A COMPARISON OF TWO DOSING REGIMENS OF INTRA-VAGINALLY ADMINISTERED MISOPROSTOL FOR PRE-INDUCTION CERVICAL RIPENING AND INDUCTION OF LABOUR

A DISSERTATION SUBMITTED TO THE NATIONAL POSTGRADUATE MEDICAL COLLEGE OF NIGERIA

BY

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NOVEMBER, 2006
DECLARATION

I hereby state that this work is original. The work has not been presented to any other College for a fellowship nor has it been submitted elsewhere for publication.

DR ADEBAYO. A. ADENIYI
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CERTIFICATION

The candidate under my supervision undertook the study reported in this dissertation. I also supervised the writing of the Dissertation.

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DR. O. OLAYEMI [FMCOG] (Nig)
CERTIFICATION

The candidate under my supervision undertook the study reported in this dissertation. I also supervised the writing of the Dissertation.

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DR. A. OLADOKUN [FMCOG (Nig)]
DEDICATION

This work is dedicated to Almighty God for His infinite wisdom and guidance at all times. To my family, especially my wife, Fola for their love, support, forbearance and encouragement.
ACKNOWLEDGEMENT

I wish to express my profound gratitude to the Head of the Department of Obstetrics and Gynaecology, University College Hospital, Ibadan, Professor A.O Adekunle for approving and supporting the conduct of this study in the Department. And the entire consultant staff for allowing the participation of their patients in the study.

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I also express my gratitude to the pharmacy unit of the Hospital for their assistance in preparing the 25 microgram and 50 microgram of misoprostol used in this study. To all I say thank you.
SUMMARY

OBJECTIVES

To compare the effectiveness of two dosing regimens (25µg and 50 µg) of misoprostol for cervical ripening/induction of labour, to compare the adverse effects on labour and fetal outcome of the two groups.

METHODOLOGY

The study was a prospective, randomized study of healthy pregnant women, with singleton fetus who registered for antenatal care and delivery at the University College Hospital (UCH) Ibadan, between 1st September 2005 and 31st May 2006 and who met the study criteria. One hundred and twenty (120) patients were recruited to participate and one hundred and eighteen (118) agreed. No patient withdrew from the study. The patients were assigned by means of table of random numbers to receive either 25 microgram or 50 microgram of misoprostol (cytotec ® tablet, Searle & Co. Chicago). Sixty-three (63) patients received 25µg and fifty-five (55) received 50µg.

RESULTS

Significantly higher number of patients achieved spontaneous labour in the 50 µg group than in 25 µg group (96.4% vs. 84% (P<0.05). The mean interval between the first dose and delivery was shorter in the 50 µg group though this did not assume statistical significance (P = 0.152).

There was no significant different between the two groups in the number of doses needed to achieve favorable cervical score of ≥ 6 or spontaneous
labour (1.8 ±1.1 vs. 1.7 ± 0.7, P = 0.689) among the patients that achieved vaginal delivery. More patients (97.9%) in the 50 µg group who achieved vaginal delivery did so within 24 hours compared to (89.6%) in the 25 µg group. However no patients in the either arm of the study received the maximum dose (200µg) of the study drug.

The need for oxytocin augmentation of labour among those that developed spontaneous labour was higher among the 25 µg group than in the 50 µg group (39.7% vs. 16.4%, P=0.007).

The incidence of caesarean section was similar in the two groups 8.0% vs. 11% for 25 µg and 50 µg respectively; with similar proportions also achieving vaginal delivery, 92% vs. 89% for 25 µg and 50 µg respectively. Overall the route of delivery did not differ significantly between the groups.

The number of neonates with 1-minute and 5 minutes Apgar score less than 7 did not differ significantly between the groups, also the number of neonates admitted into special baby care unit and the indications for admission were not statistically different. However meconium stained liquor was recorded in significantly higher number of patients in 50 µg group than in the 25 µg group (9.1% vs. 0.0%), but none of the neonate had features suggestive of meconium aspiration.

Labour complications, which included precipitate labour, tachysctole (>5 contractions in 10 minutes for two consecutive 10 minutes period), fetal distress
(fetal bradycardia or tachycardia) were more in the 50 µg groups. Two patients in 25 µg group experienced vomiting.

**CONCLUSION**

The two dose regimens 25µg and 50µg were both effective in cervical ripening / induction of labour. 50µg resulted in relatively faster delivery and less need for augmentation of labour; however it was associated with more labour complications compared to 25µg.
INTRODUCTION

In an ideal world, all pregnancies would go to term, and labour would begin spontaneously. In reality however, it is often best to deliver the infant before the onset of natural labour.\textsuperscript{1,2,3}

The exact mechanism responsible for cervical ripening and subsequent initiation of labour are currently not well understood.\textsuperscript{4,5} Over the past few years, there has been an increasing awareness that if the cervix is unfavorable, a successful vaginal birth is less likely.\textsuperscript{6} Various scoring systems for cervical assessment have been introduced. In 1964, Bishop systematically evaluated a group of multiparous women for elective induction and developed a standardized cervical scoring system. The Bishop score helps delineate patients who would be most likely to achieve a successful induction of labour.\textsuperscript{7}

A major factor that influences successful induction of labour is the state of the uterine cervix. If the cervix is unripe, closed, firm and uneffaced, with a Bishop score of less than 6, the conventional method of induction of labour by surgical amniotomy become technically difficult and intravenous infusion of oxytocin results in prolonged labour with risks of maternal and fetal complications and unsuccessful inductions, unnecessarily increasing the caesarean section rate.\textsuperscript{8} The duration and successful induction of labour is inversely correlated with the Bishop score.\textsuperscript{6}

In an attempt to improve the cervical ripening before induction of labour, many methods have been described, ranging from natural to modern methods, mechanical and pharmacological.\textsuperscript{9}

Among the commonest mechanical methods of cervical ripening is the use of extra-amniotic transcervical balloon catheter which is widely used especially in this environment.\textsuperscript{10}

Recent efforts have been focused on the pharmacological agents mainly oxytocin and prostaglandins. Although oxytocin is a safe and effective initiator
of uterine contractions, its success depends on the condition of the cervix before induction.\textsuperscript{11}

Prostaglandin $E_2$ (dinoprostone) is the only pharmacological agent approved by the Food and Drug Administration for cervical ripening and induction of labour. However, this preparation is expensive especially in low resource settings.\textsuperscript{12}

Misoprostol is a synthetic 15-deoxy 16-hydroxy, 16-methyl analogue of the naturally occurring prostaglandin $E_1$ originally manufactured for prevention and treatment of peptic ulcers, especially those induced by non-steroidal anti-inflammatory drugs (NSAIDs).\textsuperscript{13}

Several studies have found misoprostol effective as an agent for cervical ripening and induction of labour. It is inexpensive, easy to store and stable at room temperature.\textsuperscript{14}

Despite many widely reported trials on misoprostol, many practical aspects of its administration are still yet to be well established, these include; the appropriate dosage, the dosing interval and route of administration, with doses ranging from 25μg to 100μg.\textsuperscript{15,16} However, it is clear that most of the side effects associated with misoprostol are dose dependent, with smaller doses demonstrating better safety profile.\textsuperscript{16}

This study was designed to contribute to the ongoing research efforts on the appropriate use of misoprostol in obstetrics. It focused on comparison of two dosing regimens (25μg vs. 50μg) of misoprostol for pre-induction cervical ripening/induction of labour.
LITERATURE REVIEW

The uterus is a fibromuscular organ, usually divided into a lower cervix and an upper corpus or body. The uterine cervix is a tubular, connective tissue structure. It measures about 25mm to 30mm in length and slightly less in diameter. The cervix is predominantly fibrous with only 10 percent being composed of muscle fibres. Microscopic examinations of the cervical tissue show that collagen fibres dominate the cervical stroma. The distribution of the muscle fibres in the cervix ranges from 29 per cent in the upper third, 18% in the middle and 6 percent in the lower third, and often the most distal portion is almost devoid of muscle. The lower concentration of muscle fibres in the cervix is in contrast to the upper corpus with 69% composed of muscle fibres. The change from mostly fibrous tissue of the cervix to the predominantly muscular tissue of the corpus is usually abrupt.

The fibrous tissue of the cervix is made up of collagen fibres, mainly of types I and III and a small amount of type IV in the basement membrane. The collagen fibres generally determine the tensile strength of the cervix like in any other fibrous connective tissue. The non-fibrillar ground substance of the cervix within which the collagen fibres are embedded consists of glycosaminoglycan (or mucopolysaccharides), proteoglycans and water molecules. The predominant glycosaminoglycans include the dermatan sulphate (52-73%), hyaluronic acid (8-22%) and heparin sulphate (6-13%). Recent studies show that there is little or no chondroitin sulphate.
The fibrillar collagen fibres and the ground substance are arranged in an organized relationship to give the cervix the rigidity which is characteristic of a non-pregnant state and early pregnant state\textsuperscript{4, 19}. Fibronectin and elastin have also been demonstrated to run in between the collagen fibres and add to the rigidity of the non-pregnant cervix\textsuperscript{19}.

The role of the state of the cervix in relation to the progress and duration of labour has long being recognized, with poor progress and prolonged labour being associated with a rigid cervix\textsuperscript{4}. The main function of the cervix before term is to retain the conceptus, but allowing their passage at term\textsuperscript{4, 20}.

To enable this degree of dilatation to occur, the cervix undergoes morphological and biochemical changes prior to the onset of labour\textsuperscript{20, 21}. These changes are complex and poorly understood, but they basically involve the rearrangement of the collagen fibres in relation to the ground substance leading to the weakening of the rigidity of the cervical connective tissue\textsuperscript{4, 8, 20}. The collagen fibres become less densely packed, and the individual collagen fibres are separated by clear spaces and the structures appear to be dissociated\textsuperscript{4}. The amount of hydroxyproline which is a measure of the level of collagen in a tissue is decreased in pregnancy with cervix containing only about 30-50 per cent of the amount in the non-pregnant cervix. This decrease is associated with softening of the cervical tissue\textsuperscript{4, 19}.

Although absolute amount of glycosaminoglycan is increased by three folds in pregnancy with the highest level at term, the relative contents of the
different glycosaminoglycans is altered. Thus, there is an increase in the level of hyaluronic acid from about 5% in the third trimester to 49% in labour, constituting the most prominent glycosaminoglycan in the latent phase of labour.\textsuperscript{4,19} Hyaluronic acid has high water binding capacity leading to an increase in the water content of the cervix, with the most marked effect seen just prior to delivery\textsuperscript{4}. There is a decrease in the level of dermatan sulphate, the lowest amount being found in the active phase of labour. It has recently been shown that the onset of changes in the concentration of dermatan sulphate corresponds to the process of cervical ripening in late pregnancy.\textsuperscript{4,19,22} Dermatan sulphate is the most important stabilizer of the cervical consistency and it also binds to fibronectin that has high affinity for collagen. Thus a decrease in the concentration of dermatan sulphate leads to reorganization of the collagen fibres, which leads to changes associated with cervical ripening\textsuperscript{4}.

All the biochemical changes described above translate into observable physical changes in the cervix which include softening, effacement and gradual dilatation of the cervix, which are the measures of cervical ripening.\textsuperscript{4,15}

The exact mechanisms that trigger the onset of cervical ripening are unknown.\textsuperscript{4,19} However, the process has been likened to an inflammatory reaction, with polymorphonuclear neutrophil invasion of the cervix in labour.\textsuperscript{4,19} Many inflammatory mediators notably interleukins – 8 (IL-8) and monocyte chemotactic peptide (MCP-1) have received some attention in recent studies.\textsuperscript{3,10,11,12} Neutrophils are rich sources of collagenase and elastase and
matrix metalloproteinase all of which play important roles in the breakdown of cervical collagens\textsuperscript{4,19,25}.

Prostaglandins especially prostaglandin E\textsubscript{2} (PGE\textsubscript{2}) and PGF\textsubscript{2α} have been implicated in cervical ripening. The former being responsible for vasodilatation of the cervical capillaries and increase in their permeability to circulating neutrophils. Prostaglandin F\textsubscript{2α} (PG F\textsubscript{2α}) stimulates a decrease in glycosaminoglycan especially cervical dermatan sulphate which leads to degradation of collagen.\textsuperscript{4,19}

The final pathway of all these biochemical reactions is softening of the cervix which in turn allows for gradual effacement and dilatation of the cervix especially in the presence of uterine contractions.

The degree of cervical softening and ripening which in turn determines the imminence of labour and delivery and also the readiness with which labour can be induced differs in individuals.\textsuperscript{2,3} Different methods have been used to quantify this degree of ripening. Among the various scoring systems, the most widely known and used is the system developed by Bishop in 1964.\textsuperscript{4,7,21} This scoring system is based on the degree of cervical effacement, dilatation, consistency, position and the station of the presenting part.\textsuperscript{1,7}

Other methods that have been proposed include the measurement of the cervical length preferably with transvaginal ultrasound\textsuperscript{18} and the presence of fetal fibronectin in the cervical and vaginal fluids.\textsuperscript{26}
Fibronectins are a family of multifunctional glycoproteins first described in 1985.\textsuperscript{2,7} They are extracellular matrix proteins and present in fetal tissues throughout pregnancy, mainly in the amniotic fluid and the deciduas.\textsuperscript{25,27} Their presence in vaginal fluid predicts onset of labour within one to two weeks while their absence gives a high negative predictive value for preterm delivery or onset of labour.\textsuperscript{27} Their presence or absence also predicts how readily the cervix will respond to labour inducing agents like prostaglandin or oxytocin.

Recently, a computer aided texture based cervical score (TBCS) has been described. It involves the use of non-invasive computer aided texture analysis of ultrasound imaging of the cervix in assessing the degree of cervical ripening.\textsuperscript{20} However this method is still in experimental stage.

While most pregnancies run a normal course and terminate at term with spontaneous onset of labour, planned induction of labour for various reasons has become an established part of modern obstetric practice.\textsuperscript{1,2,3,48}

The chances of successful induction of labour are influenced among other things by the state of the cervix, with a favorable cervix being associated with successful outcome as demonstrated by Bishop.\textsuperscript{7} A low score of less than 6 out of the maximum score of 13 is associated with a higher failure to induce labour, prolonged labour and a higher incidence of caesarean section.\textsuperscript{1,16,28,29}

In an attempt to improve the cervical ripening, many methods have been described, ranging from natural to modern methods, mechanical and pharmacological methods.\textsuperscript{20} The use of castor oil and evening primrose oil is
widely reported in the literature especially among the midwives\textsuperscript{20,21}. Other methods include: membrane stripping, mechanical dilatation, surgical amniotomy and the use of various pharmacological preparations.\textsuperscript{18,19,22,25} Among the commonest mechanical methods of cervical ripening is the use of extra-amniotic transcervical balloon catheter which has been widely acclaimed as being effective, cheap, simple and safe, even in patients with ruptured fetal membranes\textsuperscript{23,24,49}. This is the method commonly used in this environment. Other mechanical methods include hygroscopic agents like laminaria tents\textsuperscript{6}.

The search for more effective cervical ripening agents has focused on pharmacological agents; this has brought the prostaglandins and oxytocin into limelight, however, most recent studies have been on the prostaglandins. The efficacy and safety of prostaglandins in cervical ripening have been proven in widely reported randomized controlled trials.\textsuperscript{26,27} The only prostaglandin approved for cervical ripening in the past was prostaglandin E2 (PGE\textsubscript{2}) (or dinoprostone).

However, there has been a lot of draw backs to its use which include the need for refrigeration at a narrow temperature range of 2-8\textdegree c and expiration time of 24 months.\textsuperscript{32} More importantly in a low-resource setting in developing countries, the drug is rather expensive and not readily available\textsuperscript{28}. Many studies have also demonstrated that majority of patients receiving dinoprostone (PGE\textsubscript{2}) for cervical ripening eventually require the use of oxytocin to augment labour.\textsuperscript{34,35}
To overcome these problems associated with dinoprostone, especially the cost and administration, an alternative was found in another prostaglandin derivative: prostaglandin E1 (PGE₁) (or misoprostol). Misoprostol is easy to administer since it is placed in the vagina and not in the cervical canal. It is also much cheaper²⁹,³⁵ with an excellent shelf life in environmental temperature as high as 30°C. Clinical trials have compared misoprostol with placebo, oxytocin and dinoprostone (PGE₂), with misoprostol showing superior efficacy and comparable safety.¹⁵

The initial drawback of misoprostol was the fact that it was primarily approved as a cytoprotective agent for peptic ulceration.¹⁵,²⁷ However, following extensive studies on its safety profile, its contraindication label which include pregnancy has been reviewed. The Food and Drug Administration (FDA) has thus approved its use in cervical ripening and induction of labour, though as an off label non experimental indication, which is an acceptable practice world wide¹⁵. Following this, its use is now widespread especially in the developing countries¹⁵.

Among the recognized adverse effects associated with misoprostol especially in relation to cervical ripening and induction of labour include: uterine hyperstimulation, fetal distress, precipitate labour and meconium stained liquor¹⁵. Most of these complications are dose related, and more likely to occur when doses greater than 50μg are used, or with a dosing frequency of less than 3 hours.¹⁵
Despite the widespread research on misoprostol, the ideal dosing regimen is yet to be determined with doses ranging from 25 to 100μg in different studies.\textsuperscript{15, 16, 47}

A study conducted at the University College Hospital Ibadan, comparing the efficacy and safety of transcervical balloon catheter with 50μg intravaginal misoprostol, showed a clear superiority of misoprostol over the balloon catheter.\textsuperscript{8} However, in an effort to find an effective dose of misoprostol, that does not increase the side effects, which are dose related, recent studies have focused on low dose regimen of 25μg\textsuperscript{12, 15, 16, 36, 47}

Since most of the side effects associated with misoprostol are dose related, using a lower dose, which is equally effective, may achieve the same result with a higher safety profile.

This study is designed to compare the efficacy and safety of two dosing regimens of misoprostol for cervical ripening and induction of labour i.e. 25μg and 50 μg.
AIMS AND OBJECTIVES

1. To compare the effectiveness of two dosing regimens (25 µg and 50 µg) of misoprostol in cervical ripening/induction of labour.

2. To compare the adverse effects that may be associated with the two dosing regimens.

STUDY HYPOTHESIS

It is propounded that no differences exist in effectiveness between two dosing regimens of misoprostol (25 microgram and 50 microgram) as pre-induction cervical ripening/induction of labour agents. That similar proportion of patients in each group will achieve vaginal delivery within 24 hours and that no difference exists in the complications of labour and fetal outcome in the two groups.

MATERIALS AND METHODS

The study was a prospective randomized study of healthy pregnant women, with singleton pregnancy who registered for antenatal care and delivery at the University College Hospital (UCH), Ibadan, between 1st January and 31st May 2006 and who fulfill the study criteria.

The study was approved by the University of Ibadan/University College Hospital Ibadan, Institutional Review committee.
All patients were adequately counseled and their informed consent obtained before their inclusion in the study. The antenatal records were reviewed for co-existing medical conditions and history of the index pregnancy. Thereafter, a first trimester ultrasound scan was reviewed to ascertain the estimated gestational age.

One hundred and eighteen participants were recruited into the study. No patient withdrew once admitted into the study. Sixty-three (63) received 25 microgram and fifty-five (55) received 50 microgram of intravaginal misoprostol.

The patients were assigned by means of table of random number with blocks of four to receive intra-vaginal misoprostol of 25 microgram or 50 microgram (as prepared by the pharmacy unit of the Hospital). Group allocation was predetermined and placed in consecutively numbered and sealed opaque envelopes. Once a patient was deemed eligible and had given informed consent for study participation, she was assigned a sequential study number. The primary investigator, who was responsible for maintaining the envelopes, was contacted to open the corresponding numbered envelope for the purpose of treatment allocation.

All consenting patients had clinical obstetric examination to exclude the presence of any of the exclusion criteria immediately before commitment to the treatment allocation.
Initial Bishop Score was assessed by the principal investigator and subsequently re-assessed by the same individual.

All those who fulfilled the study criteria received either 50micrograms or 25micrograms misoprostol intravaginally in the posterior fornix every 6 hours for a total of 4 doses for cervical ripening or until labour is established, with the maximum exposure time to the agent being 24 hours.

Oxytocin induction and active management of labour were commenced in those patients with satisfactory Bishop Score who did not develop spontaneous active labour after maximum exposure to either dose regimen, or had a spontaneous rupture of membranes without an ensuing adequate uterine contractile pattern.

Oxytocin infusion was not started until at least 4 hours after the last dose of misoprostol. By use of a standardized protocol, oxytocin infusion was by gravity-assisted method commencing with 4miu/min and increasing at intervals of 30 minutes to achieve adequate uterine contraction pattern i.e. at least 3 strong uterine contractions in ten minutes, each lasting 40-60 seconds.

Once in the active phase of labour, routine intrapartum management was without regard to the dose regimen. Fetal heart rate monitoring was by intermittent auscultation with Pinnard’s fetal stethoscope (or when necessary sonicaid) at intervals of 15 minutes. Evaluation of uterine contractions for frequency, intensity and duration over 10 minute periods was done at intervals of 30 minutes. Maternal vital signs were assessed every hour. This information
was charted on the partograph as recommended by the World Health Organization (WHO).

Abnormal parameters in labour were treated in accordance with standard obstetric intervention(s) appropriate for each situation.

Hyperstimulation defined greater than 5 contractions in ten minutes with associated fetal heart rate abnormality was to be managed by infusion of normal saline, maternal positional change and supplemental oxygen through intranasal catheter. Persistent cases were to be managed with irrigation of the vaginal using normal saline via a 50ml syringe (with the needle detached) with attempt to remove all the fragments of misoprostol. In addition when necessary intravenous magnesium sulphate at a loading dose of 4gram given slowly over 20 minute followed by 2gram per hour infusion as maintenance until the hyperstimulation is corrected.

**Inclusion criteria**

All consenting pregnant women with

- Singleton pregnancy at ≥ 37 weeks gestational age
- Bishop’s score of ≤ 5
- Cephalic presentation
- Normal fetal heart rate
- Intact membranes
Exclusion criteria

1. Malpresentation
2. Multiple gestation
3. Placenta praevia
4. Estimated fetal weight of > 4000gm
5. Abnormal fetal heart rate
6. Evidence of cephalo-pelvic disproportion
7. Unexplained vaginal bleeding
8. Any pre-existing medical illness like cardiovascular disease, renal or hepatic dysfunction and clotting disorders.
9. Any contraindication to receiving prostaglandins. eg, glaucoma
10. Active genital infection
11. Suspected chorioamnionitis
12. Previous caesarean delivery or uterine surgery
13. Grand multiparity
14. Non consenting patients
15. Severe pre-eclampsia/Eclampsia
16. Uterine contractions
Calculation of sample size

The sample size on each arm of the dosing regimen was calculated using the formula below. This gave a total of fifty (50) parturients, corresponding to 80% statistical power, 5% significant level and with provision for 25% non-response or dropout.

**FORMULA**

\[ N = (Z\alpha + Z\beta)^2 \left\{ P_0 (1-P_0) + P_1 (1-P_1) \right\} / (P_1-P_0)^2 \]

Where:

- \( N \) = required minimum sample size for each group.
- \( Z\alpha \) = percentage of normal distribution corresponding to the required significant level of 5% = 1.96
- \( Z\beta \) = point of normal distribution corresponding to the statistical Power of 80% = 0.842.
- \( P_0 \) = Response in the first group (from previous study) \(^{39} = 0.60\)
- \( P_1 \) = Expected response in the second group = 0.30

\[ N = (1.96+0.842)^2 \left\{ 0.30 (1-0.30) + 0.60 (1-0.60) \right\} / (0.60 -0.30)^2 \]

\[ = 40 \text{ (minimum sample size in each group) } \]

Deliberate over sampling by 25% was done to account for non-responders, drop-outs or lost to follow-up.

Therefore, the sample size for each group = 40 + 10 = 50.
DATA ANALYSIS

Baseline data included maternal age, parity, estimated gestational age, indication for induction of labour and initial Bishop Score.

Primary outcome measures included:

- Pre-induction Bishop score
- Interval to achieve ripened cervix/spontaneous labour.
- Interval from first insertion to delivery (first insertion-delivery interval)
- Requirement for oxytocin augmentation
- Route of delivery and
- Apgar scores

Secondary outcome measures would be

- Occurrence of hyperstimulation, tachystole, uterine rupture and any other direct complications.
- Data entry was into a standard proforma and statistical analysis was performed with \( \chi^2 \); student t-test, Mann – Whitney U and Fisher’s exact test when appropriate. All tests were two-tailed (or sided) with 0.05 level of significance.

Differences in age, parity, and estimated gestational age were analyzed with t-test, while differences in route of delivery, and presence of complications were analyzed with \( \chi^2 \) (chi square) and Apgar and Bishop Scores were by
Mann-Whitney U test using statistical package for social scientist version 11.0.
RESULTS

One hundred and eighteen patients were enrolled in the study, of these 63 received 25 microgram (µg) and 55 received 50 microgram (µg).

The maternal demographic characteristics were similar in both groups (Table 1).

Postdate pregnancy was the commonest indication in both groups, accounting for 71% and 76.4% for 25µg and 50µg groups respectively. (Table 2)

The pre-ripening/pre-induction cervical assessments by the Bishop Score in both groups were comparable (Table 3).

Significantly higher number of patients achieved spontaneous labour in the 50 µg group (96.4%) than 25 µg (84.1%) (P < 0.05).

The mean interval between the first dose and vaginal delivery is shorter in the 50 µg group (754 ± 362 minutes) than in the 25 µg group (885 ± 582 minutes, but this is not statistically significant (P=0.152). There is no significant difference between the number of doses to achieve favorable cervical score ≥ 6 or spontaneous labour between the two groups 1.8 ± 1.1 for 25 µg group and 1.7 ± 0.7 for 50 µg group (P=0.689).

Among the patients who achieved vaginal delivery, all the patients 48(97.9%) in the 50 µg group did so within 24 hours compared to 52 (89.6%) in the 25 µg group (P = 0.063).
No patients in the either arm of the study received the maximum dose of the drug. The need for augmentation among those who developed spontaneous labour was higher in the 25 µg group than (39.7%) than the 50 µg group (16.4%) \( P = 0.007 \). (Table 4.)

The incidence of caesarean section was similar in the two groups 8.0% and 11.0% for 25 µg group and 50 µg group respectively, more patients had caesarean section for poor progress of labour in the 25 µg group than in the 50 µg group while more patients had caesarean section on account of fetal distress in the 50 µg group but none of these difference assumed statistical significance \( P=0.682 \).

The overall rate of successful vaginal delivery and the rate of caesarean delivery were similar between the two groups (Table 4).

The birth weights of the neonates were similar in the two groups 3143 ± 475gm in 25 µg group and 3237 ± 486 in 50 µg group \( P=0.291 \). The Apgar score of the babies at one minute and five minutes were similar (Table 5).

The overall fetal outcomes were similar in the two groups.

Adverse labour outcomes were mainly tachystole (defined as the occurrence of more than five contractions in ten minutes for two consecutive ten minutes period), precipitate labour (delivery less than three hours after onset of labour), fetal distress and meconium stained liquor. All these were significantly higher in the 50 µg group \( P=0.038 \) (Table 5).
Table 1: Demographic characteristics of the study groups

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<tr>
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<th>25 µg (n=63)</th>
<th>50 µg (n=55)</th>
<th>Significance</th>
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<tr>
<td>Age (Years) (Mean + SD)</td>
<td>30.8 ± 3.4</td>
<td>30.2 ± 5.5</td>
<td>P &gt; 0.05* (NS) (0.4)</td>
</tr>
<tr>
<td>Gestational Age (Weeks)</td>
<td>40.3 ± 1.5</td>
<td>40.7 ± 1.3</td>
<td>P &gt; 0.05* (NS) (0.22)</td>
</tr>
<tr>
<td>Parity Mean</td>
<td>2.3 ± 1.6</td>
<td>2.8 ± 1.5</td>
<td>P &gt; 0.05* (NS) (0.10)</td>
</tr>
</tbody>
</table>

Data presented as mean ± SD.

NS: Not Significant

* Student t test
Table 2: Indications for induction of Labour

<table>
<thead>
<tr>
<th>Indication</th>
<th>25 µg (n=63)</th>
<th>50 µg (n=55)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postdate Pregnancy</td>
<td>45 (71.4%)</td>
<td>42 (76.4%)</td>
<td>P &gt; 0.05</td>
</tr>
<tr>
<td>Pre-eclampsia</td>
<td>6 (9.5%)</td>
<td>4 (7.3%)</td>
<td>(0.195)</td>
</tr>
<tr>
<td>Gestational Diabetes Mellitus</td>
<td>5 (7.5%)</td>
<td>3 (5.5%)</td>
<td></td>
</tr>
<tr>
<td>Intrauterine growth Restriction</td>
<td>4 (6.3%)</td>
<td>3 (5.5%)</td>
<td></td>
</tr>
<tr>
<td>Poor Obstetric history</td>
<td>2 (3.2%)</td>
<td>1 (1.8%)</td>
<td></td>
</tr>
<tr>
<td>Oligohydramnous</td>
<td>1 (1.6%)</td>
<td>2 (3.6%)</td>
<td></td>
</tr>
</tbody>
</table>

Table 3: Cervical Assessment by Bishops Score

<table>
<thead>
<tr>
<th>Bishop Score</th>
<th>25 µg (n=63)</th>
<th>50 µg (n=55)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-Ripening/Induction Score</td>
<td></td>
<td></td>
<td>***</td>
</tr>
<tr>
<td>1</td>
<td>3 (4.7%)</td>
<td>2 (3.6%)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>6 (9.5%)</td>
<td>4 (7.2%)</td>
<td>P &gt; 0.05</td>
</tr>
<tr>
<td>3</td>
<td>21 (33.3%)</td>
<td>19 (34.5%)</td>
<td>(0.67)</td>
</tr>
<tr>
<td>4</td>
<td>22 (34.9%)</td>
<td>21 (38.2%)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>10 (15.9%)</td>
<td>9 (16.4%)</td>
<td></td>
</tr>
<tr>
<td>Mean Group Bishop Score</td>
<td>3.8 ± 1.1</td>
<td>3.4 ± 1.0</td>
<td></td>
</tr>
</tbody>
</table>

Data Presented as n (%) or Mean ± SD

*** Mann-Whitney U - test
Table 4: Labour Outcome

<table>
<thead>
<tr>
<th></th>
<th>25 µg (n=63)</th>
<th>50 µg (n=55)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset of spontaneous Labour During Ripening</td>
<td>53 (84.1%)</td>
<td>52 (96.4%)</td>
<td>P &lt; 0.05* (0.049)</td>
</tr>
<tr>
<td>Need for Augmentation</td>
<td>25 (39.7%)</td>
<td>9 (16.4%)</td>
<td>P &lt; 0.05* (0.007)</td>
</tr>
<tr>
<td>Mode of Delivery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaginal Delivery</td>
<td>58 (92%)</td>
<td>49 (89.0%)</td>
<td>P &gt; 0.05* (0.580)</td>
</tr>
<tr>
<td>Caesarean Section</td>
<td>5 (8.0%)</td>
<td>6 (11.0%)</td>
<td></td>
</tr>
<tr>
<td>Indications for caesarean Section</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poor – Progress</td>
<td>3 (4.7%)</td>
<td>2 (3.6%)</td>
<td>P &gt; 0.05** (0.682)</td>
</tr>
<tr>
<td>Fetal Distress</td>
<td>2 (3.2%)</td>
<td>4 (7.2%)</td>
<td></td>
</tr>
<tr>
<td>Mean Interval between first Insertion and Delivery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 12 Hrs</td>
<td>35 (60.3%)</td>
<td>30 (61.2%)</td>
<td>P &gt;0.05* (0.063)</td>
</tr>
<tr>
<td>12 – 24hrs</td>
<td>17 (29.3%)</td>
<td>18 (36.7%)</td>
<td></td>
</tr>
<tr>
<td>&gt; 24 hrs</td>
<td>6 (10.4%)</td>
<td>1 (2.0%)</td>
<td></td>
</tr>
<tr>
<td>Mean insertion-delivery interval</td>
<td>885 ± 582</td>
<td>754 ± 362</td>
<td>P&gt; 0.05*** (0.152)</td>
</tr>
<tr>
<td>Mean (minutes)</td>
<td>14.7 ± 9.7</td>
<td>12.6 ±6.1</td>
<td></td>
</tr>
<tr>
<td>Mean (hours)</td>
<td>1.8 ± 1.1</td>
<td>1.7 ±0.7</td>
<td>P &gt; 0.05*** (0.689)</td>
</tr>
</tbody>
</table>

* Chi square – test
** Fisher’s Exact test
*** Student’s t-test
Table 5: Adverse Labour Outcome

<table>
<thead>
<tr>
<th>Adverse Effect</th>
<th>25 µg (n=63)</th>
<th>50 µg (n=55)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>54 (85.7%)</td>
<td>35 (63.6%)</td>
<td>P &lt; 0.05</td>
</tr>
<tr>
<td>Tachystole</td>
<td>0 (0.0%)</td>
<td>2 (3.6%)</td>
<td>(0.038)</td>
</tr>
<tr>
<td>Precipitate Labour</td>
<td>3 (4.8%)</td>
<td>4 (7.2%)</td>
<td></td>
</tr>
<tr>
<td>Fetal Distress</td>
<td>4 (6.4%)</td>
<td>9 (16.4%)</td>
<td></td>
</tr>
<tr>
<td>Meconium staining of liquor</td>
<td>0 (0.0%)</td>
<td>5 (9.1%)</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>2 (23.2%)</td>
<td>0 (0.0%)</td>
<td></td>
</tr>
</tbody>
</table>

*** $X^2$, Fisher’s exact Test
**Table 6: Neonatal Outcome**

<table>
<thead>
<tr>
<th>Neonatal Outcome</th>
<th>25 µg (n=63)</th>
<th>50 µg (n=55)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth Weight (gm)</td>
<td>3143.2 ± 475.4</td>
<td>3237.3 ± 486.5</td>
<td>P &gt; 0.05 * (0.291)</td>
</tr>
<tr>
<td>Apgar Score &lt;7</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 minute</td>
<td>6 (9.5%)</td>
<td>9 (16.42)</td>
<td>P &gt; 0.05** (0.321)</td>
</tr>
<tr>
<td>5 minutes</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Admission to SCBU</td>
<td>8 (12.7%)</td>
<td>9 (14.3%)</td>
<td>P &gt; 0.05 ** (0.68)</td>
</tr>
</tbody>
</table>

Data Presented as mean ± SD, n (%)  
* Student t-test  
** Chi square test
DISCUSSION

The baseline characteristics were similar in the two groups. There were no differences between indications for induction of labour, with postdate pregnancy constituting the commonest indication, this has been reported by previous studies.\textsuperscript{8,11,39} The pre-ripening/induction Bishop scores were also similar.

The results of the study demonstrate that both 25µg and 50 µg dose regimens are effective in cervical ripening/induction of labour with both groups requiring similar number doses of the drug (1.8 ± 1.1 vs. 1.7 ± 0.7). However, more patients in the 50 µg arm achieved vaginal delivery within 24 hours (97.9% vs. 89.6%). More patients also developed spontaneous labour with less need for oxytocin augmentation of labour, but the overall induction delivery interval was similar between the groups, these are similar to the results of previous studies\textsuperscript{11,13,40,41} in which more patients reportedly achieved vaginal delivery within 24 hours.\textsuperscript{42} All these findings have been adduced to the more potent effect of the higher dosage on the uterine cervix.\textsuperscript{6}

There was no significant difference in the route of delivery between the groups though more patients required caesarean section for poor progress of labour in the 25 µg groups, while presumed fetal distress, as indication for caesarean section was more in the 50 µg group. These results have been demonstrated in a previous study.\textsuperscript{43}
The incidence of labour complications such as tachystole (defined as six or more uterine contractions in 10 minutes for 2 consecutive 10 minutes period) and meconium staining of liquor have been associated with the use of misoprostol. This study demonstrates a higher rate in the 50 µg group (3.6% vs. 0.0%). This uterine contraction abnormality have been the contentious issue in the safety profile of misoprostol for cervical ripening and induction of labour. Incidence rate of between 7.1% and 36.7% have been previously reported with different doses and dosing interval of misoprostol. A lower incidence of 3.6% in this study may be due to strict protocol criteria of 6 hours dosing interval and not commencing oxytocin augmentation when necessary, earlier than at least 4 hours after the last dose of misoprostol.

However despite the significant uterine contraction anomalies associated with 50 µg dose, the overall neonatal outcomes were similar between the groups with comparable Apgar scores at one and five minutes and similar rate of special care baby unit admissions.

**LIMITATION OF THE STUDY**

The 50 µg and 25 µg misoprostol tablets are presently not available, and the doses had to be prepared from the available 100µg and 200µg tablets with the assistance of the Hospital pharmacy unit. The effect that this may have on the study could not be quantified. Availability of appropriate dosage forms in the future will remove any effect that this might have had on the study.
CONCLUSION

This study confirmed the efficacy of misoprostol for cervical ripening/induction of labour. A 25 µg dose appeared safer than 50 µg although the latter resulted in more deliveries within 24 hours and less need for oxytocin augmentation. The higher rate of uterine contractile abnormalities with 50 µg dose is of particular concerns. More studies are needed to further confirm the result of the study especially in relation to the safety profile of misoprostol for cervical ripening and modalities of Labour.
REFERENCES


18. Jone G and Maxwell D: Cervical ultrasound in pregnancy


30. Chez RA : Cervical Ripening


32. Summers L: Methods of cervical ripening and labour induction


# APPENDIX I

**PROFORMA (DATA COLLECTION FORM)**

**A COMPARISON OF TWO DOSE REGIMENS OF INTRA-VAGINALLY ADMINISTERED MISOPROSTOL FOR PRE-INDUCTION CERVICAL RIpening AND IndUCTION OF LABOUR**

<p>| | | | |</p>
<table>
<thead>
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<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Serial No</td>
<td>Hospital Number:</td>
<td>Date-</td>
<td></td>
</tr>
<tr>
<td>2. Age (Last birthday in year)</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>3. Occupation</td>
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<tr>
<td></td>
<td>House wife</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Unskilled worker</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Semi skilled worker</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>Skilled worker</td>
<td></td>
<td></td>
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<td></td>
<td>Professional</td>
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</tr>
<tr>
<td>4. Religion</td>
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<td>Christianity</td>
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</tr>
<tr>
<td></td>
<td>Islam</td>
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<td></td>
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<tr>
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<td>Others</td>
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<td>5. Educational Status</td>
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<tr>
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<td>Primary/Arabic</td>
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</tr>
<tr>
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<td>Secondary</td>
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<tr>
<td></td>
<td>Teacher Training College</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>Polytechnic/University</td>
<td></td>
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<tr>
<td>6. Marital Status</td>
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<td></td>
<td></td>
</tr>
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<td></td>
<td>Single</td>
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<tr>
<td></td>
<td>Cohabiting</td>
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<td></td>
<td>Married</td>
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<tr>
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<td>Separated</td>
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<tr>
<td></td>
<td>Divorced</td>
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<tr>
<td></td>
<td>Widowed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7. Parity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8. Gestational age at delivery (in weeks)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
(a) L.M.P.______________________________________
(b) E.D.D.______________________________________
(c) Gestational age (using earliest USS) ____________________________
D Gestational age at booking ______________________

9. Indication(s) for planned induction of labour: ____________________________

10. Dose regimen
   (a) 25µg
   (b) 50µg

11. Cervical Bishop Score:

   (a) 1st insertion __________ Time __________ Date __________

   (b) 2nd insertion __________ Time __________ Date __________

   (c) 3rd insertion __________ Time __________ Date __________

   (d) 4th insertion __________ Time __________ Date __________

   (i) Time of onset of uterine contractions __________ Date __________
   (ii) Time of Bishop’s score ≥7 (in absence of contractions) __________ Date __________

13. Time of commencement of induction of labour with oxytocin (in those without uterine contractions.) __________ Date __________

14. Total dose of oxytocin used for induction of labour.

15. Need for augmentation of labour (those with contraction with misoprostol)
   (i) Yes
   (ii) No

16. Time of commencement of augmentation __________________________

17. Total dose of oxytocin used for augmentation of labour: __________

18. Pre-induction fetal heart rate: __________________________

19. Time of delivery: __________________________ Date __________

20. Interval between insertion of first dose of misoprostol and delivery: __________

21. Route of Delivery
   i. Spontaneous vaginal
   ii. Instrumental vaginal
   iii Caesarean

22. If operative delivery from Q.21 above, please state indication:

........................................................................................................................................................................................................................................................................................................
23. Any complication(s) of labour? If any, please tick
   Hyperstimulation
   Precipitate Labour
   Fetal Distress
   Meconium stained liquor during labour
   Meconium aspiration syndrome
   Uterine rupture

24. If yes above (Q.23), Please state Obstetric intervention
   ........................................................................................................................................
   ........................................................................................................................................
   ........................................................................................................................................
   ........................................................................................................................................
   ........................................................................................................................................
   ........................................................................................................................................

25. Apgar scores at birth ......(1-minute) .......(5-minutes)........(10 minutes)

26. Birth weight  ..............................................Kg

27. Baby’s sex  Male .............................. Female: ..............................

28. Was infant admitted to SCBU?  Yes..........  No ...............  

29. Indications(s) for SCBU admission
   ........................................................................................................................................
   ........................................................................................................................................
   ........................................................................................................................................
   ........................................................................................................................................

30. Postpartum Complications (Maternal)
   i.  Postpartum Haemorrhage
   ii. Retained placenta
   iii. Wound Infection
   iv. Puerperal Sepsis
   v.  Anemia
   vi. Postpartum Depression
   vii. Maternal Death
   viii. Others (Please specify)
LABOUR SUMMARY

<table>
<thead>
<tr>
<th></th>
<th>Hour</th>
<th>Minute</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2nd stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3rd stage</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Consent Form

I,…………………………………………………………………………………………………………………………have been fully informed about the protocol for the study titled A COMPARISON OF TWO DOSE REGIMENS OF INTRA-VAGINALLY ADMINISTERED MISOPROSTOL FOR PRE-INDUCTION CERVICAL RIPENING AND INDUCTION OF LABOUR

I understand the study is towards comparing the effectiveness of two dose regimens of Misoprostol for pre-induction cervical ripening (softening of the cervix).

I have also been informed that agents of the study-Misoprostol (Cytotec) – is at present not registered for the indication and has been associated with possible risks of uterine hyperstimulation(excessive uterine contractions), fetal distress and uterine rupture, especially when oxytocin induction is commenced sooner than after four hours of the last dose of Misoprostol, but that efforts would be made to minimize these risks.

That I will suffer no consequence if I refuse to volunteer for this study and that I retain the right to decline further participation at any stage of the study.

I hereby voluntarily consent to be a participant in this study.

Patient’s Signature:___________________________
Date:________________________________________
Witness:________________________________________
Date:________________________________________
Address of Institution Review Board: Room 210 IMRAT, College of Medicine, University of Ibadan.
Address of the Principal Investigator: Department of Obstetrics and Gynaecology
University College Hospital, Ibadan.
Phone Number: 08037141492
**BISHOP SCORING SYSTEM (1964)**

**FACTORS**

<table>
<thead>
<tr>
<th>SCORE</th>
<th>DILATATION (cm)</th>
<th>EFFACEMENT (%)</th>
<th>STATION OF PRESENTING PART</th>
<th>CERVICAL CONSISTENCY</th>
<th>CERVICAL POSITION</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Closed</td>
<td>0-30</td>
<td>-3</td>
<td>Firm</td>
<td>Posterior</td>
</tr>
<tr>
<td>1</td>
<td>1-2</td>
<td>40-50</td>
<td>-2</td>
<td>Medium</td>
<td>Middle</td>
</tr>
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<td>2</td>
<td>3-4</td>
<td>60-70</td>
<td>-1, 0</td>
<td>Soft</td>
<td>Anterior</td>
</tr>
<tr>
<td>3</td>
<td>≥5</td>
<td>≥80</td>
<td>+1, +2</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
## EFFICACY OF MISOPROSTOL FOR RIPENING AND INDUCTION OF LABOUR

<table>
<thead>
<tr>
<th></th>
<th>25μg</th>
<th>50 μg</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean interval between 1st dose and onset of contractions‡</td>
<td>381.0 ± 105 minutes (6.4 hours)</td>
<td>286 ± 160 minutes (5.0 hours)</td>
<td>0.450** (NS)</td>
</tr>
<tr>
<td>Minimum interval between 1st dose and onset of contractions</td>
<td>25 minutes</td>
<td>15 minutes</td>
<td></td>
</tr>
<tr>
<td>Duration of cervical ripening‡</td>
<td>830 ± 639 minutes (13.8 Hours)</td>
<td>805± 0.00 minutes (13.4 Hours)</td>
<td>0.904*** (NS)</td>
</tr>
<tr>
<td>Mean pre-induction Bishop score†</td>
<td>7.0 ± 1.1</td>
<td>7.2 ± 1.0</td>
<td>0.125** (NS)</td>
</tr>
<tr>
<td>Vaginal delivery within 24 Hours of 1st dose</td>
<td>52 (89.6%)</td>
<td>48 (97.9 %)</td>
<td>0.16*** (NS)</td>
</tr>
<tr>
<td>No patients requiring one dose</td>
<td>30 (47%)</td>
<td>29 (53%)</td>
<td>0.74 (NS)</td>
</tr>
<tr>
<td>Duration of first stage of labour</td>
<td>482.2 ± 271 minutes (8.1 Hours)</td>
<td>452.2 ± 278 minutes (7.5 Hours)</td>
<td>0.43 (NS)</td>
</tr>
<tr>
<td>Duration of second stage of labour</td>
<td>15.23 ±1.0 minutes</td>
<td>10.0 ± 0.9 minutes</td>
<td>0.19 (NS)</td>
</tr>
<tr>
<td>Duration of third stage of labour</td>
<td>5.96 ± 3.2 minutes</td>
<td>5.08 ± 0.41 minutes</td>
<td>0.000 (S)</td>
</tr>
</tbody>
</table>

Data presented as mean ± Std. deviation and number and percent. NS = Not significant, S = Significant.  
** Student t test  
*** Chi- square test  
‡ Patients with spontaneous uterine contractions.  
† Patients who developed spontaneous labour were excluded.