A Comparative Study of Buccal Misoprostol Vs Oral Misoprostol for Induction of Labour in Prelabour Rupture of Membranes

M. Nagalakshmi[1], V. Aruna Devi[2], Mogili Archana[3]

ABSTRACT

Introduction: Prelabour rupture of membranes (PROM) is defined as the membrane rupture at term without spontaneous uterine contractions. In 10% of term pregnancies and 30-40% preterm pregnancies, foetal membranes fail to maintain their structural integrity resulting in their prelabour rupture. Study aimed to compare the safety and efficacy of misoprostol by two different route's of administration i.e., oral and buccal in women with PROM at term.

Material and Methods: 100 patients with PROM were divided into oral and buccal group equally. Both the groups received 25µg of misoprostol every 4th hourly, either orally with water or it was held in the cheek in the buccal group, maximum upto 6 doses in either group.

Result: The prevalence of PROM in the present study was 7%. All demographic varaiables are insignificant in both groups. oxytocin augmentation required was found to be statistically significant in both groups. Mean induction delivery interval was shorter in buccal group (13.966±4.68) compared to oral group(17.126±5.10) which was statistically significant. The change in the pre-induction Bishop score after 12 hours was slightly higher in the buccal group compared to oral group which was statistically. Tachysystole was higher in buccal group (8%) compared to oral group(2%), There were no cases of still births and neonatal deaths in both groups. No significant differences were found in hospital stay and NICU admissions in both the groups.

Conclusion: Buccal misoprostol is more efficacious than oral misoprostol. Women who received buccal misoprostol experienced shorter induction to delivery interval, required fewer doses of misoprostol and required oxytocin augmentation less frequently than those who received oral misoprostol.

Keywords: Buccal Misoprostol, Oral Misoprostol, Labour in Prelabour Rupture

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]

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 in PPROM. The preventive treatment awaits further elucidation of aetiology, not yet fully understood.[3]

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 or side effects[4].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 to dilate well in response to myometrial contractions.

[1]Associate Professor, [2]Associate Professor, [3]Post Graduate, Department of Obstetrics and Gynaecology, CKM Hospital, Kakatiya Medical College, Warangal, Telangana, India

Corresponding author: Dr V. Aruna Devi, Associate Professor, Department of Obstetrics and Gynaecology, CKM Hospital, Kakatiya Medical College, Warangal, Telangana, India

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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. Recently, the most fascinating synthetic prostaglandin E_1 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 the side 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. There are few clinical studies on the use of orally and buccally administered Misoprostol for induction of labour. In view of the above, this comparative study was undertaken to evaluate the safety and efficacy of oral and buccal routes of administration of Misoprostol for induction of labour in patients with PROM.

MATERIAL AND METHODS

Cases for the present study were taken from CKM Hospital Warangal, from the period January 2016 to September 2017. Cases admitted to labour ward at term with PROM were included in the study.The total number of deliveries during the period January 2016 to September 2017 was 8515 out of which 596 were PROM at term and 100 cases were enrolled for the present study.

The incidence of PROM in our institute is 7%.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.

Induction 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

Exclusive criteria

1. Cephalopelvic disproportion
2. Antepartum hemorrhage
3. Malpresentation
4. Previous uterine scar
5. Symptoms and signs suggestive of chorioamnionitis
6. Bad obstetric history

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 4th 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.

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 $p<0.05$.

RESULT

Total number of deliveries during the period January 2016 to September 2017 were 8515 out of which 596 cases were PROM and 100 cases were enrolled for the present study. The incidence of PROM in our institute was 7%.

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 (figure-1).

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. The difference between gestational age category and grouping was found to be statistically not significant. Mean GA was 38.31±0.632 (table-1). The difference between mode of delivery and grouping was found to be statistically not significant.

Age Group (Yrs)	Oral Group N(%)	Buccal Group N(%)	P-Value
<20 Yrs	0(0%)	0(0%)	P Value- 0.895, Statistically Not Significant
21-25 Yrs	25(50%)	25(50%)	
26-30yrs	22(44%)	23(46%)	
31-35 Yrs	3(6%)	2(4%)	
Mean Age-	25.42 ± 2.917		
Gestational Age			
37-38 Weeks	11(22%)	8(16%)	P Value- 0.744, Statistically Not Significant
38-39 Weeks	30(60%)	32(64%)	
39-40 Weeks	9(18%)	10(20%)	
40-41 Weeks	0(0%)	0(%)	
Mean GA (Wks) ± SD - 38.31 ± 0.632			
Mode Of Delivery			P Value- 0.440, Statistically Not Significant
Vaginal Delivery(Vd)	38(76%)	43(86%)	
Instrumental	2(4%)	1(2%)	
Caesarean Section	10(20%)	6(12%)	
Parity			
Primigravida	26(52%)	22(44%)	P Value- 0.548, Statistically Not Significant.
Multigravida	24(48%)	28(56%)	

Table-1: Demographic distribution of subjects

Doses Required For Induction	Oral	Buccal	P-Value
1	6(12%)	10(20%)	P Value- 0.166, Statistically not significant
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%)	
MEAN	2.76±1.1888	2.36±1.225	
Augmentation			
Oxytocin Required	32(64%)	18(36%)	P Value- 0.009, Statistically significant
Not Required	18(36%)	32(64%)	
Total	50(100%)	50(100%)	
Induction -Delivery			
<5hrs	0	0	
6.1-12.0hrs	12	22	P Value- 0.02, Statistically significant
12.1-18hrs	18	21	
18.1-24hrs	11	3	
>24hrs	9	4	
Total	50	50	

Table-2: Response of drug in groups

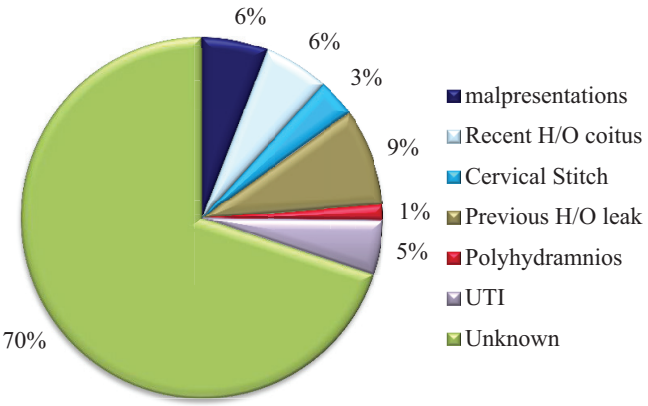
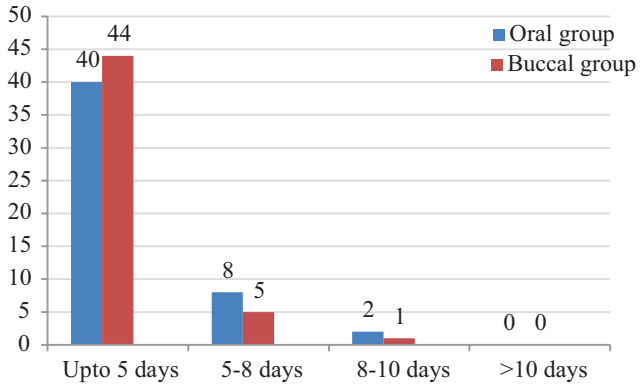


Figure-1: Risk factors of prom



Chi-square-1.5, df-2, P Value-0.472, Statistically not significant

Figure-2: Distribution of subjects based on hospital stay

Indications	Oral	Buccal
Foetal Distress	8(16%)	4(8%)
Failed Induction of Labour	2(4%)	2(4%)
Cervical Dystocia	0	0
Total	10	6
Maternal Complications		
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
Wound Infections	2(4%)	1(2%)
Chi-square- 0, df- 1, P Value- 1.00, Statistically not significant		

Table-3: Indications for caesarean section and Maternal Complications

Outcome	Oral	Buccal
Neonatal APGAR		
Min	7.20±0.45	7.08±0.34
Min	8.95±0.32	9.04±0.28
Birth Weight(Kg)	2.7958±0.28651	
Still Birth	0	0
Neonatal Resuscitation Bag And Mask Mechanical Ventilation	5(8%) 4 1	6(10%) 5 1
Neonatal Death	0	0
NICU Admission	5(10%)	6(12%)

Table-4: Neonatal Outcome:

Complication	Oral N (%)	Buccal N(%)	X^2 Value
Sepsis	0	0	1.64, df-3
Birth Asphyxia	2(4%)	3(6%)	
Neonatal Jaundice	1(2%)	-	
Neonatal Death	0	0	
Respiratory Distress	2(4%)	2(4%)	
Meconium Stained Liquor	2(4%)	4(8%)	
Total	7	9	
Chi-square- 1.64, df- 3, P Value- 0.650, Statistically not significant.			

Table-5: Neonatal Complications:

Caesarean section was planned in cases of foetal distress, cervical dystocia or failed induction of labour. The failed induction of labour in present study was referred to as "if labour didn't ensue even four hours following last dose of the drug. Cases of failed induction delivered by caesarean section. The difference between parity and grouping was found to be statically not significant.

The association between number of doses and grouping was found to be statistically not significant. The association between Oxytocin augmentation and grouping was found to be statistically significant. The association between induction-delivery interval and grouping was found to be statistically significant (table-2).

In total there were four cases of failed induction, two in the oral group and two in the buccal group. 2 cases both in the oral and buccal group underwent caesarean section due to failed induction of labour.

10 cases (20%) in oral group and 6(12%) cases in buccal group underwent caesarean section. Foetal distress was predominant reason for caesarean section in oral group. 2 cases each in both the groups underwent caesarean section because of failed induction of labour as there was no change in the initial Bishop Score even after 6 doses of the drug. No statistical significance was found among the grouping (Table-3).

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.

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-4).

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

Study and Year	Tachysystole and Hyperstimulation							
	Oral				Buccal			
	No. of Cases	Dose	Tachy-Systole	Hyper-Stimulation	No. Of Cases	Dose	Tachy-Systole	Hyper-Stimulation
Shetty[10] 2002b	50	50µg 4th hourly	0	0	50	50µg 4th hourly	0	1 (2%)
Sujata Siwatch et al[11] 2014	80	25µg 3 hourly%	1 (1.3%)	1 (1.3%)	80	25µg 4th hourly	1 (1.3%)	1 (1.3%)
Present study	50	25µg 4 hourly%	1(2%)	0	50	25µg 4th hourly	4 (8%)	0

Table-6: Tachysystole and hyperstimulation

between neonatal complications and grouping was found to be statistically not significant (table-5).

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 (figure-2).

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 4th hourly either orally with water or it was held in the cheek in the buccal group, maximum of 6 doses in either group. PROM is characterized by rupture of membranes before the onset of true labour. This occurs in 5-20% of all labours. Prevalence of PROM in present study was 7%. Indian studies (Bhalerao and Desai, 2000, Bhide 2001)[5] report an incidence of PROM in 7-12% of all labours. In 70% of the cases it occurs in pregnancies at term.

Study by Pandey et al[6] shows a prevalence of 7.7% which is comparable to the prevalence of present study (figure-1).

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[7] which included 177 cases and mean age was 26.5 years. Most common age group in their study was 15-25 years (table-1). 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. In this study, the patients of low socio-economic status were 60% and middle socio-economic status were 25% which is comparable with the study by Pandey et al[6] which is 61% and 39% respectively. Comparable to study by Arnab Mondal ISSN[8] 2016, which is 59% in low socio-economic and 32% in middle socio economic class.

In this study booked cases were 41% and unbooked cases were 59%.This is comparable to the study by Anjana Devi et al[9],1996 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, induced abortions 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[6] (9%).

From the above mentioned studies, it is concluded that more number of cases in the oral group required Oxytocin augmentation. In the present study, 32 (64%) in the Oral group and 18(36%) in the Buccal group required Oxytocin Augmentation, indicating superiority of the buccal group of administration of drug Misoprostol (table-2).

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.

In present study we had 8% rate of Tachysystole in buccal group and 2% rate in oral group (table-6). This is comparable to the study of Sujata Siwatch et al[11] 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[10] 2002b which was 0% in oral and 2% in buccal group and to those of Sujata Siwatch et al[11] 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.

The majority of cases in the present study in either group had vaginal delivery within 24 hours from the starting of induction. But more number of cases delivered vaginally within 24 hours in the buccal group. 88% as compared to 80% in the oral group indicating that buccal route for induction was more efficacious

The instrumental delivery rate was 1 (2%) in the buccal group and 2 (4%) in the oral group in the present study which is consistent with the study of Shetty et al[10] 11 (22%) in buccal group and 7(14%) in the oral group.

In the present study rate of caesarean delivery was 20% vs. 12% in oral and buccal group respectively, which is comparable to study by Shetty et al[10] 2002b, 30% vs. 16% in oral and buccal group respectively and 7.5% vs. 8.8% in oral and buccal group respectively by Sujata Siwatch et al[11] 2014 study.

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[10,11] 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[11] 2014 1.3% vs. 1.3% in oral and buccal groups respectively. Also comparable to study by Shetty et al[10] 2002b 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[12] which was Absorption kinetics of Misoprostol with oral and vaginal administration and K. Gemzel Dannielsson[13] 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 (table-4).

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.(table-5) 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 group as compared to oral group and it is consistent with the study of Shetty et al[26] 2002b 5 (10%) require NICU admissions in buccal group and 6 (12%) in oral group.

The difference between neonatal complications and grouping was found to be statistically not significant.

Failed induction of labour

Most of the comparative studies of different routes i.e., oral or buccal for induction of labour with Misoprostol have not reported failed induction as a separate entity. The present study had failed induction rate of 2 (4%) in the oral group as compared to 2 (4%) in the buccal group. In both the cases there was no change in the initial Bishop score even after maximum of 6 doses as per the study protocol and both the cases underwent caesarean section.

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 of 50 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

Present study is in aggrement with previous reports that buccal Misoprostol is more efficacious than oral Misoprostol. Women who received buccal Misoprostol experienced

- Shorter induction to delivery interval
- Required fewer doses of Misoprostol
- Required oxytocin augmentation less frequently than those who received oral Misoprostol
- No significant differences in maternal and neonatal complications.

Therefore 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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