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To compare the efficacy and safety of sublingual and vaginal dose of Misoprostol for induction of labor in term viable pregnancies

Authors
Dr Shweta Patel[1], Dr Shabd Yadav[2], Dr Kalpana Yadav[3*]
[1]Assistant Professor, Department of Obstetrics & Gynecology, AIIMS Bhopal (M.P.), India
[2]Associate Professor, Department of Pediatrics, SSMC Rewa (M.P.), India
[3]Professor & Head, Department of Obstetrics & Gynecology, SSMC Rewa (M.P.), India
*Corresponding Author
Dr Kalpana Yadav
Professor & Head, Department of Obstetrics & Gynecology, SSMC Rewa (M.P.), India

Abstract

Objective: *To compare the efficacy and safety of misoprostol by sublingual and vaginal route for induction of labor in term viable pregnancies.*

Material and Methods: *This prospective study was conducted on 200 women, who presented with indication of induction of labor. After taking informed consent cases were randomly divided into sublingual and vaginal group with 100 cases in each. Starting dose of misoprostol for induction in primigravida was 50µg and in miultigravida was 25µg followed by 25µg if required, up to maximum of 5 doses. Primary outcome was to determine efficacy of drug in term of total vaginal deliveries after induction and to determine safety in view of total number of cesarean section and fetal outcome. Secondary outcome was to compare total dose, number of doses, induction delivery interval, antepartum complications and fetal outcome in both groups.*

Result: *Total number of successful vaginal deliveries were more in sublingual group (87%). Significant number of primigravidae in sublingual group delivered with single dose of 50µg misoprostol compare with vaginal group (56.89% in s/l v/s 32.69%in p/v group). Induction delivery interval, oxytocin augmentation, meconium stained liquor, abnormal uterine action, total number of cesarean sections all were less in sublingual group than vaginal group. No significant difference was seen in neonatal outcome.*

Conclusion: *Sublingual route of misoprostol has better efficacy than vaginal route of misoprostol for induction of labor.*

Keywords: *Misoprostol, Induction of labor, Meconium stained liquor.*

Introduction

Induction of labor is widely carried out all over the world in cases, in which continuation of pregnancy is hazardous to the mother and/or her fetus. Labor induction in women with live fetus at term remains a major challenge in modern

obstetrics. In the recent past misoprostol, the wonder drug which used for management of PPH is still under trial for labor induction with various routes and doses. It has some potential advantages as compared with PGE_2 i.e. it is inexpensive, stable at room temperature, easy to administer and may be given orally.[1] Initially it was used as a vaginal dose (50µg) every 2 hourly, up to maximum total dose of 600µgbut it is associated with higher risk of uterine hyper- stimiulation.[2] Since then lower dose have been proposed to reduce adverse effect though with other routes. Ever since pharmacokinetic studies show that sublingual and oral misoprostol produces earlier and higher peak plasma concentration of misoprostol acid than vaginal or rectal misoprosto.[3]Women prefer to use misoprostol orally or sublingually instead of vaginal route, claiming that oral route is more convenient and offer greater privacy.[4]

In spite of different doses and routes of administered (sublingual, oral and vaginal), ideal doses and mode of administration still remain to be controversial. Thus, the present study is being conducted to compare efficacy and safety of sublingual and vaginal route of misoprostol for induction of labor and for establishing the best route and best dose of drug keeping in mind fetal and maternal risk.

Aim

To compare the efficacy and safety of misoprostol by sublingual and vaginal route for induction of labor.

Objectives

1. To study various demographic data like booking status, age, gravidity and various indications of induction.
2. To determine safe dose required for induction establishment.
3. To determine total dose, number of doses and induction delivery interval required for safe vaginal delivery.
4. To determine successful induction in term of vaginal deliveries within 12hours/ 24hours of initiation of labor.
5. To determine safety of drugs by total number of caesarean section and fetal outcome.

Material and Methods

The present study was conducted on 200 women, who presented with indication of induction of labor in department of Obstetrics and Gynecology, Shyam Shah Medical College and associated Gandhi Memorial Hospital, Rewa (M. P.) from July 2009 to September 2010.

Women with ≥37 weeks of gestation with varied parity after taking informed consent following exclusion/inclusion criteria were taken in the study.

Exclusion Criteria

1. Parity ≥4, Recurrent abortions ≥2.
2. Known hypersensitivity to use of prostaglandin.
3. Previous caesarean delivery or other type of uterine surgery.
4. Need for immediate delivery (such as ominous FHR, active uterine bleeding).
5. Severe oligohydramnios (AFI <5cm by USG), Severe IUGR, Chorioamnionitis, Cephalopelvic disproportion.

Inclusion Criteria

1. Single live pregnancy in cephalic presentation
2. Normal FHR tracing
3. Unfavorable cervix (Bishop score <6)
4. Pregnant woman with any of the indication for induction of labor :-
   a. Prolonged pregnancy (≥40 weeks of gestation)
   b. Prelabor rupture of membrane
   c. Gestational/chronic hypertension.
   d. IUGR
   e. Oligohydramnios (AFI 6±1cm)

After selection, detailed obstetric history complete physical and obstetric examination was done. Gestational age and AFI was assessed by

ultrasonography. Cases were randomly put in either of the two groups with 100 cases in each:-
Group A – sublingual group (s/l).Group B – Vaginal group (p/v).
Starting dose of misoprostol in primigravida was 50µg(half of 100µg)and in miultigravida was 25µg, further regimen was as follows:

a) If uterine contractions were adequate, no further action was taken;
b) If uterine contractions were inadequate and/or progress was inadequate (cervical dilatation less than 1 cm per hour), 25µg misoprostol was subsequently given at 4 hours interval up to maximum 5 doses.

A watchful monitoring of FHR and uterine contraction was done every 15 minutes and later at regular intervals. Once cases entered in active labor, further augmentation with oxytocin was required only in cases with ineffective contractions (if the frequency of contractions was <3 per 10 minutes, or the contraction pattern was dysfunctional) oxytocin was administered not earlier then 4 hour after the last misoprostol dose starting at 1 miu/minute and increased by 1 miu/minute every 15 minute until adequate contractions persisted. Cases of abnormal uterine action (tachysystole, hypertonus or hyperstimiulation) was managed by intrauterine resuscitation (which included stopping the oxytocin infusion, maternal repositioning, hydration and oxygen administration) and/or injection Terbutaline. In case of fetal distress (FHR<100 minute) or cases not responding to injection Terbutaline were managed by emergency caesarean section.
An improvement of Bishop's score by 4 points from the original score, was taken as successful induction and If patient didn't respond to the drug at the end of protocol were consider as failed medical induction and taken for caesarean section. Fetal outcome was noted on the basis of Apgar score at 1 minute and 5 minutes. Resuscitation/NICU care was documented accordingly and followed for 2 days. Resuscitation was defined as the need for positive pressure ventilation or intubation. Mother and baby monitored for at least 3 days before discharge from hospital.
The primary outcome measures were caesarean section as a measure of safety, and failure to achieve vaginal delivery in 24 hours as a measure of clinical effectiveness. Secondary outcome measures included intrapartum events, uterine activity, maternal adverse effects and maternal and neonatal complications.
The results were analyzed by statistically modified 't' test. Statistical significance was assigned to P values < 0.05.

Results

Total 200 cases were randomized for the study and allocated into two groups with 100 cases in each. As shown in Table 1, in the present study maximum women (59.5%) were unbooked and belonged to 20-25yr age group (76%) and majorities (63%) of women were primigravidae with Modified Bishop's score ≤3 prior to induction (59%). In both groups PROM was the indication of induction in maximum cases (41%).Table 2, shows that in the present study 56.89% primigravidae in sublingual group were delivered with 50µg misoprostol (single dose) compared to 32.69% in vaginal group, which was statistically significant (p<0.05). Table 3, shows that in sublingual group majority of women (37.5%) delivered within 8-12hrs, whereas in vaginal group 35.84% women delivered within 12-16hrs.As shown in Table 4, no significant difference seen between both the study groups in term of mode of delivery, need of oxytocin augmentation, intrapartum complications and fetal outcome. Table 5, shows Comparison of maternal and perinatal outcome to induction delivery interval.

Table 1: Distribution of cases according to demographic profile and indications of induction

Variable	Sublingual group (s/l) (n=100)	Vaginal group(p/v) (n=100)
Booked cases	39	42
Unbooked cases	61	58
Age group	20-35	20-35
Primigravidae	65	61
Miultipara	35	39
Modified Bishop's score ≤3	60	58
Modified Bishop's score ≥3	40	42
Indications of induction		
PROM/Leaking	44	38
Postdatism	27	30
Hypertensive disorders in Pregnancy	10	12
Oligohydramnios	12	10
IUGR	6	8
Others*	1	2

*Gestational thrombocytopenia
Gestational Diabetes

Table 2: Distribution according to total dose required for vaginal delivery

Induction delivery dose	Sublingual group(n=88)		Vaginal group (n=81)	
	Primigravida (n=58)	Miultipara (n=30)	Primigravida (n=52)	Miultipara (n=29)
25µg	3(5.17%)	15(50.0%)	1(11.92%)	11(37.93%)
50µg	33(56.89%)	9(30.0%)	17(32.69%)	9(31.03%)
75µg	7 (12.06%)	5(16.67%)	14(26.92%)	6(20.68%)
100µg	10 (17.24%)	1(3.33%)	12(23.07%)	3(10.34%)
125µg	3(5.17%)	-	5(9.61%)	-
≥150µg	2 (3.44%)	-	3(5.76%)	-

Table 3: Distribution of cases according to induction delivery interval

Induction delivery interval	Sublingual group(n=88)		Vaginal group(n=81)	
<4 hrs	3	3.49%	5	6.17%
4-8 hrs	14	14.9%	10	12.33%
8-12 hrs	33	37.5%	26	32.09%
12-16 hrs	22	25%	29	35.80%
16-20 hrs	6	6.81%	4	4.93%
20-24 hrs	6	6.81%	4	4.93%
>24 hrs	4	4.54%	3	3.7%

Table: 4 Distribution of cases according to mode of delivery, oxytocin augmentation, intrapartum complications and fetal outcome.

Variable		Sublingual group(s/l) (n=100)	Vaginal group(p/v) (n=100)
Mode of delivery	Vaginal	88(88%)	81(81%)
	Caesarean section	12(12%)	19(19%)
Oxytocin augmentation	Required	33(33%)	43(43%)
	Not required	67(67%)	57(57%)
Fetal complications	MSL	9(40.09%)	17(45.94%)
	Fetal Distress	3(13.63%)	4(10.81%)
	Hyperstimiulation	5(22.72%)	4(10.81%)
Maternal complications	APH	2(9.09%)	5(13.51%)
	DTA	1(4.54%)	2(5.4%)
	Cervical tear	-	2(5.4%)
Failed induction		2(9.09%)	3(8.1%)
Fetal outcome	Healthy	84(84%)	77(77%)
	Apgar <7 at 1 min	16(16%)	23(23%)
	NICU Admission	5(5%)	7(7%)

Table: 5 Comparison of maternal and perinatal outcome to induction delivery interval

Outcome	Induction delivery interval				Total (n=200)
	≤4-8 hrs	8-12 hrs	12-16 hrs	>16-20 hrs	No
Abnormal uterine action	7	2	-	-	9
Sublingual group	4	1	-	-	5
Vaginal group	3	1	-	-	4
$\chi^2 = 0.032$ p = 0.857 Not Significant					
Vaginal delivery	32	59	51	27	169
Sublingual group	17	33	22	16	88
Vaginal	15	26	29	11	81
$\chi^2 = 2.557$ p = 0.465 Not Significant					
Caesarean section	8	12	6	5	31
Sublingual group	4	5	1	2	12
Vaginal	4	7	5	3	19

Discussion

In the present study maximum induced women were delivered vaginally (87% in s/l v/s 79% in p/v group). Caesarean sections were needed, 12% in s/l and 19% in p/v group compare to study by Caliskan et al found 81.3% delivered vaginally and 18.7% by Caesarean section in sublingual group.[5]Bartusevicus et al found 17% Caesarean section in sublingual and 20% in vaginal group.[6] Whereas study done by Nasar et al found Caesarean section rate of 35.2% in sublingual and 28.2% in vaginal group which was almost twice more than our study.[7]

In sublingual group maximum (56.89%) primigravidae delivered with 50µg (single dose) Misoprostol, whereas with same dose in vaginal group 32.69% women delivered which is almost two times more in sublingual group and statistically significant. Similar number of women delivered in both groups up to 100µg dose. These above observations may be because of the systemic bioavailability of sublingual misoprostol avoided first pass metabolism; hence single dose was sufficient while in vaginal instillation the vaginal secretions decrease local effect of drug. In the study miultigravida women required less dose of drug for delivery due to favorable Bishop's score. Hence it is evident that single dose of misoprostol can be used for inducing the contraction and formation of lower uterine segment (without compromising the fetus) for betterment of surgery and maternal outcome during Caesarean section. Similarly, single dose can be used as trial for vaginal delivery in women for conditions as relative indications for caesarean section. In study of Bartusevicius et al mean number of doses of 50µg misoprostol was significantly lower in sublingual group.[6]

In present study out of all vaginal deliveries approximately 96% women delivered within 21hrs of induction in both groups, in s/l group maximum (31.5%) delivered within 8-12hrs induction delivery interval. Whereas in vaginal group more (35.8%) women delivered in 12-16hrs induction delivery interval. Similarly, in the study by Caliskan et al mean induction delivery interval in sublingual group was 11.8 ± 7hrs and 12.4 ± 6hrs in vaginal group.[5] Study by Bartuseviucius et al it was 15hrs in sublingual and 16.7hrs in vaginal group.[6]

As showed in the study oxytocin augmentation was needed33% in sublingual group compare to 43% in vaginal group. Similarly, study done in 2006 by Feitosa et al found that 34.6% cases in sublingual group needed augmentation.[8] In contrast study by Nassar et al, 81.1% cases in sublingual group needed augmentation.[7]

In our study intrapartum maternal and fetal complications occurred in 22% sublingual and 47% vaginal group. Most common complication was MSL, which was 9% in sublingual and 17% in vaginal group. In sublingual group out of 9 cases of MSL 6 were delivered vaginally and 3 needed caesarean section, whereas in vaginal

group out of 17 cases of MSL 11 were delivered vaginally and 6 underwent in caesarean section due to unfavorable cervix. Similarly, in study by Fisher et al, more MSL were found in vaginal group (7.8%) then in sublingual group (1.6%).[9] Hyperstimiulation was found in 4 women in sublingual and 3 women in vaginal group. Out of them one in vaginal group was managed by tocolytics (s/c Inj. terbutaline), all other were taken for caesarean section due to abnormal fetal heart rate. Study done by Bartusevicius et al found similar rate of hyperstimiulation in both groups.[6]Feitosa et al found hyperstimiulation in 7% sublingual and 1.3% vaginal group.[8] In contrast Moreas Filho found more hyperstimiulation in vaginal group i.e. 1.7% in sublingual Vs 3.2% in vaginal group.[10] Tachysystole occurred in one cases of each group, which was managed by tocolytics with subcutaneous injection terbutaline.[10]

In present study caesarean section for failed induction was done in 2% cases of sublingual and 3% cases of vaginal group. Study by Nassar et al, found 3.5% failed induction in each group.[7] Bartusevicius et al, found same rate of induction failure in both groups.[6] In contrast study by Moreas Filho et al found more failed induction in sublingual group i.e. 10.3% sublingual Vs 4.8% in vaginal group.[10]

In our study 84% in sublingual and 77% in vaginal group had healthy baby at the time of delivery. In sublingual group 16% babies had Apgar <7 at 1 min, out of them 11% needed resuscitation and 5% were admitted in NICU. Whereas, in vaginal group 23% babies had Apgar <7 at 1 min, out of the 17% needed resuscitation and 7% were admitted in NICU, but there was no still birth and all NICU admitted babies were discharge in good condition. In the study by Moreas Filho et al, Apgar <7 at 1 min found in 3.5% babies in sublingual and 4.8% in vaginal group.[10]

In our study when induction delivery interval is compared, in sublingual group 17% women delivered within 8hrs of induction with less dose, but during this interval maximum cases 75.0% (3/4) with hyperstimiulation syndrome were noted. In these cases, early decision of caesarean section was taken as associated with high risk factors i.e. postdatism, IUGR, oligohydramnions. This may be due to early rise in plasma level of drug or repetition of drug prior to subside of its first dose plasma level. Thus 25% (4/12) caesarean section were done in this period and 18.75% (3/16) babies had Apgar <7 at 1 min and one baby admitted in NICU. Whereas, in vaginal group within 8hrs of induction 15% cases delivered vaginally and 21.0% (4/19) needed caesarean section same as sublingual group maximum hyperstimiulation syndrome 66.6% (2/3) occurred in this period 17.39% (4/23) babies had Apgar <7 at 1 min and 28.5% (2/7) needed NICU admission. In 8-12hrs of induction in sublingual group maximum (37%) women delivered vaginally and 41.67% (5/12) needed caesarean section, which were mostly due to MSL (2/12) or fetal distress (2/12). These babies (6/13) had Apgar <7 at 1 min out of them 3 needed NICU admission. In vaginal group maximum caesarean section 36.84% (7/19) were done in this period, out of them mostly (6/7) were due to MSL and fetal distress. These babies were also compromised and 43.4% (10/23) babies had Apgar <7 at 1 min and 2 were needed NICU admission. After 16hrs of induction caesarean sections for failed induction were done in 2 women in sublingual and 3 women in vaginal group.

Conclusion

The secret of success in labor induction lies on replicating the process of spontaneous parturition as closely as possible. Cervical ripening is a prelude to onset of myometrial contractions. Misoprostol administered sublingually as compared to vaginally has been proved to be an effective and better method for cervical ripening and induction of labor, when combined with judiciously timed amniotomy achieving more

vaginal deliveries in women with unfavorable cervix.

But the benefits necessitate to be carefully balanced against the risk of adverse neonatal outcome due to uterine hyperstimiulation, which was observed more in initial hours of induction. There was no significant difference in both groups with respect to mode of delivery, induction delivery interval, abnormal uterine action, failed induction and neonatal outcome, bearing in mind that our sample size was not powered to evaluate these parameters for safety. However sublingual dose is attractive because of ease of administration, less frequent need for vaginal examinations, greater freedom of position, possibility of its use despite vaginal bleeding or leaking, less dose and induction delivery interval required for vaginal delivery. In conclusion Misoprostol seems to be relatively safe, cheap, easy to administer and quite effective for successful induction of labor which is boon to women of developing countries.

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