COMPARISON BETWEEN VAGINAL MISOPROSTOL AND INTRAVENOUS OXYTOCIN IN INDUCTION OF LABOR AT MUHIMBILI NATIONAL HOSPITAL, DAR ES SALAAM, TANZANIA.

By

MUNAWAR MAULID KAGUTA, MD.

A dissertation submitted in (partial) fulfillment of the requirement for the degree of Master of Medicine (Obstetrics and Gynaecology) of the University of Dar es salaam.

University of Dar e salaam.

2005

CERTIFICATION

The undersigned certify that he has read and hereby recommend for acceptance by the University of Dar es salaam a dissertation entitled: *Comparison between Vaginal Misoprostol and Intravenous Oxytocin in Induction of Labor at MNH, Dar es salaam, Tanzania,* in partial fulfilment of the requirements for the degree of Master of Medicine (Obstetrics and Gynaecology).

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Dr. Hamudu, N.A.S.

(Supervisor)

Date.....

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I, Munawar Maulid Kaguta, hereby declare that this dissertation is my own original work and that is a product of my own efforts and it has not been presented and will not be presented in any other University for similar or any other degree award.

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DEDICATION

To my mother, who taught me how to read and write, my wife Hafsa and my son Nabil.

LIST OF ABBREVIATIONS

AGOTA: Association of Gynaecologists and Obstetricians of Tanzania.

CPD: Cephalopelvic disproportion.

HIV: Human immunodeficiency virus

IUFD: Intrauterine fetal death

MNH: Muhimbili national hospital

MUCHS: Muhimbili University College of Health Sciences.

NIMR: National Institute of Medical Research

NICU: Neonatal intensive care unit

.

DEFINITION OF TERMS

Onset of labor: Starting of painful and regular palpable contractions.

Induction-to-delivery interval: The time from the beginning of induction to the time of delivery.

Bishops score: The measure of cervical ripeness, on which the consistency, position, length, and dilatation of the cervix is measured.

Hyperstimulation: Presence of more than four contractions in ten minutes, with or without an abnormal fetal heart rate pattern.

SVD: Spontaneous vertex delivery

Caesarean section: Surgical removal of the fetus from uterus by abdominal route.

Fetal distress: A fetal heart rate above 160 or below 120 beats per minutes, or with late deceleration.

PIH: pregnant induced hypertension.

Failed induction: Failure of starting or progression of uterine contractions.

Established labour: starting of regular painful contractions, increasing in intensity and frequency, and cervical dilatation.

Partograph: Is a graphic representation of cervical dilatation and descent of the presenting part against time.

Apgar score:A numerical scoring system usually applied at 1 and 5 minutes after birth to evaluate the condition of the baby, based on the heart rate, respiration, muscle tone, reflexes and colour.

PROM: Premature rupture of membrane before the onset of contractions

Prematurity: gestational age less than 37 weeks.

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ABSTRACT

Objective: To compare the safety, efficacy and cost effectiveness of vaginal misoprostol and intravenous oxytocin in induction of labor.

Design: Randomized trial.

Setting: Labor ward at Muhimbili National Hospital (MNH), Dar es Salaam Tanzania.

Methods: One hundred and forty two non-grandmultiparous (≤ gravida 4) women with indication for labor induction were randomly selected for vaginal misoprostol and intravenous oxytocin methods of induction of labor. Misoprostol was administered to 71 women at a dose of 25μg four hourly, not exceeding 4 doses, whereas oxytocin infusion was titrated based on patient response.

Main outcome measures: The main parameters measured were: induction –to-delivery interval, time from induction to onset of contraction, maternal and fetal outcomes, safety and the cost of induction between the two drugs.

Results: The median induction –delivery interval was significantly shorter in the misoprostol group as compared to the oxytocin group (10.86 versus 15.45 hours, $p<0.001$). The time from induction to beginning of contraction was also significantly shorter in the misoprostol group than in the oxytocin group (2.59 versus 3.57 hours $p<0.0015$). There was no difference in fetal and maternal morbidity between the groups. There was no single case of uterine rupture. Majority of women in the misoprostol group (70%), required less than 0.2 USD for successful induction, whereas in the oxytocin group 77% spent >2.10 USD for induction. Misoprostol was significantly cheaper ($p<0.05$).

Conclusion: Misoprostol at a dose of 25μg is safe, effective and cheaper than oxytocin for induction of labor.

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1. INTRODUCTION.

1.1: Background information

Labor is the process of uterine contraction leading to progressive effacement, dilatation of the cervix and birth of the baby. The cause of the initiation of the process of human labor remains unclear. Potential factors include changes in hormonal levels of estrogen and progesterone, increased production of prostaglandins and elevation of level of corticotrophin releasing hormone (CRH), as well as increased sensitivity of the myometrium to the endogenous oxytocin. It is most likely that interaction between these factors play an essential role in the process of labor.

It was found in one study that high level of maternal plasma CRH are associated with an increase in the uterine contractile response to infused oxytocin[1].

Some studies suggested that estrogen and relaxin are particularly involved with cervical ripening, while prostaglandin and oxytocin are more involved in regulating symmetrical uterine contractility[2].

Progesterone dominance during pregnancy is associated with a firm closed cervix, few myometrial gap junctions, low calcium levels in the cells, and a quiescent myometriumAt term, a change in the oestrogen/progesterone balance favors cervical ripening and increasing uterine activity.

Of particular importance at the level of the muscle cells are changes in the number of oxytocin receptors; a complex interaction between cAMP and phosphoinositide

metabolism governs the intercellular level of calcium, thus regulating contractile activity.

Induction of labor is an intervention whereby a delivery is preferred at a particular time rather than waiting for spontaneous labor. It is designed to artificially initiate uterine contractions leading to progressive effacement and dilatation of the cervix and birth of the baby. This includes intact membrane cases and also those with spontaneous rupture of the membrane before spontaneous labor.

The introduction of amniotomy, by Thomas Denman of the Middlesex hospital in 1756 was a major improvement for inducing labor. This method has remained a cornerstone of labor induction to the present day[3].

A further important advance in the induction of labor followed the isolation of oxytocin by Sir Henry Dales. William Blair Bell[4] reported the first study that led to the use of oxytocin for the induction of labor.

In late 1960's a number of developments in the way oxytocin was administered and the advent of pure synthetic oxytocics enabled oxytocin to be used more effectively to induce labor.

The observation of Raphael Kurzrok and Charles Lieb in 1930 established the existence of prostaglandins[5]. Von Euler first coined the term "prostaglandin" in 1936 after he had isolated it from the accessory glands of the male genital tract.

It was not until the late 1960s that prostaglandins were first used clinically for the induction of labor, when the effect of prostaglandin F2α on the pregnant human uterus in vivo was described[6] . Then in 1970, prostaglandins E1 and E2 were administered to induce labor[7].

1.2: LITERATURE REVIEWS

Induction of labor is one of the most common procedures performed in obstetrics. In western countries the induction rate may be as high as 44 %[8].Its goal is to achieve vaginal delivery by stimulating uterine contraction before spontaneous onset of labor. Generally it has merit as a therapeutic option when benefits of expeditious delivery outweigh the risk of continuing the pregnancy.

The success of an induction depends largely on the state of cervix when labor is initiated[9]. Therefore cervical ripening or preparedness for induction should be assessed before a regimen is selected.

Induction of labor is indicated when it is agreed that the fetus or mother will benefit from a higher probability of a healthy outcome than if birth is delayed. An exception to this is induction of labor at maternal request for social reasons at term.

The most common indications for induction of labor include: postterm pregnancy, pre-eclampsia, diabetic pregnancy, prelabor rupture of membrane if more than 24-48 hours without starting labour, placental separation and intrauterine fetal death.

The methods of induction in common use today are amniotomy, oxytocin and prostaglandins (PGE2). Other methods include: balloon catheter, and stripping of the membranes.

It is hypothesized that amniotomy increases the production (or causes a release) of prostaglandins locally. Risks associated with this procedure include umbilical cord prolapse or compression, maternal or neonatal infection, fetal heart deceleration, bleeding from a low lying placenta and possible fetal injury[10]. Amniotomy also increases the chances of intrapartum maternal to child transmission of HIV and other vaginal microorganisms.

Oxytocin is an octapeptide, secreted normally by the posterior pituitary. The physiology of oxytocin-stimulated labor is generally similar to that of spontaneous labor, although individual women vary in sensitivity and response to oxytocin. Based on the pharmacokinetic studies of synthetic oxytocin, uterine response starts after 3-5 minutes of infusion, and a steady state of oxytocin is achieved on plasma by 40 minutes.

The uterine response to oxytocin depends on the gestational age and is enhanced by amniotomy. As pregnancy progresses, the number of oxytocin receptors in the uterus increases by 100-fold at 32 weeks and by 300-fold at the onset of labor. The myometrium is more sensitive to the effect of oxytocin after a previous labor.

Guidelines of labor ward protocol are essential to avoid injudicious use of oxytocin that may lead to fetal distress or uterine rupture in the presence of obstructed labor, especially with a grandmultiparous pregnancy or previous scars.

Oxytocin activates the phospholipase C-inositol pathways and increases the intracellular calcium levels, stimulating contractions in the myometrial smooth muscles[9]. It is the preferred pharmacologic agent for inducing labor when the cervix is favorable or ripe.

A study done at Mulago hospital, in Uganda found that the 100% of patient with intrauterine fetal death given Misoprostol delivered within 48 hours compared to 96.7% who were induced with oxytocin[11]. In another study where misoprostol was used to induce labor in grand multiparous women with live baby and intrauterine fetal death on which 50mcg and 100mcg were inserted respectively, result showed shorter application –to-expulsion interval than women with fetal death, (10.1 versus15.4 hours) [12]

De aquino[13] in their study done in Sao Paulo, comparing oxytocin and Misoprostol for labor induction found that the cesarean section rate, latent period, and period

from induction to vaginal delivery were significantly higher for oxytocin group than Misoprostol.

Kramer RL, et al[14] found that, women with Bishops score of 3 or less who received Misoprostol had shorter median induction-to-delivery interval in comparison to women who received oxytocin. The misoprostol group was also more likely to deliver vaginally within 24 hours of the start of induction.

Prostaglandins are 20-carbon carboxylic acid derived from essential fatty acid containing 3, 4 and 5 double bonds, mostly arachidonic acid. These substances can stimulate contraction of uterus at any gestational age.

Prostaglandins directly affect the collagenase enzyme of the cervix to break down the collagen networks with an increase in hydrophilic glycosaminoglycan and hyaluronic acid and a decrease in dermatan sulfate thus resulting in softening of the cervix. Prostaglandins also allow for an increase in intracellular calcium levels, causing increased contractility of myometrial muscles[9].

Several studies have been performed, especially in developed countries; using prostaglandin E2 (dinoprostone) gel for cervical ripening and labor induction, particularly in cases where the Bishops index was lower than seven. Its effectiveness was markedly shown. However, the use of this drug is limited because of its high cost and thermal instability. The latter leads to difficult storage, plus the occasional need to use oxytocin after cervical ripening [15,16]

Misoprostol (Cytotec) is a synthetic prostaglandin E1 analogue that is registered for the treatment of gastric ulcer for patient taking non-steroidal anti-inflammatory drugs. It has been found to be a useful agent for induction of labor. It is selective for PGE1 receptors, and has no clinically significant effect on bronchi or blood vessels, in contrast to Dinoprostone, which has its marked side effects. However, a meta-analysis performed in 1998 emphasized the need for complementary studies in order to achieve safer results in relation to hyperstimulation syndrome and perinatal results[17].

Misoprostol has been shown to be useful for the following indications:

1. Induction of labor at any gestational age e.g. missed abortion,incomplete abortion, intrauterine fetal death, and severe preeclampsia.
2. Postpartum hemorrhage.

Sanchez, et al[18] performed trials investigating the use of Misoprostol vaginally for induction of labor compared with Dinoprostone or a combination of Dinoprostone and oxytocin. These trial have used various dosage intervals and maximum dosage ranging from single 25μg to 100μg dose up to a maximum dose of 600μg.[14]

A recent study on the pharmacokinetics of this drug showed that its serum levels, after vaginal administration, remain stable for at least 4 hours, suggesting that the ideal time interval between doses should be equal or more than 4 hours[20].

Misoprostol, is inexpensive, easily stored at room temperature, effective in inducing uterine contraction, and has few systemic side effects. It is more quickly absorbed orally than vaginally, but vaginally absorbed serum levels are more prolonged. Is not only a safe and effective agent for cervical ripening and labor induction but it is also more efficient than Dinoprostone[21]. Study done in the USA by Sanchez-Ramos[22] where Misoprostol was found to be more effective in inducing gravidas with PROM than oxytocin, results showed shorter induction- to-delivery time in Misoprostol group.

Bugalho A et al[22] studied the effectiveness of low dose vaginal Misoprostol for labor induction in 666 pregnant women with a fetus in cephalic presentation, 50μg of misoprostol was given every 12 hours for a maximum of 4 doses resulting in successful induction in all cases.

Despite being inserted in the posterior fornix, Misoprostol is more effective than intracervical PGE_2; it was found that the time from the start of induction to vaginal delivery was significantly shorter in PGE1 group[23].

On the other hand, some trials reported uterine contraction abnormalities (tachysystole, hypertonus and hyperstimulation), increased frequencies of meconium passage, neonatal acidemia and cesearean delivery for fetal distress in association with repeated higher doses of vaginal or oral misoprostol. However, low- dose vaginal misoprostol appears to have a more favorable profile, Hofmeyr GJ[24,] Wing

DA[25]. N. Van Gemund et al[26] showed that significantly fewer neonates were admitted to NICU in the misoprostol group compared with dinoprostone group. Uterine rupture is considered a rare complication of labor induction with misoprostol. Nausea and diarrhea are reported side effects.

Balloon catheter provides mechanical pressure directly on the cervix as the balloon is filled. A Foley catheter (26Fr) or specifically designed balloon device can be used.

Stripping of the membrane causes an increase in the activity of phospholipase A2 and PGF2α as well as mechanical dilation of the cervix which release prostaglandin. The risk of this technique include infection, bleeding, accidental rupture of membrane and patient discomfort[10]

1.3: STATEMENT OF THE PROBLEM

Oxytocin is the only approved pharmaceutical agent used for induction of labor in Tanzania. This agent is given as an intravenous infusion during induction. In this process, one must also have intravenous fluid particularly dextrose 5%, cannula, and a giving set. A 5 IU ampoule of oxytocin costs 250 Tshs, a 500ml of dextrose5% costs 500 TShs, a cannula costs 500 TShs, and one giving set is 300 TShs according to the Medical Store Department price list. For better achievement, proper titration is important. These needs enough midwives per pregnant woman On the other hand increasing the number of midwives would raise the cost of manpower.

It is difficult to monitor oxytocin titration in a busy labor ward like Muhimbili National Hospital. A woman on induction can stay for sometime before starting the

next dose of oxytocin. In ideal situation oxytocin needs availability of 1:1 nursing care. On top of that lack of infusion pump makes things more difficult in our environment. Oxytocin needs rupturing of membrane before starting induction. In this era of HIV, this increases the chances of transmission from the mother to the fetus.There is a need for an effective, safe and cost effective inducing agent that does not need intravenous infusion, cannula or giving set, and one, which will decrease working load,and leaving the membrane intact for as long as possible to reduce the chances of intrapartum HIV transmission. This agent may be Misoprostol. The agent is available in a 28 tablets packet of 200mcg or 100mcg costing 16,000 and 9,000 Tshs respectively. The drug however is not registered for this purpose.

1.4: RATIONALE OF THE STUDY

There has been no local study done to prove its safety, efficacy and cost effectiveness. Therefore, there was a need to better establish its safety so as to avoid undesired effect to the mother and fetus.

This study therefore, sought a safer, efficacious, and cost- effective alternative to oxytocin for induction of labor. The data obtained may be useful to the health policy makers particularly those dealing with pregnant women to reevaluate the policy of labor induction. Findings from this study may also form the basis for MNH department of obstetrics and gynecology on formulating guidelines on the use of misoprostol in obstetrics. Future researchers may also find these informations useful for further studies in induction of labor.

1.5: Null hypothesis.

There is no difference between oxytocin and misoprostol in labor induction.

1.6: Research question

Is there any difference in safety, efficacy and cost between Misoprostol and oxytocin in induction of labor?

2: OBJECTIVES

2.1: Broad objective:

To compare the safety, efficacy and cost effectiveness of Misoprostol and oxytocin in induction of labor

2.2: Specific objectives:

1. To compare the interval from initiation of induction to the onset of labor between the two drugs.
2. To compare the induction-to-delivery interval between vaginal misoprostol and intravenous oxytocin.
3. To compare maternal and fetal outcome between the misoprostol and oxytocin group.
4. To compare the cost of induction between misoprostol and oxytocin.

3.METHODOLOGY.

3.1:Study area

The study was conducted at Muhimbili National Hospital labor ward. This is the main consultant hospital located in Dar es Salaam, the business city of Tanzania. MNH acts as the referral center for Dar es Salaam and costal region but occasionally receives patient from upcountry. The bed capacity is 1500.The labor ward receives many pregnant women in labor. There are also those coming for induction of labor for several indications.

The number of deliveries per month lies between 600 and 900, while the average number of induction per month lies between 20-25.

3.2: Study design.

Randomized clinical trial.

3.3: Study duration.

June –December 2004

3.4: Study population

All parturient admitted in the labor ward at Muhimbili National Hospital for induction due to various indications during the study period.

3.5: Exclusion criteria for this study:

Previous surgery on the uterus (myomectomy, uteroplasty, previous C/section)

Multiple pregnancy

Parity more than 5

Malpresentations

Fetal malformations.

All participants were screened for any presence of the above contraindications before enrolling them in the study.

3.6: Sample size.

The average success following induction by oxytocin in MNH labor ward is around 63 % (0.63) of cases. Hence, an increase to 80% (0.80) of cases will be considered as a significant progress.

$$n = \frac{P1\,(1-P1) + P2\,(1-P2)\,(Z\alpha+Z\beta)^2}{(P1-P2)^2}$$

Where: n= minimum required sample size.

Zα= the standard value which correspond to 1.96 at 95% Confidence interval.

Zβ= power of the study at 80%, (0.84).

P2=0.63 (proportional delivery after oxytocin)

P1= 0.80 (needed proportion to show that misoprostol is superior)

$$n = \frac{0.80(1-0.80) + 0.63(1-0.63)\,(1.96+0.84)^2}{(0.80-0.63)^2}$$

$= 69$

$= 69$ for each group, total=138.

3.7: Sampling techniques

Pregnant women were recruited as they came for admission in the labor ward for induction; those eligible for the inclusion were involved in the study after counseling by the investigators.

3.8: Training of research assistants.

The 4 nurse midwives were trained on the purpose of the study, proper titration of oxytocin, how to fill the checklist, and intrapartum monitoring. This was achieved through a one-day training conducted by the principal investigator.

3.8: Data collections

A pilot study was conducted to check the success of sampling procedure and the application of the induction drugs before actual data collection.

A structured checklist was used for data collection.

Four research assistants (nurse midwives in labor ward) were trained on the recruitment procedures and how to fill the checklist. The resident/registrar on call in the labor ward was asked to participate in the whole procedures. The main researcher was doing a daily-based supervision of the whole process and make sure that all necessary equipments are available.

Both pregnant women who were seen in antenatal ward/clinic by other doctors and scheduled for induction and those directly admitted to the labor ward after being examined by doctor on call and planned for induction were counseled about the study

by the main researcher or research assistants and offered a participants information document.

These participants from antenatal ward/clinic include those with favorable and unfavorable cervices.

Those admitted directly from home were screened to exclude any contraindication to labor induction. Subjects were fully informed that they were going to be randomly assigned to one of the two inducing agents. Those who agreed signed the informed consent form.

The main researcher or research assistants assigned the participants to either the oxytocin or misoprostol group by means of drawing a sealed envelop which was containing the name of the drug to be used. Each participant was allowed to pick one envelope randomly. This process was done once the pregnant woman was already admitted in the labor ward.

Bishop's score was done before starting induction to all pregnant women by checking the dilatation, consistency, length, and position of the cervix; and level of presenting part. A score of less than seven was categorized as unfavorable. Fetal heart rate was checked before starting induction to ensure the fetal well being.

Intermittent fetal heart rate monitoring by auscultation or by using the doptone machine and uterine contraction monitoring by palpation were performed in all women from the moment they were considered to be in active labor. Evaluation of uterine activity was performed by palpating the abdomen to assess the possible

occurrence of hyperstimulation, which was defined as the presence of more than 40 contractions in 10 minute, with/without an abnormal fetal heart pattern.

Amniotomy was done to those who fall in the oxytocin group and proved not to be HIV positive by counterchecking their antenatal cards,and was also not done in a case of IUFD. The procedure was done during the next assessment if it was unsuccessful at the first attempt. For those known HIV positive amniotomy was done once the dilatation of the cervix was seven centimeter or above.

The oxytocin infusion was given in 500ml of 5%dextrose.5iu in 500ml equals to 10mU/ml which was infused by counting drops/min, on which 15-20 drops are equivalent to 1ml. Infusion begin at 10drops/min, dosage increased every 30 min by 10drops/min until ideal contraction pattern is achieved (i.e 3-4 contractions in 10 minutes), the maximum dosage was 60drops/min. Thus the initial dosage was approximately 6mU/min and the maximum dosage was approximately 40mU/min. If labor was not established within 12 hours of induction, this was to be regarded as a failed induction; the next step relied on the standard hospital procedure, where the resident or registrar on call decides on the management as is usually done.

At MNH in normal situation, women scheduled for induction are induced by oxytocin infusion preceded by amniotomy in case of no contraindication, in case of no contraction or poor progress for more than twelve hours; this is regarded as failed induction. The resident/registrar on call decides on whether to send the woman back to the ward or for cesarean section.Those in the misoprostol group, a 100mcg (Continental pharma Inc, Belgium) tablets were cut into 4 quadrants with a blade

(each containing 25mcg). 25mcg was administered in the posterior fornix of the vagina. The patients were asked to remain recumbent for at least 30minute after the insertion of the drug, and then they were allowed to walk and drink. The dose was repeated after every 4 hours until the appropriate contraction pattern was established. The maximum dose was 100mcg. If contractions were not established four hours after the insertion of the fourth dose, induction was considered to have failed, and the patient management was to be left to the resident or registrar on call. Once the ideal pattern of contractions was reached, misoprostol was no longer administered.

During induction, the time of starting of induction and delivery of a baby were noted in hours so as to get the time interval between them. The time a participant started to feel pain on the back and lower abdomen was noted as a start of contraction.

The participants were asked to report any occurrence of nausea, excessive vomiting or shivering as a measure of maternal morbidity.

The total number of dextrose 5% 500ml bottles and number of 5iu of oxytocin used were recorded for all participants in oxytocin group. The total dose of misoprostol used was also noted.

3.9: Data handling and analysis

All data were entered into a computer using Epinfo 6 data entry program. Analysis was done using Epi6 software. Frequency distribution and measure of location were used to summarize data. Statistical significance testing were done using chi-square test, P-value of less than 0.05 was considered statistically significant.

3.10:Ethical issue

The aim of the study was explained to all participants. They were well informed on the benefit of the study, some undesired effects and immediate actions that would be taken in case of a problem. They were all aware that at any time of the study they can decide to pull out and this could not interfere with their hospital services. Those who were not ready to participate were ensured to get same quality of care as those in the study groups..A written consent sufficed one to be included in the study.

Those agreed were carefully scrutinized to rule out any contraindication to induction. The fetal heart rate patterns were checked before induction to avoid usage of inducing agent in an already stressed fetus. In case of any undesired side effect of the drug, like hyperstimulation, no more doses was inserted, mothers were instructed to lie on the left lateral position and proper measures were done to ensure the safety of both mother and fetus. Measures were taken to avoid prolonged labor and maternal exhaustion in all groups.

3.11:Ethical clearance

This proposal was presented to the department of obstetrics and gynaecology. Ethical clearence was granted by the MUCHS reseach and publication committee.

4:RESULTS

A total of 142 pregnant women were enrolled in the study. Out of the 142 participants, 71 were randomly allocated to the use of the misoprostol and 71 to intravenous oxytocin. There were no much differences in the characteristics of the groups. No one was lost to follow up throughout the study

Table 1: Characteristics of the women studied. Values are given as n (%) or average [range].

Character	Misoprostol (n=71)	Oxytocin, (n=71)	p value.
Median maternal age (years)	26 [16-40]	26 [16-40]	
Median gestational age (weeks)	39 [21-42]	39 [26-42]	0.075
Nullipara	30 (42)	43 (60)	<0.05
Favourable Bishop score	48 (67)	50 (70)	0.76
Indications for induction of labor			
Postdate	20 (28)	18 (25	NS
PROM	6 (8)	18 (25)	0.04
IUFD	10 (15)	8 (13)	NS
PIH	23(32)	22(30)	NS
Others	12 (17)	5 (7)	NS

NS=Not Significant

The distributions of maternal and gestational age were almost similar in the misoprostol and oxytocin groups except for parity on which there were more primigravidae in the oxytocin group, 60% vs 42% in misoprostol group.

Most participants (67% and 70% respectively) had favourable cervix in both misoprostol and oxytocin groups.

Indication for induction was mostly due to PIH; 32% and 30% in misoprostol and oxytocin groups respectively.

Most of the participants were nullipara.

Table 2

Maternal and fetal morbidity.Values are given as n (%) or average [range].

Variable	Misoprostol (n=71)	Oxytocin,n(%) (N=71).	p value
Maternal morbidity			
Nausea&vomiting	15(21)	3(4)	<0.01
Shivering	7(9)	2(3)	0.07
PPH	0	0	
Chorioamnionitis	0	0	
Hyperstimulation.	4(6)	5(7)	NS
Uterine rupture	0	0	
Fetal morbidity			
Meconium stained liquor	5(7)	1(1)	0.03
Apgar<7 at 5min.	2(3)	4(6)	NS
Intrapartum fetal distress	1(1)	1(1)	NS
Perinatal mortality	0	0	
Admission to neonatal ward.	17(24)	32(45)	0.04

NS=Not significant.

Nausea and vomiting was reported by 15 women (21%) in the misoprostol group and 3 (4%) in the oxytocin group.

There were 7 (9%) cases of shivering in the misoprostol group and 2(3%) in the oxytocin group.

There was no much difference in terms of hyperstimulation. This occurred in 4(6%) in misoprostol and 5 (7) in oxytocin group.

There was no case of uterine rupture.

Those in the misoprostol group had higher incidences of meconium stained liquor, 5 (7%) than in the oxytocin group, 1(1%).

Apgar score less than 7 after 5 minutes was observed in 2 (3%) babies in the misoprostol group, and 4 (6%) in the oxytocin group.

Admission to the neonatal ward was higher in the oxytocin group, 32 (45%), than in the misoprostol group, 17 (24%).

Table 3: Delivery outcomes. Values are given as n (%) or mean

Variable	Misoprostol,n(%) (n=71)	Oxytocin,n(%) (n=71)	pvalue
Vaginal delivery (total)	64 (90)	48 (68)	<0.001
Induction-to-delivery interval (hr) mean.	10.86	15.45	<0.001
Latent period (hr) mean	2.59	3.57	<0.001
Cesarean section.	7 (10)	23 (32)	<0.001
Indication for cesarean			
Fetal distress	1	1	NS
Failed induction	3	21	< 0.001
Others	3	1	NS

Vaginal delivery was significantly more frequently in the misoprostol group (occurred in 90% of the women) versus 68% in the oxytocin group, (P<0.001).

The mean interval from induction to delivery time was shorter in the misoprostol group than in the oxytocin group; 10.86 hours and 15.45hours respectively, p<0.001.

The mean duration from induction to the beginning of contraction was shorter in the misoprostol group, (p<0.001). There were more cesarean sections in the oxytocin group than in the misoprostol group, 32% and 10%, respectively, p<0.001.

Many cesarean sections were due to failed induction.


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Table 4: Delivery outcomes of primigravidae.values are n (%)

Varibles	Misoprostol n=30	Oxytocin n=43	p-value
Induction to delivery interval (hours), mean	11.41	14.23	<0.001
Vaginal delivery	26(87)	31(72)	NS
C/section	4(13)	12(28)	0.02
Apgar score <7 at 5 min.	1	2	NS
Admission to NNW	5(17)	14(32)	<0.001

***NS=Not significant**

The mean induction to delivery time was shorter in the misoprostol group than in the oxytocin group,$p<0.05$.

Vaginal delivery was more in the misoprostol group, 87%, than in the oxytocin group, 72%.

Cases of c/section were more in the oxytocin group, 28%, than in the misoprostol group, 13%.

There were fewer admissions to neonatal ward in the misoprostol group than in the oxytocin group.

Table 5: Delivery outcome of IUFD. Values=n, (%)

Variable	Misoprostol, n=10	Oxytocin n=8	p-value
Induction to delivery interval (hrs) means.	12.35	16.17	<0.001
Vaginal delivery	9(90)	7(88)	NS
C/section	1(10)	1(12)	NS
Dose of misoprostol (average)	100mcg		

NS=Not Significant

The means induction to delivery time shorter in the misoprostol group than in the oxytocin group,p<0.001.

Vaginal delivery was almost equal in both groups

There were very few cases of c/section in both groups.

Table: 6
Outcomes of women with unfavorable cervices. Values are means,n (%).

Variable	Misoprostol n=23	oxytocin n=21	p value
Induction to delivery interval (hours)	11.26	15.52	<0.001
Vaginal delivery	19(83)	10(48)	0.03
C/section	4(17)	11(52)	0.03
Apgar score <7 at 5min.	1	1	NS

The duration from induction to delivery was shorter in the misoprostol than in the oxytocin group, p value <0.001.

Occurrence of vaginal delivery was more in the misoprostol group, p=0.03.

Almost half of participants in the oxytocin group underwent c/section.

Table 7

Indication for admission to neonatal ward. Values are given as *n* (%)

Variable	misoprostol (n=71)	oxytocin (n=71)	p-value
Care after cesearen Section.	7(10)	23 (32)	0.003
Low apgar score.	2(3)	4 (6)	0.61
Prematurity.	8(11)	5 (7)	0.33

Majority of admissions to the neonatal unit were for babies of mothers who delivered by cesarean section in both oxytocin and misoprostol groups (32% and 10%).

Babies admitted due to low score were almost equal in groups, 3% in misoprostol and 6% in oxytocin group.

Table 8. The dosage of misoprostol used till delivery.

Dose (mcg)	Number of women, n (%), [n=71]
25	16 (23)
50	38 (53)
75	4 (6)
100	13 (18)

Majority of women, 53%, required two doses of misoprostol for induction of labor.

Table 9: Comparison of cost of induction between misoprostol and oxytocin.

Cost (US dollar)	Misoprostol, [n=71]	Oxytocin [n=71]	P-value
<0.2	50 (70%)		<0.001
0.2-0.70	14 (20%)	1 (2%)	<0.001
1.5-2.10	5 (7%)	15 (21%)	<0.001
>2.10	2 (3%)	55 (77%)	<0.001

The cost of induction was less than 0.20 dollar in the majority of patients in misoprostol group, as compared to those in oxytocin group whereby the cost of induction was more than 2.10 US dollar, this was statistically significant. ($P<0.05$).

The average cost of the drug in the misoprostol group was 0.37 US dollars (range) while in the oxytocin group was 2.5 US dollars (range); this difference is statistically significant ($p<0.05$).

5.DISCUSSION

This trial was done to compare vaginal misoprostol with intravenous oxytocin (the latter is the most widely used drug for inducing labour in Tanzania). This study aimed at comparing the safety, efficacy and cost effectiveness of both drugs.

In this trial misoprostol has appeared to be a more effective, safe and cheaper induction agent than oxytocin. This is in agreement with previous studies.[13.]

The study has showed that a dose of 25mcg of misoprostol, inserted at four-hourly intervals, is safe, more effective, and cheaper than oxytocin for induction of labor.

In this study 42% of the patients enrolled in the trial had favourable bishop score, misoprostol has shown to be effective in cases of unfavorable cervices than oxytocin. The reason for having many participants with favourable Bishops score was because all planned induction cases at MNH are not brought in the labor ward without having ripe cervices unless there is obstetric indication,so during the study this policy had to be maintained. This finding is consistent to other studies addressing the efficacy of misoprostol [11,26].

The trial has shown that the average time interval to the onset of labor was significantly shorter in the misoprostol group . Those in the misoprostol group had a mean time of 2.59 hours while in the oxytocin group was 3.59 hours. These same

results have also been found by many other authors[13] .De Aquino et al[13] studied misoprostol (25mcg, vaginally) and oxytocin and found an average of 4 hours to the beginning of labor for the misoprostol group, versus 6 hours for the oxytocin group,. These findings are consistent with our results.

In this trial the average time interval from induction of labor to the occurrence of vaginal delivery was significantly shorter for misoprostol than for oxytocin (10.86 hours versus 15.45 hours), the same findings have been reported in other studies[13,28]

The finding of no significant difference in neonatal and maternal morbidity, a very low incidence of intrapartum fetal distress in misoprostol groups alleviated the fear of misoprostol and hence is a challenge to the MNH to adjust its induction methods and officially introduce misoprostol as a first line drug for induction of labour.

The low incidence of uterine hyperstimulation found in this study, is similar to a study done in Sao Paulo[13].However other studies[27,28]reported greater incidence of uterine hyperstimulation syndrome.This may be due to the differences in dosage used in their studies.

Lack of serious morbidity like uterine rupture in both groups may have been attributed by the low dose of misoprostol and proper titration of oxytocin. This signifies that misoprostol at low dose of 25mcg is safe and effective.

In this study incidences of meconium stained liquor was higher in the misoprostol group than in the oxytocin group. Similar finding has been reported in other studies,however the difference in the two groups was not statistically significant and there was no fetal compromise,once again this shows that at a dose of 25mcg misoprostol is safe to both mother and fetus.

The big difference in admission to the neonatal ward seen in this study between the two groups was mainly due to the higher cases of cesarean section in the oxytocin group than misoprostol group. At MNH every woman who undergoes caeserean section her baby is kept at the neonatal unit for a day or two til the mother recovers completely from anaesthesia. Most of these babies have no problems, they are admitted for care. Those admitted due to low Apgar score were a minority.

The finding that most women in the misoprostol group achieved vaginal delivery in comparison to those in the oxytocin group, further proves the cost effectivenness of misoprostol , a significantly higher number of participants with failed induction with oxytocin who had to undergo caesarian section made the cost increase tremendously (Oxytocin+ surgery). Comparative studies have shown that the incidence of cesarean sections is higher in the oxytocin group[14,29]. In this trial 32% in the oxytocin group underwent cesarean section in comparison to 10% in the misoprostol group, the rate was almost thrice for the oxytocin group.

In this study the main reason for cesarean section was due to failed induction. There were 24 cases of which 21 were in the oxytocin group, showing a statistically significant difference between the two groups. This is similar to other studies [30,13].

A large number in the misoprostol group, 66%, spent 9-13 hours before delivering, while most of those in the oxytocin group, 49%, spent 14-18 hours. Several studies have revealed similar findings [13, 30; 31].This shorter duration in the misoprostol group was an advantage to the patient and their families.

Misoprostol administraton has significantly reduced the work burden to the midwives, they were satisfied by this method of induction,which is easier to care, and almost all prefered misoprostol in the future so as lessen the work of continous titration of oxytocin drops in a busy MNH labour ward.

The cost of induction associated with the use of misoprostol was substantially lower than those associated with oxytocin. Most women in the misoprostol group,70%, spent less than 0.20 USD, in comparison to 77% in the oxytocin group who spent more than 2.10 USD.The same low cost of misoprostol was also reported by Nakintu N[11]. These results also imply that Misoprostol reduces the hospital expenses, nursing and monitoring time which reduces the congestion in the labor ward.

The cost associated with the use of vaginal misoprostol compares favorably with those of oxytocin infusion. In comparison with the cost of misoprostol induction,

this study has revealed that use of oxytocin was about seven times more expensive than the induction with vaginal misoprostol .

Hospital expenditure, nursing and monitoring time would be significantly reduced in case of adoption use of misoprostol.The same findings have been reported by Cassimo B et al[31].One study demonstrated that the expense of induction using vaginal misoprostol was about 25-36 times lower than that of oxytocin infusion [21]

6.CONCLUSION

Misoprostol 25mcg administered intravaginally is significantly more effective,safe and cheaper for labor induction than oxytocin. The inexpensiveness and the appropriteness of this drug testified that misoprostol in regard to financial and human resources is more valuable compared to oxytocin especially in a low income countries like Tanzania.

7.RECOMMENDATIONS

Introduction of misoprostol for induction of labour shall significantly reduce the number of unnecessary caesarean section due to failed induction.

Misoprostol should be used at a dose of 25mcg inserted at the posterior fornix every 4 hours.

Misoprostol is an important drug for induction of labour. It should be licenced by the ministry of health for obstetrics use with initiative from AGOTA.

It will be of great benefit for the country to revisit the policy of labor induction and eventually give access to the availability of this agent to all level of health system.

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9.APPENDINCES

9.1:CHECK LIST.

Comparison between vaginal misoprostol and intravenous oxytocin in induction of labor in Tanzania.

1.Name:	
2. Registration number.	
3.Age	
4.Gravidity	
5.Parity	
6.Gestational age (weeks)	
7.Bishops score	
8.Indication for labor induction	
9.State of the membrane before induction	
10.Time induction started	
11. Latent period (hours).	
12.Delivery time	
13.Interval of induction- to – delivery time	
14.Agent used for induction	
15.Total dose given	
16. Mode of delivery.	
17.Indicationfor c/section	
18.Apgar score after 5 min	

19.Nausea	
20. Vomiting.	
21.Postpartum hemorrhage	
22.Meconium stained liquor	
23,Admission to neonatal ward	
24.Reason for admission to neonatal ward.	
25.Shivering	
26.Total cost of induction	
27.Maternal satisfaction	

9.2: Patient information.

We are conducting a research to compare two inducing agents. One of them is oxytocin, which is commonly used in our labor ward, the other one is misoprostol, is not routinely used here. The aim of this study is to find out if the new drug, Misoprostol, is suitable for our country. We are trying to find out its efficacy, safety and cost effective in comparison to our common agent for induction, oxytocin. This trial is of beneficial for our country particularly pregnant women who required to be induced.

These drugs rarely can have some undesired effects if not used carefully, like hyperstimulation, which can results in fetal distress or rupture uterus. In case of these

effects every measure will be taken on time for the benefit of mother and her baby. Other side effects like nausea, vomiting, and shivering are not very severe to cause any danger.

The new agent is in the form of tablet which is administered in the vagina, will be given every 4 hours until desired contraction is achieved, but will not exceed four doses. The routine agent,oxytocin, is administered intravenously in form of drops till a desired contraction pattern is achieved.

If you are interested you will select an envelope that contains one of these two agents, then the picked agent will be used during your induction. Both patients will be treated equally regardless of agreeing or refusing to join the study.

Any question regarding this study can be directed to Dr Kaguta of department of obstetric and gynecology who is incharge of this study.

Do you have any question?

9.3: Consent form.

I……..have read and understood what is written in this form and agreed to participate in this study.

…….. ……

Name of the patient signature

Date……

Name of the witness signature

…….. ……