blood products) and conserve our already strained resources.

Prophylactic TXA use has been shown to produce a statistically significant decrease in postpartum blood loss; however, this may not convey clinical significance in terms of transfusion rates and maternal comorbidity from severe haemorrhage. Currently, there is no consensus regarding the optimal timing or dosing of prophylactic TXA for caesarean deliveries (33).

In the light of the above, this research proposes to assess the efficacy of TXA in preventing PPH after caesarean delivery in a population large enough to be adequately powered to add to the current body of evidence. Also, there are no published RCTs, in Southern Africa reporting on TXA in obstetric patients.

GOAL STATEMENT

The aim of this study is to compare the effect of a low dose of TXA (1 g) at the time of skin incision during caesarean delivery together with prophylactic oxytocin administration, versus prophylactic oxytocin alone in an open label randomized clinical trial.

RESEARCH QUESTION

Does intravenous TXA 1g plus Oxytocin 10 IU result in a lower incidence of primary postpartum haemorrhage compared to Oxytocin 10 IU alone after caesarean section?

OBJECTIVES

1. To assess the effect of TXA (1g) on postpartum blood loss at caesarean delivery.
2. To determine the potential adverse effects of intravenous TXA administered at caesarean section.

PRIMARY OUTCOME

Incidence of PPH, defined by a calculated estimated blood loss > 1000ml or a red blood cell transfusion up to day 2 postpartum

Secondary Outcomes

- Other outcome measures describing postpartum blood loss including
  - calculated blood loss,
  - visually estimated blood loss,
  - mean/median number of units of packed red blood cells transfused,
  - incidence of postpartum shock;
  - proportion of women requiring supplementary uterotonics,
  - incidence of postpartum transfusion,
  - incidence of emergency surgery for PPH including caesarean hysterectomies,
  - mean peripartum change in haemoglobin and haematocrit as well as haemoglobin drop > 2 g/dL,
  - transfer to intensive care unit (ICU),
  - or death from any cause.
- To assess potential adverse effects of TXA:
  - Hemodynamic parameters,
  - adverse gastrointestinal events, renal, hepatic, and coagulation function,
  - and any venous or arterial thrombosis at any time during the woman's postoperative course.

METHODOLOGY

Research design

Open-label parallel randomized control trial.

Target population

Women undergoing caesarean sections at Sally Mugabe and Parirenyatwa Hospitals based on set inclusion and exclusion criteria.

Inclusion criteria

- Estimated gestational age of 37 weeks or more
- Live intrauterine foetus
- Elective or emergency caesarean delivery
- Signed informed consent

Exclusion criteria including any of the following factors or conditions identified prior to surgery

- History of coagulopathies or conditions predisposing them to thromboembolic phenomena,
- seizure history,
- autoimmune disease,
- placental abruption,
- placenta praevia,
- abnormally adherent placentae if identified on prenatal ultrasound,
- eclampsia or HELLP syndrome,
- known hypersensitivity to TXA,
- planned general anaesthesia,
- caesarean delivery for the second twin or second/third triplet(s) after vaginal birth of the first twin,
- poor understanding of English/Shona languages,
- those who have received anticoagulants in the week before delivery
- persons-under-investigation for COVID-19 and confirmed COVID-19 positive women.

Women will receive individual information in late pregnancy about the trial from obstetricians and midwives during antenatal clinic visits or from anaesthetists during the pre-caesarean visit, or both. Women may be pre-included (receive information and sign consent forms) for caesareans both before and during labour when the investigator considers that the woman is likely to have a caesarean delivery. The aim of pre-inclusion is to facilitate recruitment, particularly the recruitment of caesareans during labour, which may be decided upon and performed in emergency situations. Women recruited prior to emergency caesarean delivery (in labour) sign consent to have the caesarean section while in labour. We therefore consider that having received information about the trial during the antenatal period and on the labour ward, they will also be able to provide informed consent for inclusion into the trial at the same time.

Study Setting

The study will be performed at two tertiary institutions that are affiliated to the University of Zimbabwe that serve as referral centres for clinics located in Harare as well as district and provincial hospitals in the surrounding provinces: Sally Mugabe Central Hospital Maternity Unit and Parirenyatwa Group of Hospitals i.e. Mbuya Nehanda Maternity Hospital (MNMH). Most of these patients understand both English and Shona languages.

Sample size

The sample size has been calculated assuming a proportion of 2.1% PPH in the experimental group and 5.8% (34) in the control group at 95% confidence interval and 90% power using the Fleiss formula giving a minimum sample size of

$$n = \frac{[Z_{\frac{\alpha}{2}}\sqrt{(r+1)\bar{p}\bar{q}} + Z_{\beta}\sqrt{rp_1q_1 + p_2q_2}]^2}{r(p_1 - p_2)^2}$$

$$n = \frac{\left[1.96\sqrt{(1+1)\times 0.0395\times 0.9605} + 1.28\sqrt{0.021\times 0.979 + 0.058\times 0.942}\right]^2}{(0.021-0.058)^2}$$

$= 581\ per\ group$

Thus, total minimum sample size $\boldsymbol{N} = \mathbf{1,162}$ women

Where: n = sample size

Z_{α} = 1.96 at 95% confidence interval

α = probability of a type I error (significance level) = 0.05

β = probability of a type II error (1 – power of test)

p_1 = proportion of PPH in the experimental group = 0.021

p_2 = proportion of PPH in the control group = 0.058

r = ratio of control group/population 2 to experimental group/population 1

q = 1-p

Randomization

A randomized allocation to study and control groups using computer-generated random numbers will be prepared by the trial statistician.

Pharmacy Plan

Oxytocin iv is dispensed weekly from the pharmacy to theatre, where it is stored in a refrigerator in the custody of the sister in charge. All patients undergoing caesarean delivery routinely receive 10IU oxytocin iv, administered slowly by the anaesthetist after delivery of baby at Sally Mugabe Hospital Maternity Unit and Mbuya Nehanda Maternity Hospital. Cold chain will be maintained up to the administration of drug to the patient.

TXA obtained for the study will be kept in theatre. This is to ensure an uninterrupted supply of the drug for the study. The TXA vials will be kept in theatre in a locked drug cupboard accessible to the researcher and research assistants at the authorization of the sister in charge. A dispensing register for the drugs will be kept together with the drugs. Patient details and study number, amount of TXA dispensed and wasted will be entered into the study register for accountability and to guard against abuse.

Intervention

The participants in the intervention arm will receive generally from the anaesthetist or nurse anaesthetist TXA (1g), administered slowly (over 30 – 60seconds) at the time of skin incision. Participants in both the intervention arm and control group will receive the routine prophylactic 10 IU oxytocin intravenously at birth of the baby. All other aspects of management of the caesarean section will be identical in both arms (34).

Other aspects of the caesarean delivery

- The surgical team will decide on the administration of additional uterotonics and the management of PPH, in a manner consistent with local guidelines. In particular, the use of TXA for the treatment of PPH will be allowed and left to the practitioner's discretion according to the hospital protocol.
- Because the surgeon's level of experience may affect estimated blood loss during or after a caesarean delivery, the obstetrician's experience, categorized as senior resident medical officer, senior house officer, junior registrar, senior registrar or consultant will be recorded (34).

Assessment

Data will be collected and recorded on the data collection tool. Any adverse event will to be reported on the IRB adverse event reporting form.

Primary outcome measure

Estimated blood loss (EBL) will be determined using haematocrit, haemoglobin, and visual estimates.

Calculated estimated blood loss = estimated blood volume × (preoperative haematocrit – postoperative haematocrit) / preoperative haematocrit. Where estimated blood volume (mL) = weight (kg) × 85).

The calculation is an objective measure to estimate blood loss because of the inaccuracy of other methods used to determine blood loss and caesarean delivery(35).

Preoperative haematocrit will be determined on the day before elective caesarean or on the day of emergency caesarean delivery. Postoperative haematocrit will be the haematocrit obtained by blood sampling at D2 (on the second morning after caesarean section). If haematocrit is not available at D2, then haematocrit at D3 will be considered; if it is also missing, then the postpartum haematocrit closest to D2 in the absence of transfusion will be considered (36,37).

All women who receive RBC transfusion for PPH between delivery and D2 postpartum are defined to have PPH and meet the criteria for the primary outcome. Calculated blood loss is impossible to determine for these women. Moreover, women only rarely receive an RBC transfusion for a blood loss less than 1000 ml. As a marker of significant maternal morbidity, RBC transfusion is considered equivalent or superior to blood loss greater than 1000 mL(25).

Although visual estimation is the method used frequently by anaesthetists to estimate blood loss, it has been demonstrated as inaccurate in repeated studies. The estimate of blood loss is affected by amniotic fluid as well. Its continued use in clinical practice is likely related to tradition and it being easily used. We will also take note of the visual estimate made by the anaesthetist, and by the operating surgeon, as this is the method used locally(6,38)(39)

Secondary outcome measures

Describing postpartum blood loss

1. Clinical
    a. Visually estimated blood loss
    b. proportion of women requiring supplementary uterotonic treatment
    c. incidence of postpartum transfusion
    d. mean number of RBC units transfused
    e. incidence of emergency surgery for PPH including caesarean hysterectomies
    f. incidence of hypovolemic shock related to PPH as determined by assessing BP and pulse
    g. incidence of transfer to ICU
    h. incidence of maternal death from any cause
    i. length of hospital stay.
2. Laboratory
    a. incidence of calculated blood loss > 500 mL and > 1500 mL
    b. mean total calculated blood loss
    c. mean peripartum change in haemoglobin (difference between haemoglobin before delivery and at D2)
    d. Haemoglobin drop > 2 g/dL (between haemoglobin before delivery and at D2) (34).

Describing adverse events

1. Clinical
    a. Hemodynamic parameters (heart rate, blood pressure) 15, 30, 45, 60, and 120 min after delivery

b. the occurrence of potential mild adverse effects of TXA in the operating room:
    i. nausea
    ii. vomiting
    iii. sensation of rings or spots of light in visual field
    iv. dizziness
c. the occurrence of potential severe adverse effects of TXA during the hospital stay and up to discharge
    i. deep vein thrombosis, if the diagnosis is confirmed by Doppler ultrasound
    ii. pulmonary embolism, if the diagnosis is confirmed by radiological examination
    iii. myocardial infarction
    iv. seizure
    v. renal failure requiring dialysis
d. any other unexpected adverse events

Data Management

The researcher and assistants will allocate each patient codes. No identifiers will be used. Any data collected will be stored in an office accessible only to the researcher and research assistants, as well as on a password-protected laptop computer.

data cleaning and entry

Completed questionnaires will be checked for validity, accuracy and completeness by the principal investigator before data entry into the computer.

Statistical methods and data reporting

Data analysis and reporting will be guided by the Consolidated Standards of Reporting Trials (CONSORT) and will be done by the researchers with the assistance of the statistician. (34).

The women's demographic characteristics and standard risk factors for PPH will be compared between the two groups.

The main analysis of the primary and secondary outcomes will be performed in the modified intention-to-treat (ITT) population, defined as women who undergo randomization and have a caesarean delivery (except if they withdraw consent or are deemed ineligible after randomization).

We will also analyse two separate per-protocol populations: women from the modified ITT population receiving a uterotonic and TXA (as specified in the protocol) (per-protocol group 1); the other will include women from the modified ITT population receiving a uterotonic and then tranexamic acid or no TXA in the 10min after delivery (per-protocol group 2; for a situation more consistent with routine clinical practice). The baseline characteristics of the trial participants, the management of the third stage of labour, and protocol adherence will be compared by descriptive statistics.

Quantitative variables will be expressed, as appropriate, as means with standard deviations (and compared by Student's t-test) or as medians with interquartile ranges (compared by the Wilcoxon rank-sum test). Chi-square or Fisher's exact tests will be used, as appropriate, to compare categorical variables. The effects of TXA will be expressed as relative risks with 95% confidence intervals for categorical outcomes and as mean differences with 95% confidence intervals for quantitative outcomes. The results will also be expressed as absolute risk differences with 95% confidence intervals for binary outcomes.

Two specified subgroup analyses will examine the primary outcome in subgroups of women at high risk of PPH. The subgroups will include women who undergo a caesarean during labour and those who are at risk for PPH according to a composite definition (having at least one risk factor with an odds ratio of 3 or greater in the literature (34) history of any of PPH, hypertensive disorder of pregnancy, multiple pregnancy, or caesarean during labour). Moreover, prespecified subgroup analyses will examine the secondary outcomes in the subgroup of women who undergo a caesarean during labour. We will use the Benjamini–Hochberg procedure to adjust for multiple comparisons of secondary outcomes or subgroups (34). A statistical test may be significant by chance but in reality, not significant. The Benjamini-Hochberg method is used to control for this false discovery rate in statistical tests. Statistical analysis will be conducted using Stata v16.

Feasibility

Prior to the COVID 19 pandemic HMH delivered 1,335 pregnancies while a total of 535 pregnancies per month were delivered at MNMH. On average 60 elective and 250 emergency caesarean sections were done at HMH per month, while 80 elective and 210 caesarean deliveries on average are done at MNMH. Based on a review of the theatre delivery records during the period from April 2020 to August 2020 an average of 154 emergency caesarean sections were done monthly at MNMH, while an average of 149 emergency cases were done at HMH. During this COVID period an average of 303 caesarean sections are being done per month. About 90% of these meet the inclusion criteria. Assuming a participation rate of 50% of these, an inclusion period of 8 months should make it possible to recruit 1,162 participants. Given that the lockdown conditions are being eased, with staff returning after industrial action, and that the hospitals are slowly reintroducing antenatal clinics, there should be an increase in caesarean sections (elective and emergency) across both institutions which may allow us to reach the targeted number in a shorter time period.

Impact of COVID-19

Coronavirus disease 2019 (COVID-19) has led to the deadliest pandemic observed in over 100 years (40). Healthcare workers and potentially researchers in obstetric wards are at a particularly increased risk for occupational exposure due to long periods of interaction with patients during labour, patient care involving multiple team members, the unpredictable occurrence of sudden obstetrical emergencies with their potential for unanticipated intubations in women undergoing labour and delivery. Presence on an obstetrical ward presents a real risk for infection to the research team (41).

At the point of recruitment, the researcher and team will employ a combination of standard contact and droplet precautions, with further precautions undertaken during aerosol-generating procedures such as recruitment of patients in labour (42).

The standard precautions are used to prevent or minimize transmission at all times. These include hand hygiene, appropriate use of personal protective equipment (PPE), safe handling of sharps, respiratory hygiene, occupational health and injection safety (42).

Transmission-based precautions – droplet or contact include:

- hand hygiene which is the most essential aspect

- PPE which consists of gloves, gown, and a medical mask
- Safe waste management (42).

Aerosol-generating procedures include women in labour. Precautions while recruiting and consenting women in labour include:

- Researchers wearing PPE – gloves, gown, fit-tested particulate respirator (N95 respirator) and eye-protection (goggles or face shield)
- Interviews in adequately ventilated rooms (42).

We will review the screening questionnaire for COVID-19 that is part of the standard triage form at our healthcare facilities. We will not recruit persons under investigation (PUI) or confirmed COVID-19 positive women. This is largely because of the knowledge gaps that currently exist as well as the potential for increased thrombotic events in COVID-19 patients which would potentially exacerbate or mask the potential adverse effects of TXA. High levels of d-dimers have been reported with 28-day mortality in patients with infection or sepsis. Contributory mechanisms include systemic pro-inflammatory cytokine responses that are mediators of atherosclerosis directly contributing to plaque rupture through local inflammation, induction of procoagulant factors, and haemodynamic changes, which predispose to ischaemia and thrombosis. In addition, angiotensin converting enzyme 2, the receptor for SARS-CoV-2, is expressed on myocytes and vascular endothelial cells, so there is at least theoretical potential possibility of direct cardiac involvement by the virus (43).

Independent Data and Safety Monitoring Board

An Independent Data and Safety Monitoring Board (DSMB) has been established for the study comprising of 3 individuals: Professor S. Rusakaniko (Statistician) [DSMB chair], Dr M. Madziyire (Obstetrician & Gynaecologist), and Dr T. Marere (Obstetrician & Gynaecologist).

The DSMB has been established to assess at intervals the progress of the clinical trial, the safety data, and the critical efficacy endpoints, and to recommend to the sponsor whether to continue, modify, or stop the trial.

Stopping Rules / Discontinuation Criteria

If at any stage during the trial the principal investigator, co-investigators (supervisors), DSMB, or ethical authorities are satisfied that having due regard to the initial risks, discomforts or other adverse effects caused to persons taking part in the trial it is in the public interest to stop or suspend the trial, the trial shall be stopped or suspended immediately. The DSMB or ethical authorities will notify the investigator in writing accordingly. Ethical authorities as well as the hospital authorities will be notified accordingly as well by the investigator.

ETHICAL CONSIDERATIONS

Approval to conduct the study and to use the hospital records of patients shall be sought from the following:

1. Parirenyatwa Group of Hospitals
2. Sally Mugabe Central Hospital Research and Ethics Committee
3. Medical Research Council of Zimbabwe (MRCZ)
4. Medicines Control Authority of Zimbabwe (MCAZ)

Participants will be requested to provide informed consent shall be sought from all the participants. Women in the study will receive full disclosure of the nature of the study, the risks, benefits and alternatives. They will be given an opportunity to ask questions. No participant will be coerced into participation. Participants will be assured that no punitive implication or denial of service shall be encountered in the event she declines and that at any time she can decide to withdraw her participation. The researcher will liaise with the team managing the patient to continue the usual care even when the patient is not willing or withdraws participation. The patient will be free to communicate with the researcher if she feels she did not get due treatment. The study shall only use coded numbers with no personal identifiers to ensure confidentiality.

Timeline

The clinical trial will run over 12 months. The initial four months will be used to obtain ethical approval for study. Approximately six months will be spent recruiting study participants and collecting and entering data. With the help of a bioinformatician I will analyse the data in preparation for dissemination in the last two months of the study.

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