Observational Study

Comparative study of fetomaternal outcome following induction of labour using sublingual *versus* vaginal misoprostol

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The objective of this study was to compare the efficacy and safety of sublingual with vaginal misoprostol in induction of labour. This was a tertiary hospital based interventional comparative prospective study comprising total 200 pregnant women. In Group 1, 100 women received 25 µg sublingual misoprostol and in Group 2, 100 women were given same dose intravaginally. Misoprostol in both group was repeated every 4 hourly up to maximum 3 doses. Outcome in respect of percentage of vaginal delivery, induction- delivery interval and feto-maternal parameters were observed. Statistical analysis was done applying Student 't' test, z test and Chi Square test. In 70% women delivered vaginally in sublingual and 76% women in vaginal group (p-value= 0.33). Induction delivery time was comparable in two groups (11.36 ± 3.5 hours *versus* 10.5 ± 3 hours respectively, p = 0.11). In the sublingual group, uterine hyperstimulation syndrome was observed in two cases and in one case of group 2 which occur after the second dose of misoprostol. APGAR score at 1 and 5 min was comparable in two groups (7.67 ± 1.01 *versus* 7.69 ± 1.02, p = 0.89 and 9.14 ± 0.9 Vs 9.02 ± 1.14, p - 0.41 respectively). As sublingual misoprostol is equally effective and safe but more acceptable to patient and has better ease of use in comparison to vaginal route, it may be concluded that the sublingual application is a better alternative to vaginal route.

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Key words **: Induction of labour, Misoprostol, Sublingual route, Vaginal route.**

Induction of labour is a common obstetric intervention, performed when the perceived risks to the mother or fetus associated with continuation of the pregnancy are greater than those associated with birth. Labour may be induced for medical or obstetric indications or for the convenience of mother or obstetrician (so called "social" indications). There are various methods involved in induction of labour[1].

- Pharmacological methods (Prostaglandins, Oxytocin & others)
- Non pharmacological methods (Natural, Surgical, Mechanical and others).

Method preferred should be individualized for better outcome of both fetus and mother with least complications. Prostaglandins are rapidly emerging as amazing drugs for induction of labour. Prostaglandins E_1 and E_2 both are used for induction. Recently its use in obstetric and gynecological practice has increased, being used widely in the management of first and second trimester abortion[2], and in the third trimester of pregnancy following intrauterine fetal death[3].

More recently, misoprostol has been used in the induction of labour at term in the presence of a viable fetus, with both vaginal[4] and oral[5] routes. Misoprostol is mostly used vaginally for labour induction, it requires regular vaginal administration which is associated with increase chances of infection, pain, and is also embarrassing for the patient. As we know that higher dose is required when it is used orally due to first pass metabolism, which can be bypassed by using sublingually.

Recently published pharmacokinetic studies show that sublingual and oral misoprostol used for first-trimester abortions produces earlier and higher peak plasma concentrations of misoprostol than vaginal or rectal misoprostol[6,7]. The sublingual route could thus be expected to be more effective than vaginal misoprostol and avoid-

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ing a direct effect on the cervix, might reduce the risk of uterine hyperstimulation and be safer.

From the current Cochrane Systematic Review based on only three small trials, sublingual misoprostol appears to be at least as effective as when the same dose is administered vaginally[8]. Findings of these studies have inspired us to pursue the present study in our institution.

The objective of this study was to compare the efficacy and safety of 25 µg of sublingual misoprostol with vaginal misoprostol in regards to induction- delivery time, successful vaginal delivery, maternal symptomatic complaints, uterine hyperstimulation and effect on fetal heart rate, neonatal APGAR scoring and neonatal morbidity.

Materials and Methods

Study area — Department of Obstetrics and Gynaecology, Eden Hospital; Medical College and Hospital, Kolkata.

Study population — Pregnant women at term/post dated who are admitted meeting the inclusion criteria

Study period — 1st July 2009 to 30th June 2010

Sample size — 200 cases were recruited for the study. They were divided into 2 groups-

Group 1- 100 cases for sublingual misoprostol induction

Group 2- 100 cases for vaginal misoprostol induction

Sample design – Tertiary Hospital based interventional comparative prospective study.

Study design- Exclusion criterion include Prior uterine disruption, Placenta praevia, Cephalo pelvic disproportion, Active genital herpes infection, Cervical cancer, Multiple pregnancy, Fetal macrosomia, Severe hydrocephalous, Malpresentation and Nonreassuring fetal status.

Study technique: It is a comparative prospective study performed after approval by the Institutional Ethics Committee of Medical College, Kolkata. Women were eligible for enrolment with written informed consent if they presented with obstetric or medical indications for labour induction and fulfilled inclusion criteria. Randomization was done using a table of random numbers with proper matching of different criterion in different group.

Group 1-(n-100) - sublingual misoprostol

Group 2- (n-100) - vaginal misoprostol

Each woman received 25 µg of sublingual misoprostol in group 1and 25 µg of vaginal misoprostol in group 2 every 4 hourly (maximum three doses). The subsequent dose of medication was withheld in the presence of any of the following: at least three regular uterine contractions in 10 minutes lasting >40 seconds, active phase of labour, cervix favourable for amniotomy (Bishop score ≥ 8). As soon as fetal head engaged and cervical dilation permitted, amniotomy was performed, followed by oxytocin augmentation if the contractions are inadequate. Oxytocin was administered not earlier than 4 hours after the last misoprostol dose, starting at 5 IU in 500ml @ 5 drops/ minute and increased by 5 drops/minute every 30 minute until adequate contractions achieved. Continuous fetal heart rate monitoring was done throughout the study. Uterine contraction (adequate, inadequate or uterine hyperstimulation) following the administration of misoprostol was assessed by using partogram.

The fetal heart rate changes were recorded as abnormal when there was fetal heart rate irregularity, fetal tachycardia or fetal bradycardia (fetal heart rate less than 100 beats per minute)[9]. All the episodes of hyperstimulation were included in the analysis regardless of the interval from the time of misoprostol administration.

Outcome Measure :

The primary outcomes in both groups were observed by the number of women delivered vaginally or caesarean section within 24 hours of the first dose of misoprostol. Secondary outcome variables included induction–delivery interval, number of misoprostol doses required, need for oxytocin augmentation, maternal adverse effects, uterine hyperstimulation with associated fetal heart rate changes, uterine rupture, post partum hemorrhage, serious maternal complications and maternal death. Neonatal outcomes included APGAR score in 1 min and 5 min, incidence of meconium-stained liqour, and neonatal morbidity or mortality.

Statistical analysis: In this study, test for means, standard deviation and proportions were conducted using the Data Analysis Add-in functionality of MS-Excel. Student 't' test and z-test was applied to test the significance. Chi-Square analyses of contingency tables and test for two proportions were conducted manually in MS-Excel.

Observations

Table 1 shows that both groups had similar age distributions and 59% of women in group-1 while 54% of women in group-2 are primigravida, rest belong to higher gravida (p value 0.75)

Fig 1 shows that both groups of mothers have almost similar distribution of indication for induction (p value 0.99).

Table 1 — *Distribution of cases as per Age & Gravida in two groups*

Age (in years)	Group1	Group2	Grand Total	p value
18 - 21	43 (43%)	46(46%)	89(44.5%)	
22 - 28	54(54%)	51(51%)	105(52.5%)	0.91
> 28	3(3%)	3(3%)	6(3%)	
Grand Total	100(100%)	100(100%)	200(100%)	
Gravida				
G1	59(59%)	54(54%)	103(56.5%)	
G2	27(27%)	30(30%)	57(28.5%)	0.75
G3 or more	10(10%)	12(12%)	22(11%)	
Grand Total	100(100%)	100(100%)	200(100%)	

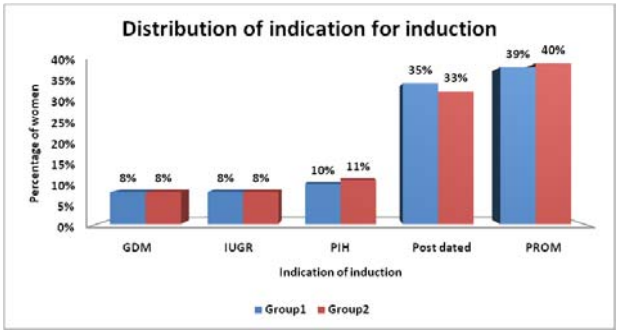

Fig 1 — Distribution of women by indication of labour induction

Table 2 shows that more than 50% women in each group is needed two doses for induction. Mean dose requirement is 2.07 ± 0.7 in sublingual group and 1.98 ± 0.68 in vaginal group which is insignificant (p = 0.71). From this table, it is seen that women in whom successful vaginal delivery had taken place have comparable Induction Delivery Interval (I-D-I) in two groups. (p value 0.11)

In our study the mode of delivery was comparable in Group 1 and Group 2 (Vaginal delivery 67% *versus* 72%, Instrumental 3% *versus* 4% and LSCS 30% *versus* 24% respectively, p =0.33).

Indication of caesarean section was mainly due to fetal distress (66.66% *versus* 7o.8% in Group 1 & 2 respectively, p =0.83). Other indications were induction failure (20% *versus* 20.8%), non progress of labour (10% *versus* 8.335) and obstructed labour (3.33% *versus* 0%).

Fig 2 shows that very few women suffered from any adverse effect by the drug administration. They were limited to milder form and were subsided on treatment. Both

Table 2 — *Comparison of number of dose of misoprostol required & induction delivery interval (I-D-I) (hours) in both groups of women*

Dose required	Group 1	Group 2	p value
1	22(22%)	24(24%)	
2	51(51%)	54(54%)	0.71
3	27(27%)	22(22%)	
Grand Total	100(100%)	100(100%)	
Induction Delivery Interval (mean)			
Time	11 hours 22 min (11.36)		0.11
	10 hours 30 min (10.50)		

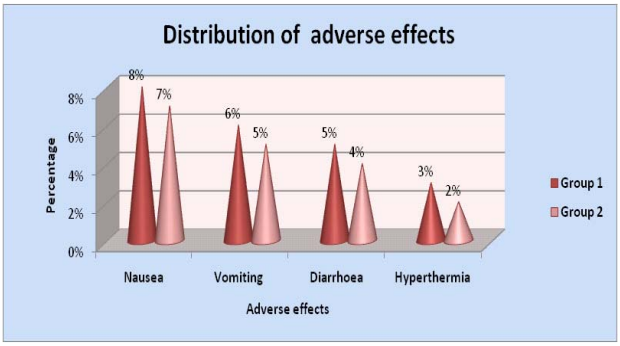

Fig 2 — Comparison of adverse effects of different routes of drug administration in two study groups

the groups did not differ much as p value was >0.05.

In our study, adequate uterine contraction following induction was almost equal in both group(65% *versus* 76% respectively, p=0.22) whereas inadequate contraction was seen in 33% and 23% in Group 1 and Group 2. Hypertonicity of uterus was comparable in both group (2% *versus* 1% respectively).

Table 3 shows that more women in sublingual group required oxytocin augmentation but the difference was not statistically significant.

Regarding the severe maternal complication, post partum hemorrhage was observed in 7 cases in group 1 and 6 cases in group 2. Third stage morbidity was in 1 and 3 cases respectively. There was no uterine rupture or maternal death in either group.

Intrapartum fetal distress and Meconium stained liquor were observed in 18% *versus* 19 % (p=0.85) and 24% versus 20% (p=0.49) in group 1 and 2 respectively.

Fig 3 shows fetal well being is comparable in two groups in respect to 1 min (p=0.89) and 5 min (p=0.41) APGAR scoring.

Table 4 shows comparable neonatal outcome in two groups. Most of the morbidities were of milder degree and were treated in ward while few required NICU admission.

Discussion

Induction of labour at term in the presence of an unfavorable cervix is associated with an increased risk of failed induction and caesarean section. The use of prostaglandin preparations with or without oxytocin infusion, has been shown to reduce induction time and the risk of failed induction. We investigated the use of misoprostol sublingually in this study, on the assumption that the sublingual route would have the higher efficacy and safety

Table 3 — *Comparison of complementary Oxytocin augmentation required for progress of labour*

Complementary oxytocin augmentation	Group 1	Group 2	Grand Total	
Not required	69(69%)	77(77%)	146(73%)	
Required	31(31%)	23(23%)	54(27%)	0.89
Grand Total	100(100%)	100(100%)	200(100%)	

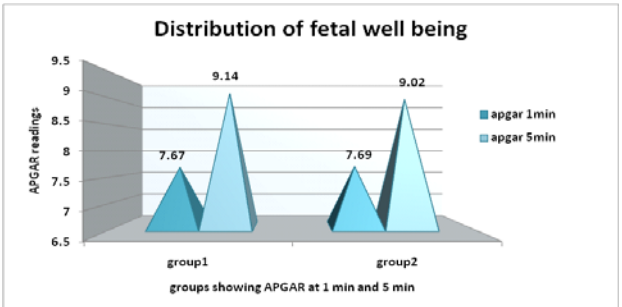

Fig 3 — Comparison of fetal well being by APGAR scoring at 1min and 5 min in two groups

than the vaginal route.

In our study we included mothers coming to our institution belonging to age group 18-35 year of comparable age (p=0.91) and parity(p=0.75)in both groups.

Table 4 — *Comparison of neonatal morbidity in two groups*

Neonatal morbidity	Group 1	Group 2
No	89(89%)	88(88%)
Yes	11(11%)	12(12%)
HIE-1	6	7
HIE-2	1	1
Convulsions	0	1
Meconium aspiration	3	4
Hypoglycemia	1	0
NICU admission	1	2

In our study common indication for induction being Premature Rupture of Membrane (39% in sublingual group and 40% in vaginal group.) and Post Dated pregnancy (35% in sublingual and 33% in vaginal group) in both the groups which was similar to the study conducted by Feitosa FE *et al*[10]. Patient having dribbling showed very good response to sublingual misoprostol as drug was washed off in case of vaginal administration.

In our study 22% in sublingual group and 24% in vaginal group required single dose administration while two doses were required in 51% and 54% cases respectively. A Bartusevicius *et al*[11] did a study to compare the efficacy and safety of 50 µg of sublingual misoprostol with 25 µg of vaginal misoprostol for labour induction at term. The mean number of misoprostol dose used was significantly lower in the sublingual group than in the vaginal group (1.5 ± 0.5 *versus* 1.8 ± 0.6, p value = 0.001). Such difference has been seen as we have used same dose sublingually and vaginally. Elhassan EM *et al*[12] in a study on 150 women in labour assigned 50 µg of misoprostol orally, vaginally, or sublingually (50 women in each group) shows that the induction to delivery time was significantly shorter in the sublingual group than in the other groups (p value = 0.003). In our study, though the dose was half (25 µg) but induction delivery time was less than the Elhassan study (11.36 ± 3.5 hrs and 10.5 ± 3 hrs in sublingual and vaginal group respectively, p- value 0.11).

In our series, 70% women delivered vaginally in sublingual and 76% women in vaginal group whereas 30% and 24% respectively delivered by caesarean section. The difference observed was not statistically significant (p-value= 0.33). In a meta-analysis[13] based on five clinical trials (n =740) comparing different misoprostol doses where two studies compared 50 micrograms of vaginal and sublingual misoprostol (n = 330), two compared the dose of 25 micrograms by both routes (n = 270) and only one compared 50 micrograms of sublingual misoprostol with 25 micrograms of vaginal misoprostol (n = 140). The rates of vaginal delivery within 24 hours, uterine hyperstimulation and caesarean section rate were similar in both routes. These findings are similar to those found in our study and other systematic review published by the Cochrane Collaborations based on evaluation of buccal/sublingual routes of misoprostol[8].

We observed that frequency of nausea (8% *versus* 7%), vomiting (6% *versus* 5%), diarrhea (5% *versus* 4%) and hyperthermia (3% *versuss* 2%) in both groups were comparable. They were of milder in degree and were subsided on treatment.

As per controlled trial[14] the incidence of maternal adverse effects was similar in the sublingual and vaginal groups (7.1 *versus* 10%; RR 0.7, 95% CI 0.2–2.1) which corroborate our observations.

Study by Ashalatha S *et al*[15] showed 1 case of uterine hyperstimulation in the sublingual group but none in oral route. As per our result, in group-1, hyperstimulation syndrome was observed in two cases and in one case in group-2 which occur after the second dose of misoprostol in all the occasions. According to Feitosa *et al*[12] there was a trend towards a higher rate of oxytocin augmentation among those given oral misoprostol as compared to vaginal. In our study, 31% in group 1 and 23% in group 2 required oxytocin augmentation. The difference observed was insignificant (p = 0.89)

Though misoprostol is feared as a drug to cause rupture of uterus but in our study we didn't had any case of rupture uterus. Various meta-analysis and reviews showed misoprostol is very safe and danger to rupture is very low in induction of labour[16,17].

Similar number of neonates in each group having APGAR score <7 at 5 minutes and an umbilical artery pH <7.16 was shown in study by Bartusevicius A *et al*[11]. While study done by EM Elhassan[12] showed that the rates of newborn referral to the pediatrician, APGAR score at 1 min less than 7, and presence of meconium stained liquor were significantly lower in the sublingual group as compared to oral and vaginal misoprostol. In our study APGAR at 1 min was comparable in two groups. Similarly there was no difference in 5 min APGAR score also.

In our study, 89% babies in sublingual group while 88% in vaginal group were healthy. While few babies suffered from minor ailments like- Hypoxic Ischemic Encephalopathy (6% *versus* 7%), Meconium aspiration (3% *versus* 4%) and Hypoglycemia (1%in group1). Three babies were very sick and were admitted in NICU. There was no neonatal mortality observed till the babies were in hospital. Neonatal admission was similar in two other studies conducted on small number of women; 2.9% by A Bartusevicius A *et al* while 1% by Feitosa FE *et al*[10,11].

Conclusion :

According to our study as the sublingual administration of misoprostol 25 µg is equally effective and safe but more acceptable to patient and has better ease of use in comparison to vaginal route, it may be concluded that the

sublingual application is a better alternative to vaginal route. Similar trials with a larger sample size should be carried out in the near future.

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