Original Article

Randomization of vaginal and sublingual misoprostol for cervical ripening and labor induction

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ABSTRACT

Background: Planned induction of labor for various indications has become an established part of modern Obstetric practice. While the efficacy of misoprostol, a prostaglandin E1 analog as a cervical ripening labor induction agent has been established, the appropriate route and dosage are still objected to ongoing research.

Objective: This study aims at comparing the efficacy of vaginally administered with sublingual misoprostol for cervical ripening and labor induction.

Methodology: One hundred (100) pregnant women at term who fulfill the inclusion criteria were equally randomized into the two arms of the study to receive either 25 μg of misoprostol sublingually or 25μg vaginally. The induction delivery interval and fetal outcomes were compared in the two arms of the study.

Results: The vaginal group required more doses of misoprostol than the sublingual group (1.68 ± 0.74 versus 1.26 ± 0.44, $P = 0.005$). Time from the administration of the first dose of misoprostol to the achievement of a Bishop score of 7 or active phase labor was shorter in the sublingual group than the vaginal route group (5.04 ± 1.77 hours versus 6.32 ± 1.36 hours, $P = 0.001$). Induction-delivery interval was shorter in the sublingual group than the vaginal route (10.02 ± 2.37 hours versus 11.12 ± 3.97 hours) although the difference was not statistically significant ($P = 0.098$). The mean Apgar scores at 1 min and 5 min were slightly better in the vaginal group than the sublingual group but the difference did not assume statistical significance (Apgar scores at 1 minute: 7.62 ± 0.83 versus 7.72 ± 0.88, at 5 minutes: 8.94 ± 1.23 versus 9.22 ± 0.46 for the sublingual versus the vaginal group, respectively, $P = 0.561$).

Conclusions: The two routes of sublingual and vaginal administration showed comparable safety and effectiveness for cervical ripening and induction of labor in low-risk pregnancies at term. However, the sublingual route appears to be superior in terms of easy administration and patients' satisfaction.

Key words: Cervical ripening; misoprostol; routes.

Introduction

While the onset of labor is spontaneous in the majority of pregnant women at term, a few, however, require artificial initiation of labor for medical, Obstetric or social reasons.[1-4] Many methods have been described for cervical ripening and induction of labor, ranging from natural to

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modern methods.[4,5] Mechanical methods include stripping or sweeping of the fetal membranes, use of hygroscopic dilators, and Foley's catheter.[6-9] Pharmacological methods like the use of prostaglandins or their analogs have been well documented and tried.[4,5,9] In an attempt to meet the demand for successful induction of labor and vaginal delivery, cervical ripening is a necessary pre-requisite.[10] The use of pharmacological agents particularly the prostaglandins or their analogs appear predominant in cervical ripening and induction of labor in many centers in modern Obstetric practice.[11]

Misoprostol was first manufactured for prophylaxis and treatment of gastric and duodenal ulcers caused by non-steroidal anti-inflammatory drugs.[12] Its uterotonic effect has propelled many studies that demonstrated its use in cervical ripening and induction of labor.[13-15] However, the ideal dose and dosing interval to be used for obstetric indications as well as different routes of administration have been the subject of different studies.[13,16-18] This study was designed to compare two routes of administration of misoprostol, viz. sublingual and transvaginal routes.

Materials and Methods

The study was a prospective randomized study of healthy pregnant women, with a singleton pregnancy who registered for antenatal care and delivery during the study period. Approval for the study was obtained from the Ethics Review Committee of the Hospital. The approval was obtained on 25-06-2014. The inclusion criteria included: valid indication for induction of labor, singleton pregnancy at ≥37 weeks gestational age, Bishop's score of ≤5, cephalic presentation, and normal fetal heart rate. The patients with the following conditions were excluded: malpresentation, unexplained vaginal bleeding, multiple gestations, placenta praevia, estimated fetal weight of >4000 gm, abnormal fetal heart rate, evidence of cephalopelvic disproportion, known allergy to prostaglandins, any pre-existing medical illness such as renal disease, cardiac disease, hepatic dysfunction, and clotting disorders, any known contraindication to receiving prostaglandins like asthma, glaucoma. Others are active genital infection, suspected chorioamnionitis, previous cesarean delivery or uterine surgery, grand multiparty, nonconsenting patients, and severe preeclampsia/eclampsia. The calculated minimum sample size to achieve a statistical power of 80% and 5% significant level was 40. A deliberate oversampling of 25% was allowed for nonresponders/dropouts. This gave a total of 50 parturient on each arm of the study. 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 the history of the index pregnancy. Thereafter, the first-trimester ultrasound scan was reviewed when available to ascertain the estimated gestational age. History taking, physical examination, and investigations were used to determine the eligibility of unbooked patients. The patients were assigned using random numbers generated, using a table of random numbers to receive intravaginal 25 μg of misoprostol or 25μg sublingual misoprostol (Evan Pharmaceuticals, Nigeria). Group allocation was predetermined and placed in consecutively numbered and sealed opaque envelopes. All eligible patients who gave informed consent for study participation were assigned sequential study numbers. The primary investigator who was responsible for maintaining the envelopes was contacted and opened the corresponding numbered envelope for treatment allocation.

All consenting patients underwent clinical Obstetric examination to exclude the presence of any of the exclusion criteria immediately before commitment to the treatment allocation. Initial Bishop Scores were assessed by a senior resident doctor and were re-assessed by the same individual. Biophysical profile, ultrasonography, blood grouping and cross-matching, and packed cell volume were also performed.

All pregnant women who fulfilled the study criteria received misoprostol in the posterior fornix of the vagina or sublingually every 4 hours for a maximum total of 6 doses for cervical ripening or until labor is established, with the maximum exposure time to the agent being 24 hours. Repeat dose of misoprostol was not administered in patients who progressed to the active phase of labor or who had adequate uterine contractions or patients who developed complications. Oxytocin induction and active management of labor were commenced in those patients with satisfactory Bishop Score who did not develop spontaneous active labor after maximum exposure to misoprostol. 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 used by gravity-assisted method commencing with 5 miu/min and increasing at intervals of 30 minutes to achieve adequate uterine contractions pattern, i.e. at least 3 strong uterine contractions in 10 minutes, each lasting 40-60 seconds. In the active phase of labor, routine intrapartum management was done. Fetal heart rate monitoring was done by intermittent auscultation with Pinnard's fetal stethoscope (or when necessary sonic aid or cardiotocograph) at intervals of 30 minutes. Evaluation of uterine contractile pattern for frequency, duration, and intensity of each contraction was done for 10 minutes at intervals of 30 minutes, while maternal vital signs—pulse rate was assessed every half hours, blood

pressure and temperature four hourly. These information were charted on partograph as recommended by the World Health Organization (WHO).

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

Data processing

Data entry was into a standard proforma and statistical analysis was performed with Chi-square (X^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 and estimated gestational age were analyzed with Student *t*-test, while differences in gravidity, parity, route of delivery, and presence of complications were analyzed with X^2 (chi square) and Apgar and Bishop's Scores were analyzed by Mann–Whitney U test using statistical package of Statistical Package for the Social Sciences (SPSS) version 21.

Results

One hundred women were randomized into the study. Fifty (50) women were randomized to receive 25 μg misoprostol via the vaginal route while another 50 received 25 μg misoprostol for cervical ripening via the sublingual route. The mean ages and other demographic characteristics were comparable, 29.4 ± 3.5 years and 29.3 ± 3.9 years ($P = 0.161$) for sublingual and vaginal group, respectively.

Postdate pregnancy, mild preeclampsia, and premature rupture of membranes were the major indications for induction of labor, accounting for 39%, 26%, and 21%, respectively. Other indications were: suspected intrauterine growth restriction, chronic hypertension, and diabetes mellitus in pregnancy [Table 1]. These indications were comparable in both the sublingual and vaginal groups. The mean Bishop score prior to commencement of cervical ripening and induction of labor were (2.56 ± 0.95 and (2.28 ± 0.88) for the vaginal and the sublingual arms, respectively ($P = 0.328$).

Figure 1 is a box plot illustrating the time required from cervical ripening to delivery in both groups. The difference in the time from onset of cervical ripening to delivery was not statistically significant in the two groups.

Table 2 compares the effectiveness of misoprostol in achieving cervical ripening and induction of labor when administered via the sublingual and vaginal route by comparing the time required to achieve uterine contractions, the time required to achieve Bishop score of greater than 7 or active phase labor, and the need for augmentation in the two groups of participants. The difference in the duration of time from administration of misoprostol to the onset of uterine contractions was statistically significant between the two groups, the mean onset of uterine contraction was earlier (2.76 ± 1.71 hours) for the sublingual group than for the vaginal group (4.04 ± 2.32 hours) (Z -2.760, *P* value = 0.005). The total number of doses of misoprostol required for cervical ripening and induction of labor was more in the vaginal group than the sublingual group with the difference being statistically significant. Two patients in the vaginal arm required a maximum dosage of 100μg (4 doses). The mean of the number of doses of misoprostol in the sublingual group was 1.26 ± 0.44 while that of the vaginal group was 1.68 ± 0.74. (*P* value = 0.001). Time from the administration of misoprostol to achievement of a Bishop score of >7 or active phase labor was significantly shorter in the sublingual group (5.04 ± 1.77 hours) than the vaginal group (6.32 ± 1.36 hours) (*P* value = 0.001).

The need for augmentation of labor was more in the sublingual group (28%) than the vaginal group (14%) although

Table 1: Indications for induction of labor

INDICATION	Number *n*	PERCENTAGE
Prolonged pregnancy	39	39
Pregnancy induced hypertension/Preeclampsia	26	26
Premature rupture of membrane (PROM)	21	21
Intrauterine growth restriction (IUGR)	8	8
Chronic hypertension	4	4
Diabetes	2	2
TOTAL	100	100

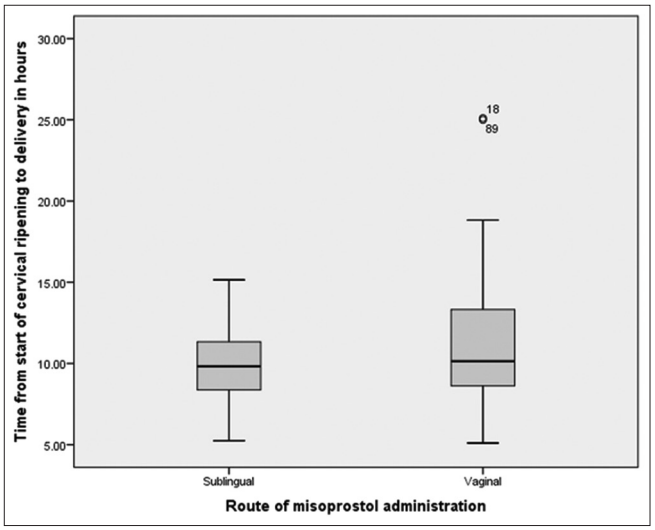

Figure 1: Box Plot showing the mean time from the start of cervical ripening to delivery (in hours) in both groups to be similar

the difference was not statistically significant (Z = 2.954, *P* value = 0.140). The interval between commencement of cervical ripening and delivery was shorter in the sublingual group (mean 10.02 ± 2.37 hours) than the vaginal group (mean 11.12 ± 3.97 hours) although the difference was not statistically significant (*P* = 0.098).

The majority of patients were satisfied with the route of administration of misoprostol and outcome of labor in the two groups (84% sublingual and 78% in the vaginal group). Although the degree of satisfaction was more in favor of the sublingual route of administration there was no statistically significant difference in patient satisfaction in the two groups (*P* value 0.636). No patient was dissatisfied with the route of administration of misoprostol. Table 3 shows the labor outcomes and complications of labor in the sublingual and vaginal route. Majority of patients in both groups had vaginal delivery following cervical ripening and induction of labor (90% in the sublingual group and 94% in the vaginal group). Six (6%) patients in each group had cesarean delivery with no statistically significant difference in the route of delivery in both groups. In the study, 98% and 94% of patients in the sublingual and vaginal route, respectively did not have any complication in labor, while 2% and 6% had complications during labor following sublingual and vaginal administration of misoprostol, respectively. While 96% of patients in both groups did not have any maternal postpartum complications, 4% had postpartum complications in each group. The route of delivery, complications during labor, and postpartum complications were similar in both groups of participants.

Table 4 shows the fetal outcomes in both groups of participants. The preinduction fetal heart rate was similar in both arms of the study prior to the administration of misoprostol for cervical ripening and induction of labor (sublingual 140.14 ± 7.18; and vaginal 142.78 ± 7.29,

Table 2: Comparison of the effectiveness of the two routes of misoprostol administration

Variable	Sublingual Group (*n*=50)	Vaginal Group (*n*=50)	*Z*	*P*
Time to onset of contractions (Hours)	2.76±1.71	4.04±2.32	-2.760	0.005†
Time from cervical ripening to Bishop score of 7 or active phase labour (Hours)	5.04±1.77	6.32±1.36	-3.205	0.001†
Cervical ripening to delivery Interval (Hours)	10.02±2.37	11.12±3.97	-1.673	0.098*
Total Number of Doses of Misoprostol used				
1 dose only (25 ug)	37 (74.0)	22 (44.0)	10.292	0.005**
2 doses (50 ug)	13 (26.0)	24 (48.0)		
3 doses (75 ug)	0 (0.0)	2 (4.0)		
4 doses (100 ug)	0 (0.0)	2 (4.0)		
Mean of the number of doses of Misoprostol (mean±SD)	1.26±0.44	1.68±0.74	-3.441	0.001*
Need for Augmentation				
Yes	14 (28.0)	7 (14.0)	2.954	0.140**
No	36 (72.0)	43 (86.0)		
Time from start to augmentation (Hours)	6.50±1.40	8.71±3.40	-2.140	0.046†

†*Z* - Mann-Whitney U test. *Independent *t*- test ** Chi-square test

Table 3: Labour outcomes and complications of labour with the route of misoprostol

	Sublingual group (*n*=50)	Vaginal group (*n*=50)	χ^2	*P*
Route of delivery				
Spontaneous Vaginal Delivery	45 (90.0)	47 (94.0)	1.754	0.598**
Instrumental Vaginal Delivery	2 (4.0)	0 (0.0)		
Caesarean Delivery	3 (6.0)	3 (6.0)		
Complications of Labour				
No Complications	49 (98.0)	47 (94.0)	1.388	0.617**
Foetal Distress	1 (2.0)	2 (4.0)		
Meconium Staining of Liquor	0 (0.0)	1 (2.0)		
Hyperstimulation	0	0		
Tachysystole	0	0		
Uterine rupture	0	0		
Maternal Postpartum Complications				
No Complications	48 (96.0)	48 (96.0)	2.553	0.495**
Wound Infection	2 (4.0)	1 (2.0)		
Puerperal Sepsis	0 (0.0)	1 (2.0)		

**Fisher's exact test

Table 4: Comparison of the Foetal outcomes

FOETAL OUTCOME	SUBLINGUAL GROUP (*n*=50)	VAGINAL GROUP (*n*=50)	*t*	*P*
Pre-induction FHR*	140.14±7.18	142.78±7.29	-1.824	0.071
APGAR Score				
Apgar Score @ 1 Min	7.62±0.83	7.72±0.88	-0.584	0.561
Apgar Score @ 5 Mins	8.94±1.23	9.22±0.46		
Birth Weight (Kg)	3.1±0.31	3.18±0.41	-1.078	0.283
SCBU Admission				
Yes	7 (14.0)	5 (10.0)	0.379	0.760**
No	43 (86.0)	45 (90.0)		

**Chi-square test. *FHR=Foetal heart rate

P value = 0.071). Mean Apgar scores at 1 min and 5 min were better in the vaginal group than the sublingual group although the difference was not statistically significant (*P* value = 0.561); the mean Apgar score at 1 minute is 7.62 ± 0.83 for the sublingual group and 7.72 ± 0.88 for the vaginal group. Mean Apgar score at 5 min was 8.94 ± 1.23 for the sublingual group and 9.22 ± 0.46 for the vaginal group (*P* value = 0.561).

The mean birth weight of babies in both groups was similar, sublingual group 3.1 ± 0.31 kg, vaginal group 3.18 ± 0.41 kg, *P* value = 0.283. The need for special care baby unit admission was slightly more following sublingual administration of misoprostol (14%) than after vaginal administration (10%), although the difference was not statistically significant (*P* = 0.760).

Discussion

The result of this study further supports the effectiveness of misoprostol as an agent for cervical ripening and induction of labor with successful vaginal delivery achieved in 94% of parturient in each arm of the study in conformity with previous studies.[16,18-23] Cesarean delivery rate was the same in both groups (6%). This is similar to the study by Adeniyi *et al*.[16] in Ibadan where 92% had vaginal delivery in the 25 µg arm of the study and about 8% cesarean delivery. A study by Siwatch *et al*.[19], which also used 25 µg misoprostol for cervical ripening and induction showed 93% and 91% vaginal delivery following administration of misoprostol by the vaginal and sublingual route, respectively. Studies by El Mehdi Hissane *et al*.[21] in Morocco showed 75% and 73% vaginal delivery following sublingual and vaginal routes of administration, respectively.

Prolonged pregnancy was the commonest indication for induction in this study, accounting for 39% and others were preeclampsia (26%) and premature rupture of membranes (21%). Suspected intrauterine growth restriction, chronic hypertension, and diabetes accounted for the remaining 14%. In a similar study comparing two dosage forms of misoprostol for cervical ripening and induction of labor by Adeniyi *et al*.[16] in Ibadan Nigeria, prolonged pregnancy was also the most common indication, and accounted for about 74% of the participants, unlike in the study by Siwatch *et al*. in India in which hypertensive disorders was the highest indication for induction (44%), while prolonged pregnancy accounted for 24%.[19]

The onset of uterine contractions was significantly faster in the sublingual group, 2.76 ± 1.71 hours than the vaginal group, 4.04 ± 2.32 hours (*P* = 0.005). Also, the mean number of doses of misoprostol in the sublingual group was smaller (1.26 ± 0.44) than that of the vaginal group (1.68 ± 0.74) (*P* = 0.005). These findings corroborate the pharmacokinetic studies by Zeiman *et al*.[20] which showed that the peak plasma concentration of misoprostol was reached in the shortest time and higher peak value in the sublingual group. This could possibly explain the faster onset of uterine contractions and the smaller mean number of doses of misoprostol observed in the sublingual group. This was in contrast to studies by Siwatch *et al*.[19] which showed that a higher mean number of doses of sublingual misoprostol 2.05 ± 0.980, than the vaginal dose 1.81 ± 0.843 was required for cervical ripening and induction of labor. Studies by Caliskan *et al.* and Filho *et al*. also showed that the number of doses required for the sublingual route of misoprostol was more than the vaginal route of misoprostol administration.[21,22]

The need for augmentation of labor was more (28%) in the sublingual group than the vaginal group (14%), which was similar to the study by Siwatch *et al*.[19] in which 38.8% and 28.8% required augmentation in the sublingual and vaginal routes respectively. There was however no statistically significant difference in the need for augmentation between the routes of administration in the Siwatch *et al*. study.[19] The less need for augmentation in the vaginal arm could be possibly explained by the local effect of vaginally administered misoprostol on the cervix which may contribute to its sustained action and hence less requirement for augmentation.[24-30] The neonatal outcomes in terms of birth weights, Apgar scores, the passage of meconium, admission to special care baby units, and indication for such admissions were comparable to other similar studies by Adeniyi *et al*.[16] and Siwatch *et al*.[19]

The pattern of patient satisfaction in both groups found in this study was similar to that previously demonstrated by Nassar A *et al*.[26] where sublingual misoprostol

(50 micrograms) was associated with a significantly higher patient satisfaction rate compared with a similar dose of vaginal misoprostol because the sublingual administration offers additional choice to women, in particular those wishing to avoid vaginal administration. The outcome of this study is in support of previous studies that found misoprostol an effective cervical ripening agent.[31-36] The generally lowlabor complications observed in the study were similar to the findings from previous studies.[16,34] The low level of complications may be due to the strict protocol criteria of 4-hour dosing interval and not commencing oxytocin augmentation earlier than 4 hours after the last dose of misoprostol. Maternal postpartum complications identified in the 2 groups were similar and were most probably not directly related to misoprostol or its route of administration. There was no statistically significant difference in the postpartum complications in both groups.

Conclusions

The two routes of sublingual and vaginal administration of misoprostol showed comparable safety and effectiveness for cervical ripening and induction of labor low-risk pregnancies at term. Both routes of administration in this study were devoid of significant side effects and have comparably favorable fetal and maternal outcomes. Although the sublingual route appears more convenient for administration and reduces the frequency of digital vaginal examination.

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.

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Conflicts of interest

There are no conflicts of interest.

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