UNIVERSITY OF NAIROBI
COLLEGE OF HEALTH SCIENCES
DEPARTMENT OF OBSTETRICS AND GYNAECOLOGY

COMPARISON OF SUBLINGUAL MISOPROSTOL AND INTRAMUSCULAR OXYTOCIN IN MANAGEMENT OF 3RD STAGE OF LABOUR IN KENYATTA NATIONAL HOSPITAL: RANDOMIZED CLINICAL TRIAL

DR. CYRUS KAMAU MUMBURA.

REGISTRATION NUMBER: H58/64033/2013

TELEPHONE NUMBER: 0727707202.

MB.ChB (UON)

A THESIS PRESENTED IN PARTIAL FULFILMENT FOR THE REQUIREMENTS FOR THE DEGREE OF MASTER OF MEDICINE IN OBSTETRICS AND GYNAECOLOGY AT THE UNIVERSITY OF NAIROBI.

DECLARATION

The records and commentaries presented in this thesis are my own original work and have not been presented in any other university for the award of an academic qualification. I further certify that the thesis was done under supervision of senior members of the department of obstetrics and gynecology, University of Nairobi.

Signed..... Date.....

Dr.Cyrus Kamau Mumbura.

Registration number: H58/64033/2013.

Phone number: 0727707202

Department of Obstetrics and Gynecology

University of Nairobi

APPROVAL OF SUPERVISORS

PROF KOIGI KAMAU Associate professor, department of obstetrics and gynecology,

University of Nairobi.

Signed.....Date.....

DR.WANYOIKE MB,ChB, M.MED

Senior Lecturer, Department of obstetrics and gynecology

University of Nairobi.

Signed.....Date.....

CERTIFICATE OF AUTHENTICITY

This is to certify that this research study was undertaken and written by Dr mumbura cyrus kamau and supervised by faculty in the department of Obstetrics and Gynaecology, University of Nairobi.

PROFESSOR OMONDI OGUTU, MB,ChB, M.MED(OBS&GYN), PGDRM

Associate professor and chairman,

Department of obstetric and gynaecology

University of Nairobi

Signature…… Date……

ACKNOWLEDGEMENT

First, I would like to thank the Almighty God for giving me courage and strength to complete this study.

My heartfelt appreciation to my supervisors for their continual guidance throughout this study.

DEDICATION

I dedicate this book to my lovely wife Ester Wangui Kamau who has been my true inspiration and my parents David Mumbura Kamau and Elizabeth Wanjiru Mumbura for their love and guidance, my lovely dughters Cynthia Wanjiru Kamau and Shanell Rengeria Kamau I love and you must work hard. God bless you all.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF ABREVIATIONS

FIGO	International Federation of Gynecology and Obstetrics.
IU	International units
IV	Intravenous
IM	Intramuscular
ICM	International confederation of midwives.
KNH	Kenyatta National Hospital
MCG	Microgram
NSAID	Non-steroidal Anti-inflammatory Drug
PPH	Post Partum Hemorrhage
SD	Standard deviation
SVD	Spontaneous vertex delivery
SPSS	Statistical Package for Social Studies
WHO	World Health Organization
RCT	Randomized controlled trial

ABSTRACT

Introduction: Third stage of labor is defined as the part of labor from the birth of the baby until the placenta (afterbirth) and fetal membranes are delivered. (1).Signs of third stage of labor includes, gush of fresh blood, and cord lengthening, globular and firm uterus and rise of the uterus anteriorly.

Everyday 800 women die from pregnancy or child birth related complications around the world, of these deaths most of them occur in developing countries. In 2013 for example 289,000 women died during and following pregnancy and child birth.(2).Of the global causes of maternal mortality;27% is attributed to severe bleeding after delivery,28% to pre-existing conditions,14% to pregnancy induced high blood pressure,8% to complications following abortion,11% to infections,9% by obstructed labor and other causes,3% to blood clots and embolism.(2).PPH is defined as blood loss of more than 500mls following vaginal delivery or more than 1000mls following cesarean section delivery. A loss of these amounts within the first 24hrs of delivery is referred to as primary PPH, whereas such an amount of blood loss occurring after 24hrs is termed as secondary PPH.WHO recommends the use of oxytocin 10i.u intramuscular in prevention of PPH. On the other hand, sublingual misoprostol is affordable, rapidly absorbed, efficacious and doesn't require refrigeration. There is little data on the effectiveness of misoprostol in comparison to oxytocin for prevention or management of third stage of labor in our set up.

Objective: To compare sublingual misoprostol 600 ug with intramuscular oxytocin 10 i.u. in management of 3rd stage of labor in low-risk vaginal birth at KNH.

Design: This study was an open blind randomized clinical trial.

Setting: Labor ward at Kenyatta National Hospital.

Sample size: 144 mothers who met the inclusion criteria were sampled out for inclusion in the study.

Methods: open blind randomized clinical trial was used at Kenyatta National Hospital from May 2016 through July 2016, 72 women were administered 10i.u oxytocin intramuscular while 72 women were given sublingual misoprostol 600mcg after the delivery of the anterior shoulder. The time taken to deliver the placenta was recorded, the amount of blood loss was estimated and the need for additional uterotonics was compared.

Data management: Data analysis was conducted using STATA version 12 (College Station, Texas. US). Initial descriptive analysis of patients was conducted according to treatment group to determine success of randomization. Continuous variables including age, were summarized using means and standard deviation and comparisons between the treatment arms was conducted using Student's t-test. The categorical variables e.g. education level were analyzed by calculating

frequencies and percentages followed by comparisons of frequency distributions conducted using Pearson's chi square test.

Main outcome measure: The primary outcome was the mean duration of third stage of labor. The mean duration (SD) of third stage was calculated in the two groups and based on tests of normality of residuals either a Student's t-test (normal distribution) or a Mann-Whitney test (skewed distribution) used for comparisons. The two secondary outcomes namely proportion of additional uterotonics used and proportion of excessive blood loss were determined through recording the respective variables into binary variables and calculating the corresponding percentages. Comparison of these outcomes and treatments were conducted using chi-square test. The magnitude of effect was presented as odds ratios and 95% confidence intervals derived from logistic regression models. For all analysis statistical significance was determined using a cut-off value of 0.05.

CHAPTER ONE

1.0INTRODUCTION

Of the estimated 287,000 maternal deaths worldwide, 85%occur in low- and middle-income countries [3]. In Kenya, the maternal mortality ratio is among the highest in the world, estimated at over 400 for every 100,000 women [4] and claiming the lives of over 6,300 mothers annually, more than Uganda which stands at 360 per 100000 women [4].

Primary Postpartum hemorrhage (PPH) is defined as blood loss of 500mls or more within 24 hours of delivery. (5) If such blood loss occurs from the genital tract after 24 hours and within first 6 weeks of delivery, then it is called Secondary PPH(6). Massive PPH is defined as blood loss of greater than 1000mls or 1500mls (7). Laboratory parameters include a drop in hemoglobin of 4gm% and acute transfusion of more than 4 units of blood. Early and accurate assessment of blood loss is important to prevent delay in management and prevention of morbidity. (8).

Oxytocin, a hormone that stimulates uterine contractions and limits uterine bleeding after birth, is the standard of care for prevention of PPH during the third stage of labor [9]. Oxytocin can be administered intramuscularly or intravenously as continuous infusion. Half-life of intravenously infused oxytocin is 3 minutes. It should not be used as a bolus as it causes a transient but marked fall in blood pressure followed by sudden rise in cardiac output which can be dangerous to already hypovolemic women (10). Oxytocin and its preservative chlorbutanol increase heart rate and have negative inotropic, antiplatelet and antidiuretic effect. Antidiuretic effect is responsible for water intoxication. It also causes nausea and vomiting. It requires storage at 15-30 degree centigrade (11).

The use of oxytocin in low-income countries, however, has historically been limited by a number of factors that includes; requirement for administration by a skilled personnel, maintenance of a cold chain storage and a requirement for sterile syringes and needles [12, 13]. Recent work has begun to challenge these limitations, as exemplified by effective administration of oxytocin by lay community health officers during home births [14].

Misoprostol is a prostaglandin E1 analogue, a methyl ester of prostaglandin E, which is methylated at C-16 (10). It is used orally for the treatment of peptic ulcer. It is a potent uterine stimulant administered orally and vaginally in the induction of abortion, cervical ripening and induction of labor. It doesn't cause hypertension and is effectively absorbed from the mucosa following oral, vaginal and rectal administration (15). It is also useful in the treatment of PPH unresponsive to oxytocin and ergometrine, (16) and its use has been suggested for the management of third stage of labor. Shivering and pyrexia are the main side effects of misoprostol, its other side effects are nausea, vomiting and diarrhea. (18)

Misoprostol has been proposed as an alternative strategy for prevention of PPH in settings where oxytocin use is not feasible. It has important advantages over oxytocin, including the potential for oral administration and a long shelf life at room temperature [21].Moreover, misoprostol can be administered sublingually, enabling a more rapid onset of action and greater bioavailability by avoiding first-pass metabolism [17]. These characteristics have led civil society organizations in Kenya to champion increased accessibility and use of misoprostol as a complementary drug to oxytocin in prevention of PPH [19]. Yet despite these advantages, sublingual misoprostol remains a second-line option to injectable uterotonics according to most recommending agencies [22, 23] because of insufficient [24] or conflicting [25] evidence about its efficacy in the active management of the third stage of labor. Although prior studies have compared injectable

oxytocin with misoprostol [23], the comparative efficacy of sublingual misoprostol versus oxytocin remains largely unknown because prior studies have focused on oral administration of misoprostol by less skilled birth attendants [26, 27], evaluated oral as opposed to sublingual administration of misoprostol [28], or evaluated suboptimal doses of either oxytocin [29], other injectable uterotonics, or misoprostol [30, 31].

Third stage of labor is defined as the part of labor from the birth of the baby until the placenta (afterbirth) and fetal membranes are delivered. (32).Signs of third stage of labor include; gush of fresh blood, cord lengthening, globular, firm uterus and rise of the uterus anteriorly.

Active management of third stage of labor is defined as use of uterotonic drugs immediately following delivery of the fetus,continuous cord traction and fundal massage immediately after delivery of the placenta, followed by massage of the uterus every 15 minutes for 2 hours. Early cord clamping has been excluded because of the benefits to the baby.(33).

Recommendations on management of 3rd stage of labor is use of uterotonic drugs within 1 minute after delivery of the baby and the abdomen has been palpated to exclude the presence of another baby. Oxytocin is the preferred uterotonic drug because its effective within 2-3 minutes after injection, has minimal side effects and can be used in all women. 10 IU is administered intramuscularly .In the absence of oxytocin ,ergometrin 0.2 mg i.m, syntometrine(1 ampoule) i.m or misoprostol 400-600 mcg orally can be administered(33).

We aimed to show the comparative benefit of oxytocin versus sublingual misoprostol at the World Health Organization recommended dose of 600 mcg [22], for prevention of PPH during active management of uncomplicated labor at a large referral hospital in a resource-limited setting. We hypothesized that sublingual misoprostol was non-inferior to oxytocin for prevention

of primary PPH.

CHAPTER TWO

2.0 LITERATURE REVIEW.

Maternal mortality rate still remains a big health concern all over the world. WHO reports almost 800 women dying every day because of pregnancy or childbirth related complications around the world. Almost all of these deaths occur in low resource setting, and most of these deaths can be prevented through active management of third stage of labor.

In a bid to reduce these rates around the world, maternal health was one of the goals developed and adopted by all the member states, committing to reduce the maternal rates by 2015.Although most of the countries have made efforts to meet these goal, WHO reports that maternal mortality rate remains still high, for example, in 2013, 289,000 women died during and following childbirth. (34).

PPH(blood loss of more than 500mls following vaginal delivery or more than 1000mls following caesarian section delivery)has been reported to be the most common cause of maternal mortality(27%)which mostly is caused by uterine atony following vaginal delivery. WHO, FIGO and ICM recommends the use of uterotonic drugs to aid in contraction of the uterus in combination with other means(active management of third stage of labor).Uterotonic agents increase the uterine tone and contractions, causing intensified uterine muscle contraction. The most used uterotonic drugs during the third stage of labor are oxytocin and misoprostol 10i.u i.v/i.m and 400-600 mcg orally/sublingually/rectally respectively.

According to WHO most of the maternal mortality rates occur in low resource setting making oxytocin, which needs to be refrigerated and also needs to be administered by a qualified trained personnel, in-efficient to be used in these low income setting. These factors require a more stable uterotonic drug to be used example misoprostol which can be taken orally and does not require refrigeration or trained health personnel to administer the drug.

2.1.1 **Global studies on uterotonic drugs**

A lot of organizations have conducted studies to find the effectiveness of oxytocin versus misoprostol. A study conducted by Gnuity health projects in five countries (Burkina Faso, Ecuador, Egypt, Turkey and Vietnam) to evaluate the safety, efficacy and acceptability of sub-lingual misoprostol found that:

Efficacy; sublingual misoprostol works well to control PPH, misoprostol and oxytocin had similar effects in treatment and prevention of PPH, both misoprostol and oxytocin stopped bleeding within 20 minutes of administration in nearly 90% of all the cases.

Safety and acceptancy; shivering and fever occurred more frequently with misoprostol. Among women given misoprostol fever of 40 degrees or more was common in one country, women reported acceptance of both oxytocin i.v/i.m and misoprostol sublingual and most of the side effects were tolerable.

Gnuity, in collaboration with the department of reproductive health and research at World Health Organization(WHO) in Argentina,Egypt,South Africa, Thailand and Vietnam on sublingual misoprostol reported that, sublingual misoprostol is safe, effective and acceptable alternative first line treatment for PPH due to uterine atony. The same study found out that misoprostol is easy to

administer and may be particularly useful in settings where administration of i.v oxytocin is not possible especially at lower level of health care systems. (35).

A study conducted in three hospitals in United States by the university of Toronto teaching hospital, to compare the efficacy of rectal misoprostol with oxytocin. In the study mothers were either given 400mcg of misoprostol per rectal or 10 i.u of oxytocin i.m or i.v. The study's primary outcome was the hemoglobin level changes from admission in early labor to a day postpartum. The study concluded that there was no difference between the efficacy of misoprostol and oxytocin and that they are equally efficient in preventing PPH (36).

A study done in Singapore to compare the oral misoprostol 400 mcg with i.m oxytocin 10 i.u in active management of third stage of labour. The primary outcome being the incidence of primary PPH and the secondary outcome a drop in hemoglobin concentration 48 hours after delivery and the need for extra uterotonic drug. The study found out that there was no occurrence of primary PPH, significant drop in hemoglobin concentration levels, there were no other significant secondary outcome measures except nausea which occurred in mothers given misoprostol. According to the researcher oral misoprostol is equally effective and as safe as i.m oxytocin in the active management of third stage of labor. (37)

Federation of Obstetrics and Gynecological Societies of India (FOGSI) conducted a study in India to compare the efficacy of 400mcg misoprostol, injection oxytocin 10i.u i.m, injection methylergometrine 0.2mg i.v and injection (0.5 mg ergometrine + 5 i.u oxytocin) on reduction of blood loss in the third stage of labor, duration of third stage of labor, effect on hemoglobin of the patient and the need for additional oxytocics or blood transfusion and associated side effects. The study showed that methylergometrine was superior to the rest of the drugs with the lowest

duration of third stage of labor and lowest incidence of PPH. There was no difference between the pre-delivery hemoglobin concentrations amongst the four groups. Misoprostol group showed significant need for oxytocic's and blood transfusion as compared to all other drugs. As regard to side effects misoprostol was associated with shivering and pyrexia in a significant number of patients as compared to the other drugs. Nausea, vomiting and headache were associated with methylergometrine and ergometrin-oxytocin group.

The study further concluded that methylergometrine had the best uterotonic drug profile as compared to the other drugs used, strongly favoring its use as an oxytocic for active management of third stage of labor. Misoprostol was found to cause a higher blood loss as compared to the other drugs hence should be used only in low resource setting where other drugs are not available. The group further suggested a research on the role of misoprostol in management of third stage of labor. (38).

Another study conducted in India to compare the efficacy of sublingual misoprostol in third stage of labor to prevent PPH with the main outcome measure being the postpartum blood loss and hemorrhage showed sublingual misoprostol is superior in minimizing blood loss postpartum as compared to im oxytocin, according to the study PPH occurrence was greater in patients who received oxytocin as compared to misoprostol 9.1% and 3.1% respectively, both drugs showed minimal blood loss less than 1000mls.Heamoglobin decrease was more in patients who received im oxytocin than sublingual misoprostol 45.6% and 9.7% respectively. The study concluded that sublingual misoprostol was a superior oxytocic agent to im oxytocin though the researcher recommended further studies to confirm these results.(39)

2.1.2 Regional studies.

A study done at a teaching and referral hospital in Harare Zimbabwe to compare oral misoprostol with intramuscular oxytocin in the management of third stage of labor with the primary outcome being incidence of PPH and any side effects. The results showed a small difference between the occurrence of PPH 15.2% in women given misoprostol and 13.3% in women given im oxytocin. The measured blood loss of more than 1000mls occurred in 3.7% of patients given misoprostol and 2% in women administered 10i.u oxytocin.

There was no significant need for additional oxytocic agent or blood transfusion in women given oral misoprostol. Shivering and pyrexia was the only side effect observed in women given misoprostol.

The study concluded that there was no difference between the effectiveness of oral misoprostol and i.m oxytocin in prevention of PPH, although the common side effects of misoprostol (shivering and pyrexia)were present, the study recommended misoprostol use to reduce the high prevalence of PPH in the developing countries which will subsequently reduce the maternal mortality rates in Africa.(40)

In a study conducted in Ghana to compare the effectiveness of oral misoprostol with i.m oxytocin 10 i.u in routine management of third stage of labor, eligible women were given 800mcg misoprostol orally or i.v oxytocin. The primary outcome being change in the hemoglobin level before and after delivery. The secondary outcome being other measure of blood loss and presumed side effects. The study found out that there was no significant difference between the oral misoprostol and oxytocin in the change of hemoglobin levels. The only significant secondary outcome was shivering and pyrexia which was common in patients given misoprostol.

The study concluded that misoprostol is as effective as oxytocin in minimizing blood loss during the third stage of labour. According to the study; misoprostol is a safe, inexpensive and effective uterotonic agent in rural and remote areas where oxytocin may be unavailable. (41)

A study done in Uganda to compare sublingual misoprostol versus intramuscular oxytocin for prevention of PPH, the primary outcome measure being PPH and the secondary outcome measure being measured blood loss of more than 1000mls,death,requirement for blood transfusion, haemoglobin changes and use of additional uterotonic agents.

The study found out that 28.6% of the women given misoprostol had primary PPH compared to 17.4% of the oxytocin group.Severe PPH occurred in 3.6% and 2.7% of participants in the misoprostol and oxytocin group respectively. There was no significant difference between the two groups in the secondary outcomes.

The study concluded that misoprostol 600 mcg is inferior to oxytocin 10 i.u for prevention of primary PPH in active management of third stage of labor. The study recommended clear documentation in which settings to use sublingual misoprostol in third stage of labour.(42)

2.2 Study rationale and the gaps.

Minimal research has been conducted to show the efficacy of sublingual misoprostol compared to oxytocin in active management of third stage of labor in Kenya. Though studies have shown that oxytocin is better in prevention of primary PPH than misoprostol, its use in low resource settings has been shown to be a disadvantage. (38)

Though a similar study was done in Mbaara Uganda, their main outcome measure was a drop in hematocrit level. This study differed from that study in that it was checking the duration of the

3rd stage of labor and the need for additional uterotonic drugs among the patients receiving the two drugs.

Research question:

Is administration of sublingual misoprostol as effective as administration of intramuscular syntocinon in management of 3rd stage of labor?

HYPOTHESIS.

Null hypothesis: sublingual misoprostol is inferior to intramuscular oxytocin in management of 3rd stage of labor.

Alternative hypothesis: sublingual misoprostol is non-inferior to intramuscular oxytocin in management of 3rd stage of labor.

Broad objective

To compare sublingual misoprostol 600 ug with intramuscular oxytocin 10 i.u. in management of 3rd stage of labor in low-risk vaginal birth at KNH.

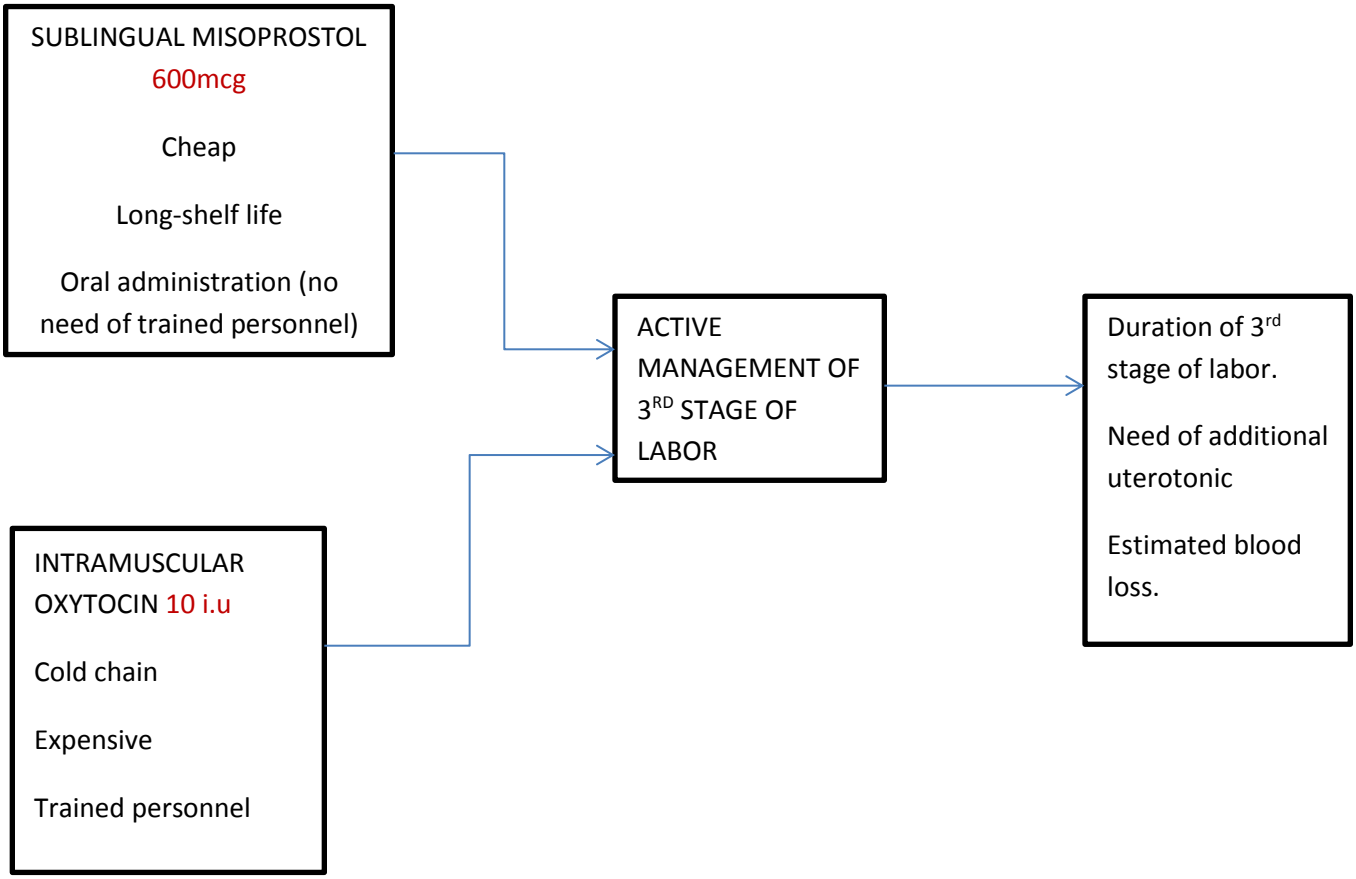
Specific objectives:

i) To compare the duration of third stage of labor in patients receiving sublingual misoprostol compared to intramuscular oxytocin

ii) To compare the use of additional uterotonic drugs among patients receiving sublingual misoprostol compared to intramuscular oxytocin during third stage of labor

iii) To compare the estimated blood loss in patients receiving sublingual misoprostol compared to intramuscular oxytocin during third stage of labor

CONCEPTUAL FRAMEWORK



3.0 METHODOLOGY.

3.1 Study design

Open blind randomized controlled trial compared oral misoprostol 600 u.g with intramuscular oxytocin 10 i.u. in management of third stage of labor in KNH. Mothers who met the study criteria were grouped into two groups, one group was given 600 mcg sublingual misoprostol

while the other was administered i.m oxytocin 10 i.u after the delivery of the anterior shoulder. Delivery was conducted by a midwife, 3rd stage of labor was managed by early cord clamping and cutting, controlled cord traction and uterine massage. Continous variables such as age, parity, weight, gestational age, duration of third stage of labor, amount of blood loss was visually estimated, the time taken during the 3rd stage of labor was taken using a stop watch and the need for additional uterotonic drug was assessed.

3.2 **Study site and setting**

Kenyatta National Hospital is the oldest hospital in Kenya, located at the capital Nairobi, it was founded in 1901 with bed capacity of 40 as the native civic hospital. In 1952 it was renamed king George VI. It was later renamed Kenyatta National Hospital in 1963.Currently it is the largest referral and teaching hospital in the country.

It covers an area of 45.7 hectares, within the complex there are institutions such as College of Health Sciences University of Nairobi, Kenya Medical Training College, Kenya Medical Research Institute and National Laboratory Services.

KNH has 50 wards, 22 outpatient clinics, 24 theatres (16 specialized) and accident and emergency departments. Total bed capacity 1800 of those 209 is private wing. It has a staff capacity of 6000 staff members.

The maternity ward has 43 nurses 3 of whom are in managerial posts. At any given time there are 13 nurses,1 registrar,1 medical officer intern,1 clinical officer intern and 2 consultants(1 junior and 1 senior).There are 700 spontaneous vaginal deliveries and an average of 400 caesarian section(emergency and elective) every month.

Rationale of study site.

Kenyatta National Hospital is a teaching and referral hospital.

Kenyatta National Hospital has large number of patients which favor's the study.

3.3 Participants and Recruitment

Midwife research assistants (MRA'S) screened laboring mothers in early labor on arrival to the prenatal ward.

Eligibility for inclusion in the study was:

- Age above 18 years
- 38-41 weeks of amenorrhea
- Anticipated uncomplicated vaginal delivery.

Exclusion criteria was:

- Confirmed intra-uterine fetal death
- Self-reported maternal heart disease
- Acute bacterial infection
- Multiple pregnancy
- Induced labor
- Elective cesarean section
- Emergency cesarean section
- Previous cesarean section
- Antepartum hemorrhage

- Reported hypersensitivity to prostaglandins
- Altered cognitive status.
- Mothers who refused to give a consent

MRAs obtained informed consent from all eligible participants after the birth was predicted to be an uncomplicated vaginal delivery. An MRA trained in human participant research conducted informed consent procedures with eligible mothers in the local language in a private area of the hospital. Only mothers in the early stages of labor (less than 6 cm dilation) were approached. All consenting participants were given written informed consent, or for those who could not write, a thumbprint was taken on the consent form.

3.4 Sample size & sample size determination.

Formula for calculating sample size in non-inferiority trials by Julios SA (40) was used to determine the required sample size:

$$n = f(\alpha, \beta) \times 2 \times \frac{\sigma^2}{d^2}$$

Where σ is the standard deviation around the duration of third stage of labour estimated as 20.4 (Elsafty MS, 2015)

$f(\alpha, \beta) = [\Phi^{-1}(\alpha) + \Phi^{-1}(\beta)]^2$

$\Phi^{-1}(\alpha)$ is the cumulative distribution function of a standardized normal deviate for 95% confidence level (5% type I error rate) estimated at 1.96

$\Phi^{-1}(\beta)$ is the cumulative distribution function of a standardized normal deviate for a power of 90% estimated as 1.24

$$n = 10.5 \times 2 \times \frac{20.4^2}{10^2}$$

n (sample size per group) =144

3.5 Data collection

A stop watch was used to measure the time taken during the 3rd stage of labor.

The need for an additional uterotonic drug was assessed and recorded. Visual estimation of blood which may have spilled on the floor was made.

3.6 Data entry – software (SPSS) for database design, database structure– coding, range and values checks for data entry fields, data entry process, data storage and archiving

3.7 Data quality assurance

There was an independent DMC which ensured there was no biasness in collection of data. We trained the MRA'S on research ethics. We developed an SOP for the study which we trained the MRA'S on them. We went through the questionnaires for data completion, any questionnaire missing this data was referred back for completion.

3.8 Drug quality assurance.

We used drugs that were outsourced by KNH i.e. sublingual misoprostol and i.m. oxytocin, the chief pharmacist through whom the drugs were procured gave a guarantee that the drugs were procured from reputable companies which were registered with the Kenya Pharmacy and Poisons Board. In collaboration with these companies they maintained the cold chain to the hospital and in the hospital they maintained the cold chain up to the wards. The hospital has laid down mechanisms to audit the potency of the drugs regularly.

3.9 Limitations

The study was conducted among few selected sample size of mothers during the 3rd stage of labor at KNH. The outcome might not have necessarily shown the drug effectiveness of all the women as there usually is a difference in drug reaction between one person to another.

The study was conducted in a short time which may have limited the researcher to few outcomes.

The data collection tool may not have exclusively given the actual amount of blood loss as there is always a margin of error in human estimation of blood loss which may vary from one person to another.

There was a chance that some participants might have developed PPH, this was dealt with according to the KNH protocols on management of PPH.

3.10 Intervention.

Eligible mothers and those consented to participate in the study were grouped into two groups through random sampling technique, one group was administered with i.m oxytocin 10 i.u while the other group was given sublingual misoprostol 600mcg.The uterotonic drugs were

administered after delivery of the baby as per the recommendations by FIGO/WHO/ICM for active management of third stage of labor.

3.11 Outcome.

Primary outcome measure: mean duration of 3rd stage of labor.

Secondary outcomes:

- Requirement for blood transfusion
- Requirement of additional uterotonic drugs
- Visually estimated blood loss.

3.12 Sequence generation.

To minimize the risk of selection bias a computer random number generator was used for random sequence generation. The allocation sequence generation was conducted by an independent statistician using STATA program with varying block sizes of between two and six.

3.13 Allocation concealment mechanism.

The statistician was responsible for ensuring allocation concealment using opaque envelopes that were delivered to the maternity unit in adequate numbers to cover anticipated allocation for each week of the study. These envelopes were stored in lockable cabinets within the unit. Patient allocation was not revealed until the patient's eligibility for the study was determined and consent for participation obtained. Once a patient was recruited the envelope with treatment allocation was opened and contained a card with either oxytocin or misoprostol.

3.14 Blinding and drug administration

This trial was an open blinded trial comparing a sublingual and injectable treatment. Due to the formulation and procedures for administering the trial drugs both investigators and patients were aware of treatment administered. The uterotonic on the card was given within one minute of delivery, delayed cord clumping was preferred, placenta was delivered by controlled cord traction or manually if not delivered within 30 minutes postpartum as per the hospital clinical guidelines. Further care was given by the hospital clinical team in collaboration with MRA'S in accordance with national guidelines which recommends (bladder emptying, management of laceration and uterine massage).All mothers were monitored upto a minimum of 24hrs postpartum.

3.15 Statistical analysis.

Data analysis was conducted using STATA version 12 (College Station, Texas. US). Initial descriptive analysis of patients was conducted according to treatment group to determine success of randomization. Continuous variables including age, were summarized using means and standard deviation and comparisons between the treatment arms were conducted using Student's t-test. The categorical variables e.g. education level were analysed by calculating frequencies and percentages followed by comparisons of frequency distributions conducted using Pearson's chi square test. The primary outcome was the mean duration of third stage labour. The mean duration (SD) of third stage was calculated in the two groups and based on tests of normality of residuals either a Student's t-test (normal distribution) or a Mann-Whitney test (skewed distribution) used for comparisons.

The two secondary outcomes namely proportion with additional uterotonic used and proportion with excessive blood loss were determined through recoding the respective variables into binary variables and calculating the corresponding percentages. Comparisons for these outcomes and treatment were conducted using chi-square test. The magnitude of effect was presented as odds ratios and 95% confidence intervals derived from logistic regression models. For all analysis statistical significance was determined using a cut-off value of 0.05.

3.16 Study measures.

MRA'S recorded;

- Vital signs
- Duration of 2nd stage of labor
- Duration of 3rd stage of labor
- Secondary use of open labeled uterotonics
- Placenta retention
- Requirement for blood transfusion
- Side effects.

All mothers will be given pre-weighed standard sanitary pads to place on the perineum at all times. These pads will be changed and weighed hourly for the first 6 hours and 6 hourly until 12 hours are over. Estimation of blood loss as 1 ml per gram of weight of the pad after subtracting the dry pad weight (37).

This estimated blood loss will be added to the volume of blood from the plastic sheet. To improve consistency in estimation of blood loss standardized electronic scales will be used to weigh soiled sanitary pad.

3.17 Ethical consideration

The research process begun by obtaining an approval from the department of obstetrics and gynecology, University of Nairobi, research permit from the Kenyatta National Hospital Research and Ethical Committee.

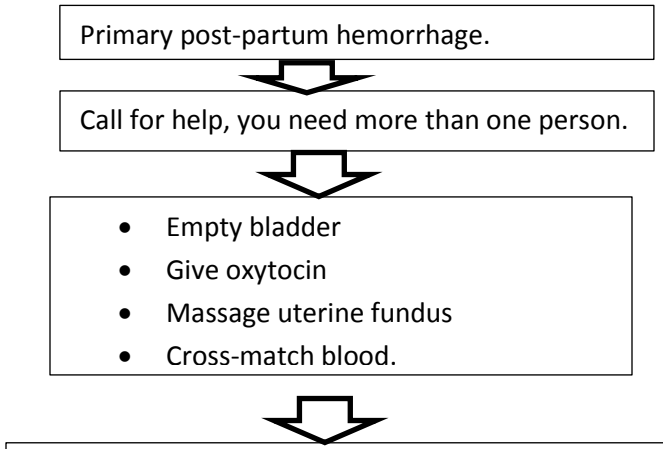
We formulated a data safety and monitoring committee, which was independent, the DMC monitored the whole research study preventing any aspect of biasness and also any leakage of the data collected.

We trained the research assistants in management of 3rd stage of labor and data collection**.**

For the patients who developed PPH we followed the laid down protocol from the hospital, which included emptying of the bladder, intramuscular oxytocin, massage of the uterine fundus and blood transfusion.

The chart below illustrates the KNH PPH management protocol which was adhered to.

KENYATTA PROTOCOL FOR MANAGEMENT OF PPH



DATA MANAGEMENT COMMITTEE

The DMC constituted of:

Chairlady

Dr.RN – clinician department of oby/gyn UoN

Email:nyokabirn@gmail.com

Phone number: 0724785403

P A – Statistician KEMRI

Email:ayiekolo@yahoo.com

Phone number: 0724236100

TK – laboratory technologist Aga Khan University Hospital Nairobi

Email:tkyalo@yahoo.com

Phone number: 0727731762

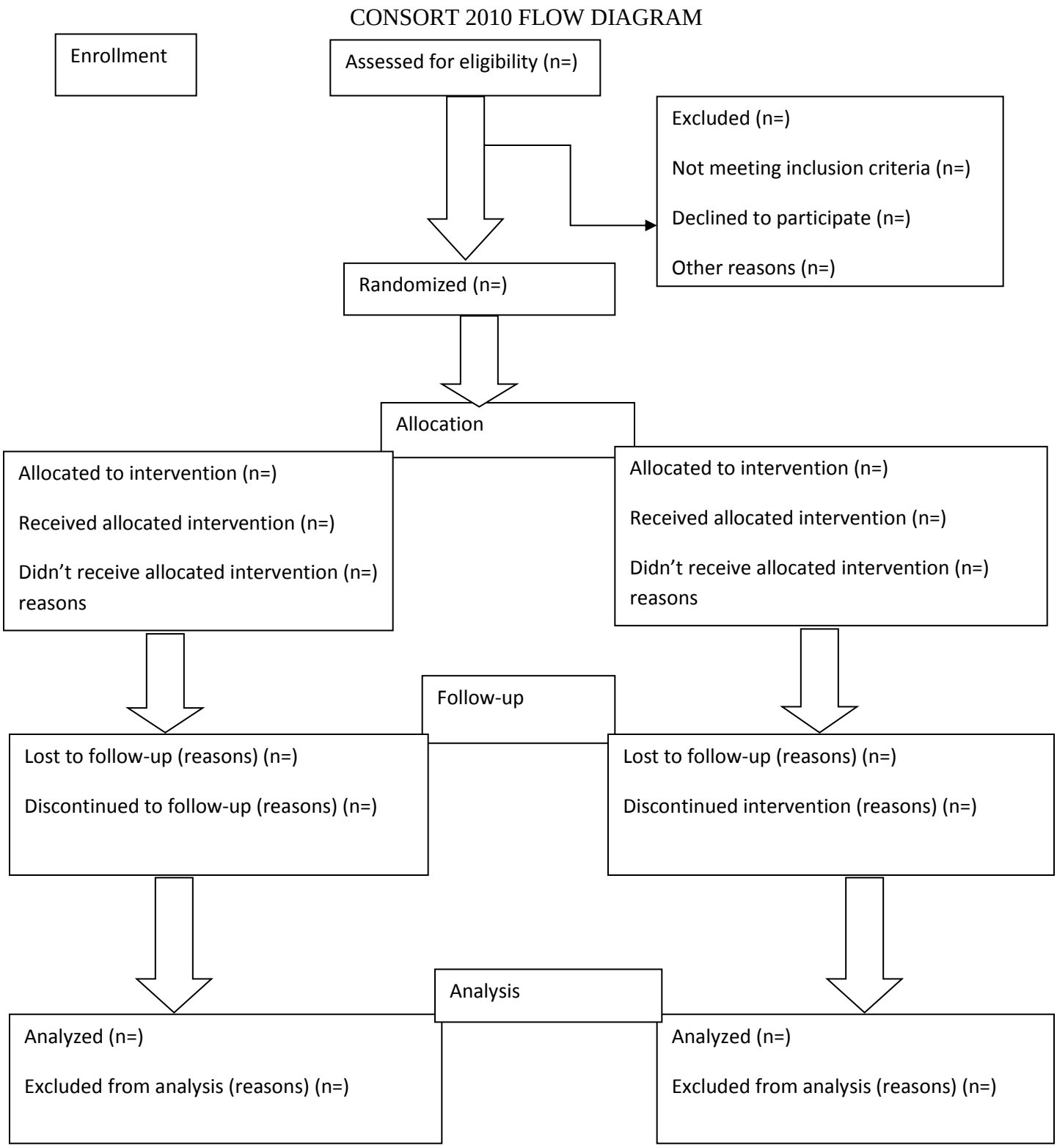
D M – clinical nurse Aga Khan University Hospital Nairobi

Email:Daniel.mbatha@aku.edu

Phone number: 0710759868.

The DMC met before the commencement of the data collection to chat a way forward on issues to include, data management, data quality, data archiving, recruitment and remuneration of MRA'S among others.

SCHEMATIC FLOW CHART OF THE STUDY DESIGN.

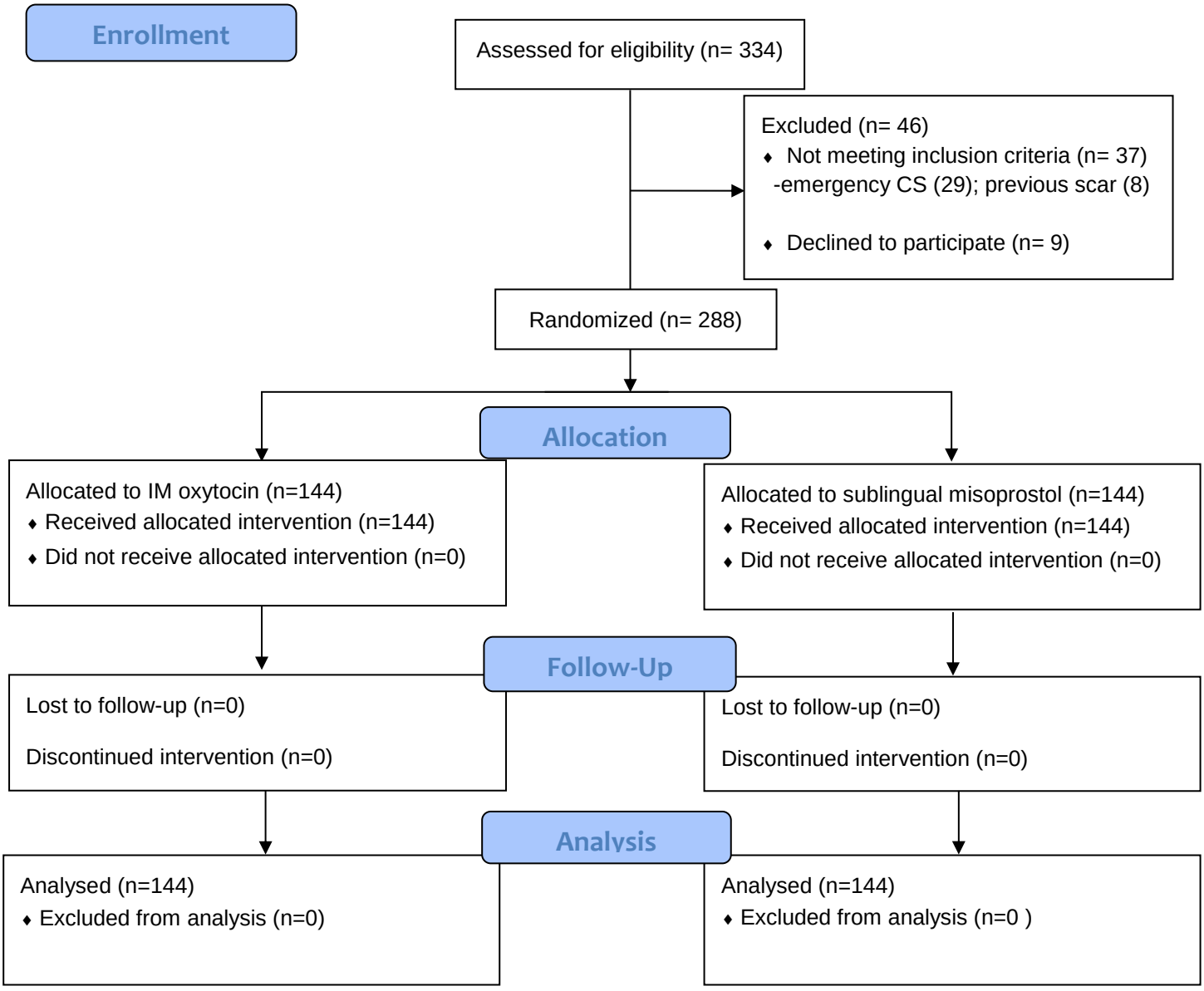


CHAPTER FOUR

RESULTS

Out of the 334 women assessed for eligibility a total of 288 met the inclusion criteria. Of these mothers 9 declined to participate and 288 were recruited into the study and allocated to sublingual misoprostol (n = 144) or intramuscular oxytocin (n = 144) for the management of 3rd stage of labor. Figure 1 shows detail of maternal enrollment, allocation to intervention, follow up and analysis.

Figure 1: Trial profile (CONSORT 2010 flow diagram)



The mean age (± SD) of mothers in the IM oxytocin group was 26.6 (± 7.7) years compared to 27.7 (± 5.5) years in the sublingual misoprostol group. Most women in both treatment arms were: aged 20-24 years (21.4 and 25.7%) or 25-29 years (32.9 and 55.7%), married (68.6 and 74.4%), and self-employed (50 and 48.6%).

There were no significant differences between the treatment arms in terms of age ($p = 0.764$), parity ($p = 0.287$), marital status ($p = 0.546$), formal education ($p = 0.081$) or occupation ($p = 0.102$), Table 1.

Table 1: Characteristics of mothers randomized to sublingual misoprostol and intramuscular oxytocin during third stage of labor

	Treatment group				
	Sublingual misoprostol n(%)	**IM oxytocin n(%)**	**Chi (χ2)**	**DF**	**P value**
Age					
<20 years	12(8.6%)	10(7.1%)	1.8	4	0.764
20-24 years	31(21.4%)	37(25.7%)			
25-29 years	47(32.9%)	51(35.7%)			
30-34 years	37(25.7%)	29(20%)			
35 years and above	16(11.4%)	16(11.4%)			
Parity					
Para 0	65(45.1%)	53(37.1%)	3.8	3	0.287
Para 1	44(30.6%)	45(31.4%)			
Para 2	23(15.7%)	25(17.1%)			
Para 3 and above	12(8.6%)	21(14.3%)			
Marital status					
Single	39(27.1%)	33(22.6%)	1.2	2	0.546
Married	99(68.6%)	107(74.4%)			
Single ever married	6(4.2%)	4(3%)			
Formal education					
Primary	29(20%)	41(28.6%)	5.0	2	0.081
Secondary	53(37.1%)	37(25.7%)			
College	62(42.8%)	66(45.7%)			
Occupation					
Formal	41(28.6%)	33(22.9%)	4.6	2	0.102
Self	72(50%)	70(48.6%)			
Not employed	31(21.4%)	41(28.6%)			

Table 2 shows that based on the primary outcome of duration of third stage of labor sublingual misoprostol was non-inferior to IM oxytocin (p = 0.185). Two patients (1.4%) in the sublingual misoprostol group had third stage labor duration longer than 30 minutes. Thirty eight percent (56/ 144) and 47.2% (68/ 144) of women in the sublingual misoprostol and IM oxytocin groups, respectively had durations of 3rd stage lasting 10-30 minutes (OR = 1.37, 95% CI 0.86-2.20) compared to durations less than 10 minutes (59.7% and 52.8%, respectively).

Table 2: Primary outcome of mothers randomized to sublingual misoprostol and intramuscular oxytocin during third stage of labor

	Treatment group			
	Sublingual misoprostol	**IM oxytocin**	**OR (95% CI)**	**P value**
Duration of third stage of labor				
< 10 minutes	86(59.7)	76(52.8)	1.0	
10-30 minutes	56(38.9)	68(47.2)	1.37(0.86-2.20)	0.185
> 30 minutes	2(1.4)	0(0.0)	NA	

Table3 shows that sublingual misoprostol was non-inferior to IM oxytocin for all the secondary outcomes (p values > 0.05). Placenta retention was rare in both the sublingual misoprostol (2/ 144; 1.4%) and IM oxytocin group (1/144, 0.7%) OR = 2.01, 95% CI 0.18-22.46. The need additional uterotonics was 4.2 and 6.3% in sublingual misoprostol and IM oxytocin group (p = 0.429) and IV fluids were required in 45.8 and 38.9% of women in labor in the two arms, respectively (p = 0.233). The estimated blood loss was not significantly different between the treatment arms, although 7/144 (4.9%) and 4/144 (2.8%) women in the IM oxytocin groups and

6/144 (4.2%) and 2 (1.4%) women in the sublingual misoprostol group had blood loss of 500-999 mls and 1000 mls or greater, respectively.

Table 3: Secondary outcomes of mothers randomized to sublingual misoprostol and intramuscular oxytocin during third stage of labor

	Treatment group		OR (95 % CI)	P value
	Sublingual misoprostol	IM oxytocin		
Placenta retention				
Yes	2(1.4)	1(0.7)	1.00	
No	142(98.6)	143(99.3)	2.01(0.18-22.46)	0.569
Added uterotonics				
Yes	6(4.2)	9(6.3)	1.00	
No	138(95.8)	135(93.8)	0.65(0.23-1.88)	0.429
Need for IV fluids				
Yes	66(45.8)	56(38.9)	1.00	
No	78(54.2)	88(61.1)	1.33(0.83-2.12)	0.233
Estimated blood loss				
0-499 mls	136(94.4)	133(92.4)	1.00	
500-999 mls	6(4.2)	7(4.9)	1.19(0.39-3.64)	0.757
1000 mls and above	2(1.4)	4(2.8)	2.05(0.37-11.35)	0.413

Table 4 presents fetal outcomes according to treatment group. Most babies in both sublingual misoprostol and IM oxytocin group had 5 minute APGAR scores above 7 out of 10 (128 [88.9%] and 124 [86.1%], respectively; p = 0.467]. There was no significant differences in fetal outcomes

with 136 (94.4%) and 135 (93.8%) of babies in the treatment groups being born alive (p = 0.777).

Table 4: Fetal outcomes among babies born to mothers in sublingual misoprostol and intramuscular oxytocin trial

	Treatment group		OR (95% CI)	P value
	Sublingual misoprostol	IM oxytocin		
Fetal outcome (n = 288)				
Still birth	6(4.2)	5(3.5)	1.00	
Fresh/Macerated baby	2(1.4)	4(2.8)	2.40(0.30-19.04)	0.407
Alive	136(94.4)	135(93.8)	1.19(0.36-4.00)	0.777
APGAR at 5 minutes (n = 271)*				
<=7	8(5.6)	11(7.6)	1.00	
>7	128(88.9)	124(86.1)	0.70(0.27-1.81)	0.467

*excludes still births and fresh/ macerated births

There were no maternal deaths in the trial (table 5).Maternal transfusion rates (2.1 and 4.2% for sublingual misoprostol and IM oxytocin, respectively) did not differ significantly across the treatment arms, p = 0.310. Most mothers in both groups did not undergo any surgical procedures during delivery (40.3% versus 48.6, p = 0.635%). Episiotomies were performed in 38 (26.4%) and 40 (27.8%) mothers allocated to sublingual misoprostol and IM oxytocin.

Table 5: Maternal outcomes among participants in sublingual misoprostol and intramuscular oxytocin trial

	Treatment group		OR (95% CI)	P value
	Sublingual misoprostol	IM oxytocin		
Mother alive	144(100.0)	144(100.0)	NA	
Blood transfusion				
Yes	3(2.1)	6(4.2)	1.00	
No	141(97.9)	138(95.8)	0.49(0.08-2.35)	0.310
Surgical procedures				
Episiotomy	38(26.4)	40(27.8)	1.00	
Perineal tears	42(29.2)	34(23.6)	0.77(0.41-1.45)	0.417
None	58(40.3)	70(48.6)	1.15(0.65-2.02)	0.635

CHAPTER FIVE

DISCUSSION

This hospital based randomized controlled trial of sublingual misoprostol administered during third stage of labor showed non-inferiority of this treatment compared to the standard intramuscular oxytocin in third stage labor. Sublingual misoprostol was also non-inferior to intramascular oxytocin in the prevention of PPH and use of additional uterotonics. There were no maternal deaths in the study.

Duration of third stage

As expected the duration of third stage for most mothers was less than 10 minutes with 59.7% and 52.8% of mothers in the sublingual misoprostol and IM oxytocin groups having durations of third stage < 10 minutes. This finding is similar to that of previous RCTs comparing duration of third stage in women receiving either oral misoprostol or IM oxytocin. At least 50% of mothers in these earlier studies had third stage durations lasting at least 5 minutes with median durations between 5 and 5.37 minutes with oxytocin and 5.23 and 5.5 minutes with misoprostol. (41, 42)

The current trial reported no difference in the duration of third stage labor in women receiving sublingual misoprostol compared to those receiving IM oxytocin. This finding agrees with earlier reports by Aziz and colleagues in Pakistani women and Oboro and Tabowei in Nigeria that showed non-inferiority of sublingual misoprostol compared to IM oxytocin in terms of duration of third stage. (41, 43) However, there are conflicting reports in literature that demonstrate that duration of third stage is shorter in IM oxytocin compared to sublingual misoprostol group. (42) Delayed third stage lasting at least 30 minutes was rare and occurred in only 1.4% of cases. Although the current trial reports no significant difference in duration of third stage it is

important to note that the two cases of delayed third stage lasting over 30 minutes were in the misoprostol group. This finding tends towards findings of longer duration of third stage in misoprostol group reported in studies that conclude inferiority of misoprostol in reducing duration of third stage. (42)

Despite the presence of several high quality systematic review and meta analyses exploring the issue of misoprostol versus oxytocin in third stage labor the duration of third stage has not been widely considered as an outcome in these comparisons hence high quality evidence on the non-inferiority of misoprostol with respect to reduction of third stage of labor is still missing. (44, 45, 46) In future meta-analysis and systematic reviews could consider including this outcome so as to synthesis existing findings and provide strong evidence on the impact of misoprostol on duration of labor.

Estimated blood loss

The risk of PPH (≥ 500 ml blood loss) was 5.7% and 7.7% of women in intervention and control groups. This compares to incidence of postpartum hemorrhage (≥ 500 mL) and postpartum blood loss in the misoprostol and oxytocin group (6% versus 5.7%) reported in an Indian RCT. (47) In common with the Indian trial there was no significant difference in the occurrence of PPH in women receiving misoprostol compared to oxytocin. High rates of PPH were reported by Kundodyiwa TW et al in 15.2% of women given misoprostol and in 13.3% of those given oxytocin, but still no significant differences were noted in PPH in the two groups. (48) In Uganda primary PPH occurred in 28.6% participants in the misoprostol group and 17.4% participants in the oxytocin group. (39) Still other studies report even lower rates of PPH: 1% for misoprostol and 0% for oxytocin (43).

The findings reported in the Ugandan trial are at variance with the report in the present trial. The trial by Atukunda and colleagues concluded that misoprostol 600 µg is inferior to oxytocin 10 IU for prevention of primary PPH in active management of labor with women receiving misoprostol experiencing a 64% increase in the risk of PPH. The findings imply that nine women need to be treated with oxytocin instead of misoprostol to prevent one case of PPH. (39)

Severe PPH occurred in 3.6% and 2.7% of participants in the misoprostol and ocytocin groups in Uganda. (39) Although severe PPH (blood loss ≥ 1000 mls) was rare in our study both studies and other African country reports indicate that there is no significant difference in the incidence of severe PPH in the oxytocin and misoprostol groups. (48) The difference in PPH (blood loss ≥ 500 mls) warrants further exploration given the similarity of patient populations and settings. In contrast to our open label non-inferiority trial the Ugandan study was a double-blind, double-dummy randomized controlled non-inferiority trial.

A systematic review conducted prior to the Ugandan trial and including two RCTs and 1787 participants compared 800 mcg sublingual misoprostol versus oxytocin. The review concluded that primary PPH rates did not differ between the two groups. (46) The RCTs included in Mousa and colleagues review used a higher dose of misoprostol compared to the 600 mcg used in the Ugandan and current trials. (46)

Use of additional uterotonics

Additional uterotonic were used in 4.2% and 6.3% of women in the misoprostol and oxytocin groups, respectively and there was no significant differences in uterotonic use across treatment groups. This finding is in agrees with documented finding in RCTs that have evaluated uterotonic use as an adjunctive treatment in women treated with oxytocin or misoprostol in third

stage. (43, 48) There is evidence in literature that misoprostol and oxytocin have similar efficacy when used after prophylactic uterotonics for treatment of primary PPH. (46)

Strengths of the study

The use of the RCT design overcomes the main challenge of alternative explanation for an intervention effect including bias, and confounding therefore providing strong evidence of non-inferiority of sublingual misoprostol in the management of third stage of labor. In this trial randomization was successful and the two treatment groups were relatively well balanced in terms of the main baseline characteristics that were assessed. The study has high internal validity which can be attributed to its design that reduced potential bias in selection of participants, allocation to intervention and assessment of outcomes. The level of external validity is high for mothers delivering within the Kenyan health system but there will be concerns in generalizing these findings to primary level facilities and the community where the majority of deliveries in Kenya occur.

Limitations of the study

A major limitation of the study was the open label design that allowed both the health providers and women participating in the trial to know the treatment arm that participants were in after assignment to intervention. This limitation is however minimized by allocation concealment which was implemented up to the point of assignment of the intervention but blinding was not feasible after the intervention assignment. Future studies that aim to completely overcome the weakness of the open label design should adopt a double-blind double-dummy RCT design. This design was not achievable in the current trial because of logistic and resource constraints.

The successfully implemented allocation concealment ensured that there was no foreknowledge of treatment assignment among participants and investigator because of the use of sequentially numbered, opaque sealed envelopes containing treatment assignment and generated by an independent statistician and open upon verification of participant eligibility for inclusion in the trial. Secondly and related to the open label design, the threat of detection or measurement bias that results from failure to blind the outcome assessors was minimal because of use of an objective primary outcome namely duration of third stage of labor. The secondary outcome measures including excessive blood loss and additional uterotonic use were also objectively measured. Despite this objective outcomes the extent to which health provider prescription practice of additional uterotonics could have been influenced by their knowledge of the treatment assignment could not be established and is a potential source of performance bias.

Conclusion

This study has demonstrated that sublingual misoprostol is non-inferior to intramuscular misoprostol in the management of third stage of labor. In particular there are no significant differences in the duration of third stage of labor among women who receive sublingual misoprostol compared to those managed using the standard treatment of intramuscular oxytocin with approximately one-half of women in both groups (59.7% for misoprostol and 52.8% for oxytocin) having third stage lasting less than 10 minutes. Similary, the need for additional uterotonics and incidence of PPH (blood loss $\geq$ 500 mls) or severe PPH (blood loss $\geq$ 1000 mls) was not significantly different between the oxytocin and misoprostol group.

Recommendations

Based on the findings of this trial it appears that sublingual misoprostol is as efficacious as intramuscular oxytocin with respect to duration of third stage labor, prevention of PPH and need for additional uterotonics. Considering the advantages in shelf life and ease of administration sublingual misoprostol should be considered for use in sub-Saharan Africa setting where climatic conditions and resource constraints preclude use of the heat labile intramuscular oxytocin preparations.

REFERENCE

1.Third stage of labor definition-medicine net-health and medical terms dictionary, 1996-2015.

2.Trends in maternal mortality:1990 to 2013,WHO,UNICEF,UNFDA,the world bank and the united nations population division, 2014, 1-14.

3.World Health Organization (2012) WHO recommendations for the prevention

and treatment of postpartum hemorrhage. Geneva: World Health Organization.

4.United Nations Department of Economic and Social Affairs Population Division

(2013) World population prospects: the 2012 revision. New York: United

Nations Department of Economic and Social Affairs Population Division.

5.Belfort MA, Dildy III GA. Postpartum hemorrhage and other problems of the third stage. In: James DK, Steer PJ, Weiner CP, Gonik B, editors. High Risk pregnancy management options. 4th ed. St. Louis: Elsevier, 2011; pp 1283-311.

6.Thompson PJ. Postpartum haemorrhage. In: Leusley DM, Baker PN, editors. Obstetrics and Gynaecology. Second ed. London: Hodder Arnold, 2010; pp 496-500.

7. Shamsi TS, Hossain N, Soomro N, Hasan JA, Noorani M, Kazi S, et al. Use of recombinant factor VIIa for massive postpartum haemhorrage: case series and review of literature. J Pak Med Assoc 2005; 55: 512-5.

8. Geller SE, Adams MG, Kelly PJ, Kodkany BS, Derman RJ. Postpartum hemorrhage in resource-poor settings. Int J Gynaecol Obstet 2006; 92: 202-11.

9. Altman DG, Schulz KF, Moher D, Egger M, Davidoff F, et al. (2001) The

revised CONSORT statement for reporting randomized trials: explanation and

elaboration. Ann Intern Med 134: 663–694.

10.Conduct of normal labour and delivery. In: Cunningham FG, Gant NF, Leveno KJ, Gilstrap LC, Hauth JC, KD. W, editors. Williams's obstetrics. 21st ed. Philapdelphia: Mc Graw Hill, 2001; pp

309-29.

11. Magann EF, Lanneau GS. Third stage of labor. Obstet Gynecol Clin North Am 2005; 32: 323-32

12. Nordstrom L, Fogelstam K, Fridman G, Larsson A, Rydhstroem H (1997)

Routine oxytocin in the third stage of labour: a placebo controlled randomised

trial. Br J Obstet Gynaecol 104: 781–786

13. . Atukunda EC, Brhlikova P, Agaba AG, Pollock AM (2013) Registration,

procurement, distribution, and use of misoprostol in Uganda: an interview-based

observational study. Lancet 382: 10.

14. Stanton CK, Newton S, Mullany LC, Cofie P, Tawiah Agyemang C, et al.

(2013) Effect on postpartum hemorrhage of prophylactic oxytocin (10 IU) by

injection by community health officers in Ghana: a community-based, cluster randomized

trial. PLoS Med 10: e1001524

15. . Lam H, Tang OS, Lee CP, Ho PC. A pilot-randomized comparison of sublingual misoprostol with syntometrine on the blood loss in third stage of labor. Acta Obstet Gynecol Scand 2004; 83: 647-50.

16. O'Brien P, El-Refaey H, Gordon A, Geary M, Rodeck CH. Rectally administered misoprostol for the treatment of postpartum hemorrhage unresponsive to oxytocin and ergometrine: a descriptive study. Obstet Gynecol 1998; 92: 212-4.

17. . Vimala N, Mittal S, Kumar S (2006) Sublingual misoprostol versus oxytocin

infusion to reduce blood loss at cesarean section. Int J Gynaecol Obstet 92: 106–110.

18. Zachariah ES, Naidu M, Seshadri L. Oral misoprostol in the third stage of labor. Int J Gynaecol Obstet 2006; 92: 23-6.

19. Tang OS, Gemzell-Danielsson K, Ho PC (2007) misoprostol: pharmacokinetic

profiles, effects on the uterus and side-effects. Int J Gynaecol Obstet 99 (Suppl

2): S160–S167.

20. World Health Organization (2012) WHO recommendations for the prevention

and treatment of postpartum hemorrhage. Geneva: World Health Organization.

21. International Federation of Gynecology and Obstetrics (2012) Prevention of

postpartum hemorrhage with misoprostol. Int J Gynaecol Obstet 119: 213–214.

doi:10.1016/j.ijgo.2012.09.002

22. Tuncalp O, Hofmeyr GJ, Gulmezoglu AM (2012) Prostaglandins for preventing

postpartum haemorrhage. Cochrane Database Syst Rev 8: CD000494.

doi:10.1002/14651858.CD000494.pub4

23. Chu CS, Brhlikova P, Pollock AM (2012) Rethinking WHO guidance: review of

evidence for misoprostol use in the prevention of postpartum haemorrhage.

J R Soc Med 105: 336–347. doi:10.1258/jrsm.2012.120044

24. . Derman RJ, Kodkany BS, Goudar SS, Geller SE, Naik VA, et al. (2006) Oral

misoprostol in preventing postpartum haemorrhage in resource-poor communities:

a randomised controlled trial. Lancet 368: 1248–1253. doi:10.1016/

S0140-6736(06)69522-6
25. Mobeen N, Durocher J, Zuberi N, Jahan N, Blum J, et al. (2011) Administration of misoprostol by trained traditional birth attendants to prevent postpartum haemorrhage in homebirths in Pakistan: a randomised placebo-controlled trial. BJOG 118: 353–361.

26. Gulmezoglu AM, Villar J, Ngoc NT, Piaggio G, Carroli G, et al. (2001) WHO multicentre randomised trial of misoprostol in the management of the third stage of labour. Lancet 358: 689–695.

27. Baskett TF, Persad VL, Clough HJ, Young DC (2007) Misoprostol versus oxytocin for the reduction of postpartum blood loss. Int J Gynaecol Obstet 97: 2–5. doi:10.1016/j.ijgo.2006.12.016

28 Vaid A, Dadhwal V, Mittal S, Deka D, Misra R, et al. (2009) A randomized controlled trial of prophylactic sublingual misoprostol versus intramuscular methyl-ergometrine versus intramuscular 15-methyl PGF2alpha in active management of third stage of labor. Arch Gynecol Obstet 280: 893–897.

29. Vimala N, Mittal S, Kumar S, Dadhwal V, Mehta S (2004) Sublingual misoprostol versus methlergometrine for active management of third stage of labor. Int J Gynaecol Obstet 87: 1–5.

30. . Postpartum hemorrhage: prevention and management toolkit/Joint statement- management of the third stage of labor to prevent PPH, international conference of midwives (ICM) international federation of gynecologist's and obstetricians (FIGO) November 2003.1-2

31. . Trends in maternal mortality:1990 to 2013,WHO,UNICEF,UNFDA,the world bank and the united nations population division, 2014, 1-14.

32. Safety and efficacy of misoprostol versus oxytocin for the prevention of PPH, Journal of pregnancy, volume 2014(2014), Article I.D 713879, 4pages.

33. Randomised controlled trial of rectal misoprostol versus oxytocin in 3rd stage management,Karkans SQ, Caloia D, Saleneiks M.E, Kingdom J, Walker M, Meffe E, Wisdom R, j Obstet Gnaecol Can.2001 feb;24(2):149-54

34. Oral misoprostol versus intramuscular oxytocin in the active management of the third stage of labor,Afolabi EO, Kuti O, Orji ED, Ogunniyi SO, Singapore med j.2010 mar,51(3);207-11

35. A study to compare the efficacy of misoprostol,oxytocin,methyl-ergometrine and ergometrine-oxytocin in reducing blood loss in active management of 3rd stage of labor,Gohi JT,Triathi B,Obstet Gynaecol India 2011 Aug;61(4):408-12.doi:10 1007/s 13224-011-0060-5 Epub 2011 sep 23.

36. Prevention of PPH with sublingual misoprostol or oxytocin:a double-blind randomized controlled trial, Bellad M,Gouder S,Kodkam B,Sloam R,Dermn R.BLOG 2012 jul;119(8);972-6.foi:10.1111/j.1471-0528.2012.03341.x.

37. Misoprostol versus oxytocin in the third stage of labor, Kundodyiwa TW, Majoko F, Rasakariko S., Int j Gynaecol Obstet.2001 Dec:75(3):235-41

38. Oral misoprostol versus oxytocin in the management of the third stage of labor. Parsons SM, Wallet RL, Ceane JM, Mathews K, Hutchers D, j Obstet Gynaecol Can.2006 jan;28(1):20-6.

39. Sublingual misoprostol versus i.m oxytocin for prevention of PPH in Uganda: a double-blind randomized non-inferiority trial.Atukunda FC,Siedner MJ,Mugyenyi GR,Twagirumukiza M,Agaba AG,Plos Med 2014 Nov 4;11(11);e 1001752.doi:10.1371/journal.pubmed.1001752.ecollection 2014

40.Julious SA. Sample sizes for clinical trials with Normal data. *Statist. Med.* 2004; **23:1921**-1986.

41. Aziz S, Kazi S, Haq G, Soomro N. Oral misoprostol versus oxytocin in the management of third stage of labour. J Pak Med Assoc. 2014; 64(4):428-32.

42. Tewatia R, Rani S, Srivastav U, Makhija B. Sublingual misoprostol versus intravenous oxytocin in prevention of post-partum hemorrhage. Arch Gynecol Obstet. 2014; 289(4):739-42.

43. Oboro VO, Tabowei TO. A randomised controlled trial of misoprostol versus oxytocin in the active management of the third stage of labour. J Obstet Gynaecol. 2003; 23(1):13-6.

44. Pantoja T, Abalos E, Chapman E, Vera C, Serrano VP.Oxytocin for preventing postpartum

haemorrhage (PPH) in non-facility birth settings.Cochrane Database Syst Rev. 2016 14;4:CD011491.

45. Hofmeyr GJ, Gülmezoglu AM, Novikova N, Lawrie TA. Postpartum misoprostol for preventing maternal mortality and morbidity. Cochrane Database Syst Rev. 2013 15;(7):CD008982.

46. Mousa HA, Alfirevic Z. Treatment for primary postpartum haemorrhage. Cochrane Database Syst Rev. 2003;(1):CD003249. Review. Update in: Cochrane Database Syst Rev. 2007;(1):CD003249.

47. Chaudhuri P, Biswas J, Mandal A. Sublingual misoprostol versus intramuscular oxytocin for prevention of postpartum hemorrhage in low-risk women. Int J Gynaecol Obstet. 2012 Feb;116(2):138-42.

48. Kundodyiwa TW, Majoko F, Rusakaniko S. Misoprostol versus oxytocin in the third stage of labor. Int J Gynaecol Obstet. 2001;75(3):235-41.

APPENDICES

Appendix I: Study questionnaire

QUESTIONAIRE FOR PARTICIPANTS IN COMPARISON OF SUBLINGUAL MISOPROSTOL WITH INTRAMUSCULAR OXYTOCIN IN THE MANAGEMENT OF 3RD STAGE OF LABOR IN KNH: RTC

SOCIO-DEMOGRAPHIC DATA.

1. Date of your birth……./……../……

2. Marital status

    a) Single

    b) Married

    c) Widow

    d) Separated

    e) Divorced

3. Parity? .....+……..

4. Highest Level of education

    A) primary

    B) Secondary

    c) College

5. What is your occupation?

    a) Formal…..

    b) Self …….

    c) Not employed……

6. Any drug allergy (specify)……

7. Mothers weight (before delivery)……..

QUESTIONAIRE FOR HEALTHCARE PROVIDER IN COMPARISON OF SUBLINGUAL MISOPROSTOL WITH INTRAMUSCULAR OXYTOCIN IN THE MANAGEMENT OF 3RD STAGE OF LABOR IN KNH: RTC

1. Type of intervention.

    a) Sublingual misoprostol

    b) Intramuscular oxytocin

2. Time taken during 2nd stage……..

3. Time taken during 3rd stage……

4. Placenta retention…….

5. Added uterotinics (specify drug and amount) …….

6. Need for i.v fluids……

7. Visually estimated blood loss……...

8. Mothers weight (after delivery)……..

9. Vital signs.

    a) After delivery of placenta…B.P…….PULSE…….RESP……..TEMP……

    b) 30 minutes post-delivery of placenta…B.P……...PULSE…….RESP……TEMP……

    c) 1 hour post-delivery of placenta…B.P…..PULSE……..RESP…….TEMP……..

10. Birth weight……

11. Foetal outcome.

    a) Still birth

    b) fresh/macerated baby

    c) Alive

12. Apgar score ……

12. Transfused (number of units)……..

13. Surgical procedures done

a) episiotomy……

b) perineal tears…….

c) Cervical tears……

d) Uterine rupture……

e) None…….

14. Death….

25

31.

Appendix II: Budget and budget justification.

NO.	ITEM	COST(KSH)
1.	**proposal writing** **typing and type setting** **printing and photocopying**	**20,000**
2.	**Data collection and entry**	**32,000**
3.	**Data analysis**	**50,000**
4.	**Final dissertation**	**21,800**
	TOTAL COST	**123,800/=**

Budget justification.

Item 1-proposal writing- ksh 20,000

Typing and type setting-50 pages @ksh.30=1,500+1,000=ksh2, 500

Printing and photocopying-50 pages@10 per page=500 x 5= ksh2, 500

Internet costs - 15 GB @ksh 1000/gb=ksh15, 000

Item 2- data collection and entry-ksh 32,000

Study questionaires-288 copies x 3 pages=864 copies @ ksh3 =2,592

Blood collection drapes-200 @ksh50=10,000

MS access data base design costs=ksh4, 000

Data entry costs-2 MRA's x 15 days @ksh500 per day=ksh15, 000

Item 3-data analysis-ksh 50, 000

SPSS software license-validity period 1 year=ksh15, 000

Data analysis charges-ksh 35, 000

Item 4-final dissertion-ksh21, 800

Typing and type setting –approx. 150 pages @ksh30=4,500+500=ksh5, 000

Printing and photocopying-approx.150 pages@ksh10 per page=1500 per copy x 10 copies=ksh15,000

Binding -6 copies@ksh300=ksh1,800 32.

12 Time lines

Activity number	Activity	Responsible	2015	2016
1	Proposal writing	Researcher Supervisors		
2	submission of proposal	Researcher	October	
3	Pretesting	Researcher		April
4	Data collection	Researcher supervisors		May, June and July
5	Data analysis	Researcher Statistician		August
6	Thesis writing	Researcher supervisors		August
7	Submission of thesis	Researcher		October

Appendix III: Informed consent form (English version)

My name is Dr.Cyrus Kamau Mumbura. I am currently doing a master's degree course in obstetrics and gynecology at the University of Nairobi. I am doing a clinical trial to compare sublingual misoprostol and intramuscular oxytocin in management of 3rd stage of labor Kenyatta National Hospital.

The information gotten from this study will be used for completion of my master's degree in obstetrics and gynecology at the same university.

The aim of this letter is to request for your participation in this research in which some participants will be given intramuscular oxytocin and others will be given sublingual misoprostol.

Please note:

- Your acceptance to participate in this study is voluntary.
- Your acceptance to participate in this study does not prevent you from withdrawing from the study.
- Declining to participate or withdrawing from this study will not warrant any punishment or penalty i.e. you will not be denied the services you are receiving
- You will not receive any token or monetary benefit by participating in this study
- Your personal details will be highly confidential.
- Part or whole of this study can be availed to you on request.
- In case you suffer from PPH an additional uterotonic will be administered to you.

You are free to ask any question that will allow you to understand the nature of the study. If you need to seek clarification you can contact me on **0727707202** or my supervisors.

Prof. Koigi kamau phone number **0722714402 email:koigikamau@kenyaweb.com** and **Dr. Wanyoike 0722522234 email:drjoewanyoike@yahoo.co.uk** at the Department of obstetrics and Gynecology University of Nairobi or SECRETARY, KNH/UoN-ERC

P.O box 19676-00202 KNH NAIROBI phone no: **2726300** ext: **44102**.

34.

Appendix IV: Informed consent form (Kiswahili)

Jina langu ni Dkt.Cyrus Kamau Mumbura. ninaendelea na masomo yangu katika somo la magonjwa ya akina mama na wanawake katika chuo kikuu cha Nairobi.Ninafanya utafiti kuhusu dawa mbili zinazotumika katika uziaji wa kuvunja damu nyingi baada ya kujifungua hospitali kuu ya Kenyatta.

Ujumbe wowote tutakao upata kwenye utafiti huu utatumika kukamilisha somo langu la masters katika masuala ya uzazi na magonjwa ya wanawake.

Barua hii ni ya kuomba ushiriki wako katika utafiti huu ambao kutakua na vikundi viwili,kimoja kitapata tembe ya kumumunya na kundi lingine litapata dawa kwa njia ya shindano kwa paja baada ya mtoto kuzaliwa.

Tafadhali kumbuka:

- Haulazimishwi kushiriki katika utafiti huu.
- Ingawa umekubali kushiriki katika utafiti huu,unaweza kujiondoa kushiriki wakati wowote
- Kukataa kushiriki katika utafiti huu haitakuwa na madhahara yoyote Kama kukatazwa kupokea huduma unazopewa
- Unaweza kupata ujumbe wowote kuhusu utafiti huu,unapohitaji
- Ikiwa utaweza kupoteza damu nyingi,dawa nyingine itaongezwa kuzuia madhara.

Unaweza kuuliza maswali yoyote yanayohusu utafiti huu na maelezo zaidi kwa kunipigia simu kwenye nambari **0727707202** au kwa wasimamizi wangu **Prof.koigi kamau 0722714402 email:koigikamau@kenyaweb.com** na **Dkt.wanyoike 0722522234 email:drjoewanyoike@yahoo.co.uk** kwenye idara ya masomo ya magonjwa ya akina mama na wanawake chuo kikuu cha Nairobi,ama karani,KNH/U.o.N ERC.

S.L.P 19676-00202 namba ya simu **2726300** laini **44102.**

KNH NAIROBI

35.

Appendix Bi: ASSENT DECLARATION FORM. (English version)

I, the undersigned, I do here by volunteer to participate in this study. The nature and purpose have been fully explained to me by

Dr.Cyrus Kamau Mumbura. Phone no. 0727707202 Email address: cyruskama@yahoo.com

I understand that all information gathered will be used for the purpose of the study only.

Name of participant.....

Signed.....Date.....

36.

Appendix Bii) ASSENT DECLEARATION FORM FOR ADULTS (Swahili version)

Mimi, mwenye sahihi, najitolea huru katika hili somo. Nimeelezewa Kwa undani kiini cha somo hili Na **Daktari Cyrus Kamau Mumbura nambari ya simu: 0727707202 barua pepe: cyruskama@yahoo.com**

Naelewa kwamba ujumbe nitakao utoa utatumika tu Kwa somo hili pekee.

Jina……

Sahihi.....Tarehe.....

Appendix V: CONSORT 2010 checklist of information to include when reporting a randomized trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomized trial in the title	i
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	v
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	1-7
	2b	Specific objectives or hypotheses	8
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	10
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	NIL
Participants	4a	Eligibility criteria for participants	11
	4b	Settings and locations where the data were collected	10-11
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	13
Outcomes	6a	completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	13
	6b	Any changes to trial outcomes after the trial commenced, with reasons	Measured blood loss at 1 and 2 hours postpartum to enable direct comparisons with other studies, which have often used those endpoints
Sample size	7a	How sample size was determined	11
	7b	When applicable, explanation of any interim analyses and stopping guidelines	11

Randomization:

Sequence generation 8a Method used to generate the random allocation sequence 14

8b Type of randomization; details of any restriction (such as blocking and block size) 14

Allocation concealment mechanism 9 Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned 14

Implementation 10 Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions 14

Blinding 11a If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how 14

11b If relevant, description of the similarity of interventions 14

Statistical methods 12a Statistical methods used to compare groups for primary and secondary outcomes 14-15

12b Methods for additional analyses, such as subgroup analyses and adjusted analyses 15

Results

Participant flow (a diagram is strongly recommended)

13a For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analyzed for the primary outcome

13b For each group, losses and exclusions after randomization, together with reasons NIL

Recruitment 14a Dates defining the periods of recruitment and follow-up

14b Why the trial ended or was stopped Completed enrolment

Baseline data 15 A table showing baseline demographic and clinical characteristics for each group

Numbers analysed 16 For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups

Outcomes and estimation 17a For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)

17b For binary outcomes, presentation of both absolute and relative effect sizes is recommended

Ancillary analyses 18 Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory

Harms 19 All important harms or unintended effects in each group (for specific guidance see CONSORT for harms) NIL

Discussion

Limitations 20 Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses

Generalisability 21 Generalizability (external validity, applicability) of the trial findings

Interpretation 22 Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence

Other information

Registration 23 Registration number and name of trial registry

Protocol 24 Where the full trial protocol can be accessed, if available Attached with the manuscript

Funding 25 Sources of funding and other support (such as supply of drugs), role of funders In the "competing interest &Financial Disclosure" section of the submission form