International Journal of Clinical Obstetrics and Gynaecology

ISSN (P): 2522-6614
ISSN (E): 2522-6622

www.gynaecologyjournal.com
2022; 6(6): 105-108
Received: 28-09-2022
Accepted: 31-10-2022

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Induction of labour with misoprostol in premature rupture of membranes after 34 weeks: Which route is better and at what dose a randomized control trial in a tertiary care hospital

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DOI: https://doi.org/10.33545/gynae.2022.v6.i6b.1243

Abstract
Background: The idea of this study was to evaluate the efficacy and safety of different routes of administration of misoprostol - 50µg oral, 25µg vaginal and 50µg sublingual for induction of labour in women with premature rupture of membranes after 34 weeks of gestation.
Design: Randomized controlled trial.
Sample: A total of 252 women with premature rupture of membranes after 34 weeks of gestation with indications of induction of labour.
Methods: Study was conducted from 01/02/2022 to 31/11/2022, Women admitted to ward with premature rupture of membranes (PROM) after 34 weeks of gestation and requiring induction of labour were randomized into three groups. A total of 252 women participated in the study and were assigned to three groups to receive either 50µg oral misoprostol (n=82) or 25µg vaginal misoprostol (n=85) or 50µg sublingual misoprostol (n=85). The doses were repeated 4 hourly till active labour was established or up to a maximum of 4 doses.
Major outcomes: 1.Induction to active labour 2.induction to delivery intervals 3.Delivery modes and 4.fetal outcomes were noted.
Results: The mean induction to active labour interval was not significantly different in the three groups (oral vs vaginal vs sublingual- 7.54±4.8 vs 7.77±4.1 h vs 7.68±5.1 h; p=0.92). There was no significant difference in the induction to delivery time interval among the three misoprostol groups (oral vs vaginal vs sublingual – 10.7± 5.5 h vs 11.2±5.0 h vs 11.2±6.4 h; p= 0.88). Spontaneous vaginal delivery rate, instrumental delivery rate and lower segment caesarean section rates were comparable among the three groups. The spontaneous vaginal delivery is more in vaginal group and least in the sublingual group. The oral group is almost equal to the sublingual group in spontaneous delivery. The number of neonates with APGAR score <7 (low APGAR) at 1 minute of birth was highest in sublingual group and lowest in vaginal group which was statistically significant (oral vs vaginal vs sublingual, 16.8% vs 9.4% vs 20%; p= 0. 04). APGAR score <7 at 5 minutes was not significantly different among the three groups (oral vs vaginal vs sublingual, 6.02% vs 3.5% vs 7.05%; p=0.2). This implies that the need for immediate resuscitation was more in the sublingual group. Neonatal intensive care admission was least in the vaginal group although the difference was not statistically significant.
Conclusion: 50µg oral misoprostol, 25µg vaginal misoprostol or 50µg sublingual misoprostol for induction of labour after 34 weeks of gestation have equal efficacy for induction of labour in women with spontaneous vaginal delivery is highest in vaginal route. The spontaneous vaginal delivery is more in vaginal route. The sublingual route having slightly higher incidence of low APGAR scores at one minute for the neonate.

Keywords: Induction of labour, oral misoprostol, premature rupture of membranes, sublingual misoprostol, vaginal misoprostol

Introduction
Premature rupture of membranes is the spontaneous rupture of membranes before the onset of labour. 5 -10% pregnancies are complicated by the premature rupture of membranes. The management of PROM is still controversial and it depends on several factors. The factors that management of PROM depend are gestational age, fetal weight, lung maturity and availability of good neonatal care balanced against the chance of developing chorioamnionitis, cord compression and neonatal infection.

The increase in the incidence of complications such as chorioamnionitis, endometritis, chronic abruption, cord compression, neonatal morbidity and neonatal sepsis is associated with the increase in time interval between rupture of membranes and onset of labour pains. Active management is preferred after 34 weeks once fetal lung maturity is achieved thus reducing maternal and fetal complications. Several methods have been used to ripen the cervix and induce labour.

Among them prostaglandins have been shown to be effective in cervical ripening as well as induction of labour. Misoprostol is a prostaglandin E1 methyl ester that stimulates myometrial contractions. Initially introduced for early pregnancy termination, in lower doses it is found to be effective for labour induction. Misoprostol is heat stable and does not require refrigeration for storage compared to the alternatives PGE2 gel or oxytocin. The cost of misoprostol tablet is also less than PGE2 gel or pessary and oxytocin injection. Studies have shown that misoprostol can be administered as various doses, at varied time intervals and through different routes such as oral, vaginal and sublingual.

The chance of iatrogenic ascending infections is decreased and the overall comfort of the patient is increased as there is reduction of vaginal examinations in oral and sublingual routes. However, the ideal dose, route and frequency of administration still remain under investigation. Most of the studies on induction of labour are conducted on women with intact membranes. Studies on women with PROM are limited. Also, there are only few studies comparing three routes of administration of misoprostol for induction of labor. Hence, the present study was undertaken with a view to compare the efficacy and safety of oral, vaginal and sublingual routes of administration of Misoprostol for induction of labour in women with PROM.

Methods

The study was done in the Department of Obstetrics and Gynecology of a tertiary care hospital for a duration of one year. The permission for the conduction of the study was granted by the institute ethics committee. This is an open label randomized controlled trial including 246 antenatal women. Participants were explained about the procedure and informed consent was obtained.

Inclusion criteria

Women who were admitted to labour ward with premature rupture of membranes after 34 weeks of gestation with a single live fetus in cephalic presentation, clear liquor, reassuring non-stress test and pre-induction Bishop score ≤6.

Exclusion criteria

Women in established labour, suspected cephalopelvic disproportion or macrosomia, history of previous uterine surgery or lower segment cesarean section, antepartum hemorrhage, chorioamnionitis, active genital infection in the present pregnancy, contraindications to prostaglandins (glaucoma, asthma) and major fetal anomalies.

The women were randomized into three groups by random selection based on computer based random numbers. PROM was confirmed based on sterile speculum examination and the color of the liquor is noted. The Bishop score was assessed before induction. All participants received prophylactic antibiotics (Ampicillin or Cephalosporin) as per the institute protocol. The time of spontaneous membrane rupture was noted. Group 1 received 50µg oral misoprostol 4th hourly, group 2 received 25µg vaginal misoprostol 4th hourly and group 3 received 50µg sublingual misoprostol 4th hourly. A maximum of 4 doses was allowed in all three groups.

The administration of doses was repeated every 4 hours until active labour was achieved (i. e. minimum three uterine contractions lasting 45 seconds or more in 10 minutes or >4cm cervical dilatation) or a maximum of 4 doses was reached. If active labour was not established with four doses of misoprostol, and bishop score was > 6, and contractions were inadequate, oxytocin infusion was commenced in some cases.

The participants and their neonates were followed until discharge and maternal and neonatal outcomes were noted.

Major outcome parameters

Induction to active labour interval, induction to delivery interval, duration of first stage, duration of second stage, duration of third stage, mode of delivery.

Minor outcome parameters

APGAR scores at 1 minute and 5 minutes of birth, neonatal unit admission.

Statistical analysis

The sample size of 246 was calculated based on previous studies assuming 80% power and 95% confidence interval. Statistical analysis was carried out at 5% level of significance and the p value <0.05 is significant.

Results

Table 1: Demographic characteristics

Parameters	Mean age (Years)	Parity		Mean duration of leaking (h)	Mean gestation age	
		Primi	Multi			
Oral Misoprostol (n = 82)	24±3.2	52	30	14±13	38.3±1.5	
Vaginal	24.5±3.5	52	33	13±9	38.2±1.8	
Misoprostol (N = 85)						
Sublingual Misoprostol (n = 85)	24.1±3.2	60	25	17±14	38.3±1.9	
P – Value	0.52	0.26	0.26	0.12	0.95 (NS)	

Demographical characteristics of the women and the indications for labour induction were similar in the three groups and the women are almost equal in the three groups (Table 1). The number of primigravida women are more than multigravida women almost in the three groups. The mean gestational age is also equal in the three groups.

The mean time taken from the induction of labour to the cervical dilatation >4cm is 7.54±4.8 (hr) in oral and 7.77±4.1 in vaginal and 7.68±5.1 in sublingual groups and the p value is not significant. So, all the three routes are equally effective in the induction of active labour.

Table 2: Major outcomes meaures

Labour characteristics	Oral	Vaginal	Sublingual	P Value
Time taken for cervical dilatation>4cm (active labour) (hr)	7.54 ±4.8	7.77±4.1	7.68±5.1	0.93
Time taken for delivery (hr)	10.7±5.5	11.2±5.0	11.2±6.4	0.87
Time from active labour to delivery (hr)	3.63±1.6	3.63±1.2	3.7±1.7	0.85
Time from prom to delivery(hr)	23±16.2	23±12.3	27.1±17.6	0.23
Duration of first stage(hr)	5±2	5.7±2.1	5.8±3.0	0.31
Duration of second stage(min)	34.5±15	34.0±13	32.6±14	0.55
Duration of third stage(min)	7.2±2.5	6.8±1.6	7±2.3	0.19

According the data in the table 2, the second major outcome is the time taken for the delivery and the p value is not significant. So, the three groups are equally effective in the in the delivery.

Table 3: Delivery mode outcomes

No. of patients	Oral misoprostol	Vaginal Misoprostol	Sublingual misoprostol
SVD	68 (81.9%)	75 (88.2%)	68 (80%)
Operative vaginal	5	4	8
LSCS	9 (10.8%)	6 (7.05%)	9 (10.5%)

The modes of delivery that are taken in the study are spontaneous vaginal delivery, operative vaginal delivery and lower segment cesarean section. The spontaneous mode of delivery is 81.9% in oral group, 88.2% in vaginal misoprostol group and 80% in sublingual misoprostol. The outcome is comparable in the three groups. The spontaneous vaginal delivery is more in the group of women that are on vaginal misoprostol than the other two groups. The spontaneous vaginal delivery is almost significantly equal in both oral and sublingual groups, with a little high in oral group than sublingual group. The LSCS is more and almost equal in both oral and sublingual group compared to vaginal misoprostol group.

Table 4: Minor outcomes

Parameter	Oral	Vaginal	Sublingual	P Value
APGAR < 7 at 1min	14 (16.8%)	8(9.4%)	17(20%)	0.04
APGAR < 4 at 5min	5 (6.02%)	3 (3.5%)	6 (7.05%)	0.2
Neonatal intensive unit admission	8 (9.6%)	3 (3.5%)	12 (14.1%)	0.055

APGAR is considered as a minor and secondary outcome in this study. APGAR at 1min, and at 5 min and neonatal intensive admission are taken into account in the study. At 1 min, APGAR <7 is more in sublingual group followed by oral group and then in the vaginal group and it is statistically significant as p value is 0.04. The APGAR score <7 at 1min is less in vaginal group. APGAR <4 at 5min is almost equal in birth oral and sublingual misoprostol group with little less in vaginal misoprostol group and this is statistically insignificant. Neonatal admissions in ICU is more in sublingual group and less in vaginal group but this is statistically insignificant. Spontaneous delivery is more significant in the vaginal group and the least in sublingual group. The spontaneous vaginal delivery between the oral and sublingual groups are almost equal with little high in oral group.

Discussion

There are many studies conducted to study the effectiveness of oral, vaginal and sublingual misoprotol in induction of labour. Some studies compared between oral &sublingual and some between sublingual & vaginal. The present study is between oral, sublingual and vaginal misoprostol. The study did not observe any significant change in the efficacy from induction to active labour or induction to delivery in all the three groups. A study by Elhassan *et al*. compared all the three routes of misoprostol for labour induction and the mean induction to delivery interval was shortest in the sublingual group which was significant in contrast to our study. A study Galidevara C *et al*. concluded that there was no significant change in the efficacy from induction to delivery in all the three routes of induction.

The spontaneous vaginal delivery rate in the present study was 81.9% in the oral group, 88.2% in the vaginal group and 80% in the sublingual group. Our results are consistent with other studies like Mehrotra *et al*. in which the spontaneous delivery rates 83.3% in the oral and 83.8% in the vaginal group. Other studies like Elhassan *et al* showed that the three group's oral, vaginal and sublingual had almost equal rates of spontaneous vaginal delivery. The results in the Bartusevicius *et al*. study found that spontaneous vaginal rates are 83% in the sublingual misoprostol group and 76% in the vaginal misoprostol group delivered vaginally within 24 hours of induction. The study by Zahran *et al*. concluded that 70.4% patients delivered vaginally in the sublingual group and 66.7% in the vaginal group with no significant difference. Our Present study is almost similar with the findings in other group.

The APGAR score <7 at 1 min is significant high in sublingual group with 20% and low in vaginal misoprostol group with 9.4%. Also, the score in the oral group with 16.8% is almost near to the sublingual group and it is statistically significant. The neonatal admission is low in vaginal group compared to other even though it is statistically insignificant. The study by Feitosa *et al* and Zahran *et al*. found no significant differences between the vaginal and sublingual misoprostol groups. A study Galidevara C *et al*. said that neonatal admission is 14.5% in sublingual group and 3.6% in vaginal route and the apgar score <7 at 1min is high in sublingual group which are consistent with our study The study by Shetty *et al* comparing oral and sublingual routes of misoprostol found the rate of admission to be 12% in the oral group and 10% in the sublingual group. These studies are in agreement with our findings.

Conclusion

Our present demonstrated the efficacy of sublingual, oral and vaginal misoprostal in premature rupture of membranes after 34 weeks of gestation. Our study showed that the three methods have significant efficacy from induction to active labour and also from induction to delivery. The need for the LSCS is low in the vaginal group and it is almost high and equal in the oral and sublingual groups. The APGAR score at 1min <7 is high in sublingual group followed by oral group and least in vaginal group which is significant. The neonatal admission is also high in sublingual group and least in vaginal group which is insignificant statistically and the need for resuscitation is more in sublingual group.

Acknowledgement

Not available

Author's Contribution
Not available

Conflict of Interest
Not available

Financial Support
Not available

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How to Cite This Article
Aravind R, Sripriya K, Sulochana M. Induction of labour with misoprostol in premature rupture of membranes after 34 weeks: Which route is better and at what dose a randomized control trial in a tertiary care hospital. International Journal of Clinical Obstetrics and Gynaecology 2022; 6(6): 105-108. DOI: https://doi.org/