OriginalResearch

SAFETY AND EFFICACY OF SUBLINGUAL MISOPROSTOL AND INTRACERVICAL DINOPROSTONE GEL AS CERVICAL RIPENING AGENT IN TERM PRELABOUR RUPTURE OF MEMBRANES : A COMPARATIVE STUDY

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ABSTRACT

Introduction: "premature rupture of membranes" (PROM) refers to the chorioamnionitis membranes spontaneously rupturing before the start of labour. This study compares the safety and effectiveness of intracervical dinoprostone gel and sublingual misoprostol for cervical ripening in term PROM.**Methods:** This is an analytical cross-sectional study including 100 term mothers with spontaneous PROM attending obstetric casualty at the Department of Obstetrics and Gynaecology, Government Raja Mirasudhar Hospital, Thanjavur, India, selected using a multistage sampling technique from the study period of February 2021 – November 2021 (10 months). One hundred samples were assigned randomly into two groups which were 50 in each group as group A (Misoprostol group) and group B (Dinoprostone gel group). **Results:** In group A, the study participants' median ages were 25 years (8.48) and 26.2 years (6.42), respectively. The difference in age averages between groups A and B was found to be 6.03, with a statistically significant p-value of 0.016. In both groups, the induction delivery interval was nearly equal. The link between the Indication for Lower Segmental Caesarean Section and both groups was statistically significant. When the two groups' delivery modes were compared, natural labour was shown to be statistically significant (p = 0.048). Normal and abnormal heart rates were statistically significant for the association between fetal heart rate and the groups, respectively, with chi-square values of 6.854 and 9.281 (p = 0.022 and 0.013, respectively). The remaining groups were not statistically significant.
Conclusion: It was concluded that though sublingual misoprostol is more efficacious than intracervical dinoprostone, its safety margin is significantly less; hence, misoprostol induction should be done only in a double setup under medical supervision.

Keywords:Misoprostol, Dinoprostone, Premature Rupture of Membranes, Efficacy

Introduction

The term "premature rupture of membranes" (PROM) refers to the chorioamnionitis membranes spontaneously rupturing before the start of labour. About 10% of all pregnancies are complicated by it(Middleton et al., 2017). PROM occurs in 7–12% of labourers, according to Indian studies (Bhalerao& Desai, 2000; Bhide, 2001). At 24, 48, and 96 hours after term PROM, spontaneous labour occurs in 70%, 85%, and 95% of women, respectively(Gaikwad H & Maskar P, 2016). The available management options in PROM are expectant management, which is waiting for the labour process to occur and induction of labour. According to this, induction of labour within 6-12 hours of membrane rupture in term PROM is advised if a woman is not in labour. This reduces the duration between the rupture of membranes and delivery, which is called a latent period, and it is essential in those with an unfavourable cervix (Middleton P et al.). Even the view of women is more favourable towards induction of labour in term PROM than expectant management(Hannah et al., 1996).

Also, WHO strongly recommends labour induction in women with prelabour rupture of membranes at term as the quality of available evidence is very high(World Health Organization, 2018). Although oxytocin is the most commonly preferred agent for induction of labour in term PROM, in a subset of women with unfavourable cervix determined by Bishops score <6, prostaglandins play a more significant role. Bishops score is a tool health care providers use to determine if the cervix is ready for labour. A score of 6 or less is considered unfavourable for induction; if induction is indicated, cervical ripening agents may be utilised. When labour begins in a previously unfavourable cervix, cervical ripening is done to facilitate softening, thinning and dilation of the cervix. This should be done to reduce failed induction as an unfavourable cervix (according to the Bishops score) at induction increases the cesarean rates and also decreases the induction-delivery interval.

Mechanical methods of cervical ripening are relatively contraindicated in ruptured membranes as it further increases the chances of chorioamnionitis. Hence pharmacological methods of cervical ripening are advised in term PROM. Pharmacological agents for cervical ripening include various formulations of prostaglandin, such as prostaglandin E1 and E2. A synthetic analogue of prostaglandin E1 called misoprostol, has been used widely as an agent for cervical ripening. Routes of administration include oral, sublingual and intravaginal routes. Misoprostol is available as a 100mcg(in scored) or a 200mcg tablet, and for cervical ripening, 25mcg or 50mcg is used by breaking the tablet(‘ACOG Practice Bulletin No. 107’, 2009). A study (Yadav & Chandwaskar, 2017)compares the efficacy and safety profile of sublingual misoprostol (PGE2) and intracervical dinoprostone (PGE1) for cervical ripening and induction of labour.

The most significant advantage of misoprostol usage lies in its storage at room temperature. There are two commercially available preparations of PGE2 for cervical ripening. 0.5mg of dinoprostone gel in a 2.5ml syringe, and the other is a vaginal insert containing 10mg of dinoprostone. 0.5mg dinoprostone gel is used either intravaginally or intracervical. This study compares the safety and

effectiveness of intracervical dinoprostone gel and sublingual misoprostol for cervical ripening in term PROM.

Methods

This is an analytical cross-sectional study including term mothers with spontaneous Prelabor Rupture Of membranes (PROM) attending obstetric casualty at the Department of Obstetrics and Gynaecology, Government Raja Mirasudhar Hospital, Thanjavur from the study period of February 2021 – November 2021 (10 months). One hundred pregnant women were selected using a multistage sampling technique, including women with singleton fetuses of cephalic presentation, gestational age >37weeks, spontaneous rupture of membranes < 6 hours, lack of uterine contractions for atleast1hour from PROM and bishops score <6. The exclusion criteria include Women with scarred uterus/with any associated medical or obstetrical complications/ with suspected cephalopelvic disproportion/with contraindications to vaginal delivery/non-reassuring foetal heart rate/meconium staining of amniotic fluid/cases being referred from PHC/GH/women with contraindications to prostaglandins.

The previous study by Nivedita et al. (Jha et al., 2015) compared the effectiveness and safety of sublingual misoprostol and intracervical dinoprostone gel for cervical ripening in prelabour rupture of membranes after 34 weeks of gestation, used to determine the sample size. Prevalence of misoprostol usage was found to be 60%; the formula calculates sample size for the cross-sectional study, n=4pq/d2 where p=prevalence = 60%, q= 100 - p = 40%, d= allowable error = 10%; therefore, n = 4×60×40/ 10x10 = 96; on rounding off, the final sample size (n) = 100. The 100 samples were assigned randomly into two groups which were 50 in each group as group A (Misoprostol group) and group B (Dinoprostone gel group).

A semi-structured validated schedule consisting of questions on basic demographic details viz., name, age, occupation, address, personal histories such as alcoholism and smoking and history of past and present medical, previous and present obstetric history, and surgical history was used. Natal history was also noted, including APGAR score and Neonatal Intensive Care Unit (NICU) admission. APGAR: this is a quick test performed on a baby at 1 and 5 minutes after birth; the provider examines the baby's: Breathing effort, Heart rate, Muscle tone, Reflexes, and skin colour. Each category is scored with 0, 1, or depending on the experimental condition. A score of 7, 8, or is typical.

Per abdominal examination, basic anthropometric measurements such as height, weight, pulse, and blood pressure were done. They were also assessed for Amniotic Fluid Index (AFI), and fetal presentation was confirmed sonographically. Temperature assessment at four hourly and pulse rate at every half-hour interval was measured. The biochemical investigations, such as total leucocyte count and c-reactive proteins, were also measured. A Swab was taken from the posterior vaginal fornix of the cervix of all women in the group. Women were allocated randomly into one of each group andinduced accordingly. Labour progress monitored with partograph. The induction delivery interval and the mode of delivery were noted and included in the study's findings. All PROM mothers were started on Inj. Cefotaxime 1g iv BD immediately after admission to our institute. All these were

measured for every mother who participated in the study, irrespective of the group they were assigned.

Group A (Misoprostol group) The mothers who were in term and with prelabour rupture of the membrane were given two doses of misoprostol (25 micrograms) four hours apart and observed for uterine contractions, fetal heart rate, cervical dilatation, mode of delivery, duration of delivery after induction and outcome and complications.

Group B (Dinoprostone gel group), the second group, the mothers were given a single dose of intra cervicalcdinoprostone gel with 0.5-milligram strength. They were also observed for uterine contractions, fetal heart rate, cervical dilatation, mode of delivery, duration after induction, outcome and complications.

Ethical considerations:

Permission was received from the institutional ethical committee. Before beginning treatment, each patient has informed written consent obtained. The mother's confidentiality and privacy were protected.

Statistical Analysis:

Data was collected in the schedule, and responses were entered in Microsoft excel. The descriptive statistics such as frequency and percentages were calculated using Epi info free software available online. The association between descriptive variables was found using the chi-square test. The difference and similarities between the groups were analysed using repeated measures of ANOVA and inferential statistics. Student t-tests and paired t-tests were done to determine the significant difference between the means of the two groups. A value less than or equal to 0.05 was inferred as statistical significance.

Results:

In group A, the study participants' median age was 25 years (8.48), while in group B, it was 26.2 years (6.42). Each of the 20 people belonged to group A or group B, depending on their age range of 26 to 30. The difference in age averages between groups A and B was found to be 6.03, with a statistically significant p-value of 0.016. The participants' average height in the intervention group was 160 centimetres, compared to 159.7 centimetres in the control group, which was considered negligible. The t value was insignificant, with a value of 0.187, because the weight between the two groups was 60.41 in the case group and 61.9 in the control group. Bishop's score was similar in both groups and statistically significant at "0" and "6" hours. The induction delivery interval was nearly the same in both groups, 8.54 hours for group A receiving misoprostol and 8.60 hours for group B receiving dinoprostone gel for induction. It was determined by the ANOVA test that there was a statistically significant difference between the two groups' means (p 0.001). (table:1)

Table 1: Comparison of various factors between dinoprostone gel and sublingual misoprostol.

		Group A (sublingual misoprostol) mean±SD	Group B (intracervical dinoprostone gel) mean±SD	P value
Age		25.0±8.48	26.2±6.42	0. 016*
Height		160±4.10	159.70±4.67	0.51
Weight		60.41±4.68	61.96±4.01	0.81
Bishops Score (time interval in hours)	at 0 hour	2.52 ±0.53	2.61±0.56	0.000*
	At 4 hours	3.61±0.61	3.54±0.58	0.01*
	At 6 hours	3.82±0.68	3.65±0.61	0.12
Induction- Delivery Interval		8.54± 1.21	8.60± 1.34	0.001*

Table 2: Association between indication for LSCS and mode of induction

Indication for LSCS	Group A (with misoprostol) n=50	Group B (with dinoprostone gel) n=50	X^2	p-value
Failed induction	2	1	5.621	0.045*
Failure to progress	3	1	7.789	0.651
Fetal distress	9	8	9.265	0.011*
Others	1	1	4.652	0.084

Failure to induce was a statistically significant indicator of LSCS with a chi-square value of 5.621 (p = 0.045), and fetal distress was found to be a statistically significant indicator of LSCS with a chi-square value of 9.265 (p = 0.011). The remaining associations were not statistically significant. (Table: 2). The correlation between PROM and delivery interval is found to be statistically significant only at less than 6 hours with a p-value of 0.053, and all the other intervals are insignificant. (Table: 3)

Table 3: Correlation between PROM and delivery interval

PROM to delivery Interval (in hours)	Mode of induction	N	Mean	Std. Deviation (±)	ANOVA	p value
< 6 hours	Group A(with misoprostol)	10	4.54	2.11	2.672	0.053*
	Group B (with dinoprostone gel)	8				
6-12 hours	Group A(with misoprostol)	30	8.12	3.14	1.567	0.132
	Group B (with dinoprostone gel)	20				
>12 hours	Group A(with misoprostol)	10	11.52	3.42	1.823	0.141
	Group B (with dinoprostone gel)	22				

Table 4: Correlation between the groups and the stages of labour, mode of delivery, and fetal heart rate.

		Mode of Induction		Mean	p-value
		Group A (with misoprostol)	Group B (with dinoprostone gel)		
First stage of labour (interval in hours)	< 6 hours	14	8	4.86	0.052*
	6-10 hours	20	12	8.54	0.731
	10-20 hours	10	18	12.42	0.062
	>20 hours	6	12	21.25	0.091
second stage of labour (interval in hours)	< 1 hour	10	12	4.21	0.021*
	>1 hour	18	20	8.65	1.221
Mode of	Normal	35	39	5.82	0.048*

delivery	Caesarean	15	11		
Fetal heart rate	Normal	35	45	6.854	0.022*
	Indeterminate	10	3	8.576	0.782
	Abnormal	5	2	9.281	0.013*

Only a time interval of fewer than 6 hours is shown to be statistically significant in the initial stage of labour, with a p-value of 0.052 with the induction medications, i.e., between the groups. (Table: 4) With a p-value of 0.021, the only time interval in the second stage of labour determined to be statistically significant was when the induction medications were taken or among the groups. When the two groups' delivery modes were compared, natural labour was shown to be statistically significant (p = 0.048). (Table: 4). Normal heart rate was found to be statistically significant with a chi-square value of 6.854 (p = 0.022). With a chi-square value of 9.281 (p = 0.013), abnormal heart rate was found to be statistically significant. The other results were not statistically significant.

Table 5: Association between mode of induction and Complications

Complications observed	**Mode of induction**		X^2	**p-value**
	Group A (with misoprostol) n=50	**Group B (with dinoprostone gel) n=50**		
Meconium stained Amniotic Fluid	3	2	6.635	0.001*
APGAR<7	3	2	2.705	0.065
NICU Admission	12	8	5.023	0.031*
Postpartum Haemorrhage	1	2	0.151	1.312
Pyrexia	10	7	7.362	0.042*
Tachycardia in baby	2	1	7.328	0.041*
GIT Effects	5	6	0.125	1.452
Oxytocin usage	1	2	0.326	0.621

Only 8 of the 12 newborns in group B's birth cohort needed NICU admission, compared to 12 of the 12 newborns in group A. 10 participants in group A and 7 in group B both complained of pyrexia. Meconium-stained Amniotic Fluid had a statistically significant χ^2value of 6.635 and a p-value of 0.001 when $\chi^2$was used to determine the connection. The same was observed in NICU admission (p =

0.031), pyrexia and induction (p = 0.042) and also tachycardia in the baby (p =0.041) was also statically significant. (Table: 5)

Discussion:

In this study, patients with term rupture of membranes who came to the hospital were given either sublingual misoprostol or intracervical dinoprostone gel to groups assigned randomly. According to this study, the indication for induction was for those presenting to obstetric casualty within 6 hours of rupture of membrane and not having uterine contractions for almost 1 hour after rupturing of membranes and with the unfavourable cervix of Bishops score <6 at the time of admission.

According to this study, induction with sublingual misoprostol results in a quicker delivery than induction with intracervical dinoprostone gel, which is the same as in the study by (Jha et al., 2015). Studies like (Denguezli et al., 2007), (Veena et al., 2016), (Chitrakar, 2012), (Wankhede et al., 2017) had inconsistent findings with induction to the delivery interval.

In the present study, those who delivered within 6 hours are 8% in grou6 hours0% in group B., 28% in group A and 30% on group B delivered within 6-12 hours of rupture of membranes, and 14% in group A and 10% in group B delivered more than 12 hours of membrane rupture. As all the women included in the study were induced, the PROM-delivery interval was less than in other studies. (P et al., 2021) did a retrospective, non-comparative, observational study and mothers were not induced in which PROM to the delivery interval was 10% in less than 12 hours, 59% in 12-24 hours and 31% in more than 24 hours. In a prospective trial by (Wankhede et al., 2017), mothers were placed into two groups and given either expectant management or intracervical PGE2 induction; the PROM to the delivery time for the expectant group was 22.36 hours, and for the intracervical PGE2 induction group was 15.5 hours.

About 35 (70%) participants in group A and 39 (78%) in group B experienced a normal delivery. Additionally, 11 (22%) of group B and 15 (30%) of group A participants underwent caesarean deliveries. Chi-square analysis revealed a statistically significant value of 5.911 with a p-value of 0.05. Moreover, from all the available studies comparing expectant management versus any method of induction in PROM, the rate of vaginal delivery is high. This shows that only a tiny proportion of PROM mothers will go for LSCS. In this present study also, the majority delivered vaginally. In the study by (P et al., 2021), 50.81% were delivered vaginally, and 49.19% were delivered via LSCS. It was found not to be statistically significant as there is a higher incidence of LSCS related to high induction rates and maternal co-morbidities.

In this study, at 4 hours after induction means Bishop's score in group A is 3.61, whereas in group B is 3.54, which is statistically significant. This indirectly shows that more women induced with misoprostol have progressed well into the active phase of labour. In the present study, 28% in group A had a duration of 1st stage <6 hours, whereas in group B it is 16%, which is only statistically significant and it implies that among people induced with misoprostol, more people had a duration of 1st stage < 6 hours than those induced with intracervical dinoprostone gel. Moreover, 12% in group B and 10% in group A had a duration of 2^{nd} stage < 1 hour which is statistically significant, implying that dinoprostone gel had a shorter 2nd stage of labour.

Regarding failed induction, in this study, 2 in group A and 1 in group B failed, which is statistically significant, implying that failed induction with misoprostol was more. The most common indication for LSCS in this study is fetal distress. 9 in group A,8 in group B had been taken for LSCS because of fetal distress. This shows that sublingual misoprostol has got more rate of fetal distress. Similar findings like non-reassuring fetal status (29.6%), fetal distress (25.6%) and failure to progress (45.45%) were found as the most common indication for LSCS with the studies by (Geethanjali et al., 2020), (P et al., 2021) and (Surayapalem et al., 2017). respectively.

In the current study, most cases occurred in women between the ages of 26 and 30. The median age of the participants was 25 years, with a standard deviation of 8.48 years in group A (sublingual misoprostol), but 26.2 years with a standard deviation of 6.42 in group B (intracervical dinoprostone gel). Our investigation determined the mean difference between the two groups was 6.03, with a statistically significant p-value of 0.016. In a study conducted by (Gupta et al., 2018) and another study by (Surayapalem et al., 2017), the most common age group was 20-24 years. (Gaikwad H & Maskar P, 2016) study had a majority (64%) of the study participants within the age group of 21-25 years.

These are the postpartum haemorrhage, pyrexia, and GIT consequences documented in the current study. 10 (20%) of the individuals who were given misoprostol sublingually (Group A) and 7 (14%) of the participants who were given dinoprostone gel (Group B) experienced pyrexia, which had a statistically significant chi-square value of 7.362 and a p-value of 0.042. Hence maternal pyrexia is more familiar with misoprostol in this study. GIT effects like diarrhoea are more common with dinoprostone gel. At the same time, misoprostol has lower rates of postpartum haemorrhage than dinoprostone. All cases of postpartum haemorrhage were managed medically. No other significant maternal morbidity was observed in the study group.

Likewise, fetal complications like meconium-stained amniotic fluid and cases of NICU admission were reported. It was concluded that misoprostol induction is associated more with meconium-stained amniotic fluid. With a chi-square value of 5.023 and a statistically significant p-value of 0.031, only 12 (24%) of the babies delivered to mothers who were induced by misoprostol sublingually (Group A) and 8 (16%) of the babies born to mothers who were induced by dinoprostone gel (Group B) had to

be admitted in NICU. (Surayapalem et al., 2017) reported 17.5% of febrile morbidity being the most common maternal complication and 26% of birth asphyxia as the most common fetal complication. (Gupta et al., 2018) reported 26% of NICU admission as fetal complications. (Jaiswal et al., 2017) documented 26% of chorioamnionitis as a maternal complication and 30% of early-onset neonatal sepsis as a fetal complication. (Endale et al., 2016) found that 22% of puerperal sepsis was a maternal complication, and 33.5% had fetal complications.

The study has a few limitations. Firstly, the sample size is not large enough to favour generalizability. Secondly, not all studies used the same drugs to compare. Additionally, as only one referral hospital was used for the study, the findings might need to be more generalisable to other organisations and the community. Further, the study findings can be elaborated in a better study design.

Conclusion:

It has been observed that though there is no significant difference between the group induced with misoprostol by sublingual route or in the group induced with Intracervical application of dinoprostone gel, the induction delivery time is less in the group administered with sublingual misoprostol than dinoprostone and misoprostol given sublingually is having higher maternal febrile morbidity and fetal distress. Thus, it was concluded that though sublingual misoprostol is more efficacious than intracervical dinoprostone, its safety margin is significantly less; hence, misoprostol induction should be done only in a double setup under medical supervision.

Conflicts of Interest

The author declares no conflicts of interest.

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