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COMPARATIVE ANALYSIS OF SUBLINGUAL VS. VAGINAL MISOPROSTOL FOR LABOR INDUCTION: A STUDY ON SAFETY AND EFFICACY

Obstetrics & Gynecology

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ABSTRACT

The study aimed to investigate the efficacy, tolerability, and safety of administering 25 micrograms of misoprostol via sublingual and vaginal routes for term labor induction. Two hundred primigravida with singleton pregnancies were randomly assigned to sublingual (Group 1) and vaginal (Group 2) misoprostol groups. Up to four doses of 25 micrograms were given at four-hour intervals. The study assessed cervical ripening, induction-to-delivery time, maternal and fetal outcomes, labor augmentation necessity, and the number of misoprostol doses. Group 1 showed a higher rate of achieving vaginal delivery within 24 hours (55% vs. 45%, p=0.05). Cesarean section rates were 16% in Group 1 and 12% in Group 2 (p=0.391). Group 1 had a lower pre-induction modified Bishop's score (3.08 vs. 3.62, p=0.022). The mean misoprostol dose was lower in Group 1 (2.14 vs. 3.10, p=0.001). The induction-to-active phase interval was longer in Group 1 (8.52 hours vs. 5.01 hours, p=0.001). Group 2 had a longer induction-to-delivery interval (14.80 hours vs. 11.28 hours, p=0.024). SNCU admission rates were lower in Group 1 (16% vs. 36%, p=0.02). Labor augmentation was more needed in Group 1 (80% vs. 56%). Group 1 required fewer misoprostol tablets (mean 2.14) and fewer vaginal examinations (mean 5.24) compared to Group 2 (mean 3.10 tablets and mean 7.10 examinations, respectively, p<0.05). In conclusion, sublingual misoprostol proved as effective as vaginal misoprostol for term labor induction, offering convenience and reducing meconium liquor incidence, vaginal examinations, and SNCU admission rates.

KEYWORDS

Misoprostol, Labor Induction, Sublingual Administration, Vaginal Administration

INTRODUCTION

Induction of labor is a dynamic medical intervention aimed at achieving favorable feto-maternal outcomes. It is typically undertaken when the risks associated with continuing pregnancy outweigh the benefits of delivery [1], [2]. Indications for induction commonly encompass scenarios such as membrane rupture without labor, gestational hypertension, oligohydramnios, featal distress, post-term pregnancy, and diabetes, as detailed in the 2016 ACOG guidelines. A range of techniques, both mechanical (such as osmotic dilators, trans-cervical balloon catheter, membrane stripping, amniotomy, extra-amniotic saline infusion, and hygroscopic cervical dilators) and pharmacological (including Misoprostol, Dinoprostone, Oxytocin, Estrogen, Relaxin, Nitric Oxide donors, and Progesterone receptor antagonists), have been utilized for this objective [3]. Among prostaglandins, Misoprostol (PGE1) has gained widespread use for cervical ripening and labor induction [4], [5]. Recent FDA approval has removed pregnancy as a contraindication for its use. Misoprostol can be administered through various routes, including oral, sublingual, buccal, and vaginal. Its pharmacokinetics vary with administration route, with the sublingual and vaginal routes bypassing the enterohepatic circulation. Notably, a sublingual dose of 50 mg every 4 hours has demonstrated efficacy in inducing vaginal delivery within 24 hours, requiring less oxytocin augmentation compared to an equivalent oral dose [6]. This study seeks to evaluate the effectiveness and safety of sublingual versus vaginal misoprostol, administered at four-hour intervals for a maximum of four doses, in cervical ripening and labor induction, in accordance with our hospital policy following the FIGO guidelines (2017) for misoprostol.

OBJECTIVE

To compare the efficacy, tolerability, and safety of 25 micrograms of misoprostol administered through two routes, sublingual and vaginal, for term labor induction.

MATERIAL AND METHOD

This comparative study was performed in the labor room with emergency settings and CTG monitoring under the Dept. of Obstetrics and Gynecology, VIMSAR Medical college, from November 2018 to November 2020.

The hypothesis formulated was that the sublingual route of misoprostol for labor induction would exhibit superiority compared to the per-vaginal route. The superiority margin was established at 5% (δ=0.05). Assuming that the genuine mean cure rates of the treatment and active control are 85% (pT=0.85) and 65% (pC=0.65) respectively, the study was designed to attain 80% power (1−β=0.8) at the 5% significance level (α=0.05) with equal allocation (k=1). Consequently, the sample size required for both the treatment and active control groups was set at 98 participants each. For analysis, it was decided to round up the numbers to 100 in each category.

The inclusion criteria were comprised of live Singleton pregnancy, cephalic presentation, longitudinal lie, BISHOP'S score ≤ 5, elective induction, prolonged pregnancy, Premature rupture of membranes, Fetal growth restriction, Maternal medical disorders such as pre-eclampsia, eclampsia, and Gestational Diabetes Mellitus (GDM).

The exclusion criteria comprised Multiple pregnancy, Malpresentation, Grand multiparity (more than 5), Fetal macrosomia, Chorioamnionitis, Previous classical or multiple caesarean sections, Infections like HIV, active genital herpes, Major degree placenta previa, Cord prolapse, Previous myomectomy, Medical disease e.g., heart disease and renal disease, known contraindications to prostaglandins (asthma), Uterine anomalies, Cephalopelvic disproportion (as determined from history and pelvic exam), Woman on active labor during admission, abnormal fetal heart rate detected through stethoscope.

From 254 pregnant women initially assessed for eligibility, 29 women were excluded because they did not meet the inclusion criteria and 24 women declined to participate. Finally, 200 women in their third trimester of pregnancy with obstetric or medical indications for the induction of labor were enrolled into predetermined randomization method to assign them to either the sublingual or per-vaginal misoprostol group.

Randomization and allocation sequence was previously generated through computer-generated random numbers, ensuring equitable distribution of participants between the interventions by a separate researcher not directly engaged in the surgical procedure. The participants' CONSORT flow diagram is depicted in **Fig 1**.

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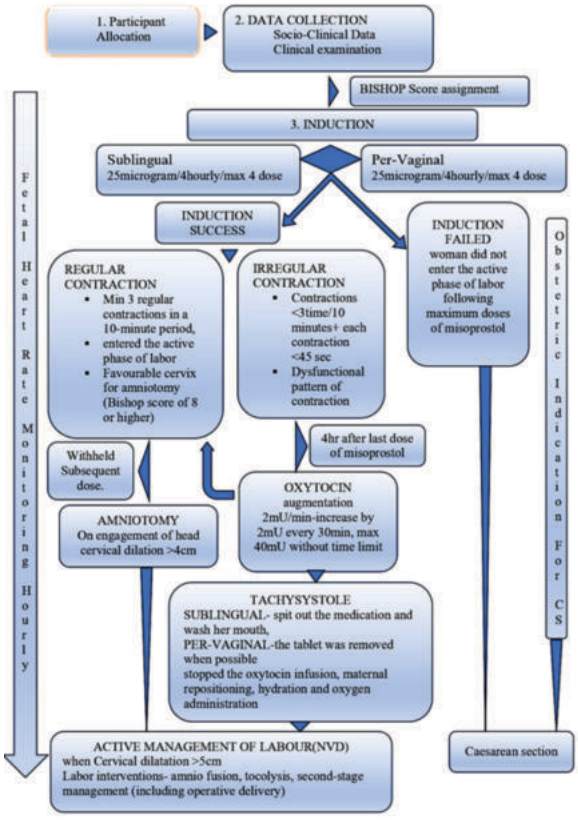

Fig.1 Consort (2010) Flow Diagram

Clinical details including demographic data, presenting complaints, previous obstetrics and menstrual history of subjects were noted. A thorough clinical examination including general physical examination, systemic examination, per abdomen, per speculum and pelvic examination was done. At time of induction, Bishop's score was assigned. Each participant in Group A received 25 micrograms of sublingual misoprostol every 4 hours for a maximum of 4 doses, while those in Group B were administered 25 micrograms of vaginal misoprostol every 4 hours for a maximum of 4 doses. If a patient experienced at least three regular contractions in a 10-minute period, entered the active phase of labor (defined as having regular uterine contractions and cervical dilatation of 6 cm or more), and had a favorable cervix for amniotomy (Bishop score of 8 or higher), any subsequent misoprostol doses were withheld. Once fetal head engagement and cervical dilation allowed, amniotomy was performed. Irregular contraction warranted oxytocin administration until regular uterine contractions were established. Our hospital's oxytocin protocol, starting at 2 milliunits per minute and increasing by 2 milliunits every 30 minutes until regular contractions ensued, was followed for all participants. In cases where the patient's membranes were still intact and the cervix was 4 cm or more dilated, amniotomy was performed to augment induction. Once cervical dilation reached 5 cm or more, the active labor management protocol was initiated, although active labor itself was defined as cervical dilation of 6 cm or more. Various labor interventions, such as amnioinfusion, tocolysis, and second-stage management (including operative delivery), were carried out as needed. Continuous fetal monitoring with stethoscope was performed throughout the induction, labor, and delivery processes considering the resource limitation. Cesarean delivery was conducted based on obstetric indications. Specific recommendations for this study included considering a cesarean if the patient remained undelivered after 24 hours of cervical ripening or if active labor had not been achieved within 12 hours. A clinically meaningful outcome was defined as a 4-hour reduction in time to delivery. All the episodes of tachysystole were included in the analysis regardless of the interval from the time of misoprostol administration to the occurrence of the abnormal FHR pattern. Recognized episodes of tachysystole were managed by stopping the oxytocin infusion, maternal repositioning, hydration and oxygen administration. In the sublingual group, the woman was advised to spit out the medication and wash her mouth, and for those in the vaginal group, the tablet was removed when possible. Labor induction was considered a failure if a woman did not enter the active phase of labor following maximum doses of misoprostol. The woman was then offered a caesarean section.

The outcome between the two group was measured as the number of women delivered vaginally within 24 hours of the first dose of misoprostol, interval from the start of induction to vaginal delivery / induction delivery interval, cesarean rates, number of misoprostol doses given, need for oxytocin augmentation, number of vaginal examination, uterine tachysystole rate (at least six contractions per 10 minutes during two consecutive 10-minute periods), hypertonus (a single uterine contraction lasting for 2 minutes or more), birth weight of baby, incidence of meconium-stained amniotic fluid, Neonatal intensive care unit (NICU) admissions, 5 min APGAR <7.

The data were collected and entered in Excel and analysed with Jamovi and R software (R Core Team (2020)). The independent-samples *t*-test was used for the analysis of equality of means, and the categorical variables were analysed using the chi-square test/Fisher exact test. A $P<0.05$ was considered significant.

The study was approved by the institutional Ethics Committee (003/19-I-S-004/Dt.25.01.2019) along with the Clinical Trial Registry of India (CTRI/2019/03/018335- The study protocol is available under this ID). Informed written consent was obtained from all participants prior to their enrollment in the study.

RESULTS

This study aimed to assess the comparative efficacy and safety of a novel sublingual misoprostol dosing regimen for cervical ripening and labor induction. Demographic characteristics of the study population are presented in **Table 1**. The mean maternal age was 26.0 years (SD 4.79) in the sublingual group and 25.2 years (SD 4.99) in the vaginal group, with no significant difference between the two groups (p = o.24). All cases in both groups were booked, with a statistically significant difference observed in the proportion of booked cases (exact test=0.006, $p<0.05$). Gestational age was categorized into <37 weeks, 37-40 weeks, and >40 weeks. More than half of the participants in both groups presented around their estimated due date (EDD), while about one-third reported being post-due date. There was no significant difference in gestational age distribution between the two groups (p = 0.44, 2=1.60). Most of the cases in both groups were rural (78%, 156), and 24% (48) held Below Poverty Line (BPL) cards. About 16% of the participants were graduates, 32% had completed high school, and 10% were illiterate.

Table 1: Demographic characteristics

	Sublingual	Vaginal	Statistical test (chi square/ fisher exact/ t test)	P value
	N=100	N=100		
Maternal age [mean, (SD)]	26.0 (4.79)	25.2 (4.99)	1.157	0.24
Booked cases	100	92	0.006*	
Gestational age (weeks)				
<37 week	12	8	1.6	0.44
37-40 week	56	64		
>40 week	32	28		

*$p<0.05$= statistically significant

The **Fig 2** suggests that the clinical indications for induction of labor were consistent between the two groups. Additionally, postdated pregnancies and oligohydramnios were found to be similar between the groups, although statistical significance was not provided (p= 0.382, 2=7.467).

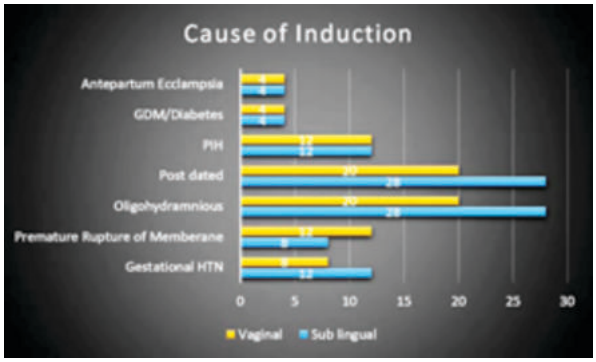

Figure 2: Clinical Indications for the Induction of labor

The pregnant women had varied clinic presentations listed in **Fig 3**, including abdominal pain, leakage, general complaints, hypertension, diabetes, and antepartum eclampsia. No significant difference was noted (p=0.224, $\chi 2$=6.953) between the two groups in these aspects.

Figure 3: Presenting complaints of the participants

Table 2 presents maternal characteristics, complications, and outcomes in the study patients. The mean Bishop's score was statistically significant (p = 0.019) among the vaginal group compared to the sublingual group. The need for Cesarean section due to failed induction was similar in both groups, while the vaginal group experienced more tachysystole and meconium-stained liquor (known side effect of vaginal misoprostol), whereas the sublingual group had a higher incidence of fetal distress (p = 0.019, 2 = 9.92). Need for oxytocin augmentation due to the irregular contractions following misoprostol was significantly higher in the sublingual group (p = 0.010, 2 = 6.62).

Table 2: Maternal Characteristics, Complications, and Outcomes

	Sublingual	Vaginal	Statistical test (chi square/t-test)	P value
Bishop score at misoprostol commencement [mean, SD]	3.08 (1.02)	3.64 (1.32)	2.367	0.019*
Mean time interval between starting misoprostol and active phase of labor (mean, SD)	8.52 (7.06)	5.01 (2.59)	3.299	0.001 *
Mean time interval between starting misoprostol and delivery (mean, SD)	11.28 (8.66)	14.80 (6.65)	2.279	0.024 *
Mean number of vaginal examination	5.24 (1.71)	7.10 (4.11)	2.95	0.004 *
Mode of delivery:				
Normal vaginal delivery	80	76	3.004	0.391
Assisted/instrumental	4	12		
Cesarean delivery	16	12		
Indications for cesarean:				
Tachysystole	0	4	9.92	0.019 *
Failed induction	4	4		
Meconium-stained liquor	0	4		
Abnormal FHR	12	0		
Need for oxytocin augmentation	80	56	6.62	0.010 *
number of doses of Misoprostol (mean, SD)	2.14 (1.0)	3.10 (0.8)	5.047	0.001 *
Successful induction	84	88	0.332	0.564
Caesarean section rate for failed induction	16	12		
Duration of hospital stay	3.12 (1.92)	2.92 (1.61)	0.563	0.575

*p<0.05 =statistically significant

A multinomial logistic regression analysis was performed to evaluate the influence of several factors, including the BISHOP score, the number of vaginal examinations, the cause of induction, meconium liquor, blood-stained liquor, and the need for augmentation with oxytocin, on the "Mode of Delivery" **(Table 3)**. Collectively, these variables explained a substantial 63.66% of the variation observed in the mode of delivery, and the impact was highly statistically significant (F=27.16, p < 0.001, R2 = 0.64).

Table 3: Logistic Regression Model for The Mode of Delivery

	Unstandardized Coefficients	Standardized Coefficients				95% CI B	
Model	B	Beta	Standard error	t	p	lower	upper
Constant	0.66		0.15	4.33	<.001	0.36	0.97
BISHOP Score	0.08	0.15	0.03	2.41	.018*	0.01	0.14
Number of Vaginal Examinations	0.03	0.2	0.01	3.13	.002*	0.01	0.06
Cause Of Induction	-0.06	-0.18	0.02	-2.75	.007*	-0.1	-0.02
Meconium Liquor	1.15	0.68	0.11	10.12	<.001**	0.92	1.37
Blood-Stained Liquor	0.21	0.08	0.16	1.28	0.204	-0.11	0.53
Need Of Augmentation with Oxytocin	0.24	0.2	0.08	2.84	.005*	0.07	0.41

*p<0.05 =statistically significant, **p<0.001 = highly significant

In the logistic regression analysis of various indications of caesarean section (R^2_{McF}=1.0, df=48, p<0.001), Meconium-stained liquor was significantly high in un-booked cases and mothers >30 year of age. Failed induction was significantly high in pregnancies with meconium and blood-stained liquor and un-booked cases whereas the high or low age group was negatively related to the success of induction. The post-dated pregnancy, frequent vaginal examination, increased misoprostol dose, un-booked cases, underage pregnancy, low BISHOP score were predictive of significantly high chance of Non-reassuring FHR in the pregnant women.

Probability of tachysystole was high in case of blood-stained liquor, among un-booked cases and increased number of vaginal examinations. It was negatively related to the BISHOP score, underage and older women, and misoprostol dose.

The bishop score at misoprostol commencement **(Fig. 4)** was higher in

the vaginal group (mean 3.64, SD 1.32) compared to the sublingual group (mean 3.08, SD 1.02), with a significant difference ($p = 0.019$, t = 2.367). The distribution of the mode of delivery, including normal vaginal delivery, assisted/instrumental delivery, and cesarean delivery, did not differ significantly between the two groups.

Figure 4: Bishop score at misoprostol commencement

The indications for cesarean section included tachysystole, failed induction, meconium-stained liquor, and non-reassuring fetal heart rate (FHR). Tachysystole was more prevalent in the vaginal group ($p = 0.019$, 2= 9.92), while the need for oxytocin augmentation was significantly higher in the sublingual group ($p = 0.010$, 2= 6.62). The mean number of doses of misoprostol was significantly higher in the vaginal group ($p < 0.05$). There was no significant relationship found between the mode of induction and the mode of delivery. Failure of induction was comparable between the two groups, but decreased fetal heart rate was more predominant in the sublingual group, while the vaginal group had a higher incidence of tachysystole and meconium-stained liquor, leading to cesarean delivery. The study revealed contrasting trends in the timing of labor progression between the sublingual and vaginal misoprostol administration groups. Although the onset of the active phase of labor occurred more rapidly in the vaginal group, the sublingual group experienced a shorter overall duration from induction to delivery **(Figure 5)**. Furthermore, the vaginal group necessitated a significantly higher frequency of repeated pelvic examinations following induction, indicating a greater need for clinical assessment, and monitoring during the labor process.

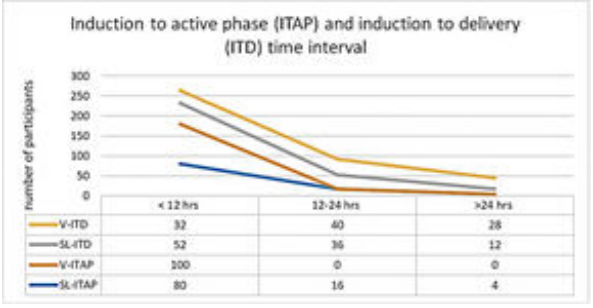

Figure 5: Induction to active phase (ITAP) and Induction to Delivery (ITD) time

The two-factor analysis of variance (ANOVA) without repeated measures showed that there is a significant difference between the number of misoprostol administered with the induction to pain and induction to delivery time among the two groups (F=95.05, df=2, p<0.001, $Eta_p^2 = 0.39$). Subsequently the Bonferroni Post-hoc-Tests on the Number of misoprostol-Induction to pain interval-Induction to delivery time also found to be statistically significant among two groups as per the **Table 4.**

Table 4: ANOVA among the dose of misoprostol-ITAP-ITD

		Mean Difference	SE	t	p
No. of misoprostol	Induction to pain interval	-4.82	0.77	-6.27	<.001**
No. of misoprostol	Induction-delivery time	-10.6	0.77	-13.77	<.001**
Induction to pain interval	Induction-delivery time	-5.78	0.77	-7.5	<.001**

*p<0.001 = highly significant

Regarding maternal outcomes, there were no significant differences (2=0.091, p=0.091) in the occurrence of side effects following induction. However, some cases of post-partum hemorrhage (26), fever (16), vomiting (4), and rigor (20) were noted among the study participants following the intervention **(Figure 6)**. The participants had a mean hospital stay of approximately 3 days in both groups.

Figure 6: Maternal complications associated with sublingual and vaginal misoprostol.

As evident from the **Table 5,** Various side effects seen in the mothers had significant association (R^2_{McF}=0.462, df=35, p<0.001) with the un-booked cases, GA less than or more than the 37-40 week window, cases presented because of referral from periphery hospitals, preterm gestation on per abdomen exam, repeated vaginal examination prior to delivery (shivering and diarrhoea) and increasing number of misoprostol tablet.

Table 5: Regression analysis of side effects in mother with socio-clinical variables

Side effect of mother	Predictor	Estimate	SE	Z	p	Odds ratio
Fever	Intercept	-9.27	0.65	-14.33	<.001*	9.44e0-5
	Booking status	-40.28	0.65	-62.30	<.001*	3.21E-18
	GA in weeks: 1 – 2	-75.22	NaN	NaN	NaN	2.14E-33
	3 – 2	46.85	0.65	72.46	<.001*	2.23E+20
	Referral	-0.01	1.09	-0.01	0.99	0.99118
	Per abdomen:					
	2 – 1	68.61	2.00e0-	3.42E+10	<.001*	6.24E+29
	No.of vaginal	0.01	0.18	0.07	0.95	1.01
	No.of misoprostol	0.69	0.60	1.14	0.25	2.00
Vomitin	Intercept	-12.32	0.78	-15.86	<.001*	4.44e0-6
	Booking status	-11.51	0.78	-14.81	<.001*	1.00e0-5
	GA in weeks:					
	1 – 2	-8.34	0.00	-2.61e-17	<.001*	2.38e0-4
	3 – 2	34.22	0.78	44.03	<.001*	7.28E+14
	Referral	-14.65	0.78	-18.86	<.001*	4.32e0-7
	Per abdomen:					
	2 – 1	-5.44	0.00	-2.54e-16	<.001*	0.00
	No.of vaginal	0.45	0.40	1.13	0.26	1.57
	No.of misoprostol	-0.71	1.17	-0.61	0.54	0.49
Shiverin	Intercept	-4.80	0.93	-5.16	<.001*	0.01
	Booking status	-1.18	0.93	-1.27	0.21	0.31
	GA in weeks:					
	1 – 2	-28.10	0.00	-6.54e-38	<.001*	6.27E-13
	3 – 2	-0.66	1.14	-0.58	0.56	0.52
	Referral	2.66	1.02	2.60	0.009*	14.26
	Per abdomen:					
	2 – 1	-57.81	0.00	-6.46e-27	<.001*	7.80E-26
	No.of vaginal	-0.57	0.24	-2.43	0.015*	0.56
	No.of misoprostol	1.78	0.76	2.36	0.018*	5.93

PPH	Intercept	56.13	0.34	165.31	<.001*	4.91E+15
	Booking status	-2.97	0.34	-8.66	<.001*	0.05
	GA in weeks:					
	1 – 2	27.27	0.57	48.25	<.001*	6.95E+11
	3 – 2	-1.09	1.08	-1.02	0.31	0.34
	Referral	-36.07	0.34	-105.12	<.001*	2.17E-16
	Per abdomen:					
	2 – 1	-26.12	0.57	-46.23	<.001*	4.52E-12
	No.of vaginal	-0.25	0.15	-1.67	0.10	0.78
	No.of misoprostol	1.58	0.54	2.93	0.003*	4.85
Diarrhea	Intercept	-156.82	0.00	-4.35e-16	<.001*	7.87E-69
	Booking status	70.75	0.00	1.96E+16	<.001*	5.32E+30
	GA in weeks:					
	1 – 2	-3.70	0.00	-1.86e-35	<.001*	0.02
	3 – 2	1.99	0.00	5.52E+14	<.001*	7.30
	Referral	6.10	0.00	1.72E+15	<.001*	446.86
	Per abdomen:					
	2 – 1	-39.02	0.00	-1.12e-27	<.001*	1.14E-17
	No.of vaginal	4.51	0.00	1.04E+14	<.001*	90.78
	No.of misoprostol	-4.45	0.00	-6.23e-14	<.001*	0.01

The study indicated no significant difference in birth outcomes, live births, and intrauterine deaths between the groups **(Table 6).** All cases of intrauterine deaths were linked to misoprostol-induced antepartum hemorrhage, a known adverse effect of the drug. APGAR scores at 5 minutes showed no significant difference between the groups. However, a significantly higher number of babies in the vaginal group required admission to the Neonatal Intensive Care Unit (NICU), compared to the sublingual group (p = 0.023, 2=5.20). NICU admission criteria was based on the APGAR score, birth weight of the newborns. Birth weight of newborns was distributed between ≤2.5 kg and >2.5 kg, with no significant difference between the two groups (p = 0.166, T = 1.397). The mean birth weight was comparable between the two. Liquor status at delivery showed a significant difference, with a higher proportion of clear liquor in the sublingual group and meconium-stained liquor associated with the vaginal group.

Table 6: Fetal and Neonatal Outcomes

	Sublingual	Vaginal	Statistical test(t test/chi square test)	P value
Birth outcome:				
Live Birth	96	96	0.000	1.00
Still birth or IUD	4	4		
Apgar score at 5 minutes:				
< 7	20	8	3.010	0.22
≥ 7	76	88		
NICU admission				
NO	84	64	5.20	0.023 *
YES	16	36		
Birth weight of Newborn in Kg				
≤2.5	56	52	1.397	0.166
>2.5	44	48		
Mean birth weight	2.77 (0.59)	2.58 (0.718)	1.397	0.166
Liquor status:				
Clear	80	56	6.63	0.036 *
Meconium-stained liquor	16	36		
Blood stained	4	8		

*p<0.05 =statistically significant

Gestational age at presentation was positively corelated to the weight of baby on delivery ($\mathbf{R^2}_{McF}$=0.191, F=2.12, p<0.001, OR=8.33). The negative birth outcome (stillbirth/IUGR) was not significantly related to any socio-clinical parameter except the side effects experienced by the mother like PPH and diarrhoea ($\mathbf{R^2}_{McF}$=0.384, F=1.38, p=0.033) as evident from the **Fig 7**.

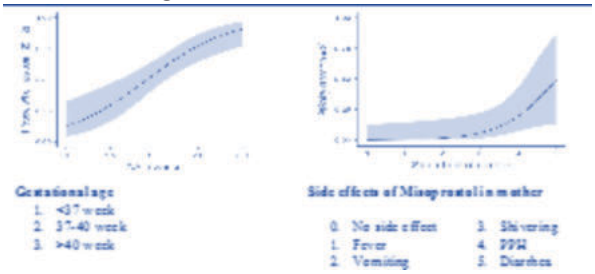

Figure 7: Correlation of weight of newborn to mothers gestational age and baby outcome with misoprostol induced side effects in the mother.

The binomial logistic regression model (R^2_{McF}=0.496, df=4, p < 0.001) for the SNCU admission of the newborn was found to have significant positive relation with the mode of delivery and the increased time interval between induction to the pain, whereas it was negatively related to the APGAR score at 5min and the dose of misoprostol **(Table 7).**

Table 7: Regression model for the SNCU admission

		95% Confidence Interval					
Predictor	Estimate	Lower	Upper	SE	Z	p	Odds ratio
Intercept	2.09	-1.441	5.621	1.802	1.16	0.246	8.082
Apgar score at 5mins	-2.482	-3.93	-1.033	0.739	-3.36	< .001	0.084
Mode of delivery	2.302	1.008	3.597	0.661	3.49	< .001	9.997
No. of misoprostol	-2.68	-4.351	-1.008	0.853	-3.14	0.002	0.069
Induction to pain interval	0.301	0.114	0.488	0.095	3.16	0.002	1.352
Note. Estimates represent the log odds of "Admission to SNCU = 1" vs. "Admission to SNCU = 0"							

DISCUSSION

Numerous clinical trials have already established the effectiveness of misoprostol in cervical ripening and labor induction. Both vaginal and sublingual routes of misoprostol administration have been explored, with the regimen of 25 micrograms every 4 hours gaining wide acceptance due to its efficacy and minimal complications. Labor induction is a common practice in modern obstetrics, with approximately 20% of pregnant women worldwide undergoing this procedure. The WHO Global Survey on Maternal and Perinatal Health found that 9.6% of deliveries involved labor induction, with regional variations.[7]

Over a two-year study period at our hospital, which included 16,870 deliveries, the majority (58.13%) resulted in vaginal deliveries, while 47.13% ended in cesarean sections. The overall induction rate was 23%, with various methods employed, most commonly oxytocin. Notably, government initiatives such as the MAMATA scheme in Odisha [8]and the PMSMA program in India [9] have encouraged patients to seek antenatal care, leading to increased bookings. The majority of patients in both study groups fell within the 21-30-year age bracket. This demographic trend could potentially be attributed to societal pressures to marry and start families within this age range, particularly among individuals from lower to middle socioeconomic backgrounds residing in rural areas [10]. When assessing educational backgrounds, a large proportion of our study participants had completed higher secondary education, which is in line with similar studies in the literature [10], [11]. Importantly, no significant differences were observed between the two groups in terms of education or socioeconomic status.

Gestational age distribution revealed that most patients were in the 37-

40-week range, a finding consistent with other studies [12]. It is noteworthy that the pre-induction Bishop's score was significantly higher in the vaginal group. The primary indications for labor induction, namely postdated pregnancy and oligohydramnios, were consistent with literature findings [12]. Notably, the need for oxytocin augmentation was significantly higher in the sublingual group [13]. Most patients in both study groups achieved active labor within 12 hours of induction, with a shorter induction-to-delivery interval observed in the sublingual group [14], [15], [16], [17].

The average number of misoprostol doses administred was significantly lower in the sublingual group. Mean dose of required misoprostol was 2.14±1.009 & 3.10±0.889 among sublingual and vaginal group patients respectively which was in similar to study done by **Van*athi*** [18] and contradictory to study done by ***Wing D et al.*** [19] Importantly, the induction-to-active labor interval was shorter in the sublingual group, with a mean interval of 8.52 hours compared to 5.01 hours in the vaginal group.

The mode of delivery did not significantly differ between the two groups, with most patients delivering vaginally (78%), a trend in line with literature reports [14]. However, the specific indications for cesarean sections (16%) varied, with non-reassuring fetal heart rate being the predominant indication in the sublingual group [11], [20]. There are also concerns expressed in the **Cochrane database** [5] regarding excessive uterine activity, particularly uterine rupture, associated with vaginal misoprostol use. The rate of failed inductions was consistent between the groups, with most patients achieving vaginal deliveries successfully. cross the studies, failed induction was consistently defined as failure to initiate labor with more than 3 cm cervical dilatation after 24 h of induction [21] as opposed to ***Banos N*** [22]who defined failed induction as inability to go into active labor after 36 h or failure to deliver within 12 h after active phase of labor. Maternal complications, including side effects, did not differ significantly between the groups, although specific cases of fever, vomiting, shivering, postpartum hemorrhage, and diarrhea were documented [16].

Multinomial logistic regression assessed factors influencing delivery mode, revealing a substantial collective influence of variables like BISHOP score, vaginal examinations, induction cause, meconium or blood-stained liquor, and oxytocin augmentation, explaining 63.66% of delivery mode variance significantly ($F=27.16$, $p < 0.001$, $R2 = 0.64$). Meconium-stained liquor was notably high in unbooked cases and older mothers for caesarean sections. Failed inductions were linked to meconium or blood-stained liquor and unbooked cases, while age affected induction success. Post-dated pregnancies, vaginal exams, misoprostol doses, unbooked status, underage pregnancies, and low BISHOP scores indicated higher non-reassuring fetal heart rates (FHR). Tachysystole probability was elevated in cases with certain factors but negatively associated with BISHOP scores and age.

ANOVA highlighted significant misoprostol-induced induction to delivery time differences ($F=95.05$, $df=2$, $p<0.001$, $Etap2 = 0.39$). Side effects in mothers correlated with unbooked status, gestational age, periphery hospital referrals, preterm gestation, and misoprostol use ($R^2McF=0.462$, $df=35$, $p<0.001$). Gestational age related positively to baby weight at delivery ($R^2McF=0.191$, $F=2.12$, $p<0.001$, $OR=8.33$). Negative birth outcomes tied significantly to maternal side effects ($R^2McF=0.384$, $F=1.38$, $p=0.033$).

Neonatal outcomes, as assessed by Apgar scores, were favourable, with only a small proportion of babies having scores below 7. Admission to the Special Newborn Care Unit (SNCU) was significantly higher in the vaginal group, which may be attributed to the longer induction-to-delivery interval in this group [18] Birth weight and the length of hospital stay did not significantly differ between the groups. Binomial regression unveiled associations between SNCU newborn admissions, delivery mode, induction-to-pain interval, APGAR score, and misoprostol dose ($R^2McF=0.496$, $df=4$, $p < 0.001$). Notably, SNCU admissions were positively linked to certain factors but negatively related to APGAR scores and misoprostol doses.

Remarkably, the number of pelvic examinations was substantially lower in the sublingual group, indicating potential advantages in terms of patient comfort and a reduced risk of infection, especially in cases of premature rupture of membranes (PROM) [18].While patient satisfaction was not formally assessed in our study, it is a noteworthy parameter that has been extensively examined in the literature [23].

The study has several limitations. Firstly, it had a limited sample size, potentially impacting the statistical robustness and generalizability of the findings. Secondly, being a single-centre study, it may not fully represent the diversity of patient populations and practices in different healthcare settings. The study's relatively short duration and the predominance of primigravida with singleton pregnancies among participants could further limit its applicability. Additionally, the lack of blinding and potential biases due to both patients and clinicians being aware of the treatment received is noteworthy. Other limitations include the potential for publication bias, unaccounted changes in clinical practice or guidelines, and the absence of data on long-term outcomes or complications associated with labor induction methods. Addressing these limitations in future research would enhance the quality and relevance of findings in this field.

CONCLUSION

Our study compared sublingual and vaginal misoprostol for labor induction in primigravida with singleton pregnancies. Sublingual misoprostol was more effective in shortening the induction-to-delivery interval, reducing misoprostol doses, and minimizing pelvic examinations. There was no significant difference in neonatal outcomes, maternal safety, or Caesarean section rates. However, fetal distress, uterine tachysystole, and failed inductions were more common with vaginal misoprostol. To comprehensively evaluate the clinical implications of this dosing regimen, further research should focus on assessing patient satisfaction and conducting robust comparative analyses with existing literature data. This will provide a more comprehensive understanding of the potential advantages and drawbacks of sublingual misoprostol in the context of labor induction.

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