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To Study the Perinatal Outcome in Women with Labor Induction by Sublingual *vs*. Vaginal Misoprostol

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Abstract

Background: Induction of labor indicated when the benefit to either mother or fetus outweighs those of continuing pregnancy. Pharmacological methods used for induction includes oxytocin, prostaglandin (E1, E2) and mifepristone. However the ideal dose, route and frequency of administration of misoprostol and its perinatal outcome are still under investigation. Hence we plan to do a comparative study between sublingual and vaginal misoprostol for inducing labor and its perinatal outcome.

Methodology: A prospective randomized interventional study was conducted on 70 pregnant women with singleton pregnancy with vertex presentation with period of gestation 37 to 42 weeks, who met the inclusion criteria and were willing to participate the study. They were explained in detail about the study on admission and were randomized into 2 groups: Group I (sublingual) and Group II (vaginal). Bishop score at start of induction, doses required, mode of delivery, duration of different stages of labor and perinatal outcome of the women were recorded.

Results: Out of 35 women in each group, 29 women (82.8%) in both normal vaginal delivery, 1 woman in group I and 3 women in group II had instrumental delivery. Emergency cesarean section was done in 5 women (14.28%) in sublingual group and 3 women (8.57%) in vaginal group. Meconium passage was seen in 4 women (11.42%) in sublingual group as compared to 2 women (5.71%) in vaginal group. Non-reassuring fetal heart rate was noted in 2 women (5.71%) in sublingual group and 5 women (14.28%) in vaginal group. Though more number of women in vaginal group had not reassuring fetal heart rate, but the difference between two groups in relation to fetal side effects was not statistically significant (P=0.23).

Conclusion: Sublingual route represents a valid alternative to vaginal route with the advantage of convenience of administration. However, it appears to offer no additional clinical advantage over the vaginal route with respect to perinatal outcome. In view of limited sample size of our study, we cannot reach definitive conclusions in regard to the preference of sublingual or vaginal route of misoprostol administration for induction of labor and its perinatal outcome.

Keywords: Prostaglandins; Oxytocin; Sublingual; Vaginal; PROM; Bishop score

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Introduction

Induction of labor implies stimulation of uterine contractions before spontaneous onset of labor, with or without ruptured membranes [1]. Induction is indicated when the benefits to either mother or fetus outweighs those of continuing pregnancy [2]. In 2006, 22.5% of births were pharmacologically induced in USA, a 50% increase since 1990. In developing countries the rates of induction are generally lower, but in some settings they can be as high as those observed in developed countries [3]. From the 2nd century through the end of 17th century numerous non-pharmacological methods have been used for the labor induction including stripping of membranes, amniotomy, transcervical catheter, extra-amniotic saline infusion and hygroscopic dilatation of cervix. Recently pharmacological methods have gained importance which includes oxytocin, prostaglandin (E1, E2) and Mifepristone. Prostaglandins were used clinically to induce labor in late 1960's with subsequent administration of various formulations of prostaglandins like PGE1 tablets and PGE2 gel. Misoprostol is a synthetic prostaglandin E1 methyl ester that stimulates myometrium contractions in pregnant uterus by binding to EP2 and EP3 prostanoid receptors. The use of misoprostol for induction of labor with live fetus was 1st described in 1992 in the pioneering study by Margulies et al. [4]. It can be used orally, vaginally and sublingually. However the ideal dose, route, frequency of administration and its perinatal outcome are still under investigation. Vaginal misoprostol appears

Table 1: Mean of baseline characteristics, Bishop Score at induction, Doses of misoprostol and Augmentation requited.

Demographic Data	Group I	Group II	p value	significance
Age	25.10+3.58	25.21+ 3.56	P=0.30	NS
Residence R/U	85.71/14.28	94.28/5.71	P=0.74	NS
BMI	23 ± 2.64	23 ± 3.04		NS
Clinical Data				
Gravidity	1.51 ± 0.91	1.49 ± 0.78	0.89	NS
Parity	1.25 ± 0.50	1.25 ± 0.61	0.65	NS
POG	39.42 ± 1.11	39.80 ± 1.05		NS
Bishop score at induction At completion	4.49 ± 0.76 8.13 ± 1.35	4.44 ± 0.79 8.13 ± 1.33	0.77 0.79	
Doses of misoprostol required	2.21 ± 1.29	2.4 ± 1.11	0.89	NS
Augmentation required	65.71	57.14	0.45	NS

Tables 2: According to Perinatal Outcomes.

Outcome Measure	Group I (sublingual)		Group II (vaginal)		P value	Significance
	N=35	%	N=35	%		
Live birth	35	100	35	100		NS
Avg birth wt	2.9 ± 0.5		3.0 ± 0.4		>0.05	NS
Ante/intra partum fetal distress	6	17.14	7	20	0.75	NS
NICU admission for <24 hours	2	5.71	5	14.28	0.39	NS
NICU admission >24 hours	4	11.42	2	5.71	0.39	NS
Mean APGAR score						
At 1 min	7.54+0.78		7.68+1.07		0.53	NS
At 5 min	9.45+0.88		9.62+0.87		0.42	NS
Apgar score <7 at 5 minutes	6	17.14	7	20	0.55	NS
Mean hospital stay	3.68+1.79		3.65+1.37		0.74	NS

to be more effective than the equivalent dosage administered orally but is associated with a higher risk of uterine hyper stimulation both without and with Fetal Heart Rate (FHR) changes. The sublingual route could thus be expected to be more effective than vaginal misoprostol, and by avoiding a direct effect on the cervix, it might reduce the risk of uterine hyper stimulation. Despite of large body of literature on the subject, there are very few randomized control trials comparing sublingual misoprostol with vaginal misoprostol for induction of labor. Hence we plan to do a comparative study between sublingual and vaginal misoprostol for inducing labor and its perinatal outcome.

Materials and Methods

A prospective randomized interventional study was conducted in the Department of Obstetrics and Gynecology, Dr. Rajendra Prasad Government Medical College, Kangra at Tanda (Himachal Pradesh) after taking approval of Protocol Review and Institutional Ethics Committee. A total of seventy women requiring induction of labor for various indications, who met the inclusion criteria were recruited into the study. Women >18 yrs of age admitted for induction of labor, singleton pregnancy, vertex presentation, gestational age 37 to 42 weeks with Bishop's score <6, Amniotic fluid index >5 and reactive non-stress test were included for study. Exclusion criteria include any contra-indications to vaginal delivery, previous LSCS and scarred uterus, severe IUGR, severe oligohydramnios, severe pre-eclampsia, eclampsia, grand multipara, intrauterine fetal death, fetal congenital malformation and known hypersensitivity to prostaglandins.

Methods

All the women who met the inclusion criteria were explained in detail about the study on admission and were randomized into 2 groups: Group I (sublingual) and Group II (vaginal) by a computer generated randomization table. The randomization sequence was kept in a sealed opaque envelope to be opened by the investigator after enrollment of woman into the study. A thorough clinical examination including general physical examination, systemic examination, per abdomen, per speculum and pelvic examination was done. Subjects were investigated; dating confirmed, non-stress test and Amniotic Fluid Index (AFI) were done. At time of induction, per abdomen, per speculum and pelvic examination was done again. Bishop's score was assigned. The women in group I were given tablet misoprostol 25 µg sublingually, while in group II women induction was done by vaginal insertion of tablet misoprostol 25 µg. Repeated doses were given every 4 h for a maximum of 5 doses. Repeat dosing was withheld at labor onset or entry into active labor (cervical dilatation of 3 cm or more) and when there was intolerance to medication. Once misoprostol was stopped, membranes were ruptured artificially and labor augmentation with intravenous oxytocin was started if necessary after 4 h to 6 h of last dose of misoprostol. Active stage of labor was monitored partographically according to institutional protocol. Mode of delivery, induction to delivery interval, and perinatal outcome were recorded.

Results

As shown in Table 1 there was no significant difference in the

Table 3: Comparison of Mean Age, BMI and Parity.

Study	Mean Age		Mean BMI		Parity	
	Sublingual	Vaginal	Sublingual	Vaginal	Sublingual	Vaginal
Calisken et al. [5]	27.5+5.3	27.2+5.4	27.9+4.6	28.1+4.8	2.3+1.9	2.2+1.5
Bartusevicius et al. [6]	27+5.2	29+5.3	25+5.8	24+5.9	1.5+0.8	1.5+0.7
Nassar et al. [9]	30.7+6.1	29.3+6.0	-	-	1+1	1+1
Ayati et al. [10]	24.6+4.4	24.3+4.0	-	-	1.5+0.8	1.3+0.6
Zahran et al. [7]	28.2+2.5	26.7+2.8	-	-	2.2+0.9	2.4+1.1
Fakhir et al. [11]	29.5+5.4	29.5+5.4	27.9+4.6	28.1+4.8	-	-
Tayyba et al. [8]	27+4	27+4	-	-	1.5+0.8	1.5+0.7
Present Study	25.1+3.5	25.2+3.5	23.0+2.6	23+3.4	1.2+0.5	1.2+0.6

Table 4: Comparison of various modes of delivery in study group.

Study (in percentage)	Spontaneous Vaginal Delivery		P value	Instrumental Delivery		P value	Cesarean Section		P value
	s/l	Vag		s/l	vag		s/l	vag	
Calisken et al. [5]	78.8	81.3	NS	2.5	1.3	NS	18.8	17.5	NS
Bartusevicius et al. [6]	76	77	NS	7.1	2.9	NS	17	20	NS
Nassar et al. [9]	58.8	57.7	NS	5.9	14.1	NS	35.3	28.2	NS
Ayati et al. [10]	84.8	90	NS	1.1	0	NS	14.1	10	NS
Zahran et al. [7]	70.4	66.7	NS	-	-	-	29.6	33.3	NS
Fakhir et al. [11]	66.7	68.4	NS	15.8	12.3	NS	17.5	19.3	NS
Tayyba et al. [8]	76	77	NS	7.1	2.9	NS	17	20	NS
Prabha et al. [12]	62	58	NS	10		NS	28	36	NS
Present study	82.8	82.8	NS	2.8		NS	14.2	8.5	NS

average age of the patients in two groups (P>0.05). The mean BMI in sublingual group was 23.02+2.64 and in vaginal group was 23+3.40. Although more number of patients in group I were from rural as compared to group II but that is not statistically significant. Among both groups there was no difference in respect to gravidity and parity, with mean gravidity 1.51+0.91 and 1.49+0.78 (P=0.89) respectively and parity between two groups was also not statistically significant (P=0.65). The mean POG at induction in sublingual group 39.42+1.11 and in vaginal group was 39.80+1.05 (P>0.05). At the time of start of induction bishop score of all seventy women was less than six with the average bishop score was 4.49+0.76 and 4.44+0.79, respectively (P>0.77). The average number of doses of misoprostol required in sublingual group was 2.2+1.29 and in vaginal group was 2.4+1.11 (P>0.89), (Table 1). In sublingual group 23 (65.71%) needed oxytocin infusion as compared to 20 (57.14%) in vaginal group required labor augmentation with oxytocin (P=0.45). In both the interval between induction and onset of active labor was (P=0.36). With respect to delivery, 54.28% women in group I and 48.57% women in group II delivered within 12 h after starting induction. Mean induction to delivery interval was 13.20+7.56 hours in sublingual group and 14.35+6.68 hours in vaginal group (P=0.67). The average duration of first stage of labor was 4.73+2.59 hours in sublingual group as compared to 4.82+2.47 hours in vaginal group (P=0.89). The average duration of second stage in sublingual and vaginal group was 26.82+16.03 and 27+18.50 minutes (P=0.58). Similarly the average duration of third stage in sublingual and vaginal group was 6.02+2.29 minutes and 5.77+2.75 minutes, respectively (P=0.67). Out of 35 women in each group, 29 women (82.8%) in both sublingual group and vaginal group had normal vaginal delivery. One woman in sublingual group (group I) and three women in vaginal group (group II) had instrumental delivery. Emergency cesarean section was done in 5 women (14.28%) in sublingual group and 3 women (8.57%) in vaginal group means more number of women were delivered by cesarean section in sublingual group (P=0.45). Table 2 shows amongst fetal side-effects meconium stained liquor and non-reassuring fetal heart rate were of major concern. Meconium passage was seen in 4 women (11.42%) in sublingual group as compared to 2 women (5.71%) in vaginal group. Non-reassuring fetal heart rate was noted in 2 women (5.71%) in sublingual group and 5 women (14.28%) in vaginal group. Though more number of women in vaginal group had not reassuring fetal heart rate, but the difference between two groups in relation to fetal side effects was not statistically significant (P=0.23). There is no still birth or early neonatal death noted in either of the group. The average birth weight of neonates in sublingual group was 2.9+0.5 kg and in vaginal group was 3.0+0.4 kg (P>0.05). Six neonates born to women induced sublingually and seven neonates born to women induced vaginally were admitted in NICU, out of these neonates, nearly 2/3rd were admitted for more than 24 h in sublingual group as compared to 1/3rd in case of vaginal group (P=0.39). The mean Apgar score at 1 min was 7.54+0.78 in sublingual group and 7.68+1.07 in vaginal group. Mean Apgar score at 5 min was 9.45+0.88 in sublingual group and 9.62+0.87 in vaginal group. Six newborn (17.14%) in sublingual group and seven (20%) in vaginal group had low Apgar score at the end of 5 min (P>0.05).

Discussion

The onset of spontaneous labor is a robust and effective mechanism which is preceded by the maturation of several fetal systems, and should be given every opportunity to operate on its own. We should only induce labor when we are sure that we can do better.

Table 5: Comparison of Perinatal Outcome.

Study (in percentage)	Mean Number of IUD/ Stillbirths		Mean Birth Weight (kg)		Apgar Score <7 at 5 min (%age)		NICU Admissions (%age)	
	s/l	Vag	s/l	vag	s/l	Vag	s/l	Vag
Calisken et al. [5]	-	-	3.2+0.5	3.3+0.5	0	0	3.8	2.5
Bartusevicius et al. [6]	-	-	3.5+0.3	3.5+0.3	2.9	2.9	2.9	2.9
Zahran et al. [7]	-	-	-	-	0.8	1.6	1.6	2.1
Fakhir et al. [11]	-	-	-	-	0	1.7	6.3	8.8
Prabha et al. [12]	-	-	-	-	2	2	6	18
Present study	0	0	2.9+0.5	3.0+0.4	2.85	5.71	17.1	20

So, for these indications, induction of labor is often the principal medical intervention utilized to decrease both maternal and fetal morbidity and mortality. Misoprostol is a synthetic prostaglandin E1 analogue used in cervical ripening and labor induction at term in developed as well as developing countries. It is a low cost product, easily available, affordable and stable at room temperature. It can be used orally, vaginally and sublingually for labor induction. Oral and sublingual misoprostol have a rapid onset of action. Sublingual and vaginal misoprostol may perhaps be compared as both have mucosal uptake, have prolonged activity and possess a greater bioavailability. The present prospective, randomized, interventional study done on two groups, group I (sublingual group) and group II (vaginal group) according to computer generated randomization table with each group containing 35 women. The various antenatal characteristics were taken into account like maternal age, weight, BMI, booking status; gravidity and parity of women in both the groups were comparable. In our study the mean age of the women in Group I (sublingual group) was 25.10+3.58 and in group II (vaginal group) was 25.21+3.56 (P=0.30). In the study done by Calisken et al. [5], Bartusevicius et al. [6], Zahran et al. [7] and Tayyba et al. [8] for comparing sublingual and vaginal misoprostol, the mean age was similar to our study. And also the mean BMI of women in sublingual group was 23.02+2.64 and in vaginal group it was 23+3.4 (P=0.74). Which is comparable to study by Bartusevicius et al. [6] was 25+5.8 in sublingual group and 24+5.9 in vaginal group (Table 3). The mean parity in our study was 1.25+0.5 in sublingual group and 1.25+0.6 in vaginal group which is comparable to; Bartusevicius et al. [6], Nassar et al. [9] and Ayati et al. [10]. The average gestational age at the time of induction of labor in our study was 39.4+1.1 weeks in sublingual group and 39.8+1.0 weeks in vaginal group (P=0.16). In the similar studies by Nassar et al. [9], Ayati et al. [10] and Fakhir et al. [11], the mean gestational age was comparable to our study. However, in the study conducted by Bartusevicius et al. [6] and Zahran et al. [7], the average gestational age was (S/L: 41+0.9 weeks; Vag: 40+1.1 weeks) and (S/L: 40.5+2 weeks; Vag: 40.7+1.8 weeks) respectively, which was slightly higher than our study. Table 4 shows in our study 85.6% women in sublingual group and 91.3% women in vaginal group had vaginal delivery (P>0.05) with slightly higher incidence of instrumental delivery in vaginal group (8.57%) as compared to sublingual group (2.81%). Calisken et al. [5], Bartusevicius et al. [6], Ayati et al. [10] and Tayyba et al. [8], similar number of women had vaginal delivery after induction with misoprostol. In our study 14.2% women in sublingual group and 8.5% women in vaginal group had cesarean section (P>0.05). However in all the above studies there was no significant difference between rate of cesarean section after induction with sublingual and vaginal misoprostol (P>0.05). There were some differences between the sublingual and vaginal group in the various perinatal characteristics like birth weight, low Apgar score at 5 min and NICU admissions but the difference between the two groups was not statistically significant. In the present study the average birth weight of the newborns in two groups was almost similar (2.9+0.5 kg in sublingual and 3.0+0.4 kg in vaginal group. However, a higher birth weight was noted in the studies conducted by Calisken et al. [5] and Bartusevicius et al. [6]. More number of newborns in group I had low Apgar score of less than 7 at 5 min (5.7%) as compared to babies born to women in group II (2.8%). Similar observations were made in the studies by Zahran et al. [7] and Fakhir et al. [1] where slightly higher number of babies in vaginal group had low 5 min Apgar score. However, in the study by Bartusevicius et al. [6] low Apgar at 5 min was noted in equal number of babies born to women in sublingual and vaginal group. Seven neonates (20%) in vaginal group as compared to six neonates (17.1%) born to sublingual group were admitted to NICU (P>0.05) similar no. by Fakhir et al. [11] and Prabha et al. [12]. Compared to our study, a significantly lesser number of neonates in both groups were admitted to the NICU in the studies by Calisken et al. [7], Bartusevicius et al. [6] and Zahran et al. [7]. Because plasma levels of misoprostol and the area under the curve are significantly greater when the same dose is administered sublingually rather than vaginally, the sublingual route could be expected to be more effective. No difference was found between sublingual and vaginal groups in relation to the number of doses required, induction to delivery interval and mode of delivery. There was no significant difference in the maternal and fetal side-effects and perinatal outcomes though meconium passage was noted more in sublingual group (Table 5). It was noted that the sublingual misoprostol is as safe as vaginal misoprostol in induction of labor in term pregnancies but more studies with larger sample size are recommended to confirm or negate this possibility.

Conclusion

Overall, induction of labor using prostaglandins seem to improve the rate of patient going into active labor, reduce the need for oxytocin augmentation leading to successful vaginal delivery, lower the rate of cesarean sections and to be associated with improved maternal satisfaction. Misoprostol (PGE1) administered locally in genital tract or taken orally or sublingually induces cervical ripening and facilitates labor induction. No significant difference was found between sublingual and vaginal administration of misoprostol in relation to the number of doses required, induction to delivery interval and mode of delivery. With regard to perinatal outcomes slightly more number of women in vaginal group experienced hyper stimulation while sublingual route was associated with more meconium passage. In view of limited sample size of our study, we cannot reach definitive conclusions in regard to the preference of sublingual or vaginal route of misoprostol administration for induction of labor and its perinatal outcome.

Statistical Analysis

The statistical difference between two groups was compared using appropriate statistical tests. The p value of <0.05 was considered as statistically significant.

Ethical Issues

Approval of Protocol Review and Institutional Ethics committee was taken for the study and guidelines set up by ICMR (1994) and Helsinki Declaration (modified 2000) was followed.

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