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A comparative study of 25mcg of oral and vaginal misoprostol in induction of labour at term gestation in primigravida

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Abstract
Background: Labour induction is one of the common medical procedures in obstetrics. The aim is to end the pregnancy when continuity is a risk to mother or fetus. Prostaglandins have been used successively for cervical ripening and for induction of labour since early 1970's.This comparative study is undertaken to evaluate the safety and efficacy of oral and vaginal routes of administation of misoprostol for induction of labor.
Material and Methods: A prospective randomised controlled trial done on 196 Patients of admitted in Rajkiya Mahila chikitsalaya, JLN Medical College, Ajmer as per inclusion and exclusion criteria, informed consent was taken and randomization into two groups. The women in the oral group were 25 µg of misoprostol with a sip of water, and vaginal group had one 25 µg of misoprostol tablet inserted in the posterior vaginal fornix without use of lubricant (maximum upto 6 doses).
Results: Our study showed that Full term (26.5%), followed by severe preeclampsia (24.4%), post-dated (16.3%), Mild PE (12.2%), Antepartum eclampsia (10.2%) and Polyhydramnios (10.2%) were indication for induction of labor. High rate of caesarean section in oral group than vaginal group 32 (32.6%) vs 16(16.3%). The commonest indication of caesarean section was fetal distress in both the groups. Failed induction was also higher in oral group than vaginal group 8(8.1%) vs 4(4%).
Conclusion: Our study shows that for induction of labour vaginal route is preferable to oral route when used in equivalent dosage of 25 µg in primigravida. In vaginal route of administration compared to oral route number of dosage required is less, induction delivery interval is less, less incidence of failed induction, less rate of caesarean section, less requirement of oxytocin augmentation, less maternal side effects of the drug. The onset of uterine activity was earlier in oral group. Neonatal outcome is comparable in both groups. The increase efficacy associated with vaginal misoprostol raises the possibility of a local cervical effect with the vaginal administration.

Keywords: Bishop's score, misoprostol, vaginal, oral

Introduction
Labour induction is one of the common medical procedures in obstetrics. The aim is to end the pregnancy when continuity is a risk to mother or fetus. In the U.S. its frequency has increases steadily from 9.5% in 1990; to 19.4% in 1998 [1] and 23.8% in 2015 [2]. Induction of labor is the non- spontaneous initiation of uterine contractions, prior to their spontaneous onset leading to progressive effacement and dilatation of cervix and delivery of the baby.
In this modern era of healthcare reform and cost containment, the identification of therapeutic strategies to enhance the success and cost-effectiveness of labour induction are of great interest [3]. Attempts to induce cervical ripening have involved the use of mechanical methods, estrogen and estrogen precursors, relaxin and prostaglandins [4].
At term gestation about 15% of pregnant women require aid in cervical ripening and labour induction. Half of them will have an unfavorable cervix a topically applied prostaglandin, containing either prostaglandin E2 or prostaglandin E1 is the most popular means to soften and dilate the cervix [5].
Prostaglandins have been shown to induce cervical ripening and stimulate uterine contractions and have been found to be effective in numerous clinical trials at a variety of doses and routes of administration [5]. PGE_2 gel preparations have been commercially available in India in 2ml and 3ml syringe containing 0.5mg of dinoprostone. However they are expensive and unstable at room temperature, requiring refrigerated storage.

Uterine hyper stimulation has been identified as a particular problem during labour induction with prostaglandins, and has to be treated with tocolytics [6].

Thus there is a need for less costly and less temperature sensitive alternative which is safe and effective. A proposed alternative is misoprostol, a prostaglandin E_1 analogue.

Misoprostol has several advantages over the other prostaglandins on the market:

1. Being an E_1analogue, it has no effect on the bronchi or blood vessels so can be used safely in hypertensive and asthmatic patients.
2. It can be stored at room temperature for many years (shelf life: 3 years)
3. It is cheap: A single 25µg tablet (Cipla) costs Rs.4.75.(india)
4. Modes of administration: Oral[11], vaginal [12, 13], intracervical [14], intrauterine [15], sublingual [16, 17], buccal [18].
5. The only notable side effects are diarrhea, pyrexia and shivering, which are dose dependent and self-limiting.

Synthetic analogue misoprostol, Prostaglanding E1 originally used as gastroprotective [6] agent up coming as cervical ripener and labour inducer [7] and is being tried enthusiastically by obstetricians world wide. A Large number of studies have shown that misoprostol is effective in first and second trimester abortion, late pregnancy labor induction and third stage of labor management [8].

Misoprostol is now being used clinically in different off label situations other than what has been approved by US Food and Drug Administration and Drug Controller of India. Yet FDA recognizes in certain circumstances, off label uses of rational products are appropriate, rational and accepted medical practice [19]. Furthermore, prescribing a medicine for an off label indication is common in the treatment of pregnant women and it is not considered experimental if based on sound scientific evidence [20].

The WHO manual 'Managing Complications in Pregnancy and Childbirth'[21] recommends the use of misoprostol for induction of labour and places it in its list of 'Essential Drugs' and also present in the official WHO list of essential drugs [22].

The American college of obstetricians & gynaecologists (2016), Reaffirmed its recommendation for use of drug for induction because of proven safety and efficacy.

During the past years the introduction of misoprostol has been a major focus of attention of induction of labour. Multiple trials have proved that misoprostol is an effective agent for cervical ripening and inducing agent [10].

To date, several studies have shown that vaginal misoprostol is to be as effective or even more effective, than traditional methods of cervical ripening and induction of labor using dinoprostone and oxytocin [11-14].

Therefore, now a days, the gold standard for the cervical ripening and induction of labour is vaginal misoprostol at doses of 25mcg every 4-6 hours [10, 18, 19]. The oral route is also effective and also has several benefits like faster onset and easier administration. Investigations have predominantly focussed on the dosing and timing of administration with intravaginal application. There are few studies on the use of orally administered misoprostol for induction of labor [20].

In view of the above, this comparative study is undertaken to evaluate the safety and efficacy of oral and vaginal routes of administation of misoprostol for induction of labor.

Material and Methodology

The study is conducted in the labour room and maternity ward from JLN medical college and hospital. All patients admitted through emergency and outpatient department with an indication for induction of labour at term gestation.

Inclusion Criteria: Patients with Primigravida, Term gestation 37-42weeks, Singleton viable pregnancy, Bishops score <6, Cephalic presentation, Clinically adequate pelvis are included in this study.

Exclusion Criteria: Patients with Cephalopelvic disproportion, Abruptio placenta, Placenta previa, Malpresentation, Previous uterine scar, Post caesarean pregnancy, Twin pregnancy, Foetal distress are excluded from this study.

Methodology

The women in the oral group were 25 µg of misoprostol with a sip of water, and vaginal group had one 25 µg of misoprostol tablet inserted in the posterior vaginal fornix without use of lubricant. In all patients the cervical status was assessed by using of Bishop Score prior to Induction. Bishop score was reassessed the end of sixth dose. Dosage was repeated every 4th hourly until an adequate contraction pattern set in (Establishment of 3 uterine contraction in period of 10 min) or once the cervical dilatation reaches 4 cms, maximum upto 6 doses. After induction the patients were monitored for maternal vitals, onset of labour, uterine contractions, uterine hyperstimulation, fever, nausea, vomiting, diarrhoea, progress of the labour was recorded by using a partogram. FHR which was monitored intermittently by auscultation every 15 min regularly. If the labour was established or Bishop score 7 or more the woman was transferred to the labour ward and membranes were ruptured when the cervix was completely effaced with a cervical dilatation of <4 cm, if spontaneous rupture of membranes did not occurred. Labour was established when painful uterine contractions were accompanied by ruptured membranes, a bloody "show", cervical effacement and / dilatation. In women in either study group with inadequate uterine contractions, oxytocin was used for augmentation of labour according to our department protocol. The primary outcomes used to evaluate efficacy were the induction to delivery interval in the women who delivered vaginally and the rate of vaginal delivery within 24 hours. The secondary outcome measures used to evaluate efficacy or safety of treatment included the number of doses of misoprostol required to effect delivery, requirement of oxytocin, incidence of failed induction, the rate of caesarean section, maternal adverse effects (nausea/vomiting, fever, diarrhoea, post partum haemorrhage), and neonatal outcomes comprising low APGAR score (1 & 5 min), need for NICU admission.

Observations and Results: After randomizing 98 women had received 25µg of misoprostol orally and 98 received vaginally.

Full term (26.5%), followed by severe preeclampsia (24.4%), post-dated (16.3%), Mild PE (12.2%), Antepartum eclampsia (10.2%) and Polyhydramnios (10.2%) were indication for induction of labour in this study. There was a non-significant difference between the two groups. The indications of caesarean section in this study are fetal distress, non-progress of labor, failed induction which was statistically non-significant. High rate of caesarean section in oral group than vaginal group 32 (32.6%) vs16 (16.3%). The commonest indication of caesarean

section was fetal distress in both the groups. Fetal distress is higher in oral group than vaginal group 16(16.3%) vs 8(8.1%). Non progress of labour is higher in oral group than in vaginal group 8(8.1%) VS (4%). Failed induction was also higher in oral group than vaginal group 8(8.1%) vs 4(4%).

More number of patients in oral group 32(32.6%) underwent caesarean section as compared to vaginal group 16 (16.3%) which is significant (p-0.008S).

In total there were 16 cases of antepartum eclampsia, 10 in the oral group and 6 in the vaginal group. The mean number of doses required oral group 3.9+/-1.5 was higher than in the vaginal group 3.8+/-1.6. This can be explained by the fact that the Bishop score prior to induction in the oral group 1.4+/-1.2 was lower than the vaginal group 1.8+/-1.8 but not significant. The mean induction delivery interval in the oral group was 19.0+/-8.6 as compared to 16.2+/-6.4 hours in the vaginal group. 3 cases in oral and 1 case in vaginal group underwent cesarean section. All cases of oral group were due to failed induction and in vaginal group due to fetal distress. 1 case in oral group and 4 cases in the vaginal group needed oxytocin augmentation. Meconium was encountered in 9 cases, 4 cases had thin and 4 cases had thick in the oral group and 1 in the vaginal group had thick meconium stained liquor. 2 babies in the vaginal group required NICU admission because of respiratory distress (Table: 1).

Table 1.

	Characteristics	Oral		Vaginal		
		Range	Mean+/-SD	Range	Mean+/-SD	P-value
Antepartum eclampsia	No. of cases	10		6		
	No. of doses required	2-6	3.9+/-1.5	1-6	3.8+/-1.6	0.65NS
	Bishop score Prior to induction	0-4	1.4+/-1.1	0-5	1.8+/-1.8	0.06NS
	Bishop score 12hrs after induction	1-12	7.6+/-3.1	3-12	8.6+/-3.4	0.03S
	Induction to delivery interval (hrs)	9.5-8.62	19.0+/8.6	7--26.5	16.2+/-6.1	0.009S
Severe preeclama	No. of cases	24		20		
	No. of doses required	1-6	3.4+/-1.5	2-6	2.7+/-1.7	0.002S
	Bishop score Prior to induction	0-5	1.7+/-1.4	0-5	2.0+/-1.0	0.1NS
	Bishop score 12hrs after induction	4-13	8.1+/-3.3	3-12	9.2+/-1.4	0.002S
	Induction to delivery interval (hrs)	6.5-28.5	15.9+/-5.8	8-25.5	13.5+/-6.8	0.008S
Mild preeclama	No. of cases	12		14		
	No. of doses required	1-6	3.3+/-1.5	2-3	3.1+/-1.2	0.3NS
	Bishop score Prior to induction	2-6	3.2+/-1.6	0-5	2.9+/-1.4	0.1NS
	Bishop score 12hrs after induction	1-10	8.0+/-1.4	3-12	8.8+/-2.6	0.008S
	Induction to delivery interval (hrs)	9.5+/-5.64	15.2+/-5.6	1-12	14.5+/-5.6	0.3NS

There were 44 cases of severe pre-eclampsia out of which 24 cases in the oral group and 20 cases in the vaginal group. The mean no. of doses required were higher in the oral group than vaginal group (3.4+/-1.5) vs (2.75+/-1.7) which was statistically significant. The pre- induction Bishop score was higher in oral group than in vaginal group (1.7+/-1.4) vs. (2.0+/-1.0) which is non- significant. The induction delivery interval was less in vaginal group than in oral group 13.5+/-6.8 vs (13.5+/-6.8) hours respectively which was statistically significant. 10 cases in the oral group 3 cases in the vaginal group underwent caesarean section. Of them 3 cases in oral and 2 cases in vaginal were due to failed induction. 5 cases in oral and 3 cases in vaginal group required oxytocin augmentation. 8 babies in the oral group and 3 cases in the vaginal group were admitted to NICU because of respiratory distress. There was 2 neonatal death in the oral group and 3 in the vaginal group because of asphyxia (Table:1).

There were 26 cases of pre- eclampsia, 12 in the oral group and 14 in the vaginal group. The mean number of doses requires for the oral group was 3.3 +/-1.5 which was higher than the vaginal group 3.1+/- 1.29 but not significant. The mean pre-induction Bishop score was higher in oral (3.2+/-1.6) than in vaginal group (2.9+/-1.4). The mean induction delivery interval was higher in oral group (15.2+/- 5.6) than vaginal group (14.5 +/- 45.6) but not significant. 3 cases in the oral group and 3 cases in vaginal group required augmentation with oxytocin. 3 cases in oral and 1 case in vaginal group underwent caesarean section due to fetal distress. Liquor was thin in 4 cases and thick in 3 cases in oral group and thin 6 cases and thick in 1 case in vaginal group. 2 babies in vaginal group in admitted in NICU (Table: 1).

20 cases diagnosed as polyhydramnios based on clinical examination and ultrasound report were taken for study.10 in the oral group and 10 in the vaginal group. Mean dosage of misoprostol in was higher in the oral group (2.8+/-1.3) than in the vaginal group (2.6+/-1.6) which is non- significant. The mean pre-induction bishop score was higher in the oral group 3.3+/-1.2 as compared to vaginal group 3.0+/-1.1. The induction delivery interval is the oral group 14.6+/-6.13 and vaginal group 14.4+/-8.5 hrs which is non- significant. 4 cases in vaginal group required augmentation with oxytocin drip. 3 cases in oral and 1 case in vaginal group underwent cesarean section due to fetal distress. The liquor was thin in 6 cases, thick in 3 cases in the oral group and 2 cases thick in vaginal group. 2 babies in the vaginal group had NICU admission (Table:2).

Table 2.

	Characteristics	Oral		Vaginal		
		Range	Mean+/-SD	Range	Mean+/-SD	P-value
Polyhydramnios	No. of cases	10		10		
	No. of doses required	01-Jun	2.8+/-1.3	01-Apr	2.6+/-1.6	0.3NS
	Bishop score Prior to induction	0-5	3.3+/-1.2	01-May	3.0+/-1.1	0.06NS
	Bishop score 12hrs after induction	01-Dec	9.6+/-0.5	0-12	9.0+/-2.2	0.009S
	Induction to delivery interval (hrs)	5-26.5	14.6+/-6.3	6.5-29.5	14.4+/-8.5	0.8NS

Postdated Pregnancy	No. of cases	16		18		
	No. of doses required	02-Jun	4.1+/-1.4	01-Jun	2.8+/-1.8	0.0001S
	Bishop score Prior to induction	0-5	2.7+/-1.5	0-5	2.7+/-1.6	1.0NS
	Bishop score 12hrs after induction	05-Oct	7.0+/-1.6	07-Dec	9.8+/-2.4	<0.001S
	Induction to delivery interval (hrs)	8.5-30.5	19.3+/-7.2	5-30.5	13.44+/-8.1	<0.0001S
Full term	No. of cases	26		30		
	No. of doses required	01-Jun	4.4+/-1.2	01-Jun	2.7+/-1.08	<0.001S
	Bishop score Prior to induction	0-3	2.2+/-1.0	01-Apr	2.5+/-1.2	0.2NS
	Bishop score 12hrs after induction	02-Sep	7.9+/-1.3	04-Dec	8.7+/-1.7	0.0003S
	Induction to delivery interval (hrs)	10--36.5	20.1+/-6.1	6.5-16.5	12.2+/-5.0	<0.001S

Postdated pregnancy in this study was considered when duration of pregnancy extended 14 days after crossing EDD in patients who knew their dates exactly. There were total 34 cases enrolled in the study, 16 in the oral group and 18 in the vaginal group. The mean number of doses required were 4.1+/-1.4 in the oral group as compared to 2.8+/-1.8 in the vaginal group. The induction delivery interval was 19.3+/- 7.2 in oral and 13.4+/-8.1 in the vaginal group. 3 cases in the oral and 2 cases in the vaginal group underwent caesarean section. 8 cases in the oral and 2 cases in vaginal group required augmentation with oxytocin. The meconium was thin in 7 cases in oral group and 8 in vaginal group, thick in 3 cases in oral group and 6 cases in vaginal group. One baby each in the oral group and vaginal group which was delivered by caesarean section required NICU admission because of birth asphyxia and was discharged after 5 days (Table:2).

There were total of 56 cases of term gestation enrolled in the study, 26 in the oral group and 30 in the vaginal group. The mean number of doses required were 4.4+/-1.2 in the oral and 2.7+/- 1.8 in the vaginal group. The Bishop score prior to induction was 2.2 +/-1.0 in oral and 2.5+/-1.2 in the vaginal group. The induction delivery interval was shorter in the vaginal group 20.15+/-6.1 as compared to oral group 12.2+/-5.0 hours which was highly significant. 17 cases in the oral group as compared to 7 cases in the vaginal group required oxytocin augmentation. 9 cases in oral and 3 cases in vaginal group underwent caesarean section due to fetal distress. 5 cases in oral and 9 cases in vaginal group required NICU admission. 3 cases had thin and 12 cases had thick meconium stained liquor in the oral group and 3 cases had thin and 8 cases had thick meconium in the vaginal group (Table:2).

42% of cases in the oral group and 55% of cases in the vaginal group had clear liquor which is non- significant. 28% in the oral and 20% in the vaginal group had thin meconium stained liquor and is not significant. 28% of cases in the oral and 24% of cases in the vaginal group had thick meconium stained liquor. Thick meconium stained liquor was particularly seen in the cases of full term and post dated pregnancy. 4 babies in oral group and 7 in vaginal group who required NICU admission for mild birth asphyxia and respiratory distress had thick meconium (Fig:1)

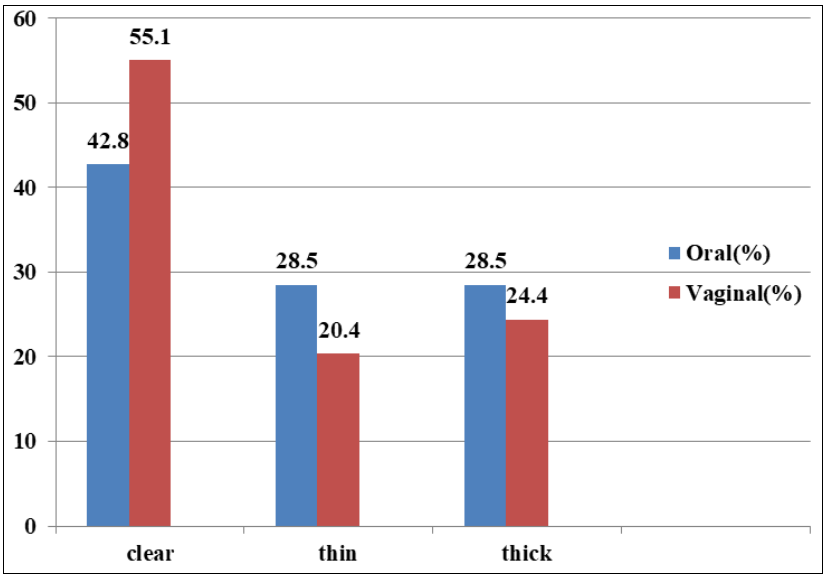

Fig 1: Liquor characteristics

There is no statistical significance between two groups regarding birth weight. Out of total 196 cases, 14.2% of cases in the oral group and 20.4% in the vaginal group required NICU admission for the mild asphyxia, and respiratory distress.2(2%) neonatal death in the oral group as compared to 3(3%) in the vaginal group. NICU admission was highest in full term 14 out of 56 (25%). The incidence of mean APGAR score at 1 min <6 was higher in the vaginal group 26(26%) versus 14 (14%) in the oral group and is significant. 2% neonatal death in the oral group 3% in the vaginal group due to asphyxia in severe preeclampsia cases (Table:3).

Table 3.

Outcome	Oral	Vaginal	P-Value
Birth weight (mean+/-SD)	2.38+/-0.67	2.43+/-0.72	0.61NS
NICU admission	14(14.2%)	20(20.4%)	0.2NS
Apgar score			
1 min <6	14(14.2%)	26(26%.5%)	0.03S
5 min <6	6(6.1%)	12(12.2%)	0.1NS
Neonatal death	2(2%)	3(3%)	0.65 NS

Discussion

In the present study, 196 cases with indication of induction of

labour were divided into oral and vaginal group equally. From the all above mentioned studies, it is concluded that more number of cases in the oral group required oxytocin augmentation.In present study oxytocin augmentation highly required in full term gestation. In the present study 35 (35%) in the oral group and 22 (22%) in the vaginal group required oxytocin augmentation (P-0.04 S), indicating superiority of the vaginal route of administration of the drug misoprostol which is statistically significant which is further supported by study Mahajan M, Gupta KB, Sharma R, Jyothi R [23]. In present study oral administration of misoprostol resulted in quicker onset of uterine activity 234+/-216 versus 249+/-177(P-0.622) minutes in oral and vaginal groups respectively. This clinically observation is further strengthened by the study of Zieman *et al.* [24] who found out maximum plasma concentration at 34 minutes after oral dosing and at 80 minutes after vaginal administration of misoprostol. The mean induction vaginal delivery interval was 816+/-390 in the vaginal, as compared to 1038+/-414 (P=0.0001) in the oral group statistically highly significant, Indicating that the vaginal route resulted in shorter mean induction vaginal delivery interval. In vaginal group 72.4% cases delivered within 24 hours compared to 44.8% cases in oral group statistically highly significant (P- 0.001).Majority of cases delivered within 12 hrs in vaginal is also highly significant when compared to oral group 23.4% vs 53%(P=0.0001). Number of cases delivered after 24hrs is higher in oral group than vaginal group 22.4% vs 11.2% which is significant (P-0.03). In present study rate of caesarean delivery was 32.6% versus 16.3% in the oral and vaginal group respectively which is significant (P-0.008) and is similar to C. David Adair *et al.* [25], (1998) of 18.3% in oral and 15.3% in the vaginal group.

Neonatal complications

14.2% neonates in the oral group and 20.4% in the vaginal group a required NICU admission for mild birth asphyxia and respiratory distress.

Failed induction

The present study had failed induction rate of 8.1% in the oral and 4% vaginal group of failed induction similar to the observations of Ashalatha Shetty *et al.* [26]. In both the cases there was no change in the initial Bishop score even after maximum of 4 doses as per the study protocol and both the cases underwent caesarean section.

Conclusion

Our study shows that for induction of labour vaginal route is preferable to oral route when used in equivalent dosage of 25 µg in primigravida. In vaginal route of administration compared to oral route number of dosage required is less, induction delivery interval is less, less incidence of failed induction, less rate of caesarean section, less requirement of oxytocin augmentation, less maternal side effects of the drug. The onset of uterine activity was earlier in oral group. Neonatal outcome is comparable in both groups. The increase efficacy associated with vaginal misoprostol raises the possibility of a local cervical effect with the vaginal administration.

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