EFFICACY OF TRANEXAMIC ACID IN PREVENTING POSTPARTUM HAEMORRHAGE AFTER ELECTIVE CAESAREAN SECTION

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NCT03463993

STUDY PROTOCOL AND STATISTICAL ANALYSIS PLAN

PRINCIPAL INVESTIGATOR

DR CHIPO GWANZURA

CO-INVESTIGATORS

DR TAAZADZA NHEMACHEMA & PROFESSOR TSUNGAI CHIPATO

DEPARTMENT OF OBSTETRICS AND GYNAECOLOGY

COLLEGE OF HEALTH SCIENCES

UNIVERSITY OF ZIMBABWE

30 June 2019

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ABBREVIATIONS

ACOG	The American College of Obstetricians and Gynaecologists
AIDS	Acquired Immune Deficiency Syndrome
AMCHA	1-(aminomethyl)-cyclohexane-4-carboxylic acid
AMTSL	Active management of the third stage of labour
ANW	Antenatal Ward
BMI	Body Mass Index
BNF	British National Formulary
BP	Blood Pressure
CI	Confidence Interval
CONSORT	Consolidated Standards of Reporting Trials
DSMB	Data and Safety Monitoring Board
EACA	Epsilon-amino-caproic acid
EBL	Estimated blood loss
EBV	Estimated blood volume
ELW	Early Labour Ward
FBC	Full Blood Count
FIGO	International Federation of Gynaecologists and Obstetricians
g	gram
Hb	Haemoglobin
HCT	Haematocrit
HMH	Harare Maternity Hospital
IM	Intramuscularly
IQR	Interquartile range
IU	International Units
IV	Intravenously
JREC	Joint Research and Ethics Committee for the University of Zimbabwe, College of Health Sciences and Parirenyatwa Group of Hospitals

kg	kilogram
LFT	Liver Function Test
LW	Labour Ward
MCAZ	Medicines Control Authority of Zimbabwe
µg	microgram
mg	milligram
ml	millilitre
MMR	Maternal Mortality Ratio
MNMH	Mbuya Nehanda Maternity Hospital
MRCZ	Medical Research Council of Zimbabwe
mRNA	messenger ribonucleic acid
NICE	National Institute of Health and Care Excellence
NICU	Neonatal Intensive Care Unit
NNU	Neonatal Unit
PCW	Post-caesarean section Ward
PNA	Postnatal ward A
PNB	Postnatal ward B
PPH	Postpartum Haemorrhage
Pvt Ltd	Private Limited
RAMOS	Reproductive Age Mortality Studies
RCOG	Royal College of Obstetricians and Gynaecologists
RCT	Randomized Controlled Trial
RR	Relative risk
SD	Standard deviation
SDG	Sustainable Development Goal
SRMO	Senior resident medical officer (intern)
SHO	Senior House Officer
TRAAP	Tranexamic Acid for Prevention of Postpartum haemorrhage
TXA	Tranexamic Acid

U&E	Urea and Electrolytes
WHO	World Health Organization
WMD	Weighted mean difference
WOMAN	World Maternal Antifibrinolytic
ZMPMS	Zimbabwe Maternal and Perinatal Mortality Study

CHAPTER 1. INTRODUCTION

1.1. POSTPARTUM HAEMORRHAGE

1.1.1. THE SCALE OF THE PROBLEM OF POSTPARTUM HAEMORRHAGE

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]. At 546 per 100, 000 live births, the maternal mortality ratio (MMR) for the Sub-Saharan region is the highest in the world [2]. This makes fulfilling the third Sustainable Development Goal (SDG3) a monumental task. Target 3.1 aims to decrease the worldwide MMR to less than 70 per 100,000 by 2030 by ending preventable maternal mortality [2].

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 extremely high [4]. However, these statistics are derived from the sisterhood method, an indirect method recommended by the World Health Organization (WHO) for developing countries. The costs of full surveillance programs in these countries would be expensive and unrealistic. The estimate may therefore not be accurate [5]. PPH is the second most common cause of maternal death, contributing 14.4% of maternal deaths second to AIDS-defining conditions based on a Zimbabwean cross-sectional study in 2007 [6]. It is important to note that this study was done 12 years ago and data collection was done using a facility birth survey as well as the Reproductive Age Mortality Studies (RAMOS) method, which made the estimate reliable [7]. The update of this study will be available soon from the ongoing Zimbabwe Maternal and Perinatal Mortality Study (ZMPMS 2018-9). Given the magnitude of the problem of PPH in Zimbabwe, its prevention would go a long way in reducing the MMR in Zimbabwe.

Caesarean sections are associated with greater blood loss than vaginal deliveries. Worldwide there has been an increase in the caesarean section rate. This could increase the risk of morbidity and mortality from PPH especially among anaemic women [8]. PPH affects about 5% of all woman giving birth globally, 3.9% of women after vaginal delivery and 6,4% of women after caesarean delivery, and it occurs in any setting [3, 9]. PPH at caesarean section is frequently underestimated. It is documented as occurring in more than 5 - 10% of caesarean deliveries [10]. The incidence of PPH in Zimbabwe is not known. In a retrospective descriptive study done at Mpilo Central Hospital in Bulawayo, the incidence was found to be 1.6%. This was low in comparison to 4.5%, in a low-resource hospital in Nigeria, 9% in Uganda, and 6.4% in a developed country, the Netherlands [11].

It is not an effective health strategy to screen for high-risk women to deliver in specialized facilities as most women who succumb to PPH have no identifiable risk factor. Patients with risk factors for PPH however would do well to deliver in a facility that at least has access to blood and an operating theatre. What is efficacious is immediate access to quality care for all women giving birth. This includes providing adequate vital medications, stocks and equipment at any location to enable the delivery of first-line PPH management [12].

Endeavours to prevent and decrease morbidity and mortality due to PPH by using interventions such as uterotonics and tranexamic acid (TXA), can assist in addressing the profound inequities in maternal and perinatal health globally [13].

1.1.2. PREVENTION OF POSTPARTUM HAEMORRHAGE AT CAESAREAN SECTION

There are various strategies employed to manage the third stage of labour to prevent excessive bleeding from the genital tract. For PPH prevention, the only intervention shown to be effective is the

administration of uterotonics [3]. The World Health Organization recommends one of the following uterotonics during caesarean births:

- Oxytocin 10IU IM/IV
- Carbetocin 100µg IM/IV where it is cost effective to use it
- Misoprostol 400 or 600 µg orally
- Where hypertensive disorders have been safely excluded
    - Ergometrine/methylergometrine (200 µg, IM/IV)
    - Fixed-dose combination of oxytocin and ergometrine (5 IU/500 µg, IM) [3].

Clinicians often extend prophylaxis where high-risk factors such as multiple pregnancy, fibroid uterus, and manual removal of the placenta are present. The prophylaxis includes infusions of 40IU of oxytocin in a crystalloid over 4 hours [27]. The effectiveness of this has not been proven in randomized controlled trials. In addition, many patients who deliver at emergency caesarean section have been shown to have a loss of oxytocin receptors within the myometrium evidenced by the decrease in binding sites and very low mRNA concentrations [27]. This could be the reason why there is likely to be more bleeding at emergency caesarean delivery.

The Royal College of Obstetricians and Gynaecologists of the United Kingdom (RCOG) recommends practitioners to consider TXA (0.5 - 1.0g) in addition to oxytocin at caesarean delivery to prevent PPH [28]. TXA was effective in decreasing the incidence of blood loss greater than 1,000 ml in women who had undergone caesarean section (relative risk (RR) 0.43, 95% confidence interval (CI) 0.23–0.78) in four studies with 1,534 women [29]. The authors of the Cochrane review, however, concluded that more studies needed to be done. TXA could, therefore, be added to the current uterotonic drugs given in the third stage of labour, particularly in women at high risk of PPH, for instance, those with multiple pregnancy, anaemia, placenta praevia and placental abruption [29].

1.2. TRANEXAMIC ACID

1.2.1. RATIONALE OF USING THE DRUG AT CAESAREAN DELIVERY

The chemical 1-(aminomethyl)- cyclohexane-4-carboxylic acid (AMCHA), commonly known as tranexamic acid, or the common trade name of Cyklokapron, or Lysteda, is a synthetic derivative of the amino acid lysine [30, 31].

In the haemostatic process, the balance between the coagulation and fibrinolytic systems maintains an intact vascular system. Once damage occurs to a vessel, coagulation occurs rapidly to form a tight net of fibrin at the site. Concurrently the fibrinolytic system removes fibrin deposits that could cause vascular occlusion permanently once repair of the vessels has occurred. As a potent antifibrinolytic agent, TXA acts by blocking the lysine-binding sites on plasminogen molecules, thereby displacing them from fibrin, effectively competitively inhibiting the activation of plasminogen. It has the potential to enhance the patient's haemostatic mechanisms. Consequently, clot breakdown is inhibited and bleeding is reduced [1].

1.3. STATEMENT OF THE PROBLEM

As is the case in other developing countries, PPH is a major cause of mortality in Zimbabwe. PPH is the second most common cause of maternal death, contributing 14.4% of maternal deaths second to AIDS-defining conditions based on a Zimbabwean cross-sectional study in 2007[6]. 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 extremely high [4]. This makes fulfilling the third Sustainable Development Goal (SDG3) a monumental task. Target 3.1 aims to decrease the worldwide MMR to less than 70 per 100,000 by 2030 by ending preventable maternal mortality [2].

In confidential enquiries into maternal deaths in South Africa from 2005 to 2007, 383 maternal deaths due to PPH were reported with the majority considered preventable. Of the deaths, 17.5 % (67) were due

to uterine atony, where uterotonics would have been effective to control the bleeding, 21 % due to uterine rupture, 23% due to retained placenta, 0.02% due to uterine inversion, and 37% due to genital trauma including Caesarean section [29]. Uterine atony contributed to a small proportion of the deaths. Therefore, attempts to address the problem should go beyond the use of uterotonic drugs.

1.4. RESEARCH QUESTION

Does intravenous Tranexamic Acid (TXA) 10mg/kg plus Oxytocin 5IU result in a lower incidence of primary postpartum haemorrhage compared to Oxytocin alone after elective caesarean section?

CHAPTER 2. LITERATURE REVIEW

2.1. LITERATURE SEARCH STRATEGY

Interest in the research topic was triggered after a review of the article published in the British Journal of Anaesthesia 'Tranexamic acid for the prevention and treatment of postpartum haemorrhage' [(1)]. Therefore, the initial literature search was directed at the trials quoted and references listed in the systematic review article. Subsequently, further articles were accessed after searching Google and PubMed in April 2017 initially, and in 2019 using the search words 'Tranexamic acid' and 'Tranexamic acid for the prevention of PPH'. Relevant articles on the use of tranexamic acid and its use in obstetrics were identified.

2.2. LITERATURE REVIEW

2.2.1. CAESAREAN BIRTH INCREASES PPH RISK

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 according to Ononge et. al. [(39)]. In a local unpublished study in 2017, virtually all of the peripartum hysterectomies were due to PPH, with the majority (67%) of the deliveries being by been by caesarean section [(40)].

2.2.2. 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 asserts that this is a weak recommendation supported by moderate-quality evidence [(3, 12)].

2.2.3. EVIDENCE ON USE OF TRANEXAMIC ACID IN OTHER SURGICAL CONTEXTS

Regardless of the type of surgery (cardiac, orthopaedic, hepatic, urological, and vascular), in a systematic review of RCTs including 20,781 participants, TXA was shown to reduce the risk of transfusion of blood by 39% [RR 0.61 (95% CI 0.54–0.69)], and the number of units transfused by 1.1 units (95% CI 0.64–1.59). The review also showed a statistically insignificant trend towards benefit on the need for re-laparotomy due to haemorrhage [RR 0.67 (95% CI 0.41–1.09)] [(1)].

A meta-analysis of 129 RCTs evaluating the impact of TXA in the prevention of bleeding at elective surgery of 10,488 participants showed a reduction of the need for a blood transfusion by 38% [RR 0.62(95%CI 0.58–0.65)]; regardless of the type of surgery [(1)].

The administration of TXA reduced mortality in bleeding trauma patients in high-, middle-, and low-income countries in the Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage (CRASH-2) trial [(1)].

Treatment with TXA has also been shown to reduce by 26 – 54% (a material reduction) bleeding in women with menorrhagia[(1)]. This suggests that TXA can reduce bleeding from the uterus even in low amounts in a non-surgical scenario. The latter provides evidence to support the hypothesis that TXA is useful for the prevention of PPH after vaginal and caesarean births.

2.2.4. CURRENT EVIDENCE ON THE USE OF TRANEXAMIC ACID IN PREVENTING PPH

In a randomized controlled trial (RCT) by Sujata and colleagues in 2016 of TXA among 60 parturients at increased risk of PPH undergoing elective or emergency caesarean delivery at a tertiary centre in India from August 2012 to April 2013, intravenous TXA 10mg/kg administered 10 minutes before skin incision significantly reduced the requirement for additional uterotonics within 24 hours (the primary outcome). Additional uterotonics were required in 23% of the patients assigned to TXA compared to 83% of patients given placebo (P<0.001). The trial, however, was small with only 60 participants, and anaesthetists were not blinded even though the patients and obstetricians were blinded to the interventions [(41)].

A Cochrane database review by Sentilhes et. al. in 2015 found 10 RCTs evaluating the use of TXA in preventing PPH after caesarean birth. In all except one, caesareans were elective. The 10 RCTs all reported that women who received TXA had significantly less blood loss without any change in blood pressure, pulse and respiratory rate, or thrombosis. However, all the studies had several limitations that included being single-centre trials, not having a placebo in three, eight not clearly stating the primary outcome, and some quasi-randomized [1].

The two most reliable studies in the review are summarized.

1. The first large double-blind RCT was reported by Gungorduk and colleagues in Turkey. The trial had an intention-to-treat analysis that included 660 women. This study had the most robust methodology. The primary outcome, estimated blood loss (EBL), was calculated by comparing the difference in haematocrits prior to and 48 hours after caesarean section. The reduction in bleeding at ceasarean delivery attributed to TXA was significant [mean 499.9 (SD 206.4) ml vs 600.7 (215.7), P=0.001]. It also reduced the percentage of patients with blood loss more than 1000 ml [2.1% vs 5.8%; RR 2.7] (95% CI 1.1–6.3), P=0.03], and the requirement for supplementary uterotonics [8.5% vs 14.5%; RR 1.7 (95% CI 1.1–2.6), P=0.02]. The study enrolled 88% of eligible patients and had no patients lost to follow-up. The findings suggest TXA may be beneficial in decreasing blood loss after caesarean delivery and haemorrhage [1, 38].
2. In Egypt, a large (740 participants), open RCT was conducted by Abdel-Aleem and associates. The decrease in the average blood loss in the experimental group was statistically significant [241.61 (SE 6.77) ml], compared to the control group [510.66 (SE 7.72) ml; weighted mean difference (WMD) - 269.0 (95% CI 288.6 to -249.5)]. When assessed 24 hours after the caesarean section, haemoglobin [- 0.48 (SD 0.87) vs -1.42 (1.16) g/dl, P=0.001] and haematocrit [-1.82% (SD 2.93) vs -4.30% (3.64), P=0.001] values had decreased less significantly in the TXA group compared to the control group. Nevertheless, the trial was not blinded and did not use a placebo [1].

Sentilhes and colleagues recommended adequately powered large multicentre RCTs as the quality of the evidence from the trials in their systematic review was unclear. They recommended interpreting the results with caution before the widespread use of TXA to prevent and treat PPH is recommended [(1)].

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 [(42)]. Also, in the context of this research, the trial looked at vaginal births as opposed to caesarean birth.

Currently ongoing is the TRAAP 2 trial which started on March 3, 2018, and is expected to be complete on June 30, 2020. The targeted sample size is 4,524, in a multicentre double-blind randomized placebo-controlled trial. One gram of TXA or placebo is being administered slowly over 30 – 60 seconds intravenously to the woman 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 [(43)].

In a prospective RCT in Nepal published in 2019, a developing country like Zimbabwe, the use of 1g of TXA administered intravenously 10 minutes before caesarean section, was associated with a significantly lower blood loss intra- and post-operatively when compared to placebo (392.13 ml±10.06 vs 498.69 ml±15.87, respectively; $p<0.001$). However, the sample size of 160 was small, and the trial was not adequately

powered to reach conclusions on the incidence of thromboembolic complications, use of additional oxytocics, and the need for blood transfusion [44].

The use of an intravenous dose of 15mg/kg 10 minutes before caesarean TXA combined with 100 µg of carbetocin intravenously after cutting the cord, and technical support (argon plasma coagulation) was noted to be effective in reducing haemorrhage around the time of surgery, duration of surgery, and postoperative stay in hospital in patients having repeat caesarean deliveries in a prospective cohort study in Ukraine that comprised 71 participants [45]. This study, however, looked at the use of three different interventions, 2 medical, and one newer intervention in caesarean sections, argon plasma coagulation which is a non-contact thermal method of haemostasis currently being studied in Russia. The technology is known to produce prompt haemostasis, to decrease blood loss and pain as well as hospital stay, effects which may be difficult to attribute to TXA solely in this study [46].

Uterine atony is the most common cause of PPH [13]. Uterotonics already address this as they have an effect on the myometrium. Their contractile effects close off the large spiral arteries pouring with blood from the placental bed. 40 – 70% of women with marked clotting disorders will not have PPH as the main mechanism for achieving haemostasis after childbirth is myometrial contraction compressing the uterine vessels rather than clotting. Clotting is the primary mechanism that would be useful where women have the deadly form of ongoing or delayed PPH. In this subgroup of women, bleeding is from spontaneous or iatrogenic lacerations to the genital tract, or trauma and they tend to bleed vaginally or into the abdomen. With its antifibrinolytic activity, TXA potentiates clotting thereby preventing PPH in this subset. This is the group of women who tend to collapse 1 – 3 hours after delivery from the deadly ooze. This subgroup of women is the group in which TXA was found to have the maximum effect in the WOMAN Trial [13]. It follows, therefore, that women with iatrogenic trauma at caesarean section are also likely to benefit from this intervention.

2.3. JUSTIFICATION

TXA is already widely used in surgery to prevent clot breakdown to reduce blood loss. However, at present, there is little reliable evidence from randomized trials of the effectiveness of TXA in preventing PPH at caesarean section.

Bleeding during and after caesarean section contributed the majority of deaths (34.9% i.e. 218 of 624 deaths) due to obstetric haemorrhage in South Africa in the period 2014 – 2016, and has been quoted as a national emergency [47, 48]. Therefore, TXA as an additional measure to reduce blood loss at caesarean delivery should be considered [48].

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 [24]. Its actions would therefore potentiate the effect of uterotonics already in use in reducing blood loss at caesarean section.

TXA is cheap, readily available, easily administered, easily stored (does not require refrigeration), and would be easy to add to routine protocols [29]. See A in **Error! Reference source not found.**. It would 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 preventing PPH may contribute to the reduction of 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 would not afford it as only 30% of Zimbabweans are in formal employment and the majority (72.3%) are below the poverty datum line [49]. A unit of packed cells that costs $120 ($335 in private hospitals), platelets $90 ($251), and fresh frozen plasma $90 ($251) means more resources can be diverted to other health service expenditures. Refer to B in **Error! Reference source not found.**.

PPH contributes to near-miss cases due to the serious illness that can occur as a consequence that includes adult respiratory distress syndrome, coagulopathy, shock, loss of fertility, and pituitary necrosis (Sheehan syndrome) [14, 27]. 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.

In the light of the above, this research attempts to assess the efficacy of TXA in preventing PPH after caesarean delivery in a large enough population to be adequately powered to add to the current body of evidence, in Southern Africa where no regional studies have been done to assess TXA in obstetric patients.

2.4. RESEARCH OBJECTIVES

1. To determine the effect of TXA (10mg/kg) given intravenously 10 minutes prior to an elective caesarean section on postpartum blood loss.
2. To determine the potential adverse effects of intravenous TXA given 10 minutes prior to elective caesarean section.

CHAPTER 3. RESEARCH METHODS

1.1. RESEARCH DESIGN

Open-label parallel randomized control trial in which women included in the trial were assigned either TXA or no TXA. No changes were made to the trial design after commencement.

1.2. PARTICIPANTS

The participants were women undergoing elective caesarean sections at Harare and Parirenyatwa Hospitals.

Inclusion criteria

- Pregnant woman with signed informed consent***
- Understand English and/or Shona
- Estimated gestational age of 38 weeks or more
- Requiring Elective Caesarean Section defined as caesarean section performed before onset of labour
- Live intrauterine foetus

***The study enrolled participants who met the inclusion criteria including minors. Consent was sought from legally authorized representatives such as the parent or guardian where possible. Where this was not possible the pregnant participants who were under the age of 18 were considered emancipated minors by them having assumed adult responsibilities (becoming a mother) before 18 years of age [50].

Exclusion criteria

Women with the following characteristics were excluded from the study:

- Placental Abruption

- Emergency caesarean section
- Current or previous history of significant disease including heart disease, liver, renal disorders
- Known coagulopathy or history of deep venous thrombosis and/or pulmonary embolism, or arterial thrombosis (angina pectoris, myocardial infarction, stroke)
- History of epilepsy or seizures
- Autoimmune disease
- Sickle cell disease
- Intrauterine foetal demise
- Eclampsia/HELLP syndrome
- Administration of anticoagulants – clexane or antiplatelet agents in the week before delivery

1.3. STUDY SETTING

The trial was conducted at two tertiary institutions that are affiliated to the University of Zimbabwe. These serve as referral centres for 12 local authority clinics located in Harare as well as district and provincial hospitals in the surrounding provinces: Harare Central Hospital i.e. Harare Maternity Hospital (HMH) and Parirenyatwa Group of Hospitals i.e. Mbuya Nehanda Maternity Hospital (MNMH). Most of the patients understood at least one of either English or Shona languages.

Located in the Southerton suburb, HMH is the referral centre for pregnant women mainly from the southern and western suburbs of Harare. The unit has an Antenatal Ward (ANW), Labour Ward (LW), Early Labour Ward (ELW), Post Natal Ward A (PNA) for patients after vaginal delivery and Post Natal Ward B (PNB) for patients post caesarean delivery. Babies with complications are admitted in the Neonatal Unit (NNU).

The northern and eastern suburbs are served by MNMH which is located in Avondale suburb. The unit has an ANW, a LW, Post Caesarean Section Ward (PCW) and a Postnatal Ward (PNW). Ill babies are admitted in the Neonatal Intensive Care Unit (NICU).

There are five teams with 3 to 4 consultants each at MNMH and 5 teams at HMH each with 2 to 4 consultants. MNMH delivers a total of 535 pregnancies per month while HMH delivers 1,335. On average 60 elective and 250 emergency caesarean sections are done at HMH per month, while 80 elective and 210 caesarean deliveries on average are done at MNMH. Refer to C in **Error! Reference source not found.**.

Elective caesarean sections are performed by Senior House Officers and Registrars (including the principal investigator) mainly, with some cases performed by Senior Resident Medical Officers (in their second year of internship) or Consultants (usually in cases that have complications or serious concurrent medical/obstetric indications).

1.4. SAMPLE SIZE

The sample size was calculated assuming a proportion of 2.1% PPH in the experimental group and 5.8% in the control group [38] at 95% confidence interval and 90% power using the Fleiss formula giving a minimum sample size of

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

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

$$= 581\ per\ group$$

Thus, total minimum sample size $N = 1,162$ women

Where: n = sample size

Zα = 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

1.5. RECRUITMENT AND ALLOCATION

Women who satisfied the inclusion criteria were provided with information about the trial in a language they understood by the researcher or research assistants.

Informed consent was signed on the day before elective caesarean section.

They were randomized to either the group that received TXA or the group which did not receive TXA. There was no blinding of staff or the patient.

1.6. RANDOMIZATION

A randomized allocation to study and control groups using computer-generated random numbers was done by the trial statistician.

Equal numbers were randomly allocated to the two groups for the two hospitals.

Based on the sample size the plan was for the statistician to prepare random numbers for 1,162 patients. Half of these numbers were labelled with A which represented the intervention 10mg/kg TXA and oxytocin 5IU e.g. random number 4A, represented random number 4, allocated to group A. The other half had the extension B (control group) to receive Oxytocin 5IU only.

The computer-generated numbers assigned the trial group and also a unique participant number. The numbered folded slips of paper were placed into sealed identical envelopes by the principal investigator. The sealed envelopes were kept in a box at each hospital in a locked-up room. At the beginning of the trial, TXA for 200 patients was available. The statistician therefore initially prepared random numbers for 400 patients (200 with the extension A and 200 with the extension B), half of which were prepared for HMH (1 – 200) and the other half for MNMH (1 – 200). A further 106 were prepared when the 400 numbers were used up to make the total number recruited 506 during the initial trial period.

The patients were enrolled by the principal investigator or the research assistants on the day before their scheduled caesarean section. Once they met the study criteria per the screening tool (see **Error!**

Reference source not found.), informed consent was obtained (**Error! Reference source not found.** & **Error! Reference source not found.**). The participant was asked to pick an envelope from the box. The envelope would then be opened by either the participant or the researcher.

The study number would then be entered on the data collection tool as the study serial number. A unique study sticker labelled 'Group A'/ 'TXA' or 'Control' would be attached to the patient's notes. The data tool would then be inserted into the notes together with a prescription form if in group A for the attention of the theatre staff and anaesthetists. (Refer to **Error! Reference source not found.**). Only the data tool was attached to the control group patient's notes. (**Error! Reference source not found.**). A list matching the serial number to the allocated group was compiled to match the original randomization.

1.7. BLINDING

There was no blinding after the sealed envelopes had been opened. After randomization, the participants and trial staff were aware of the trial group to which the patient had been allocated.

A completely blinded trial would have required fully dedicated staff. Such a trial would have put pressure on already busy anaesthetists. However, there was an agreement from the departments that the TXA would be given according to the study protocol.

1.8. INTERVENTION

The participants in the intervention arm received TXA (10mg/kg) administered slowly over 5 minutes intravenously (iv) 10 minutes prior to skin incision and prophylactic oxytocin (5 IU iv) slow administration by the anaesthetists on delivery of the baby. Participants in the control group received prophylactic oxytocin (5 IU iv) only on delivery of the baby. 5IU of Oxytocin were administered slowly intravenously as recommended by the WHO in 2012 [12]. Updated recommendations were then published by WHO in 2018

after ethical approvals had been obtained and came to the attention of the principal investigator after the initial planned period of data collection (1 January 2018 to 31 December 2018) recommending the use of 10IU of oxytocin in the third stage. No change was made to the protocol during the data collection period [3]. All patients continued to receive 5IU of prophylactic oxytocin.

TXA (10mg/kg) solution for injection from the vial was diluted with 100 – 200ml electrolyte solution such as Normal Saline, Ringers Lactate solution, dextrose/water for injection on the same day it was to be used by the anaesthetist at the dose prescribed. Intravenous administration at a rate of 100mg or fraction thereof over at least 1 minute – usually at least 5 minutes for each patient was done. The administration was to be done at least 10 minutes before skin incision [32, 33, 37, 38].

No additional prophylactic uterotonics were to be administered to the patient based on the anaesthetist's or surgeon's subjective preferences. Several local surgeons routinely add misoprostol for select cases at caesarean section. A recent local unpublished study conducted in 2017 concluded that adding misoprostol to the routine prophylactic oxytocin did not reduce the occurrence of PPH in patients undergoing low risk elective caesarean section [51]. Therefore, additional uterotonics were to be administered only if clinically indicated.

1.9. PHARMACY PLAN

Intravenous oxytocin 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 5IU oxytocin intravenously, administered slowly by the anaesthetist after delivery of the baby at HMH and MNMH. The cold chain is maintained up to the administration of the drug to the patient.

TXA obtained for the study was purchased from Sky Pharmaceuticals (Tranexamic acid 0.1g/ml injection from Pfizer Laboratories, registration number: 75/10.4/574)) was kept in theatre. This was done to ensure

an uninterrupted supply of the drug for the trial. The TXA vials were kept in a lockable drug cupboard accessible to the sister-in-charge only, who would only dispense them to the anaesthetist on presentation of a study prescription form. A dispensing register for the TXA was kept in the same cupboard. Patient details and study number, amount of TXA dispensed and wasted were entered into the study register for accountability and to guard against abuse. Please refer to the detailed Pharmacy Plan in **Error! Reference source not found.**.

1.10. ASSESSMENT

Data were collected and recorded on the data collection tool. Any adverse event was to be reported on the MCAZ/MRCZ adverse event reporting form.

Vital signs (heart rate, blood pressure, respiratory rate) were recorded before surgery, immediately after placental delivery, and 1 to 2 hours after birth.

Full blood count (FBC), urea & electrolytes (U&E) and liver function tests (LFTs) were performed a day before delivery and on the second day after delivery.

Estimated blood loss (EBL) was determined using the difference in haematocrit values taken before and 48 hours after caesarean delivery according to the formula:

$$= \text{EBV} \times \frac{\text{(Preoperative haematocrit – Postoperative haematocrit)}}{\text{Preoperative haematocrit}}$$

Where EBV (estimated blood volume) in ml is equal to the woman's weight in kg × 85 [38].

As haematocrit values were not consistently available, EBL was also determined using the haemoglobin (Hb) value using the Meunier's formula BV × [(Hb_i – Hb_e)/(Hb_e)], where BV is blood volume, Hb_i is initial Hb, and Hb_e is end Hb [52].

Standard EBL based on visual estimates made by anaesthetist after assessment of patient's linen and abdominal swabs was also recorded.

The calculated method and visual estimation of blood loss were used in this study. Although visual estimation is the method used frequently by anaesthetists to estimate blood loss, it has been demonstrated as inaccurate in repeated studies. Its continued use in clinical practice is related to tradition and ease of use. This method was compared with the calculated method by Stafford et. al. who noted that these calculations could be inaccurate based on the hydration status of women, particularly related to intravenous loading conducted during regional anaesthesia (>90% had an epidural), or with pregnancy-induced hypertension. They also acknowledged that maternal physiologic changes may alter the haematocrit changes. Plasma volume increases by on average 1.25 litres in all pregnant women, and all will undergo fluid changes post-delivery [23, 53, 54]. In addition, all of the participants received intravenous fluids as they are surgical patients. Therefore, any effects on the haematocrit of the physiological changes or IV fluids happened in all the participants as the plasma volume changes were universal to all pregnant women. Secondly, we intended to do a subgroup analysis of women who had pregnancy-induced-hypertension. Women with Eclampsia/HELLP syndrome were excluded from the study. As visual estimation is the method traditionally used at both hospitals, we used this together with the more objective calculated method for comparison to determine blood loss.

Refer to **Error! Reference source not found.** for the patient flow in the study.

1.11. STATISTICAL METHODS

Data analysis was conducted using Stata v15 (Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC) following the CONSORT guidelines for reporting RCTs [55].

The primary analysis compared women given a low dose of TXA (10mg/kg) administered 10 minutes before elective caesarean section with prophylactic oxytocin administration to those given prophylactic oxytocin alone.

Baseline characteristics were compared between the groups to check the adequacy of randomization. Differences between patients lost to follow-up and included patients were also assessed. The intention-to-treat analysis was followed. This is a statistical concept whereby every participant in the study is accounted for in the analysis according to the randomization treatment assignment regardless of whether there is noncompliance, protocol deviations, withdrawal from the study, and anything happens after randomization [56].

Categorical data were reported using frequencies and proportions while continuous data were summarized using means and standard deviations for normally distributed data, and medians and quartile range where data was not normally distributed. Comparisons for categorical data were done using the chi-square test or Fisher's exact test when the sample size was small.

For continuous data, the t-test was used to compare differences between the groups and the analysis of variance (ANOVA) was used for comparing more than two groups. Where data were not normally distributed, the nonparametric Kruskal Wallis test was used to compare differences in continuous outcome for more than two groups. The Mann-Whitney U test was used to compare two groups where data were not normally distributed. Effect estimates were presented with relative risk measures and associated 95% confidence intervals. Any subgroup analysis was conducted as the primary analysis.

An analysis was conducted after 506 participants had been recruited to check if there are any significant differences in adverse events in the two groups.

1.12. DATA MANAGEMENT

The researcher and assistants allocated the patient a study serial number. No identifiers were used.

1.13. DATA CLEANING AND ENTRY

Completed questionnaires were checked for validity, accuracy and completeness by the principal investigator before data entry into the computer by the research assistant

1.14. OUTCOMES

1.14.1. Primary Outcome

1. Incidence of PPH defined by blood loss equal to or exceeding 1,000 ml following elective caesarean section
    - Based on calculated estimates.

1.14.2. Secondary Outcomes

1. Incidence of PPH defined by blood loss equal to or exceeding 1000 ml following elective caesarean section
    - Based on visual estimation
2. Estimated blood loss during caesarean section
    - Based on visual estimate of blood loss and calculated estimates
3. Need for blood transfusion
    - Mean or median number of units of red blood cells transfused up to day 2 postpartum
4. Use of additional uterotonics (such as oxytocin infusion or prostaglandins)

- Number of participants who required additional uterotonics

5. Incidence of emergency surgical interventions for PPH up to day 2 post-surgery
6. Mean change in HCT up to day 2 post-surgery
    - Difference between the HCT on the day before surgery and day 2 post-surgery
7. Mean peripartum change in haemoglobin up to day 2 post-surgery
    - Difference between the haemoglobin on the day before surgery and at day 2 post-delivery
8. Duration of mother's hospital stay
9. TXA side effects
    - number of participants with headache, anaphylaxis, nausea, diarrhoea, dizziness, fatigue, nasal sinus complaints, transient visual disturbances, abdominal pain, complaints of feeling faint, reported by anaesthetists and theatre staff [time frame: up to discharge from the recovery ward on day of surgery]
    - number of participants with deep venous thrombosis, pulmonary embolism, myocardial infarction, or any thrombotic event confirmed by laboratory investigations up to day 2 post-surgery
    - number of participants with seizures up to day 2 post-surgery
    - number of participants with renal failure (defined by the need for dialysis) up to day 2 post-surgery
    - number of participants with hypotension reported by anaesthetists and theatre staff [time frame: up to discharge from the recovery ward on day of surgery]
    - Vital signs before surgery
        - Heart rate before surgery
        - Systolic BP before surgery
        - Diastolic BP before surgery

- Vital signs after placental delivery
    - Heart rate after delivery of the placenta
    - Systolic BP after delivery of the placenta
    - Diastolic BP after delivery of the placenta
- Post-caesarean delivery creatinine (mg/dL)
- Postoperative urea g/L
- Postoperative aspartate transaminase (IU/L)
- Postoperative alanine transaminase (IU/L)
- Postoperative total bilirubin (IU/L)

10. Neonatal outcomes
    - Birth weight in grams determined on the date of delivery
    - Apgar scores at 1 and 5 minutes on the date of delivery
    - Reason for admission to NNU/NICU [time frame: up to discharge from NNU/NICU]
    - Number of neonates with neonatal jaundice determined clinically [time frame: up to discharge from NNU/NICU]
    - Number of neonates with thromboembolic events determined clinically [time frame: up to discharge from NNU/NICU]
    - Number of neonates who died [time frame: up to the day of discharge of the mother]

3.15. DATA REPORTING

The study is reported according to the Consolidated Standards of Reporting Trials (CONSORT) which ensures that RCTs are reported in a standardized manner internationally and that all study participants are accounted for clearly and transparently [55].

3.16. INDEPENDENT DATA AND SAFETY MONITORING BOARD

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

The DSMB was established to assess at intervals the progress of the clinical trial, the safety data, and the critical efficacy endpoints, and to recommend to the sponsors and researchers whether to continue, modify, or stop the trial. The DSMB reviewed the analysis prepared for this report.

3.17. STOPPING RULES / DISCONTINUATION CRITERIA

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

3.18. ETHICAL CONSIDERATIONS

Approval to conduct the study and to use the hospital records of patients was sought and obtained from the following:

Table 1 Ethical approvals

Ethical Body	Approval Number
Harare Hospital Research and Ethics Committee	HCHEC 300817/61
Joint Research and Ethics Committee (JREC) at Parirenyatwa Group of Hospitals	JREC/239/17
Medical Research Council of Zimbabwe (MRCZ)	MRCZ/B/1386
Medicines Control Authority of Zimbabwe (MCAZ)	B/279/5/35/2018

Refer to **Error! Reference source not found.**.

Participants were requested to provide written informed consent. Refer to **Error! Reference source not found.** and **Error! Reference source not found.**. Participants were given full disclosure of the nature of the study, the risks, benefits and alternatives. They were given an opportunity to ask questions. No participant was coerced into participation. Participants were assured that no punitive implication or denial of service would be encountered if they did not agree to enter the trial and were permitted at any time to withdraw their participation. Women in the study were not given any material benefits.

The researcher liaised with the team managing the patient to continue the usual care even when the patient was not willing to enter or withdrew their participation. The patient was free to communicate with the researcher if they felt they did not get due treatment. The study used only coded numbers with no personal identifiers to ensure confidentiality.

3.19. TRIAL REGISTRATION

The trial was registered on clinicaltrials.gov NCT03463993.

3.20. PROTOCOL

The full trial protocol can be accessed at:

The Department of Obstetrics and Gynaecology, University of Zimbabwe College of Health Sciences,

P.O. Box A178, Avondale, Harare, Zimbabwe

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