THE JOURNAL OF OBSTETRICS AND GYNECOLOGY OF INDIA

The Journal of Obstetrics and Gynecology of India (September–October 2011) 61(5):538–542
DOI 10.1007/s13224-011-0081-0

ORIGINAL ARTICLE

A Comparison of Vaginal vs. Oral Misoprostol for Induction of Labor–Double Blind Randomized Trial

Jindal Promila · Avasthi Kumkum · Kaur Maninder

Received: 24 June 2009 / Accepted: 27 July 2011 / Published online: 26 October 2011

Abstract

Objective To compare efficacy and safety of 50 µgm misoprostol vaginal with oral for labor induction.

Methods 110 women at term gestation, Bishop score ≤4, with various indications for labor induction were randomized and double blinded. After decoding 51 women had received misoprostol orally and 52 vaginally, four hourly (maximum six doses) or till woman went into active labor.

Results Statistical analysis was done with SPSS 11.0. In vaginal misoprostol group induction delivery interval was significantly less (9.79 vs. 16.47 h) and successful induction was significantly higher (90.38 vs. 74.51%) than oral group, with in 24 h of induction. As for as dose required is concerned in vaginal group 40.38% women needed two doses for delivery, in contrast 35.29% in oral group maximum six doses were required.

Conclusion Vaginal route of misoprostol is more effective labor inducing agent than oral.

Keywords Vaginal misoprostol · Oral misoprostol · Induction of labor

Jindal P. (✉), Professor · Kaur M., Resident
Department of Obstetrics and Gynecology, Dayanand Medical College and Hospital, 20-B, Rishi Nagar, Ludhiana 141001, Punjab, India
e-mail: jindal_promila@rediffmail.com

Avasthi K., Professor
Department of Obstetrics and Gynecology, Christian Medical College and Hospital, Ludhiana 141001, Punjab, India

Introduction

Induction of labor at term with unfavorable cervix is associated with increased risk of failed induction and cesarean sections. Conventional methods for cervical ripening (oxytocin, Foley's catheter) are being used since ages but have their own merits and demerits, hence there is a need for more efficient inducing agent with less limitations. Till today no ideal agent has been found. Prostaglandin is new drug of interest in this field. Out of all prostaglandins PGE_1 and PGE_2 have been tried for induction of labor.

PGE_2 is being used as gel and tablet, has the advantage of being used intracervical or vaginally [1–3] but is expensive and needs refrigeration.

PGE_1's synthetic analogue, misoprostol, originally used as gastroprotective agent [4], its use as cervical ripener and labor inducer is upcoming [5] and is being tried enthusiastically by obstetricians worldwide. With time it has crossed the legal hurdles in western as well as developing countries including India. It has advantage of being cheap, stable at room temperature and easy to be administered by various routes i.e. vaginal, oral, sublingual or rectal [6]. Absorption by oral route is erratic at the same time it is more rapid than vaginally administered misoprostol reaching peak serum concentrations within 30 min compared to one hour with vaginal route. Oral misoprostol is eliminated rapidly (2–3 h) [4] than vaginal (≥4 h) [4]. Hence, vaginal route seems to be more efficacious than oral and should result in shorter

induction–delivery interval and reduced need for oxytocin augmentation [5] but at the cost of little more complications.

We have taken up this study to compare vaginal and oral routes of 50 μgm misoprostol for cervical ripening and induction of labor. To eliminate the subjective biasness we have randomized and double blinded the study.

Materials and Methods

This randomized double blind study is undertaken to compare 50 μg misoprostol oral with vaginal route. A pharmaceutical company, India, supplied two vials A and B containing tablets of same size, shape and color but one vial had placebo and other had active drug. The company coded the study for 120 women. Code list indicated which woman is to receive tablet from which vial and by which route. Accordingly every woman received one tablet orally and one vaginally simultaneously, four hourly to the maximum of six tablets. At the end of the study decoding was done according to the decoding list which determined finally which women received active drug misoprostol vaginally and which received orally, accordingly grouped as vaginal or oral for analysis.

All women with term gestation who were admitted in labor room of Dayanand Medical College and Hospital, Ludhiana with various indications for induction of labor were randomly included in the study after informed written consent.

Total 110 women with term gestation, singleton pregnancy, cephalic presentation, no fetal congenital malformation, reactive fetal heart rate pattern, bishop score ≤ 4 and rupture of membranes <4 h duration were recruited in the study. Women with bishop score >4, Cephalopelvic disproportion, placenta praevia or unexplained vaginal bleeding, previous caesarian section/or other uterine surgery, active herpes simplex, carcinoma cervix, chorioamnionitis and any contraindication to use of prostaglandins e.g. hypersensitivity, asthma, acute PID etc. were excluded. Out of these 110 women recruited seven got excluded hence only 103 women could complete the study (Fig. 1).

After detailed history, systemic and local examination included woman was allocated the code number according to code list and according to the code one tablet from one vial was given orally and at the same time one tablet from other vial was inserted vaginally in posterior fornix. Progress of labor was monitored especially for uterine contractions its frequency, intensity and duration, fetal heart rate and other fetal and maternal complications like nausea, vomiting, diarrhea, distress etc. Complications were managed symptomatically with antiemetics, I/V fluids etc. Woman was said to be in 'active labor' if she had three uterine contractions per 10 min, lasting for $\geq$60 s and of good intensity which was judged subjectively. Both oral and vaginal tablet were repeated every four hourly till either she went into active labor or maximum dose six tablets have been consumed. Once she went into active labor no further tablet was given orally or vaginally. Induction was said to be a "failure" if woman did not go into active labor four hours after 6th dose. Once labeled as 'failure' and there was no obstetric indication to terminate the pregnancy by LSCS, then augmentation with oxytocin by escalation method was done. In these women labor was also monitored in the same way.

During the course of induction uterus was said to be hypertonic if uterine contractions lasted for >120 s, tachysystole if >6 contraction per 10 min for two consecutive 10 min or hyperstimulation if either or both hypertonus tachysystole associated with abnormal fetal heart rate pattern, occurred then vaginal tablet was removed from the posterior fornix and no further dose oral or vaginal due was given, if needed Terbutaline 0.25 mg was given I/V or S/C. Fetal heart was monitored by fetal doppler and if abnormal fetal heart detected then women was put on continuous external tocodynamometry and before terminating the pregnancy by caesarean section, artificial rupture of membranes was done and the caesarean section was decided on the basis of obstetrical indications. Note was made especially for mode of delivery, intrapartum and postpartum maternal and fetal complications. After delivery both mother and the neonate were observed throughout the hospital stay for any complication especially nursery admission.

The main measure of efficacy was successful induction i.e. number of women who achieved active labor within 24 h of induction and their induction delivery interval. Other measures were number of deliveries within 24 h, total dose of misoprostol/oxytocin required for delivery and mode of delivery. The measures of safety included the uterine tachysystole, uterine hypertonus, abnormal fetal heart tracings, incidence of meconium passage and the neonatal outcome. Baseline data included maternal age, socioeconomic status, parity, gestation, indication for induction and pre-induction cervical score.

Finally after decoding women who had received misoprostol vaginally were grouped as vaginal group and those who received orally were grouped as oral group (Fig. 1).

Statistical Analysis

Both groups were analyzed statistically by applying Student's unpaired *t*-test, *Z*-test, χ^2 test with Yate's correction using statistical SPSS Software version 11.0. With 35 variables, comparison in two groups to make it 95%

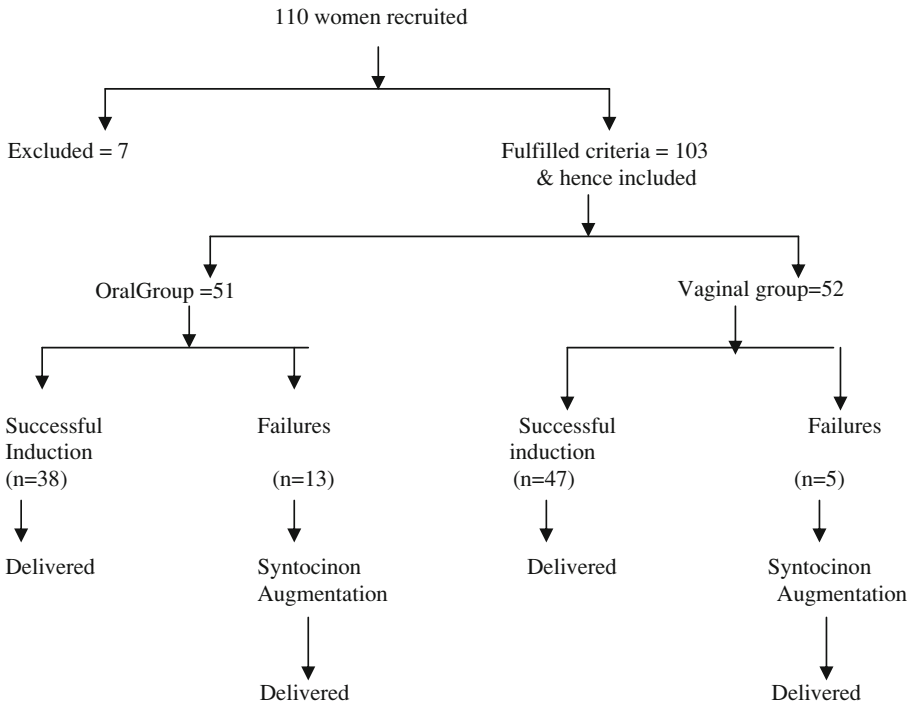

Fig. 1 Schematic representation of women studied

statistically powerful and for detecting significance of <0.05 number of subjects to be studied should have been 144. However due to time constraint and limited availability of cases (our institution being unaided private tertiary centre) study size could be 103 making power of study 70.04%.

Results

After decoding 51 women had received 50 μg misoprostol orally and 52 vaginally (Fig. 1). Seven women were excluded because of active herpes simplex (1 woman), premature rupture of membranes >4 h (1 woman) undiagnosed breech (1 woman), erroneously enrolled with a Bishop score of five (1 woman), for other protocol violation or clinical concerns (1 woman) and two women voluntarily voted out after one tablet insertion hence only 103 women could complete the study (Fig. 1). Maternal demographic characteristics and indications for induction were comparable in both the groups (Table 1). Commonest indication for induction of labor was hypertensive disorders in both vaginal and oral groups.

The successful induction rate was 90.38% in vaginal group and 74.51% in oral group (Table 2) which is statistically significant ($P = 0.0426$).

Induction active labor interval was significantly shorter in vaginal group (median 6 h (range 2–20.45) vs. 9.25 h (range 2–25.15) $P = 0.0049$) so was induction delivery interval (9.79 h (range 3.24–26.32) vs. 16.47 h (range 4–28) $P = 0.0033$).

Also greater number of women (47/52) delivered within 24 h of induction with vaginal misoprostol than with oral (37/51) (Table 2). 13/51 women did not achieve active labor within 24 h of induction in oral group as compared to 5/52 in vaginal group ($P = 0.0426$) and these were labeled as 'failures' (Table 2). All 'failures' achieved active labor with median dose of 14 mU/min (range 10–18) of oxytocin.

Greater number of women delivered with two doses of vaginal misoprostol (40.38 vs. 25.49%) in oral group 5/51 (9.8%) required six doses to go into active labor while no

Table 1 Demographic characteristics and indications for labor induction. Values are expressed as median (range) or (percentage)

	Oral Misoprostol group ($N = 51$)	Vaginal Misoprostol group ($N = 52$)
Demography		
Age (years)	26 (20–40)	25 (20–40)
Primigravida	32 (62.75%)	24 (46.16%)
Gestation (weeks)	39 (37–42)	39 (37–42)
Indication for induction		
Hypertensive disorders	43 (84.31%)	47 (90.38%)
Intrauterine growth restriction	6 (11.76%)	3 (5.77%)
Oligohydramnios	2 (3.92%)	2 (3.85%)
Diabetes mellitus	1 (1.96%)	0 (0%)

Table 2 Outcome of labor induction. Values are expressed as median (range) or (percent)

	Oral group ($N = 51$)	Vaginal group ($N = 52$)	P value
Successful induction	38 (74.51%)[a]	47 (90.38%)[a]	0.0426*
Failures	13 (25.49)[a]	5 (9.62)[a]	0.0426*
Induction–active labor interval	9.25 (2–25.15)[b]	6 (2–20.45)[b]	0.0049*
Induction–delivery interval	16.47 (4–28)[b]	9.79 (3.24–26.32)[b]	0.0033*
Number delivered within 24 h	37 (72.54)[a]	47 (90.38)[a]	0.0032*
Median dose required	6 (1–6)[b]	2 (1–6)[b]	0.00044*
Tachysystole	5 (9.80)[a]	14 (26.92)[a]	0.0431*
Hypertonus	0 (0)	0 (0)	
Hyperstimulation	0 (0)	0 (0)	
Uterine rupture	0 (0)	0 (0)	

[a] Percentage

[b] Range

* Statistically significant

woman in vaginal group (Table 3) required this maximum dose and highest dose required in vaginal group was five tablets in 3/52 women (5.77%).

Lesser fetal heart rate abnormalities (Table 4) were observed with vaginal misoprostol than with oral (5/52 vs. 10/51) but the difference is not statistically significant ($P = 0.1147$). Incidence of uterine contractile abnormalities were statistically more with vaginal misoprostol (14/52 vs. 5/51 $P = 0.0431$) (Table 2).

The majority of women in both the groups (85/103) delivered vaginally (Table 5) but overall incidence of vaginal births being significantly greater in vaginal group 47/52 vs. 38/51 in oral group ($P = 0.0462$) however cesarean section rate was significantly more in oral group (25.49 vs. 9.62% $P = 0.0462$) and commonest indication for cesarean section was fetal distress in both the groups (12/13 in oral group vs. 5/5 in vaginal group; $P = 0.4434$) (Table 5).

Table 4 Neonatal outcome

	Oral group ($n = 51$)	Vaginal Group ($n = 52$)	P value
Birth weight (kg)	2.89 (1.5–4)	2.8 (1.5–4)	0.2947
Apgar at/minute	8 (0–10)	8 (0–10)	0.1707
Apgar at 5 min	9 (0–10)	9 (0–10)	0.1793
Meconium staining of liquor	1	1	0.8994
Uterine contractile abnormalities	5/51	14/52	0.0437*
Fetal heart abnormalities	10	5	0.1147
Admission to NICU	2	0	
Live birth	51/51	52/52	
Still birth	0	0	

* Statistically significant

Neonatal outcome in both groups was good as all the neonates were born alive with median Apgar score of 8, 9 at 1 and 5 min, respectively (Table 4). Two neonates from oral group required neonatal ICU admission one for low birth weight with tachypnoea and other for RDS (Table 4).

Discussion

Misoprostol is a wonderful drug in the armamentarium of obstetricians for induction of labor. Vaginal misoprostol is an effective cervical ripener and labor inducing agent [7]. In our study successful induction with 50 μg vaginal misoprostol was higher (90.38 vs. 74.51%, RR 2.6, 95% CI

Table 3 Misoprostol dose requirement

Total dose of Misoprostol		Oral group		Vaginal group	
Number of Tablets	μgm	Delivered No. (%)	Not delivered No. (%)	Delivered No. (%)	Not delivered No. (%)
1	50	3 (5.88)	–	6 (11.54)	–
2	100	13 (25.49)	–	21 (40.38)	–
3	150	8 (15.69)	–	10 (19.23)	–
4	200	3 (5.88)	–	7 (13.46)	–
5	250	6 (11.77)	–	3 (5.77)	–
6	300	5 (9.80)	13 (25.49)	–	5 (9.62)
Total		51 (100)	–	52 (100)	–

Table 5 Mode of delivery

Mode of delivery	Oral group ($N = 51$)	Vaginal group ($N = 52$)	P value	Failures	
				Oral ($n-13$)	Vaginal ($n-5$)
Vaginal	38/51	47/52	0.0462*	13	5
Normal	36/51	44/52	0.0765	13	5
Forceps	2/51	3/52	0.3782	–	–
Cesarean section	13/51	5/52	0.0462*	–	–
Indication of cesarean section					
Fetal distress	12/13	5/5	0.4434	0	0
Cervical dystocia	0	0	–	0	0
Maternal distress	1/13	0	0.2585	0	0

* Statistically significant

0. 78–4.42). Shetty et al. [5] reported lower failure (2.4 vs. 6.76%, RR 2.7, 95% CI 0. 7–10.0) with 50 μg vaginal misoprostol as compared to oral and at the same time reported shorter induction delivery interval by 10.1 h [5]. Even Latika et al. [1] observed 100% success rate with 50 μg vaginal misoprostol [1] and 100 μg oral misoprostol [8]. In our study also induction delivery interval was shorter by 5.28 h with 50 μg vaginal misoprostol (9.79 h vs. 16.47 h, RR 0.79, 95% CI, 0.27–1.31). While comparing 50 μg vaginal misoprostol with Foley's catheter/oxytocin successful induction was 90.61 vs. 78.44% and induction delivery interval shorter by 7.87 h in vaginal misoprostol group [9].

As vaginal misoprostol is absorbed rapidly and eliminated slowly from body making it available to act for a longer time as compare to oral [4] resulting in rapid progression of labor leading to greater number of women delivering within 24 h of induction (69.5 vs. 56.4%) [5]. In our study more women (90.38 vs. 72.54%) delivered within 24 h in vaginal group.

Main fear with this drug is excessive uterine contractions and uterine rupture in both scarred and unscarred uterus. These complications are dose related higher the dose; more is uterine stimulation but shorter is the induction delivery interval [6]. With 50 μg vaginal misoprostol incidence of uterine contractile abnormalities have been reported to be 4.9% [5], 9% [9], 12% [1] and 26.92% in our study Ewert etal [10] observed these complications incidence as 3, 6.25, 10% with 25,100 and 200 μg controlled release vaginal inserts of misoprostol. While with 50 and 100 μg oral misoprostol uterine hyperstimulation incidence of 0.8% [5], 6.4% [11], respectively are reported. Oxytocin which has been considered safer than misoprostol [9] is also not devoid of uterine abnormalities incidence being 19.2% [12]. Apart from this PGE_2 also has lesser complications (12% [1]) than misoprostol. One uterine rupture was reported in scarred [9] and one in unscarred [13] uterus with vaginal misoprostol and one with dinoprostone [2].

In our observation despite of high incidence of uterine contractile abnormalities with vaginal route it does not increase in cesarean section rate rather LSCS rate in our oral group was significantly more 25.49 vs. 9.62%, which is consistent with Shetty etal [5] (24.6 vs. 22.8%) and How et al. [6] (33 vs. 17%). Commonest indication for cesarean section in our study was fetal distress irrespective of route used for misoprostol where as fetal distress contributed 2.4% with oral and 13% with vaginal use [5]. Misoprostol and its use by vaginal and oral route does not adversely affect neonatal and maternal outcome [5, 6, 9].

Conclusion

Vaginally administered 50 μg misoprostol is highly effective cervical ripener and labor inducing agent than oral misoprostol, but its use demands close monitoring for uterine contractile abnormalities.

Acknowledgments The concerned pharmaceutical company helped in double blinding and coding and decoding the material.

References

1. Latika S, Biswajit C. Comparison of prostaglandin E_1 (misoprostol) with prostagladin E_2 (dinoprostone) for labour induction. J Obstet Gynecol 2nd. 2004;54:139–42.
2. Gemund NV, Seherjon S, Classie SL, et al. A randomized trial comparing low dose vaginal misoprostol and dinoprostone for labour induction. Br J Obstet Gynaecol. 2004;111:42–9.
3. Chuck J, Huffaker BJ. Labour induction with intravaginal misoprostol versus intracervical PGE2 gel (prepidil gel): randomized comparison. Am J Obstet Gynaecol. 1995;173:137–42.
4. Drug Review. Misoprostol an old drug, new indications. Br J Postgrad Med. 2002; 48 (4): 336-9.
5. Shetty A, Danielian P, Templeton A. A comparison or oral and vaginal misoprostol tablets in induction of labour at term. Br J Obstet Gynaecol. 2001;100:238–43.
6. How HY, Leasebevrge L, Khoury JC, et al. A comparison of various routes and dosages of misoprostol for cervical ripening and the induction of labour. Am J Obstet Gynaecol. 2001;185: 911–5.
7. Wing DA, Paul RH. A comparison of different dosing regimens of vaginally administered misoprostol for pre-induction cervical ripening and labour induction. Am J Obstet Gynaecol. 1996;175: 158–64.
8. Nagai SW, Chan YM, Lam SW, et al. Labour characteristics and uterine activity: misoprostol compared with oxytocin in women at term with pre labour rupture of membranes. Br J Obstet Gynecol. 2000;107:222–7.
9. Jindal P, Avasthi K, Bala T. A comparison of vaginal misoprostol verus Foley's Catheter with oxytocin for induction of labour. J Obstet Gynaecol India. 2007;57:42–7.
10. Evert K, Powers B, Robertson S, et al. Controlled release misoprostol vaginal insert in parous women for labour induction. Obstet Gynaecol. 2006;108:1130–7.
11. Wing DA, Fasett MJ, Guberman C, et al. A comparison of orally administered misoprostol to intravenous oxytocin for labour induction in women with favourable cervical examinations. Am J Obstet Gynaecol. 2004;190:1689–96.
12. Abramovici D, Goldwasser S, Mabie BC, et al. A randomized comparison of oral misoprostol vs. Foleys catheter and oxytocin for induction of labour at term. Am J Obstet Gynaecol. 1999; 181:1108–12.
13. Blanchette HA, Nayak S, Erasmus S. Comparison of the safety & efficacy of intravaginal misoprostol (prostaglandin $E_{1)}$ with those of Dinoprostone (prostaglandin E_2) for cervical ripening & induction of labor in a community hospital. Am J Obstet Gynaecol. 1999;180:1551–9.