Original Research Article

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Comparison of 25 Microgram of Sublingual Misoprostol with 25 Microgram Vaginal Misoprostol for Induction of Labour at Term

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Abstract

Introduction: To compare 25 microgram of misoprostol with two different routes [sublingual and vaginal] for induction of labour at term in terms of efficacy, tolerability and safety. *Material and Method:* After getting approval from ethical committee, 180 patients those for labour induction at term were included in this study. 90 patients were administered sublingual misoprostol and remaining 90 patients were administered vaginal misoprostol after considering inclusion and exclusion criteria. Outcome measures like mode of delivery, induction-delivery interval, maternal complications, fetal outcome and complications were compared using an unpaired, two-tailed Student's *t* test and chi-square test.

Results: 25 μg of sublingual misoprostol patients had shortened induction delivery interval and needed less number of misoprostol tablets and pelvic examination than vaginal misoprostol ($p<0.05$) with no significant difference in mode of delivery and fetomaternal complications. *Conclusion:* we conclude that 25 μg of sublingual misoprostol is better in efficacy than 25 μg of vaginal misoprostol for term induction with no difference in tolerability and safety.

Keywords: Induction; Labour; Misoprostol; Sublingual; Term; Vaginal.

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Introduction

Induction of labour at term is always in changing trend in search for best drug and method in terms of successful fetomaternal outcome. Though lot of methods are available at present, induction using drugs are commonly practiced. Commonly used drugs include oxytocin, misoprostol, dinoprostone and mifepristone. Misoprostol, a prostaglandin E1 analogue has added advantage of cervical ripening [1] when compared to oxytocin. Though misoprostol and dinoprostone can help in cervical ripening, misoprostol is cheaper, more stable, easily storable [2] and has multiple routes of administration [3] when compared to dinoprostone. There is always a search for better and safer route of administration for misoprostol. Though misoprostol is used as off label drug [4] in these conditions; vaginal route is still practiced. Nowadays few clinical trials are focusing on sublingual route, stating rapid peak concentration, avoidance of first pass metabolism [5], less chance of uterine hyperstimulation due to direct contact and ease of administration [4]. This study is to compare the efficacy and safety of 25 microgram of sublingual misoprostol with 25 microgram of vaginal misoprostol administered at 4-hour intervals for maximum of 6 doses for labour induction in term pregnancy with an unripe cervix.

Materials and Methods

After getting approval from ethical committee, 180 patients those for labour induction at term were included in this study. 90 patients were administered sublingual misoprostol and remaining 90 patients were

administered vaginal misoprostol. Inclusion criteria includes nulliparous and multiparous women with live singleton pregnancy at a gestational age of 37 completed weeks or more with a medical or obstetric indication for induction including postdated pregnancy, prelabour rupture of membrane (PROM), mild preeclampsia (MPE) and gestational diabetes mellitus (GDM) with cephalic presentation and unfavorable cervix with reassuring fetal heart tracing.

Exclusion Criteria includes multiple gestation, malpresentation, previous uterine surgery including cesarean surgery, known contraindications to the use of prostaglandins (e.g. asthma), grandmultiparity, need for immediate delivery, chorioamnionitis or hyperthermia > 38°C, active vaginal bleeding, ultrasonically estimated oligohydramnios, polyhydramnios, suspicion of fetal malformation, macrosomia or growth restriction.

Randomization was done by computer prepared data. They had been divided into 2 groups.

Group A: sublingual misoprostol (SLM)

90 patients for labour induction were randomly allocated for 25 microgram (µg) sublingual misoprostol administration every 4th hourly for maximum of 6 doses.

Group B: vaginal misoprostol (VM)

90 patients for labour induction were randomly allocated for 25 microgram vaginal misoprostol administration every 4th hourly for maximum of 6 doses.

Method

Each women was allocated to receive 25 ìg sublingual misoprostol every 4th hourly for maximum of 6 doses in group A and 25 microgram vaginal misoprostol administration every 4th hourly for maximum of 6 doses. If patient had atleast three regular contraction in 10 minutes, enters active phase of labour [regular uterine contraction and cervical dilatation greater than or equal to 3 cms] and cervix favourable for amniotomy (Bishop score greater than or equal to 8), then subsequent dose of misoprostol was withheld. As soon as fetal head engagement and cervical dilation permitted, amniotomy was performed, followed by oxytocin augmentation if the frequency of contractions was less than three per 10 minutes each lasting for 45 seconds or the contractions pattern was dysfunctional. Oxytocin was administered not earlier than 4 hours after the last misoprostol dose, starting at 1 milli international Units(mU)/minute and increased by 1 mU/minute every 15 minute until adequate contractions persisted. Continuous fetal cardiotocography was used throughout the study.

Tachysystole was defined as at least six contractions per 10 minutes during two consecutive 10-minute periods. Hypertonus was defined as a single uterine contraction lasting for 2 minutes or more. Hyperstimulation syndrome was defined as the presence of tachysystole or hypertonus associated with a nonreassuring FHR pattern (fetal tachycardia, late decelerations, severe variable decelerations or loss of FHR variability). All the episodes of hyperstimulation syndrome were included in the analysis regardless of the interval from the time of misoprostol administration to the occurrence of the abnormal FHR pattern. Recognised episodes of hyperstimulation were managed by stopping the oxytocin infusion, maternal repositioning, hydration and oxygen administration. In the sublingual group, the woman was advised to spit out the medication and wash her mouth, and for those in the vaginal group, the tablet was removed when possible. Labour induction was considered a failure if a woman did not enter the active phase of labour following six doses of misoprostol. The woman was then offered a caesarean section.

Following outcome Variables were Measured.

1. Number of women delivered vaginally within 24 hours of the first dose of misoprostol.
2. Interval from the start of induction to vaginal delivery / induction delivery interval.
3. Cesarean rates
4. Number of misoprostol doses given
5. Need for oxytocin augmentation
6. Number of per vaginal examination
7. Uterine tachysystole rates
8. Uterine hypertonus rates
9. Uterine hyperstimulation rates
10. Other Maternal adverse effects
11. Birth weight of baby
12. Incidence of meconium-stained amniotic fluid
13. Neonatal intensive care unit (NICU) admissions.
14. 5 min APGAR score less than 7.

The means between the groups were compared using an unpaired, two-tailed Student's *t* test. Categorical variables were analysed using chi-square test. $P < 0.05$ was considered statistically significant. For discrete data, relative risk (RR) with 95% confidence intervals (CI) was used.

Results

During the study period, 212 patients were enrolled for labour induction and after proper selection, 180 patients were included. Patients in both groups were comparable for age (Years), parity, gestation age (Weeks), Bishop Score and Indication for induction (Table 1). Sublingual group required significantly less number of misoprostol dose for successful delivery when compared to vaginal group (p=0.02). Sublingual group patients needed significantly less number of Pelvic examination than vaginal route of administration (p=0.04) (Table 2). Average number of Misoprostol tablet used was 1.85±1.02 in sublingual route and 2.20±1.00 in vaginal route with significant difference among the group (P= 0.02).

Oxytocin was used for augmentation in 67 patients in sublingual group and 70 patients in vaginal group which is comparable. (P > 0.05). All patients in both groups had delivered within 24 hours either by vaginal or caesarean section. Regarding the mode of delivery, there was no significant difference among the group.78 patients had vaginal delivery in sublingual group compared to 75 patients in vaginal misoprostol group (P > 0.05). Among vaginal delivery in sublingual group there was 73 spontaneous delivery and 5 instrument delivery compared to 67 spontaneous and 8 instrument delivery in vaginal group which is not significant (P > 0.05). Indication for caesarean section includes fetal distress, non-progress of labour/arrest of labour and failed induction. 3 patients with fetal distress, 6 patients with non progress of labour and 3 patients with failed induction had undergone caesarean section in sublingual group when compared 5 patients with fetal distress, 6 patients with non progress of labour and 4 patients with failed induction in vaginal group with no significant difference(P>0.05) (Table 3).

Table 1: Table showing demography, parity, gestational age, Bishop score and indication for induction

Parameters	Group A[SLM]	Group B [VM]	P value; Relative risk[95% Confidence interval]
Age [Years]	25.07 ± 3.97	25.08 ± 3.70	0.99
Parity	1.38 ± 0.72	1.32 ± 0.57	0.54
Primigravida	63[70]	65[72]	0.74; 0.97[0.80-1.17]
Multigravida	27[30]	25[28]	0.74; 1.08[0.68-1.71]
Gestational age [Weeks]	39.92±2.45	39.32±2.66	0.12
Bishop score	4.03±0.81	4.05±0.59	0.85
	Indication for induction		
Post term [>41 weeks]	42[46.7]	38[42.2]	0.55; 1.11[0.80-1.53]
Mild preeclampsia	16[17.8]	20[22.2]	0.46; 0.80[0.44-1.44]
Gestational diabetes mellitus	6[6.7]	5[5.6]	0.76; 1.20[0.38-3.79]
Prelabour rupture of membrane	26[28.8]	27[30]	0.87; 0.96[0.61-1.51]

Values as mean±SD, numbers [percentage]

Table 2: Table showing vaginal delivery, misoprostol dose, delivery interval and pelvic examinations

Parameters	Group A[SLM]	Group B [VM]	P value; Relative risk[95% Confidence interval]
Vaginal delivery <24 hours	78(86.7)	75(83.3)	0.53; 1.04 (0.92 -1.18)
Total doses of misoprostol	1.85 ± 1.02	2.20 ± 1.00	0.02
Induction delivery interval(minutes)	650.98 ± 250.83	738.45 ± 230.97	0.01
Number of pelvic examination	6.25±2.70	7.15±3.11	0.04

Values as mean±SD, numbers [percentage]

Table 3: Table showing oxytocin usage, mode of delivery and indication for caesarean section

Parameters	Group A[SLM]	Group B [VM]	P value; Relative risk[95% Confidence interval]
Oxytocin use	67 (74.4)	70 (77.8)	0.60; 0.95 (0.81 - 1.13)
Total Vaginal delivery	78 (86.7)	75 (83.3)	0.53; 1.04 (0.92 - 1.18)
Spontaneous Vaginal delivery	73 (81.1)	67 (74.4)	0.28; 1.09 (0.93 - 1.27)
InstrumentalVaginal delivery	5 (5.6)	8 (8.9)	0.39; 0.63 (0.21 – 1.84)
Caesarean section	12 (13.3)	15 (16.7)	0.53; 0.80(0.40 -1.61)
Indication for caesarean section			
Fetal distress	3 (25.0)	5 (33.3)	0.47; 0.60 (0.15 – 2.44)
Non progress of labour	6 (50.0)	6 (40.0)	1.00; 1.00 (0.34 – 2.98)
Failed induction	3 (25.0)	4(26.7)	0.70; 0.75(0.17-3.26)

Values as mean±SD, numbers [percentage]

Table 4: Table showing maternal and fetal complications

Parameters	Group A[SLM]	Group B [VM]	P value; Relative risk[95% Confidence interval]
Maternal complications			
Tachysystole	9 (10.0)	7 (7.80)	0.60; 1.29(0.50 -3.30)
Hypertonus	4(4.4)	3 (3.3)	0.70; 1.33(0.31 – 5.79)
Hyperstimulation syndrome	4 (4.4)	4 (4.4)	1.00; 1.00 (0.26 – 3.87)
Vomiting	3 (3.3)	2 (2.2)	0.65; 1.50(0.26 - 8.76)
Fetal parameters and complications			
Birth weight [Kgs]	2.89±0.23	2.90±0.19	0.75
Apgar score <7 at 5 minutes	3 (3.3)	4 (4.4)	0.70; 0.75 (0.17 - 3.26)
Meconium passage	7 (7.7)	5 (5.5)	0.55; 1.40(0.46-4.25)
NICU admission	2 (2.2)	3 (3.3)	0.65; 0.67 (0.11 – 3.90)

Values as mean±SD, numbers [percentage]

Regarding maternal uterine complications that include tachysystole, hypertonus and hyperstimulation syndrome, 9 patients in sublingual group and 7 patients in vaginal group had tachysystole with no need of intervention.4 patients in sublingual group and 3 patients in vaginal group had hypertonus with no need of intervention. 4 patients in each group had hyperstimulation syndrome. There was no significant difference among the groups regarding maternal complications (P>0.05). Hyperstimulation syndrome was treated by maternal left lateral position, O2 administration and infusing intravenous fluids. All the patients had responded well and were delivered vaginally except one patient who was delivered by outlet forceps for failed maternal effort in vaginal group. Other maternal complication noted was vomiting and was there in 3 patients in sublingual group and 2 patient in vaginal group which does not need any intervention.

The average birth weight (kilograms) of baby is 2.89±0.23 in sublingual group and 2.90±0.19 in vaginal group with no significant variation among the group. 7 babies had meconium passage in sublingual group compared to 5 babies in vaginal group. 3 babies had APGAR score of less than 7 in sublingual group and 5 babies in vaginal group, out of which 2 babies in each group needed NICU stay. One more baby in vaginal group with meconium aspiration needed NICU admission thus total of 3 babies in vaginal group needed NICU admission. There was no significant complication (P>0.05) on babies irrespective of mode of misoprostol administration (Table 4).

Discussion

Though misoprostol had been used as off label drug for term induction, lot of studies were showing better results than other drugs. There was no difference in age, parity and gestational age among the both groups in our study. Bishop scoring was comparable in both groups. Though in our study more post term patients were in sublingual group, it did not have significant difference with vaginal group and also it did not affect mean gestational age.

The results had showed that 25μg of sublingual misoprostol administration resulted in significantly shorter induction to delivery interval, with a lower number of misoprostol doses required and lesser number of pelvic examination required as compared with those administered 25 μg of vaginal misoprostol. In Tang et al [6] study, the sublingual route has been shown to produce significantly higher serum peak concentration of misoprostol than either oral or vaginal administration. In addition, the area under the curve for plasma levels over 4 and 6 hours was significantly greater following sublingual administration than for either oral or vaginal administration. Aronssonet al [7] had evaluated the effects of misoprostol on uterine contractility following different routes of administration. The sublingual application of misoprostol has, with regard to effects on the myometrium, had rapid effect on uterine contractility as oral administration and the bioavailability was similar to that following vaginal administration. We had administered sublingual dosage every 4th hourly. These findings may explain the significant reduction in induction delivery interval with sublingual misoprostol in our study than vaginal group. A Bartuseviciuset al [5] had also observed same result in their study. They had used 50 μg of sublingual misoprostol in contrast to 25 μg in our study. Our study had showed that 25 μg administered sublingually was more effective in shortening the induction delivery interval and also reducing total misoprostol tablets used for induction which may decrease the cost of management.

Studies done in indian population [2,8,9] with same dosage had shown highly significant reduction

in induction delivery time, total number of misoprostol doses and pelvic examination required [P<0.01] but our study showed only significant difference [P= 0.01-0.05]. This needs large sample studies to confirm. There was no significant difference between the groups regarding mode of delivery which is comparable to studies done on indian and iran population. But Feitossa et al [10] had observed significantly less vaginal delivery rates and more fetal distress in sublingual group than vaginal group. They had used 25 μg of sublingual misoprostol every 6 hourly. Tang et al [8] on studying pharmacokinetics of misoprostol in different route of administration had found that at the end of 6 h, the serum levels of MPA in the vaginal groups were higher than those of the sublingual and oral routes. It may be due to their higher dosing interval (6 hours Vs 4 hours) than our study. Sublingual misoprostol [25 μg] administered 4th hourly may be optimal dose for term induction.

Our study had showed a significant reduction in number of pelvic examination before delivery. Patient would be comfortable when number of pelvic examination was reduced. We had not taken satisfaction parameter in our study as it was beyond our scope. Nasser et al [8] had studied on patient satisfaction criteria and they had concluded that sublingual misoprostol was satisfactory route of administration than vaginal route. This route of administration may reduce the chance of infection particularly in PROM cases because of less number of vaginal examinations required. On considering these facts and our observation on significant decrease in number of pelvic examination sublingual route may be a satisfactory route of administering misoprostol.

Different routes of misoprostol administration for labour induction necessitate carefully balancing the benefit (shorter time until delivery) against the risk (uterine hyperstimulation, adverse neonatal and maternal outcomes). Incidence of tachysystole, hypertonus and hyperstimulation syndrome was not significant in our study. BartuseviciusA et al[5] had used 50 μg of sublingual misoprostol had noted three fold higher incidence of tachysystole in the sublingual than in the vaginal group. In our study we had observed no significant value for tachysystole with 25 μg of sublingual misoprostol, still we cannot conclude on adverse effect due to our sample size.

The neonatal outcomes were similar in both the trial groups. There was no significant difference in birth weight of baby among the study groups. In term of other maternal complication, in our study patient had developed vomiting in three patients in sublingual group and two patients in vaginal group. Though number of patient varies, it was not significant. From our study, we found that vomiting can occur irrespective of route of administration. It might be due to systemic action of absorbed misoprostol.

Sublingual dosing for labour induction is attractive because of ease of administration, less frequent need for vaginal examination, greater freedom of position and the possibility of its use despite vaginal bleeding or ruptured membranes. Cost of management is also low when comparing to other modes of induction. Even though this was not assessed in the present study, we assume higher patient acceptance of sublingual route, which was observed with oral when compared with vaginal administration.

Conclusion

We conclude that 25 μg of sublingual misoprostol administered every 4th hourly for maximum of 6 doses was more effective for induction in full term pregnancy than 25 μg of vaginal misoprostol administered every 4th hourly for maximum of 6 doses in terms of shortened induction delivery interval, less number of misoprostol tablets required and less number of pelvic examination required. It neither alters vaginal delivery rate and caesarean section rate nor produce significant complications like hypertonus, tachysystole and hyperstimulation syndrome than vaginal route of administration. We believe further studies on safety with larger numbers of women need to be conducted before we advocate sublingual misoprostol as routine labour induction agent.

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