A RANDOMIZED CLINICAL TRIAL COMPARING ORAL AND VAGINAL MISOPROSTOL FOR INDUCTION OF LABOUR AT TERM IN KENYATTA NATIONAL HOSPITAL(K.N.H.)

Submitted by:

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A DISSERTATION PRESENTED IN PART FULFILMENT OF THE REQUIREMENT FOR THE AWARD OF THE DEGREE OF MASTER OF MEDICINE IN OBSTETRICS AND GYNECOLOGY

UNIVERSITY OF NAIROBI

DECLARATION

I hereby declare that this is my original work. It has not been presented for a degree award or any other award in any other university.

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ABBREVIATIONS AND ACRONYMS

ANC- Antenatal clinic

ARM- Artificial rupture of membranes

DSMB- Data and safety and monitoring board

IUGR- Intrauterine growth restriction

IV- Intravenous

LNMP- Last normal monthly period

NSAID- Non-steroidal anti-inflammatory drugs

PGE1- Prostaglandin E1

PGE2- Prostaglandin E2

PGF2α- Prostaglandin $F2_{\alpha}$

PROM- pre labour rupture of membranes

WHO- World Health Organization

ABSTRACT

Introduction

Induction of labour is the process of artificially stimulating the uterus so as to start labour. It's usually done at the age of viability to avert a foreseen adverse outcome associated with continuation of the pregnancy. The indications for induction of labour differ. The incidence varies from country to country. In developed countries for instance, induction of labour varies between 20-35% but it has been found to be much lower in developing countries. In Niger for example, induction of labour is as low as 1.4%. Globally, an average of 9.6% of pregnant women will require induction of labour. Misoprostol (PGE1) has proved very effective in induction of labour. In addition, it's cheap, heat stable therefore easy to store and transport and widely available. However, the ideal route of administration, dose and frequency are yet to be determined. Generally, women all over the world find vaginal examination uncomfortable. Therefore oral administration may be more comfortable and acceptable. A dose given less frequently than the current 2hourly solution will be better for the already constrained low resource settings.

Broad objective

To compare the efficacy of 25µg vaginal misoprostol 4hourly and 50µg oral misoprostol 4hourly for induction of labour, neonatal and maternal outcomes.

Methodology

Study participants were randomly assigned to 2 groups; oral misoprostol 50µg 4hourly and the other group assigned to vaginal misoprostol 25µg 4hourly to a maximum of 4 and 5doses respectively. The average duration from induction to delivery and proportion of deliveries occurring within 24hours of induction was determined. The primary dependent variable was the proportion of deliveries within 24hours of induction, while the secondary dependent variables were the maternal and perinatal outcomes. The independent variables include; the route and the dosage of administration of misoprostol and the socio-demographic characteristics.

Results

In this study, 77 study subjects received oral misoprostol while 75 received vaginal misoprostol for induction of labour. Among the participants who received vaginal misoprostol 52 (68.0) had a successful vaginal delivery within 24 hours compared to 40 (53.0%) of those that received oral misoprostol (P-value =0.09). The average duration taken from the onset of induction of labour until delivery was 17.9 hours for the participants who received oral misoprostol as compared to 21.7 hours in the group that received vaginal misoprostol (P-value =0.024). There was no statistically significant difference observed in the maternal and early perinatal outcomes between the two groups.

Conclusion

Oral misoprostol at 50µg 4hourly is as effective as vaginal misoprostol 25µg 4 hourly for induction of labour at term.

1.0 INTRODUCTION

Induction of labour is the process of artificially stimulating the uterus so as to start labour(1). The age of viability varies from developed countries to low resource settings. The incidence varies from one place to another. In developed countries induction of labour varies between 20-35% but it's much lower in developing countries. The rate of induction of labour in Africa is 4.4% being as low as 1.4% in Niger (16). On average, 9.6% of pregnant women will require induction of labour globally(1).

Induction of labour should be done to avert an anticipated neonatal or maternal adverse outcome when absolutely necessary especially in limited resource setting with a challenge in monitoring of the process. It should be safe to the mother resulting in a safe birthing process and a healthy neonate within an acceptable timeframe. Induction of labour is usually achieved by pharmacological methods such as prostaglandins and oxytocin or non-pharmacological methods such as a balloon catheter. The process is not risk free and therefore it should only be done where the benefits outweigh the risk associated with induction of labour. Because of these risks, the woman and her baby should be monitored closely during this process. This can cause a constraint in the limited resource setting. Successful induction of labour depends on interplay between co-ordinated myometrial contractions and progressive cervical effacement and dilatation. The pharmaceutical products used for induction of labour include oxytocin and misoprostol (PGE1). However, in women with unfavourable cervix it is easier to achieve vaginal delivery within a reasonable time with misoprostol than with oxytocin. In addition misoprostol is cheap, heat stable at room temperature, easy to transport and store. Misoprostol can be given orally or vaginally for induction of labour. Nevertheless, the ideal dosage, route and frequency of administration are yet to be established.

2.0 LITERATURE REVIEW

Induction of labour started a while back. It dates back to Hippocratic days when the original descriptions of mammary stimulation and mechanical dilation of the cervical canal was done. But it was not until the second century AD that Soranus practiced artificial rupture of the membranes for induction of labour(2). Other labor induction methods were introduced during this period including manual cervical dilatation.

In a meeting held in London during 1700's, clinicians discussed the efficacy and ethics of early delivery by artificial rupture of membranes for induction of labor .In 1810, amniotomy was introduced in the United States for induction labor. Until the 20th century, amniotomy, manual cervical dilatation and other mechanical methods remained most commonly employed methods for induction of labour.

Pharmacological methods for induction of labour were mainly discovered during the 20th Century. In 1906, Dale observed that extracts from the infundibular lobe of the pituitary gland (now known to be oxytocin) caused myometrial contractions. Three years later, Bell reported the first experience with use of oxytocin for labor induction. With the introduction of pituitary extract as a hormonal method of labor induction in 1913, the use of this method gained acceptance among obstetricians. However, due to the use of large doses and the impurity of the extract, numerous adverse effects were reported. Gradually, as the number of reported cases of uterine rupture increased, the use of this impure form of oxytocin became discredited in many centers(2).

Initially, oxytocin was administered via intramuscular or subcutaneous routes. The use of oxytocin as an intravenous infusion was initiated in the 1940's and in 1949, Theobald reported

his initial results with this form of administration. The structural formula of oxytocin was discovered in 1953. Prior to this, it was known as a pituitary extract but without an identified chemical structure. It was during this time that synthetic oxytocin was introduced and it has been in use since 1955. For more than ten years, oxytocin was the main pharmacological method used for induction of labour.

However in 1968, Karim and colleagues introduced the use of prostaglandins for labor induction. Since then, the use of prostaglandins, in different varieties and forms of administration, has become a common method of labor induction. Among them include prostaglandin F2α, PGE1 and PGE2. In 1980's the synthetic prostaglandin analogue misoprostol (PGE1) started gaining acceptance as an effective and safe method of labor induction.

Misoprostol was originally used to treat gastric ulcers especially the NSAID induced ones in 1980s. It was then noted to cause uterine contraction and the studies on its use for abortion induction and induction of labour began. Oxytocin has been found to be less effective than misoprostol in induction of labour especially in patients with poor Bishop Score. Many studies have been conducted on use of misoprostol for induction of labour at different doses, frequencies and routes of administration. Misoprostol has been given orally, sublingual, buccal, vaginally and intracervically for induction of labour with different results. However, up to date, the ideal dosage, route of administration and frequency of misoprostol administration for induction of labour is not yet known.

There are few studies on buccal misoprostol for induction of labour and therefore limited data on its efficacy and safety in induction of labour. Nevertheless, it has been shown to have higher rates of uterine hyperstimulation and a higher failure to achieve delivery within 24 hours

compared to oral and vaginal misoprostol. This could be due to its rapid absorption and a low first pass effect(3,4).

Sublingual misoprostol has also been given for induction of labour. A study by Gatta D.S. et al in 2009 found that sublingual misoprostol at a low dose of 12.5µg given 6 hourly achieved 60% vaginal deliveries with 7% cases of uterine hypersystole. In addition, meconium stained liquor was found in 12% of the participants(3),(4). Generally, sublingual misoprostol has been found to have a higher frequency of uterine hyperstimulation / hypersystole than oral and vaginal misoprostol when used for induction of labour. Just like buccal misoprostol, sublingual misoprostol is rapidly absorbed into the body and this could be the reason for the high association with uterine hyperstimulation(5)(6).

Vaginal misoprostol has been widely used for induction of labour. It has been found to be highly effective in successful induction of labour. It also allows for cervical assessment at the time of drug insertion. Studies have shown that vaginal misoprostol has a higher bioavailability probably due to the low first pass effect associated with the route of administration. Nevertheless, it has been associated with more cases of uterine hyperstimulation than oral misoprostol. Studies done using vaginal misoprostol at 100µg 4 or 6 hourly have shown that it's associated with higher rates of uterine hyperstimulation compared to lower doses. Given more frequently than 4 hourly, vaginal misoprostol has been associated with abnormal fetal heart rates and uterine hypersystole even at doses lower than 100µg.The current WHO guidelines on induction of labour recommends use of vaginal misoprostol at 25µg given 6 hourly for induction of labour.

Induction of labour with oral misoprostol has been studied. It has been found to be effective and safe with lower incidences of uterine hyperstimulation and changes in fetal heart rate changes.

However, just like the other routes of misoprostol administration, the ideal dosage, frequency and drug form is yet to be determined. The current protocols recommend use of oral solution 2 hourly in divided dosages. In low resource settings, this proves challenging due to the frequency of administration and difficulties in accurate dose measurement. A study using oral misoprostol 50µg and vaginal misoprostol 25µg given 4-6 hourly to a maximum of 5 doses showed that the oral group had more delivery rates than the vaginal group within 24 hours(7). Komala et al in their clinical trial reported that oral misoprostol achieved 94 percent vaginal deliveries compared to 86 percent for vaginal misoprostol group, though this difference was not statistically significant (7). The vaginal group was associated with more cases of uterine hyperactivity. However, there was no statistically significant difference in the duration of induction from onset until delivery. The maternal and neonatal outcomes were comparable in both groups(7). A study by Rahman et al in 2013 found that 25µg vaginal misoprostol was as safe and as effective as 50µg oral misoprostol each given 4 hourly to a maximum of 5 doses(13).

Apart from misoprostol and oxytocin, several other methods have been used successfully for induction of labour. These include PGE2, $PGF2_{\alpha}$, balloon or Foley's catheter, laminaria, amniotomy and membrane stripping, sexual intercourse, membrane striping, acupuncture, hygroscopic dilators, herbs and castor oil.(8) (9)(10). Among the pharmacological methods used for induction of labour besides Misoprostol include prostaglandin F2α (PGF2α) and

Mifepristone,a synthetic steroid that acts as progesterone receptor antagonist (11). $PGF2_{\alpha}$ has been successfully used for induction of labour with good results.

Indications for induction of labour can be done for medical and non-medical reasons. These include postdatism, prelabour rupture of membranes, polyhydramnious, oligohydramnious,

hypertensive disease in pregnancy, diabetes mellitus, chorioamnionitis, IUGR, intrauterine fetal demise, and placental insufficiency (1)(12).

Contraindications for induction of labour include previous uterine scar, transverse lie, malpresentation, non-reassuring fetal status, invasive cervical cancer, active genital herpes, extensive genital warts, pelvic structural abnormality, placenta praevia,and cord prolapse(1)(12).

3.0CONCEPTUAL FRAMEWORK

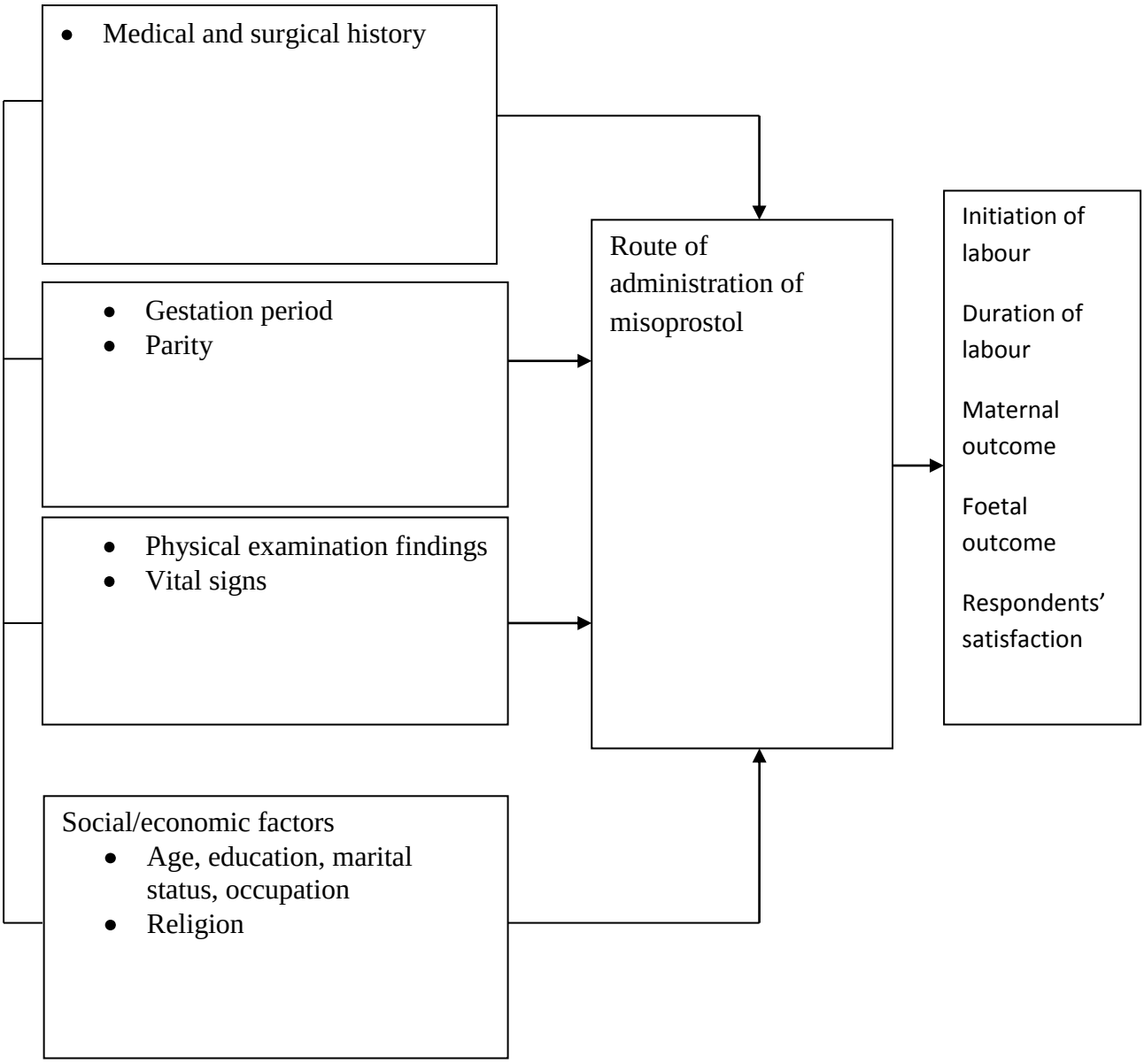

Chart 3.1: Conceptual framework

The independent variables including the age, marital status, occupation, gestational age, religion and parity may affect the primary and secondary outcomes of induction of labour in this study ie maternal and perinatal outcomes as well as the proportion of deliveries achieved within the first cycle of induction. The route of misoprostol administration and the dose was expected to have an effect on these variables.

4.0 STUDY JUSTIFICATION

Induction of labour is necessary in about 9.6% of pregnant women globally (1). This is in order to avoid an adverse outcome that may be associated with continuation of the pregnancy. Misoprostol has proven very useful for this purpose. It can be given by sublingual, buccal, oral or vaginal routes for induction of labour. Nevertheless, the ideal route and dosage of misoprostol administration for induction of labour is yet to be established. The current WHO protocols on induction of labour recommend use of Misoprostol 25µg 6 hourly per vagina or as an oral solution 25µg 2 hourly(1).

Vaginal misoprostol may be uncomfortable to administer to women and it's also associated with a risk of ascending infection. Studies have shown that it has a higher risk of uterine hyper stimulation due to its high bioavailability. Therefore, oral misoprostol may be more acceptable to women and it has a lower risk of uterine hyperstimulation at low doses as compared to vaginal misoprostol. In low resource setting where trained personnel are few, giving the drug 2 hourly is a challenge. Besides, the current protocol that uses misoprostol oral solution makes it cumbersome and involving in diluting the drug and dividing it into 10 doses without spills. Therefore a dosage that will be given less frequently and in tablet form may be more appropriate.

5.0 RESEARCH QUESTION

What is the efficacy of oral misoprostol compared with vaginal misoprostol in induction of labour at term and the immediate perinatal and maternal outcomes?

6.0 NULL HYPOTHESIS

Vaginal misoprostol at 25µg 4 hourly is not more effective than oral misoprostol 50µg given

4 hourly

7.0 OBJECTIVES

7.1 Broad objective

To compare the efficacy of 25µg vaginal misoprostol 4 hourly and 50µg oral misoprostol 4 hourly for induction of labour, perinatal and maternal outcomes in women with term pregnancies

7.2 Specific objectives

1. To compare the proportion of vaginal deliveries achieved by the two methods within 24 hours of induction of labour
2. Compare the average time taken by the two methods from induction of labour to delivery
3. Compare safety with the two methods, maternal outcomes especially maternal uterine hyperstimulation and the immediate perinatal outcomes between the two groups

8.0 METHODOLOGY

8.1 Study design

This study was a randomized clinical trial comparing oral and vaginal misoprostol for induction of labour in which 75 and 77women were randomized into vaginal and oral groups respectively. Pregnant women at 38-42wks gestation were recruited as the study population. They were aged between 18-49 years with a clear indication for induction of labour, of sound mind and able to give an informed written consent

8.2 Study site

This study was conducted in Kenyatta National hospital (K.N.H.), the largest and oldest referral hospital in Kenya and the larger East African region. This is one of the two referral hospitals receiving patients from all over the country. The hospital is located in Nairobi city, the capital city of Kenya that is within Nairobi County. It also serves as the teaching hospital for the University of Nairobi- Medical School and the Kenya Medical Training college. K.N.H. has 50 wards, 24 theatres and 22 out-patient clinics and an Accident and Emergency. It has a bed capacity of 1800. The maternity department is quite busy with a labour ward, acute gynecological ward, cold gynecological ward, 2 maternity theatres, antenatal and postnatal wards. On average, 500 deliveries are recorded every month in the hospital.

8.3 Study Population

Eligible pregnant women between 38- 42wks were recruited to the study in the labour ward. A written consent was then obtained from the participants. Each participant had an entry interview on admission to get their socio-demographic data and their obstetric history including the LNMP. A physical exam was then performed and the Bishop Score determined by a digital vaginal

exam. All the participants had an obstetric ultrasound done at least once during this pregnancy. The participants were randomly assigned to either oral misoprostol 50µg 4 hourly or vaginal misoprostol 25 µg 4 hourly after a reactive non stress test. Randomization was simple through computer generated allocations in opaque envelopes. The oral group received 2 tablets 25µg each 4 hourly while the vaginal group received 1 tablet 25µg each 4 hourly. The participants in the oral group were given up to a maximum of 5 doses while the vaginal group received a maximum of 6 doses. The primary investigator and the assistants keenly monitored the administration of the drugs to ensure compliance to the medication during induction of labour. A digital vaginal exam was done at 8 hours for the oral group unless there was an indication to do it earlier such as lower abdominal pain, vaginal bleeding or drainage of liquor. After the first 8 hours, a vaginal exam was performed as necessary or after the last dose of misoprostol if not in labour. The participants who had not gone into labour 24 hours from the onset of induction were reassessed for either a second cycle of induction after the last dose of misoprostol, or cesarean section or ARM and IV oxytocin if the Bishop Score was favourable. The maternal pulse and blood pressure were assessed every 6 hourly and fetal heart rate assessed 4 hourly before the onset of labour and as per the partograph during labour. ARM and augmentation of labour was done with oxytocin from 4cm cervical dilatation if no adequate contractions after 4-6 hours from the last dose. Monitoring of labour was done by use of the partograph. In case of uterine hyperstimulation, the induction of labour was supposed to be stopped and $MgSO_4$ 1g / hour to be given in normal saline and a CTG done as the patient is being prepared for an emergency Caesarean section. Women with non-reassuring fetal status and other indications for Caesarean section were also attended to appropriately. The occurences and outcomes of induction of labour were recorded in the patient's records and in a questionnaire attached to the patient's file on

admission. The primary outcome was the proportion of deliveries (%) within 24 hours on each mode of induction. The average time from induction to delivery, the mode of delivery and neonatal outcomes were also recorded in a similar manner. All study participants were followed up until delivery and the neonates observed for 12 hours post partum.

8.4 Inclusion criteria

Pregnant women between 38-42 weeks gestation with singleton pregnancies, in cephalic presentation, gravida 1-4, controlled Diabetes mellitus, pregnancy induced hypertension, mild and controlled severe Pre-eclampsia, pre labour rupture of membranes, mild oligohydramnious, polyhydramnious, post term pregnancies, IUGR and rhesus negative mothers.

8.5 Exclusion criteria

Patients with a previous uterine scar, severe systemic disease such as uncontrolled diabetes, cardiac disease, uncontrolled severe pre-eclampsia and eclampsia, antepartum hemorrhage, non-reassuring fetal status, malpresentation and IUFD.

8.6 Sampling technique

All eligible pregnant women giving consent to participate in the study were randomly allocated to either vaginal or oral misoprostol on admission. Randomization was done using numbered opaque envelopes with a code that would link the participant to either method of induction of labour.

8.7 Sample size calculation

The sample size for each arm was calculated using the equivalence method as follows (13):

$$n = 2 \text{ x } \frac{Z_{1-\frac{\alpha}{2}} + Z_{1-\beta}}{\delta_0}^2 \text{ x p x (1-p)}$$

$$n = 2 \text{ x } \frac{1.64 + 1.28}{0.18}^2 \text{ x } 0.86 \text{ x } (0.14)$$

$$= 63.4 + (10\% \text{x} 63.4)$$

$$n = 69.7$$

8.8 Parameter definitions

- n=size per group; p=the proportion of women who achieve vaginal delivery within 24 hours of induction on standard treatment =86% (7,13); z_x = the standard normal deviate for a one or two sided x;
- δ_0 = a clinically acceptable margin (13)
- This formula is for equivalence study designs comparing a standard treatment against a new intervention to ascertain that they have the same efficacy. It has been obtained from the Journal of Thoracic Disease Vol.1, No.1 (December 2009) on practical biostatistics and sample size calculation in Randomized Clinical Trial (13). It assumes a sample size power of 90% and a response rate of 86% with the standard treatment. It also assumes that there will be 10% drop outs during the study. The value of P (response to standard treatment) was derived from previous studies (7).

8.9 Participant recruitment and randomization chart

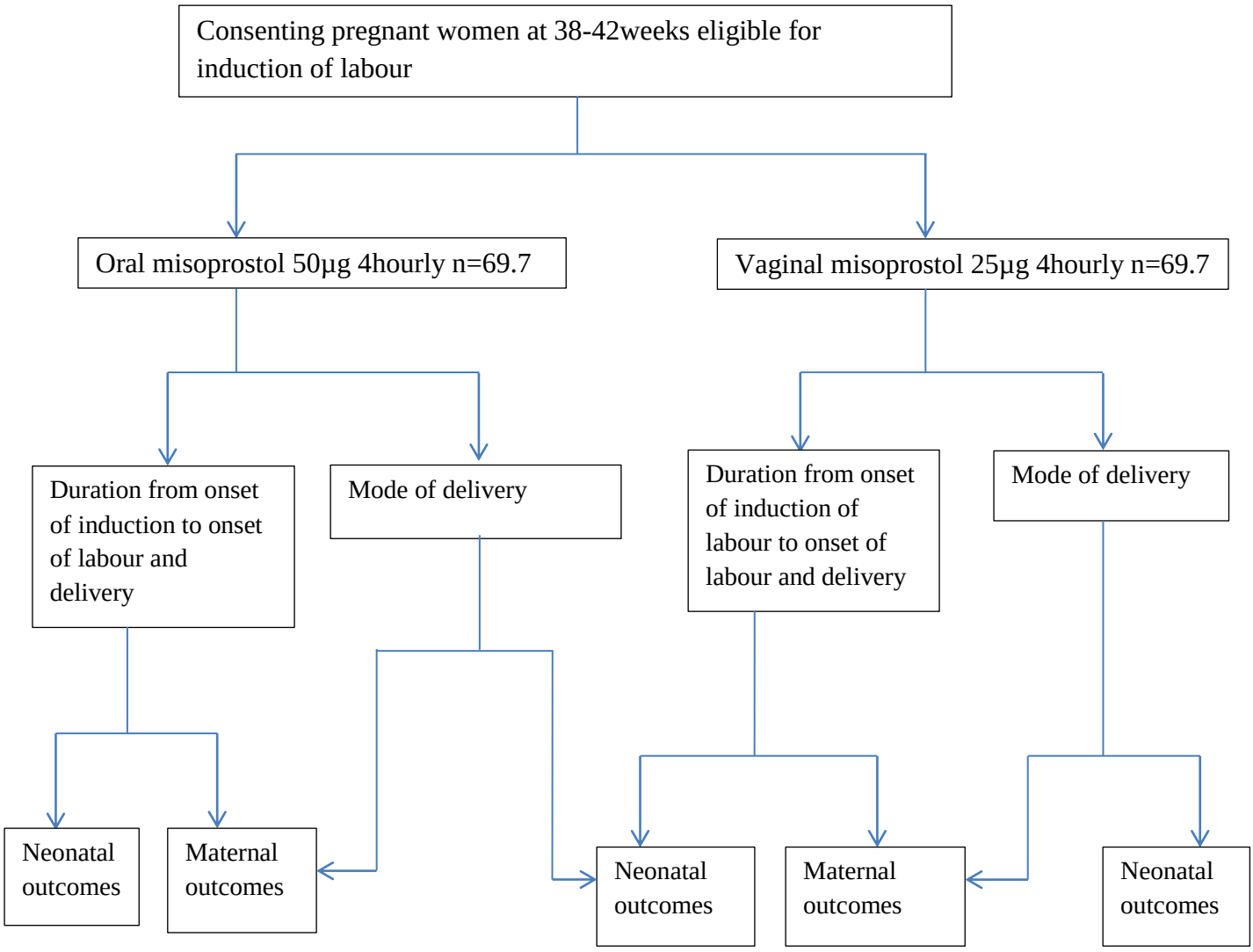

Chart 8.9: Participant recruitment and randomization chart

8.10 Allocation of interventions

Participants were randomly allocated to oral or vaginal misoprostol. Block randomization was done. This was done in order to ensure a balanced participant recruitment in both arms during the interim analysis. The numbers were generated using a computer software and sealed in opaque envelopes. This study was not blinded.

8.11 Research instruments

Questionnaires were filled through verbal interviews on admission prior to induction of labour. Further information was obtained from the patient records including outcomes of induction, maternal and fetal outcomes and recorded in the questionnaire.

8.12 Data collection techniques and management

The eligible participants were recruited in labour ward following an informed consent. An entry interview to get their socio-demographic data and obstetric history was conducted and a physical exam performed. The Bishop score was determined by a digital vaginal exam. Induction of labour was then initiated with either oral or vaginal misoprostol. The monitoring of labour was done using the partograph. The occurences of induction of labour and the outcomes were recorded in the partograph and also in a questionnaire attached to the patient's file.

8.13 Data analysis

Raw data was entered into Red cap software and checked for completeness, errors and outliers. Data analysis was done using STATA programme and SPSS. Data analysis was done using Pearson Chi-square. The samples of mean for numerical data were subjected to a t- test for difference of means and Kwallis test for a difference in medians. A p-value of <0.05 was considered to be statistically significant. The results are presented in chapter 9 in tables and bar graphs.

8.14 Data and Safety Monitoring Board (DSMB)

A DSMB was constituted to include members from other institutions who so as to provide the requisite expertise for conducting a drug clinical trial in the department. The DSMB was an independent group of experts composed inorder to advise the KNH-UoN Ethics and Research

Committee, Department of Obstetrics and Gynaecology, University of Nairobi, Kenyatta National Hospital and the study investigators. The members of the DSMB provided their expertise and recommendations. The primary responsibilities of the DSMB included to: 1) periodically review and evaluate the accumulated study data for participant safety, study conduct and progress, and, when appropriate, efficacy, and 2) make recommendations to KNH-UoN Ethics and Research Committee, Department of Obstetrics And Gynaecology, University of Nairobi, Kenyatta National Hospital and the study investigators, concerning the continuation, modification, or termination of the trial. Terms of reference for the team will be developed defining the mandate of the DSMB. However, no modifications were done during the study.

8.15 Stopping rules

The DSMB agreed on some rules that would be applied to ensure participant protection. This was to be implemented in stopping the study to avoid harm to the study participants. An interim analysis was done at 60% of study participant recruitment and data collection to compare the efficacy and safety of both drugs. However, any serious adverse effect was to be reported to the DSMB and to the head of the department, Obstetrics and Gynecology, University of Nairobi and the assistant director, department of reproductive health, K.N.H. within 24 hours. The immediate/ early stopping rule was uterine rupture. Other stopping rules included: Significantly high efficacy or safety on one treatment arm as compared to the other, significantly high frequency of serious adverse effect(s) on oral misoprostol as compared to vaginal misoprostol.

8.16 Serious adverse effects

There were no serious adverse effects reported during this study. The primary investigator was responsible for reporting any case of a serious adverse event occurring to the participants during this study to the data and safety monitoring committee, Head of Reproductive health services-

K.N.H. and Head of department Obstetrics & Gynecology-UoN and the supervisors within 24 hours. A written report was supposed to be submitted to the same within 48 hours. The possible serious adverse effects in this study included; uterine hyperstimulation, uterine rupture, poor perinatal outcomes and death. Immediate management of these serious adverse effects was to be instituted. In case of any suspected uterine hyperstimulation, induction of labour was supposed to be stopped immediately, $MgSO_4$ at 1g/hour in normal saline started and a CTG done as the participant was being prepared for an emergency caesarean section. A serious adverse event (S.A.E.) form was to be completed with details of the event and the outcome after the management.

8.17 Ethical consideration

This study was designed to comply with international ethical guidelines that govern human research. It was carried out after an approval from the department of Obstetrics and Gynaecology and the KNH-UoN Ethics & Research Committee.

Since this study involved human subjects, it was anticipated that some ethical issues may arise. These included; serious adverse effects such as uterine rupture, poor maternal and neonatal outcomes or significantly low efficacy on one of the methods. To mitigate this, participants were well counseled at enrollment and vigilant monitoring was done during induction till delivery to ensure early intervention. An interim analysis was also done at 60% of study participant recruitment and data collection and the results were shared with the data and safety monitoring committee to decide on whether to carry on with the study or not. There were no ethical issues that arose during this study and so no modification or termination of the study needed to be done.

8.18 Confidentiality

All the study participants' information was treated with utmost confidentiality. Each participant was assigned a unique number that was used for identification while concealing their real identity. Data was only available to investigators and only for the purpose of this study.

8.19 Risks and benefits

Induction of labour is done to avert an anticipated adverse effects associated with carrying on with the pregnancy such as fetal demise. However the process is not without risks. During the study period, the following risks were taken in to consideration (There are no globally acceptable definitions for some of the terms).

- Uterine hyperstimulation – occurrence of uterine contractions lasting more than 2 minutes, occurrence of more than 4 contractions within 10 minutes averaged over 30 minutes or contractions of normal duration occurring within 60 seconds of each other with or without fetal heart changes. (This term is becoming obsolete and being replaced by tachysystole).
- Tachysystole – More than 5 contractions within 10 minutes averaged over 30 minutes
- Hypersystole (Hypertonus) – Single contraction lasting more than 2 minutes
- Sepsis – Ascending infection
- Uterine rupture
- Failed induction of labour and subsequent Caesarean section
- Non reassuring fetal status
- Umbilical cord accidents

8.20 Consent

A written consent was provided to each of the participants in English or Kiswahili. It was also explained to them in a language that they could understand. The participants will be told what the research entails, the procedure, the risks and benefits. They were also be given time to read through the copy. Participation was done willingly without any coercion. The participants were also aware that they were free to withdraw from the study at any stage without victimization or denial of treatment whatsoever.

8.21 Limitations

i. This study was not blinded and this could have introduced a bias.

ii. Drug stock outs during the study

8.22 Information sharing

At the onset of the study, the relevance of the study was shared with all the labour ward staff in K.N.H. especially in labour ward in order to enhance co-operation. Relevant protocols were shared with them and appropriate up dates were given during the study, including study progress. The clinically significant results are going to be shared with the relevant teams. These include; K.N.H. maternity staff, University of Nairobi (department of Obstetrics and Gynaecology) and the Ministry of Medical services.

9.0 RESULTS

This study was conducted over a period of 3 months at Kenyatta National Hospital. The study comprised 75 women and 77 women at term who received 25 µg and 50 µg of vaginal and oral misoprostol 4 hourly respectively. The mean age of the women who received oral misoprostol was 26.2 years and 27.0 years for those who received vaginal misoprostol (table 9.1). Most of the study subjects were primigravidae with a median gestational age of 41 weeks vide the last normal menstrual period. Except for educational attainment in which the group receiving oral misoprostol had more subjects with secondary and above education level compared to the group that received vaginal misoprostol (χ^2 for trend = 6.0, *P*-val = 0.014), marital status was equally distributed among the study participants. The frequency distribution of the sociodemographic characteristics of the study participants is shown in table 9.1

Table 9.1 Frequency distribution of the socio-demographic characteristics

	Oral	**Vaginal**	***P*-val**
Age (years)			
Mean (SD)	26.2 (5.0)	27.0 (5.2)	***P*-val. = 0.333**
Parity live births	**Oral**	**Vaginal**	**Overall**
Median (IQR)	0 (0_1)	0 (0_1)	0 (0_1)
Gestational age (weeks)			
Median (IQR)	41(40_41)	41(41_41)	41(41_41)
Marital status			
Single	10 (13.2)	13 (17.3)	χ^2 **= 0.44**
Married	66 (86.8)	61 (81.3)	***P*-val.= 0.543**
Divorced	0 (0.0)	1 (1.3)	
Education level			
Primary	7 (9.1)	15 (20.0)	χ^2 **for trend = 6.0**
Secondary	32 (41.6)	33 (44.0)	***P*-val = 0.014**
College	35 (45.5)	26 (34.7)	
University	3 (3.9)	1 (1.3)	

Table 9.2 shows the distribution of indication for induction of labour by either oral or vaginal misoprostol. Postdatism was the commonest indication for induction of labour on both vaginal and oral routes. Overall, it accounts for 80% of all the participants who had induction of labour. In the oral group, postdatism accounts for 76.6% of all the indications for induction of labour and 83.8% of all the patients induced by vaginal route.

Table 9.2 Frequency distribution for the indications of induction of labour

Indication for induction of labour	**Oral**	**Vaginal**	χ^2 **= 9.860** ***p*-val. = 0.043**
Postdatism	59 (76.6)	62 (83.8)	
Hypertension in pregnancy	0 (0.0)	5 (6.4)	
PROM	13 (16.9)	5 (6.8)	
Others	5 (6.5)	2 (2.7)	

In table 9.3 the women who received oral misoprostol were 1.3 times likely to achieve vaginal delivery within 24 hours compared to those who received by vaginal route although this difference did not attain statistical significance. The mean time from induction of labour to delivery was 17.9 hours in those who received oral misoprostol and 21.7 hours among the women receiving vaginal misoprostol.

Table 9.3 Frequency distribution of vaginal deliveries achieved within 24 hours of induction and the average number of hours from induction to delivery

Route of misoprostol administration	**Achieved vaginal delivery within 24 hours**		**Relative risk, (95% CI)**
	Yes	**No**	**1.3 (0.97-1.64)**
Oral	52 (68.0%)	25 (32.0%)	
Vaginal	40 (53.0%)	35 (47.0)	**p- value =0.09**
Total no. of hours from induction to delivery	**Oral misoprosol**	**Vaginal misoprostol**	
Mean (SD)	17.9 (10.4)	21.7 (12.9)	***P*- value = 0.024**

Among the women who received oral misoprostol 28.7% delivered by caesarean section while those that got vaginal misoprostol were 30.7%. Table 9.4 shows the distribution of indications for the caesarean section.

Table 9.4 Frequency of distribution for the indications for Caesarean section

Indication for CS	**Oral**	**Vaginal**	
Failed induction	4 (18.2)	6 (26.1)	χ^2 **= 1.337**
Poor progress	9 (40.9)	8 (34.8)	***P*-value = 0.72**
NRFS	6 (27.3)	4 (17.4)	
Other	3 (13.6)	5 (21.7)	

The proportion of women who achieved delivery by either vaginal or caesarean section within 24hours following oral misoprostol were 87% while 68% of those who received vaginal misoprostol had delivered within 24 hours from the onset of induction of labour as shown in Figure 1.

Figure 1 A bar graph showing the proportion of total deliveries (by vaginal or caesarean section) that were achieved within 24 hours by either oral or vaginal misoprostol

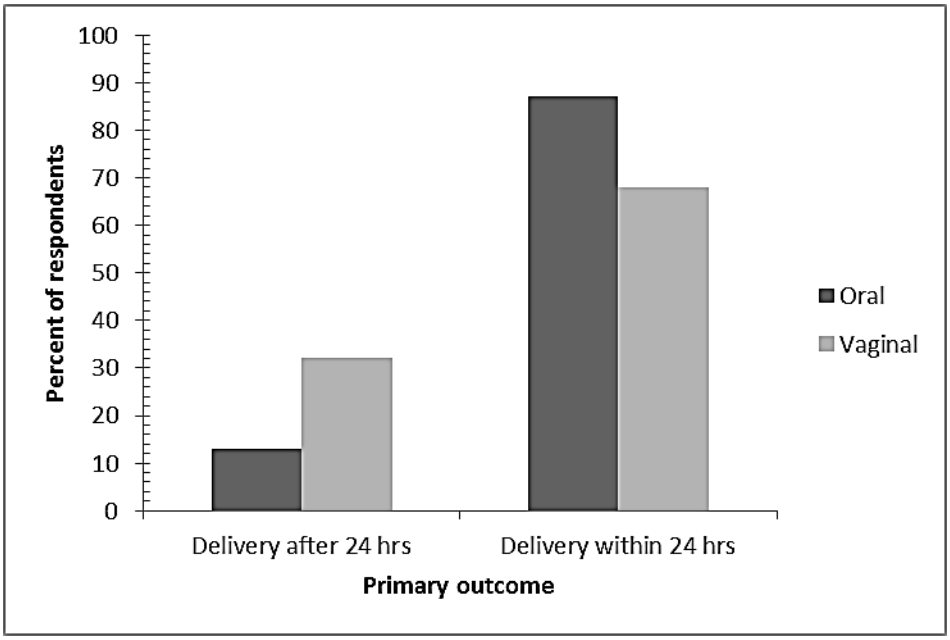

Figure 1: P-value= 0.005

The median number of misoprostol doses received by oral route was 2 while in those receiving vaginal misoprostol, the median dose was 3. Oxytocin augmentation was done for 55.8% of those that received oral misoprostol and in 54.7% of the participants who received vaginal misoprostol. Meconium stained liquor occured in 9.1% of the participants on oral misoprostol and in 16% of those in the vaginal group**.** The distribution is as shown in table 9.5

Table 9.5 Other intrapartum occurrences

Number of doses given	**Oral**	**Vaginal**	
Median (IQR)	2(2_4)	3 (2_4)	***P*- value = 0.065**
Oxytocin Augmentation			
No	34 (44.2)	34 (45.3)	χ^2 **= 0.21**
Yes	43 (55.8)	41 (54.7)	***P*- val. = 0.884**
Meconium stained liquor			
No	70 (90.9)	63 (84.0)	χ^2 **= 1.658**
Yes	7 (9.1)	12 (16.0)	**P-value = 0.198**

The mean birth weight in the oral group was 3252g and 3213.2g in the women receiving vaginal misoprostol with no significant statistical difference. There were no perinatal mortalities or admissions to NICU during the study period. However, 6 neonates on each arm needed resuscitation as shown in table 9.6

Table 9.6: Frequency distribution of perinatal outcomes

Birth weight	**Oral**	**Vaginal**	**Overall**
Mean (SD)	3252.6(460.5)	3213.2 (399.4)	***P*-value = 0.577**
Median (IQR)	10 (9_10)	10 (9_10)	10 (9_10)
APGAR 5 min	**Oral**	**Vaginal**	**Overall**
Median (IQR)	10 (9_10)	10 (9_10)	10 (9_10)
Neonate resuscitated			
No	71 (92.2)	69 (92.0)	χ^2 **= 0.02**
Yes	6 (7.8)	6 (8.0)	***P*-val. = 0.962**
Neonate admitted to NICU			**Overall**
No	77 (100.0)	75 (100.0)	152(100.0)
Perinatal mortality			**Overall**
No	77 (100.0)	75 (100.0)	152(100.0)

As shown in table 9.7 below, there was no incidence of uterine hyperstimulation, hypersystole or tachysystole. In addition, there was no diarrhoea or hyperpyrexia reported on either oral or vaginal misoprostol but there was vomiting in 13% of those that received oral misoprostol and 16% of those that received vaginal misoprostol as shown in table 9.7. Nausea occurred in 12% of the women receiving vaginal misoprostol and 7.8% of those that received oral misoprostol.

Table 9.7: Frequency distribution of maternal outcomes

Uterine Hyperstimulation		**Oral**	**Vaginal**	**Overall**
No		77 (100.0)	75 (100.0)	152(100.0)
Hypersystole				
No		76 (100.0)	75 (100.0)	151(100.0)
Tachysystole				
No		77 (100.0)	75 (100.0)	152(100.0)
Hyperpyrexia		Oral	Vaginal	Overall
	No	77 (100.0)	75 (100.0)	152(100.0)
Vomiting				
	No	67 (87.0)	59 (78.7)	***P*- value = 0.172**
	Yes	10 (13.0)	16 (21.3)	
Diarrhoea				
	No	77 (100.0)	73 (100.0)	150(100.0)
Nausea				
	No	71 (92.2)	66 (88.0)	***P*- value = 0.384**
	Yes	6 (7.8)	9 (12.0)	

In table 9.8 the predictors of delivery within 24 hours were the route of misoprostol administration, the mode of delivery and the number of misoprostol doses given. For example, the participants who received vaginal misoprostol were 3.26 more likely to deliver within 24hours compared to those that received oral misoprostol. In addition, the participants who delivered by Caesarean section were 3.90 more likely to deliver within 24 hours as compared to those that had vaginal delivery.

Table 9.8 Multivariable model for predictors of delivery within 24 hours after induction

	Odds ratio	95% CI		P value	LRT
Route of misoprostol administration					<0.001
Oral	Ref				
Vaginal	3.26	1.12	9.47	0.030	
Mode of delivery					
Vaginal	Ref				
Caesarean	3.90	1.33	11.40	0.013	
Doses of misoprostol given					
No of doses	3.85	2.33	6.36	<0.001	

10.0 DISCUSSION

Misoprostol was initially approved for the treatment of peptic ulcer disease. It is during its use that it was observed to initiate uterine contractions among pregnant women. The use of misoprostol for induction of labour started in 1980's in South America.

Many studies on the use of misoprostol for induction of labour have been done since then. A few studies comparing oral and vaginal misoprostol at 50µg and 25µg respectively, given 4 hourly have been done in Asia.

The purpose of this study was to compare the efficacy of 25µg vaginal misoprostol and 50µg oral misoprostol 4 hourly for induction of labour, perinatal and maternal outcomes in women with term pregnancies. Most of the outcomes in this study are comparable to similar studies done mainly in Asia (7, 14, 15,17). The randomization process was effective for age, marital status, parity and gestational age. However, the oral group had statistically significant more educated participants compared to the vaginal group. This may have confounded the difference observed in response to treatment.

Majority of the women who were induced by either oral or vaginal misoprostol were primigravida and the median gestational age for both arms was 41weeks. In addition the median number of misoprostol doses received by oral route was 2 and in those receiving vaginal misoprostol, the median dose was 3. The mean birth weight in the oral group was 3252g and 3213.2g in the women receiving vaginal misoprostol. There was no statistical difference observed between the two groups. This might have helped in reducing bias and confounders in the study.

The average time taken from induction of labour to delivery in the oral group was 17.9 hours, which was significantly less than in the vaginal group at 21.7 hours (P-value = 0.024).

This could partially be due to the difference in the maximum number of doses given though only 8 participants received more than 5 doses of vaginal misoprostol. The response is comparable to a similar study by Rahman et al in which the participants receiving 50µg oral misoprostol delivered within 21.22 hours while those on vaginal misoprostol 25µg delivered within 20.15 hours of induction of labour. However, the duration on both arms is longer than the study by Komala et al in their comparative study between oral and vaginal misoprostol for induction of labour in which the oral group took an average of 12.92 hours from induction to delivery while the vaginal group took an average of 14.04 hours. This could be due to the long waiting time for theatre for participants who required caesarean section since the time includes both normal deliveries and caesarean deliveries.

Postdatism was the commonest indication for induction of labour on both vaginal and oral routes. Overall, it accounted for 80% of all the participants who had induction of labour. In the oral group, postdatism accounted for 76.6% of all the indications for induction of labour and 83.8% of all the patients induced by vaginal route. Other indications for induction included hypertensive disease in pregnancy and PROM. This is comparable to a study done in 2013 by Joshua P. Vogel et al on patterns and outcomes of induction of labour in Africa and Asia (16). In their study, they observed that the commonest indication for induction of labour was elective and unplanned induction for postdatism and post term pregnancies. A small difference was observed in stratification for indications for induction of labour with the oral group having slightly more PROM participants and vaginal group with more participants with postdatism. Since amniotomy

contributes to cervical ripening, this difference may have introduced a confounder in the outcomes observed.

There was a difference observed in the overall rate of deliveries achieved by both vaginal and caesarean section within 24 hours of initiation of induction of labour between vaginal and oral misoprostol. Among the women receiving vaginal misoprostol, the rate of deliveries achieved in 24 hours was 87% while in the vaginal group, the rate of deliveries was 68.0% with a risk difference of 19%. Among the women who received oral misoprostol, 68% achieved vaginal deliveries within 24 hours compared to 53.3% in the vaginal group with the women who received oral misoprostol 1.3 times more likely to achieve a vaginal delivery within 24 hours. However, there was no statistically significant difference observed in the vaginal deliveries achieved within 24 hours on either oral or vaginal misoprostol. These rates are slightly lower compared to a few other studies. Nevertheless the rate of deliveries in 24 hours on oral misoprostol was comparable to the study done by Sultana et al (14). This could partially be due to the difference in the maximum number of doses given though only 8 participants received more than 5 doses of vaginal misoprostol. In addition, vaginal misoprostol used on PROM participants may have been flushed out of the posterior fornix by the liquor contributing to the longer duration from induction to delivery.

Nevertheless, there was no significant difference in the rate of vaginal and caesarean deliveries observed between the two methods. The rate of vaginal deliveries achieved in the women receiving oral misoprostol was 71.4% while in the vaginal group, the rate of vaginal deliveries was 69.3%. This is comparable to a study done by N. Sultana et al (14) in which the vaginal delivery rate was 70%in those receiving oral misoprostol and 66% among the women getting vaginal misoprostol. The main indication for caesarean section was poor progress of labour

accounting for 40.9% of all the indications for caesarean sections in the oral group and 34.8% in the vaginal group. The proportion of the participants who had failed induction of labour in the oral group was 5% while those who received vaginal misoprostol it was 8%. This compares with similar study done by Sultana et al in which 6% of the women who received oral misoprostol had failed induction of labour compared to 8% in those receiving vaginal misoprostol. In another study by Komala et al (7) among those that received vaginal misoprostol, l 6% had failed induction of labour compared to 2% of those that received oral misoprostol. These similar findings in these studies, including this study, could be because the participants were randomly allocated to each arm and therefore the confounding factors were almost evenly distributed between the two groups.

During labour, there was no difference in the rate of oxytocin augmentation between the two groups. Augmentation of labour with oxytocin was done for 55.8% of those that received oral misoprostol and in 54.7% of the vaginal group. However, the women on vaginal misoprostol had a higher incidence of meconium stained liquor (16%) compared to those on oral misoprostol (9.1%). This is comparable to most studies (7, 14, 15, 17) and it could be due to the high bioavailability of vaginal misoprostol compared to oral misoprostol as a result of reduced first pass effect in the liver and gut.

There was no uterine hyperstimulation reported during this study. This is unlike most studies (7, 14, 15, 17) where one or two cases of uterine hyperstimulation are reported. This could be due to inaccurate assessment for uterine contractions using clinical method as opposed to CTG. In addition, there was no diarrhea or hyperpyrexia reported on either oral or vaginal misoprostol but there was a difference in the two arms with vomiting in 13% of those that received oral misoprostol and 16% of those that received vaginal misoprostol. In addition, nausea occurred in

12% of the women receiving vaginal misoprostol and 7.8% of those that received oral misoprostol.

In perinatal outcomes, there was no significant difference observed between those on vaginal or oral misoprostol. The neonatal outcomes were comparable on both arms. There were no perinatal mortalities or admissions to NICU during the study period. However, 6 neonates on each arm needed resuscitation due to an APGAR score of ≤ 7. One neonate in each study arm had an APGAR score < 7 and the one neonate from the oral group had an APGAR score < 7 at 5 minutes. This could be due to cord compression following PROM. The baby was delivered by an emergency caesarean section.

CONCLUSION

Misoprostol is an effective agent for induction of labour given orally or vaginally. There is no significant difference between 25µg vaginal misoprostol and 50µg oral misoprostol given 4hourly to maximum of 6 and 5 doses respectively, the maternal and perinatal outcomes are comparable. Although the women who received oral misoprostol 1.3 times more likely to deliver within 24 hours compared to those that received vaginal misoprostol, there was no significant difference. The rate of failed induction was low and almost the same in the two arms and compared well with the studies conducted elsewhere. The safety and efficacy at the stated dosages seems to be comparable for both oral and vaginal misoprostol

RECOMMENDATIONS

Based on this study Kenyatta National hospital and the Ministry of Health should consider adopting oral misoprostol tablets at 50µg 4 hourly to a maximum of 5 doses for induction of labour at term. This is much easier to administer and both provider and patient friendly as compared to the current guidelines on oral solution that needs to be given 2 hourly in an already lean human resource in our set up. This will be very useful especially in patients with PROM who need induction of labour.

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APPENDICES

APPENDIX 1: QUESTIONNAIRE

Enrolment

Initials: Tel.:

Age: Parity:

LMP: EDD:

Gestational age:

Marital status:

Nationality:

County of residence:

Education level:

Religion:

Occupation:

Tel. no.:

Medical history: DM Yes ☐ No ☐ HTN Yes ☐ No ☐

Other chronic disease: If yes, specify:

Indication for induction of labour:

Have you had a normal delivery before? Yes ☐ No ☐

Ever heard about induction of labour?

History of previous induction of labour: Yes ☐ No ☐

If yes the previous route of induction:

Was this a planned pregnancy?

Current route of misoprostol administration: Oral Vaginal

Oxytocin augmentation: Yes ☐ No ☐

Uterine hyperstimulation:

Hypersystole:

Tachysystole:

Meconium stained liquor: Yes ☐ No ☐

Total no. of misoprostol doses given:

Maternal outcomes

Hyperpyrexia: Yes ☐ No ☐

Vomiting: Yes ☐ No ☐

Diarrhoea: Yes ☐ No ☐

Intrapartum

Mode of delivery: ☐ Vaginal ☐ Caesarean

Birth weight:

Indication for C/S:

Total no. of hours from induction to delivery:

Neonatal outcomes

APGAR score: At 1min ☐ At 5min ☐

Neonate resuscitated: Yes ☐ No ☐

Neonate intubated/Admitted to NICU : Yes ☐ No ☐

Neonatal mortality: Yes ☐ No ☐

Others

For any subsequent induction, what would be the preferred mode of induction? :

☐ Same ☐ Different ☐ Unsure

If different, specify which one?

Was the labour experience better than expected?

Was the labour experience worse than expected?

Was the pelvic exam extremely painful?

Do you have a positive attitude towards a subsequent induction of labour?

APPENDIX 2

CLINICAL REPORT FORMS

2.1 SUBJECT ENROLMENT FORM

In patient no.:

Participant's Unique no.:

Tel. no.:

Age:

Nationality:

Race:

Weight:

Height:

Date enrolled:

Time first dose given:

2.2 PARTICIPANT ELIGIBILITY FORM

Age:

Of sound mind: Yes No

Gestational age 38-42weeks: Yes No

If yes,specify:

Parity between 0-3: Yes No

Specify:

Singleton gestation: Yes No

Cephalic presentation: Yes No

Indication for induction of labour (tick appropriately):

Inclusion criteria

- Hypertensive disease in pregnancy
- Postdatism(specify the gestational age)
- Intrauterine growth restriction
- Oligohydramnious
- Polyhydramnious
- Controlled Diabetes Mellitus at term
- Pre-labour rupture of membranes
- Rhesus negative at term
- Any other(specify):

Exclusion criteria

- Cardiac disease
- Previous uterine scar
- Intra uterine fetal death
- Severe systemic disease
- Malpresentation
- Antepartum hemorrhage
- Eclampsia

2.3 MEDICAL/SURGICAL HISTORY

History of any of the following:

Hypertension:

Diabetes mellitus:

Cardiac disease:

Asthma:

Epilepsy:

Thyroid disease:

Known food or drug allergies:

History of previous surgeries:

If yes, specify:

Other:

If yes, specify:

2.4 PHYSICAL EXAMINATION FORM

Blood pressure:

Pulse rate:

Temperature:

Respiratory rate

Pallor:

Jaundice:

Oedema:

Fundal height:

Lie:

Presentation:

Fetal heart rate:

Any other significant finding:

2.5 CLINICAL LABORATORY DATA FORM

Hemoglobin:

Blood group:

VDRL:

Serology-status:

2.6 SERIOUS ADVERSE EFFECT (S.A.E.) REPORT FORM

Participant Serial No.:

Participant I.P. No.:

Date of adverse effect:

Date reported:

Reported by:

Reported to:

The nature of S.A.E.:

Uterine hyperstimulation
Uterine rupture
Perinatal mortality

Is the S.A.E. due to misoprostol administration:

Yes	No	Not sure

Description of the S.A.E.:

Effect on misoprostol administration:

Withheld	Discontinued permanently	No change

The treatment/intervention given:

Outcome of the S.A.E.

- Fatal/death
- Life threatening
- Leads to disability
- Prolonged hospital stay
- Poor neonatal outcome

Comments by the attending clinician

Comments by the monitoring committee:

APPENDIX 3: STUDY PARTICIPATION CONSENT FORM

This is an informed consent form inviting you to participate in my research on comparison between oral and vaginal misoprostol for induction of labour.

Name of the principal investigator: Dr. Victoria Muviku

Institution: University of Nairobi

Department: Obstetrics and Gynaecology

Registration no.: H58/64040/2013

Contacts: 0734885080

Introduction:

Induction of labour is the process of artificially stimulating the uterus so as to start labour. It's usually done at the age of viability to avert a foreseen adverse outcome associated with continuation of the pregnancy. The indications for induction of labour differ. The incidence varies from country to country. In developed countries induction of labour varies between 20-35% but it's much lower in developing countries, being as low as 1.4% in Niger. On average, 9.6% of pregnant women will require induction of labour. Misoprostol (PGE1) has proved very effective in induction of labour. In addition, it's cheap, heat stable therefore easy to store and transport and widely available.

Purpose of the study:

Misoprostol has been used for induction of labour for several decades. However, the ideal dosage, route and frequency of administration are yet to be established. In addition, some women find vaginal exams including administration of vaginal misoprostol uncomfortable. This study will compare oral and vaginal misoprostol efficacy, maternal and neonatal outcomes.

Ethical consideration:

The study is designed to comply with international ethical guidelines that govern human research and will be carried out after approval by the department of Obstetrics and Gynaecology and the KNH-UoN Ethics& Research Committee.

Since this study involves human subjects, ethical issues may arise. These include severe adverse effects such as uterine hyperstimulation, poor maternal and neonatal outcomes or significantly low efficacy on one of the methods. To mitigate this, patient will be well counseled at enrollment, vigilant monitoring during induction till delivery to ensure early intervention. An interim analysis will also be done at 50% in conjunction with the monitoring committee to decide on whether to carry on with the study or not.

Risks and Benefits:

Induction of labour helps to avert adverse effects associated with carrying on with the pregnancy such as fetal demise. However the process is not without risks. This study will take into consideration and look out for the following risks. (There are no globally acceptable definitions for some of the terms).

- Uterine hyperstimulation – occurrence of uterine contractions lasting more than 2minutes, occurrence of more than 4contractions within 10 minutes over 30minutes or contractions of normal duration occurring within 60seconds of each other with or without fetal heart changes. (This term is becoming obsolete and being replaced by tachysystole).
- Tachysystole – More than 5contractions within 10minutes averaged over 30minutes
- Hypersystole (Hypertonus) – Single contraction lasting more than 2minutes
- Sepsis – Ascending infection
- Uterine rupture
- Failed induction of labour and subsequent Caesarean section
- Non reassuring fetal status

Umbilical cord accidents

Confidentiality:

Participants will be treated with utmost confidentiality and no names will be used.

Voluntary participation:

The study is voluntary and participants will be free to ask any questions or clarifications. Anyone wishing to withdraw from the study will be free to do so at any stage without any victimization.

Dr. Victoria Muviku : ……..

Signature: ……

Date: ……

Consent to participate in the study:

I the undersigned have read the foregoing information and voluntarily consent to this study. I am aware of the process of induction of labour and the procedures involved as explained to me. Am also aware of the available routes of the drug administration, the benefits and risks associated with this process. I have asked questions which have been answered to my satisfaction. I have also been assured of confidentiality and freedom to withdraw at will and at any stage of the study without any victimization. If I have more questions later about the study I will ask the investigator, and if I have any questions on my rights as a research subject, I can call the KNH-UoN Ethics& Research Committee at 02 726 300. I will receive a copy of this consent form.

Name of participant ……

Signature ……

Date ……

Swahili translation of the consent form

Ridhaa ya kushiriki katika utafiti:
Mimi aliyetia sahihi kwa hiari yangu bila kulazimishwa ridhaa ya utafiti huu. Nafahamu mambo yanayohusisha huu utafiti kama vile yameelezwa kwangu. Pia, nafahamu faida na hatari zinazohusiana na utafiti huu. Yale ambayo sikuelewa vizuri kuhusiana na huu utafiti, nimeuliza maswali na kujibiwa kikamilifu vilivyo. Nimehakikishiwa ya kwamba mambo ambayo yananihusu kwa huu utafiti yatawekwa kama siri. Pia, nimehakikishiwa ya kwamba niko huru kujiondoa kwa huu utafiti bila kunyimwa matibabu ipasavyo. Kama nina maswali zaidi baadaye kuhusu utafiti nitamwuliza mchunguzi na kama niko maswali yoyote juu ya haki zangu katika huu utafiti, naweza kupiga simu KNH-UoN Kamati ya Utafiti na Maadili katika 02 726 300. Nitapokea hii fomu ya ridhaa.
Jina la mshiriki .....
Sahihi .....
Tarehe .....

APPENDIX 4: BUDGET

	BUDGET FOR INDUCTION OF LABOUR STUDY IN KENYATTA NATIONAL HOSPITAL			
Item	**Description**	**Quantity**	**Unit price(Ksh)**	**Total(Ksh)**
	Office supplies			
1	Biro pens	10	20	200
2	Notebook	1	150	150
3	Pencils	5	10	50
4	Pencil sharpener	1	50	50
5	Diary	1	150	150
6	White out pen	1	150	150
7	Stapler	1	500	500
8	Staple remover	1	250	250
9	Paper punch	1	600	600
10	Folders	4	50	200
11	Box files	4	300	1200
12	Spring files	4	150	600
13	Dictaphone	1	15000	15000
	Others			
1	Misoprostol	1440	60	86400
2	Fetoscopes	3	500	1500
3	Printing	10	1000	10000
4	Photocopying	3	1500	4500
5	Final proposal booklet	4	1000	4000
6	Final dissertation	4	1000	4000
7	Protocols	5	100	500
8	Transport	20	3000	60000
9	Research assistants	30	2000	60000
10	Communication		10000	10000
11	Statistician	1	30000	30000
12	Accommodation	2000	60	120000
13	Miscellaneous			14000
	Total (Ksh)			424000