e-ISSN: 0976-822X, p-ISSN:2961-6042

Available online on http://www.ijcpr.com/

International Journal of Current Pharmaceutical Review and Research 2023; 15(9); 190-196

Original Research Article

Study of Sublingual Misoprostol and Oral Misoprostol for Induction of Labor at Term- an Open Label Randomized Prospective Study

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Received: 10-06-2023 Revised: 20-07-2023 / Accepted: 30-08-2023
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Conflict of interest: Nil

Abstract

Background: Misoprostol, an oral prostaglandin compound, is being increasingly used for induction of labor by vaginal, oral and sublingual route, though unlicensed for this use. This study was undertaken to compare the efficacy of sublingual misoprostol to oral misoprostol in induction of labor at term.

Materials and Methods: This prospective study was done from 1st December 2020 to 15th September 2021. Study included total 160 patients admitted to Tata Main Hospital for induction of labor at 37-42 weeks of gestation, who were randomized into two groups of 80 women each as Group A (Oral misoprostol) and Group B (Sublingual misoprostol). Age, pre- and post- induction Bishop score, maternal side effects, dose requirement induction to delivery interval, mode of delivery, 3rd stage complication, incidence of tachysystole/ hyperstimulation/ hypertonus, gain in Bishop Score ≥6, success rate were all recorded.

Results: The mean number of doses of misoprostol was significantly lower in the sublingual group (p=<0.001). Mean induction interval was significantly lower in Sublingual group when compared to the Oral group. Significantly faster gain in Bishop score was observed in Sublingual group. Success rate was similar n both groups.

Conclusion: Although the Sublingual route of misoprostol led to a faster improvement of Bishop score, overall success rate of induction by both the routes of misoprostol was comparable.

Keywords: Induction of labor, Misoprostol, Sublingual.

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Introduction

Induction of labor (IOL) is a common intervention, performed for medical, obstetric, or social indications. Induction of labor is indicated when the mother and fetus are benefited with higher chance of healthy outcome than with the birth being delayed. Even today, thousands of women die or suffer high levels of morbidity because of complications related to delivery. Many of these deaths are avoidable. One of the greatest challenges in obstetric care is induction of labor.[1] The aim of IOL is to stimulate adequate uterine contractions before the spontaneous onset of labor leading to vaginal delivery. There are several methods of induction of labor which are categorized into pharmacological and non-pharmacological methods. Non-pharmacological methods of induction are amniotomy, mechanical dilatation with a balloon catheter. Pharmacological inductions include prostaglandin E1 (misoprostol), prostaglandin E2 (dinoprostone) or oxytocin.[2] Prostaglandins (PG) are being used in cervical ripening and induction of labor ever since its first use in 1987 and is used in 23% of all confinements.[3]

Several studies have documented the use of misoprostol as being safe and inexpensive.[4,5] It is being increasingly used for induction of labor by vaginal, oral and sublingual route, though unlicensed for this use. Vaginal misoprostol has been shown to be more efficacious than oral misoprostol in equivalent doses.[1] However, there has been the worry of excessive uterine contractility with vaginal doses of 50 µg or higher. The higher efficacy after sublingual administration may be explained by the pharmacokinetics of the drug.[6] With faster onset of action and shorter induction to delivery interval, sublingual use of misoprostol for induction of labor at term has been found to be an attractive approach to the commonly used oral/vaginal routes for induction of labor. Therefore, this study was undertaken to compare the efficacy of sublingual misoprostol to oral misoprostol in induction of labor at term.

Materials and Methods:

This prospective hospital based non-blinded comparative clinical study was conducted in the

Department of Obstetrics and Gynecology at Tata Main Hospital, Jamshedpur from 1st December 2020 to 15th September 2021 after obtaining approval from Institutional Ethical Committee. Study included total 160 patients admitted to Tata Main Hospital for induction of labor at 37-42 weeks of gestation, fulfilling following inclusion and exclusion criteria.

Inclusion Criteria:

1. Primigravida at term
2. Cephalic presentation
3. Unfavorable cervix (Bishop Score <6)
4. Reassuring fetal heart tracing

Exclusion criteria:

1. Cephalopelvic disproportion
2. Previous cesarean section or any uterine surgery
3. Multiple gestation
4. Abnormal fetal presentation
5. Active genital herpes infection
6. Placenta Previa
7. Need for immediate delivery

Methodology:

Written informed consent was obtained from each patient prior to their enrollment in the study. Study patients were randomized into two groups of 80 patients each as follows:

Group A: 80 pregnant women induced by 50 microgram oral misoprostol administered 4 hourly for a maximum of 5 doses.

Group B: 80 pregnant women induced by 50 microgram sublingual misoprostol administered 4 hourly for a maximum of 5 doses.

On admission, a thorough history was taken and a detailed general examination was done. The fundal height, the lie and presentation of fetus was determined, Fetal heart rate (FHR) was auscultated and ultrasound was done to evaluate of amniotic fluid index, to confirm the lie and presentation of fetus. A pelvic examination was done to determine the bishop score and was done to rule out contracted pelvis and cephalopelvic disproportion. Non stress test (NST) was done for 20 minutes and if NST was reassuring the process of preinduction cervical priming was initiated. Misoprostol dose was withheld when there were at least three regular contractions in 10 minutes, active phase of labor was reached [regular uterine contraction and cervical dilatation greater than or equal to 3 cm] and cervix favorable for amniotomy [Bishop score greater than or equal to 8]. As soon as fetal head engagement and cervical dilation permitted, amniotomy was performed, followed by oxytocin augmentation if the frequency of contractions was less than three per 10 minutes each lasting for 45 seconds or the contractions pattern was dysfunctional. Oxytocin was administered not earlier than 6 hours after the last misoprostol dose, starting at 1 mU/minute and increased by 1 mU/ minute every 15 minutes until adequate contractions persisted. Intermittent fetal cardiotocography and intermittent fetal heart rate auscultation were done. Monitoring was done to look for tachysystole/hyperstimulation/hypertonus. In the sublingual group, the woman was advised to spit out the medication and wash her mouth. The woman was then offered a caesarean section. Following outcome variables were measured.

Outcome parameters:

Primary outcomes:

1. Gain in Bishop Score >/-6
2. Number of women entering active phase of labor

Secondary outcomes:

1. Induction to delivery interval
2. Rate of failed inductions
3. Mode of delivery - Incidence of caesarean sections
4. Third stage complications - postpartum hemorrhage, meconium-stained amniotic fluid, non- reassuring fetal heart rate
5. Adverse effects

Hyperstimulation syndrome was defined as the presence of tachysystole or hypertonus associated with a non-reassuring FHR pattern (fetal tachycardia, late decelerations, severe variable decelerations or loss of FHR variability).

Labor induction was considered a failure, if a woman did not enter the active phase of labour following six doses of misoprostol.

Success of preinduction cervical ripening was defined as achievement of a bishop score >/= 6 at the end of 24 hours of misoprostol or achieved vaginal delivery.

Failure of preinduction cervical ripening was defined as failure to achieve a bishop score of > 6 at the end of 24 hours of administration of misoprostol.

Labour induction was considered a failure if a woman did not enter the active phase of labor following six doses of misoprostol.

Active phase of labour was defined as time between the end of latent phase (4-5) cm dilatation and full dilatation (10cm).

Tachysystole defined as >5 contractions in 10 minutes period averaged over 30 minutes with or without fetal heart rate changes.

Hyperstimulation defined as excessive uterine contractions with abnormal fetal heart changes.

Bishop score used for assessing the cervical status is shown in the Table 1. A score of <6 was considered unfavorable. Artificial rupture of membranes was done when bishop score was >/= 8.

Table: 1: Modified Bishop score

Cervical factor	Score			
	0	1	2	3
Dilatation	closed	1-2	3-4	5
Length	>4	3-4	1-2	0
Consistency	Firm	Medium	Soft	-
Position	Posterior	Midline	Anterior	-
Head: station	-3	-2	-1,0	+1, +2

Results

The mean age in Group-A was 27.1± 3.8 years and in Group-B was 27.2 ± 4.4 years. This difference was not statistically significant. Mean gestational age in Group A was 38.4±1.06 years and in Group B was 38.6±1.05 years. Patients in both the study groups were comparable in terms of age and pre-induction Bishop score. (Table 2)

Table 2: Comparison of age and pre-induction Bishop score between the two study groups

Parameters		Group A (Oral)		Group B (Sublingual)		p-value
		n=80	%	N=80	%	
Age (in years)	18-20	3	3.8	6	7.5	0.1585
	21-25	25	31.3	20	25.0	0.2937
	26-30	37	46.3	34	42.5	0.6170
	31-35	15	18.8	20	25.0	0.2301
	Mean	27.1± 3.8		27.2 ± 4.4		0.93
Mean Gestational age (years)		38.4±1.06		38.6±1.05		0.23
Pre- Induction Bishop Score	0-3	47		40		0.26
	>3 -<6	33		40		0.26

The mean dose requirement of Misoprostol in Group A was 2.94±0.97 and in Group B was 2.13±0.92 (p<0.001). More women had successful induction with 1 dose of sublingual misoprostol in Group B, while in Group A majority (80%) of patients had successful induction with </= 3 doses. This difference was statistically significant. (Table 3)

Table 3: Dosage requirement of misoprostol

Dose requirement of Misoprostol	Group-A (Oral)		Group-B (Sublingual)		Total (N=160)	p-value
	N=80	%	N=80	%		
1	5	6.3	21	26.3	26	<0.0001
2	33	41.3	35	43.8	68	0.7278
3	26	32.5	18	22.5	44	0.0872
4	14	17.5	5	6.3	19	0.0035
5	2	2.5	1	1.3	3	0.4122
Mean	2.94±0.97		2.13±0.92		<0.001	
Median	3.00		2.00			

The incidence of maternal side effects of misoprostol was 20% (16 0f 80) in Group A and 12.5% (10 of 80) in Group B. This difference was statistically not significant(p=0.19). Gastrointestinal effects were the most common side effects observed in both the groups, followed by pyrexia. (Figure 1)

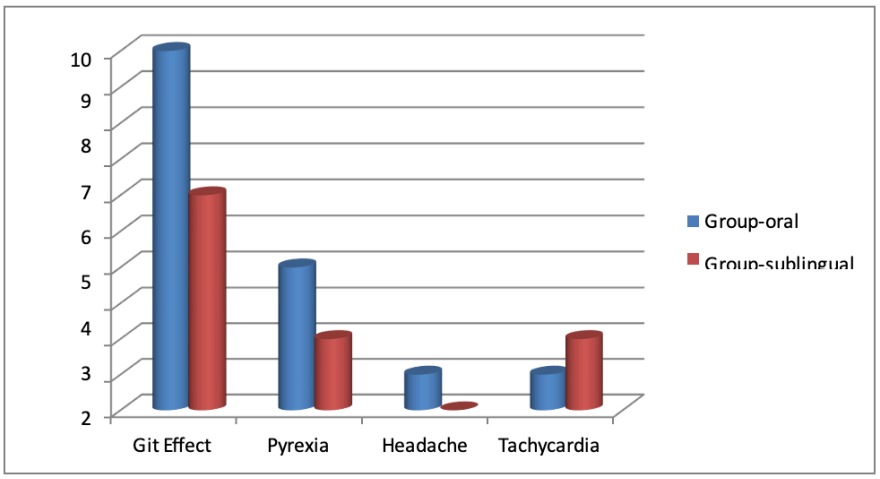

Figure 1: Maternal side effects in Study patients

Tachysystole/ hyperstimulation was observed in only 3 patients, out of which two were in Group A and 1 was in Group B. Incidence of tachysystole/ hyperstimulation was similar in both the groups (p=0.58). (Figure 2)

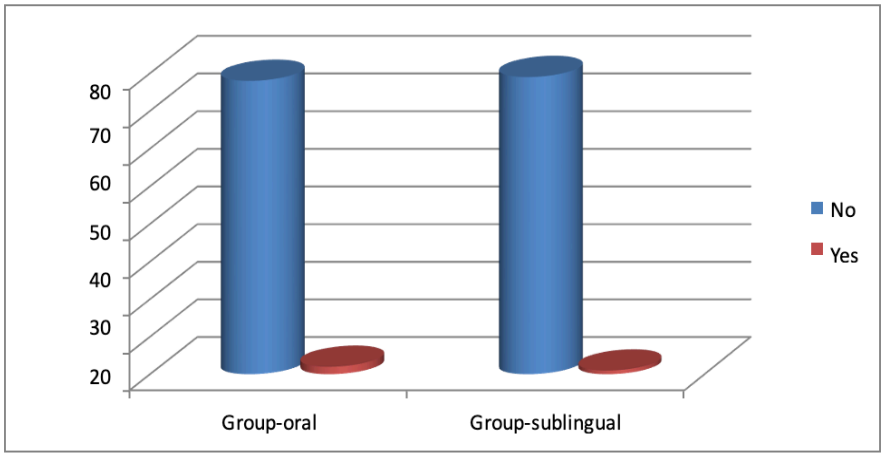

Figure 2: Incidence of tachysystole/hyper stimulation in the two study groups

Lower segment caesarean section (LSCS) rate was higher in Group-A (30% vs 20 %, p = 0.15), while vaginal delivery was higher in Group-B (72.5% vs 60%, p =0.09). However, this difference was not statistically significant. Mean induction delivery interval in Group B was 8.72±4.42 hours, which was significantly lower than Group A where it was 11.44±4.74 hours. (Table 5)

Table 4: Mode of Delivery and Induction Delivery Interval in two study groups

Parameters		Group A (Oral)		Group B (Sublingual)		P value
		N=80	%	N=80	%	
Mode of Delivery	Vaginal Delivery	48	60.0	58	72.5	0.09
	LSCS*	24	30	16	20.0	0.15
	Forceps	8	10.0	6	7.5	0.58
Induction delivery interval (hours)	Mean	11.44±4.74		8.72±4.42		<0.001
	Median	11.50		8.00		
	Range	3.20-23.00		2.50-23.10		

3rd stage of labor complications were observed in only 6 patients, out of which postpartum haemorrhage (PPH) was seen in 5 patients and cervical tear in 1 patient. The incidence of 3rd stage of labor complications was similar in both groups (p=0.64). (Figure 3)

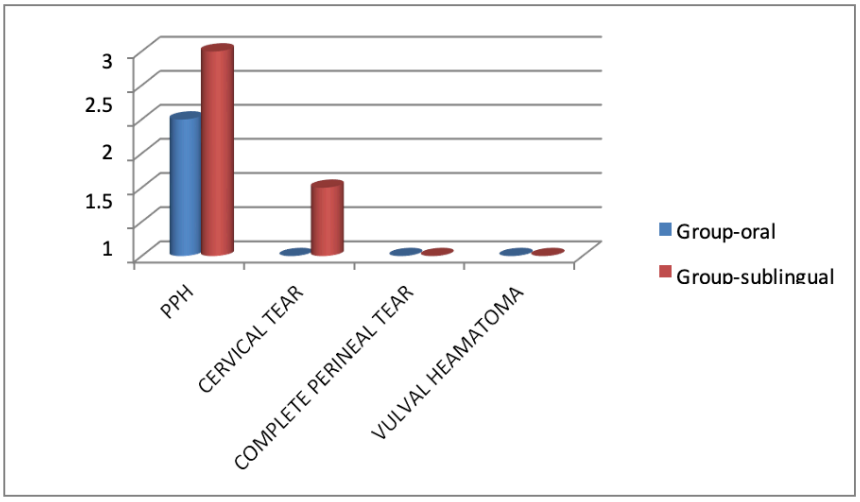

Figure 3: Incidence of 3rd stage of labor complications in Study Patients

After 4 hours (post 1 dose) and after 8 hours (post 2 doses), the change in mean Bishop score was significantly higher in Group B as compared to Group A (p 0.001 and 0.015, respectively). (Table 5) Success rate of induction of labor was similar in both Group A and Group B. (Figure 4)

Table 5: Misoprostol dosage and mean Bishop score change

Time in hours	Study Groups	Bishop Score			
		Mean	SD	Median	p-value
0	Group-A	3.32	1.11	3	0.1469
	Group-B	3.58	1.16	3.5	
4	Group-A	3.52	2.14	5	0.001
	Group-B	4.68	2.34	7	
8	Group-A	10.48	2.59	11	0.015
	Group-B	11.39	2.06	12	

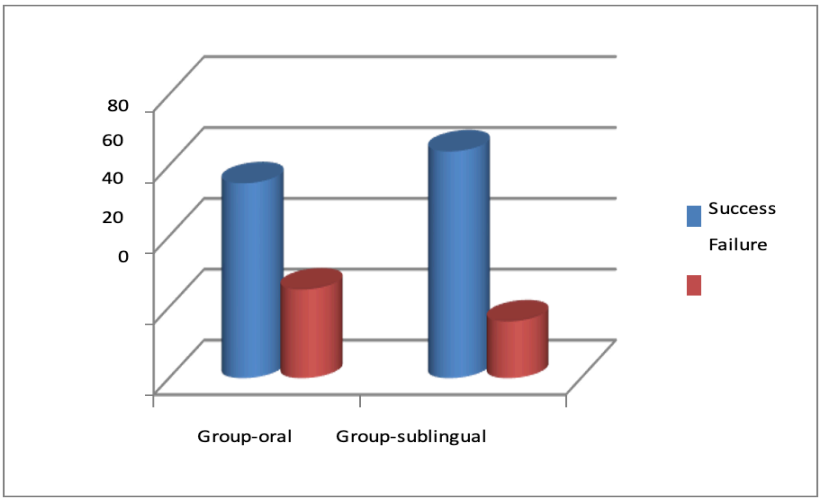

Figure 4: Success rate of induction of labor in both the study groups

Discussion:

Misoprostol is an oral prostaglandin compound, structurally related to prostaglandin E1. It was manufactured as a treatment for peptic ulcer disease.[1] Its proven efficacy in uterine contractility and cervical ripening has led to this drug currently being used for termination of unwanted pregnancy, management of incomplete and spontaneous abortions, induction of labor, augmentation of labor and treatment of postpartum hemorrhage (PPH). Misoprostol has advantages in being cheap, widely available even in most resource-poor settings and remaining stable at room temperature. It is included in the World Health Organization (WHO) essential medicine list on several indications including labor induction.[7-9] This study was done to compare the safety and efficacy of Oral misoprostol and Sublingual misoprostol for induction of labor in term

pregnancy.

In Oral misoprostol group, mean age of patient was 27.1± 3.8 years and in Sublingual misoprostol group, mean age was 27.2 ± 4.4 years in our study. Majority of patients in our study were in the age group of 21-30 years. On the other hand, mean gestational age in Oral misoprostol group and Sublingual misoprostol group was 38.4±1.06 years and 38.6±1.05 years, respectively. Thus, patients in both Oral misoprostol and Sublingual misoprostol groups were comparable in terms of chronological and gestational age in our study. (Table 2) Out of 160 patients, 47 patients in Oral misoprostol group and 40 patients in Sublingual misoprostol group had bishop score of <3 while 33 patients in Oral and 40 patients in Sublingual group had bishop score between 3 and 6. The distribution of bishop score was similar in both the groups(p=0.26). (Table 2)

In our study, mean dose requirement of misoprostol in Oral group was 2.94±0.97 and in Sublingual group was 2.13±0.92 (p<0.001). Median dose in Oral group was 3 and in Sublingual group was 2. Majority of patients in Sublingual group had successful induction with ≤2 doses of misoprostol, while in Oral group, most of the patients had successful induction with ≥2 doses of drug. (Table 3) The mean dose of misoprostol in Sublingual group was significantly lower than Oral group. Similar observations were made by Parimkayala R et al[10] who observed that sublingual group had lesser number of women requiring more than 1 dose of misoprostol compared to the oral group in their study.

Maternal side effects of misoprostol were observed in 16 patients in Oral group and 10 patients in Sublingual group in our study. Gastrointestinal effects were most commonly observed in both the Oral (12.5%) and Sublingual (7.5%) groups, followed by pyrexia (5% Vs 2.5%), tachycardia (1.3% Vs 2.5%) and headache (1.3% Vs 0%). (Figure 1) Malini S et al[11] reported the incidence of Gastrointestinal tract effects were more with vaginal misoprostol. In our study, tachysystole was observed in 2 patients (2.5%) in Oral group and one patient (1.3%) in Sublingual group (p=0.56). (Figure 2) Shetty A et al[12] reported that there was a higher incidence of uterine hyperstimulation in the vaginal group (4.9%). Owolabi AT et al[13] reported that was a higher incidence of tachysystole and hyperstimulation with use of misoprostol than with catheter use for induction of labor. Caliskan E et al[14] reported a higher rate of tachysystole (17.5 %) in the sublingual group when compared with the vaginal group (3.8%).

60% of patients in Oral group and 72.5% of patients in Sublingual group had delivered vaginally (p 0.09) in our study. Cesarean section was required in 30% patients in Oral group and 20% patients in Sublingual group (p=0.14). 10% patients in Oral group and 7.5% patients in sublingual group had forceps delivery. (Table 4) Owolabi AT et al[13] reported no significant difference in the caesarean or other operative delivery rates among patients in the two treatment groups (p 50.03). Deepika TH et al[15] reported a vaginal delivery rate was 66% with sublingual misoprostol. Induction to delivery interval was significantly lower in Sublingual group (8.72±4.42 hours) when compared to the Oral group (11.44±4.74 hours). Shetty A et al[12] reported that the mean induction to vaginal delivery interval was significantly shorter in the vaginal group as compared to oral group. Owolabi AT et al[13] reported that induction to delivery interval was significantly shorter in the misoprostol group than in the catheter group. Caliskan E et al[14] reported that the mean induction to delivery time was higher in Vaginal group than Sublingual group (p = 0.56). The mean number of misoprostol doses required was significantly higher in the Sublingual group than Vaginal group (1.1 +/- 0.4; p- 0.001) in their study.

The incidence of postpartum haemorrhage in Oral group was 2.5% as compared to 3.8% in Sublingual group (p=0.64). One patient in Sublingual group had cervical tear. (Figure 3) Similarly, Wallstrom T et al[16] reported that the incidence of postpartum haemorrhage was similar in Oral and Sublingual misoprostol groups (p=0.4). In Sublingual misoprostol group, there was significantly faster change in mean Bishop score after 1st and 2nd dose of misoprostol as compared to Oral group (p=0.001). (Table 5) Owolabi AT et al[13] reported there was significant change in Bishop score in the two groups. Significantly greater number of patients in the Sublingual group had favourable Bishop score and had entered into active phase of labor after 1st dose of misoprostol. Success rate of induction of labor was significantly higher in Sublingual group as compared to Oral group (p<0.001). (Figure 4) The major limitation of this study was small sample size. This was a single center study and the simultaneous COVID 19 pandemic and lockdown had further hampered the sample size.

Conclusion

This study showed that Sublingual route of misoprostol had significantly lower drug dosage requirement, lesser induction to delivery interval and faster improvement in Bishop score as compared to Oral route. Although the Sublingual route of misoprostol led to a faster improvement of Bishop score, overall success rate of induction by both the routes of misoprostol was comparable.

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