TRANEXAMIC ACID USE AMONGST WOMEN AT HIGH VERSUS LOW RISK OF POST-PARTUM HAEMORRHAGE DELIVERING AT KENYATTA NATIONAL HOSPITAL: A RETROSPECTIVE COHORT STUDY

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DECLARATION:

This research work and dissertation is my original work and to the best of my knowledge it contains no materials previously published or written by another person. It has not been submitted for award of a degree in any other university. References of work done by others have been clearly indicated.

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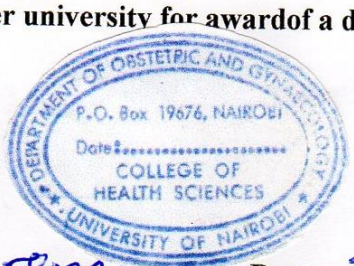

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TABLE OF CONTENTS

Table of Contents

DEFINITION OF ABBREVIATIONS

AE – Adverse Effects

AMSTL – Active Management of Third Stage of Labour

CCT – Controlled Cord Traction

CS – Cesarean Section

KNH – Kenyatta National Hospital

KNH-UoNERC – Kenyatta National Hospital / University of Nairobi Ethics Review Committee

PI – Principal Investigator

PPH – Postpartum haemorrhage

RCT – Randomized Clinical Trial / Randomized Controlled Trial

SAE – Severe Adverse Effects

TXA – Tranexamic acid

WHO – World Health Organization

DVT – Deep Venous Thrombosis

PTE – Pulmonary Thromboembolism

EUA – Examination under anaesthesia

OPERATIONAL DEFINITION OF TERMS

Low Multiparity – Parity between 1 and 3

Grand Multiparity – Parity of 4 and above

LIST OF FIGURES

LIST OF TABLES

ABSTRACT

Background:

Post-partum haemorrhage (PPH) tops the list amongst causes of maternal deaths globally. PPH accounts for approximately one in every four pregnancy-and-childbirth-related deaths that occur globally and remains the leading cause in most low- and middle-income countries. In Kenya, it accounts for 44% of maternal mortalities.

The World Health Organization (WHO) recommends the Active Management of Third Stage of Labour (AMSTL) package as a post-partum haemorrhageprevention strategy. Among the components of AMSTL, the use of uterotonics is proposed to be the main intervention. Oxytocin remains the main uterotonic for preventing primary postpartum haemorrhage in both cesarean, other operative, and vaginal deliveries. Intravenous Tranexamic Acid (TXA), an antifibrinolytic agent that prevents plasminogen from being activated to plasmin, has recently been recommended by WHO for use in treatment of all PPH cases, regardless of the cause, and this is the practice in our setting. Whether or not TXA can be used prophylactically in obstetric setting remains unclear due to limitation of data from either retrospective studies and/or clinical trials given that it has largely been studied in surgical set-ups rather than obstetric.

Studying the patterns of use of TXA amongst different obstetric groups from available data therefore becomes a necessary step that will inform future trials that may wish to investigate prophylactic use of TXA amongst different obstetric groups to prevent PPH.

Objective:

To determine the association between the presence of risk factors for postpartum haemorrhage at the time of birth and use of tranexamic acid among parturients at Kenyatta National Hospital.

Methodology:

This was a retrospective cohort study of in which 437 files randomly selected out of those who delivered at Kenyatta National Hospital maternity between January and December 2019. The study assessed the incidence of TXA use, use of additional uterotonics, blood transfusion, additional surgical interventions, and ICU/HDU admission between the women with risk factors for PPH (exposed) and those without (unexposed). Their records were retrieved and information on their socio-demographics, PPH-risk-factor status, use of Tranexamic acid, additional management for PPH, and the maternal outcomes were obtained and documented. The data was cleaned, analyzed and managed using STATA. Crude and adjusted Relative Risk (RR) was used to assess the association between the different variables and risk factors. A *P*-value of <0.05 was considered to be statistically significant.

Study Significance:

This study addsto the available pool, valuable information on the use of TXA amongst women with high risk of PPH. This will inform future clinical trials that would want to look into the possible use of TXA prophylactically in obstetric settings.

Results:

437 participants who were eligible were recruited into the study, and 222 were exposed, while 215 were allocated to the control group. The mean age was 29yrs (30 vs 28 for Exposed vs Unexposed). TXA use was found to be higher in those with risk factors (11.24%) than those without (3.72%) *(RR 3.026, P-value 0.003)* but not of statistical significance after adjusting for confounders. A similar pattern was observed in the use of additional Uterotonics, blood products and HDU/ICU admission between the two groups. Surgical interventions were observed to be less in the exposed (3.15%) than in the unexposed (7.98%) group*(RR* 0.395*, P-value 0.022)*.

Recommendation:

We recommend for additional studies, preferably randomized trials, to look prospectively into the prophylactic of use TXA among those having PPH risk factors.

Key words: Postpartum haemorrhage, Risk factors, Tranexamic acid.

1. INTRODUCTION

1.1. BACKGROUND

1.1.1. Epidemiology

The traditional definition of postpartum haemorrhage has beenthe loss of 500 ml or more of blood within 24 hours following parturition.The definition of severe PPH, on the other hand,has been the loss of 1000 ml or more of blood within the a similar timeframe [1,2]. Estimates in literature of its incidence varies widely from region to region being lowest in the developed countries and highest in the developing countries, and largely depends on the criterion used to diagnose the disorder. While WHO estimates that approximately 5% of women giving birth will be affected by PPH globally [2], a 2012 systematic review and metanalysis found the prevalence of PPH ranging between 7.2% (Oceania)and 25.7% (Africa).In the systematic review severe post-partum haemorrhagewas most prevalent in Africa (5.1%) and least in Asia (1.9%) [3]. In rural Uganda, Ononge et al, in a prospective study done between 2013 and 2014, found a prevalence rate of 9% [4]. There is no literature available to give estimates of its magnitude locally in Kenya.

Almost 20% of the PPH cases will progress to severe forms where risks of death or further interventions like use of additional uterotonics, blood transfusion, surgery, and ICU admission increases greatly [5].

Post-partum haemorrhage (PPH) is top on the list of causes of maternal deaths globally. It accounts for about one in every four maternal deaths that occurs globally [1,2,7]. It still is the leading cause in most low-income countries, and in Kenya itis responsible for about 4 out of 10[7,8,].

The risk factors for PPH include very young and advanced maternal age, multiple pregnancy, polyhydramnios, fibroids, hypertensive diseases of pregnancy, chorioamnionitis, placenta previa, placenta abruptio, cervical tears, retained placenta, rupture of the uterus, vaginal instrumental delivery, and delivery via cesarean section [5,6].

1.1.2. Risk Factors for PPH

The Royal College of Obstetricians and Gynaecologists (RCOG) appreciates the lack of appreciable risk factors to predict the likelihood of the occurrence of PPH, and that any woman remains at risk. However, they identify some to include: pre-existing coagulopathies, multi-fetal

pregnancy, pre-eclampsia, prolonged labour, a previous history of Post-partum haemorrhage, general anaesthesia, placental abnormalities, perineal and vaginal tears and episiotomy [53].

Bhavana et al in a cross-sectional study looking at PPH risk factors and CS indications among 100 women at term identified Gestational Diabetes being the highest risk factor (10%), followed by hypertensive disorders of pregnancy (6%) [54].

Tatsuya and associates, through a prospective cohort study that was done in a Japanese tertiary perinatal facility between June, 2013 and July, 2016, identified use Artificial Reproductive Technology (ART), gestational hypertension and macrosomic fetal delivery as the risk factors for post-partum haemorrhage [55].

1.1.3. PPH prevention:

Active management of the third stage of labour (AMSTL), which currently remains the main proven preventive intervention for postpartum haemorrhage, mainly combines mechanical interventions.These include: prophylactic use of uterotonics soon after expulsion of the baby, early umbilical cord clamping and cutting, controlled cord traction (CCT), and, uterine massage– as observed by some authors [9,10]. Nonetheless, administration of uterotonics,particularly oxytocin, after birth has been clearly shown to be the only component of AMTSL that effectively leads to the prevention of PPH [11–15]. However, a synergistic biochemical hemostatic effect would be expected from the additional use of pro-hemostatic drugs such asTXA, in addition to this mechanical hemostatic enhancement produced by AMSTL.

1.2. TRANEXAMIC ACID (TXA)

TXA is a an effective anti-fibrinolytic agent that preventsthe breakdown of clots (fibrinolysis) and consequently cause a reduction in bleeding proportions. It achieves this by blocking lysine binding sites on plasminogen molecules. It also has the potential to augment the effectiveness of the hemostatic mechanismsof the individual [16].

Traditionally, it has been used in major trauma, after-birth bleeding, surgery, dental extractions, nosebleeds, and heavy menstrual bleeding to either treat or prevent excessive bleeding [17,18]. It is also used in the management of hereditary angioedema [19].

It can be administered topically, orally or intravenously [17].

Results from trials done previously have demonstrated that Tranexamic acid use in electiveoperationslowers the risk of being transfused with blood, the mean volume of blood transfused, and need for repeat surgeries due to haemorrhage, without increasing the occurrence of thrombotic events. They also further demonstrated overall reduction in mortality [20, 21]. The CRASH-2 trial, carried out in high-, middle-, and low-income countries, demonstrated that TXA when administered early (within 3 hours)reducedmortality from all causesamongst trauma patients who were bleeding without an increase in thrombotic events [22]. They further made observation that TXA significantly lowered the probability of death due to bleeding. They had strong evidence that effect of TXA on deaths attributable to bleeding mainy depended on how soon it was administered from the time from injury. A systematic review that looked at non-surgical management options for heavy menstrual bleeding found TXA to be an effective therapy for the reducing menstrual bleeding in women with Abnormal uterine bleeding, when compared to those women treated with control or placebo [23]. The effectiveness of tranexamic acid in treating menorrhagia is an important observation as it suggests TXA can lower blood loss from the uterus, even of low amounts, and also in non-surgical settings [24].

1.2.1. Tranexamic acid for Postpartum Haemorrhage

In normal pregnancies,usually the hemostatic balance changes towards a hypercoagulable state in order to reduce haemorrhagic complications that would be associated with birth. However, myometrial contraction, which interrupt blood flow, remains the most crucial initial factor for immediate hemostasis at birth. After placental separation from the uterus during delivery, stepwise physiologic and hemostatic eventsusually come into play to lower blood loss.Strong contractions of the myometrium occur, platelet activity increases and coagulation factors are released en-masse.However, there is increased fibrinolysisat the same time [25]. As oxytocin usepromotesmyometrial contraction, tranexamic acid may be able to negate the fibrinolysis and consequentlypromote haemostasis. Charbit et al in their study looking at fibrinogen levels as an early predictor of PPH found a close association between low levels of fibrinogen and severity and outcome among the women who had PPH [26, 27]. This may, in addition, suggest that tranexamic acid could be an effective drug to be used in the prevention of PPH.

1.3. PPH TREATMENT

Amulticenter open-label randomized controlled trial thatlooked atthe use of TXA for the treatmentof PPH demonstrated that a high TXA dose reduced bleeding in women who had Post-

partum haemorrhage [33]. However, because of its open design, low sample size, issues pertaining the harm-benefit ratio, andconflicting findings from studies done before and after using the same protocol [34], the use of Tranexamic acid to treat obstetric post-delivery bleeding remained debatable at the time.

The WOMAN trial (a randomized, double-blinded, placebo-controlled trial in women with a clinical diagnosis of PPH), was, therefore, designed to rectify this clinical dilemma [18]. In 21 countries, they managed to recruit 20,060 women between March, 2010 and April, 2016. These were women of 16 years ormorehaving clinically diagnosedPPHfollowing vaginal delivery or CS. They were randomly allocated to be giveneither TXA (n=10051) or placebo (n=10 009), out of whom 10036 and 9985, respectively, were analyzed. TXA significantly reduced death that was attributable to bleeding (TXA: 155 [1·5%] of 10 036 patients vs Placebo: 191 [1·9%] of 9985 with a risk ratio (RR) of 0·81, 95% confidence interval of 0·65–1·00; p value was 0·045). This effect was more pronounced in those who received treatment within three hours of delivery (89 [1·2%] in the TXA group as compared to 127 [1·7%] in the placebo group, with a risk ratioof 0·69, 95% confidence interval between 0·52 and 0·91; p-value of 0·008). No significant difference was observed in all other causes of death between the two groups. They also found that TXA did not reduce the risk of hysterectomy, as the occurrence was almost similar in both groups (358 women [3·6%] in the TXA group versus 351 women [3·5%] in the placebo group, with the risk ratio at 1·02, 95% confidence interval from 0·88 to 1·07; and p-value at 0·84). Death from all causes or hysterectomy, which was their composite primary endpoint, was not reduced with TXA (534 [5·3%] deaths or hysterectomies in the tranexamic acid group in comparison with 546 [5·5%] in the placebo group, Risk Ratio 0·97, 95% Confidence interval 0·87 to 1·09; p-value 0·65). The occurrence of adverse events between the two groups was found not to be significantly different.

It is these findings of the WOMAN trial that led to the WHO's recommendations for the use of TXA to treat PPH regardless of the cause. This would imply that TXA may also be beneficial if given prophylactically for the prevention of PPH.

2. LITERATURE REVIEW

2.1. Tranexamic acid use in obstetrics

In our literature review, we came across 3 systematic reviews, 3 RCTs looking at the use of intravenous tranexamic acid as prophylaxis for the prevention of PPH in vaginal births, 10 RCTs looking at similar use of TXAas prophylaxis to prevent PPH during cesarean section, and 2 protocols for RCTs investigating the use of prophylactic intravenous TXA for preventing of post-partum haemorrhagein vaginal births. The methodologies and analysis differed amongst the studies: variation in the definition of PPH, variations in the primary outcomes, some had blinding while others didn't, some placebo controlled and others not, differences in the methods of determining blood loss, amongst other differences. Despite these, the common finding was that less blood was lost in the groups that received TXA, compared to the control groups, and no increased risk of severe adverse effects was observed. These have been highlighted in the discussion below.

In 2015, a Cochrane review ofthe use TXA for the prevention of PPH was updated and published [28]. 12 trials that involved 3285 women whose risk of excessive haemorrhage was low, undergoing elective cesarean section (9 trials, 2453 participants)or vaginaldelivery (3 trials, 832 participants) attained the inclusion criterion and were analysed in the metanalysis. They allreceived either TXA or placebo or no intervention,these interventions being additional to theroutine prophylactic uterotonics that were prescribed in theirlocal guideline(s). The studies that took part had an overall low risk of bias for incomplete data, and a moderaterisk of bias for allocation concealment,random sequencegeneration, blinding, and selective reporting.The quality of evidence was assessed using GRADE.Based on mixed-quality studies, the authors concluded that TXA (being additional to the standard uterotonic drugs) lowers the magnitude of haemorrhagepostpartum.They also were able to make conclusion that TXA prevents post-partum haemorrhage and transfusion with blood productsafter vaginaldelivery and cesarean

sectionamongst women whose risk of post-partum haemorrhage is low. TXA exerted more pronounced effect on blood loss above 500ml or 400ml in thevaginal delivery group than those that underwent cesarean section. When compared to those who were given placebo or no intervention,the women who received TXA had a lowermean blood loss(the mean difference was - 77.79 mL with 95%confidence interval -97.95, -57.64 - five trials, 1186 women) with similar effectsin both vaginal delivery and cesarean section. Evidence to make conclusions onserious adverse effects was insufficient, though they found higheroccurrence ofminor adverse effects with the use of TXA. They proposed further investigations on TXA's effects on thromboticevents and mortality and also the use of TXAamong high-risk women.

Chunbo Li et al published in 2017 a systematic review and metanalysis on the effectiveness and safety of prophylactic TXA preventing PPH [29]. They included 25 articles with 4747 participants. They found that TXA led to a reduction in the intraoperative,post-operative, and total blood loss by a mean volume of 141.25mL (95% CI 186.72 - 95.79, P value <0.00001),36.42mL (95% CI -46.50 to -26.34, P value <0.00001), and 154.25mL (95% CI -182.04 to -126.47, P value <0.00001) respectivelyamong women who had Cesarean Section. Prophylactic TXA given in vaginal deliveries led to a reduction in the intraoperative, postoperative, and total blood loss by an average volume of 22.88mL (95% CI -50.54 to 4.77, P value0.10), 41.24mL (95% CI -55.50 to -26.98, P value 0.00001), and 84.79mL (95% CI -109.93 to -59.65, P value < 0.00001) respectively.Further, they found that TXA could lower the incidence of PPH and severe PPH, and also reduce the needforblood transfusions. In cesarean and vaginal deliveries, the risk for deep vein thrombosis (DVT) after Cesarean Section or Vaginal Deliverywas not increased with tranexamic acid usage, though minorside effects occurred more commonly.

Chunbo Li et al made conclusion thatprophylactic intravenous TXA given to women undergoing cesarean section was effective and safe. Although TXA given prophylactically led to reduction inpost-partum blood loss, they observed that the current data that existed wasnot sufficient to makeauthoritative recommendations about itsclinical importance. This was because the quality of the included literature was the poor to moderate. Therefore, to validate their findings, they identified a need forRCTs of high qualityand having samples that arelarger.

Massimo et al pre-published an updated systematic review and metanalysis on the safety and efficacy of TXA for preventing obstetric-relatedbleeding following cesarean sections in 2018 [30]. 18 RCTs met their criterion for inclusion into the metanalysis.These translated to an enrolment of 1,764 participants in the experimental group(given intravenous prophylactic TXAto prevent bleeding following CS and 1,793 participants in the control group(received placebo or no intervention)for evaluation. They found that TXA use compared to controls had reducedPPH>400 mL (risk ratio was found to be 0.40, 95% confidence interval between 0.24 and 0.65. This was fromfive trials which had 786participants in total), severe PPH>1,000 mL (risk ratio at 0.32, 95% confidence interval from 0.12 to 0.84; five trials that had 1,850 participants in total), and the requirement for transfusion with blood products (risk ratio 0.30, 95% confidence interval: 0.18-0.49; 10trials analyzedhaving asum of 1,873 women). They did not find any particular safety concerns on the TXA-use. Overall, the findings supported TXA having beneficial effect in loweringhaemorrhage and the need for red cell transfusion in women planned to undergo cesarean delivery.

Another RCT was published in 2001 by Yang et al. They looked at 400 puerperants and grouped them into four for comparison as follows:Group Iwith 94 participantswas givenone dose of intravenous 1 g TXA as an infusion; Group II with 92 participantswere givena single intravenous dose of 0.5 g TXA;Group IIIwith 92 participants received a single intravenous dose of 0.5 g amino- methylbenzoic acid, and Group IVwith 87 was not given anyto serve as the control group [31]. They found the average blood loss to be significantly lower infirst and second groups than in the third and fourth groups (P value being< 0.01).However, there was no significant difference between the first and second groupsthat received different dosages of TXA(P value > 0.05).Themagnitude of blood lost immediately after the expulsion of placenta was not of significant difference among the 4 groups (P value> 0.05). However, the mean blood lost at two hoursafter birth was found to be 129.7 ml, 133.9 ml, 168.5 ml and 178.2 ml for the first, second, third and fourth groups respectively, which is lower for group I and II as compared to III and IV. The total blood lost for the four groups was recorded as 243.3 ml, 242.9 ml, 308.1 ml, and 314.8 ml respectively, exhibiting a similar picture as that found at 2 hours postpartum.Having their definition forpost-partum haemorrhage as blood loss ≥ 400 mL, the authors reported its occurrence as 6.4%, 13.3%, 20.7% and 25.3% for group I, II, III and IV respectively.There were no major adverse events thatwere reported to haveappeared.The main limitation for this study

was itsabsence of placebo and blinding as much as it was a it was a multicenter, randomized controlled study. Moreover, they did not describe the randomization method that was used.

Gungorduk et al. sought to check the effects of having additionalIV TXA to the standard AMSTL to lower vaginal haemorrhage during the 3rd and 4th stages of labour in a more recent randomized controlled trial that was published in 2013 [32]. This was a prospective, double-blind, equivalence RCT that had 454 women randomly allocated to either get an IV infusion of TXA (n = 228) or five percent dextrose glucose (n = 226) at the delivery of the anterior shoulder with both groups usingAMSTL (included prophylactic injection of 10 IU of oxytocin within 2 minutes of delivery, early cord clamping, and controlled cord traction afterdelivery. Having their primary outcome as the mean blood loss in the 3rd and 4th labor stages, the investigators found the itto be significantly lower in the interventional than that in the control group (261.5 ± 146.8 mL versus 349.98 ± 188.85 mL, respectively; p value < 0.001). The interventional group also had a lower frequency of PPH > 500 mL (4, 1.8%) in comparison to that in the control group (15, [6.8%]; relative risk, 3.76; 95% confidence interval, 1.27-11.15; p value = 0.01). They, therefore, concluded that blood loss, postpartum,was reduced by TXA usein addition to the standard AMSTLwith no increasedoccurrence of thromboembolic events.

In Iran, Mirghafourvand et al set out to look at the effects ofpreventive TXA on the calculated and measured blood loss followingvaginal birth amongstPPH-low-risk through a double-blinded RCT that was published in 2013 [36].120 women who had a singleton pregnancy were recruitedandwere randomized to either get 1gof IV TXA or placebo, thisbeing additional to the standard 10 International Units of oxytocin followingfetal delivery.They established the calculated blood loss using the haematocrit levels prior to delivery and 12–24h following parturition. In addition, they quantified blood loss through measurements doneat2 time periods: from fetal delivery to when the placenta is expelled and from the time the placenta is expelled to the end of the 2nd hour post-delivery.They found the intervention group to have a significantly lower mean (SD) calculated total blood lost (519 (320) vs 659 (402) mL, P = 0.036) and the measured blood lostbetweenthe delivery of the placentaand 2hours post-delivery (69 (39) vs 108 (53) mL, P < 0.001) in comparison to the control group.The blood loss measured betweenfetal expulsionandthedelivery of the placenta was not significantly different between the 2arms. The occurrence of calculated blood loss > 1000 mL was lower in the group that received TXAthan in

the control (7% vs 18%, P value = 0.048). Their study had minimal allocation, and measurement bias because of the double blinding procedures.

Most of the trials looking at the use of prophylactic TXA to prevent PPH have been done on Cesarean delivery, and offer evidence that TXA reduces the incidence of PPH [37-46]. 7 out of 10 were double-blind and placebo-controlled. Sample size varied. Though the mode and timeframe of estimation was not clearly specified, they all measured postpartum blood loss as the primary outcome and demonstrated lower loss of blood in the experimental than in the control groups. Only Abdel-Aleem et al specified that they measured their blood loss 2 hours postpartum [45]. All, except Xu et al, reported no thromboembolic side effects, while two studies reported more gastrointestinal (GI) side effects in their experimental than in the control group(s).

Gai et al in China, 2004, looked at 180 primiparous women in a multicenter prospective RCT [37]. 91 of these in the experimental group received infusion of 1g IV Tranexamic acid 10minutes before CS, while the rest who formed the control group only received standard care with no placebo. Their primary outcome was postpartum blood loss, though the method used to determine this was not clear. They found this to be 359.3ml vs 439.3ml (p value 0.002) in the experimental and control groups respectively. Nil thrombotic or other side effects were reported in this study.

In 2007, Gohel et al published a prospective RCT done in India [38]. They recruited 100 primiparas, 50 of whom were in the experimental group and received Infusion of 1g IV TXA 20min before CS. The other 50 in the control group did not receive placebo. Though not clearly specified, their primary outcome was postpartum blood loss as well. The experimental group had an average blood loss of 374.9ml while the control group had 472.8ml (p value 0.003). They did not report any thrombotic or other side effects.

In Iran in 2009, Sekhavat et al, carried out a prospective RCTamongst 90 primiparous women who had cesarean delivery [39]. They were put in 2 groups: the experimental groupbeing made up of 45 participantswho were given intravenous TXA immediately before cesarean section, and the controlgroup also comprising of 45 participants thatwere given placebo. They measured the volume of blood lost from the end of the CS to two hours after delivery and compared the outcome between the 2 groups. They also measured Haemoglobin and haematocrit which they compared between the 2 groups. Their findings were that TXA significantly lowered the volume

blood lost from the end of cesarean section to 2 hoursafter delivery(28.02 +/- 5.53 mL in the TXA group vs 37.12 +/- 8.97 mL in the control group, p value = 0.000). The level of haemoglobin 24 hours after cesarean section was found to be significantly higher haemoglobinin the TXA group than in the control (TXA group: 12.57 +/- 1.33 and Control group: 11.74 +/- 1, p value 0.002). Both groups did not report any complications or side effects. From these findings they were able to conclude that TXA statistically lowered blood lost from the completion of cesarean section to 2 h afterwardswith no complication or side effects associated with itsuse.

Gungorduk et al, published an RCT that was done in Turkey in 2011 [40]. Seeking to look at TXA's safety and efficacy in loweringhaemorrhagein elective CS, theycarried out anRCT that was double-blind and placebo-controlled among 660 participants planned to have elective CS.These participants were randomly allocatedfor administration of eitherIVtranexamic acid (1 g/10 mL in 20 mL of 5% dextrose) or placebo (30 mL of 5% dextrose) prior to cesarean section.The experimental group had 330 participants while the rest formed the control group. The estimated blood loss post-cesarean formed their primary outcome. They foundTXA tosignificantly reduce the loss of blood during CS (The mean estimated blood loss 499.9 ± 206.4 mL in TXA grp versus 600.7 ± 215.7 mL in the placebo group; $P < 0.001$), the proportion of patients having bleeding>1000 mL in volume (7 [2.1%] versus 19 [5.8%], in the experimental and placebo groups respectively; relative risk 2.7, 95% confidence interval 1.1 to 6.3 and P value< 0.03), and the need to use additional uterotonic drugs(48 [14.5%] compared to 28 [8.5%], respectively; relative risk 1.7; 95% confidence interval 1.1 to 2.6; P value = 0.02). The demographic features and maternal and fetal outcomes did not show any significant variation between the two groups. Their findings were, therefore, suggestive that TXA could be of use to reduce bleeding post-cesarean effectively and safely.

In Iran, Movafegh et al, in 2011, assessed the effect of intravenous tranexamic acid on blood-loss during and after cesarean section [41]. Through a double-blindedRCT, they recruited 100 pregnant women who were randomized into either experimental or control groups in a ratio of 1:1. Participants in the experimental arm were given 10 mg/kg of tranexamic acid while those in the controlwere given an intravenous placebo, 20 minutes before incision. They recorded the volume of blood lost post-placental delivery, postoperative hemorrhage 2 hrs after the operation, and the amount of oxytocin administered. The two groups had similardemographics,

includingthe mean maternal age, the maternal weight, and the duration of the operation. Their results demonstrated that intravenous TXA decreased intraoperative (Mean intraoperative blood loss 262.5 ± 39.6 in the tranexamic acid group compared with 404.7 ± 94.4 mL in the placebo group) and postoperative blood loss (67.1 ± 6.5 versus 141.0 ± 33.9 mL in the experimental and placebo groups respectively; P value <0.001) and cumulative international units of oxytocin given to the who patients delivered via cesarean (39 ± 5.8 versus 43 ± 5.4 units in the experimental group and controls respectively; P value =0.001).

In China, 2013, Xu et al recruited 174 to acase-controlled study that was randomized and double-blinded [42]. They compared blood loss (calculated from blood collected and measured in 2intervals: the 1stbeing from the time of placental delivery to the completion of cesarean section and the 2ndbeing from the completion of cesarean to 2 hours after delivery)between 88 who weregiven 10 mg/kg of TXA immediately prior tocesareanandthe 86 others to whom TXA was not given. In addition, to they also measured Blood Pressure, Heart Rate, Respiratory Rate, haemoglobin, platelet count, post-operative PT and PPT which they compared between the 2arms. Their findings were that the experimental group had significantly lower volume of blood lostfrom end of cesarean to two hours post-delivery (46.6 ± 42.7) (p value < 0.01) when compared to the controls (84.7 ± 80.2); and the same picture was observed in thevolume of blood lost from delivery of the placenta to two hourspost-delivery (379.2 ± 160.1in the Tranexamic acidarm versus in the441.7 ± 189.5 in the control arm; p value= 0.02). However, the two arms did notshow any difference in the amount of blood lost in the intervalbetween delivery of the placentaand the end of cesarean section p value = 0.17. Although in mild form, the tranexamic arm experienced transient side effects more frequently than the controls.The administration oftranexamic acid did not lead to significant abnormalities in vital signs as observed in this study.

Sentürk et al conducted a double-blinded and placebo-controlled RCT in Turkey and published its findings in 2013 [43]. Their an objective ofassessingTXA for its effectiveness and safety in reducing intra- and post-partum blood lossamongstdelivering via CS,they enrolled 223 women who were healthy,having a normal pregnancyof any gestation, and whom theycarried outcesarean section on. The experimental groupwhich had 101 participants received 20cc TXAwhile the control group having 122 participants received 20cc of 5% dextrose solution

intravenously 10 min prior to the beginning of CS. Thereafter, they determined their outcomes by measuring the volume of blood lost in the post-surgical periods, and thedrop in haemoglobin and haematocrit levels after CS. They followed-up their participants for a meanperiod oftwo weeks post-surgery. They found that TXAlowered boththe intra- and post-surgical blood loss, but they did not find any complicationscaused by TXA.

Shahid et al, in Lyari General Hospital, Karachi, Pakistan, did a double-blinded and placebo-controlled RCTbetween March 2009 and April 2011with an objective of determiningTXA's efficacy and safety in lowering blood lost during and after cesarean section[44]. They enrolled 74 women (primi- and multiparous)who had been scheduled to undergo lower segment caesarean section (LSCS)then had themrandomizedto get either tranexamic acidor distilled waterfor injection just before commencement of the surgery.Their findingsdemonstrated that TXA significantly lowered the quantity of blood lost during LSCS (the volume of blood lostbetween delivery of the placenta and the end of LSCS was 356.44 ± 143.2 milliliters in the experimental armcompared to 710.22 ± 216.72 milliliters in the controlarm; p value < 0.001).However, the blood lost after CS was not significantly reduced (the amount of blood lostbetween the end of LSCS andtwo hours post-delivery was 35.68 ± 23.29 millilitersin the experimentalarmand 43.63 ± 28.04 millilitersin the controlarm; p value = 0.188).The use of TXA was not linkedto any adverseevents or complicationssuch as thrombosis.

In Egypt at the Women's Health Hospital, located in Assiut University, Assiut, Abdel-Aleem et al assessed the possible effectiveness of TXA on blood loss amongstwomen scheduled to undergo elective CS through an open, single-centre, randomized clinical trialthat was published in 2013 [45]. 740 women pregnant with a singleton fetus, attending the hospital, andscheduled to undergo elective CS at ≥37 weeks gestation (n = 740) were recruited into the study and subjected to randomization into either a group that was given 1 gram ofTXA intravenously as a slow infusionover 10 min before elective CS(n = 373) or another which did not receive any additional treatment to the standard care (n = 367). Thereafterthey measured the blood lost during surgery and for two hours after the operation. They got a mean total blood-loss volumeof 241.6 (SE 6.77) milliliters in the TXAarmwhich was significantly lower when compared to the control armthat had 510 (SE 7.72) milliliters. Theyalso found that the haematocrit and haemoglobin levels

dropped by a mean valuestatistically significantly lower value in the experimental group than in the controls.

Goswami et al, through a monocenter case-control study that wasprospective,and double-blinding randomization,compared the effectiveness and safety of two doses of TXA with placebo in lowering intraoperative bleeding and the occurrence of post-partum haemorrhage when used prophylactically. Three random groups (Groups T1, T2, and C) were formed:T1 with 30 participantsgiven10mg/kg of tranexamic acid in 20 milliliters of 5% glucose administeredIV;T2 also with 30 participants given 15mg/kg of tranexamic acid in 20 milliliters of 5% glucose administeredIV; and C30 participants given a placebo. The study drug was prophylactically infusedtwenty minutesprior to incising the skin and later blood lost was measured between the delivery of the placentaand 24 hours post-partumusing of weight and volume determinations. The results showed that tranexamic acid was efficacious in loweringhaemorrhage and the need for blood transfusion amongst anaemic parturients having LSCS, with the 15mg/kg dose of tranexamic acidbeing more effective than the 10mg/kg dosage, without any unnecessary increasing of the occurrence of adverse events. This effect can be clearly seen in theprimary outcome of the study, which was the mean total blood loss, and which was found to be527.17±88.666 milliliters, 376.83±31.961milliliters and 261.17±56.777 millilitersin group C, T1, and T2 respectively. While the blood-loss drop in the T1 group in comparison with the control group was 146.34±56.32 milliliters, it was found to be 262±31.51 millilitersforthe T2 group when compared to controls as well, giving a difference of 115.66±24.81 milliliters between T1 and T2. With a P value <0.05, this difference was concluded to be significantstatistically. Their findings on postoperative blood loss was insignificant throughout all the3arms. No significant adverse outcomes were observed in all the groups.

In our literature search, we came across protocols for two multicenter randomized clinical trials designed to address the prophylactictranexamic acid use to prevent post-partum haemorrhage: TRAAP Study, TAPPH-1 Study.

The TRAAP trial is an RCT that has been designed to be double-blinded, randomized and done in multiple countries and centres. They plan to recruit 4000 women who are labor and favourable for asingleton vaginal birth, and at a gestation of ≥ 35 weeks [47]. They intend to offer treatment that would be either 1g of TXAor a placebo IVsoon after deliverybeing additional to the

preventive oxytocin usuallygiven to all women during delivery. The occurrence of post-partum haemorrhage (blood loss volume ≥500 milliliters)will be used as their primary outcome, and this would be determined using collector bags that are graduated. To demonstrate a 30 % drop in the post-partum haemorrhage incidence from 10.0 % to 7.0 %, they have powered the study at 80%.

The TAPPH-1 trial is a pilot trial that will be double-blind and controlled by a placebo [48]. They plan to recruit58 pregnant mothers with a singleton gestation of more than 32 weeks delivering either vaginally or via CS. They will berandomly allocated to be intravenously given either 1gramof TXA or0.9% saline. They will primarily be looking at how feasible it is to administer tranexamic acidas well as collect data on the safety of administering drug. They will also analyze the groups on the effectiveness of mitigating the start of post-partum haemorrhage as well as othervariables that are relevant clinicallywill also be analysed.

Although the current information availed is suggestive that the use of TXA in a patient with post-partum haemorrhage reduces blood loss, the administration of blood products, and the requirement for operative intervention, our literature review highlights that conducting conclusive meta-analyses on the available studies proves difficult because of the significant heterogeneity between the studies, including the methods of measuring blood loss, the definition of PPH and the patient inclusion criterion. Reporting on severe adverse events, including mortality, also would pose a challenge because of the small sizes of the reported studies. Therefore, larger or more trials are needed to look at the safety and efficacy of using tranexamic acid in obstetric blood loss.

It is also evident that studies that looked at the use of tranexamic acid in vaginal births are greatly missing and this is an area that would require extensive evaluation for better and conclusive evidence. Riana et al also noted the need for further evaluation of TXA use in vaginal delivery in the article they published in 2018 [52]. Our study offers valuable evidence from the already available data that may inform the need for future trials to test the effectiveness and safety of prophylactic TXA in preventing PPH.

2.2. Retrospective studies on Tranexamic acid

In our search, we have not come across retrospective studies similar to this. However, there are many retrospective studies that have been done on TXA in other non-obstetric settings, especially orthopedic.

Stoicea et al, for instance, retrospectively looked at 564 total hip arthroplasties – both primary and revision – at a single teaching centre between January, 2013 to July, 2015 and published their article in 2018. These patients would either be given no tranexamic acid, or 1g when the operation starts and a second bolus when closing the wound at the discretion of the surgeon. Between the 2 groups, they compared differences in levels of Haemoglobin, haematocrit, the estimated blood loss and adverse outcomes within two days post-operation. They found significantly higher haemoglobin and haematocrit levels amongst those who received Tranexamic acid than those who didn't, in addition to lower rates of blood transfusion. Out of the overall 564 Total Hip Arthroplasty patients, 394 (69.86%) were giventranexamic acidand 170 (30.14%) were not.

In China, 2013, Guorui et al, in a multi-center retrospective study, also looked at the effectiveness and efficacy of TXA in lowering loss of blood following simultaneous bilateral total knee arthroplasty. The team compared three groups, one being given only 1g of IV TXA, the other combining 1g of IV TXA in combination with intra-articular 1g TXA, and a control group that received no TXA. They looked at the total blood lost as the primary outcome while the highest haematocrit and Haemoglobin drops, blood product transfusion rates, volume of drainage, hospital-stay length and expenditures and occurrence of complications formed secondary outcomes. Their findings indicated that tranexamic acid could be useful in lowering blood loss during subsequent bilateral total knee arthroplasty without increasing the occurrence of complications. Both the total blood lost and the highest Haemoglobin and haematrocrit drop was was observed to be less amongst the intervention group in comparison to those who received no treatment, but with no significant difference between the group that only received IV and the one that combined IV and intra-articular TXA. The secondary outcome measures done also had a similar trend, while the occurrence of complications was not significantly different between the 3 groups ($P>0.05$).

2.3. PPH Risk Factors versus TXA use

In our search, we did not come across such a study for comparison.

2.4. PPH Risk Factors versus other PPH interventions

Although there we haven't found a study directly comparing Risk factors for PPH against the use of uterotonics, several researchers have observed in different studies that majority of those who use uterotonics have at least one form of risk factor for PPH, thereby suggesting that the presence of risk factors for PPH could have an association with the use of uterotonics to manage PPH.For instance, Kochand associates, 2020,looked at 717 prescriptions of misoprostol, in total, and found a tenth of these to have been for treatment of PPH [56]. The majority of those who were given were multiparous (68.1%) and 25% had pastCS. The mean gestational age was found to be 39 weeks and 51.4% of them had a caesarean section.

Kollin et al and Ekeronma et al both made observation that the presence of risk factors for PPH predisposed one to the likelihood or receiving blood transfusion [57,58]. The former analyzed the Crash-2 and WOMANS trials and found that PPH patients had a higher chance of transfusion if they had a CS (ARR 1.16; 95% CI 1.08–1.25), and if they had any existing identifiable cause(s) of obstetric bleedingbesides atony of the uterus. The latter, on the other hand, observed that antenatally, Placenta Previa was the most strongly identifiable risk factor for all red cell transfusions in Obstetrics accounting between 7% and 37%.

3. CONCEPTUAL FRAMEWORK

3.1. Conceptual Framework Narrative

The conceptual framework shown below (figure 1) illustrates how presence or absence of risk factors (the independent variable) might influence the use of tranexamic acid (the dependent variable), and how other external (personal and institutional) factors may also interact with them to cause influence on the use of TXA.

We postulate that presence of risk factors for PPH at the time of delivery, regardless of the mode, is likely to lead to the administration of TXA (and other interventions of Post-partum haemorrhage) by the caregivers at in the immediate post-partum period. However institutional factors (such as stock-outs, presence or absence of PPH protocols in place, ordering and procurement procedures, patient-caregiver ratios) and personal factors (such as knowledge and skills in the proper management of PPH, cadre) may influence both the decision of when to give Tranexamic acid, uterotonics and/or blood products, and whether they are administered or not.

Institutional factors will not be looked at in this study, though they may influence the use of TXA and other forms of intervention for PPH.

3.2. Conceptual Framework flow chart

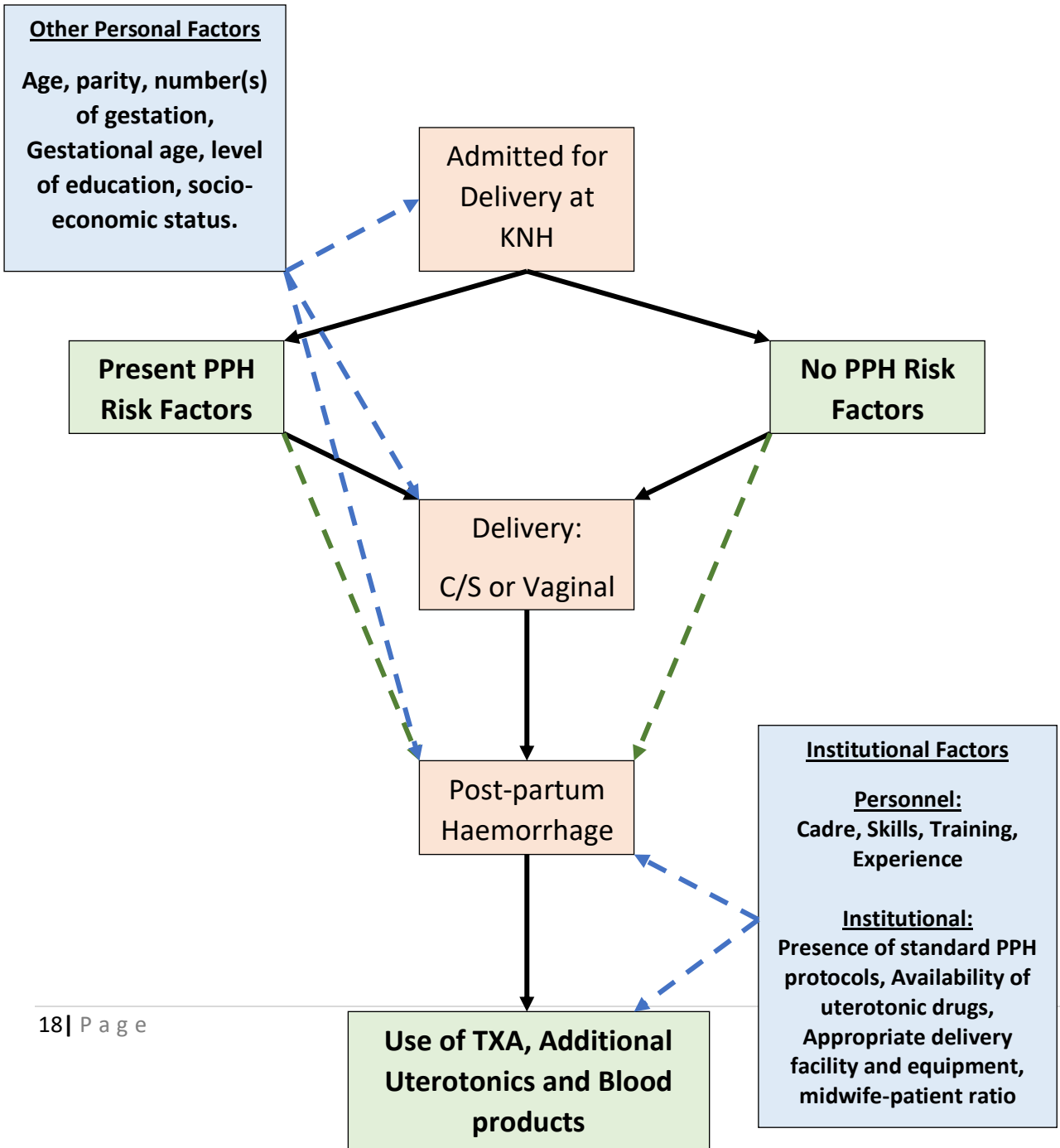

Figure 1:Conceptual Framework

4. STUDY JUSTIFICATION

PPH tops the global list of maternal mortality-causes and accounts for almost one in every four maternal mortalities that occurs globally [7]. It remains the foremost cause of maternal deathsamongstmajority of the low-income countries, and in Kenya, accounting for 44% [7,8]. Being a major cause of maternal deaths globally and locally in the current age, there still is need for innovation of better ways to reduce the burden of PPH.

Among the components of the AMSTL strategy for preventing PPH, WHO recommends that uterotonic use is the main preventive intervention [1,10] and oxytocin still remains the main uterotonic for preventing primary post-partum haemorrhage in both vaginal birth and cesarean section, as much as others like Carbetocin have been shown to be equally efficacious in preventing obstetric haemorrhage [1].

Intravenous TXA has recently been recommended by WHO for use in all obstetric haemorrhage cases, regardless of the cause [2,18] mainly following the WOMAN Trial's findings. It showed that TXA may be a beneficial intervention in preventing death from bleeding in patients with postpartum hemorrhage without increasing the risk of Venous Thromboembolism [18]. Being inexpensive and easy to administer, TXA is, therefore, a promising drug which could be simply incorporated into the regular management protocols for deliveries in hospitals, if proven to be beneficial. This study provides a platform for future trials that may want to consider the use of prophylactic TXA amongst women facing high risk for post-partum bleeding. It informs clinicians and researchers in whether particular groups of parturients – stratification being based on specified characteristics, which in our case becomes presence of PPH risk factors – may benefit from TXA more than others, if not all.

A combination of both theoretical arguments and the results obtained from clinical trials carried out in other clinical settings suggest that tranexamic acid seems to be a promising medicationto be used in preventingpost-partum bleeding. However, studies conducted on vaginal delivery are largely lacking and the evidence available is insufficient to reach any definitive conclusion on whether prophylactic TXA-use not only lowers postpartum bleeding but also the need for more interventions for controlling blood loss.

Through this study, we hope to provide information on the use of TXA amongst women having a high risk of post-partum hemorrhage, with the aim of determining their likelihood of using TXA. If found to be more likely to use TXA, our study can recommend further studies to evaluate whether routine use may lower PPH burden amongst those at high risk of PPH.

5. STUDY OBJECTIVES

5.1. Research Question

Is there an association between the presence of risk factors for postpartum haemorrhage at the time of delivery and use of tranexamic acid in women who are admitted for delivery at Kenyatta National Hospital?

5.2. Null Hypothesis

Amongst Women who are admitted and deliver at the Kenyatta National Hospital, having risk factors for PPH at the time of delivery is not associated with use of tranexamic acid.

5.3. Objectives

5.3.1. Broad Objective

To determine the association between the presence of risk factors for postpartum haemorrhage at the time of birth and use of tranexamic acid among parturients at Kenyatta National Hospital.

5.3.2. Specific Objectives

Amongst women who were admitted and delivered at Kenyatta National Hospital in 2019:

1. to compare the use of TXA between those with and without risk factors for PPH at the time of delivery.
2. to compare the use of additional PPH management interventions (in addition to the standard Oxytocin) among those with and without risk factors for PPH at the time of delivery.

3. to compare the incidence of adverse maternal outcomes between those with and without risk factors for PPH at the time of delivery.

6. METHODOLOGY

6.1. Study Design

This was aretrospective cohort studydone amongwomenattending the Kenyatta National Hospital maternity for delivery.

6.2. Study Setting

The study wascarried out in Kenyatta National Hospital (KNH) Maternity Unit.

KNH is theoldest and one of the Kenya's national teaching and referral hospitals. It is located in Kenya's capital city, Nairobi, and is managed as a Semi-autonomous Government Agency. It is the largest public referral and teaching hospital for the University of Nairobi and the Kenya Medical Training College, and houses some of the most specialized medical services within the country. The maternity unit, where this study will be conducted, is part of the Reproductive Health Department in the Hospital.

The hospital, located 2km south west of the Nairobi central business district,has a bed capacity of 1,800 and receives patients from Nairobi and its environs as well as referrals from all other hospitals in Kenya.

The KNH Maternity Unit operates 24 hours a day, 7 days a week throughout the year and conducted about 1,000 deliveries every month in 2019. This would, however, vary in special circumstances like during health workers' industrial strikes. Uncomplicated and most of the complicated maternity cases are admitted directly in the department without passing though Accident and Emergency. A team of midwives and the Obstetrics and Gynaecology Registrar on-

call handle the triage and admission of these patient into this unit, where they are monitored till delivery, and handled for any complications that may arise.

6.3. Study Period

This study wasconducted at KNHbetween January, 2020and June, 2020, and looked at the women who delivered in KNH between January and December, 2019.

6.4. Study Population

The participants for the study weredrawn from amongst women who attended the Kenyatta National Hospital's maternity for delivery between January and December, 2019. This included both vaginal and cesarean deliveries.Their records were retrieved from the Kenyatta National Hospital's Health Records and Information unit.

The KNH maternity conducts about 1,000 deliveries every month.

Those with risk factors for PPH at admission into the unit formed the exposed group and they were be compared with those without the risk factors.

The outcomes for this study were the use of Tranexamic acid, additional PPH management interventions apart from standard prophylactic oxytocin, and any adverse maternal outcomes documented.

6.4.1. Inclusion criteria:

In order to facilitate recruitment of appropriate participants, those to be included in the study were women who attended the Kenyatta National Hospital maternity for delivery in the year 2019, regardless of their indication, and meet the following criterion:

- Spontaneous Vertex delivery
- Breech delivery
- Cesarean delivery
- Assisted Vaginal delivery
- Mixed delivery methods (as in multifetal gestations)

6.4.2. Exclusion criteria:

Those with presence of one or more of the followingwere be excluded:

- Missing records
- Delivery at a gestation less than 28weeks, determined by the best available evidence.

6.5. Study Groups

6.5.1. Exposed Group

These were the parturients who had one or more of the risk factors for PPH. These risk factors included: one or more previous uterine surgery, a previous history of PPH, Placenta previa, Placenta abruptio, Morbidly adherent placenta, Multifetal pregnancy, Gestational hypertension, Gestational Diabetes Mellitus, Prolonged Labor, and pre-existing coagulopathy.

6.5.2. Unexposed Group

These were the parturients who had none of the risk factors for PPH

6.6. Sample Size Determination

The formula for the calculation of the sample size for a retrospective or prospective cohort study is given by the following formula [50,51]; Z^2

$$n = \frac{\mathrm{N} \,.\, \mathrm{Z} \,.\, \mathrm{p}.\,(1 - \mathrm{p})}{Z^2 \,.\, p \,.\, (1 - p) + \, e^2 \,.\, (N - 1)}$$

(*n - Calculated sample; N - Population; Z - Normal standardized variable associated with the confidence level; p - True probability of the event; e - Sample error*)

Sample size was calculated using open access program such as EpiInfo5 and OpenEpi6 with:

Two-sided significance level(1-alpha): 95

Power (1-beta, % chance of detecting): 80

Ratio of sample size, Unexposed/Exposed: 1

Percent of Unexposed with Outcome:5

Percent of Exposed with Outcome: 14

Odds Ratio: 3

Risk/Prevalence Ratio: 2.7

Risk/Prevalence difference: 8.7

	Kelsey	Fleiss	Fleiss with CC
Sample Size: Exposed	178	177	200
Sample Size: Non-exposed	178	177	200
Total sample size:	356	354	400

CC – Continuity Correction

Results rounded off to the nearest integer. Using the highest estimates from Fleiss with CC, with an additional 10% to cater for attrition, the total sample size would be 420, with 210 per arm.

6.7. Study Procedures

6.7.1. Participant Recruitment

Once approval was obtained from the KNH-UON Ethics committee and other relevant departments within KNH, records of the women who delivered at the Kenyatta National Hospital between January and December, 2019were retrieved from the KNH Health Records and Information Department. They were be checked for completeness and those which met the inclusion criterion and do not fit in the exclusion criterion were included in the study. The information needed will be checked for from the files and captured in a questionnaire.

The patients' files will be examined the presence of one or more of the risk factors for PPH– which included A previous history of post-partum haemorrhage, Previous obstetric surgery like Cesarian Section and Myomectomy, and presence of bleeding disorders, Hypertensive disorders, diabetes mellitus, prolonged labor, placenta abruption, placenta previa, morbidly invasive placenta, Multifetal pregnancy, Intrauterine fetal demise and grand multiparity in the current pregnancy – to group them into the exposed groups. Those without any of the above risk factors were categorized under the unexposed group.

Information captured from their records included socio-demographics, maternal and currentcharacteristics, whether tranexamic acid was administered or not, and the dosage used, the estimated volume of blood lost, presence of a clinical diagnosis of post-partum haemorrhage, transfusion with blood products, use of additional forms of management for PPH, and the occurrence of adverse maternal outcomes.

6.7.2. Sampling

Simple random sampling technique was used to select the participants of the study from the population in the study period.

6.7.3. Consent

Consent was not required in this study since the data was retrieved from past records. However, permission to collect information from patient's records was obtained from the KNH-UON ERC, and the relevant departments that were involved in the study. We also endeavored to conform to the standards of both KNH-UON ERC and KNH where the study was conducted.

Randomization

There were no randomization procedures required in this study because of the nature of its study-design. However, the study participants were randomly selected from the pool of those who delivered in KNH between January and December, 2019.

6.7.4. Blinding

Being a retrospective cohort study, blinding was not required.

6.7.5. Interventions

Given that this was a retrospective cohort study, there were no interventions given, but instead we had exposed and unexposed groups. The former were those women having one or more of the risk factors for PPH while the latter comprised those without the risk factors. The risk factors for PPH that were looked at in this study will included: Previous history of PPH, previous uterine surgery, and current presence of placenta abruptio, placenta previa, bleeding disorder, hypertensive disorders, diabetes mellitus, prolonged labor, grand multiparity, multifetal pregnancy, morbidly invasive placenta and intrauterine fetal demise.

6.7.6. Data Collection

The participants' biodata was captured from the patient's file. This included antenatal, for those who attended ANC at KNH, intrapartum and post-partum.The data captured includedSocio-demographic and maternal attributes of the participants such as age, parity, level of education, medical and surgical history, previous obstetric history, physical examination findings, education and counselling information, present pregnancy information and laboratory test results. This data was collected by trained research assistantsand/or the principal investigator and was recorded in

the study data collection tool (questionnaire). Measurements of primary and secondary outcomes were also documented in the questionnaire.

At the end of each day, each questionnaire was counter-checked for completeness before being stored in a secure place, to minimize attrition due to incompleteness of data.

Data collected was kept confidential, until the completion of the study. The Data was then entered into the data management software for analysis.

Confidentiality was maintained through all these processes.

6.8. Data Variables

6.8.1. Data Variables table

Table 1:Data Variables used in the study

Objective	**Independent**	**Dependent**	**Source**
To compare the use of TXA between those with and without risk factors for PPH	Presence or absence of Risk factors for PPH	Use of Tranexamic acid to treat PPH	Patients' files
To determine the use of additional PPH management interventions (in addition to TXA) among those with and without risk factors for PPH	Presence or absence of Risk factors for PPH	Use of additional PPH management interventions (Additional Uterotonics, Blood transfusion, Surgical interventions)	Patients' files
To compare the incidence of adverse maternal outcomes between those with and without risk factors for PPH	Presence or absence of Risk factors for PPH	Presence of adverse maternal outcomes (ICU/HDU admissions, Prolonged Hospital Stay)	Patients' files

6.8.2. Outcome Measures

Our outcome measures included the following:

1. The use of Tranexamic acid
2. The cumulative dosage of TXA used in the treatment of PPH. This was grouped into two:

a. Less than or equal to 1g
b. More than 1g

3. The use of additional intervention(s) for PPH.
    a. The use of additional Uterotonics, besides the standard oxytocin as prescribed by standard operating procedures where available, or by common practice.
    b. Administration of blood products for management of PPH
    c. The use of Surgical interventions (Examination under Anaesthesia (EUA) and/or repair of perineal and/or cervical tears, intrauterine tamponade, arterial embolization, B-lynch sutures, uterine artery ligation, peri-partum hysterectomy, andlaparotomycarried out to control haemorrhage)
4. Adverse maternal outcomes [18]. These will include:
    a. Thromboembolic events such as Thrombosis of Deep veins, pulmonary thromboembolism, Myocardial infarct, and Cerebrovascular accidents
    b. Complications (kidney failure, heart failure, respiratory failure, liver failure, sepsis,and convulsions)
    c. Intensive Care Unit (ICU) and/or High Dependency Unit (HDU) admissions
    d. Prolonged Hospital Stay
    e. Any other documented adverse medical occurrence

6.9. Data Management and Analysis

6.9.1. Data Management

Data was collected using specially designed data collection questionnaires. This was done by the principal investigator or the trained research assistants. The collected data was verified by the data manager on a daily basis before uploading to a password protected excel sheet.

6.9.2. Data Analysis

Data was cleanedand analyzed using Stata 14 SE analysis package.

Socio-demographic and maternal characteristics of the participants, such as age, parity, level of education,werecompared between the two groups and presented in form of tables of frequencies and/or means.

Crude and adjusted Relative Risk was used to compare the use of TXA, the use of additional intervention(s) for PPH and the adverse maternal outcomes between the 2 groups.

p-value less than or equal to 0.05 was considered statistically significant.

6.10. Ethical Considerations

6.10.1. Ethical Review

This study sought the approval of the Kenyatta National Hospital and University of Nairobi Ethical Review Committee (KNH-UoN ERC) before commencement. Thereafter, further authorization was obtained from KNH administration to collect data at the hospital's Health Records and Information Unit using our data collection tools. The questionnaires were stored in a secure location.

The KNH-UoN ERC will reviewed and approved this proposal and the data collection tools prior to initiation of the study,as far as scientific content and how we comply with the applicable research and human subjects' regulations is concerned. There were no methodological changes that were required in the course of the study that would have required further review and approval from the committee.

The final report will be submitted to the KNH-UoN ERCafter the study. The reports will capture the total subjects enrolled into the study, the number that completed the study, all the changes in the research activity, and all other challenges that were not anticipated.

6.10.2. Informed consent

Being a retrospective study, with data being obtained from patients' records, informed consent was not a pre-requisite in the study. However, Approval from the Ethics committee, together with that from the relevant departments formed important checks to ensure that the study met the ethical standards required, and that the information captured would be safely and confidentially handled during and after the study.

There were no personal identifiers that were used to identify for participants. A unique study identification number wasallocated to each participant for the purpose of concealing identity. This identification number linked them to a log with their personal details. This information was be stored in a password-protected data base that would only be accessible to the principal investigator and/or authorized persons.

6.10.3. Risks

No particular risks, were anticipated during the study since it did not involve any human subjects, or any procedures. However, if any were to be faced, this would have been addressed accordingly. We ensured the participants privacy and confidentiality was maintained at all times.

It is possible that others could have knowledgea participant's involvement in the study, and consequently have access to their health information.We, however, believe there would be no stigma related to this and hence no harm in future care for the study participants.

6.10.4. Benefits

The participants will not get direct benefits from the study due to the non-human involvement. The information learnt from this study will benefit others in the future as it will inform the standard practices of preventing PPH.

Information derived from this study will as well form basis for future studies related to tranexamic acid and/or post-partum haemorrhage

6.10.5. Confidentiality

The information obtainedwas handled with Belmont's principles of confidentiality (Respect for persons, Beneficence and Justice). Each study participant wasgiven a unique study identity number to maintain confidentiality. The coded number identified all reports, data collected and other administrative forms. All the information on the participants and the study as a whole waskeptsecure and only accessible by study staff. All databases wereprotected with password(s).

During result dissemination, patient identities will still be kept confidential

6.10.6. Study Discontinuation

Since the study did not involve human or animal subjects, withdrawal from the study was not an issue to deal with.

However, the KNH-UoN-ERC had the right to terminate the study at any stage if deemed fit as per their regulations.

6.10.7. Training

Training of research assistantstook place in the week prior to commencement and during the course of the study. They were initially be observedas they collected the data and filled in the questionnaires, and thereafter allowed to work under supervision until when the principal investigator was satisfied with their understanding of the process. The principal investigator constantly reviewed the questionnaires for completion and accuracy.

6.10.8. Study Strength

The main strength of this study is that it was the first of its kind, and it was well powered for the main objective, despite having no prior study for estimation of proportions. It provides valuable information on the patterns of use of Tranexamic acid and other interventions for PPH, that may help in stratification of patients that may benefit from such interventions, both in clinical and research settings.

6.10.9. Study Limitations

Being a retrospective study, we did not have the control of accuracy of information captured. It is, therefore, expected that missing, or unverifiable, incomplete and/or inaccurate data would be a limitation in this study. However, due diligence was done to capture as much information from the records available as possible and our observation from the study was that this was minimal. Most of the data required was available in the records. Records missing more than 50% of the required information was excluded from the study.

6.10.10. Dissemination of Research Findings

A report of the findings of this trial shall be availed to all, who will be encouraged to give comment(s) on it.

In addition to the above, dissemination of the results will be carried out in 3ways:

- Compilation of a report that will be shared with the Department of Obstetrics and Gynaecology, and the KNH-UoN-ERC.
- Publication in a recognized and reputable journal.
- Presentation of the findings in national and/or international conferences.

7. RESULTS

7.1. Risk Factors for Post-partum Haemorrhage

The figure below shows the risk factors for PPH that were assessed for and used to categorize into either exposed or unexposed groups. Those who had one or more of these at the time of admission were categorized into the exposed arm while those without any formed the unexposed group. The most prevalent risk factor amongst the participants in the exposed group (n=222) was found to be a previous uterine surgery, followed by hypertensive disorders in pregnancy then prolonged labor in the current pregnancy. The sample did not have anyone with morbidly adherent placental disorders.

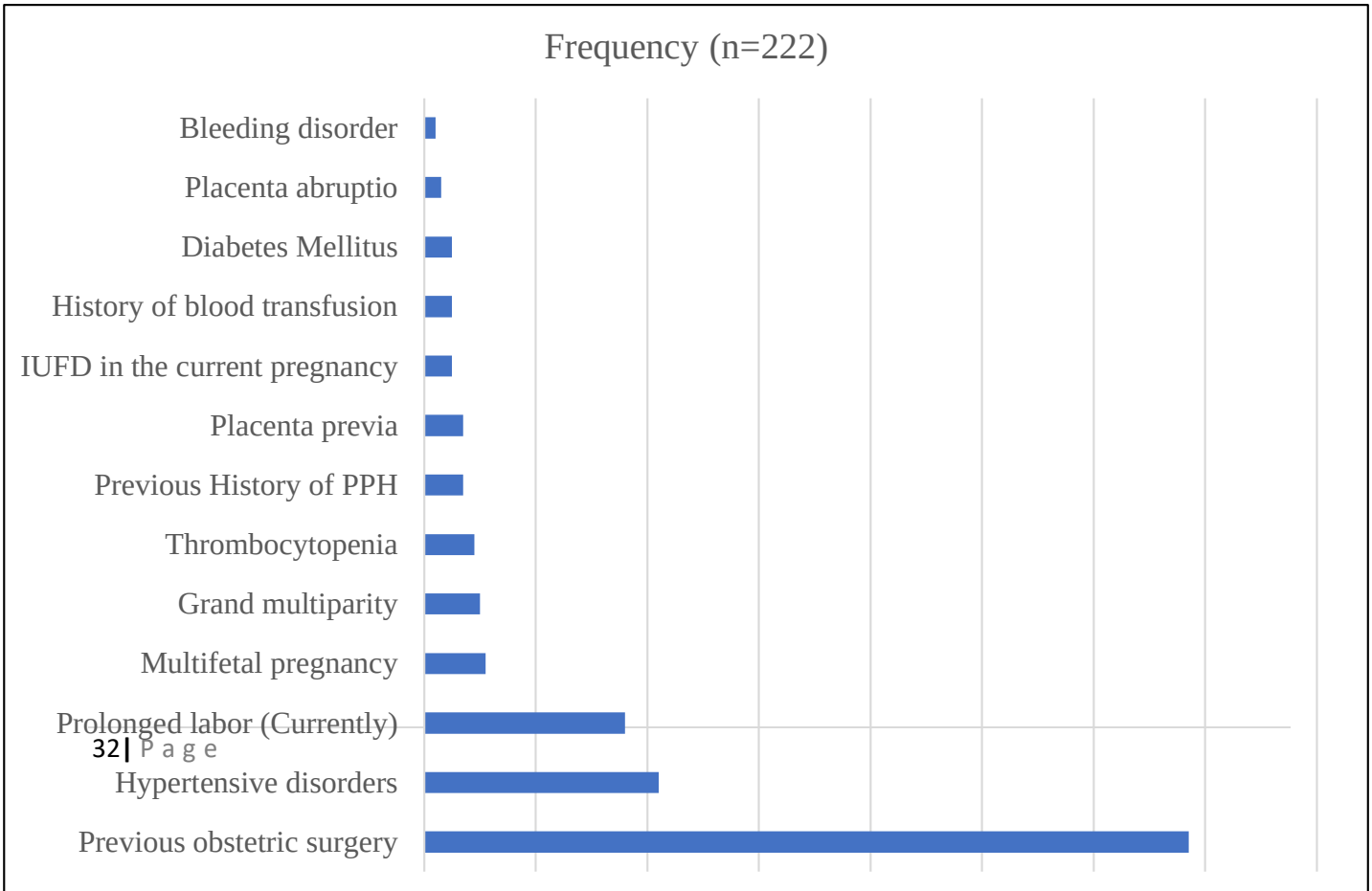

Figure 2: Risk factors observed amongst the exposed group

7.2. Characteristics of the Enrolled Participants

During period under which the study took place, there were 13, 806 deliveries in total, with 131,124 live births and 682 still births.Out of these, we randomlyselected 449 records of eligible participants, 12 of which were excluded (5 due to significantly missing data and 7 because the delivery was at a gestation less than 28weeks). Therefore, a final total of 437 participants were enrolled into the study and allocated into either the exposed (n=222) or the unexposed group (n=215) based on their risk status, and their data captured and subjected to analysis as shown in the figure 2 below:

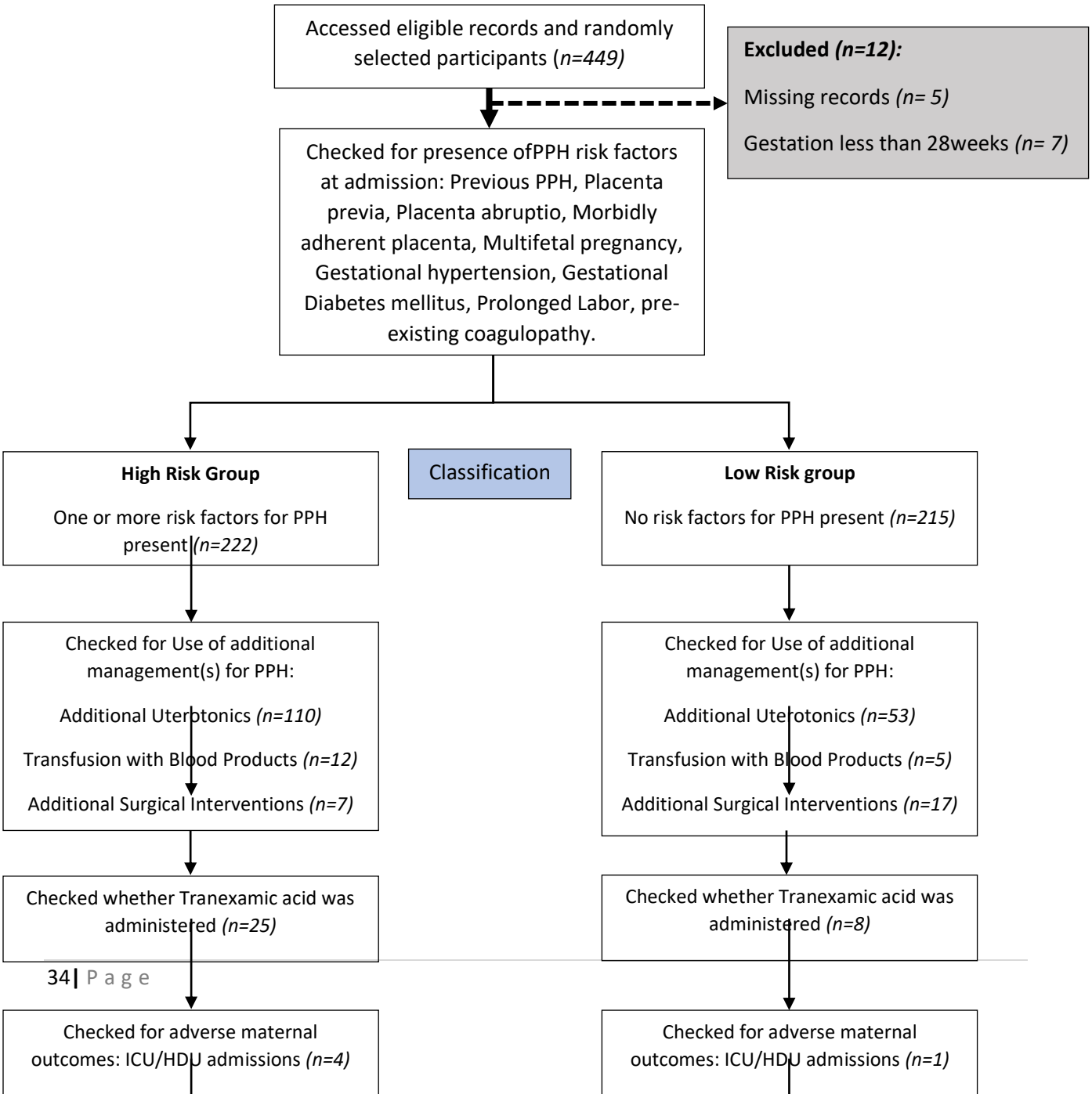
Accessed eligible records and randomly selected participants (n=449)
Excluded (n=12):
Missing records (n= 5)
Gestation less than 28weeks (n= 7)
Checked for presence ofPPH risk factors at admission: Previous PPH, Placenta previa, Placenta abruptio, Morbidly adherent placenta, Multifetal pregnancy, Gestational hypertension, Gestational Diabetes mellitus, Prolonged Labor, pre-existing coagulopathy.
High Risk Group
One or more risk factors for PPH present (n=222)
Classification
Low Risk group
No risk factors for PPH present (n=215)
Checked for Use of additional management(s) for PPH:
Additional Uterotonics (n=110)
Transfusion with Blood Products (n=12)
Additional Surgical Interventions (n=7)
Checked for Use of additional management(s) for PPH:
Additional Uterotonics (n=53)
Transfusion with Blood Products (n=5)
Additional Surgical Interventions (n=17)
Checked whether Tranexamic acid was administered (n=25)
Checked whether Tranexamic acid was administered (n=8)
Checked for adverse maternal outcomes: ICU/HDU admissions (n=4)
Checked for adverse maternal outcomes: ICU/HDU admissions (n=1)

Figure 3: Study flow chart showing the characteristics of the enrolled participants

7.3. Socio-demographic and Maternal Characteristics

The characteristics, both socio-demographic and maternal, of the 437 participants have been summarized in the table 1 below. The similarity in characteristics between the two groups demonstrates effective randomization when enrolling for participation. At the time of recruitment into the study, the distribution of marital statuses, levels of education and occupation was comparable between the 2 groups.

The mean age for the study participants was 29yrs, with the high-risk group having a mean of 30years versus 28years in the low-risk group. Majority of the participants were in the age category 26-35 years and this comprised 52.09% of the exposed arm which is almost similar to the same group in the unexposed arm that comprised 56.76%.

The total number of cesareans versus vaginal deliveries was almost equal (54.23% vs 45.77%) which mirrors well the distribution by mode of delivery in the year 2019 in KNH. Majority of those who delivered via cesarean section fell in the high-risk group (77.93% vs 29.77%), while for those who delivered vaginally, majority fell in the low-risk group (70.23% vs 22.07%).

Table 2: **Socio-demographic and maternal characteristicsby risk group**

Variable		**Risk Factor Status**		***p* - value**
		Low Risk (n=215)	**High Risk (n=222)**	
Age Group	**<=25 (n=136)**	79 (36.92%)	57 (25.68 %)	0.020
	26-35 (n=238)	112 (52.34%)	126 (56.76%)	
	>35 (n=62)	23 (10.73%)	39 (17.57 %)	
Mean Age	**29 (n=437)**	30	28	
Economic Status	**Unemployed (n=233)**	120(56.07%)	113 (50.90 %)	0.260
	Employed (n=203)	94 (43.93%)	109 (49.10%)	
Level of Education	**None (n=5)**	3 (1.43%)	2 (0.91%)	< 0.001
	Primary (n=97)	40 (19.05%)	57 (26.03%)	
	Secondary (n=176)	99 (47.14%)	77 (35.16%)	
	College/University(n=151)	68 (32.38%)	83 (37.90%)	
Mode of Delivery	**CS (n=237)**	64(29.77%)	173(77.93 %)	
	SVD (n=200)	151 (70.23%)	49 (22.07%)	
Parity	**Nulli-parity (n=137)**	82 (38.14%)	55 (24.77%)	0.003
	Low Multi-parity (n=284)	129 (60.00%)	155 (69.82%)	
	Grand multi-parity (n=16)	4 (1.86%)	12 (5.41%)	

7.4. Tranexamic use

Table 3: Tranexamic use, Additional uterotonic use, Surgical interventions, Blood products transfusionand HDU/ICU admissions by risk group

Variable	**PPH Risk Status: n (%)**		**Relative Risk (95%CI)** ***p-value***	
	High Risk (*n=222*)	**Low Risk (*n=215*)**	**Crude**	**Adjusted**
The incidence of use of IV 1g Tranexamic acid	25 (11.28%)	8 (3.72%)	3.026 (1.40-6.56) *p – 0.003*	1.84 (0.79-4.29) *p - 0.782*
The incidence of use additional uterotonics	110 (49.55%)	53 (24.77%)	2.00 (1.53-2.62) *p – <0.001*	0.85 (0.70-1.03) *P=0.09*
The incidence of surgical intervention(s) for PPH	7 (3.15%)	17 (7.91%)	0.42 (0.18-1.00) *p – 0.022*	0.98 (0.46-2.07) *p - 0.810*
The incidence of transfusion with blood products	12(5.88%)	5 (2.33%)	2.53 (0.92-6.97) *p – 0.062*	2.00 (0.80-5.03) *p - 0.013*
The incidence of HDU/ICU admissions	4(1.80%)	1(0.47%)	3.90 (0.44-34.54) *p – 0.187*	1.36 (0.13-14.54)

As shown in Table 3, those parturients who had risk factors for PPH were three times more likely to use tranexamic acid compared to those without (11.28% vs 3.72%, *RR 3.026, p-value 0.003*). When adjusted for age, parity and mode of delivery, however, the risk for use of TXA reduces to 1.9 times, and not statistically significant (*RR 1.84, p-value 0.782*).

7.5. Use of additional interventions for postpartum haemorrhage

7.5.1. Use of additional uterotonics

The comparison between presence of risk factors for post-partum bleedingversus the lack of them with the use of additional uterotonics has been illustrated in Table 3. The high-risk group was found to have been twice more likely to be given additional uterotonics in comparison with the low-risk group (49.55% vs 24.77%, *RR 2.00, 95%CI: 1.53-2.62, p-value <0.001*). Adjusting for age, parity and mode of delivery eliminates the higher risk for use of using additional uterotonics amongst the exposed group, though not statistically significant (*RR 1.85, 95%CI: 0.70-1.03,p-value 0.775*).

As shown below (Table 4), we found that different combinations of additional uterotonics were used, the commonest being additional oxytocin alone (*n=105*), followed by additional misoprostol alone (*n=32*), then combination of oxytocin, misoprostol and ergometrine (*n=17*). The least used was Ergometrine alone (*n=1*), in combination with oxytocin, misoprostol and Carbetocin (*n=1*), and the combination of misoprostol and Carbetocin (*n=1*)

Table 4:Additional uterotonics used

Variable	**Risk Factor Status: n (%)**		***p-value (Fisher's Exact)***
	High Risk (*n=222*)	**Low Risk (*n=215*)**	
Oxytocin (n=105)	73 (32.88%)	32 (14.88%)	0.008
Misoprostol (n=32)	26 (11.71%)	5 (2.33%)	
Oxytocin and Misoprostol (n=17)	9 (4.05%)	8 (3.72%)	

Oxytocin, Misoprostol and Ergometrine (n=4)	2 (0.90%)	2 (0.93%)	
Oxytocin and Carbetocin (n=2)	0 (0%)	2 (0.93%)	
Oxytocin, Carbetocin and Ergometrine (n=2)	0 (0%)	2 (0.93%)	
Oxytocin, Misoprostol, Carbetocin and Ergometrine (n=1)	0 (0%)	1 (0.47%)	
Misoprostol and Carbetocin (n=1)	0 (0%)	1 (0.47%)	
Ergometrine (n=1)	0 (0%)	1 (0.47%)	
Total	**110**	**53**	

7.5.2. Transfusion with blood products

As illustrated in Table 3 above, having risk factors for PPH was associated with a 2.5 times higher chance of being transfused with blood products when compared to those without risk factors (5.88% vs 2.33%, *RR 2.53, 95%CI: 0.92-6.97, p-value - 0.062*).The adjusted relative risk was slightly lower and statistically significant (*RR 2.00, 95%CI: 0.80-5.03,p-value 0.013*).

7.5.3. Surgical Interventions for postpartum haemorrhage

As shown in Table 3 above, the presence of risk factors for PPH was not associated with a higher risk of having surgical intervention(s)for PPH. The exposed group had an almost 3 times lower chance of undergoing surgical intervention(s) for PPH compared to the unexposed group. (3.15% vs 7.91%, *RR 0.420, 95%CI: 0.18-1.00, p-value - 0.022*). When adjusted for confounders,the relative risk was rises to almost 1though statistically not significant *(RR 0.98, 95%CI: 0.46-2.07,p-value 0.810)*.

The most common surgical intervention observed in the study was EUA and repair of cervical and/or perineal tear(s) (Table 5). We did not find any emergency hysterectomy done in the sample.

Table 5:Surgical interventions by risk group

Variable	**PPH Risk status: n (%)**		***p-value (Fisher's Exact)***
	High Risk (*n=222*)	**Low Risk (*n=215*)**	
EUA + repair of tear (n=20)	6 (2.7%)	14 (6.5%)	0.741
Haemostatic/Compression suture (n=2)	1 (0.45%)	1 (0.47%)	

Other Surgical interventions (n=1)	0 (0%)	1(0.47%)	
Repair of the Uterus (n=1)	0 (0%)	1(0.47%)	
Total	**7 (3.15%)**	**17 (7.91%)**	

7.6. Adverse Maternal Outcomes

Having PPH risk factors was associated with a higher probability of ICU/HDU admission {1.80% for the high-risk group vs 0.47% for the low-risk group *(Crude RR* 3.90, *95%CI: 0.44 – 34.54, p-value 0.187 and adjusted RR 1.36, 95%CI: 0.13 – 14.54)*}. Statistically, this was not a significant association.

This can be seen in the summary in Table 3

Only two participants were identified to have had prolonged hospital stay, and the number was too small to be subjected to analysis.

We did not assess for death in this study.

8. DISCUSSION, CONCLUSION AND RECOMMENDATIONS

8.1. DISCUSSION

In our study, we found a positive association between the presence of risk factors for PPHand the use of TXA. Those with the risk factors were twice as much likely to be given tranexamic acid as compared to those without. This could be explained by the pre-existence of some of the risk factors which put the caregivers on a high alert for PPH. This may prompt early interventions by the caregivers at the slightest provocation. It was also observed that a slightly bigger proportion of those with risk factors delivered via cesarean. One likely reason for this observation made may be that cesarean deliveriesare more likely to be carried outin the more complicated pregnancies, in whichthere is compromise of hemodynamic stability by the additional pathologic condition. The other possibility is that cesarean deliveries are usuallyrequiredin circumstances where already there is poorly controlled bleeding. Some of the factors whichwould increase the higher chance of Cesarean delivery include antepartum haemorrhage, prolonged labour and fetal distress, malpresentations, and macrosomia Tranexamic acid was more likely to be administered during cesarian than vaginal delivery. No studies have been identified for comparison with previous findings.

The presence of risk factors for PPH was associated with a twice as much higher risk of use of additional uterotonics (49.55%) as compared to those without (24.77%). This could also be explained by the presence of risk factors which would prompt early interventions at the earliest signs of significant bleeding, just like in the case of tranexamic acid. In our study we looked at both the use of additional individual and combined uterotonics. This finding was comparable to whatKoch et al, 2020, found after looking at a total of 717 prescriptions of misoprostol [56]. They found that 10% of thesehad been used for the treatment of PPH. The majority of those who

received the drug were multiparous (68.1%) and 25% had pastCS. The mean gestational age was 39 weeks and 51.4% had a CS. They also observed that 79.2% were also given oxytocin and 54.2% given additional methylergonovine. These observations support the finding that presence of risk factors would be associated with the use of uterotonics other than the standard prophylactic oxytocin.

The presence of risk factors for PPH also had a positive association with transfusion with blood products with an almost double risk of receiving transfusion with blood products with the presence of PPH risk factors (5.88% vs 2.33% for high vs low risk groups). Kolin et al, in their analysis of Crash-2 and WOMANS trial had a closer observation that PPH patients had a higher probability of transfusion with blood products if they had a CS (ARR 1.16; 95% CI 1.08–1.25), and if they were found to have any identifiable causes of obstetric bleeding other than uterine atony such as including surgical trauma or tears, placenta previa or accreta. [57].Ekeroma et al, in a 1997 RCOG article, cite Placenta Previa as being the most strongly identified antenatal risk factor for all red blood cell transfusions in Obstetrics, accounting for between 7% and 37%. Our observation of 6% is close to the minimum they observed in those with placenta previa. [58]. A number of epidemiological, retrospective and case-control studies were also able to identify other antenatal risk factors for blood transfusion. These included: pre-eclampsia, antepartum haemorrhage, multiple gestation, polyhydramniosand coagulation disorders. Intrapartum risk factors that were identified included: operative delivery, CS and labouraugmentation [58].

We further made observation that the presence of risk factors for PPH was associated with less chance of additional surgical interventions for PPH (3.15% for the high-risk group vs 7.98% for the low-risk group). This finding could be explained by the fact that majority of those without risk factors for PPH would be allowed to have a vaginal delivery, and hence these are more likely to end up having complications such as higher degree tear(s), retained placenta, cervical tear(s), among others and end up having EUA which was observed to be the most common surgical intervention. Abedzadeh-Kalahroudi et al, 2016, support this observation with their finding that the incidence of genital trauma was higher in younger age, those with lower parity and with increasing gestational age. These are likely to be of the lower risk group [59].Christianson et al, 2003, also found nulliparous women to be at higher probability of

sustaining tears (adjusted odds ratio, 10.0; 95% CI, 3.0-33.3) in comparison to the multiparous women [60].

Although the number was low there was an observed positive association between the presence of risk factors for PPH and HDU/ICU admissions {4 (1.80%) for the high-risk group vs 1 (0.47%) for the low-risk group} similar to what Selo-Ojeme et al, 2005, in a retrospective case-control study found. They observed that the main reasons for being admittedincluded hypertensive disorders (39.4%), and obstetric bleeding (36.4%) [61].They also observed that the women who were admitted to the ICU had significantly higher likelihood of being black ($P<0.05$), having a shorter mean duration of pregnancy (36.6 vs. 39.2 weeks; $P=0.006$), delivered via emergency CS($P<0.001$), and had a higher mean volume of blood lost at delivery (1,173 vs. 296 ml; $P<0.001$) supporting the likelihood of risk factors for PPH predisposing one to ICU admissions.

The main strength of this study is that it is the first of its kind, and was well powered for the main objective. It provides valuable information on the patterns of use of Tranexamic acid and other interventions for PPH, that may help in stratification of patients that may benefit from such interventions, both in clinical and research settings.

Being a retrospective study, we did not have the control of accuracy of information captured. It is, therefore, expected that missing, or unverifiable, incomplete and/or inaccurate data would be a limitation in this study. However, due diligence was done to capture as much information from the records available as possible and our observation from the study was that this was minimal. Most of the data required was available in the records. Records missing more than 50% of the required information was excluded from the study.

The presence of risk factors for PPH was associated with a 3 times higher risk of use of Tranexamic acid (in this case IV 1g) with {11.24% vs 3.72% *(RR 3.026, P-value 0.003)*}. When adjusted for confounders, the risk reduces to 2 times but not statistically significant *(RR 1.85, P-value 0.775)*.

8.2. CONCLUSION

TXA use is and use of additional uterotonics is higher in those with risk factors for PPH, but not statistically significant.

The presence of risk factors for PPH has a statistically significant higher rate of transfusion with blood products

Additional surgical interventions for PPH were lower in those with risk factors for PPH.

8.3. RECOMMENDATION

Our study suggests a positive relationship between the presence of risk factors for PPH at parturition and subsequent TXA and additional uterotonic use, and transfusion with blood products.

We, therefore, recommend more powered studies to validate this relationship, further studies to look at the feasibility of use TXA amongst the high-risk group and further additional studies to look prospectively, probably RCT, at the possibility of prophylactic use of TXA among those having PPH risk factors at the time of parturition.

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10.APPENDICES

10.1. APPENDIX I: DATA COLLECTION TOOL (QUESTIONNAIRE)

Study Title:RISK OF TRANEXAMIC ACID USE AMONGST WOMEN AT HIGH RISK OF POST-PARTUM HAEMORRHAGE DELIVERING AT KENYATTA NATIONAL HOSPITAL: A RETROSPECTIVE COHORT STUDY

DATE: _____Enrollment identification number: _____

Part 1: Biodata

Age: _____ Gravida: _____ Parity: _____

LMP: _____ EDD: _____ Gestational Age: _____

Marital status: _____ Highest level of education: _____

Occupation: _____ Residence: _____

Part 2: Antenatal Profile:

Hb: _____ g/dl Blood Group: _____ Rhesus: _____

VDRL: _____ HIV: _____ RBS: _____

Urinalysis: _____

Hepatitis B screening: _____ Any other test done: _____

Part 3: Medical and Surgical History (Risk profile for PPH): Indicate 'yes' or 'no'

Previous History of PPH _____

Previous Surgical operation (specify): _____

Bleeding Disorder: _____ Placenta previa: _____

Abnormally invasive placenta (placenta accreta/increta/percreta): _____

Abruptio placentae: _____ Eclampsia, HELLP syndrome: _____

Multiple pregnancy: _____ In utero fetal death: _____

Blood transfusion: _____ Diabetes: _____

Prolonged labor

Grand multiparity

Part 5: Delivery and Blood Loss measurement

Type of delivery: _____ Was there operative delivery?_____

Estimated blood loss:

Birth Weight:

Part 6: Any drugs given during Labour? (Specify Dosage and total amount administered): _

_____

_____

_____

_____

Part 7: Additional Interventions for Bleeding (Tick where appropriate):

Were additional uterotonic(s) used? _____ If yes, specify: _____

Were additional haemostat(s) used? _____ If yes, specify: _____

Was there blood transfusion?_____ If yes, how many Pints: _____

Were there any surgical intervention(s) for PPH? _____ If yes, specify: _____

_____

HDU/ICU admission related to PPH: _____

Was the hospital stay prolonged? _____

Outcome (Death or recovered): _____

Part 8: Adverse Events –any that is documented within 6 weeks post-partum (Indicate whether yes or no):

Deep vein thrombosis, **if the diagnosis is confirmed by Doppler ultrasound**: _____

Pulmonary embolism, **if the diagnosis is confirmed by radiological examinations**: _____

Myocardial infarction: _____ Seizure: _____

Renal failure needing dialysis: _____

Any other unexpected adverse events: _____

Part 8: Assessors comments:

Any comments about this assessment? _____

_____

_____

_____