



To Compare the Efficacy and Safety of Misoprostol for Induction of Labour at Term Singleton Pregnancies by Intravaginal versus Sublingual Route

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Abstract

Background: Induction of labour implies stimulation of contractions before the spontaneous onset of labour, with or without rupture of membranes. Common indications of labour induction include post-dated pregnancies, intra-uterine growth restriction, pregnancy induced hypertension, non-reassuring fetal status and various medical conditions such as chronic hypertension and diabetes. In routine clinical practice, there are only two classes of drugs which are seriously considered for cervical ripening and induction of labour, namely prostaglandins (E1 and E2) and oxytocin.

Materials and Method: The study was a prospective randomized study comprising of all women above 18 years with singleton term gestation in cephalic presentation with parity 1 to 3 with normal FHR and no contraindication for induction both for mother and the fetus admitted in JNIMS between October 2017 and September 2019.

Results: Delivery with a single dose was almost same in both the two groups. Normal vaginal delivery was more among intravaginal group but ventouse and LSCS was more among sublingual group but the finding was statistically insignificant. Maternal and fetal complications were comparable in between the two study groups.

Conclusion: The sublingual route of administration of misoprostol is comparable in efficacy and safety to the vaginal route for induction of labour.

Keywords: Induction, Misoprostol, Sublingual, Intravaginal.

Background

Induction of labour implies stimulation of contractions before the spontaneous onset of labour, with or without rupture of membranes. Common indication of labour induction includes post-dated pregnancies, intra-uterine growth restriction, pregnancy induced hypertension, non-reassuring fetal states and various medical conditions such as chronic hypertension and diabetes.¹

In routine clinical practice, there are only two classes of drugs which are seriously considered for cervical ripening and induction of labour, namely prostaglandins and oxytocin.

Misoprostol is a prostaglandin E₁ which stimulates remodeling of extracellular collagen with activation of collagenase, increasing the water content and changes in the glycosaminoglycan of the extracellular matrix, with an increase in the amount of hydrophilic

glycosaminoglycan and hyaluronic acid and a decrease in dermatan sulfate. It can also directly increase myometrial contractility. All of these changes result in softening, effacement, and marked relaxation of the smooth muscle fibers and dilatation of the cervix. Misoprostol is extensively absorbed and rapidly metabolized, with approximately 80% excreted by the kidney with a terminal half-life of less than 1 hour when introduced vaginally and sublingually, and peak plasma levels noted at around 5-9 hours.² It is cheap and stable at room temperature.

Induction of labour has become a very popular practice in modern obstetrics, and keeping in view the various advantages and disadvantages of the different methods, the present study was undertaken to find out the safety and efficacy of vaginal versus sublingual misoprostol for induction of labour at term.

Methodology

The study was carried out in department of Obstetrics and Gynaecology, Jawaharlal Nehru Institute of Medical Sciences (JNIMS), Imphal, Manipur, between September 2017 to August 2019, to compare the efficacy and safety of misoprostol for induction of labour at term singleton pregnancies by intravaginal versus sublingual route with 25mcg, 3 doses at 4 hours interval. It was a prospective randomized study comprising of all women above 18 years with singleton term gestation in cephalic presentation with parity 1 to 3 with normal FHR and no contraindication for induction both for mother and the fetus. We excluded pregnant women with previous uterine surgery, cephalopelvic disproportion, women in active labour, grand multiparity, antepartum hemorrhage, twin pregnancy, preterm labour, history of cervical encirclage, malpresentation and known hypersensitivity to prostaglandins.

After proper history taking, general and obstetrical examination, condition at the time of admission, during labour and mode of delivery was noted.

After delivery, the mother and the babies were examined and findings were noted. Mother and babies were followed up.

Study Tools or Procedure

Pregnant women at term pregnancy fulfilling the inclusion criteria were admitted in the ward and the efficacy and safety of misoprostol in induction of labour by intravaginal versus sublingual route with 25mcg, 3 doses at 4 hours interval were compared.

Timing of drug given, frequency of drug administration, rate of cervical dilatation, duration of first stage of labour, color of liquor, oxytocin augmentation if the induction fails after 3rd dose of tablet misoprostol, mode of delivery, induction to delivery time interval, birth weight of neonates in grams, neonatal condition at birth and incidence of hyperstimulation were noted.

Sample Size: Based on the study of Caliskan E et al³, sample size was calculated from the following parameters:

$\alpha=0.05$

Power= 80% (2 sided)

Treatment effect=21%

Deliveries with 24 hours=91.3%

Sample size was found to be 60 patients in each group.

Statistical Analysis

Data collected were entered in Microsoft excel 2008. Data were then checked for accuracy and correctness. Data were analyzed using SPSS version 18 (statistical package for social science) and were presented in tabulated manner. Mean and percentages were used for descriptive data. For test of significance chi-square test and t-test was used. Probability value of less than 0.05 was taken as significant.

Result

Table 1: Age distribution of the respondents

Age in years	Misoprostol Intravaginal n(%)	Misoprostol Sublingual n(%)	Total N(%)	Chi-square test
<20	9(15.0)	10(16.6)	19(15.8)	Value=0.342 df=2 p=0.842
20-30	43(71.4)	41(68.4)	84(70.0)	
>30	7(11.6)	9(15.0)	16(13.2)	
Total	60(100.0)	60(100.0)	120(100.0)	
Mean ±SD	24.1±3.3	23.9±3.4	-	

Table 1 and figure 1 show that there was a little difference in various age group. This difference was not statistically significant (p>0.05). So, both

the groups were comparable regarding age. Both the mean age was also almost similar.

Table 2: Distribution of the respondents by parity

Parity	Misoprostol Intravaginal n(%)	Misoprostol Sublingual n(%)	Total N(%)	Chi-square test
Primipara (1)	34(56.6)	38(63.3)	72(60.0)	Value=0.556 df=1 p=0.455
Multipara(1-2)	26(43.4)	22(36.7)	48(40.0)	
Total	60(100.0)	60(100.0)	120(100.0)	

Among the intravaginal group, primipara was 56.6% and among the sublingual group it was 63.3% but the difference observed was

statistically insignificant as p>0.05. Parity was also comparable between the two groups.

Table 3: Distribution of the respondents by indication of induction

Indication for induction	Misoprostol Intravaginal n(%)	Misoprostol Sublingual n(%)	Total N(%)	Chi-square test (yates corrected)
Post term	28(46.6)	30(50.0)	58(48.4)	Value=0.683 df=3 p=0.877
Mild Oligohydranmnios	9(15.0)	12(20.0)	21(17.5)	
PROM	17(28.4)	15(25.0)	32(26.6)	
Mild PIH	6(10.0)	3(5.0)	9(7.5)	
Total	60(100.0)	60(100.0)	120(100.0)	

Post term was the most common indication in all the cases and after stratification it was 46.6% among intravaginal group and 50% among

sublingual. Mild-oligohydranmnios, PROM and mild eclampsia were almost similar among the two groups

Table 4: Distribution of the respondents by number of doses

Number of doses of misoprostol	Misoprostol Intravaginal n(%)	Misoprostol Sublingual n(%)	Total N(%)	Chi-square test Yates corrected
One dose	28(46.4)	26(43.4)	54(45.0)	Value=1.273 df=2 p=0.529
Two doses	19(31.5)	15(25.0)	34(28.3)	
Three doses	4(6.5)	7(11.6)	11(9.1)	
Induced (total)	51(85.0)	48(80.0)	99(82.5)	Value=0.519* df=2 p=0.471
Oxytoxin augmentation*	9(15.0)	12(20.0)	20(15.7)	
Total	60(100.0)	60(100.0)	120(100.0)	

Single dose was required in 46.4% of respondents among intravaginal group and in case of sublingual group it was 43.4%. And for two doses, 31.5% among intravaginal and 25% among

sublingual group. Oxytocin augmentation was required in 15% among intravaginal group and 20% among sublingual group. This finding was found to be statistically insignificant ($p>0.05$).

Table 5: Distribution of the respondents by rate of cervical dilatation, duration of first stage

Acceleration effect	Misoprostol Intravaginal Mean±SD	Misoprostol Sublingual Mean±SD	t-test
Rate of cervical dilation cm/hr	2.66±0.80	2.32±0.27	Value=3.1192 df=118 p-0.0023
Duration of 1 st stage in minute	178.29±57.4	190±61.39	Value=1.106 df=118 p-0.271
Induction to delivery interval in minute	496.54±94.37	531.64±119.98	Value=1.78.1 df=118 p-0.077

Rate of dilatation was a little difference in intravaginal group (2.66±0.80 cm/hr) than sublingual group (2.32±0.27 cm/hr). This finding was statistically significant ($p<0.05$). Duration of 1st stage (178.29±57.4 vs. 190±61.39 minutes) and

induction to delivery interval (496.54±94.37 vs. 531.64±119.98 minutes) was reduced in intravaginal group than sublingual group but found to be statistically insignificant.

Table 6: Distribution of the respondents by mode of delivery

Mode of delivery	Misoprostol Intravaginal n(%)	Misoprostol Sublingual n(%)	Total N(%)	Chi-square test (Yates corrected)
NVD (±RMLE)	48(80.0)	43(71.6)	91(75.8)	Value=1.217 df=2 p-0.544
Ventouse	7(11.6)	9(15.0)	16(13.3)	
LSCS	5(8.4)	8(13.4)	13(10.9)	
Total	60(100.0)	60(100.0)	120(100.0)	

NVD was more among intravaginal group (80% vs. 71.6%) but ventouse and LSCS was more

among sublingual group but the finding was statistically insignificant ($p>0.05$).

Table 7: Distribution of the respondents by indication of LSCS

Indication of LSCS	Misoprostol Intravaginal n(%)	Misoprostol Sublingual n(%)	Total N(%)	Chi-square test (Yates corrected)
Fetal distress	3(60.0)	4(50.0)	7(53.8)	Value=0.167 df=2 p-0.919
Non-progression of labour	1(20.0)	3(37.5)	4(30.7)	
Failure of dilatation and effacement of cervix	1(20.0)	1(12.5)	2(15.5)	
Total	5(100.0)	8(100.0)	13(100.0)	

Fetal distress was a bit higher among intravaginal group (60% vs. 50%), non-progression was more among sublingual group and failure of induction

was more in intravaginal group. But this finding was found to be statistically insignificant.

Table 8: Distribution of the respondents by maternal complications

Maternal complications	Misoprostol Intravaginal n(%)	Misoprostol Sublingual n(%)	Total N(%)	Fisher exact test
Yes*	7(11.6)	9(15.0)	16(26.6)	Value=0.288 df=1 p=0.591
1)Nausea and vomiting	3(5.0)	4(6.7)	7(5.8)	
2)Tachysystole	3(5.0)	4(6.7)	7(5.8)	
3)Hyperstimulation	1(1.6)	1(1.6)	2(3.4)	
No*	53(88.4)	51(85.0)	88(88.0)	
Total	60(100.0)	60(100.0)	120(100.0)	

Maternal complication was present in 11.6% of cases among intravaginal group and among sublingual group it was 15%. But the finding was statistically insignificant. Nausea and vomiting

were 5% among sublingual group but among intravaginal it was 6.7%, tachysystole was more among sublingual (5% vs 6.7%) and same finding for hyperstimulation in both the groups.

Table 9: Distribution of the respondents by fetal complications

Fetal complications	Misoprostol Intravaginal n(%)	Misoprostol Sublingual n(%)	Total N(%)	Chi-square test (Yates corrected)
Yes*	8(13.3)	9(15.0)	17(14.1)	Value=0.0 df=1 p=1.0
1)Meconium staining of liquor	5(8.3)	6(10.0)	11(9.3)	
2)Non reactive heart rate (Bradycardia)	3(5.0)	3(5.0)	6(5.0)	
No*	52(86.7)	59(98.3)	111(92.6)	
Total	60(100.0)	60(100.0)	120(100.0)	

Out of 11 cases of meconium stained liquor, 6 of them were in sublingual group and 5 among intravaginal group. Non-reactive fetal heart rate (fetal bradycardia) was same among the two groups. Though fetal complications were more among sublingual group but it was found to be insignificant ($p>0.05$).

Discussion

The use of misoprostol for induction of labour has been quite promising. It is inexpensive can be stored at room temperature, has minimal side effects at low doses, can be administered with ease by various routes like oral, sublingual, vagina, buccal and rectal and more importantly acts to promote cervical ripening and uterine contractions. Doses ranging from 25 mcg to 200 mcg have been used but doses more than 50 mcg is associated with uterine contraction abnormalities, meconium passage and uterine rupture.⁴

This prospective randomized control trial was conducted to compare the efficacy and safety of misoprostol for induction of labour at term by intravaginal versus sublingual route among 120 cases (60 cases each).

Most of the respondents were from the age group 20-30 years and also for the two groups. So, both the groups were comparable regarding age.

Parity was also comparable between the two groups. More than half of the respondents were primipara.

Single dose was required in 46.4% of respondents among intravaginal group and in case of sublingual group it was 43.4%. And for two doses, 31.5% among intravaginal and 25% among sublingual group. Oxytocin augmentation was required in 15% among intravaginal group and 20% among sublingual group. This finding was found to be statistically insignificant ($p>0.05$). Hissane EM et al⁵ in their study observed that there were no significant differences in the number of doses needed. Insignificant difference

was also observed in the study by Akare MD et al⁶ regarding risk of failed induction, reduced time from initiation to induction, reduced induction to delivery interval.

Rate of dilatation was a little difference in intravaginal group (2.66±0.80 cm/hr) than sublingual group (2.32±0.27 cm/hr). This finding was statistically significant (p<0.05). Souza AS et al⁷ in their study found no statistically significant difference between the sublingual and the vaginal misoprostol groups with respect to the rate of vaginal delivery within 24 hours. But duration of 1st stage and induction to delivery interval was reduced in intravaginal group than sublingual group but found to be statistically insignificant so comparable. The mean induction to delivery time was 748 +/-379 min in the sublingual group and 711 +/- 425 min in the intravaginal group, p= 0.560. So, comparable in the study by Caliskan E et al³. Mean induction-to-delivery interval was similar in both groups (21.22 hours in the oral group vs. 20.15 hours in the vaginal group; P = 0.58).⁸ Mean induction delivery interval was shortest (10:35 hrs) in vaginal misoprostol group in a study undertaken to compare the safety and efficacy of intra-vaginal misoprostol, oral misoprostol and intra cervical catheter balloon for induction of labour at term in terms of interval from induction to birth, mode of delivery, maternal complication, neonatal outcome and to find out failure rate in induction of labour in all the group by Sheiker C et al⁹.

NVD was more among intravaginal group (80% vs. 71.6%) but asst. Ventouse and LSCS was more among sublingual group (8.4% vs.13.3%) but the finding was statistically insignificant (p>0.05). The rate of vaginal delivery in <24 hours was higher in the vaginal group (58.6% vs 39.2%, P = .001) in the study by Haas DM et al¹⁰. The rate of cesarean deliveries for non-reassuring fetal status was 3.3% for the vaginal misoprostol group and 9.5% for the buccal misoprostol group (P = .033).¹⁰ In the study by Muzonzini G et al¹¹, the buccal route was associated with a trend to fewer caesarean sections than with the vaginal route

(18/73 versus 28/79; relative risk (RR) 0.70; 95% confidence interval (CI) 0.42 to 1.15).

Total induced after 3 doses was 99 (82.5%), 85% among intravaginal and 80% among sublingual. This finding was in concordance with the study by Gatta DS et al¹² where labour was successfully induced in 90% of pregnant women. Seven women in the group 1 (8.8%) and 12 women in the group 2 (15%) required emergent caesarean delivery for fetal heart rate abnormalities (p= 0.22) in the study by Caliskan E et al³ which is almost similar to this study. Hissane EM et al⁵ in their study observed vaginal delivery rates were 75% in the sublingual group and 73% in the intravaginal group.

Maternal complication was present in 11.6% of cases among intravaginal group and among sublingual group it was 15%. But the finding was statistically insignificant. Nausea and vomiting were 5% among sublingual group but among intravaginal it was 6.7%, tachysystole was more among sublingual (5% vs 6.7%) and same finding for hyperstimulation in both the groups. In the study by Souza AS et al⁷ it was observed there was no significant difference in uterine hyper stimulation syndrome among the two groups which was same with this study. An increased risk of uterine tachysystole was found in the sublingual misoprostol group like our study. Caliskan E et al³ in their study concluded that sublingual misoprostol is as efficacious as vaginal misoprostol for induction of labour but more frequent tachysystole is observed with sublingual misoprostol group. No statistically significant difference was found between both groups as regards the number of misoprostol doses used, need for oxytocin augmentation, mode of delivery, neonatal outcome, or the occurrence of tachysystole, hypertonus, or hyperstimulation in the study by El Kattan EA et al¹³.

Out of 11 cases of meconium stained liquor, 6 of them were in sublingual group and 5 among intravaginal group. Sublingual and vaginal misoprostol had similar effectiveness; however, meconium-stained liquor was observed

considerably more frequently with sublingual misoprostol than with vaginal misoprostol in study by Jahromi BN et al¹⁴. Late fetal heart rate deceleration was observed in 8 women in the sublingual group and 4 in the vaginal group (P=0.22) in the above study. But fetal bradycardia was same among the two groups. Though fetal complications were more among sublingual group, it was found to be insignificant (p>0.05).

Fetal distress was same in both the cases, non-progression was more among sublingual group and failure of induction was more in intravaginal group. But this finding was found to be insignificant.

Similar finding was observed in the study by Hissane EM et al⁵ that there were no significant differences in the incidence of contractility disturbances, and neonatal results.

The sublingual route of misoprostol was associated with a reduced risk of failed induction, reduced time from initiation to induction, reduced induction to delivery interval and a higher incidence of maternal and fetal side effects which was a bit contradictory to this study. However, the differences were not statistically significant. The sublingual route of administration of misoprostol is comparable in efficacy and safety to the vaginal route for induction.

Conclusion

Induction of labour is usually performed when the risks of continuing pregnancy are higher than the benefits of delivery. A prospective randomised control trial was conducted to compare the efficacy and safety of misoprostol for induction of labour at term by intravaginal versus sublingual route with single live fetus (25mcg, 3 doses at 4 hours interval) among 120 cases (60 cases each) in the department of Obs and Gynae, JNIMS, Imphal. Age, address, parity and booked status were comparable between the study groups. Delivery with a single dose was almost same in both the two groups. Oxytocin augmentation though little more among sublingual group was statistically insignificant. Rate of dilatation was

significantly more among intravaginal group but the induction of delivery and mean 1st stage of labour was insignificant. Normal vaginal delivery (NVD) was more among intravaginal group but ventouse and LSCS was more among sublingual group but the finding was statistically insignificant. Maternal and fetal complications were comparable in between the two study groups. The sublingual route of administration of misoprostol is comparable in efficacy and safety to the vaginal route for induction. Further study with a bigger sample is recommended to a robust significant finding.

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