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# A Comparison of 25 µg with 50 µg Misoprostol for Cervical Ripening and Induction of Labor

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## Abstract

**Background:** Misoprostol is increasingly being accepted as a standard agent for cervical ripening and induction of labor. The lowest effective dose is still not known.

**Materials and Methods:** This was an open label clinical trial of one hundred and eighty four women with obstetrics or medical indications for induction of labor at University of Abuja Teaching Hospital, Abuja. Women were grouped to receive either 25 µg or 50 µg of intravaginal misoprostol. The main outcome measure was induction-vaginal delivery interval while the secondary outcome measures were requirements for oxytocin augmentation, mode of delivery, frequency of tachsystole/hyperstimulation, as well as feto-maternal outcomes. Data was analyzed using SPSS version 21.0. Chi-square test was used to compare categorical variables. Mann-Whitney test was used to analyze continuous variables of the two treatment groups. P-value of less than 0.05 was accepted as indicating statistical significance.

**Results:** Mean induction delivery interval was 13.8 ± 5.9 and 14.0 ± 5.7 hours (P=0.842) with the 25 µg and 50 µg misoprostol respectively. The delivery rate within 24 hours of 66.3% (61/92,) in 25 µg group was lower than 67.4% (62/92) recorded in the 50 µg group but the difference was not statistically significant (P=0.156). The rates of caesarean section and operative vaginal delivery were similar in both groups. There were no significant difference in maternal side effects and neonatal outcomes among the women in the two groups.

**Conclusion:** There were no statistically significant differences in the effectiveness and safety of either of the dose regimen over the other. The choice may therefore be guided by the physician's experience, availability and/or departmental protocol.

**Keywords:** Misoprostol; Labor; Pregnancy; Delivery; Cervical ripening

## Introduction

Situations arise in obstetrics where it becomes necessary to end a pregnancy in the interest of the mother and/or baby. Thus, induction of labor (IOL) has merit as a therapeutic option when the benefit of expeditious delivery outweighs the risks of continuing the pregnancy. The benefits of cervical ripening and induction of labor therefore must be weighed against the potential maternal and fetal risks associated with this procedure [1-3]. Induction of labor usually involves not a single intervention but a complex set of interventions with a tendency of posing challenges for both the obstetrician and mother [4,5].

The search for an ideal agent, timing and dosage interval to convert an unfavorable cervix to one receptive to delivery is an ongoing process [6]. The ideal induction agent would be one that is efficient, cost effective, easy to store, non-invasive, without side effects, and whose effects on mother and fetus can be readily monitored [7].

The well documented effectiveness of misoprostol in several gynecological and obstetric applications has resulted in enthusiasm for its use. The purpose of induction of labor is to achieve vaginal delivery by stimulating uterine contractions before the spontaneous onset of labor. However, it does appears challenging to a obstetricians when the cervix is not favorable [8,9]. There is paucity of data about the use of preformed 25 µg intravaginal misoprostol for cervical ripening and labor induction in West African Sub-region especially in Nigeria.

With the availability of the 25 µg preparation, it may become objectively feasible to compare the effectiveness and efficacy of the 25 µg with 50 µg in cervical ripening and induction of labor. This study was designed to compare the efficacy and safety of 25 µg and 50 µg intravaginal misoprostol tablets for cervical ripening and induction of labor when administered at an interval of 6 hours.

## Materials and Methods

This was a clinical trial of one hundred and eighty four women with obstetrics or medical indications for induction of labor at University of Abuja Teaching Hospital, Abuja. Women were randomized to receive either 25 µg or 50 µg of intravaginal misoprostol. The study population comprised of all eligible pregnant women admitted for induction of labour at term with unfavorable cervix during the study period.

Included were all pregnant women who had given consent and with; singleton cephalic presenting pregnancy at term with no contraindication for vaginal delivery. Other inclusion criteria were pre-

requisite reactive Cardiotocograph (CTG) and, intact membrane with unfavorable cervix for induction (Bishop's score of ≤ 5).

Patients who refused consent to participate were excluded alongside those with singleton fetus with weight greater or equal to 4 kg and multiple gestation. Other exclusion criteria were patient with ruptured membrane, unsatisfactory CTG and contraindication to vaginal delivery.

Enrolled patients were randomly allocated to one of the two therapeutic regimens of 25 µg or 50 µg misoprostol tablets. Randomization was performed using computer-generated list by means of sequentially numbered, opaque, sealed envelopes indicating their medication. One group of patients received 25 µg misoprostol and the other group 50 µg misoprostol (two 25 µg misoprostol).

The sample size on each arm of the dosing regimen was calculated using the formula [10]:

Sample size, N=2M

M=required minimum sample size for each study arm

$M=(Z\alpha+Z\beta)^2\{H0(1-H0)+H1(1-H1)\}/(H1-H0)^2$

Where; Zα=percentage of normal distribution corresponding to the required significant level of 5%

=1.96

Zβ=point of normal distribution corresponding to the statistical power of 90%

=1.28

H0=Response in the first group (From previous study)39=0.97

H1=Expected response in the second group=0.82

Thus $N=(1.96+1.28)^2\{0.97(1-0.97)+0.82(1-0.82)\}/(0.97-0.82)^2$

N=82.4

Therefore, the minimum sample size in each group was 83.

Adding 10% attrition rate to the value obtained above, each trial group was allocated 92 patients. The total sample size was 184 pregnant women for both arms.

Data were analyzed using Statistical Package for Social Science (SPSS version 21) categorical variables using Chi square test. P-value of less than 0.05 was accepted as indicating statistical significance. Comparison of means was done using a Student's t-test. Mann-Whitney U test and Fisher's exact test was also employed as found appropriate. The ethical clearance was obtained from the Research Ethics Committee of the University of Abuja Teaching Hospital and signed consent for participation was obtained for all the patients.

## Results

A total of 1318 deliveries were recorded during the period of study and out of which 189 were assessed for eligibility. One hundred and eighty four met inclusion criteria and were enrolled into the study. Five women did not meet the inclusion criteria and were excluded. There were neither opt out cases nor incidence of protocol violations. All 184 enrolled were available for final analysis. Patient population was divided into two groups; group A received 25 µg misoprostol per vaginally and group B received 50 µg. Thus, the rate of cervical ripening and induction of labor was 14.3%.

Table 1 shows maternal demographic profile of the women included in the study. Both groups were comparable with respect to maternal age, parity, mean gestational age at the time of induction and Bishop's score at commencement of cervical ripening and labor induction. The mean age of patients in the 25 µg group was 29.28 ± 4.71, while the mean age in the 50 µ 29.39 ± 4.00, P=0.85; Nulliparity (47.8% *vs.* 45.7%, P=0.09) and multiparity (52.2% *vs.* 54.3%) respectively for 25 µg and 50 µg were not statistically different. The mean gestational age (40.30 ± 1.92 *vs.* 39.54 ± 4.50, P=0.14); and initial Bishop's scores (3.84 ± 0.97 *vs.* 3.88 ± 1.06, P=0.37) were similar respectively for 25 µg and 50 µg groups.

| Characteristic | 25 µg Misoprostol | 50 µg Misoprostol | P-value |
|---|---|---|---|
| | n=92 (%) | | |
| Age[a] (Years) (Mean ± SD) | 29.28 ± 4.71 | 29.39 ± 4.00 | 0.85 |
| Parity[b] | | | |
| Nulliparous | 44 (47.8) | 42 (45.7) | 0.09 |
| Multiparous | 48 (52.2) | 50 (54.3) | - |
| Gestational age (Weeks) (Mean ± SD)[c] | 40.30 ± 1.92 | 39.54 ± 4.50 | 0.14 |
| Initial Bishop Score (Mean ± SD)[c] | 3.84 ± 0.97 | 3.88 ± 1.06 | 0.37 |

**Table 1:** Maternal characteristics of the study groups [[a]Mann-Whitney U test; [b]Chi square; [c]Student's t-test].

The indications for cervical ripening and induction of labor were similarly distributed in both groups. Postdate is the single most frequent indication constituting more than 50% in both groups of the study (Table 2).

| Indication for labor induction[b] | 25 µg Misoprostol | 50 µg Misoprostol | P-value |
|---|---|---|---|
| | n=92 (%) | | |
| Post date | 60 (65.1) | 46 (50.0) | 0.28 |
| Hypertensive disorder of pregnancy | 20 (21.8) | 26 (28.2) | 0.43 |
| IUFD | 3 (3.3) | 1 (1.1) | 0.32 |
| IUGR | 1 (1.1) | 3 (3.3) | 0.32 |
| Others | 8 (8.7) | 16 (17.4) | 0.12 |

**Table 2:** Indications for induction [[b]Chi square].

Majority of women in both groups delivered vaginally (86.9% in 25 µg group and 88% in the 50 µg group). The 25 µg misoprostol group had a lower delivery rate with a single dose compared with the 50 µg group (32.6% and 39.1% respectively). However, 25 µg group had more deliveries than 50 µg group with increasing number of misoprostol doses (39.1% *vs.* 34.8%, and 17.4% *vs.* 16.3% for 2 doses and 3 doses respectively). The need for oxytocin augmentation among participants was higher in the 25 µg group (20.4%) than in 50 µg group (17.4%). This was however not statistically significant (P=0.64) (Table 3).

| Variables | 25 µg Misoprostol | 50 µg Misoprostol | P-value |
|---|---|---|---|
| | n=92 (%) | | |
| Number of Misoprostol doses[b] | | | |
| 1 | 30 (32.6) | 36 (39.1) | 0.53 |
| 2 | 36 (39.1) | 32 (34.8) | 0.68 |
| 3 | 16 (17.4) | 15(16.3) | 0.87 |
| 4 | 10 (10.9) | 9(9.8) | 0.83 |
| Induction vaginal delivery interval[a] | 13.8 ± 5.9 | 14.0 ± 5.7 | 0.84 |
| <12 hrs (n,%)[b] | 28 (30.4) | 32 (34.8) | 0.78 |
| 12- < 24 hrs (n,%)[b] | 38 (41.3) | 40 (43.4) | 0.81 |
| ≥ 24 hrs (n,%)[b] | 14 (15.2) | 9 ( 9.8) | 0.32 |
| Oxytocin augmentation[b] | 19 (20.6) | 16 (17.4) | 0.64 |

**Table 3:** Intrapartum variables [[a]Mann-whitney U test; [b]Chi square test].

There was no difference between the two groups with regard to the proportion of patients who had a successful induction. Eighty percent of patients allocated to 25 µg group and 76.1% of those in 50 µg group had spontaneous vaginal delivery while 6.5% and 11.9% of participants had instrumental vaginal delivery in 25 µg and 50 µg respectively (Tables 4 and 5).

| Delivery[b] | 25 µg Misoprostol | 50 µg Misoprostol | P-value |
|---|---|---|---|
| | n=92 (%) | | |
| Spontaneous vaginal delivery | 74 (80.4) | 70 (76.1) | 0.8 |
| Instrumental vaginal delivery | 6 (6.5) | 11 (11.9) | 0.25 |
| Caesarean section | 12 (13.1) | 10 (10.9) | 0.69 |
| Others (Laparotomy)[c] | - | 1 (1.1) | 0.32 |

**Table 4:** Outcome of induction of labor [[b]Chi-square test; [c]Fisher's Exact test].

| Indication | 25 µg Misoprostol | 50 µg Misoprostol | P-value |
|---|---|---|---|
| | n=12 (%) | n=10 (%) | |
| Fetal distress[b] | 7 (7.6) | 5 (5.4) | 0.82 |
| Non progress of labor[c] | 3 (3.3) | 1 (1.1) | 0.32 |
| Others[c] | 2 (2.2) | 4 (4.3) | 0.42 |

**Table 5:** Indications for caesarean delivery [[b]Chi square; [c]Fisher's Exact test].

The incidence of caesarean section was similar in the two groups, twelve women (13.0%) in the 25 µg group and ten women (10.9%) in the 50 µg required emergency caesarean delivery for one reason or the other (P=0.82). No differences were noted in the overall incidence of caesarean section.

As highlighted in Tables 6 and 7, there was no significant difference in the secondary outcomes variable such as neonatal outcomes and intrapartum complications. No significant differences were found in both groups regarding intrapartum stillbirth, Apgar scores of less than 7 at 5 minutes and the number of neonates admitted to the Special Care Baby Unit.

The only recorded still birth in the 50 µg group was a consequence of ruptured uterus. The 50 µg misoprostol group recorded the highest number of cases with abnormal uterine contractions (2.2%) compared with misoprostol 25 µg group (1.1%).

| Outcome | 25 µg Misoprostol | 50 µg Misoprostol | P-value |
|---|---|---|---|
| | n=89 (92-3 IUFD) (%) | n=91 (92-1 IUFD) (%) | |
| Foetal outcome | | | |
| Alive[b] | 89 (96.7) | 90 (97.8) | 0.96 |
| Dead[d] | - | 1 (1.1) | 0.32 |
| Apgar score < 7 | | | |
| At 1 min[b] | 7 (7.6) | 7 (7.6) | 0.97 |
| At 5 min[d] | 5 (5.4) | 2 (2.2) | 0.25 |
| SCBU admission[d] | 5 (5.4) | 3 (3.3) | 0.47 |

**Table 6:** Fetal outcome [[b]Chi square; [d]Fisher's Exact test].

| Complication[d] | 25 µg Misoprostol | 50 µg Misoprostol | P-value |
|---|---|---|---|
| | n=2 (%) | n=7 (%) | |
| Uterine contraction abnormalities | 1 (1.1) | 0.567 | 0.567 |
| Uterine tachysystole | 1 (1.1) | 0.75 | 0.75 |
| Uterine hyperstimulation syndrome | - | 0.32 | 0.32 |
| Ruptured uterus | - | 0.32 | 0.32 |
| Postpartum hemorrhage | - | 2 (2.2) | 0.16 |
| Perineal laceration | - | 2 (2.2) | 0.16 |

**Table 7:** Intrapartum complications [[d]Fisher's Exact test].

With regards to potential adverse effects, no patient in any group had nausea, vomiting, diarrhea and fever in the study population. No case of hypertonus was recorded. Fetal distress requiring surgical intervention occurred in 12 patients. In each of these patients, management was initially conservative using nasal oxygen, adequate hydration and nursing on the left side. Caesarean sections were done when these measures failed to correct the adverse fetal cardiac activity. Uterine abnormalities were observed in both regimens; one case each while a case of uterine tachysystole was seen in 50 µg group. However, the observations were not significant statistically (P=0.57).

One multigravida in the 50 µg group had uterine rupture accounting for 0.54% of patients in the whole study. It was later discovered that she had a previous termination of pregnancy that was associated with complications. Two women in the 50 µg group developed postpartum hemorrhage compared to none in the 25 µg group (P=0.16). No maternal death was recorded in the study. All results tended to be more favorable in 25 µg group, but did not reach statistical significance.

## Discussion

Misoprostol is increasingly being used for cervical ripening and induction of labour more than ever before. This was also observed in this study where there was an increase in rate from 13% recorded previously to 14.3% in the same institution [11]. The explanation for this could be attributed mainly to a rise in patients acceptability of induction of labour with misoprostol compared to 'painful' oxytocin. It is also lower to that of more developed nations like UK, United States and Canada. (18% UK, 20% US and 19% Canada) [12].

The women in the study were homogenous in terms of age, gestational age and parity in both groups. The most common indication for cervical ripening and induction of labour was postdate, accounting for 57.6%, followed by preeclampsia, accounting for 13.0%. This is similar to that obtained in a prospective study of labour induction [5] The same commonest indication was recorded in Korle Bu, Ghana [7], however, the second indication was sickle cell disease as against preeclampsia in Nigeria. These trends may be due to the fact that there are more postdated pregnancy now than before, probably due to better dating of gestational age and earlier booking.

The results of this study indicate that 25 µg of intravaginal misoprostol every 6 hours was as efficacious as 50 µg for cervical ripening and labor induction. There was no statistical significant difference between the two misoprostol regimens in terms of clinical efficacy. Although the study found that induction delivery interval was similar among the two groups, other investigators [13-18] had demonstrated that it was shorter in the 50 µg group. In a meta-analysis comparing 25 µg with 50 µg misoprostol, the induction vaginal delivery interval was nearly five hours shorter in the 50 µg group [19]. This difference as against meta-analysis may be due to small sample size and non-blinding of the study.

The proportion of women delivering within the first twelve hours and next twelve hours of induction were similar among the groups, which is consistent with the finding by other investigators [14,17]. This is contrast to the finding of Meydanli et al. [19] and Elhassan et al. [17] Meydanli reported that more women delivered between 12-24 hours in the 25 µg group while El-hassan reported that fewer delivered vaginally in the 25 µg group. The explanation for the differences may be in the methodology. Both researchers used compounded misoprostol prepared by different methods.

There was no difference in the overall caesarean section delivery rates unlike increase in caesarean section rate in the 50 µg group reported by Has et al. [14] Elhassan et al. [17] showed an increase in caesarean section rate in 25 µg group. In this study, there was no significant difference in occurrence of uterine contraction abnormalities among regimens, although some researchers have demonstrated an increase incidence of uterine contraction abnormalities in the 50 µg groups [13-15]. The higher incidence of hyper stimulation in Diro et al. [13] study is possibly due to higher dose of misoprostol received by most women. Although not statistically significant, the incidence of haemorrhage due to perinear laceration was more in the 50 µg group in this study. However, both El-hassan and El-sherbiny et al. [15] reported significantly increased incidence of atonic postpartum hemorrhage in 50 µg group.

Even though higher dose misoprostol (50 µg) enhance cervical ripening and labor during induction in a more efficient way than lower dose (25 µg), concern persist with respect to intrapartum fetal wellbeing. The price for using a higher misoprostol dosage to achieve higher delivery rate is increased risk of hyper stimulation syndrome, abnormal fetal heart rate, meconium staining liquor and perinatal mortality and morbidity from asphyxia. In this study, though not statistically significant, the 50 µg misoprostol group accounted for a high number of cases with abnormal uterine contraction (1.1% *vs.* 2.2%, Fisher exact test=0.375). However, the caesarean section for suspected fetal distress was not significant for both groups (7.6% *vs.* 5.4%, P=0.821). This may be due to early detection of abnormal fetal heart rate and early corrections.

The concern about safety of misoprostol is not limited to the fetus alone but extends to the mother. There was a case of uterine rupture in the 50 µg misoprostol group. Statistical analysis comparing this effect showed no significant difference. Even though the use of misoprostol for cervical ripening and induction of labor has been associated with uterine rupture, most reviews found no difference with other conventional methods.

Attempting an explanation for the aforementioned side effects in misoprostol use and taken into account other reports, it appears that the increase in clinically relevant adverse effects may be dose dependent rather than misoprostol related. The relationship between previous uterine evacuation and posterior uterine ruptured has previously been documented [20-22] as in this study. However, it is not strong evidence to exclude such patients from misoprostol use.

## Conclusion

It appears that 25 µg of intravaginal misoprostol is as safe as 50 µg for cervical ripening and induction of labor. The choice may therefore be guided by the physician's experiences, availability and/or departmental protocol. It may also appeared safe to suggest that WHO recommendation on the use of low dose 25 µg misoprostol be applicable to our pregnant population provided strict selection criteria are upheld.

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