COMPARING VAGINAL AND ORAL ADMINISTRATION OF MISOPROSTOL FOR CERVICAL RIPENING AND INDUCTION OF LABOUR IN PROLONGED PREGNANCIES

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Abstract

***Background*:** Dinoprostone (prostaglandin E2), is presently used as the approved standard protocol for cervical ripening and labour induction. In search for a cheaper alternative, misoprostol (prostaglandin E1) has been found to be a good substitute. The ideal dose, route and frequency of administration of misoprostol are, however, still under investigation. Although, vaginal application of misoprostol has been validated as a reasonable means of induction, there is patient resistance to digital vaginal examination and there is a risk of ascending infection. For these reasons, oral administration of misoprostol for cervical ripening and labour induction has been tried.

***Objective*:** The efficacy and safety of oral and vaginal misoprostol for the elective induction of labour with prolonged pregnancy and unfavourable cervix was compared through a prospective study over a period of one year at the Military Hospital, Accra.

***Methods*:** A prospective, non-blinded randomised study of 148 women with prolonged pregnancy. Data was collected using a prepared structured case record form (data profoma). The study population was randomized into two groups and given 50 µg misoprostol orally in one group and 50 µg vaginally in the other. The main outcomes were measured as induction to delivery time, vaginal delivery achieved within 24 hours and the incidence of uterine hyperstimulation with fetal heart rate (FHR) changes.

***Results*:** The mean induction to delivery interval was shorter in vaginal group than oral group but the differences did not reach statistical significance (12.9hrs vs 14.3hrs; mean difference -1.42, *P* value = 0.24). The shorter duration of vaginal misoprostol, however, was significant for nulliparous women (13.4hrs vs 17.9hrs; mean difference 4.53, p<0.05). There was less failure to achieve vaginal delivery within 24 hours of induction in the vaginal route group, but the differences did not reach statistical significance (6.1% vs. 6.8%; p = 0.81). Fewer women needed oxytocin augmentation in the vaginal group (24.2% vs.17.4%, p = 0.11). There was a higher incidence of uterine hyperstimulation in the vaginal group but not significant (14.7% vs 6.1%, p = 0.10). APGAR scores at 5 minutes showed no difference between the two groups (1.49% vs. 2.99%, p =0.42).

***Conclusions*:** Compared with oral misoprostol, vaginal misoprostol for induction of labour at term resulted in a shorter induction-to-delivery time and a lesser need of oxytocin for women to deliver within 24 hours of induction. Both maternal and neonatal safety outcome were comparable in both groups. However, the more frequent occurrence of hyperstimulation in the vaginal group could lessen its preference to the oral route. More trials are needed to determine the right oral dosage that combines efficacy with safety.

Key Words: Induction of labour, vaginal misoprostol, oral misoprostol, induction delivery interval.

Introduction

Induction of labour is extensively used all over the world in cases in which continuation of pregnancy is hazardous to the mother and/or her fetus. Data from the WHO Global Survey on Maternal and Perinatal Health showed that 9.6% of the deliveries involved labour induction[1].

Over the years, various professional societies have recommended the use of induction of labour in circumstances in which the risks of waiting for the onset of spontaneous labour are judged by clinicians to be greater than the risks associated with shortening the duration of pregnancy by induction. One of these is pregnancy beyond 41 weeks, due to the increased risk of perinatal death[2,3].

Many evidences have highlighted the importance of prostaglandins to induce cervical ripening and stimulate uterine contractions at a variety of doses and routes of administration i.e. orally or vaginally[4-6]. However, prostaglandin preparations (Prostaglandin E2-dinoprostone) that have been registered for cervical ripening and labour induction are expensive and unstable, requiring refrigerated storage. In the developing countries with high average parity, there is an urgent need for an affordable drug to optimize induction outcome. Misoprostol (a prostaglandin E1 analogue) is a methyl ester of prostaglandin El additionally methylated at C-16[5,7] with several potential advantages: it is stable at room temperature, it is

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relatively inexpensive and it can be given via several routes (oral, vaginal, sublingual and buccal). These properties make misoprostol an ideal agent for induction of labour, particularly in settings where the use of prostaglandin E2 is not possible owing to lack of available facilities for storage, or financial constraints. Misoprostol has been compared satisfactorily with the presently agreed agent dinoprostone (prostaglandin E2), the most advantageous dosing regimen, timing, and route of administration lingered the focus of enduring research[4,7,8].

Recently, some studies have demonstrated the efficacy of oral misoprostol for cervical ripening, comparable with that of vaginal misoprostol[9–11].The use of an oral medication for cervical ripening is appealing due to reduction in repeated digital examination necessary for placement of the agent and also reduction in the risk of ascending infection.

This study aimed to compare the efficacy and safety of misoprostol when administered in equivalent doses, (orally and vaginally) for cervical ripening and labour induction in prolonged pregnancy with a live fetus.

Materials and Methods

***Research setting*:** The study was carried out at The Military Hospital from May 2014 to January 2015. The hospital is the second biggest hospital in the city situated almost at the centre of Accra. Although it is primarily a military hospital, it provides services to both military personnel and the general civilian population. The hospital has a 600-bed capacity with the Obstetrics and Gynaecology Department having 65 Beds.

Sample Size Determination: A sample size of 148 (74 women in each group) was calculated using a two-tailed alpha of 0.05 and a power of 95%. A standard deviation of 506 minutes was derived from a previous publication describing vaginal misoprostol for induction of labour[12]. A 300-minute (5-hour) difference in induction-to-delivery time between the two groups was considered clinically significant.

Inclusion Criteria: The study population was all patients with gestational age between 41–43 weeks who were receiving antenatal care at the Military Hospital between May 2014 and January 2015, and without contraindication to vaginal delivery. These included all eligible and consenting patients with the following characteristics: Age between 20–40 years, accurately dated gestation by ultrasound biometry via Crown rump length (CRL) measurements in the first trimester of pregnancy or according to the date of the last menstrual period preceded by regular cycles without use of oral contraceptives, singleton viable pregnancy and cephalic presentation.

Exclusion Criteria: These included Patients with known contraindications to receiving prostaglandins, premature rupture of membranes, multiple pregnancies, previous uterine surgery, any other contraindication to vaginal delivery or induction of labour and those who refused to consent.

Study Design: The study was a prospective, randomized clinical trial. It was not placebo-controlled and once randomisation was completed, neither the staff nor the patients were blinded to the route of administration.

Participation in the study was voluntary and patients were free to withdraw consent at any time during the study. Withdrawal of consent did not result to a difference in the care received compared to those that did not withdraw consent.

A detailed history and general physical examination including abdominal examination were done to confirm the presentation of the fetus. Digital vaginal examination was also done to confirm the Bishop Score. Baseline investigations included complete blood count, blood grouping and Rh factor. A fetal cardiotocogram (CTG) trace to confirm fetal well-being was performed as well as ultrasound for fetal weight and liquor volume.

The participants were subsequently randomized into group A and group B for induction with oral or vaginal misoprostol respectively. The randomization was done by placing 148 numbered cards each in an opaque envelope stating the route for induction. These sealed envelopes were put in a box and drawn by lottery in a consecutive order by the participants, who were unaware of the route allocated until the envelope was opened.

Study Protocol: *Treatment schedules*- The attending doctor administered the drug. The oral solution was prepared immediately before administration by mixing the 200µg with 200 ml of water. The woman then took a 50ml aliquot of solution (50µg). The vaginal misoprostol of 50µg was administered in the posterior fornix. These were repeated after every four hours to a maximum of four doses if there was no uterine activity.

When uterine activity suggested the onset of labour, vaginal assessment was performed and the participant was sent to the labour ward for further monitoring by trained midwives. All care was according to local hospital guidelines.

The data was collected using a prepared structured case record form (data proforma) after administration of the misoprostol. Data collection was done by the investigator and trained personnel. The time of dose introduction, beginning of significant uterine contractions (significant uterine contractions mean 3–5 contractions of moderate to severe intensity in 10 minutes) and deliveries times were also noted.

Failed induction of labour was defined as vaginal delivery not achieved within 24 hours of initiating induction of labour[13]. Patients deemed to have failed induction were managed by local protocol of 4 doses of 4 hourly 50ug misoprostol vaginally after a rest period of 24 hours or offered caesarean section according to patients wish. The indications for Caesarean section

(CS) were maternal request after 24 hours of induction or an obstetric indication. Any complication encountered during the induction procedure was recorded and managed accordingly.

Main Outcome Measures- The primary outcomes used to evaluate efficacy were the induction-to-delivery interval in women who delivered vaginally and successful induction in 24 hours. The primary measures used to evaluate safety were the incidence of uterine hyperstimulation with fetal heart rate (FHR) abnormalities and neonatal outcome of low Apgar score (6 or less at 5 minutes).

Secondary outcomes related to measures of efficacy and safety included requirement for oxytocin and the rate of CS.

Ethical and Legal Considerations: Ethical clearance for the study was obtained from The Institutional Review Board of the Military Hospital (Appendix III). A written informed consent was obtained from all patients after a general description of the study and the essence of their participation was verbally explained to them in a language they understood.

Data Analysis: The data was collected and entered into epi-data for analysis. Statistical analysis included calculation of mean differences with 95% confidence interval for continuous data using STATA 12. The unpaired t-test was used to test the mean difference for induction-to-delivery times and all continuous variables, while chi-square test was used in cases of difference of absolute numbers. All statistical tests were evaluated at the 0.05 significance level.

Results

One hundred and forty eight participants were recruited for the trial. Of these, 74 received misoprostol orally and 74 vaginally. None of the women recruited requested to be withdrawn after enrolment and there were no cases of post-randomisation protocol violations. Of the 74 participants that received vaginal misoprostol route, 68 were analysed for the primary endpoint. Similarly, 66 were analysed for the primary endpoint out of the 74 participants that received the oral misoprostol.

This is because 6 and 8 persons respectively for vaginal and oral route had failed induction.

Some demographic characteristics and primary induction outcomes are presented in Table 1 while table 2 shows secondary induction outcomes and the chi-square test.

From Table 1, there were no significant differences in maternal demographic characteristics in terms of age and parity. It was however observed that the mean birth weight was significantly more for the oral route compared to the vaginal route when the two arms were compared. ($p = 0.001$).

From the same table, the mean induction to delivery interval was shorter in the vaginal misoprostol group (12.9hrs vs 14.3hrs; mean difference -1.42). This was however not statistically significant ($p = 0.24$).

The shorter duration of vaginal misoprostol, however, was held true when nulliparous and multiparous women were analysed separately. Whereas the nulliparous women had significantly shorter mean induction to delivery interval in the vaginal misoprostol group (13.4hrs vs 17.9hrs; mean difference -4.5 and $p = 0.01$); the mean induction to delivery interval in the vaginal misoprostol group was marginally longer for parous women (12.5hrs vs 11.4hrs; mean difference 1.1216). This was however not statistically significant ($p = 0.46$).

From Table 2, it was observed that achieving vaginal delivery within 24 hours of induction in the oral group was less (6.8% vs. 6.1 %, $p = 0.81$), the number of women who received oxytocin augmentation was higher in the oral group (24.2% vs.17.4%, $p = 0.11$) and failed induction was also observed to be high in the oral group (4.5% vs. 5.9%, $p = 0.53$). The differences did not however reach statistical significance in all these observations.

Uterine hyperstimulation without FHR changes was more frequent in women treated with vaginal misoprostol compared with the oral route (7.46% vs.2.99%, $p = 0.10$). It was observed again that, uterine hyperstimulation with FHR changes was more frequent in the vaginal group than those who received the oral misoprostol (4.5% vs.3.7%, $p = 0.53$). The difference in both findings were however not statistically significant.

Five women in the vaginal group (3.7%) delivered by emergency caesarean sections compared with six (4.5%) in the oral. This difference was again not statistically significant. In the women who had caesarean sections, fetal distress and failure to progress were the indications; fetal distress was suspected on the basis of worrying fetal heart tracings alone or with the presence of meconium.

The Apgar scores <7 at 5 minutes and NICU admission were similar represented as 2 (1.49%) infants in the oral group compared with 4 (2.99%) infants in the vaginal group.

Table 1: Some Demographic Characteristics and Primary Induction Outcomes

Characteristics	Vaginal Misoprostol N=74	Oral Misoprostol N=74	Mean Diff, T-Test	*P Value*
Maternal age(years)	29.7[4.5]	30.0[3.5]	0.38	0.57
Mean Birth weight (grams)	3101.5 [414.0]	3343.8 [442.7]	-242.2	0.001
Parity Nulliparous Multiparous	 38 **{**51.4%**}** 36 **{**48.6%**}**	 35 **{**47.3%**}** 39 **{**52.7%**}**	 0.243	 0.622
Induction-to-delivery (*hr*)	12.91 [6.31]	14.33 [7.00]	-1.42	0.24
Induction-to-delivery (*hr*) Nulliparous Multiparous	 13.4 [5.99] 12.5 [6.61]	 17.96 [6.58] 11.38 [5.90]	 -4.531 1.121	 0.01 0.46

Table 2: Secondary Induction Outcomes and The Chi-Square Test.

Characteristics	Vaginal Misoprostol	Oral Misoprostol	Chi-Square value	*P- Value*
Vaginal delivery not achieved in <24 h	9(6.08%)	10(6.76%)	0.0604	0.81
Failed induction	6 (4.48%)	8 (5.97%)	0.3893	0.53
Oxytocin augmentation	23 (17.42%)	32 (24.24%)	2.5247	0.11
Uterine hyperstimulation without FHR changes	10 (7.46%)	4 (2.99%)	2.6755	0.10
Uterine hyperstimulation with FHR changes	6 (4.48%)	5(3.73%)	0.3893	0.53
Caesarean section	5(3.73%)	6(4.48%)	0.1343	0.71
Apgar score <7 at 5 min	4 (2.99%)	2 (1.49%)	0.6370	0.42
NICU admission required	4 (2.99%)	2 (1.49%)	0.6370	0.42

There was no statistical difference between oral and vaginal misoprostol with respect to 5-minute Apgar scores and NICU admissions (p = 0.42). There were no perinatal deaths in both arms.

Discussion

There is increasing evidence that misoprostol, administered either vaginally or orally, is as effective as conventional methods for induction of labour at term[4,6,8]. Interest in oral misoprostol for cervical ripening and labour induction is also growing day by day[7,9–11]. This study compared oral and vaginal misoprostol in well homogenized groups where all of the women were with intact membranes, had Bishop's score <6 and were at more than forty weeks' gestation with no antenatal complications. The rationale was to identify efficacy and safety of oral misoprostol regimen compared with intravaginal regimen.

The results of this study showed that in equivalent doses, the vaginal route of administration of misoprostol, although not statistically significant, resulted in a shorter induction to delivery interval, and more women were delivered with fewer doses of vaginal misoprostol within 24 hours of the induction with less need for oxytocin. This may be because, vaginal misoprostol is steadily absorbed and slowly eliminated from the body making it available to act for a longer time as compare to oral, resulting in rapid progression of labour and leading to greater number of women delivering within 24 h of induction[14]. The findings agreed with different systematic reviews[7,15] which showed that both oral and vaginal misoprostol were similar with regard to the priority outcomes including induction to delivery time.

The shorter duration of vaginal misoprostol, however, was held true when nulliparous and multiparous women were analysed separately where the difference was statistically significant (13.4hrs vs. 17.9hrs; mean difference -4.53, p-value <0.05) for the nulliparous participants. In other previous studies,[5,16] 50µg of oral misoprostol given every 4 hours was associated with longer intervals to delivery compared with vaginal misoprostol. This further indicates the efficacy of the vaginal administration especially for nulliparous women.

The finding however contrasted that of Kambhampati K. et al.,[17] where the oral group, though not statistically different, had a shorter induction to delivery interval of 12.92 hours as compared to 14.04 hours in vaginal group. The reason for the disparity may be because that study compared 50µg of oral misoprostol versus 25µg of intravaginal misoprostol whereas this study used 50µg of misoprostol for both routes.

In this study, vaginal misoprostol was associated with a less need for oxytocin augmentation (17.4% vs. 24.2%, p = 0.11), reduced risk of not achieving vaginal birth within 24 hours of labour induction (6.1% vs. 6.8%, p = 0.81) and less failed induction rate (4.5% vs. 5.9%, p = 0.53). All these differences between the two groups were however not statistically significant.

These results were consistent with different systematic review,[7] which showed that both oral and vaginal misoprostol were similar with regard to these priority outcomes. It however contrasted with that of Kambhampati K. et al.,[17] where the oral group showed a tendency of less need of oxytocin augmentation, less failed induction and a reduced risk of not achieving vaginal birth within 24 hours of labour induction. Kambhampati K. et al. however compared 50µg of oral misoprostol and 25µg of intravaginal misoprostol whereas this study used 50µg of misoprostol for both routes.

Although vaginal misoprostol has been shown to be effective compared with other traditional methods of labour induction in terms of a shorter induction delivery interval and less oxytocin need,[4,8] there is however an increasing concern about the higher incidence of uterine tachysystole and hyperstimulation[4,7]. This fear of uterine tachysystole and hyperstimulation is dose related; higher doses result in greater uterine stimulation but shorter induction delivery interval[18]. The relatively long half-life of misoprostol and its metabolites in maternal serum after vaginal administration might account for the tachysystole in these women than those who received the medication orally[14].

In this study, uterine tachysystole or hypertonus abnormality was more frequent in women treated with vaginal misoprostol compared with the oral route (7.5% vs.3.0%). It was observed again that uterine hyperstimulation with FHR changes uterine (hyperstimulation syndrome) was more frequent in the vaginal group than those who received the oral misoprostol (4.5% vs.3.7%). The difference in both findings were however not statistically significant. Oxytocin, which has been considered safer than misoprostol, is also not devoid of uterine abnormalities incidence being 19.2%[19].

Other studies have also reported higher rates of non-reassuring fetal heart tracings and uterine hyperstimulation associated with vaginal misoprostol compared with oral misoprostol[16,19]. Toppazada *et al*[19] noted an increase in abnormal fetal heart patterns and uterine hyperstimulation with the vaginal route. Bennett *et al*[16] also found oral misoprostol in a dose of 50µg to be less effective when compared with an equivalent dose vaginally, but noticed a trend of increasing hyperstimulation in the vaginal group.

The relationship between misoprostol use and caesarean section is a complex one. The trend in previous randomized trials has been an increase in caesarean sections for fetal heart rate abnormality and a reduction for poor progress of labour. Despite high incidence of uterine contractile abnormalities with vaginal route, there was no significant difference between oral and vaginal misoprostol with respect to emergency caesarean sections. It is important to note that, there were more emergency caesarean sections in the oral group (4.5% vs. 3.7%). The indications for emergency caesarean section included non-reassuring fetal heart tracings such as the presence of late decelerations or prolonged bradycardia and failure of labour to progress. This is consistent with Shetty et al[20]. (24.6 vs. 22.8%) and How et al[18]. (33.0 Vs. 17.0%).

The treatment in this study was not blinded. Under the circumstance, there could be a real possibility of bias in the clinical decision-making. A clinician who is anxious about possible risks of the new treatment may be more likely to intervene.

Misoprostol whether by vaginal and oral route do not adversely affect neonatal outcome despite increases in uterine hyperstimulation[18,20]. A Cochrane review that compared oral and vaginal misoprostol suggested that the oral route was associated with a reduction in Apgar score of less than seven at five minutes[7].

Similarly, in this study, although not significant, there was higher number of infants in the vaginal misoprostol group with Apgar scores less than 7 at 5 minute. Four infants (3.0%) in the vaginal group compared with two infants (1.5%) in the oral group. These infants, admitted to NICU, required positive pressure ventilation at delivery but they had no clinical sequelae of asphyxia. They required no investigations and at the time of writing, none has had any further admissions to hospital. This finding concur with a Cochrane review[7] where there was a lower risk of Apgar score being less than seven at 5 minutes of life for the oral group.

Conclusions

The results of this study suggested that, in equivalent doses, vaginal misoprostol was associated with shorter induction-to-delivery times than oral misoprostol. Both maternal and neonatal safety outcome were comparable in both groups.

The results supported the use of 50µg doses of oral misoprostol for pre-induction cervical ripening and labour initiation because it had almost same efficacy and safety as its vaginal analogue. Oral route approach offered convenience and ease of administration.

Recommendation

Oral or vaginal misoprostol for cervical ripening and labour initiation in doses of 50µg four hourly is recommended. However more randomized controlled trials, preferably double-blinded, with a larger sample size is needed to categorically determine the right oral regimen and intervals that combines safety with efficacy.

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