ORIGINAL ARTICLE

Oral Misoprostol Solution more Effective than a Sublingual Route for Induction of Labor: A Prospective Comparative Trial at Tertiary Care Center

Jyothi Shetty[1], Rekha Upadhya[2], Rishpana Rajendran[3]

Received on: 07 November 2022; *Accepted on*: 14 December 2022; *Published on*: 11 May 2023

Abstract

Objective: To assess the safety and effectiveness of 25 µg of oral misoprostol solution at the same dose as sublingual misoprostol for labor induction.

Design: A prospective comparative trial.

Materials and methods: The study included 82 women with term singleton pregnancies who were selected for labor induction. Forty-two patients received sublingual misoprostol every 3 hours, and 40 patients had oral misoprostol solution every 2 hours (six doses).

Results: Within 24 hours of induction, 82.5% of the oral group's women delivered vaginally. The sublingual group had 66% women. The Chi-square test was applied to compare two routes, and the result revealed no statistically considerable difference with a *p*-value of 0.101. In comparison to the oral group (4.43 ± 2.8 hours), the sublingual group (6.25 ± 3.7 hours) had a longer mean interval between the last misoprostol dosage and the onset of labor. Sublingual and oral groups had mean induction to vaginal delivery intervals of 12 ± 5.2 hours and 9 ± 4.5 hours, respectively. A *p*-value of 0.02 indicated that the difference was statistically considerable. In the sublingual group, 14.2% of patients had meconium-stained liquor, and in the oral group, 10% of patients had meconium-stained liquor.

Conclusion: As per the study outcomes, oral misoprostol solution and 25 µg of sublingual misoprostol are both secure and reliable approaches to induce labor in females with an unfavorable cervix. For several measurements, including induction time and vaginal birth rate, we discovered that oral misoprostol solution was more efficient than the sublingual method.

Keywords: Labor induction, Misoprostol, Oral misoprostol solution, Sublingual administration.

Journal of South Asian Federation of Obstetrics and Gynaecology (2023): 10.5005/jp-journals-10006-2205

Introduction

Over the last 25 years, the incidence of labor induction has substantially grown, with approximately 25% of gravid women receiving the procedure. Labor induction aims to induce uterine contractions and cervical ripening in order to facilitate vaginal birth.[1] Labor induction is known to increase the risk of cesarean delivery; induced women are at a higher risk of cesarean than women in spontaneous labor. Population-based studies have demonstrated that as a pregnancy advances beyond 39 weeks of gestation, the frequency of maternal and fetal problems rises. Both groups with risk factors and unselected populations show the same trend.[2] A Randomized Trial of Induction Versus Expectant Management (ARRIVE) trial and a recent meta-analysis found that planned induction of labor in normal singleton pregnancy at 39 weeks gestation is not related to perinatal or maternal problems and may decrease the cesarean section need, risk of hypertensive condition of pregnancy, and need for neonatal respite. Evidence suggests that elective birth from 39 weeks reduces the fetal and maternal risk.[3,4] To ripen the cervix and induce labor, misoprostol is utilized. The ideal dosage and method to use to increase the incidence of vaginal delivery remain unclear. Misoprostol delivered vaginally is more effective than the same amount taken orally. It still has a greater risk of uterine hyperstimulation, with and without alterations in the fetal heart rate (FHR), and vaginal administration is more inconvenient.[5] Women prefer to take misoprostol orally because they feel it is more convenient and provides more privacy, even though the vaginal administration route seems to be just as efficient as the oral route. However, there has not been any agreement regarding the best route of administration in the literature up to this point. A low-dose misoprostol tablet was not commercially produced. So, obstetricians used several methods to prepare and provide the needed dosage. Some clinicians distributed 200 or 100 µg tablets into smaller fragments by deliberately crumbling them. There are now 25 µg pills available for purchase (Cipla, India). A recent pharmacokinetic investigation by Tang et al.[6] evaluated the absorption kinetics of misoprostol administered orally, vaginally, and sublingually. The fastest time to peak blood drug concentration for misoprostol delivery is through oral and sublingual routes. The section under the curve

[1–3]Department of Obstetrics and Gynaecology, Kasturba Medical College, Manipal, Karnataka, India

Corresponding Author: Rekha Upadhya, Department of Obstetrics and Gynaecology, Kasturba Medical College, Manipal, Karnataka, India, Phone: +91 9986143120, e-mail: rex2000@rediffmail.com

How to cite this article: Shetty J, Upadhya R, Rajendran R. Oral Misoprostol Solution more Effective than a Sublingual Route for Induction of Labor: A Prospective Comparative Trial at Tertiary Care Center. J South Asian Feder Obst Gynae 2023;15(2):167–171.

Source of support: Nil

Conflict of interest: None

for plasma concentrations over 6 hours after sublingual delivery was much higher than it was after vaginal and oral administration. Compared with the vaginal route, the sublingual misoprostol could be expected to have more efficacy and avoid a direct impact on the cervix. Uterine hyperstimulation risk might be safer and reduced. In comparison to vaginal dinoprostone or oxytocin, oral misoprostol is equally effective as vaginal misoprostol, according to a recent systematic study.[7] Evidence supports that the oral regimen is safer than the vaginal regimen, especially when there is a greater chance of infection rising, as in the case of pre-labor rupture of the membrane. They advise using 25 µg of the solution of oral misoprostol every 2 hours as the ideal dosage. The "World Health Organization" (WHO)[8] and the "International Federation of Gynecology and Obstetrics"[9] both suggest oral misoprostol for labor induction. Additionally, compared to other methods, the sublingual and oral routes are simpler to give and have the benefit of having no restrictions on movement after administration. The large range of oral and sublingual misoprostol protocol variations has proven difficult for systematic reviewers to handle. There are several different misoprostol dosages (20–200 µg) and administration frequencies (1–6 hourly) in published randomized studies.[5] This study administered misoprostol dosing by pharmacokinetic data.[10] To induce labor and induce cervical ripening, this research compared the effectiveness of oral misoprostol solution 25 µg given every 2 hours to an identical amount given sublingually every 3 hours.

Materials and Methods

This prospective comparative trial was conducted at a University Teaching Hospital from September 2016 to July 2018. The Ethics Committee (IEC 471/2016) approved the study, and informed and written consent was acquired. Participants were nulliparous and multiparous women who were full-term and had a live singleton fetus, cephalic presentation, an unfavorable cervix, and a medical or obstetric rationale for induction. Parity larger than three, abnormal cardiotocography at the time of admission, prior cesarean delivery, and breech presentation were the criteria for exclusion from the research. Before allocating, the resident physician performed a vaginal checkup to determine the modified Bishop score. The consultant decided the route of misoprostol administration at the time of recruitment. Women received 25 µg of misoprostol (Misoprostol; Cipla Pharmaceuticals, Mumbai, India), and if necessary, the dosage was repeated up to six times. The doctor decided whether to provide the women 25 µg of misoprostol sublingually or orally. Misoprostol 25 µg tablets were mixed in 25 mL of water and given orally to the oral group every 2 hours until sufficient uterine contractions were attained. If the participant is assigned to the sublingual arm, the attending nurse placed 25 µg of misoprostol tablet under the woman's tongue every 3 hours. Every hour, the frequency of uterine contractions was measured, and for the women in both groups, a vaginal checkup was performed every 4 hours to measure cervical dilation. Misoprostol was administered until cervical dilatation of >3 cm or sufficient uterine contractions occurred (i.e., 3–4 cm which lasts 45 seconds in 10 minutes). Cardiotocography was used to check the health of the fetus before and after misoprostol administration. At a 4 cm cervical dilation, an amniotomy was done. Further doses of misoprostol were withheld in patients who entered the active labor phase. In instances with infrequent uterine contractions, intravenous oxytocin infusion augmentation was started. An 8-hour maximum oxytocin infusion was provided at least 4 hours following the administration of misoprostol. With or without a nonreasoning FHR pattern, tachysystole is described as more than five contractions in 10 minutes for at least two intervals of the same duration. Until the FHR recovered to normal, episodes of hyperstimulation were treated with left maternal repositioning and intravenous fluid resuscitation. If the cervix was unfavorable for artificial membrane rupture after six dosages of misoprostol, the induction was said to have failed. The clinical team chose to continue managing. The primary outcome metric for women who delivered vaginally was induction to the delivery period. The number of misoprostol dosages, surgical delivery rates, the frequency of side effects, and neonatal results were considered secondary outcome variables. Uterine contractions were observed every 30 minutes, and patients were subjected to continuous cardiotocography monitoring for 20 minutes every 2 hours.

Statistical Analysis

To compare qualitative data, analysis was conducted by applying the SPSS 16.0 statistical software program (SPSS Inc, Chicago, USA). The Mann–Whitney *U* test was employed after making sure that everything was normal; if it was not, an independent *t*-test was applied. According to their distributions, we analyzed continuous measures by Mann–Whitney *U* test with median differences or using an independent sample *t*-test with mean differences. A 0.05 *p*-value is regarded as statistically significant. The sample size was determined using the same induction procedure and results from this research by Shetty et al.[11] and a comparison of the mean time spent in the labor ward in active labor across groups; we had taken a standard deviation of 4.72 for the time spent. Assuming a clinically significant difference of 3 hours between groups, the sample size needed is 40 in each arm at a 5% level of significance and 80% power. Considering 3 hours differences as significant to differentiate between the oral and sublingual groups, this study will require 40 patients in each group.

Results

About 90 women showed up for labor induction throughout the research period; however, 8 were ineligible because they matched the criteria for exclusion. Flowchart 1 depicts the flowchart of participants. This experiment included a total of 82 women. Out of these, 42 received misoprostol sublingually and 40 orally. The demographic characteristics were similar among groups (Table 1). The primary indicators for labor induction in the present research were postdated pregnancy and pre-labor membrane rupture at the admission time (Table 2). With a mean gestational age of 39.2 weeks, the majority of the women were nulliparous. In the oral group, 13 (32.5%) received two doses, whereas, in the sublingual group, 14 (33.3%) required three doses of misoprostol, as depicted in Table 3. Table 4 compared the delivery mode in the sublingual and oral misoprostol groups. In the entire cohort, overall, there were 61 vaginal deliveries. In the oral group, 33 women (82.5%) delivered vaginally. A Chi-square test comparison of the two routes revealed no statistically significant difference between them, with a *p*-value of 0.1. In comparison to the sublingual group, the oral group's mean time from induction to vaginal birth was considerably shorter ($p = 0.02$). Table 5 lists the reasons for cesarean delivery. Table 6 illustrates the maternal complications and neonatal outcomes in these two groups. Between the two groups, there was no noticeable variation in the rate of meconium passing.

Flowchart 1: Consort chart

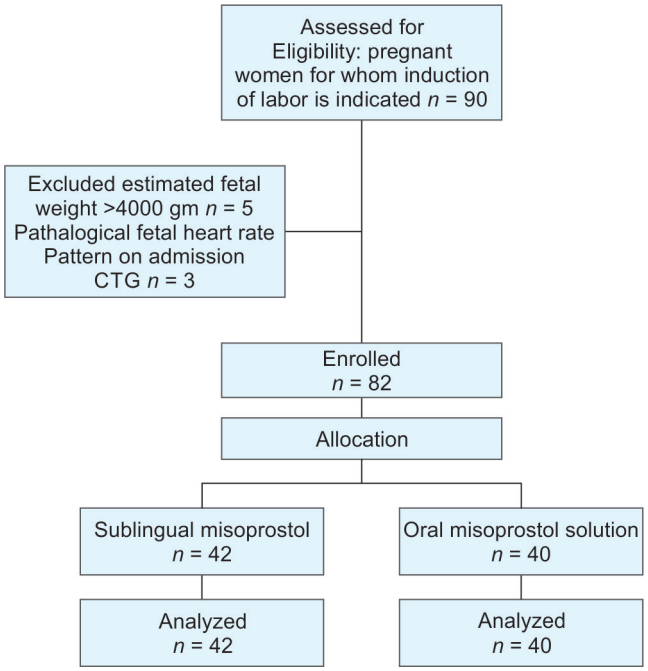

Table 1: Baseline characteristics of the women

	Oral solution n = 40	*Sublingual n = 42*	*Significance*
Age (years) Mean (SD)	28.7 (4.0)	27.6 (3.7)	0.21
Height (cm) Mean (SD)	157.7 (4.5)	157.1 (6.0)	0.61
Weight (kg) Mean (SD)	62.5 (9.4)	65 (1.1)	0.28
Mean BMI ± SD	23.9 ± 3.2	25.9 ± 4.7	0.03
Bishop score Mean (SD)	2.9 (0.9)	2.2 (1.1)	0.005
Primigravida (%)	29 (72.5)	38 (90.5)	
Multigravida (%)	11 (27.5)	4 (9.5)	

Table 2: Indications for induction of labor

Indication	*Oral solution n = 40 (%)*	*Sublingual n = 42 (%)*
Post dates	10 (25)	18 (42.8)
Prelabor rupture of membranes	19 (47.5)	6 (14.2)
Low normal liquor	2 (5)	2 (4.7)
Hypertension: gestational hypertension	5 (5)	2 (4.7)
Diabetes:	1 (2.5)	1 (2.3)
GDM	0	1 (2.3)
Overt DM		
IUGR	1 (2.5)	2 (4.7)
Decreased fetal movements	1 (2.5)	2 (4.7)
Maternal request	0	2 (4.7)

Discussion

Although several studies support misoprostol's effectiveness in inducing labor, further study is needed to determine the best dosage and protocol. The outcomes of this trial demonstrated that women who had their labors induced with an oral misoprostol solution went into labor more quickly and were more likely to give birth vaginally than women who had their labors started sublingually. The vaginal delivery rate was comparable with other studies.[12–14] This is the first study using low-dosage oral misoprostol in solution (25 µg) as recommended by WHO. In the present study, misoprostol was administered as an oral solution in 25 mL of water given every 2 hours based on the Cochrane recommendation for labor induction. Women were made to drink oral misoprostol solution in studies done by Thaisomboon,[12] Aalami-Harandi,[13] and Deshmukh.[14] And where they used a maximum of 10–12 doses. However, in this study, we could deliver them using less than six doses of misoprostol solution orally. Multiple studies have been done, with the dose of misoprostol varying from 25 µg every 2 hours to 100 µg as a single dose. Misoprostol taken orally causes persistent uterine activity within 90 minutes and lasts for around 2 hours.[10] An inaccurate notion that the oral pharmacokinetic data for vaginal dosages is the same has led to the use of dosing regimens with 4–6 hours intervals.[10] According to Shetty et al.,[11] the sublingual method demonstrated comparable effectiveness to the vaginal route while causing less hyperstimulation. The sublingual method was more effective with no rise in hyperstimulation rates or negative effects, according to a comparison of 50 µg of oral misoprostol with an equal dosage of sublingual misoprostol. In comparison to all other modes of administration, sublingual administration might produce the greatest plasma concentration.[6] According to the research, sublingual misoprostol is just as efficient for inducing labor as vaginal misoprostol when administered in doses of 50 µg. Misoprostol 50 µg sublingually caused more frequent tachysystole, although neonatal outcomes were comparable. In the sublingual group, there was a rising prevalence of uterine tachysystole (17.5%) compared to 3.8% in the vaginal group, which might be due to increased bioavailability and higher doses. Every 4 hours, misoprostol 25 µg was given sublingually in multiple studies by Sharami,[15] Ayati,[16] and Jahromi.[17] The present study is the first study in the literature in which sublingual misoprostol was administered every 3 hours by pharmacokinetics. This will reduce the induction to vaginal delivery interval and enhances the satisfaction among induced women as this will reduce the time of stay in the labor ward. Pre-labor membrane rupture was the main cause of labor induction in the oral group in the current investigation. Early labor induction may lower the risk of infection in both the mother and the newborn since the premature rupture of the membranes occurs in 6–19% of all term births. The major advantage of administration of the drug orally or sublingually compared to the vaginal administration route of dinoprostone or misoprostol gel is that the drug does not

Table 3: Number of doses of misoprostol used

Dose	*Oral solution n = 40 (%)*	*Sublingual n = 42 (%)*	*Significance*
1	7 (17.5)	4 (9.5)	
2	13 (32.5)	4 (9.5)	
3	9 (22.5)	14 (33.3)	
4	5 (12.5)	10 (23.8)	
5	2 (5)	4 (9.5)	
6	4 (10)	6 (14)	
Mean (SD)	2.85 ± 1.5	3.57 ± 1.4	0.30*

*Independent *t*-test

Table 4: Mode of delivery

Outcome	*Oral solution n = 40*	*Sublingual n = 42*	*Absolute difference (95% CI)*	*p-value*
Delivered vaginally in ≤24 hours (%)	33 (82.5)	28 (66.6)	0.158 (–0.032–0.333)	0.101*
Cesarean section (%)	7 (17.5)	14 (33)		
First dose to vaginal birth in hours (mean ± SD)	4.43 ± 2.8	6.25 ± 3.76	1.817 (0.339–3.296)	0.017**
Induction to vaginal delivery intervals (hours)				
Mean hours (mean ± SD)	9 ± 4.5	12 ± 5.2	3.00 (0.496–5.50)	0.020*

*Independent *t*-test, **Mann–Whitney *U* test

Table 5: Indications for cesarean section

Indication	*Oral solution n = 7 (%)*	*Sublingual n = 14 (%)*
FHR abnormality	2 (28.5)	5 (35.7)
Failure to progress	2 (28.5)	2 (28.5)
Meconium-stained liquor	2 (28.5)	2 (14.2)
Arrest of descent in 2nd stage	0	1 (7.1)
Failed induction	1 (14.2)	2 (14.2)

Table 6: Maternal and neonatal outcome

	Oral solution n = 40	*Sublingual n = 42*
Uterine tachysystole	0	0
Postpartum hemorrhage (%)	0	1 (2.3)
Perineal tear (%)	1 (2.5)	2 (4.7)
Mean birth weight mean ± SD	2.9 ± 0.487	3.03 ± 0.406
Apgar score <9 at 5 minutes	1 (2.5)	1 (2.4)

wash off with the leaking of liquor. The present study is important because it offers attractive benefits of the sublingual route of administration, including easier administration as compared to the vaginal route. The sublingual and oral administration routes might be preferred to the vaginal routes in certain clinical situations, such as when early rupture of the membranes occurs, with the possible advantage of avoiding vaginal checkups and lowering the risk of chorioamnionitis. In a low-resource situation with an unfavorable doctor–patient ratio, oral misoprostol solution is an appealing and convenient choice. It is often impossible to closely monitor intravenous oxytocin infusions. The function of oral misoprostol for labor induction is expanded by the findings of the Mundle et al. INFORM investigation, which was published in The Lancet.[18] The INFORM randomized control experiment was carried out in two hospitals with overloaded work and limited resources in India. Misoprostol does not need cold chain storage, unlike dinoprostone gel, which is expensive and has to be refrigerated. Misoprostol is easy to use and may be quickly incorporated into clinical practice due to its inexpensive cost and the small size of the tablet. Misoprostol aids in uterine stimulation and cervix ripening, which lessens the requirement for oxytocin infusion.[19,20]

Conclusion

From the results of the current research, it can be inferred that the 25 µg oral misoprostol solution and the same dose of sublingual misoprostol are both secure and reliable ways to induce labor in females with an unfavorable cervix. The current study used a dosing regimen consistent with the pharmacokinetics of misoprostol. We found that misoprostol given as a solution to drink was more effective than the sublingual route for various indicators, such as induction time and vaginal birth rate.

Compliance with Ethical Standards

- Ethical approval and consent to participate: Approved IEC no. 471 by the hospital ethical committee. Written consent was taken from participants.
- Human and animal rights: None of the authors of this paper conducted any investigations on animals. Standard care of treatment is given as per hospital standards and ethical committee approval.

Acknowledgments

Authors acknowledge the cooperation from patients and the "Department of Obstetrics and Gynecology".

Orcid

Jyothi Shetty https://orcid.org/0000-0002-4523-7437
Rekha Upadhya https://orcid.org/0000-0003-3336-9616

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