10.5005/jp-journals-10028-1031
ORIGINAL ARTICLE

Sublingual *vs* Vaginal Misoprostol for Labor Induction

Sujata Siwatch, Jasvinder Kalra, Rashmi Bagga, Vanita Jain

ABSTRACT

Background: This study is a randomized controlled trial comparing the efficacy and safety of sublingual *vs* vaginal misoprostol for induction of labor.

Materials and methods: A total of 160 women admitted for induction of labor at the PGIMER, Chandigarh, India were randomized to receive 25 µg of vaginal or sublingual misoprostol for labor induction. The two groups were compared for mode of delivery, induction delivery interval, misoprostol dose required, uterine contraction abnormalities and neonatal outcomes.

Results: Majority of women in both groups delivered vaginally (91 and 89% in vaginal and sublingual misoprostol groups respectively). Mean number of doses of misoprostol required for induction of labor was similar in vaginal misoprostol group and sublingual misoprostol group (1.81 ± 0.84 *vs* 2.05 ± 0.98). The occurrence of uterine contraction abnormalities and neonatal outcome was similar in both groups.

Conclusion: The low dose of 25 µg is equally efficacious and safe by both vaginal and sublingual routes.

Keywords: Misoprostol, Labor induction, Sublingual, Vaginal.

How to cite this article: Siwatch S, Kalra J, Bagga R, Jain V. Sublingual *vs* Vaginal Misoprostol for Labor Induction. J Postgrad Med Edu Res 2012;46(3):138-143.

Source of support: Nil

Conflict of interest: None

INTRODUCTION

Misoprostol, a prostaglandin E1 analog, has been used for cervical ripening and labor induction by a variety of routes including oral, buccal, sublingual and vaginal routes. Although the efficacy of misoprostol has been proved by various randomized trials, the search for an ideal route of administration is still ongoing. There have been few studies comparing the efficacy of low dose sublingual and vaginal misoprostol.[1-8]

The present study was planned to evaluate the efficacy and suitability of sublingual misoprostol for induction of labor when compared with an equivalent low dose (25 µg) given vaginally. Clearance from the Ethics Committee of the institute was taken. Considering the vaginal delivery rate of 73.8% with sublingual misoprostol by Shetty et al,[1] a study with 80% power and α error of 5% required a sample size of 138 women to detect a difference of 20% between the two groups.

PATIENTS AND METHODS

A total of 160 pregnant women admitted in the labor room in Postgraduate Institute of Medical Education and Research, Chandigarh, India, for induction of labor over a 2 years period were recruited in the study, provided they fulfilled the following inclusion and exclusion criteria and were willing to participate in the study.

Inclusion criteria included pregnancy with singleton live fetus with cephalic presentation, gestational age ≥32 weeks, Bishop's score <5 with intact membranes. Exclusion criteria included previous uterine surgery, major fetal malformation, parity >3, premature rupture of membranes, antepartum hemorrhage, severe renal, hepatic failure, any medical disorder such as cardiac disease, glaucoma, convulsive disorder, asthma, severe anemia, any contraindication to vaginal delivery like cephalopelvic disproportion, severe intrauterine growth induction (IUGR), oligohydramnios (<3 cm), clinically suspected chorioamnionitis or history of unclean vaginal examination, known hypersensitivity to prostaglandin, any oral pathology and acid peptic disease.

On admission, a detailed history of present pregnancy, past medical and obstetric history was taken. A general physical examination and an obstetrical examination were done to ascertain fundal height, lie and presentation of the fetus and the Bishop's score. An informed consent was taken from the subjects willing to participate in the study. They were then allocated according to a computer generated randomization chart into two groups of 80 women each for labor induction. Group 1 received 25 µg of misoprostol vaginally 4 hourly up to a maximum of six doses. Group 2 received 25 µg of misoprostol 4 hourly sublingually up to a maximum of six doses. The recruitment was done by the investigator or resident in the labor room. Misoprostol used was one-fourth tablet of 100 µg misoprostol (Cytotec).

A vaginal examination was performed to assess the Bishop score followed by administration of 25 µg of misoprostol, vaginally in group 1 and sublingually in group 2. Progress of labor and fetal heart rate pattern was monitored and subsequent doses of misoprostol given every 4 hours until there were regular uterine contractions (i.e. 3 contractions every 10 minutes), cervical dilatation >3 cm, Bishop score of >8 or evidence of tachysystole, hypertonus or hyperstimulation. In the event of tachysystole, uterine hypertonus or hyperstimulation, the woman was placed in left lateral position and oxygen was administered by facemask at the rate of 8 liters per minute. Injection terbutaline 250 µg was given by subcutaneous route in case of hyperstimulation and hypertonus. The uterine contraction was monitored by palpation and fetal heart rate was

monitored by intermittent auscultation as per protocol. Cardiotocographic tracing was taken in the event of features suggestive of fetal distress. With nonreassuring fetal heart rate tracing, further doses were withheld. Once in active phase of labor, routine intrapartum management was performed as per the protocol of the labor room. If the patient was undelivered at the end of 24 hours, the decision about further management was as per the clinician in charge. The presence of any side effect (fever, gastrointestinal side effects) was noted.

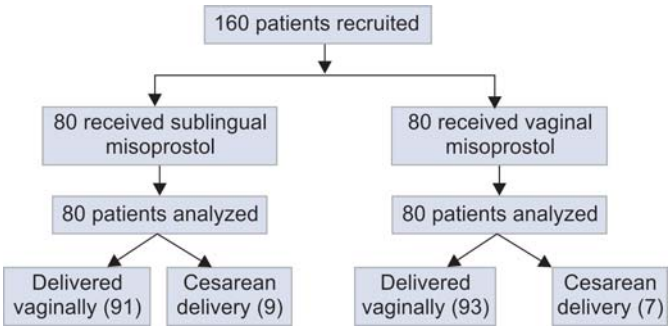
Primary outcome of the study was percentage of women delivering vaginally. Secondary outcomes included total number of doses of 25 µg of misoprostol required, percentage of women not delivered within 24 hours, induction delivery interval, rate of uterine tachysystole, uterine hypertonus and hyperstimulation, side effects/ adverse events, percentage of fetal distress (meconium stained liquor or fetal heart rate abnormality), neonatal Apgar score and admission to neonatal intensive care unit.

STATISTICAL ANALYSIS

Statistical analysis was done by using Chi-square test, Student t-test and Fisher exact test by SPSS software (version 11.0). Intention to treat analysis was done. However, there were no dropouts.

RESULTS

Flow chart 1 shows the flow of participants through each stage. The demographic features, indications for induction and pre-induction scores were comparable between the two arms (Table 1). The mean age of the women was 25.01 ± 2.83 years with majority of them being primiparous (77.5%) and at term gestation (93.75%). The mean preinduction Bishop's score at the start of induction was comparable in both groups, being 3.04 ± 0.892 in group 1 and 3.14 ± 0.838 in group 2.



Flow Chart 1: Consort diagram showing that 160 women were recruited and randomized to receive vaginal (group 1) and sublingual misoprostol (group 2). There were no dropouts in the study

Outcomes of labor and fetal outcomes in the two groups are shown in Tables 2 and 3 respectively. Majority of women in both groups delivered vaginally (91.0% in vaginal misoprostol and 89% in sublingual misoprostol group). Among those who delivered vaginally, comparable number of women in both vaginal and sublingual misoprostol groups delivered within 24 hours of induction (91.8% and 94.3% respectively). Mean induction delivery were similar in both vaginal misoprostol and sublingual misoprostol groups (16.17 ± 5.96 hours *vs* 15.25 ± 5.03 hours). Majority and comparable number of women in both vaginal and sublingual misoprostol groups did not require oxytocin augmentation (71.2 and 61.2% respectively) and the mean dose of oxytocin required in both groups was also comparable. Mean number of doses of misoprostol required for induction of labor was similar in vaginal misoprostol group and sublingual misoprostol group (1.81 ± 0.84 *vs* 2.05 ± 0.98). The incidence of abnormal uterine contraction (tachysystole and hyperstimulation) was low and comparable in both the groups. Neonatal outcome in terms of birth weight, Apgar score at 1 and 5 minutes, cord pH and admission and stay in neonatal intensive care unit was comparable in both the groups. However, there was one case of neonatal death due to birth asphyxia in the vaginal group though no uterine contraction abnormalities were seen in the same patient. This patient was a primigravida induced for postdates. She required three doses of vaginal misoprostol to initiate labor and was in second stage after 10 hours and 30 minutes when a low-mid cavity forceps delivery was carried out on noticing fetal bradycardia in second stage of labor. No uterine hyperstimulation was observed during labor. The newborn weighing 2.9 kg had poor Apgar scores of 0, 2, 2 at 0, 5 and 10 minutes and developed hypoxic ischemic encephalopathy (HIE) and expired after 5 hours. The woman had severe postpartum hemorrhage. She required cervical tear suturing followed by laparotomy. As the uterine atony did not respond to oxytocics, B-lynch suture was placed along with internal iliac artery ligation. She required multiple blood transfusions, ventilatory support for 1 day and was subsequently discharged in a satisfactory condition.

DISCUSSION

The use of prostaglandin E1 analog, misoprostol for induction of labor has proved to be quite promising. It is inexpensive, can be stored at room temperature, has few side effects at low dose, can be administered with ease by various routes like oral, vaginal, sublingual, buccal and rectal and more importantly, acts to promote both cervical ripening and uterine contractions. Doses from 25 to 200 µg have been used but dose of 50 µg or more is associated

with uterine contraction abnormalities, meconium passage and uterine rupture.[1-7] There is paucity of literature on comparison of low dose (25 µg) sublingual misoprostol with an equal dose of vaginal misoprostol. We did a PubMed search using the words 'misoprostol, sublingual, vaginal, induction, labor' on 5th January 2011. The few studies comparing the sublingual and vaginal misoprostol for labor induction are mentioned in Table 3.[2-6,8-9] Of a total of seven studies that have compared sublingual *vs* vaginal misoprostol, three used 50 µg misoprostol, one compared 50 µg sublingual with 25 µg vaginal misoprostol and three used 25 µg misoprostol for induction of labor (Table 4). Figures 1A to C show the meta-analysis of women not delivered vaginally in 24 hours, oxytocin use and of hyperstimulation between sublingual and vaginal route of misoprostol administration reported in these studies.

The mean number of doses of misoprostol required for induction was comparable in both groups in the present study. However, there were eight women (10%) in the sublingual group who required up to four doses. The dose requirement for misoprostol in the sublingual misoprostol group was reported to be more as compared to the vaginal misoprostol group in studies by Caliskan et al[4] and Moraes Filho et al,[3] although the difference was less appreciable in the present study. The pharmacokinetic study by Zeiman et al showed that the peak plasma concentration of misoprostol was reached in the shortest time with a higher peak value in the sublingual group.[10] However,

Table 1: The demographic profile of subjects in the study was comparable between the vaginal (group 1) and sublingual misoprostol (group 2)

	Group 1 (n = 80)	*Group 2 (n = 80)*	*Total (n = 160)*	*p-value*
Age in years (mean ± SD)	25.03 ± 2.723	24.99 ± 2.953		0.934
Nullipara	64 (80.0%)	60 (75.0%)	125 (78.1%)	0.566
Period of gestation in weeks (mean ± SD)	38.55 ± 1.37	38.13 ± 1.40		0.054
Induction for hypertensive disorders	37 (46.3%))	33 (41.3%)	70 (43.8%)	0.52
Induction for postdates	21 (26.3%)	18 (22.5%)	39 (24.4%)	0.58
Mean preinduction score	3.04 ± 0.892	3.14 ± 0.838		0.466

Table 2: Characteristics and outcomes of labor. Group 1—vaginal misoprostol, group 2—sublingual misoprostol

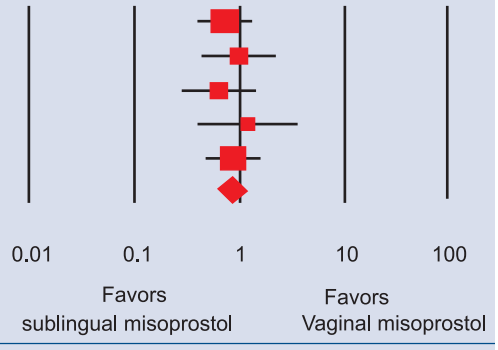
	Group 1 (n = 80)	*Group 2 (n = 80)*	*p-value*
Vaginal delivery	73 (91.2%)	71 (88.7%)	0.598
No vaginal delivery in 24 hours	17 (21%)	17 (21%)	1.0
Cesarean section	7 (8.8%)	9 (11.3%)	0.832
Indications for cesarean sections			
a. MSL	2 (28.57%)	5 (55.55%)	0.357
b. Fetal bradycardia	3 (42.85%)	1 (11.11%)	0.26
c. NPL	2 (28.57%)	3 (33.33%)	1.0
Mean doses of 25 mg misoprostol used	1.81 ± 0.843	2.05 ± 0.980	0.102
Women requiring oxytocin	23 (28.8%)	31 (38.8% 0)	0.18
Mean dose of oxytocin required	40.7 ± 22.4	35.61 ± 21.91	0.404
Maternal/labor complications			
Hypertonus	1 (0.01%)	1 (0.01%)	1.0
Tachysystole	1 (0.01%)	0	1.0
Hyperstimulation	1 (0.01%)	1 (0.01%)	1.0
Terbutaline use	1 (0.01%)	1 (0.01%)	1.0
Meconium stained liquor	3 (0.04%)	5 (0.06%)	0.72
Fetal bradycardia	4 (0.05%)	2 (0.025%)	0.68
Meconium stained liquor with fetal bradycardia	1 (0.01%)	0	1.0
Postpartum hemorrhage	1 (0.01%)	—	1.0
Vomiting, nausea	2	3	1.0

Table 3: Neonatal outcomes in group 1 (vaginal misoprostol) and group 2 (sublingual misoprostol) were comparable

	Group 1 (n = 80)	*Group 2 (n = 80)*	*p-value*
Mean birth weight (kg)	2.79 ± 0.389	2.68 ± 0.333	0.058
Mean Apgar score (AS)			
1 minute	8.00 ± 1.396	8.20 ± 0.537	0.234
5 minutes	8.93 ± 0.823	9.11 ± 0.356	0.063
Neonatal death	1 (0.01%)	0	1.0
Neonatal hyperbilirubinemia	2 (0.02%)	2 (0.02%)	1.0

Meta-analysis

Study name	Comparison	Odds ratio	Lower limit	Upper limit	z-value	p-value
Feitosa	25 μg *vs* 25 μg 6 hourly	0.726	0.382	1.379	– 0.979	0.328
Siwatch	25 μg *vs* 25 μg 4 hourly	1.000	0.432	2.316	0.000	1.000
Bartusevicius	50 μg *vs* 25 μg 4 hourly	0.645	0.282	1.475	– 1.038	0.299
Caliskan	50 μg *vs* 50 μg 4 hourly	1.183	0.379	3.688	0.289	0.773
Nassar	50 μg *vs* 50 μg 4 hourly	0.853	0.451	1.615	0.487	0.626
		0.822	0.583	1.157	– 1.126	0.260



A

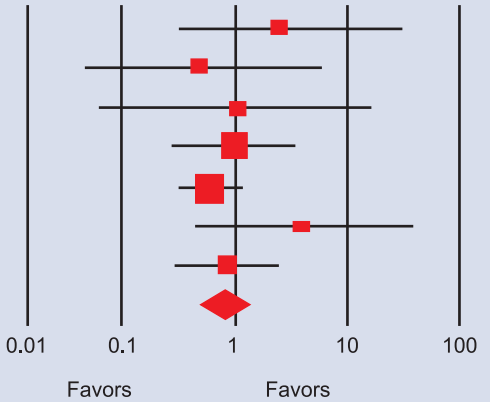
Meta-analysis

Study name	Comparison	Odds ratio	Lower limit	Upper limit	z-value	p-value
Feitosa	25 μg *vs* 25 μg 6 hourly	1.000	0.510	1.959	0.000	1.000
Filho	25 μg *vs* 25 μg 6 hourly	0.729	0.348	1.527	– 0.838	0.402
Siwatch	25 μg *vs* 25 μg 4 hourly	0.638	0.329	1.235	– 1.334	0.182
Bartusevicius	50 μg *vs* 25 μg 4 hourly	1.000	0.515	1.940	0.000	1.000
Zahran	50 μg *vs* 50 μg 6 hourly	0.931	0.644	1.348	– 0.377	0.706
Caliskan	50 μg *vs* 50 μg 4 hourly	1.422	0.762	2.653	1.108	0.268
Nassar	50 μg *vs* 50 μg 4 hourly	1.506	0.727	3.122	1.101	0.271
		0.978	0.784	1.221	– 0.196	0.845

B

Meta-analysis

Study name	Comparison	Odds ratio	Lower limit	Upper limit	z-value	p-value
Feitosa	25 μg *vs* 25 μg 6 hourly	3.083	0.313	30.336	3.965	0.334
Filho	25 μg *vs* 25 μg 6 hourly	0.526	0.046	5.964	– 0.518	0.604
Siwatch	25 μg *vs* 25 μg 4 hourly	1.000	0.061	16.270	0.000	1.000
Bartusevicius	50 μg *vs* 25 μg 4 hourly	1.000	0.279	3.620	0.000	–1.000
Zahran	50 μg *vs* 50 μg 6 hourly	0.614	0.319	1.182	–1.459	–0.145
Caliskan	50 μg *vs* 50 μg 4 hourly	4.158	0.454	38.047	1.262	0.207
Nassar	50 μg *vs* 50 μg 4 hourly	0.864	0.299	2.498	– 0.270	0.787
		0.825	0.515	1.321	– 0.801	



C

Figs 1A to C: Meta-analysis comparing sublingual and vaginal misoprostol groups for (A) women not delivered vaginally in 24 hours, (B) use of oxytocin for labor augmentation and (C) hyperstimulation during labor

Table 4: Overview of quality of study determinants, doses and preinduction Bishop's scores of various studies that compared sublingual and vaginal misoprostol for labor induction.

Name of authors	*Subject number*	*Dose administered (sublingual vs vaginal)*	*Bishop's score (sublingual-s, vaginal-v)*	*Random-ization*	*Allo-cation conceal-ment*	*Ad hoc/ a priori analysis*	*Intention to treat analysis*	*Blinding*	*Lost to follow-up/drop-out*
Siwatch (present study)	160 (80 + 80)	25 µg *vs* 25 µg 4 hourly	s-3.14 ± 0.84 v-3.04 ± 0.89	+		+	+		+
Feitosa 2005	150 (75 + 75)	25 µg *vs* 25 µg 6 hourly		+	+	+	+	+	+
Filho 2005*	123 (60 + 63)	25 µg *vs* 25 µg 6 hourly	s-BS <4 = 31 v-BS <4 = 32	+					+
Nassar 2007	170 (85 + 85)	50 µg *vs* 50 µg 4 hourly	s-2.6 ± 1.6 v-3.0 ± 1.7	+	+	+	+		+
Bartusevicius 2006	140 (70 + 70)	50 µg *vs* 25 µg 4 hourly	s-4.1 ± 1.0 v-4.1 ± 1.0	+		+	+	+	+
Caliskan 2005	160 (80 + 80)	50 µg *vs* 50 µg 4 hourly	s-1.7 ± 1 v-1.9 ± 1.1	+	+			+	+
Zahran 2009	480 (240 + 240)	50 µg *vs* 50 µg 6 hourly	s-2.2 ± 1.2 v-2.4 ± 1.2	+	+	+	+	+	

*Study quality assessment is limited as the study is not published in English language

Abdeel-Aleem et al showed that serum concentration of misoprostol fell abruptly by the 120th minute and was about 10% of the peak serum concentration at the 240th minute.[11] Vaginal administration of misoprostol however, maintains 60% of the peak serum concentration at 240 minutes. Thus, more doses of misoprostol would be required. The local effect in case of vaginal misoprostol may also be responsible for sustained contractions, thus requiring lesser doses.

Uterine tachysystole or hyperstimulation is a source of concern for fetal well being. In the present study, using a low dose of 25 µg misoprostol there was one case each of uterine hypertonus and hyperstimulation in both the vaginal and sublingual misoprostol groups. There was one case of tachysystole in the vaginal misoprostol group. The overall uterine contraction abnormalities were found to be comparable in both the groups (3.7% and 2.5% respectively). The higher rate of uterine contraction abnormalities reported by Nassar et al[8] and Caliskan et al[4] (8% and 22.5% respectively) could be due to the higher dose used. There are no significant differences in the neonatal outcome between the vaginal and sublingual misoprostol groups with regard to mean birth weight, Apgar score, card pH and rate of NICU admission and neonatal hyperbilirubinemia or meconium passage.

Body mass index (BMI) is an important maternal factor that can conceivably influence the dose-response characteristics for sublingually or vaginally administered misoprostol. An obese woman might be expected to require higher dose of misoprostol or more frequent dosing when compared with a petite woman with similar pregnancy characteristics.[4] The present study did not take into account the weight or BMI of the women.

CONCLUSION

The study concludes that both vaginal misoprostol and sublingual misoprostol are equally safe and effective methods of labor induction in women with unfavorable cervix in third trimester of pregnancy. A low dose of 25 µg sublingual or vaginal misoprostol is also as effective and has low incidence of side effects relating to uterine contraction abnormalities as reported with a higher dose in the literature. Majority of the women do not need any oxytocin augmentation of labor. However, a larger number of women need to be studied in order to achieve a statistical power sufficient to compare the occurrence of infrequent events.

REFERENCES

1. Shetty A, Danielian P, Templeton A. Sublingual misoprostol for the induction of labor at term. Am J Obstet Gynecol 2002; 186:72-76.
2. Shetty A, Mackie L, Danielian P, Rice P, Templeton A. Sublingual compared with oral misoprostol in term labour induction: Randomized controlled trial. Br J Obstet Gynecol 2002;109:645-50.
3. Filho M, Olímpio Barbosa de, Albuquerque, Rivaldo Mendes de, Pacheco, Álvaro José Correia, et al. Sublingual versus vaginal misoprostol for labor induction of term pregnancies. Rev Bras Ginecol Obstet 2005;27:24-31.
4. Caliskan E, Bodur H, Ozeren S, Corakci A, Qzkan S, Yucesoy I. Misoprostol 50 microgram sublingually versus vaginally for labor induction at term. Gynecol Obstet Invest 2005;59:155-61.
5. Feitosa FE, Sampaio ZS, Alencar CA Jr, Amorim MM, Passini R Jr. Sublingual *vs* vaginal misoprostol for induction of labor. Int J Gynaecol Obstet 2006;94:91-95.
6. Bartusevicius A, Barcaite E, Kriksolaitis R, Gintautas V, Nadisauskiene R. Sublingual compared with vaginal misoprostol for labor induction at term: A randomized control trial. BJOG 2006;113(12):1431-37.

7. Bartusevicius A, Barcaite E, Nadisauskiene. Oral, vaginal and sublingual misoprostol for induction of labor. Int J Gynaecol Obstet 2005;91(1):2-9.
8. Nassar A, Awwad J, Khalil A, Abu-Musa A, Mehio G, Usta I. A randomised comparison of patient satisfaction with vaginal and sublingual misoprostol for induction of labour at term. BJOG 2007;114:1215-21.
9. Zahran KM, Shahin AY, Abdellah MS, Elsayh KI. Sublingual versus vaginal misoprostol for induction of labor at term: A randomized prospective placebo-controlled study. J Obstet Gynaecol Res 2009;35(6):1054-60.
10. Zieman M, Fong SK, Benowitz NL, Banster D, Darney PD. Absorption kinetics of misoprostol with oral and vaginal administration. Obstet Gynecol 1997;90:88-92.
11. Abdel-Aleem H, Villar J, Gulmezoglu AM, Mostafa SA, Youssef AA, Shokry M, et al. The pharmacokinetics of the prostaglandin E1 analogue misoprostol in plasma and colostrums after postpartum oral administration. Eur J Obstet Gycecol Reprod Biol 2003;108:25-28.

ABOUT THE AUTHORS

Sujata Siwatch (Corresponding Author)

Senior Research Associate, Department of Obstetrics and Gynecology Postgraduate Institute of Medical Education and Research, Chandigarh India, e-mail: siwatch1@yahoo.com

Jasvinder Kalra

Professor, Department of Obstetrics and Gynecology, Postgraduate Institute of Medical Education and Research, Chandigarh, India

Rashmi Bagga

Professor, Department of Obstetrics and Gynecology, Postgraduate Institute of Medical Education and Research, Chandigarh, India

Vanita Jain

Professor, Department of Obstetrics and Gynecology, Postgraduate Institute of Medical Education and Research, Chandigarh, India