

A comparison of oral versus vaginal misoprostol for induction of labor at term, at the Ahmadu Bello University Teaching Hospital, Zaria

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ABSTRACT

Background: The comparison of same, equal and low dose of misoprostol by the oral and vaginal routes for induction of labour at term requires further elucidation.

Objective: To compare the efficacy and safety of 25 micrograms (ug) of oral misoprostol with 25ug vaginal misoprostol for induction of labor at term.

Methods: A randomised control trial that involved 169 consented women with indication for induction of labor. A total of 85 women had oral misoprostol while 84 women had vaginal misoprostol. The oral misoprostol dose (25ug) was repeated every 2 hours, while the vaginal dose (25ug) was repeated every 6 hours for a maximum duration of 24 hours or when need arose for intervention. Data was analysed using SPSS version 20.

Results: The mean induction-delivery interval was significantly shorter (18.48 +/- 2.01 vs. 22.82 +/- 2.50, $P = 0.00$), with more vaginal deliveries (88.2% vs. 85.7%, $P = 0.00$) in the oral group compared to the vaginal group respectively. The cardiotocographic abnormalities in the vaginal group were significantly higher than the oral group (8.3% vs. 1.2%, $P = 0.03$). There were more foetal distress and meconium stained liquor in the vaginal group but not statistically significant.

Key words: Efficacy; oral misoprostol; safety; vaginal misoprostol.

Background

Induction of labor is the artificial initiation of labor at a viable gestational age with the aim of achieving a vaginal delivery in a pregnant woman with intact membranes.^[1] In developed countries, induction of labor involves up to 25% of all deliveries at term, while African countries tend to have lower rates between the range of 1.4% and 6.8%.^[2-4] The rate of induction of labor differs from one institution in Nigeria to another with an overall rate of 6.3%.^[2,3] Induction of labor helps in reducing perinatal mortality, maternal complications, and improving maternal outcome.^[5] However,


it can be associated with risks, such as excessive uterine activity, abnormal fetal heart rate (FHR) patterns, and uterine rupture.^[6,7] For successful induction, certain factors, such as parity, gestational age, and cervical status should be considered.^[8] Indications for induction of labor can be maternal such as pregnancy-induced hypertension or fetal such as intrauterine growth restriction.^[3]

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Prostaglandins remain the single most effective means of achieving cervical ripening and induction labor, but they should be avoided in cases of scarred uteri and used with caution in grand multipara.^[3] Misoprostol unlike dinoprostone is stable at room temperature, cheaper, effective, easy to administer, and can be given through several routes (oral, vaginal, sublingual, rectal, and buccal).^[9,10]

In 2011, World Health Organization issued guidelines on induction of labor, which includes the use of oral and vaginal misoprostol for induction of labor and is applicable to all clinical settings.^[3,9] Similarly, the Federal Ministry Of Health in Nigeria had approved the use of misoprostol for induction of labor and issued guidelines regarding its use.^[11]

Oral misoprostol is more effective than intracervical prostaglandins and the current gold standard vaginal dinoprostone in achieving vaginal delivery within 24 h with fewer cesarean sections.^[3,9] For women with ruptured membranes, it exhibits similar efficacy to oxytocin.^[9] The comparison between oral misoprostol and vaginal prostaglandins favored oral misoprostol with reduced risk of caesarean births and without increase in the risks of adverse maternal or perinatal outcome.^[3,9,12] However, dreadful side effects can occur with high dose oral misoprostol, but with low dose the rates were equivalent to both placebo and the current gold standard: vaginal dinoprostone and may be lower compared with vaginal misoprostol.^[3] Also, the few local studies done on induction of labor at term were with only vaginal misoprostol, while the majority of international studies done compared the two routes but with high doses of misoprostol ($\geq 50 \mu\text{g}$), with associated dreadful side effects of uterine hyperstimulation and tachysystole.^[5,7,9-15]

In view of the above evidences that lower dose misoprostol is associated with less dreadful side-effects and the paucity of studies that compared equal and low dose misoprostol via the oral and vaginal route, this study aims to compare the safety and efficacy of 25 μg tablet misoprostol (Vanprazole by Cipla-Evans pharmaceuticals India) administered in equivalent doses via the oral and the vaginal routes.

Methodology

Setting

The study was conducted in the delivery suite of the Obstetrics and Gynaecology department of Ahmadu Bello University Teaching Hospital Zaria (ABUTH), North Western Nigeria from May 2014 to June 2015. This hospital provides antenatal, intrapartum, postnatal, neonatal, pediatric inpatient and outpatient care with emergency obstetric and neonatal

care. Some local cultural practices like early marriage, early pregnancies with high fertility rate are associated with medical conditions like hypertension in pregnancy, which frequently demand interventions like induction of labor.

Study population

The study population were pregnant women of parity less than 5 (para 0 to para 4) admitted into the labor ward with indication for induction of labor at term (38–42 weeks) and who gave a written informed consent.

Study design

The study was a randomized controlled trial. It involved eligible, consented patients who were randomly assigned into oral or vaginal misoprostol group. The allocation was done by sequentially opening numbered and folded forms with already stamped routes of administration based on a computer-generated randomization table. The forms were sealed in opaque envelopes and picked at random from a basket by each patient.

Inclusion criteria

Women with term singleton fetuses, vertex presentation, a specific indication for induction of labor, parity of zero to four, bishop score of zero to five, and cardiotocographic evidence of a reactive fetal cardiac activity.

Exclusion criteria

Women with multiple gestation, malpresentation, nonreactive fetal cardiac activity, previous uterine surgeries, those already in labor, women with medical conditions, such as sickle cell anemia, mitral valve stenosis, glaucoma, and known hypersensitivity to prostaglandins.

Materials and Procedure

A written informed consent was obtained from every participant. Demographic data of the women including age, parity, reason for induction, gestational age, and admitting Bishop Score were recorded. Routine clinical evaluation and laboratory investigations including urinalysis, hematocrit, and at least one pint of compatible blood were obtained. A preliminary cardiotocographic (CTG) was done to assess the fetal condition, while a repeat CTG was done whenever abnormality in the FHR was detected and more frequently in the high-risk patients.

The 25 μg misoprostol (by Pantoprazole Cipla-Evans pharmaceuticals, India) was given to each participant in the oral group to be swallowed every 2 h with 20 ml of Nestle water, under direct observation for a maximum of 24 h (12 doses). The vaginal study group received similar dose of misoprostol

(25 µg) placed in the posterior vaginal fornix every 6 h for a maximum of 24 h (four doses). However, the next dose of misoprostol was withheld and the process terminated if the parturient transits into active phase of labor or when untoward observation was made requiring intervention, such as fetal distress, vaginal bleeding, or uterine hyperstimulation (a contraction lasting at least 2–3 min or more than five contractions per 10 min lasting greater than 45 s).

The interval from the last dose of misoprostol was at least 6 h before labor augmentation with oxytocin was considered, whenever it was adjudged necessary.^[16] Induction of labor was declared failed when active labor was not established after 24 h or the process abandoned (prior to onset of active labor) due to maternal or fetal complication. The woman was then given option for induction of labor after resting and further evaluations or an alternative mode of delivery based on the prevailing obstetric and clinical conditions. For women who proceeded into active phase of labor, partographs were opened and duly completed as their labor progressed.

Each parturient was monitored for uterine hyperstimulation, nausea, vomiting, diarrhea, fever, need for analgesia, genital tract lacerations, primary postpartum hemorrhages, need for intensive care admission, and fetal complications like cardiotocographic changes, meconium stained liquor, fetal distress, fetal demise, still birth, birth asphyxia, and need for admission into the special care baby unit (SCBU).

The efficacy outcomes of the induction were recorded as induction – delivery interval unchanged cervix after 24 h, need for oxytocin augmentation, vaginal delivery not achieved within 24 h, operative vaginal deliveries, caesarean section rates, cumulative doses of misoprostol needed, and duration of latent phase of labor and retained placentae.

Besides standard management of patient in labor, uterine contractions, pulse, and FHR were recorded hourly in latent phase and 1/4 hourly in the active phase of labor. CTG was repeated whenever abnormal FHR (<120 or >160 bpm) was observed with the sonicaid and more frequently in the high-risk pregnancies (such as bad outcome in previous pregnancy and gestational diabetes) and in those with evidence of fetal distress. The partograph was opened for each parturient as soon as they commenced active phase of labor and ensuing first, second, third, and fourth stages of labor were managed according to the departmental and national labor management protocols.

Sample size

The minimum sample size was determined by using the proportion outcome formula for a two-sided test of 5%:

$$m = c \times \frac{\pi_1(1-\pi_1) + \pi_2(1-\pi_2)}{(\pi_1 - \pi_2)^2}$$

Where

m = Size per group

c = 7.9 for 80% power

The proportion estimates were taken as:

$\pi_1 = 0.82$ and $\pi_2 = 0.62$, when the proportion of women that achieved a vaginal delivery on induction with vaginal misoprostol from previous Zaria study was taken as 82% (28/34) at a power of 80% to obtain a proportion difference of 20% (i.e., 62%) between the two groups given a statistical significance of 0.05.^[14]

Thus, m (size per group) = 7.9 X

$$\frac{\{0.82(1-0.82) + 0.62(1-0.62)\}}{(0.82 - 0.62)^2} = 75.68$$

Size per the two groups = $76 \times 2 = 152$

The minimum of 167 subjects was needed, when an attrition rate of 10% was added to the calculated sample size. Thus, a total of 170 subjects were randomized.

Data analysis

Data was analyzed using Statistical Packages for Social Science (SPSS) version 20 software. The mean induction delivery interval and other efficacy outcomes were compared using the student t-test. Complications of misoprostol due to different routes of administration were analyzed by their percentages and compared by Fisher's test of proportions. A P value of < 0.05 was considered statistically significant.

Ethical consideration

Approval for this study was obtained from the Ethical Committee of Ahmadu Bello University Teaching Hospital Shika, Zaria.

Funding

All the expenses incurred in carrying out this study were borne by the researcher.

Results

A total of 1,383 deliveries were conducted during the study period. Among the 192 women slated for induction of labor, 170 were eligible at the point of entry into the study. However, one woman defaulted after allocation into the vaginal group, leaving 169 to receive treatment (an attrition

rate of less than 1%). A total of 85 pregnant women had 25 µg oral misoprostol and 84 had 25 µg vaginal misoprostol. The induction rate using misoprostol was 12.22% [Figure 1].

The gestational age, bishop score, and parity of the pregnant women were within the same mean and standard deviation of the mean for both groups. These parameters were restricted by the study design (gestational age: 38–42 weeks, Bishop score: 0–5, and parity: 0–4). The mean Bishop score was not significantly different for both groups: 2.93 and 2.90 in the oral and vaginal groups, respectively [Table 1].

The commonest indication for induction of labor was prolonged pregnancy (83.5% and 78.5%) in both the oral and vaginal groups, respectively. The second commonest indication for induction of labor for both routes was pregnancy-induced hypertension (15.3% vs. 17.9%).

The mean duration of labor was not significantly different for both routes (9.80 ± 1.06 vs. 10.45 ± 1.14 , $P = 0.18$) for the oral and vaginal routes, respectively. The mean induction - delivery interval was significantly shorter in the oral group compared to the vaginal group (18.48 ± 2.01 vs. 22.82 ± 2.50 , $P < 0.001$). The need for oxytocin augmentation was nearly the same for both groups. More doses of misoprostol were required to achieve delivery in the oral group than the vaginal (4.66 ± 0.51 vs. 2.62 ± 0.29 , $P = 0.00$), respectively [Table 2].

The number of women who delivered by spontaneous vaginal delivery was significantly higher in the oral group compared to the vaginal group (relative risk, RR = 1.20; 95% confidence interval, CI: 0.97–1.49, $P = 0.00$). On the contrary, the cesarean section rate was significantly higher in the vaginal group when compared to the oral route. The main indication for caesarean section was fetal distress, but was not statistically significant between the two groups. The percentage of failed induction of labor was not significantly different in both groups [Table 3].

There was a significant difference in the cardiotocographic (CTG) changes (three variable decelerations, two early decelerations, one late deceleration, and one sinusoidal tracing in the vaginal group against one variable deceleration in the oral group (RR = 0.14; 95% CI: 0.02–1.12 $P = 0.03$). More meconium stained liquor, fetal distress, and SCBU admissions were in the vaginal group.

The major indication for the neonatal admissions was birth asphyxia (more from the vaginal group), whereas the other two SCBU admissions were due to neonatal jaundice (from oral group) and risk of neonatal sepsis (from vaginal group).

There was no uterine hyperstimulation, intensive care unit admission, maternal death or still birth in both groups. One woman had primary postpartum hemorrhage from a cervical tear in the vaginal group. Maternal gastrointestinal complications were not significantly different between the two groups. One woman in the oral group had diarrhea as the side effect, whereas another woman in the vaginal group had nausea. The need for analgesia was also not significantly different for both routes [Table 4].

Table 1: The characteristics of the pregnant women who had induction of labor with 25 µg misoprostol by the oral and vaginal routes

Outcome	Oral group (mean±SD)	Vaginal group (mean±SD)	CI (95%)	P
Age	28.86±3.15	28.37±3.11	(25.47-28.76)	0.43
Height	1.64±0.18	1.63±0.18	(1.61-1.66)	0.62
Weight	77.61±8.47	76.76±8.43	(71.65-85.47)	0.74
Parity	2.19±0.24	1.86±0.21	(0.88-2.18)	0.10
Gestational age	39.19±4.28	38.71±4.25	(38.24-41.17)	0.66
Bishop score	2.93±0.32	2.90±0.32	(2.47-3.35)	0.86

Table 2: Comparison of the efficacy of both the oral and vaginal routes of administration of misoprostol

	Oral routes (mean±SD)	Vaginal routes (mean±SD)	P
Duration of labor	9.80±1.06	10.45±1.14	0.18
Induction delivery interval	18.48±2.01	22.82±2.50	0.00
Oxytocin augmentation	1.53±0.18	1.58±0.17	0.77
No. of doses of misoprostol	4.66±0.51	2.62±0.29	0.00

Table 3: Outcome of induction of labor following misoprostol administration by the oral and vaginal routes

Outcome	Oral route, n=85	Vaginal route, n=84	RR (95% CI)	P
Spontaneous vaginal deliveries	75 (88.2)	72 (85.7)	1.20 (0.97-1.49)	0.00
Cesarean section	10 (11.8)	12 (14.3)	1.04 (0.18-1.22)	0.00
Failed induction of labor	9 (10.6)	10 (11.9)	1.10 (0.47-2.57)	0.22

Table 4: Fetal and maternal complications following misoprostol administration by oral and vaginal routes

Parameters	Oral route, n=85	Vaginal route, n=84	RR (95% CI)	P
Meconium stained liquor	1 (1.2)	2 (2.4)	0.49 (0.05-5.35)	0.55
*CTG changes	1 (1.2)	7 (8.3)	0.14 (0.02-1.12)	0.03
Fetal distress	3 (3.5)	8 (9.5)	0.37 (0.10-1.35)	0.11
Apgar score <7 at 5 min	1 (1.2)	2 (2.4)	0.63 (0.05-6.65)	0.16
SCBU admission	2 (2.4)	3 (3.6)	1.84 (0.32-10.47)	0.72
Birth asphyxia	3 (3.5)	5 (6.0)	3.68 (0.40-33.98)	0.22
Need for analgesia	15 (17.6)	15 (17.6)	0.99 (0.52-1.90)	0.97

*CTG=Cardiotocographic changes: 3 variable decelerations, 2 early decelerations, 1 late deceleration, and 1 sinusoidal tracing in the vaginal group, whereas in the oral group only one variable deceleration. SCBU=Special care baby unit

Discussion

Literature has shown that the route of administration of misoprostol has a strong impact on the pharmacokinetic profile that results in different clinical efficacy with bioavailability of the oral misoprostol declining after 2 h and that of vaginal misoprostol detectable after 6 h.^[16] Therefore, this study used the protocol for oral dosing of misoprostol every 2 h and vaginal dosing every 6 h.^[3,16] Kundodyiwa *et al.* in a systematic review that used the same low and equal dose misoprostol (20 µg) via the oral and vaginal route reported significant differences in terms of less uterine hyperstimulation with FHR changes in the oral group but with no significant differences in other outcomes.^[17]

Prolonged pregnancy was the most common indication for induction of labor as similarly reported by Bako *et al.* and Ekele *et al.*^[13,18] However, an earlier Zaria study by Abdul *et al.* reported hypertension in pregnancy as the commonest indication unlike the present study where hypertension in pregnancy was the second commonest indication. This disparity could be explained by the fact that only term pregnancies were used in this study, whereas the modal gestational age of the women with pregnancy-induced hypertension in the previous study was 36 week gestation.^[14]

A shorter induction delivery- interval for the oral route was similarly reported by Kombhampati *et al.*^[19] However, Rasheed *et al.* and Shetty *et al.* reported shorter induction delivery interval for the vaginal route against the oral route.^[20,21] These variations in the induction delivery interval can be explained by the lack of homogeneity in the dosing frequency for the oral route. For example, the same doses of 50 µg were used for both the oral and the vaginal routes by Rasheed *et al.* but their dosing frequency was every 4–6 h, which was too long for the bioavailability of the oral drug of just 2 h.^[20]

Other parameters like Bishop scores, gestational ages, and parity can affect the induction delivery interval if not carefully selected as in this study.^[8] However in this study, these parameters were restricted by the study design (gestational age: 38–42 weeks, Bishop score: 0–5, and parity: 0–4). Similar to the report by Khadija *et al.* the mean gestational age, Bishop score and parity for both routes in this study were comparable with no significant difference.^[22]

The more number of doses of oral misoprostol administered in this study was similar to the findings of Rasheed *et al.*, Khadija *et al.*, and Shetty *et al.*^[22,20] However, differ from that of Hall *et al.* who reported consistency in the number of doses for both routes of administration, which can be explained by the use of a higher oral dose (100 µg) compared to a lower

vaginal dose (25 µg).^[23] The study by Khadija *et al.* showed similar needs for oxytocin augmentation for both routes of misoprostol administration.^[22] However, Shetty *et al.* and Rasheed *et al.* showed more oxytocin requirement for the oral route than the vaginal route.^[20,21] Both Rasheed *et al.* and Shetty *et al.* used a dosing frequency (4 hourly) which could not keep up to the recommended levels in the plasma to maintain contractions and hence the need for additional oxytocin augmentations in order to achieve deliveries. The oral route of misoprostol exhibits less bioavailability and requires more frequent dosing (2 hourly) to maintain the plasma peak volume required to sustain the adequate number of contractions needed.^[16]

The higher success rate in achieving vaginal deliveries in the oral route compared to the vaginal was similarly reported by Kombhampati *et al.*, Ratna *et al.*, and Sultana *et al.*^[24,25] However, caesarean section rate was significantly lower in the oral group compared to the vaginal group which was similar to the report by Kombhampati *et al.*, Ratna *et al.*, and Sultana *et al.*^[19,24,25]

More cesarean sections were done in the vaginal group on account of fetal distress as similarly reported by Kombhampati *et al.*^[19] This can be explained by the greater bioavailability of the vaginal dose of misoprostol.^[16]

Regarding fetal safety outcomes, Kombhampati *et al.* similarly reported more clear liquor in the oral group compared to the vaginal group as in this study, where more meconium stained liquor was seen in the vaginal group.^[19] The meconium stained liquor could be explained by the longer bioavailability of the vaginal route of administration of misoprostol which had been associated with uterine hyperstimulation, fetal distress, and meconium stained liquor.^[16,19] Contrary, the Cochrane review showed more meconium stained liquor in the oral group.^[26] However, meconium staining has been associated with prolonged pregnancy rather than the mode of the induction.^[19]

The significant higher rate of cardiotocographic changes in the vaginal group compared to the oral group was similarly reported by Khadija *et al.*^[22] Similarly, most studies reported increased rate of fetal distress in the vaginal group and uterine hyperstimulation.^[3,21,26] The overall fetal safety outcomes were better with the oral route. Similarly, more safer fetal outcomes with the oral route were reported by Kombhampati *et al.*, Ratna *et al.*, and Khadija *et al.*^[22,19,24] When the safety outcome of induction of labor with misoprostol is been contemplated upon, then the oral route has proved by this research and many others to be the safer option.

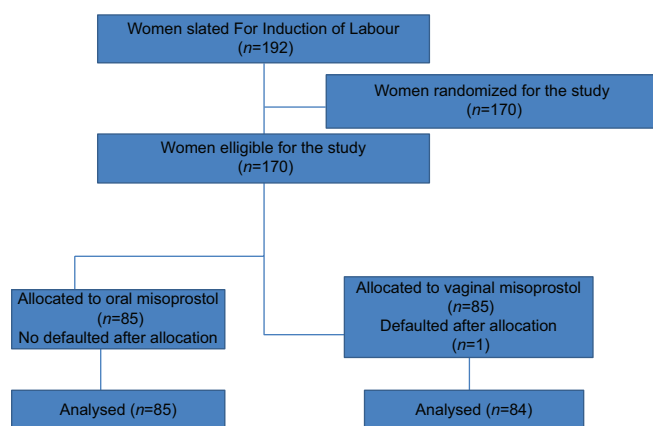


Figure 1: Women flow chart of the study. Excluded ($n = 22$). Women eligible for the study ($n = 170$)

Maternal gastrointestinal side-effects of misoprostol were not common in this study as reported by most studies, where diarrhea is the commonest side effect of the oral route.^[2,3,25,26] This could probably be due to the low dose used ($25 \mu\text{g}$) in this research.

Conclusion

The oral route of administration of misoprostol ($25 \mu\text{g}$) for the induction of labor at term is more effective than the vaginal route, by virtue of the higher rates of vaginal deliveries, lower rate of cesarean section, and shorter induction delivery interval. The oral route is also safer than the vaginal route for fetuses.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Limitations of the study

1. The neonates were not followed-up over a long-term period, in order to detect the rare and remote side effects that maybe related to the misoprostol
2. The method of analgesia used in the process of the induction of labor was intramuscular pentazocine unlike most international studies that used epidural analgesia for pain alleviation during labor induction.

Recommendations

1. The $25 \mu\text{g}$ misoprostol should be added to the essential drug list in our settings, to discourage the breaking of $200 \mu\text{g}$ misoprostol, or dissolving it in water before use

2. The administration of the $25 \mu\text{g}$ oral dose of misoprostol, for induction of labor, can be a better choice in centers where continuous fetal monitoring cannot be ensured
3. The dosing regimen ($25 \mu\text{g}$ every 2 h) for the oral route should be adhered to, rather than a higher oral dose with a longer dosing interval: for example $50 \mu\text{g}$ every 4 h to comply with bioavailability of the oral route.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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