A COMBINATION OF FOLEYS BALOON AND MISOPROSTOL VERSUS MISOPROSTOL ALONE FOR INDUCTION OF LABOUR AT KENYATTA NATIONAL HOSPITAL, A RANDOMIZED CONTROLLED TRIAL

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THIS DISSERTATION IS SUBMITTED IN PARTIAL FULFILLMENT FOR THE AWARD OF DEGREE IN MASTER OF MEDICINE IN OBSTETRICS AND GYNECOLOGY

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I also sincerely appreciate the KNH research and programs unit for the financial support towards this study.

DEDICATION

I dedicate this book to my dear wife Belinda and my son Dylan, you have been my inspiration. My parents, Mr. and Mrs. Kibii who have raised me to be the person I am today. God bless you all.

DECLARATION

This is to certify that the work presented herein is my original work, has not been presented for a degree course in any other university and was supervised by senior members of the Department of Obstetrics and Gynecology, University of Nairobi, School of Health Sciences, Faculty of Medicine, Kenyatta National Hospital, Nairobi, Kenya.

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CERTIFICATION OF SUPERVISION

This is to certify that this project by Dr. Davies Kiprop Kibii was researched upon under my supervision and that this book is submitted with my approval.

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LIST OF ABBREVIATIONS

ACOG – American College of Obstetricians and Gynecology

APGAR-Appearance Pulse Grimace Activity Respiration

GAGs– Glycosaminoglycan's.

ICU – Intensive Care Unit.

IUFD– Intrauterine Fetal Demise.

FGR – Fetal Growth Restriction.

KNH – Kenyatta National Hospital.

NICU – Neonatal Intensive Care Unit.

RCT– Randomized Clinical Trial.

USA– United States of America

WHO– World Health Organization

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ABSTRACT

Introduction

The World Health Organization (WHO) defines induction of labor as the initiation of labor by artificial means prior to its spontaneous onset at a viable gestational age with the aim of achieving vaginal delivery in a pregnant woman with intact membranes. Successful labor induction leads to vaginal birth while failed induction is the inability to achieve more than 3 cm cervical dilatation after 24 hours of induction of labor. after using the standard WHO protocol. In developed countries, up to 25% of term deliveries involve induction of labor compared to about 9.6% in the developing countries. Failed induction is an expected outcome of induction of labor. Failed induction or prolonged duration of induction to delivery may increase costs, patient anxiety, and if not monitored well especially in the setting of heavy workload may lead to poor neonatal outcomes.Misoprostol versus Foley balloon alone had no significant difference between induction to delivery time.Combination methods of induction of labor may reduce the high failed induction rates reported by misoprostol or Foley catheter balloon alone. If induction of labor using combined Foley and misoprostol can reverse or reduce these outcomes, then it can change guidelines on induction of labor or for those patients at risk of failed induction.

Methods

In this randomized clinical trial, we aimed to find out if combined methods using misoprostol with Foley's catheter versus misoprostol alone have a higher success rate

and lower the incidence of failed induction. Participants comprised pregnant women admitted for induction of labor at gestational age of 28 weeks and beyond at Kenyatta National Hospital antenatal and labor wards. The primary outcome was the incidence of failed induction or successful induction and secondary outcomes induction to delivery interval, and incidence of adverse maternal and perinatal outcomes. We conducted intent-to-treat analysis using SPSS version 21. For each outcome, proportions were compared using Chi2 test, 95% CI, two tailed hypotheses and p value considered significant at <0.05.

Results

Between February and May 2016, we enrolled 180 (76%) of 237 pregnant women who were scheduled for induction of labor at 28 weeks or higher gestational age. Of these, one half were randomized to induction of labour using a combination of intracervical extramniotic Foley catheter and 25 micrograms of misoprostol (n = 90) and the other half randomized to 25 micrograms of misoprostol alone (n = 90). There were no post randomization withdrawals; all participants received the assigned treatment. There were no statistically significant differences in the socio-demographic or obstetric characteristics of women between the two groups. The mean Bishops score was similar between the two groups 2.8 (± 1.1) versus 2.1 (± 1.5) for the combined versus misoprostol alone respectively (p=0.143). Combined Foley and misoprostol group had a significantly shorter induction-to-delivery interval compared to those in the misoprostol only group. (Log rank chi = 15.82; p = 0.0001=). There were no significant differences in the rates of failed induction, 8.9% for the combined Foley and misoprostol versus 11.1%

for the misoprostol alone (p=0.619). Although more complications occurred in the misoprostol alone arm (8.9%) compared to the combined misoprostol and Foleys arm (4.4%), these differences were not statistically significant. Admissions to neonatal intensive care unit were similar between the two groups (p = 0.697).

Conclusions

Compared to misoprostol only, use of combination of misoprostol and Foley Catheter for induction of labor significantly shortened the induction to delivery time but did not reduce the rates of failed induction, or increase maternal or neonatal adverse outcomes.

Recommendation

In the setting of poor Bishops score and urgent need to achieved delivery, pregnant women should be offered combination of Foley catheter and misoprostol rather than misoprostol alone for induction of labor. Larger trials can further evaluate if combination methods can reduce failed induction rates.

INTRODUCTION AND LITERATURE REVIEW

Induction of Labor

Induction of labor is a procedure used to stimulate uterine contractions during pregnancy before spontaneous onset of labor with an aim to achieve vaginal birth. A health care provider might recommend labor induction for various indications, primarily when there's concern for a mother's health or a baby's health. In developed countries, up to 25% of all deliveries at term now involve induction of labor. In developing countries, the rates are generally lower, due to lack of drugs, staffing and lack of access to cesarean delivery services, but in some settings they can be as high as those observed in developed countries, (World Health Organization, WHO)(1).

Induction of labor is not risk-free and many women find it to be uncomfortable. With a view to promoting the best-known clinical practices in labor and childbirth and to improving maternal outcomes worldwide, the WHO has developed the present recommendations using the procedures outlined in the *WHO Handbook for guideline development*

General principles related to the practice of induction of labor

Induction of labor should be performed only when there is a clear medical indication for it and the expected benefits outweigh its potential harms.

In applying the recommendations, consideration must be given to the actual condition, wishes and preferences of each woman, with emphasis being placed on cervical status, the specific method of induction of labor and associated conditions such as parity and rupture of membranes.

Induction of labor should be performed with caution since the procedure carries the risk of uterine hyper stimulation, uterine rupture and fetal distress.

Wherever induction of labor is carried out, facilities should be available for assessing maternal and fetal well-being. Women receiving oxytocin, misoprostol or other prostaglandins should never be left unattended because complications may arise and should be promptly managed. Failed induction of labor does not necessarily indicate caesarean section. Some settings may allow a repeat of the process provided maternal and fetal factors are suitable for the same. Wherever possible, induction of labor should be carried out in facilities where caesarean section can be performed.

The indication for induction of labor therefore must be convincing, compelling, consented to and documented. These conditions are not met when the proposed indication is solely for the convenience of the physician or the woman alone.

Specific recommendations for induction of labor

Induction of labor is recommended for women who are known with certainty to have reached 41 weeks (>40 weeks + 7 days) of gestation. It is however not recommended in women with an uncomplicated pregnancy at gestational age less than 41 weeks. Women with gestational diabetes should not give birth later than 41 weeks and 6 days and should be offered elective induction of labor or cesarean section(2)If gestational diabetes is the only abnormality, induction of labor before 41 weeks of gestation is not recommended. Induction of labor at term is not recommended for suspected fetal macrosomia because of the likelihood of complications during the delivery which commonly include shoulder dystocia, and birth injuries(3).

Induction of labor is recommended for women with prelabor rupture of membranes at term. In women with an uncomplicated twin pregnancy at or near term, no recommendation was made, as there was insufficient evidence to issue a recommendation(1). If prostaglandins are not available, intravenous oxytocin alone should be used for induction of labor. Amniotomy alone or with oxytocin is however not recommended for induction of labor unless there are particular risks with use of prostaglandins like uterine hyper stimulation(2).

According to WHO (2011) recommendations, if prostaglandins are not available, intravenous oxytocin alone should be used for induction of labor. It also recommends low-dose vaginal misoprostol (25 µg, 6-hourly) for induction of labor (10). Misoprostol is not recommended for induction of labor in women with previous caesarean section because of there is a higher risk of developing complications the most common being uterine rupture.

Methods of induction of labor

Methods of labor induction include mechanical and pharmacological means. Optimal choice of these depends on the pre-induction status of the cervix. The three factors most likely to lead to success include favorable cervix, multiparity and prior vaginal delivery. The cervix is considered unfavorable if the bishop score is less than 6.The most important element of bishop score is dilation, followed by effacement, station and position, with the least useful element being cervical consistency.Xenakis et.al clearly demonstrated in his prospective study between 1993 to 1995 involving five hundred and

ninety seven pregnancies that those who had a bishop score of 3 or less at onset of induction had significantly higher rates of failed induction and caesarean delivery then those with a bishop score above 3(4).

Table 1-Bishop scoring system.

Factor	0	1	2	3
Dilatation (cm)	0	1-2	3-4	>5
Effacement (%)	0-30	40-50	60-70	>80
Consistency	Firm	Medium	Soft	
Position	Posterior	Central	Anterior	
Station	-3	-2	-1 or 0	+1 or lower

Balloon Foley Catheter can be inserted either digitally or via direct visualization using a sterile Speculum(5). No data supports one over the other. It works by exerting traction as well a local pressure at the cervix causing production of local prostaglandins, which then initiate the process of cervical dilatation. Balloon (Foley) catheter is strongly recommended for induction of labor by the WHO (2012)(1).

Karjane et al in a randomized clinical trial in 2006 involving 140 women at term in Virginia medical center, Richmond USA found out that women who had extramniotic saline infusion In the Foley balloon had a shorted induction to delivery time compare with use of Foley balloon without saline infusion but this had no effect on the cesarean section rates and the neonatal outcomes.(3)

A similar study comparing extramniotic catheter with saline infusion,intracervical catheter and prostaglandin E2 done by Mandana and colleagues between 2007 and 2009 at Alzahra hospital Iran involving 363 women showed that pre-induction cervical ripening by Extra Amniotic catheter with Saline Infusion with concurrent oxytocin is better than prostaglandins in cervical ripening, shortening time to delivery and shorter time to active phase of labor without increasing the cesarean rate or maternal complications (6).

Misoprostol is a synthetic prostaglandin E1 analogue. It works by altering the extracellular ground substance of the cervix. They then cause an increase in elastase, glycosaminoglycan, dermatan sulfate, and hyaluronic acid levels in the cervix. A relaxation of cervical smooth muscle facilitates dilation. Secondly prostaglandins allow for an increase in intracellular calcium levels, causing contraction of myometrial muscle. It can be administered orally, vaginally, rectally sublingually and bucally(7).

A systematic review done by Hofmeyr and colleagues at the university of Witwatersrand south Africa in 2000 showed that misoprostol was effective at doses ranging from 25mg 3 hourly to 50 mg 4 hourly and 100mg 12 hourly were more effective than oxytocin and dinoprostone recommended doses but had increased incidences of uterine hyper stimulation with the higher doses(8).

The combination of balloon catheter plus oxytocin is recommended as an alternative method of induction of labor when prostaglandins (including misoprostol) are not available or are contraindicated. In the third trimester, in women with a dead or an anomalous fetus, oral or vaginal misoprostol are recommended for induction of labor.

Natural processes like sweeping membranes are recommended for reducing formal induction of labor.

A combination of isosorbide mononitrate and misoprostol has also been used for induction of labour.Nitric oxide has been shown to stimulate prostaglandin production in the human cervix which then lead to cervical softening and dilatation(9).

A randomized clinical trail by Carbone end colleagues at the university of Washington comparing Foley balloon filled with 60mls of water for injection with misoprostol 25 micrograms versus misoprostol alone in 2013 involving 123 women at a gestation of 24 weeks or greater found that combined Foley balloon with misoprostol shortened induction to delivery time by 3.1 hours(10). A similar randomized controlled trial done in 2009 by Hill et all comparing Foley balloon with oral misoprostol versus vaginal misoprostol alone among 232 women found out that the combination group had a shorter induction to delivery time(11).

A comparative study by Dahiya and colleagues in India found out that combination of Foley balloon and vaginal misoprostol quickens cervical ripening and reduces the induction to delivery time.

A randomized controlled trial done by Mohamad and colleagues at woman health center Assuit university in 2009 showed that a combination of isosorbide mononitrate and misoprostol is effective than misoprostol alone in hastening cervical ripening and had a shorter induction-labor interval(12). In a randomized trial at the university of Pennsylvania by Levine and colleagues (‘FOR MOMI’ trial) 492 women were randomized and overally the combination methods achieved faster median time to

delivery compared to single methods. Misoprostol-Foley 13.1 hours, Foley-oxytocin 14.5 hours, misoprostol alone 17.6 and Foley alone 17.7 hours(13).Above study was done in a university hospital and 25 micrograms misoprostol was administered every 3 hours up to 24 hours. The shorter time could be due to the synergistic effect provided by the two methods(13).

MATERNAL AND NEONATAL ADVERSE EFFECTS ASSOCIATED WITH INDUCTION OF LABOUR

Betamimetics are recommended for women with uterine hyper- stimulation during induction of labor. Uterine hyper stimulation (tachysystole) may occur with or without FHR changes and is defined as: 4 or more contractions in 10 minutes over a 30 min period or Contractions lasting more than 2 minutes in duration or Contractions of normal duration occurring within 60 seconds of each other(14). Early recognition is essential as hyper stimulation of the uterus causes poor uterine placental perfusion leading to a decrease in fetal oxygenation and eventually fetal compromise. When assessing for hyper stimulation consideration should be given to both the duration and frequency of the contractions. Contractions normally vary in duration from 30-60 seconds during the first stage of labor, to 90 seconds during the second stage of labor. The fetus needs 60-90 seconds between each contraction to restore normal fetal oxygenation. Hyper stimulation is frequently associated with oxytocin infusions, therefore judicious use of oxytocin and continuous cardiotocograph (CTG) is required whenever an oxytocin infusion is being administered(14).

Terbutaline is the main beta mimetic used. However in Kenyatta National Hospital, nifedipine is the most available as well as the commonly used tocolytic. Tocolytics like

magnesium sulfate, atosiban and nitroglycerin have a small effect (3).The decision to manage the adverse effects will be instituted after the input from the consultant managing labor ward is obtained.

Misoprostol is also associated with other side effects including nausea, vomiting,diarrhoea and dizziness. The women should be reassured if any of these side effects occur and the medication stopped if they are overwhelming.

Outpatient induction of labor is not recommended for improving birth outcomes. This because induction of labor requires facilities for monitoring maternal and fetal well-being. Secondly induction should be done in a facility, which has the capacity of doing a cesarean section (3).

Failed Induction

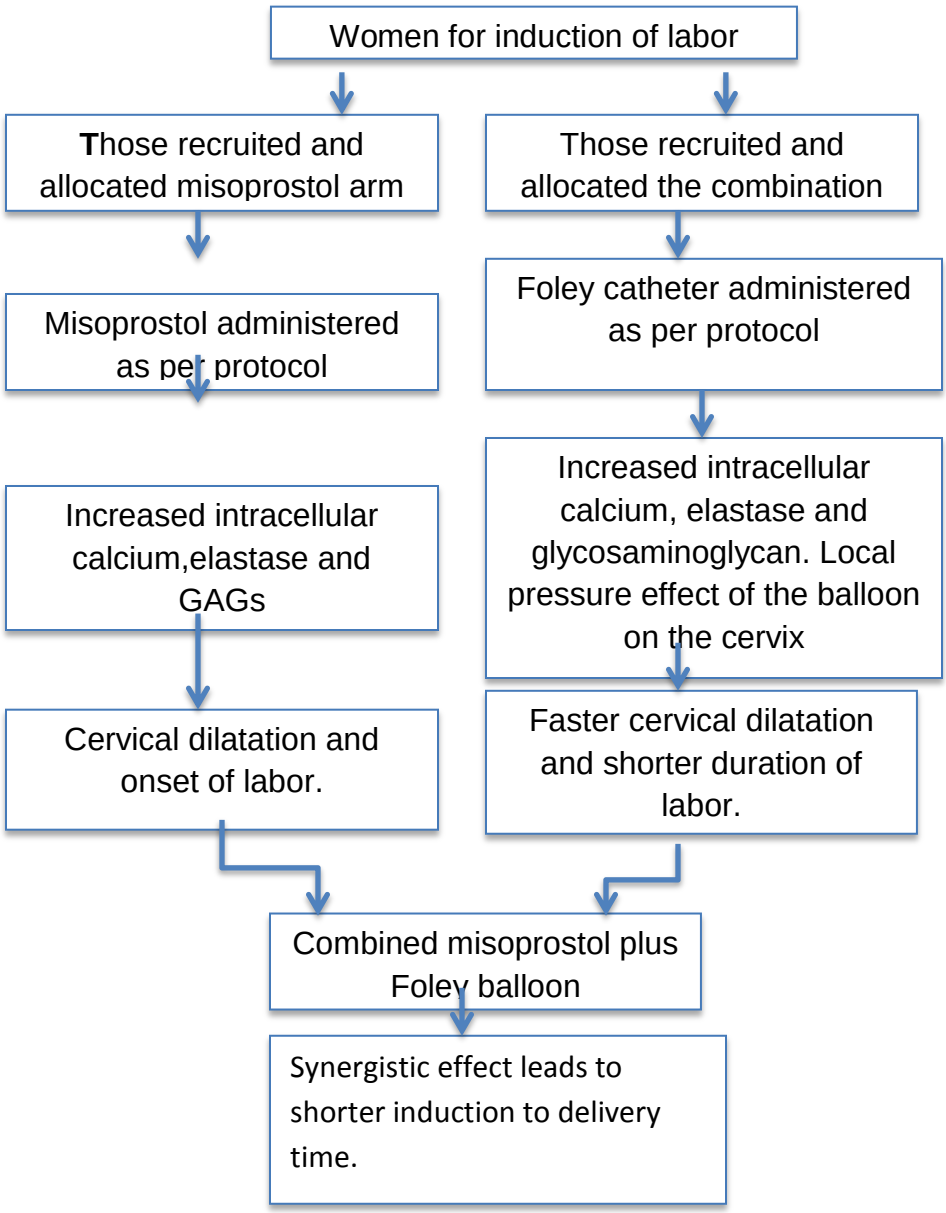
Failed induction is defined as labor not starting after one cycle of treatment or after 24 hours and cervical dilatation less than 4cm(15). If induction fails, healthcare professionals should discuss this with the woman and provide support. The woman's condition and the pregnancy in general should be fully reassessed, and fetal wellbeing should be assessed using electronic fetal monitoring. If induction fails, decisions about further management should be made in accordance with the woman's wishes, and should take into account the clinical circumstances. The subsequent management options include: a further attempt to induce labor (the timing should depend on the clinical situation and the woman's wishes) or caesarean section. Lawani et al in their retrospective study done in a low resource setting of west Africa found out 24.1% rate of failed induction(16). Locally, a cross sectional descriptive study done by Esiromo in

2011 involving two hundred and sixty two women at or more that 34 weeks gestation found out 26% rates of failed induction(17). The study also found out 77.7% success rate with misoprostol alone and 40% success with Foleys catheter alone.

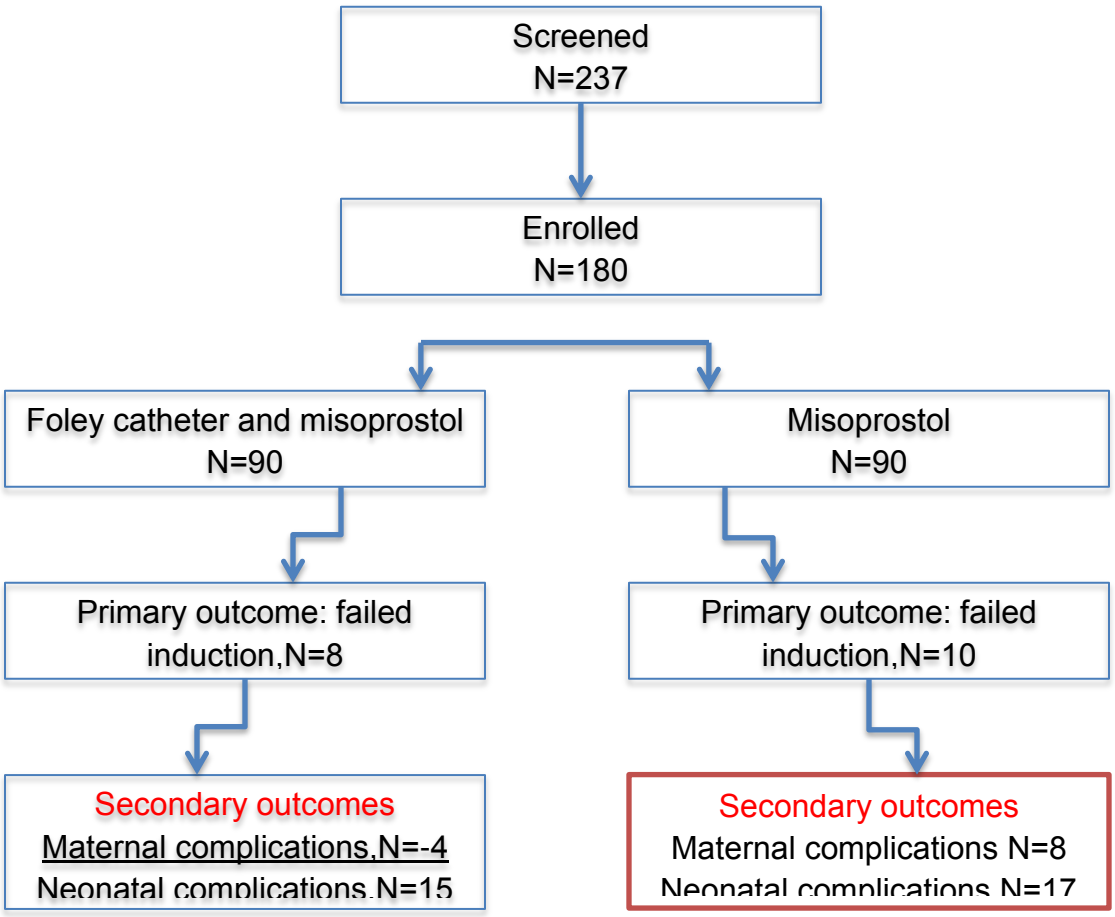
Predictors of successful induction of labor.

Successful induction of labor is more likely if there is a Bishop score more than 3, multiparity and prior vaginal delivery. Xenakis et.al clearly demonstrated in his prospective study between 1993 to 1995 among five hundred and ninety seven pregnancies that those who had a bishop score of 3 or less at onset of induction had significantly higher rates of failed induction and caesarean delivery then those with a bishop score above 3(4).

CONCEPTUAL FRAMEWORK



SCHEMA OF TRIAL



STUDY JUSTIFICATION

Failed induction or prolonged duration of induction to delivery may increase costs, patient anxiety, and if not monitored well especially in the setting of heavy workload may lead to poor neonatal outcomes.

If induction of labor using combined Foley and misoprostol can reverse or reduce these outcomes then it can change guidelines on induction of labor for all or specifically for those patients at risk of failed induction. Women who required urgent delivery may also benefit from a shorter induction to delivery time. Although used separately, a combination of misoprostol and Foley catheter have not been studied or used in our setting.

RESEARCH QUESTION

Is there a difference in the incidence of failed induction if combined Foley catheter plus misoprostol versus misoprostol alone is used for cervical ripening and induction of labor?

HYPOTHESIS

There is no difference in the incidence of failed induction when combined Foley catheter plus misoprostol versus misoprostol alone is used cervical ripening and induction of labor.

OBJECTIVES

BROAD OBJECTIVE:

To evaluate the efficacy of combined mechanical (Foley balloon catheter) and pharmacologic (misoprostol) administration in reducing the incidence of failed induction.

SPECIFIC OBJECTIVES

1. Compare the incidence of failed induction between women randomized to combined misoprostol and Foley balloon versus those randomized to misoprostol alone for cervical ripening and induction of labor.
2. Compare the differences in induction-to-delivery time between women randomized to combined misoprostol and Foley balloon catheter versus those randomized to misoprostol alone for cervical ripening and induction of labor.
3. Compare the incidence of immediate adverse maternal and perinatal outcomes between women randomized to combined misoprostol and Foley balloon versus those randomized to misoprostol alone for cervical ripening and induction of labor.

METHODS

Study design.

Two-arm open label (non blind) randomized clinical trial.

Study site and setting.

This study was carried out at the Kenyatta Hospital (KNH) antenatal and labor wards. KNH is the largest teaching and referral hospital in Kenya. It receives patients from Nairobi and its environs as well as referrals from all other hospitals in Kenya as well as international patients. It has a bed capacity of 1800 beds and is located 2km southwest of the Nairobi Central Business District. Each year, KNH conduct about 15577 deliveries of which 1800 are induced.

Study population

The study population comprised pregnant women admitted for induction of labor at KNH at gestational age of 28 weeks and beyond. Eligible consenting women also had a Bishop's score of less than 6. Every consecutive eligible participant was enrolled after simple random sampling.

Inclusion & exclusion criteria:

Inclusion:

0.All pregnant women scheduled for induction of labor were included if they had any of the following indications:; late term or post term pregnancies, hypertension, gestational diabetes, oligohydramnios, or intrauterine fetal demise.

Exclusion:

We excluded women who had clinical and ultrasound finding of fetal growth restriction, previous cesarean sections, multiple gestation, contraindication to prostaglandins, fetal anomalies, other uterine surgeries, estimated fetal weight more than 4000G, placenta previa, non-reassuring fetal status, grand multiparity (more than 5) and HIV infection.

SAMPLE SIZE AND SAMPLING PROCEDURE

Sample size calculation

In a recent Kenyan study conducted in 2011, Esiromo reported failed induction rate of 26%. In this study, only pharmacological cervical ripening and induction methods were reported, including misoprostol or dinoprostone alone, oxytocin infusion alone or a combination of artificial rupture of membranes with oxytocin infusion. The study conducted among 262 participants concluded that the pharmacological induction alone took an average of 19.1 hours and that this was abit long and posed risk to both mother and fetus. Karjane and colleagues assessed induction outcomes among 140 women using trans cervical Foley bulb with and without extra-amniotic saline infusion concluded that use of Foley bulb with extra amniotic saline infusion reduced the induction to delivery time compared to trans cervical Foley bulb alone without altering the caesarean section rates.(18)

We postulated that offering a combined use of misoprostol and Foley catheter would reduce this proportion to 16%. This 10% difference is clinically significant as it may reduce length of hospitalization, caesarean section rates and eventually the cost of care.

Therefore to detect a 10% difference in the successful induction following the use of Foley with misoprostol versus misoprostol alone, sample size was calculated using the formula used by Allan Donner(19),

Sample size formula $n = \frac{2\left(z_{1-\alpha_{/2}}\sqrt{2\bar{p}(1-\bar{p})} + z_{1-\beta}\sqrt{p_c(1-p_c)+p_a(1-p_a)}\right)^2}{(p_c - p_a)^2}$

A total of 180 women (90 per group) were needed to achieve an 80% power to detect the stated difference of 10% at a two-sided alpha=0.05 level of significance. An assumption of a 10% loss to follow-up or missing data 200 women were enrolled (100 in each arm) where we defined p_c=74% proportions of women in the misoprostol alone and p_a=84% proportions of women in combined misoprostol and Foley and

$\bar{p}$ = (p_C + p_a)/2 ($Z_{0.25}$ =1.960, and $Z_{0.8}$ =0.842

Sampling procedure

Pregnant women were admitted to the labor ward from home or from the daily antenatal clinics. The decision to do induction of labor was done by the team comprising of the consultant covering labor ward or the antenatal ward. Trained research assistants then approached the women to obtain informed consent and conduct study procedures. Block randomization of all eligible consenting subjects by computer generated random sequences and a randomization ratio of 1:1.Upon enrollment, an opaque envelope containing the participant's enrollment number and assignment to either the Foley plus vaginal misoprostol or vaginal misoprostol alone was opened. Each participant was assigned a unique subject number for identity and confidentiality. Participants and health provider were aware of the treatment allocation at the time of assignment of treatment. Clinical decisions were made during the major ward rounds, which were done twice a day in labor ward, in the morning and in the evening. During the day, the resident carried out frequent reviews and made decisions as necessary.

Intervention arm

This was the combination arm whereby Foley balloon plus misoprostol were used concurrently.

Control arm

Misoprostol alone-women received misoprostol alone plus any other intervention without insertion of Foleys catheter.

Outcomes

The primary outcome in the study was failed induction, which was defined as the failure to achieve more than 3cm cervical dilatation after 24 hours.

Secondary outcomes

These comprised: induction to delivery time, mode of delivery, immediate maternal outcomes including, postpartum hemorrhage, chorioamnionitis, hyper stimulation (5 contractions in 5mins) and uterine rupture and early perinatal outcomes (poor APGAR score, Neonatal Intensives Care Unit admission and Non Reassuring Fetal Status)

Description of interventions.

Pregnant women who were assigned to the misoprostol alone arm for induction of labour were given 25 mcg vaginally 6hourly up to a maximum of 4 doses, bishop score more than 6 or when they went into active labor(20). Later amniotomy and augmentation was done as per KNH protocol.

In the Combination arm, we inserted an 18-French Foley catheter with a 30 cc balloon placed just above the internal cervical os and then inflated with 30 cc of sterile water for injection. The Foley balloons were bought by the funding agency, Kenyatta National Hospital and stored in a locked cupboard at the doctor resting room at the labor ward. The research assistants were able to access the cupboard when they needed the materials. The tip of the length of the Foley catheter was strapped to the subject's inner right thigh under slight tension so that the balloon exerts some pressure at the cervical os. At the same time 25 mcg of misoprostol was inserted at the posterior fornix of the vagina 6 hourly up to a maximum of 4 doses, Bishop score >6 or active labor. If difficult, Foley catheter insertion was attempted every 6 hours unless Bishop scores more than 6 or in active labor. When Foley balloon fell off, labor was augmented or amniotomy performed as per the existing protocol.

Data collection, management and analysis.

Data was collected by use of questionnaires by the principal investigator and 4 trained research assistants. The research assistants were postgraduate residents in the department of Obstetrics and Gynecology. Information was obtained from history, review of medical records and clinical examination. The information was stored safely in

a password-protected computer and backed up on a dedicated USB drive. Any hard copy records carried for analysis were stored under lock and key and patients confidentiality observed. A qualified statistician did the analysis as per protocol with intent to treat analysis using SPSS version 21.The research assistants together with the principal investigator held sessions in labor ward on counseling, obtaining an informed consent and to standardize speculum examinations and insertion of Foley's catheter and vaginal misoprostol.

Demographic, clinical and laboratory characteristics were summarized and compared between study arms. Continuous variables were summarized using means (SD) and compared using the two-sample t-test if normality assumptions are met; or summarized using medians and interquartile ranges and compared using nonparametric Wilcoxon rank sum test. Categorical variables were summarized using counts and proportions and compared between study groups using Pearson's chi-square tests or Fisher's exact tests as appropriate. Primary outcome was failed (or successful induction) and secondary outcomes: time to delivery, maternal and perinatal outcomes. Proportions were compared using Chi2 test, 95% Confidence Interval, two tailed hypotheses with p significant at <0.05.

Primary outcomes

We conducted intent-to-treat analysis in which for the primary effectiveness analysis included all mother-child pairs at randomization. The final statistical analysis was conducted at the time when the last pregnant woman was delivered. The effect of combined Foley and misoprostol versus misoprostol alone in reducing the failed

induction was evaluated using a Z-statistic with Greenwood's formula to estimate the standard errors.

Secondary outcomes

We also used intent-to-treat analysis for secondary outcome included Induction-to-delivery time, mode of delivery, maternal outcomes like PPH, chorioamnionitis, hyper stimulation (5 contractions in 5mins) and uterine rupture and Perinatal outcomes (APGAR, Neonatal Intensives Care Unit admission and Non Reassuring Fetal Status, NRFS. The outcomes were compared between the two arms using Z-statistic with Greenwood's formula to estimate the standard errors.

The study results were presented to the department of obstetrics and gynecology of the school of medicine, University of Nairobi that comprises the faculty and fellow colleagues before being submitted to the Ethics committee. Presentation was in form of table and graphs.

ETHICAL CONSIDERATIONS

Ethical Review

This protocol and the template informed consent form found in Appendix II, and any subsequent modifications to this form, was reviewed and approved by the Kenyatta National Hospital/University of Nairobi Ethics Research Committee (ERC) prior to initiation of the study with respect to scientific content and compliance with applicable research and human subjects regulations. The study was registered with Pan African Clinical Trials registry (PACTR201604001535825).

The protocol, informed consent form, and any other requested documents, as well as any subsequent modifications, were also reviewed and approved by the ethical review committee.

The investigator submitted safety and progress reports to the ERC at least annually and within three months of study completion. These reports included the total number of participants enrolled in the study, the number of participants who completed the study, all changes in the research activity, and all unanticipated problems involving risks to human subjects or others. In addition, all open DSMB reports were provided to the ERC.

Informed Consent

Written informed consent was obtained from adult female pregnant participants and from the parents or legal guardians of participants who could not consent for themselves. The participants in the study were not in labor and therefore were less

stressed and adequate counseling was offered before consenting. If the partner was available they were equally informed of the study and if the pregnant woman prefers a discussion with the pregnancy partner who was within the facility she was given the opportunity to seek advice from him. The partner after that then appended a signature or thumbprint as a witness as provided for in the informed consent.

However, the mother's approval was considered as tacit approval from the father, unless otherwise specified. The informed consent form found in Appendix II, was translated into Swahili as well as independently back translated to evaluate the veracity. This form described the purpose of the study, the procedures to be followed, and the risks and benefits of participation, in accordance with all applicable regulations.

Literate participants documented their provision of informed consent by signing their informed consent forms. Non-literate participants were requested to document their informed consent by marking their informed consent forms with a thumbprint in the presence of a literate third party witness. Any other local ERC requirements for obtaining informed consent from non-literate persons was followed.

Risks

The potential risks were anticipated and addressed. Misoprostol use is associated with hyper stimulation of the uterus leading to fetal heart rate irregularities. Misoprostol is routinely used in this setting and our experienced nurses easily pick such abnormalities an institute appropriate management with the residents and consultants on duty. The consultant covering labor ward was informed of any adverse effect within 15 minutes

and tocolysis with nifedipine was instituted as soon as the adverse effect is picked up. If the tocolysis is not achieved, the patient was taken to theatre for an emergency caesarean section. A previous similar by Carbone et al study did not find clinically significantly different rates of hyper stimulation and fetal heart rate abnormalities.

Insertion of Foley Catheter may be uncomfortable as it involves speculum examination. However, this is the standard way to use Foley catheter for mechanical induction. We ensured adequate preparation of women and lubrication to minimize discomfort and prevent any unintended trauma. Residents who are well trained normally conduct this procedure.

Participation in the study will require participants to commit their time for additional questioning. Consenting process and completing questions at exit may take 20-30 minutes.

Although study assistants made every effort to protect participant privacy and confidentiality, it is possible that others knew participants' involvement in the study. However, there was no stigma related to this and we made every effort to prevent such events and alleviate any potential harm caused if they did occur.

Benefits

We believe that combination of Foley and misoprostol conveyed direct benefit to participants, mothers and infants, and their partners. Those who had successful induction and who would have experienced failed induction had reduced hospitalization, cost of hospitalization. Other than potential direct benefits to participants from this study, others may benefit in the future from information learned from this study.

Specifically, information obtained from this study may lead to the implementation of combined methods improving outcomes of induced labor.

Confidentiality

All study-related information was stored securely at the study site. All participant information was stored in locked file cabinets in areas with access limited to study staff. A coded number identifies all reports, collected data, and administrative forms in order to maintain participant confidentiality. All local databases were secured with password-protected access systems.

Participant's study information will not be released without the written permission of the participant, except as necessary for monitoring by the DMSB, or Kenyatta National Hospital Ethical Review Committee (ERC).

Study Discontinuation

The study made every reasonable effort to retain any enrolled study participant until completion of study period. The goal is to achieve greater than 95% participant retention. The Principal Investigator (PI) may withdraw participants from the study in order to protect their safety and/or if they are unwilling or unable to comply with required study procedures.

Additionally, participants may withdraw from the study for any reason at any time. However, every reasonable effort was made to complete a final evaluation of participants who terminate from the study prior to delivery, and study staff recorded the reason(s) for all withdrawals from the study in participants' study records.

The study also may be discontinued at any time by the ERC.

Data Safety and Monitoring Board (DSMB)

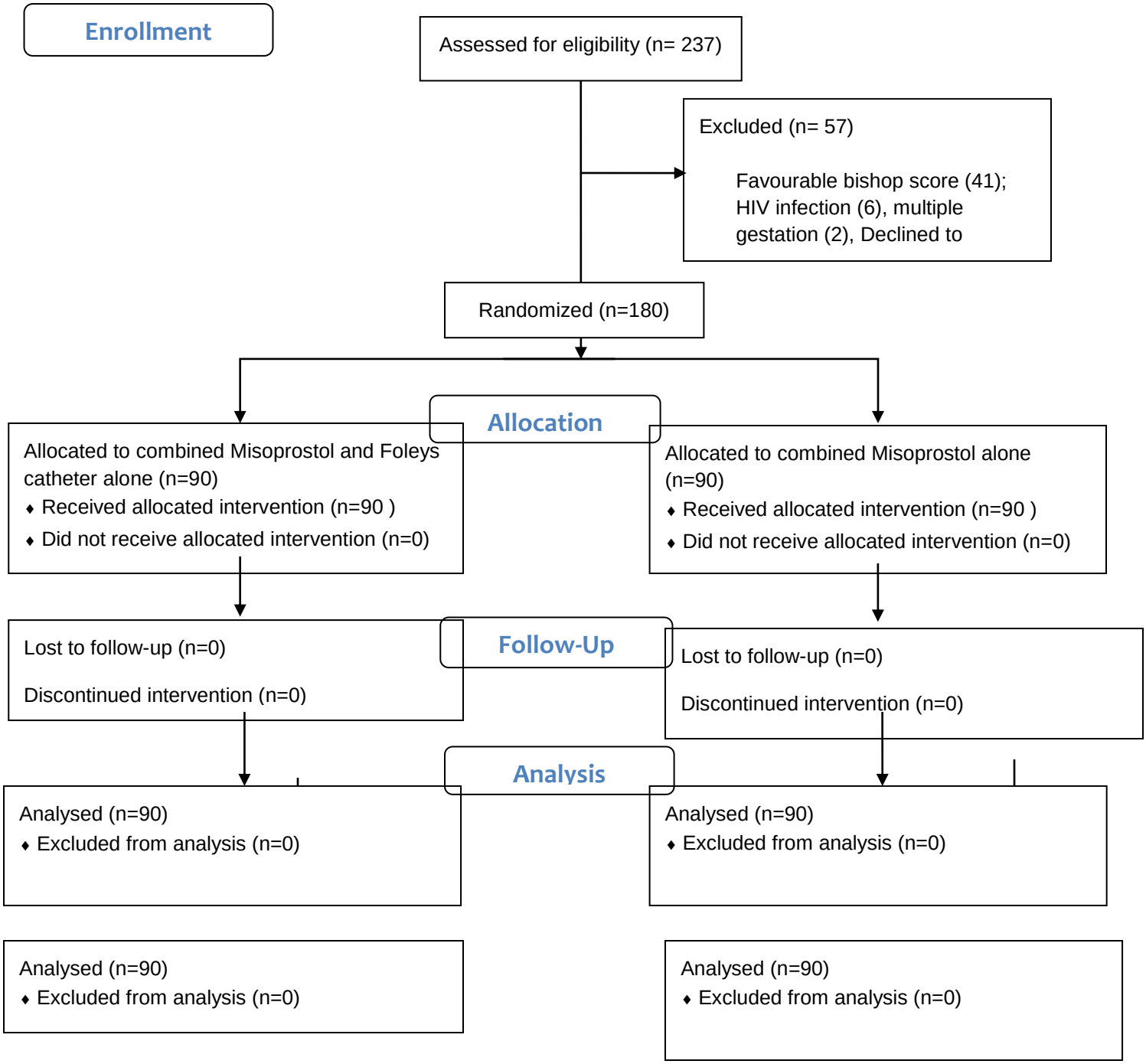
This study was subject to monitoring by an independent Data Safety and Monitoring Board (DSMB), which met once every month, checking initially for balance in randomization and later monitoring patient safety and signals of efficacy, futility or harm at each interim analysis. Formal interim analyses for efficacy and/or effectiveness was conducted when 25%, 50% and 75% of participants had completed follow-up.

The DSMB also provided a recommendation to terminate or alter the design or conduct of the trial if unacceptable safety results emerged. If significant safety concerns emerge, the DSMB had full access to relevant efficacy and safety data to assess the relative benefit-to-risk profiles of the study regimens when developing their recommendations.

CHAPTER FOUR: RESULTS

Between February and May 2016, 237 pregnant women scheduled for induction of labor at Kenyatta National Hospital (KNH) were approached and screened for eligibility. A total of 57 (23.2%) were excluded because of: favorable bishop score 41 (17.3%), refusal 8 (3.4%), maternal HIV infection 6 (2.5%) and multiple gestations 2 (0.8%). After enrolment into the study, 180 women were randomized to cervical ripening with misoprostol alone (n = 90) or combined Foley and misoprostol (n = 90). There were no protocol deviations and all recruited patients were included in the analysis using Intention To Treat (Figure 1).

Figure 1: Flow Diagram



There were no statistically significant differences in the socio-demographic characteristics of women according to intervention group. The mean age of women in the combined misoprostol and Foleys group was 27.8 ± 5.9 compared to the misoprostol alone group 26.9 ± 4.7 years. Most pregnant women belonged to the age group 25-29 years, 37.8% in the combined misoprostol and Foley group versus 41.1% misoprostol group. Majority of women were married 70 (77.8%) in the combined versus 72 (80%) in the misoprostol arm. More than three-quarters of mothers had either secondary or higher education level 74.5% in the combined versus 83.3 % in misoprostol alone (Table 1). More than half of the mothers reported that they were currently engaged in employment and 56 [62.2%] in combined misoprostol and Foleys arm compared to 52[57.8%] in misoprostol arm).

Table 1: Characteristics of mothers enrolled in misoprostol trial according to intervention group

	Combination (Misoprostol + Foleys)	Misoprostol alone		
	n (%)	n (%)	RR (95% CI)	P
Maternal age				
Mean age (SD)	27.8(SD 5.9)	26.9(SD 4.7)	NA	NA
17-19 years	3(3.3)	3(3.3)	1.0	
20-24 years	22(24.4)	27(30.0)	0.90(0.38-2.12)	0.806
25-29 years	34(37.8)	37(41.1)	0.96(0.41-2.22)	0.92
30-34 years	17(18.9)	14(15.6)	1.10(0.46-2.60)	0.834
35 years and above	14(15.6)	9(10.0)	1.22(0.51-2.90)	0.657
Marital status				
Single	16(17.8)	17(18.9)	1.0	
Married	70(77.8)	72(80.0)	1.02(0.69-1.50)	0.934
Separated/ divorced	4(4.4)	1(1.1)	1.65(0.94-2.90)	0.082
Education level				
Primary	23(25.6)	15(16.7)	1.0	
Secondary	34(37.8)	33(36.7)	0.84(0.59-1.19)	0.323
Post-secondary	33(36.7)	42(46.7)	0.73(0.51-1.05)	0.085
Employment status in past 12 months				
Currently employed	52(57.8)	56(62.2)	1.0	
Not currently employed but worked in past 12 months	6(6.7)	7(7.8)	0.96(0.52-1.78)	0.892
Did not work in past 12 months	32(35.6)	27(30)	1.13(0.83-1.53)	0.452

The obstetric histories of mothers randomized to intervention and control treatment were similar (Table 2). Majority of the women were primigravida, 61.1% in combined misoprostol group (p = 0.292) and about half (53.3%) in the misoprostol group. Most mothers were at term (37 week of gestation and above) and this did not vary by arm (73.2% vs. 74.4%, p = 0.939). In both arms, the most common indication for labor induction in was post term pregnancy accounting for 54 (60%) in the combined misoprostol and Foleys group and 51(56.7%) in the misoprostol group.

Table 2: Obstetric history of mothers enrolled in misoprostol trial according to intervention group

	Combination (Misoprostol + Foleys)	Misoprostol alone	
	n (%)	n (%)	P
Parity			
Multigravida	55(61.1)	48(53.3)	0.292
Primigravida	35(38.9)	42(46.7)	
Gestation (weeks)			
>28	9(10)	6(6.7)	0.939
29-32	8(8.9)	8(8.9)	
33-36	7(7.8)	9(10)	
37+ to 38	3(3.3)	2(2.2)	
38+ to 40	7(7.8)	11(12.2)	
40+ to 41	40(44.4)	45(50)	
≥42	16(17.7)	9(10)	
Indication for induction			
Postdate	54(60)	51(56.7)	0.650
Hypertension	12(13.3)	17(18.9)	0.311
Rhesus incompatibility	3(3.3)	5(5.6)	0.469
History of PROM	9(10)	6(6.7)	0.418
IUFD	12(13.3)	11(12.2)	0.823
Mean bishops score (± SD)	2.1 ± 1.5	2.8 ± 1.1	0.143

Primary outcome: Failed induction rates

Table 3 shows that mothers in the combined misoprostol and Foleys group were less likely to receive a second (66.7% versus 88.9%, p = 0.001) and third (26.7% versus 46.7, p = 0.006) dose of misoprostol compared to those in the misoprostol alone group (OR 0.25; 95% CI 0.11-0.55 and 0.42; 0.22-0.78, respectively). There was no significant

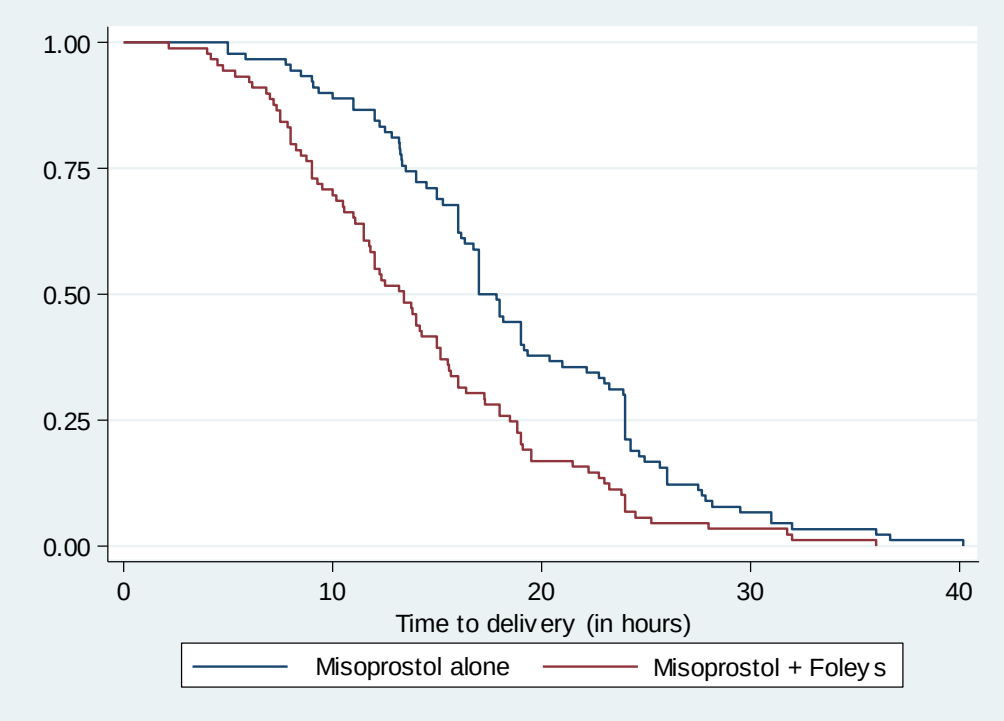
difference in the rates of failed induction in either arm, combined method at 8.9 % and misoprostol alone at 11.1 %.

There was no significant difference in the caesarean section rate in the combined group 18 (20%) compared to the misoprostol alone group 14 (15.6%) OR = 1.36; 95% CI 0.59-3.18; p = 0.437 (Table 3).

Table 3: Number of failed induction plus the doses in women randomized to misoprostol or misoprostol + Foleys

	Combination (Misoprostol + Foleys)	Misoprostol alone		
	n (%)	n (%)	OR(95% CI)	P
Failed induction				
Yes	8(8.9)	10(11.1)	1.28(0.43-3.94)	0.619
No	82(91.1)	80(89.9)	NA	NA
Number of misoprostol doses administered				
One	90(100)	90(100)	NA	NA
Two	60(66.7)	80(88.9)	0.25(0.11-0.55)	0.001
Three	24(26.7)	42(46.7)	0.42(0.22-0.78)	0.006
Four	8(8.9)	16(17.8)	0.45(0.18-1.12)	0.085
Mode of delivery				
SVD	72(80.0)	76(84.4)	1.0 (ref)	
C/section	18(20.0)	14(15.6)	1.36(0.59-3.18)	0.437

Figure 2: Kaplan–Meier time curve for induction to delivery comparing women in the misoprostol + Foley versus misoprostol alone



As presented in Figure 2 mothers in the combined group had a relatively shorter duration of time between induction of labor and delivery compared to those in the control group (Log rank chi = 15.82; p = 0.001**).** Half (50%) of mothers in the combined group delivered within 14.1 hours of induction compared to 18.9 hours for the mothers in the misoprostol alone arm.

There was statistically significant difference in the mean duration of time between induction of labor and delivery. The mean duration of time from induction to delivery was significantly shorter in the combination of Foley balloon and misoprostol (14.1 hours)

compared to the misoprostol alone (18.9 hours), mean difference CI and p value p < 0.001 (Table 4).

Table 4: Labor duration among women in misoprostol alone and misoprostol + Foley groups

	Combination (Misoprostol + Foleys)	Misoprostol alone	Difference (95% CI)	P
n	90	90		
Mean time to delivery	14.1 hrs. SD(6.9)	18.9 hrs. SD(7.2)	4.8(2.7-6.8)	< 0.001
Delivery within 24 hours among SVD (n=148)	69(90.8%)	57(79.2%)	OR 0.4(0.1-1.1)	0.064
Delivery within 24 hours among CS (n=32)	12(85.7%)	6(33.3%)	OR 0.1(0.01-0.06)	0.003

Secondary outcomes: maternal and perinatal outcomes

Maternal outcomes

Table 5 shows that there were no significant differences in maternal complications in the combined misoprostol and misoprostol alone groups. Complications occurred in 8 (8.9%) women in misoprostol group and 4 (4.4%) women in the combined misoprostol and Foleys group.

Table 5: Maternal delivery outcomes and complications according to treatment arm

	Combination (Misoprostol + Foleys)	Misoprostol alone	OR	P
Maternal complications	**n (%)**	**n (%)**		
Yes	4(4.4)	8(8.9)	1.0 (ref)	
No	86(95.6)	82(91.1)	0.48(0.14-1.64)	0.241
Type of complications				
PPH	3(3.3)	4(4.4)	1.35(0.29-6.21)	0.701
Uterine hyper stimulation	1(1.1)	3(3.3)	2.02(0.18-22.71)	0.568
Uterine rupture	0(0.0)	1(1.1)	NA	NA
APH	0(0)	0(0)	NA	NA

Perinatal outcomes

As shown in Table 6, 17 (18.9%) babies delivered by women in the misoprostol alone group were admitted to neonatal intensive care compared to 15 (16.7%) of babies in the combined misoprostol and Foley group who were also admitted to neonatal ICU (p = 0.697). The complications that led to NICU admissions in the two groups included: birth asphyxia (6.7 versus 7.8 in the misoprostol alone and combined arms, respectively), prematurity (12.2 versus 8.9%), and fetal anomalies (1.1% versus none).

Table 6: Neonatal complications among babies born to mothers in misoprostol trial

		Intervention			
	Combination (Misoprostol + Foleys)	Misoprostol alone		OR (95% CI)	P
NICU admission					
No	75(83.3)	73(81.1)		1.0 (ref)	
Yes	15(16.7)	17(18.9)		0.86(0.37-1.98)	0.697
Types of complications					
Birth asphyxia	7(7.8)	6(6.7)		1.18(0.32-4.44)	0.773
Prematurity	8(8.9)	11(12.2)		1.43(0.55-3.73)	0.468
Fetal anomaly	0(0)	1(1.1)		NA	`NA

DISCUSSION

The study found out that there was no significant difference in the rates of failed induction between the two groups. There are however no comparable studies in Kenya. These were similar with the findings from a study done in Kwale Nigeria, which showed no difference in the rate of failed induction, (22.3%) for misoprostol and 21.7% for combined Foley and oxytocin, among 32 584 women at between 28 to 42 weeks gestation(21).

We found significant reduction of induction to delivery time. In this study, induction of labor with combination of Foley balloon plus misoprostol shortened the overall induction time by 4.8 hours in comparison to misoprostol alone. A randomized controlled trial by Carbone et al found out a 3.1-hour reduction in time from induction to delivery for combined method compared to misoprostol alone (10). Similarly, Charaya et al reported that combined methods reduced induction to delivery interval by 2.78 hours compared to misoprostol alone (22).

There was no significant difference in the rates of cesarean sections, maternal and neonatal outcomes and or complications in our study. This finding is in keeping by an RCT conducted by Matonhodze BB et al which established that although the rates of cesarean section was more common in the combined group (45.4%) compared to 39.8% of misoprostol alone, this difference was not statistically significant. Similarly, Charaya et al and Matonhodze BB et al found no significant difference in maternal and neonatal outcomes as well as complications between the combined and Foley alone arms(23). Its important to note that the study by Matonhodze and colleagues was done in a South African university hospital, which is a similar setting as our study(23).

In a recent trial at the university of Pennsylvania, Levine and colleagues ('FOR MOMI' trial) randomized 492 women at 37 weeks and above and reported that the combination methods achieved faster median time to delivery compared to single methods. The time to delivery intervals were: misoprostol-Foley 13.1 hours, Foley-oxytocin 14.5 hours, misoprostol alone 17.6 and Foley alone 17.7 hours(13). The finding of shorter induction to delivery time could be due to the synergistic effect provided by the two methods(13).

Our study had several strengths. We had a very high retention in our study and this ensured a high adherence to the study protocol. The RCT design also protected against selection bias, known and unknown confounders. There was a minimal risk of information and classification bias because data was obtained from medical records and a team comprising both consultants and obstetrics and gynecology residents who delivered the care.There was good documentation of the primary outcome both in the medical records and with independent verification from the study team.

Our study had limitations in the study size since it allowed for detection of relatively large effect size for failed induction; larger studies would help in determining whether small effect sizes would provide information on any potential role of combined methods in failed induction. The large interval period between 28 weeks to term could be a biasing factor and therefore we propose future studies with shorter intervals of gestation at induction. We therefore propose larger future studies, which may address the limitations above. We also recommend health care policy makers and staff to adopt the combined methods of induction of labor since it takes a shorted time between induction to delivery and this in turn reduces hospital anxiety and even the total cost of health care.

In conclusion, this RCT suggests that the synergistic effects of combination methods may safely reduce the induction to delivery time interval in this setting and has no significant effect on induction failure. These findings may have significant impact on the management of labor and should be offered to women with poor bishop scores requiring shorter time from induction to delivery interval.

Study Budget

The expenses during this study included the following: -

Item	Role	Number	Unit cost	Total (ksh)
Research Assistants	Collect data	200 patients	500/patient	100000
Foleys catheter	Mechanical induction	90	100	9 000
Misoprostol (25mcg)	Pharmacological induction	200	200	40000
Statistician fee ERC fees	Analysis ERC	30000 2000	30000 2000	30000 2000
Printing of the proposal, questionnaires and other paper work	5000	5000	50000	5000
Grand total				Ksh186, 000

Patient information and Consent form

This document is to be read by or read to every participant in a language she understands best before the onset of the intervention.

Principal investigator-Dr. Davies Kibii

Iam a resident doctor specializing in Obstetrics and Gynecology at the university of Nairobi. Am conducting a study on induction of labor using 2 different methods so as to compare their success and other factors. It will involve a total of 180 participants. The information will help you know about the research so that you make a decision to participate or not. You have the right to ask any questions at any point. Once you have read through and all questions clarified, you will be humbly requested to sign (or thumb print) the consent form as evidence that you voluntarily agreed to participate.

Participant right

Participation is voluntary, you may chose to participate or not. You may ask any question any time. It is also your right to drop from the study any time you wish without any penalty whatsoever. If you decline to participate, the normal standard of care will be provided.

Purpose of study

Information obtained from the study will help us improve the management of women undergoing induction of labor at our facilities.

Procedure

If you agree to participate there will be 2 arms, one arm involve use of a vaginal tablet alone every 6 hours while the other arm involve use of the same tablet plus a Foley catheter inserted once onto your cervix with some 30 ml of fluid in it. The midwife and the doctor who performed the procedure will do monitoring of the mother and the baby and you will be informed of the progress accordingly. Incase of any complications, you will be informed about it together with the alternatives to delivery, which may or may not include being performed a cesarean section.

Benefits and compensation

Mothers who participate will be given a stipend of 200 KSH on completion of the study. The information will help us improve on the management of other women who may need induction of labor.

Confidentiality

All information collected from the study will be strictly confidential. Your name will not appear on any document and the principal investigator with research assistants will have access to the information provided.

Who to contact

If you have any questions later, please reach me on my number 0721578173 at any time of the day or night. If am unreachable please contact the midwife or the doctor attending to you.

Consent form

I have read the information (or it has been read and explained to me) concerning the research study and I fully understand all about it and I voluntarily agree to take part in the study.

Patient signature (or thumb print)..... Date.....

Witness signature ..... Date.....

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