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Original Research Article

Oral and vaginal route of misoprostol for induction of labour: a comparative study

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ABSTRACT

Background: Induction of labour can be defined as "Artificial initiation of uterine contractions before the onset of spontaneous labour, after the period of viability, by any methods, for purpose of vaginal delivery." The key factor for a successful induction is the status of cervix, its form, consistency and dilatation which is determined by the Bishop score. In case of unfavourable cervix or in the pregnancies remote from the term; prostaglandins are more effective than any other method of induction. Introduction of misoprostol, PGE1 analogue, for the induction of labour in 1993 and its approval for clinical use by ACOG (American College of Obstetrics and Gynecology) in 1999 has been the most significant advancement. It is the latest drug for induction of labour which is cheap and stable at room temperature and is being used worldwide in different doses and by various routes. We compared the most commonly preferred two routes; vaginal and oral in terms of success of induction and noted the adverse events and side effects in both routes.

Methods: This was a prospective comparative study carried out at SBKSMIRC (Shrimati Bhikhiben Kanjibhai Shah Medical Institute and Research Centre), Dhiraj general hospital, Vadodara, Gujarat, 200 patients who required induction of labour were recruited after applying inclusion and exclusion criteria and were randomly divided in two groups- Group A meant to receive 50µg oral misoprostol, Group B - meant to receive 25µg vaginal misoprostol repeated 4 hourly up to maximum of five doses. Progress of labour was charted on the partograph. The mean induction delivery interval, mode of delivery, maternal and neonatal outcomes and complications were observed.

Results: The mean induction to delivery interval was significantly less in vaginal group than oral (23.3±12.4 hours in oral vs. 17.3±10 hours in vaginal). Vaginal delivery and cesarean section rates were comparable in both groups (76% in Group A vs. 72% in Group B for vaginal delivery, 18% vs. 20% for Cesarean section, respectively). 58% patients in Group A required more than two doses as compared to 39% in group B, though the difference was statistically not significant. Significant number of patients required added oxytocin administration in Group A (72%). No major complications or adverse events were observed. Neonatal hyperbilirubinemia was seen more in Group A.

Conclusions: Both Oral misoprostol in a dose of 50µg and vaginal misoprostol 25 µg every four hours, to a maximum of five doses, have the potential to induce labour safely and effectively. The vaginal route however is beneficial in effecting delivery in lesser time with few numbers of doses as compared to oral route.

Keywords: Induction of labour, Misoprostol, Oral route, Vaginal route

INTRODUCTION

Induction of labour is one of the most important procedures in today's obstetrics. It has been a baffling problem since time immemorial and is most debatable when done prior to attainment of maturity or at term in normal patient, just to deliver her at the convenience of patient and the doctor, as failure of induction or meconium staining of liquor following induction can lead to increased incidence of cesarean sections. Normally, all

pregnancies should continue to term and labour should begin spontaneously resulting in vaginal delivery, however Induction of labour is widely performed when continuation of pregnancy is hazardous to the mother or fetus.[1] Induction of labour is the artificial initiation of uterine contractions before its spontaneous onset for the purpose of delivery of the fetoplacental unit using mechanical or pharmacological methods.[2] The success of labour induction largely depends on the cervical status or Bishop's score at the time of induction. It is generally predicted that the patients with a poor Bishop's score at the initiation of induction have higher chances of failure of induction.[3]

A successful induction of labour refers to vaginal delivery of healthy baby, in an acceptable time frame with minimum maternal discomfort or side effects.[4] The search for ideal agent, timing and route of administration for the induction of labour has been an ongoing process. The drugs commonly available for purpose of induction are oxytocin, dinoprostone gel and misoprostol.

Prostaglandin E2 has been the agent of choice for pre-induction cervical ripening for several decades and is one of the pharmacologic agents approved by the United States Food and Drug Administration for this indication. However, it has several disadvantages: it is expensive, requires intracervical application, and continuous refrigeration.[5,6] Induction of labour with oxytocin is unlikely to lead to vaginal delivery in an unripe cervix.[7]

Misoprostol (a prostaglandin E1 analogue) is a comparatively new agent for pre-induction cervical ripening and labour induction. It has excellent cervical ripening and uterotonic properties.[8] Although, misoprostol currently is approved by U.S. FDA for the prevention and healing of peptic ulcers induced by NSAIDs, in 2002, the U.S Food and Drug Administration approved a new label on the use of misoprostol during pregnancy for cervical ripening and for induction of labour.[9,10] It is economical, stable at room temperature, with very few side effects and can be easily administered through oral, sublingual, vaginal , buccal or rectal routes.[11] Most clinical trials have used doses ranging from 25µg to 100µg, inserted intra-vaginally into the posterior fornix.[3,10-14] The most common vaginal dose used has been 50µg, inserted once or administered every four to six hours; inserting 25µg every six hours intra-vaginally has been associated with the fewest side effects.[5,14,15]

Oral vs. vaginal route: Maximum plasma concentration of orally administered misoprostol is produced faster than vaginal method (30 minutes vs. 1 hour), but the plasma concentration of the medication in vaginal method stay longer, so that oral misoprostol is removed after 2-3 hours, but vaginal misoprostol removal takes more than 4 hours. Although vaginal application of misoprostol has been validated as a reasonable means of induction, 5 there is patient resistance to repeated digital examination necessary for placement of the agent. There is also a risk of ascending infection because of repeated vaginal examinations.[16]

Oral misoprostol is well tolerated when used for the management of upper gastrointestinal tract dysfunction.[9] For these reasons, oral administration of misoprostol has been introduced for cervical ripening and labour induction.[17,18] It is not only easier, but mother satisfaction and acceptance is higher. There have been few trials assessing efficacy and tolerability of oral misoprostol for induction with varying conclusions.

Considering the routine use of both vaginal and oral routes, uncertainty regarding the preferred dose and route, lack of accurate statistics, advantages and disadvantages on the effectiveness of both methods, we designed this study to assess and compare the efficacy of oral misoprostol 50µg and vaginal misoprostol 25µg for induction of labour at term. And to compare maternal and neonatal complications and side effects of the drug.

METHODS

This was a prospective comparative study conducted in department of Obstetrics and Gynecology at SBKSMIRC (Shrimati Bhikhiben Kanjibhai Shah Medical Institute and research Centre), Dhiraj general hospital, Vadodara, from January 2010 to March 2011. Study population comprised of 200 subsequent pregnant women admitted through the emergency or outpatient department with an indication for induction of labour at term. After confirming eligibility criteria, informed written consent was obtained. To avoid observer bias, the patients were randomly assigned, by means of sealed envelopes handed over to designated staff unaware of dose and route written inside the envelope, to two groups -Group A, received tab misoprostol 50µg orally repeated every 4 hours for maximum five doses, group B received 25µg misoprostol vaginally every 4 hours for maximum of five doses.

Inclusion criteria

- Singleton pregnancy beyond 37 weeks gestation
- Vertex presentation
- Clinically adequate pelvis
- Bishop score <6
- Reactive Non stress test
- Absence of uterine contractions.

Exclusion criteria

- Malpresentation
- Presence of uterine contractions >= 3/10 min
- Cephalo–pelvic disproportion
- Favourable cervix (Bishop score > 6)
- Previous Caesarean section or uterine scar
- Multiple gestation

- Placenta previa
- Non reactive non stress test
- Contraindication to vaginal delivery
- Hypersensitivity to prostaglandins
- Parity -5 or more.

A detailed history, followed by general physical examinations was done. Obstetrical examination included fundal height, lie, presentation, fetal heart sound, per vaginal examination for assessing bishop's score and pelvis. Routine blood investigations and antenatal Ultrasound was done to ensure gestational age. Demographic characteristics were noted. Maternal vitals were monitored. Duration, frequency and intensity of uterine contractions were observed. Resident doctors on duty were instructed to ascertain proper execution of induction protocols. Study population was examined and misoprostol vaginally was placed in posterior fornix after moistening with saline by an assigned senior most resident only, at proper intervals. Per Vaginum examination was done every 4 hourly to note the changes in the status of cervix in both groups. Unnecessary PV examinations were strictly avoided to minimize the rate of infection. Fetal heart rate monitoring was done especially before each successive dose of misoprostol and induction continued only if fetal heart rate was normal. All parameters were charted on the partograph and progress of labour was assessed. Induction was discontinued when the patient entered in active labour which was considered if, either she had adequate uterine contractions rated as at least 3 contractions /10 min each of 40 sec duration or the cervix was >3cm dilated. A further dose was withheld in cases of tachysystole, hyper tonus or hyper stimulation or non reactive CTG not corrected by primary measures which demanded intervention. If the patient did not enter active labour four hours after last dose, the induction was considered to have failed and cesarean section was performed. Amniotomy was done when cervix >4cm dilated, augmentation with oxytocin was done if patient failed to have good uterine contraction with frequency of at least 3 per 10 minutes 4 hours after last dose of misoprostol. Side effects and complications were noted. The outcomes were noted as

Primary outcomes to evaluate efficacy were

- Mode of delivery
- Induction-to-delivery interval in vaginal delivery
- Vaginal delivery within 24 hours.

The primary measures used to evaluate safety were the incidence of tachysystole (contraction pattern of more than six contractions in ten minutes), hypertonus (prolonged uterine contraction lasting more than two minutes), uterine hyper stimulation (hypertonus or tachysystole in the context of an abnormal fetal heart rate tracing requiring intervention); and non-reassuring FHR.[19]

The secondary outcome measures included

- Number of doses of misoprostol needed to effect vaginal delivery
- Augmentation with oxytocin
- Incidence of failed induction
- Maternal adverse effects (nausea/vomiting, diarrhea, fever, postpartum hemorrhage, uterine rupture)
- Neonatal outcomes.

Statistical analysis

Data was compiled tabulated and analyzed using SPSS vn 15. Chi square test was applied with p value of <0.05 considered as significant. Mean and standard deviation was calculated for descriptive statistics.

RESULTS

Table 1 depicts the demographic variables of the study group with regards to age, gestational age, parity and pre induction Bishop Score, which were comparable in both the groups. Mean age of patients was 25.10±3.4 years in Group A (oral group) and 24.05±2.88 years in Group B (vaginal group). Average gestational age was 39.81±1.06 weeks and 40.07±1.00 weeks in Group A and B, respectively. The mean Pre induction Bishop Score was 3.98 in oral group and 4.04 in vaginal group which was again comparable. Most women in each group were nulliparous (65% in Group A, 68% in group B).

Table 1: Demographic distribution of study population.

Characteristics	Group A (n=100)	Group B (n=100)
Maternal age, years mean±SD	25.10±3.4	24.05±2.88
Gestational age, weeks mean±SD	39.81±1.06	40.07±1.00
Pre induction Bishop score, mean±SD	3.98±1.55	4.06±1.35
Parity		
Primigravida	65	68
Multigravida	35	32

Table 2: Indications for induction of labour.

Indication for induction	Group A (N%)	Group B (N%)
Post date	40	48
IUGR	15	16
Severe PET	17	14
Oligohydramnios	20	14
IUFD	3	2
Eclampsia	2	4
Congenital anomalies	03	02

Table 2 enumerates indications for induction of labour. Post datism was the commonest indication for induction of labour comprising 48% and 40% in vaginal and oral group respectively, followed by oligohydramnios and IUGR.

Among the primary outcomes compared (Table 3), spontaneous vaginal delivery and caesarean section rates were almost similar in both the groups, 76% in group A and 72% in group B, 18% in group A and 20% in group B, respectively. There was no significant difference in the mode of delivery in two groups, however the induction to delivery interval was significantly less in vaginal group, group B, (P=0.0014). Among the patients delivered vaginally more than 50% patients delivered in less than 24 hours in both the groups (P=0.69 i.e. not significant).

Secondary outcomes are shown in Table 4. More than 50% patients in group A required more than two doses of misoprostol to effect delivery which was comparable to 44% in group B. 72% patients required oxytocin augmentation in oral group whereas only 48% in vaginal group which was significantly less (P=0.001). This was either due to ineffective or in-coordinate uterine contractions or poor effacement of cervix encountered in oral group.

Very few adverse events were encountered. Tachysystole developed in two women in group A and one women in group B (P = 0.38). Uterine hyper stimulation occurred in two women (2%) in the vaginal misoprostol group only. Both of these (nulliparous) women received tocolysis and underwent urgent delivery by CS. None of the patients developed hypertonus. Non-reassuring FHR patterns were defined as late deceleration, variable deceleration, prolonged deceleration, tachycardia, or reduced FHR variability which was comparable in both groups.

Table 3: Primary outcome variables.

Characteristics	Group A	Group B	P value
Mode of delivery			
Vaginal delivery	76%	72%	0.41
Cesarean section	18%	20%	0.88
Instrumental delivery	6%	8%	0.73
Induction-vaginal delivery interval, hours, mean±SD	23.3±12.4	17.3±10.9	0.0014
Vaginal delivery within 24 hours	55	62	0.69

Table 4: Secondary outcome variables.

Characteristics	Group A	Group B	P value
No. of doses			
1	12	17	
2	30	44	
>2	58	39	0.085
Oxytocin administration (n= %)	72	48	0.001
Failed induction	9	12	0.73
Maternal side effects, n=%			
Nausea/vomiting	15	2	0.33
Diarrhea	2	4	0.72
Fever	2	4	0.6
PPH	0	1	
Adverse events, n=%			
Tachysystole	2	1	0.38
Hyperstimulation	0	2	0.42
Hypertonus	0	0	
Nonreassuring FHR	12	8	0.84
Neonatal outcome, n=%			
Meconium stained liquor	15	11	0.32
NICU admission	9	4	
1 min APGAR <7	2	2	
5 min APGAR <7	6	3	

Table 5: Comparison with other studies

Outcome	Route	Rehman et al (50 µg PO vs. 25µg PV)	Janice et al (50 µg PO vs. PV	Jindal et al (50 µg PO vs. PV)	Present study (50µg PO vs. 25 µg PV
Vaginal delivery	Oral	58%	83.3%	74.5%	76%
	Vaginal (25µg)	64%	76.8%	90.38%	72%
Cesarean section	Oral	30%	16%	25.49%	18%
	Vaginal	29%	19%	9.62%	20%
Induction to vaginal delivery interval, mean (SD), hours	Oral	21.22±2.4	27.3 (18.8)	16.47	23.3 (12.4)
	Vaginal	20.15±3.1	19.3 (11.9)	9.79	17.3 (10.9)
Oxytocin administration	Oral	27.27%	78%	-	72%
	Vaginal	23.6%	50%	-	48%
Number of delivered within 24 hours	Oral	49%	56%	72.54%	55%
	Vaginal	52%	69.5%	90.38%	62%

Incidence of LSCS done for failed induction in oral group (A) was 9% whereas in vaginal group (B) was 12% (P=0.73). With regards to the neonatal outcome, no significant differences between the groups were found in the proportion of neonates with Apgar score <7 at 5 minutes, incidence of meconium-stained amniotic fluid, or the proportion admitted to NICU. Meconium stained liquor was seen in 15% in oral group and 11% in vaginal group. Nine babies from group A were admitted to NICU among which four had hyperbilirubinemia, two had mild respiratory distress, and two had feeding difficulties and one because of intrauterine growth restriction. In Group B, the vaginal misoprostol group, three babies were admitted to NICU with suspected neonatal sepsis and one having had a seizure. The higher incidence of hyperbilirubinemia may be due to more requirement of oxytocin in Group A whereas neonatal sepsis in Group B may be attributed to frequent vaginal examinations needed. Maternal side effects were minimal and manageable with minimum interventions. PPH occurred in only one patient in vaginal group. Comparison with different studies is shown in Table 5. Our results were almost similar to that studied by, Janice et al, however, they had compared equivalent doses (50 ug) of misoprostol by oral and vaginal routes. Rehman et al, compared 50 µg orally administered to 25 µg vaginally administered misoprostol and our findings were comparable with theirs.[20,21]

DISCUSSION

Preeclampsia The use of prostaglandin E1 analogue, Misoprostol for induction of labour has been quite promising. There is increasing evidence that misoprostol, administered either vaginally or orally, is as effective as conventional methods for induction of labour at term.[22] Doses from 25 µg to 200 µg have been used but more than 50 µg is associated with hyper stimulation, hypertonus, meconium stained liquor and uterine rupture.[22]

Distribution according to demographic characteristics in our study population was almost similar to study by Janice Sk et al, Rehman et al, and Shetty et al.[20,21,23] This study shows that women who receive misoprostol vaginally experience faster induction-to-delivery times with less need for oxytocin augmentation when compared with a similar group of women receiving oral misoprostol. These findings concur with those of others.[18,20] Though the total number of doses of misoprostol required in vaginal groups was lower as compared to oral, when average was derived, the difference was not statistically significant in our study which was in contrast to studies done by Wing DA et al, Janice SK et al, and Jindal et al.[14,20,24] This may be due to the reason that sometimes the vaginal dose did not dissolute completely by the time of next dose which increased the requirement of dose. Induction to vaginal delivery interval was significantly lower in vaginal group as shown by Janice et al and Jindal et al, as vaginal misoprostol is absorbed rapidly and eliminated slowly from body making it available to act for a longer time as compare to oral resulting in rapid progression of labour.[25] Main fear with this drug is sometimes excessive uterine contractions and possibility of uterine rupture in both scarred and unscarred uterus, however, by and large, use of this drug in previously scarred uterus is almost negligible and rupture is not common in primigravida and in multipara patients misoprostol is used very cautiously. These complications are dose related, higher the dose; more is uterine stimulation but shorter is the induction delivery interval.[26] With 50µg vaginal misoprostol, incidence of uterine contractile abnormalities has been reported to be 4.9%, 9% and 12% in different studies.[21,24,27] Ewert et al, observed these complications incidence as 6.25, 10% with 100 and 200 µg controlled

release vaginal inserts of misoprostol, respectively.[3,25,28] Higher incidence of fetal distress and meconium staining of liquor could be due to increase in hyper stimulation of uterus. Significantly increased number of patients required oxytocin augmentation in oral group compared to vaginal group in our study, an observation also noted by Rasheed R et al.[29]

There is extensive clinical experience with this agent (misoprostol) and a large body of published reports supporting its safety and efficacy when used appropriately. No studies indicate that intrapartum exposure to misoprostol or other PG cervical ripening agents does not have any long term adverse health consequences to the fetus in the absence of fetal distress nor there is a plausible biologic basis for such a concern.[10] A limitation of our study may be no placebo control group; however certain indications definitely demand intervention in terms of induction of labour whatever be the preferred route and dose. Vaginal misoprostol significantly reduces the time interval to delivery and increases chances of vaginal delivery with less requirement of oxytocin, although cesarean section rates are no different from orally used misoprostol, making both routes comparable in outcomes, though higher dose is required when used orally due to reduced bioavailability and high first pass metabolism. Our study compared 50 µg misoprostol orally vs. 25 µg vaginally and findings were comparable with other studies. The acceptability to women of the different routes of administration should also be evaluated. Considering wide variation in preferences of dose and routes of misoprostol, recently, FIGO (2017) has come up with recent recommended regimens for misoprostol in different indications which allow inductions to be done with 25 µg misoprostol vaginally every 6 hours or orally every 2 hours.[30] Clinical trials have shown that at an equivalent dosage the vaginal route produces greater clinical efficacy than oral route. Approximately, 25µg of misoprostol should be considered as the initial dose for cervical ripening and labour induction. The frequency of administration should be not more than 3-6 hours. (Level A recommendation).[10]

CONCLUSION

The results of this study suggest that vaginal misoprostol is associated with shorter induction-to-delivery times than oral misoprostol. Mode of delivery may not be affected by the route preferred, but as on one side higher dose is required in oral route due to less bioavailability, vaginal administration on other hand may be bothersome and uncomfortable to the patient, thus affecting the compliance. Hence, there is a need for a greater number of appropriately designed double-blinded randomized controlled trials with a larger sample size to validate the efficacy and safety of 50 µg oral misoprostol in comparison with 25 µg vaginal misoprostol.

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