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Original Research Article

"A COMPARATIVE STUDY OF BUCCAL MISOPROSTOL Vs ORAL MISOPROSTOL FOR INDUCTION OF LABOUR IN PRELABOUR RUPTURE OF MEMBRANES"

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ABSTRACT:

Background: Prelabour rupture of membranes (PROM) is defined as the membrane rupture at term without spontaneous uterine contractions.[1] It is rupture of membranes with at least 2 hours latent period before active labour, latent period being the time elapsing from the time of rupture of membranes to the onset of labour. If rupture of membranes (ROM) occur before 37 weeks of gestation it is termed as the preterm prelabour rupture of membranes (PPROM).

OBJECTIVES:

• To compare the safety and efficacy of Misoprostol by two different routes of administration i.e., oral and buccal in women with PROM at term.

• To achieve a safe vaginal delivery of patients by inducing labour with Misoprostol either by oral or buccal route and to make a clinical study regarding the induction-delivery intervals, maternal and neonatal complications and adverse effects of the drug by the two different routes.

MATERIAL & METHODS: Study Design:A prospective comparative study.**Study area:**Department of Obstetrics and Gynaecology, Integral Institute of Medical Sciences and Research, Lucknow, Uttar Pradesh.**Study Period:** June 2021 – June 2022.**Study population**: Cases admitted to labour ward at term with PROM were included in the study.**Sample size:** study consisted a total of 100 cases.**Sampling method:** Simple random method. **Study tools and Data collection procedure:**100 cases of pregnant women with PROM at term were approached for the study and were divided into two groups of 50 each for 25 microgram Misoprostol for oral and buccal route. Thorough history taking, examination, foetal evaluation by reactive CTG, assessment of cervical status by bishop score was done prior to induction. Informed consent was obtained.The cases were divided into two groups 50 each to receive Misoprostol 25µg(1/4 of 100 µg tablet) 4th hourly either by buccal or oral route. In all patients, the cervical status was assessed by using bishop score prior to induction.

Results: In the present study tachysystole was 8% and 2% in women of buccal and oral Misoprostol group respectively.In present study there was no case of hyperstimulation. 10%

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presently studied women experienced Vomiting.Fever 4%, chills 12% were reported in the overall group.

CONCLUSION: From our study, it can be concluded that buccal route of administration of Misoprostol for induction of labour in Term Prelabour rupture of membranes (PROM) is more efficacious compared to the oral route of administration and might be the preferred route.

Keywords: Prelabour rupture of membranes (PROM), Misoprostol, tachysystole

INTRODUCTION:

Prelabour rupture of membranes (PROM) is defined as the membrane rupture at term without spontaneous uterine contractions.[1] It is rupture of membranes with at least 2 hours latent period before active labour, latent period being the time elapsing from the time of rupture of membranes to the onset of labour. If rupture of membranes (ROM) occur before 37 weeks of gestation it is termed as the preterm prelabour rupture of membranes (PPROM).[1]

Indeed, in most pregnancies labour begins at term in the presence of intact foetal membranes. Without interventions their spontaneous rupture usually occurs near the end of the first stage of labour. However, in 10% of term pregnancies and 30- 40% preterm pregnancies, foetal membranes fail to maintain their structural integrity resulting in their prelabour rupture and of these, approximately 50% will go into labour within 12 hours, 70% within 24 hours, 85% within 48 hours and 95% within 72 hours in the absence of obstetric intervention. [(2,3,4)]

The management of prelabour rupture of membranes has gone through various cycles of obstetric activity from benign neglect to immediate intervention. Paralleling these cycles of activity there have been varying degrees of concern about infection. Meanwhile incidence has remained unabated and is still responsible for large number of neonatal mortality. Preterm prelabour rupture of membranes (PPROM) is associated with intrauterine infection. Early detection of intrauterine infection may help prevent neonatal sepsis. C-reactive protein (CRP) is an acute phase protein often elevated when inflammation is present and has been found elevated in cases of PPROM. CRP is commonly used for the early diagnosis of chorioamnionitis inPPROM. The preventive treatment awaits further elucidation of aetiology, not yet fully understood. [(5,6,7)]

In most instances either it is obvious from the release of clear amniotic fluid from cervix by speculum examination or by simple labouratory test like Nitrazine test. The key to the management is an accurate assessment of gestational age and the presence or absence of sepsis.

Three decades ago the main worry of prelabour rupture of membranes was intrauterine infection and this led to the wide spread adoption of a policy of induction of delivery to prevent such infection.A successful induction of labour leads to vaginal delivery of the neonate in a good condition, in an acceptable time frame and with minimum maternal discomfort orside effects.[8]

It has been known for years, that achievement of these goals is largely dependent upon the condition of the cervix. A “ripe” soft yielding cervix requires a lower quantum of uterine work than an unripe hard and rigid one. An unripe cervix fails todilate well in response to myometrial contractions.[9]

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Prostaglandins have been used successfully for cervical ripening and subsequent labour induction in the clinical environment since the early 1970's. The mode of administration that have been studied include intravenous, intramuscular, oral,vaginal and intracervical.[10]

Recently, the most fascinating synthetic prostaglandin E1 analog Misoprostol has been focus of attention in the arena of various labour inducing agents. Misoprostol was originally made for healing of gastric ulcers induced by NSAID's. [11,12]

It is theside effect of the drug which has been exploited by the obstetricians for the purpose of cervical ripening and induction of labour. Labour induction with Misoprostol has become an intensely investigate topic. Various authors have reported its excellent efficacy, minimal side effects and cost saving benefits.

Investigations have predominantly focused on the dosing and timing of administration with intravaginal application. In view of the above, this comparative study is undertaken to evaluate the safety and efficacy of oral and buccal routes of administration of Misoprostol for induction of labour in patients with PROM.

OBJECTIVES:

• To compare the safety and efficacy of Misoprostol by two different routes of administration i.e., oral and buccal in women with PROM at term.

• To achieve a safe vaginal delivery of patients by inducing labour with Misoprostol either by oral or buccal route and to make a clinical study regarding the induction-delivery intervals, maternal and neonatal complications and adverse effects of the drug by the two different routes.

MATERIAL & METHODS:

Study Design:A prospective comparative study.

Study area: Department of Obstetrics and Gynaecology, Integral Institute of Medical Sciences and Research, Lucknow, Uttar Pradesh.

Study Period: June 2021 – June 2022.

Study population: Cases admitted to labour ward at term with PROM were included in the study.

Sample size: study consisted a total of 100 cases.

Sampling method: Simple random method.

Inclusion criteria:

1. 37 weeks or more gestation.
2. Single ton gestation
3. Original bishop score less than 6
4. Spontaneous rupture of membranes
5. Vertex presentation
6. Reactive cardiotocography

Exclusion criteria:

1. Cephalopelvic disproportion
2. Antepartum hemorrhage
3. Malpresentation

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4. Previous uterine scar
5. Symptoms and signs suggestive of chorioamnionitis
6. Bad obstetric history

Ethical consideration: Institutional Ethical committee permission was taken prior to the commencement of the study.

Study tools and Data collection procedure:

100 cases of pregnant women with PROM at term were approached for the study and were divided into two groups of 50 each for 25 microgram Misoprostol for oral and buccal route. Thorough history taking, examination, foetal evaluation by reactive CTG, assessment of cervical status by bishop score was done prior to induction. Informed consent was obtained.

The cases were divided into two groups 50 each to receive Misoprostol 25µg(1/4 of 100 µg tablet) 4th hourly either by buccal or oral route. In all patients, the cervical status was assessed by using bishop score prior to induction.

Bishop Score:

	0	1	2	3
Dilatation(cm)	0	1-2	3-4	≥5
Effacement(%)	0-30	40-60	60-80	>80
Station	-3	-2	-1,0	+1,+2
Consistency	Firm	Medium	Soft	-
Position	Posterior	Mid	anterior	-

Repeat Bishop Scores were assessed prior to each dose. Dosage was repeated every 4^{th} hourly until an adequate contraction pattern set in (establishment of 3 uterine contractions in a period of 10 minutes) or once the cervical dilatation reaches 4 cm, maximum up to 6 doses. After induction, the patients were monitored for maternal vital signs, progress of labour and foetal heart rate which was monitored by intermittent auscultation in majority of cases.

Maximum allowable doses were 6 i.e. 150 µg of the drug Misoprostol either by buccal or oral route. If labour did not ensue even after 4 hours following the last dose, it was considered as failed induction and other methods was tried.

Following parameters were recorded -number of doses, and the interval between induction to onset of uterine contraction, induction-delivery interval, mode of delivery, maternal and neonatal complications and adverse effects of the drug like fever, diarrhoea, nausea and others.

Tachysystole was defined as more than 5 uterine contractions per 10 minutes without foetal heart rate changes for 2 consecutive 10 minute periods.Hyperstimulation was defined as exaggerated Uterine response (tachysystole or prolonged uterine contraction of >90 seconds) accompanied by FHR deceleration or tachycardia.

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Statistical analysis: Data entry and statistical analysis was performed with the help of Microsoft excel 2007 and SPSS version 17.0, while categorical variables are presented as number and percentages. Independent sample T test was applied to compare means of two groups. Chi-square test is used to compare differences in categorical variables. The statistical significance level was fixed at $p<0.05$.

OBSERVATIONS & RESULTS:

TABLE-1: RISK FACTORS OF PROM

RISKFACTORS	PROM	PERCENTAGE
Malpresentation	35	6
RecentH/oCoitus	35	6
CervicalStitch	20	3
Previous H/oLeak	52	8.8
Polyhydramnios	8	1.2
UTI	29	5
Unknown	417	70
Total	596	100

In our study previous history of leak was the most common risk factor (8.8%) followed by recent history of coitus and malpresentation being 6.0% each. 70% cases had no risk factors.

Cases are considered booked if the patient had 3 antenatal checkups of which at least one in the third trimester. PROM incidence was higher in unbooked cases being 59%. In this study booked cases were 41% and unbooked were 59%.

Out of 50 cases in the oral group, majority 26(52%) were primigravida. out of 50 cases in the buccal group, majority were multigravida 28(56%). The difference between parity and grouping was found to be statically not significant.

TABLE 2- DISTRIBUTION OF SUBJECTS BASED ON AGE:

AGE GROUP (YRS)	ORAL GROUP n(%)	BUCCALGROUP n(%)	MEAN±SD
<20YRS	0(0%)	0(0%)	
21-25YRS	25(50%)	25(50%)	

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26-30YRS	22(44%)	23(46%)	25.42±2.917
31-35YRS	3(6%)	2(4%)	
TOTAL	50(100%)	50(100%)	

Chi-square- 0.22, df- 2, P Value- 0.895, Statistically not significant

Majority of cases in both the groups belong to age 21-25 years. (MEAN AGE-25.42 ± 2.917). The difference between age category and group was found to be statistically not significant.

TABLE 3- RESPONSE TO DOSAGE OF DRUG:

DOSESREQUIREDFOR INDUCTION	**ORAL**	**BUCCAL**
1	6(12%)	10(20%)
2	16(32%)	25(50%)
3	18(36%)	8(16%)
4	6(12%)	3(6%)
5	2(4%)	2(4%)
6	2(4%)	2(4%)
TOTAL	50(100)	50(100)
MEAN	2.76±1.1888	2.36±1.225

Chi-square- 7.822, df- 5, P Value- 0.166, Statistically not significant.

Out of 50 cases in oral group, majority 18(36%) required 3 doses .out of 50 cases in buccal group majority 25(50%) required 2 doses. The association between number of doses and grouping was found to be statistically not significant.

TABLE 4–DISTRIBUTION OF SUBJECTS BASED ON OXYTOCIN AUGMENTATION:

AUGMENTATION	**ORAL**	**BUCCAL**
OXYTOCINREQUIRED	32(64%)	18(36%)
NOTREQUIRED	18(36%)	32(64%)
TOTAL	50(100%)	50(100%)

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Chi-square- 6.76, df- 1, P Value- 0.009, Statistically significant

Out of 50 cases in oral group, 32(64%) required Oxytocin augmentation. Out of 50 cases in buccal group, 18(36%) required Oxytocin augmentation.The association between Oxytocin augmentation and grouping was found to be statistically significant.

TABLE 5- INDUCTION-DELIVERY INTERVAL:

INDUCTION-DELIVERY	**ORAL**	**BUCCAL**
<5HRS	0	0
6.1-12.0HRS	12	22
12.1-18HRS	18	21
18.1-24HRS	11	3
>24HRS	9	4
TOTAL	50	50

Chi-square- 9.67, df- 3, P Value- 0.02, Statistically significant.

Out of 50 cases in the oral group, majority 18(36%) delivered within 12.1-18hrs.Out of 50 cases in the buccal group majority 22(44%) delivered within 6.1-12 hrs. The association between induction-delivery interval and grouping was found to be statistically significant.

TABLE 6-MATERNAL COMPLICATIONS:

	ORAL	BUCCAL
TACHYSYSTOLE	1(2%)	4(8%)
HYPERSTIMULATION	0	0
DIARRHOEA	1(2%)	1(2%)
FEVER	2(4%)	-
CHILLS	6(12%)	2(4%)
VOMITINGS	5(10%)	5(10%)
PPH	0	0
CERVICAL TEARS	0	0
WOUNDINFECTIONS	2(4%)	1(2%)

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In the present study tachysystole was 8% and 2% in women of buccal and oral Misoprostol group respectively.In present study there was no case of hyperstimulation. 10% presently studied women experienced Vomiting.Fever 4%, chills 12% were reported in the overall group.

TABLE 7- NEONATAL OUTCOME:

Outcome	**ORAL**	**BUCCAL**
NEONATALAPGAR		
1 MIN	7.20±0.45	7.08 ±0.34
5 MIN	8.95±0.32	9.04±0.28
BIRTHWEIGHT(kg)	2.7958±0.28651	
STILLBIRTH	0	0
NEONATAL RESUSCITATION • BAGANDMASK • MECHANICAL VENTILATION	5(8%) 4 1	6(10%) 5 1
NEONATALDEATH	0	0
NICUADMISSION	5(10%)	6(12%)

Out of total 100 cases, 10% cases of neonates in oral group and 12% cases of neonates in buccal group required NICU admission for birth asphyxia, respiratory distress. There were no still births and neonatal deaths in both the groups.Mean APGAR score at 1min 7.20±0.45 at 5 min 8.95±0.32 in the oral group and 7.08±0.34 at 1 min 9.04±0.28 at 5 min in the buccal group.

TABLE 8-NEONATAL COMPLICATIONS:

COMPLICATION	**ORALn (%)**	**BUCCALn(%)**	**X^2VALUE**
SEPSIS	0	0	

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BIRTHASPHYXIA	2(4%)	3(6%)	
NEONATAL JAUNDICE	1(2%)	-	
NEONATAL DEATH	0	0	
RESPIRATORY DISTRESS	2(4%)	2(4%)	**1.64,df-3**
MECONIUM STAINEDLIQUOR	2(4%)	4(8%)	
TOTAL	7	9	

Chi-square- 1.64, df- 3, P Value- 0.650, Statistically not significant.

Out of total 100 cases, 2 (4%) cases in oral group and 3(6%) cases in buccal group and 2(4%)cases in each group had birth asphyxia and respiratory distress respectively which was managed by neonatal resuscitation of Bag and mask ventilation and mechanical ventilation accordingly. Meconium stained liquor was noted in 2 (4%) cases in the oral group and 4(8%) in the buccal group. The association between neonatal complications and grouping was found to be statistically not significant.

Out of 50 cases in oral group, 6(12%) neonates had apgar score≤ 7 at 1minute. Out of 50 cases in buccal group, 8(16%) neonates had apgar score ≤ 7 at 1minute.The difference between apgar score at 1minute and grouping was found to be statistically not significant.

APGAR Score <7 at 5 min of birth in oral group were 1out of 50 and 1 out of 50 in buccal group. The difference between apgar score at 5minute and grouping was found to be statistically not significant.

80% of cases in oral group and 88% of cases in buccal group had hospital stay of<5 days. 16% in oral group and 10% in buccal group had hospital stay of 5-8 days.On applying chi square test no significant difference was found in hospital stay of both the groups.

DISCUSSION:

In the present study, 100 cases of PROM were divided in to oral and buccal group equally. Both the groups received 25µg of Misoprostol every 4^{th} hourly either orally with water or it was held in the cheek in the buccal group, maximum of 6 doses in either group.

In present study mean age was 24 years. Majority of cases were in the age group of 21 to 25 years.This is comparable with the results of published series by **Boskabadi et al**[13]which included 177 cases and mean age was 26.5 years. Most common age group in their study was 15-25 years. Many studies have reported a higher mean age in their study. The lower common age group in this study is probably due to early marriages and pregnancy in India.

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In this study booked cases were 41% and unbooked cases were 59%.This is comparable to the study by **Anjana Devi et al** [14], which showed unbooked cases as 52%.In unbooked cases there is lack of antenatal case leading to lack of identification of recurrent risk factors like PPROM, PROM, preterm delivery, inducedabortions and their managements. Also urogenital infections are not detected and treated due to lack of antenatal care leading to premature rupture of membranes.

In the present study maternal morbidity was reported in 11% of cases of PROM which correlates with the study by **Pandey et al**[15] (9%).

INDUCTION VAGINAL DELIVERY INTERVAL

Study andyear	InductionVaginalDeliveryInterval (hours)					
	No.ofcases	Dose	Oral	No.ofcases	Dose	Buccal
Sujata et al[16] 2014	80	25□g 3rdhrly	17.67 ±7.32	80	25□g 4thhrly	14.8 ±6.2
PRESENT STUDY	50	25□g 4th hrly	17.126 ±5.104	50	25□g 4th hrly	13.96 ±4.684

In the present study the mean induction vaginal delivery interval was 17.126 ±5.104 in the oral group, as compared to 13.96± 4.68 in the buccal group which is consistent with the observation of the above mentioned studies. Indicating that the buccal route resulted in shorter mean induction vaginal delivery interval compared to oral group.

TACHYSYSTOLE AND HYPERSTIMULATION

Study AndYear	TachysystoleandHyperstimulation							
	Oral				Buccal			
	No. OfCases	Dose	Tachy-Systole	Hyper-Stimulation	No. OfCases	Dose	Tachy-Systole	Hyper-Stimulation
Shetty[17]2002b	50	50□g 4thhourly	0	0	50	50□g 4th hourly	0	1(2%)

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SujataSiwatchetal[16]2014	80	25□g3hourly%	1 (1.3%)	1 (1.3%)	80	25□ g 4th hourly	1 (1.3%)	1 (1.3%)
PRESENTSTUDY	50	25□g4hourly%	1(2%)	0	50	25□g 4 thhourly	4(8%)	0

In present study we had 8% rate of Tachysystole in buccal group and 2% rate in oral group. This is comparable to the study of **Sujata Siwatch et al[16] 2014**, which was 1.3% in oral group.There was no case of hyperstimulation in both groups. This can be compared to study of **Shetty[17] 2002b** which was 0% in oral and 2% in buccal group and to those of **Sujata Siwatch et al[16] 2014** 1.3% vs. 1.3% in oral and buccal group respectively.Increased incidence of tachysystole and hyperstimulation could be related to dosage, frequency of dosing and its cumulative effect.

A concern with Misoprostol induction of labour has been excessive uterine activity namely tachysystole and hyperstimulation.No adverse events as a consequence of tachysystole have been reported in any of the comparative studies of two routes by Misoprostol.

In present study we had 1 (2%) and 4 (8%) cases of tachysystole in oral and buccal group respectively. No cases of hyperstimulation was reported in both groups. The rates were similar to study by **Sujata siwatch et al[16] 2014** 1.3% vs. 1.3% in oral and buccal groups respectively. Also comparable to study by **Shetty et al[17] 2002**where hyperstimulation was 0% in oral group and 1(2%)in buccal group.

Out of 4 cases in buccal group, 1 underwent instrumental delivery and others delivered vaginally after being treated for tachysystole. Out of 1 case in oral group in which tachysystole was noted delivered by instrumental delivery. All the cases were managed with left lateral position and oxygen inhalation and further administration of drug was stopped.

The higher rate of tachysystole in buccal group can be explained by the fact that the systemic bioavailability of buccal administered Misoprostol is 3 times that of Misoprostol administered orally. This greater bioavailability of buccal Misoprostol might explain the increased incidence of foetal heart rate abnormalities in this group, which might be the result of excessive uterine activity, a fact that has been stated by the study of **Zieman et al[18] which** was "Absorption kinetics of Misoprostol with oral and vaginal administration" and **K. Gemzel Dannielsson[19]**"Comparision between oral and vaginal administration of Misoprostol on uterine contractility".In present study, 2 cases in oral group had fever which is a known side effect of prostaglandins.1 case each in oral and buccal group had diarrhoea, which was treated symptomatically.

There were no cases of still births and neonatal deaths in both groups.5 neonates in oral group and 6 in the buccal group required NICU admission, for birth asphyxia and respiratory distress.The incidence of apgar score at 1 min < 7 and 5 min < 7 was 6(12%) and 1(2%) in oral group versus 8 (16%) and 1 (2%) in buccal group respectively which was higher in the buccal

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group as compared to oral group and it is consistent with the study of **Shetty et al[17]2002**5 (10%) require NICUadmissions in buccal group and 6 (12%) in oral group.

Recently Sanchez-Ramos and Andrew M. Kauntiz in their metaanalysis of various comparative studies of the two routes of Misoprostol administration found no difference for the incidence of abnormal apgar score and rates of admission to NICU. Mean birth weight was 2.7958±0.28651. Placenta in all the cases in both the groups was complete. 2 cases in the oral group and 4 in the buccal group had meconium stained liquor. But none of the neonates suffered from meconium aspiration. The difference between neonatal complications and grouping was found to be statistically not significant.

The mean number of doses required for induction was slightly higher in the oral group 2.76 ± 1.88 versus 2.36 ± 1.225 in buccal group.The change in the pre-induction Bishop score after 12 hours was slightly higher in the buccal group 10.428 ± 1.16 versus 8.0263 ± 2.05 in the oral group, which can be partly explained by the fact that the systemic bio- availability of buccal administered Misoprostol is three times higher than the oral route.

Out of 50 cases in oral group, 32(64%) required oxytocin augmentation. Out of50 cases in buccal group, 18(36%) required oxytocin augmentation. The association between oxytocin augmentation and grouping was found to be statistically significant.

The mean induction delivery interval was shorter in the buccal group 13.966±4.678 versus 17.126±5.104 hrs in the oral group.On applying chi square test and Independent sample 'T' test , the correlation between grouping and induction-delivery interval was found to be statistically significant ($p<0.002$) implying buccal route of administration is more efficacious and resulted in shorter induction-delivery interval.

On applying chi square test and Independent sample 'T' test, the correlation between grouping and Bishop score after 12 hours was found to be statistically significant ($p<0.0001$) indicating the superiority of buccal route.

CONCLUSION:

From our study, it can be concluded that buccal route of administration of Misoprostol for induction of labour in Term Prelabour rupture of membranes (PROM) is more efficacious compared to the oral route of administration and might be the preferred route.

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