Original Article

Comparison of 25 µg Sublingual and 50 µg Intravaginal Misoprostol for Cervical Ripening and Labor: A Randomized Controlled Equivalence Trial

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Abstract

Background: Sublingual misoprostol, used for labor induction, produces earlier and higher peak plasma concentrations of misoprostol than vaginal or rectal misoprostol. The sublingual route could be expected to be more effective and safer than the vaginal route and by avoiding a direct effect on the cervix, it might reduce the risk of uterine hyperstimulation and be safer. This study aimed to compare the efficacy of 25-µg sublingual misoprostol with 50-µg intravaginal misoprostol for cervical ripening prior to labor induction in primiparous women.

Methods: In a double-blind, parallel randomized controlled equivalence trial, we recruited 131 primiparous women at 36–42 weeks of gestation requiring labor induction who referred to Alzahara hospital in Rasht, Iran. The women were randomly assigned to receive 25-µg sublingual misoprostol with vaginal placebo (n = 63) or 50-µg intravaginal misoprostol with sublingual placebo (n = 63). The dose was repeated every 4 h (maximum 4 doses). The primary outcome was the interval from the start of induction to vaginal delivery.

Results: There were no significant differences between the two groups with regard to the interval from the start of induction to vaginal delivery (13.2 ± 3.07 h in the vaginal group vs. 13.1 ± 3.46 h in the sublingual group), duration of active phase, Bishop Scores after 4h, and rate of the vaginal delivery under 12 h. Also, the rate of hyperstimulation, tachysystole, type of delivery, cause of cesarean section, Apgar scores less than 7 and admission to the NICU were similar in these two groups. The mean dose of misoprostol applied was significantly lower in the sublingual group ($P = 0.001$).

Conclusion: Sublingual administration of 25-µg of misoprostol appears to be as effective as 50 µg intravaginal misoprostol for cervical ripening and labor induction.

Trial Registration: This trial has been registered under IRCT 38903131096N3

Keywords: Cervical ripening, labor, misoprostol

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Introduction

Labor induction is the most common medical intervention in pregnancy. The success rate of labor induction depends on the state of cervix before initiation of induction. Induction of labor in the case of unfavorable cervix leads to prolonged labor, increased rate of cesarean delivery and fetal distress.[1] In order to improve the rate of successful induction, different methods are used for ripening of cervix before labor induction. These include mechanical devices and medications such as prostaglandins (PGs). PGs are the most common methods for cervical ripening used in a variety of forms, dosages and application routes.[2,3]

Misoprostol, a synthetic PGE1 analogue, is currently used for labor induction at term. It has a number of advantages for clinical use. It is cheaper than the other PGs, easy to administer, does not require refrigeration, and can be administered vaginally, buccally, sublingually, and rectally.[4] Several studies have evaluated the efficacy, feasibility, and safety

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of misoprostol for induction of labor in women with an unfavorable cervix. However, the optimal dosage and route of administration have not been established yet.[3,5,6]

The use of sublingual misoprostol for cervical ripening at term was recently investigated in some studies. The sublingual route would have the higher efficacy than the vaginal route by avoiding the first pass effect of the hepatic system, while having lower uterine hyperstimulation and tachysystole rates by avoiding direct effects on the cervix. In addition, the sublingual route is easier than other routes with the advantage of no restriction of mobility after administration. Also, misoprostol is absorbed as rapidly following this route of administration as after oral and vaginal treatment and plasma levels are elevated significantly longer. [3] Due to the higher bioavailability of sublingual administration, measured as the area under the curve, the direct effect on the cervix could be expected to be more pronounced than oral and vaginal treatment.

In one study, a sublingual dose of 50-µg every 4h resulted in more women delivering vaginally within 24 h and required less

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oxytocin augmentation, compared to vaginal misoprostol.[7] Sublingual misoprostol used for labor induction produces earlier and higher peak plasma concentrations of misoprostol than vaginal or rectal misoprostol.[8,9] Therefore, the sublingual route could be expected to be more effective than the vaginal route and by avoiding a direct effect on the cervix, it might reduce the risk of uterine hyperstimulation and be safer.

This study aimed to compare the efficacy of 25-µg sublingual misoprostol with 50-µg intravaginal misoprostol for cervical ripening prior to labor induction in primiparous women. We decided to compare the effectiveness and safety of 25 µg sublingual misoprostol dose vs. standard dose (50 µg) of intravaginal misoprostol for cervical ripening and labor induction.

Materials and Methods

This double-blinded parallel randomized controlled equivalence trial was conducted on pregnant women who referred to Al-Zahra hospital in Rasht, the capital of Guilan Province, North of Iran, from July 2010 to September 2011.

Nulliparous women were eligible for enrollment if they presented with obstetric or medical indications for labor induction, including gestational age > 41 weeks (dates confirmed by first trimester ultrasound); oligohydramnios, abnormal biophysical profile score, gestational diabetes mellitus without the need for insulin therapy, and intrauterine growth restriction. The inclusion criteria were gestational age of 36–42 weeks confirmed by first trimester ultrasound, singleton live pregnancy, vertex presentation, intact membranes, an unfavorable cervix (Bishop Score ≤4), absence of spontaneous uterine contraction, estimated fetal weight less than 4000 g, and normal fetal heart rate.

The exclusion criteria were: 1) cephalopelvic disproportion, 2) previous cesarean delivery or other type of uterine scars, 3) known hypersensitivity to the use of PGs, 4) preeclampsia (characterized by BP ≥ 140/90 and proteinuria ≥ 300 mg/L), 5) the need for immediate birth (such as active uterine bleeding or fetal heart rate (FHR) abnormalities, and 6) any contraindication to vaginal delivery.

This study was approved by the Ethical Committee of Guilan University of Medical Sciences. All participants provided written informed consent before entry into the study.

We used blocked randomization method for generating the randomization sequence. The permuted block randomization method for a block of size 4 was used. Opaque envelopes labeled A and B were provided and after assignment, one of them was delivered to the labor room based on the participants' group. Two packages of pills, one labeled sublingual and another labeled vaginal medication (placebo or misoprostol) were put in each envelope. In this trial, participants, labor staff, and outcome assessor were blinded and did not know the allocation of A and B groups.

In order to prepare 50-µg or 25-µg misoprostol, one 200-µg tablet was divided into 4 or 8 pieces, respectively. The placebo that was produced by Sobhan Company was similar in appearance, texture, and taste to misoprostol. The placebo was divided into 4 or 8 pieces like misoprostol.

The pill labeled vaginal medication was put in the posterior vaginal fornix and another labeled sublingual medication was put under the tongue.

The women were randomly assigned to receive either 50 µg of vaginal misoprostol with sublingual placebo (group I) or 25 µg of sublingual misoprostol with vaginal placebo (group II) every 4 hours for a maximum of 4 doses. Prior to every dose administration, a fetal cardiotocography was performed for 20 min to confirm fetal wellbeing and a vaginal examination was done to assess the Bishop score.

A subsequent dose of medication was not given if the frequency of contractions was more than thour see in 10 minutes, or active phase of labor (defined as cervical dilation ≥ 4 cm) on vaginal examination. Amniotomy was performed in the active phase of labor (cervical dilation ≥ 4 cm). Labor was augmented with oxytocin in the active phase of labor, if the frequency of contractions was less than thoursee per 10 minutes or had an arrest of dilation (no change in cervical dilation in 2 h). Oxytocin was administered not earlier than 4 h after the last dose of misoprostol, and starting at 1 MU/min and increased by 1MU/min every 20 min until adequate contractions persisted.

Tachysystole was defined as six or more uterine contractions in 10 min. Uterine hyperstimulation was defined as tachysystole associated with a non-reassuring FHOURS pattern, (fetal tachycardia, late decelerations or less of FHOURS variability). Hyperstimulation was treated by the left lateral position, intravenous fluid bolus, oxygen supplementation, cessation of oxytocin infusion, removal of misoprostol tablet and vaginal irrigation.

Primary outcome was defined as the time from the start of induction (first dose of misoprostol) to vaginal delivery. The frequency of delivery within 12 h and 24 h of indication, mode of delivery [cesarean section (C/S)] or normal vaginal delivery (NVD), indications of C/S, doses of administered misoprostol, the rate of uterine hyperstimulation and tachysystole, need for oxytocin augmentation and FHR abnormalities, changes in Bishop score after 4 h, duration from indication initiation to the active phase and premature rupture of membrane were indicated as maternal secondary outcome. Also, neonatal outcomes included birth weight, 1 and 5 min Apgar score, meconium stained amniotic fluid, and neonatal intensive care unit (NICU) admission rate.

To detect a difference in 2 h in the induction-to-delivery interval between two groups with an error probability of 5% and a power of 80%, assuming a standard deviation (SD) of 4 h, at least 63 women were necessary per group.

Statistical analysis

Data were analyzed using IBM SPSS Software Version 16. For numeric variables, data were described as mean and SD and for categorical variables, data were shown as number and percentage. For statistical analysis, 2-tiled independent *t*-test was used to compare means between the two groups. Also, chi-square and Fisher's exact tests were used to compare proportions between the two groups. A *P* value less than 0.05 was considered statistically significant.

Results

Sixty thoursee women were assigned to the 25 µg sublingual misoprostol (group I) and 63 to the 50 µg vaginal misoprostol group (group II). Two women from the sublingual group and thoursee from the vaginal arm were excluded. One had spontaneous labor and four patients required emergent intervention. Demographical characteristics of the women and the indications for labor induction were similar in the two groups. All patients were primipara, there was no significant difference in the mean initial

Table 1. Demographical characteristics of the women and the indications for labor induction

Variables	25 µg sublingual misoprostol (*n* = 63)	50 µg vaginal mioprostol group (*n* = 63)	*P*-value
Age (years)	25 ± 4.6	23.5 ± 4.3	0.078
Gestational age(weeks)	39 ± 0.8	39 ± 1	0.357
Initial Bishop score	2.3 ± 0.6	2.1 ± 0.7	0.088
Indication for induction			
Post term	21 (33.3)	25 (39.7)	0.579
Abnormal fetal testing	29 (46.0)	26 (41.3)	0.720
Oligohydramnios	6 (9.5)	3 (4.8)	0.491
Gestational diabetes	4 (6.3)	5 (7.9)	1
Intrauterine fetal restriction	3 (4.8)	4 (6.3)	1
*Data are Mean ± SD or numbers (%).			

Table 2. Labor characteristics

Variables	25 µg sublingual misoprostol (*n* = 63)	50 µg vaginal misoprostol (*n* = 63)	Difference (95% CI) between two groups	*P*-value
Changes in Bishop score after 4 hours	3.7 ± 2.4	4.1 ± 2.1	-0.4 (-1.19, 0.39)	0.321
Success of induction	58 (92.6)	52 (82.5)	9.5 (-2, 21)	0.180
Interval to active phase (hours)	7.6 ± 3.2	7.3 ± 3	0.3 (-0.79, 1.39)	0.588
Interval to rupture of membranes	6.1 ± 2.5	6.8 ± 2.9	-0.7 (-1.66, 0.26)	0.149
Tachysystole	0	2 (3.2)	-3.2 (-7.5, 1.2)	0.496
Hyperstimulation	5 (7.9)	2 (3.2)	4.8 (-3.2, 12.7)	0.440
Need to oxytocin	13 (20.6)	6 (9.5)	11.1 (-1.2, 23.5)	0.137
Mean dose of misoprostol applied	38.5 ± 14	84.9 ± 33	-46.4 (-55.4, -37.4)	0.0001
*Data are Mean ± SD or numbers (%).				

Table 3. Delivery outcomes in both study groups

Variables	25 µg sublingual misoprostol (*n* = 63)	50 µg vaginal misoprostol (*n* = 63)	Difference (95% CI) between two groups	*P*-value
Mean interval to vaginal delivery	13.2 ± 3.4	13.1 ± 3.1	0.1 (-1.05, 1.25)	0.863
Mode of delivery				
-C/S	10(15.9)	18(28.6)	-12.7 (-27, 1.6)	0.133
-NVD	53(84.1)	45(71.4)	12.7 (-1.6, 27)	0.133
Indications for cesarean				
-FHR abnormalities	2(3.2)	5(7.9)	-4.8 (-12.7, 3.2)	0.440
-Failure to progress	4(6.3)	5(7.9)	-1.6 (-10.6, 7.4)	1
-Meconium passage	4(6.3)	8(12.7)	-6.3 (-16.5, 3.8)	0.363
Vaginal delivery before 12 hours	28(52.8)	24(53.3)	-0.5 (-20.3, 19.3)	1
Vaginal delivery before 24 hours	53(100)	45(100)	0	1
*Data are Mean ± SD or numbers (%). NVD = normal vaginal delivery; FHR = fetal heart rate				

Table 4. Neonatal outcomes

Variables	25 µg sublingual misoprostol (*n* = 63)	50 µg vaginal misoprostol (*n* = 63)	Difference (95% CI) between two groups	*P*-value
Neonatal birth weight	3237 ± 389	3268 ± 314	-31 (-155.7, 93.7)	0.623
1-min Apgar score less than 7	9 (14.3)	4 (6.3)	7.9 (-2.6, 18.5)	0.241
5-min Apgar score less than 7	0	1 (1.6)	-1.6 (-4.7, 1.5)	1
Admission to NICU	1 (1.6)	2 (3.2)	-1.6 (-6.9, 3.7)	1
*Data are Mean ± SD or numbers (%).				

Bishop score between the two groups. The common cause for pregnancy termination in both groups was the abnormal biophysical profile score (Table 1).

In both groups, a considerable improvement occurred in Bishop Score 4h after initiation of labor induction. Also, there were no significant differences in the interval from initiation of induction to the active phase of labor, success of induction rate, changes in cervical dilation after 4h, the rate of vaginal delivery before 12 h, and 24 h, the incidence of cesarean delivery, the rate of cesarean for failed induction and fetal distress, between the two groups. There were no significant differences in the interval (± SD) from the start of induction to vaginal delivery in the two groups (13.**2** ± 3.07 h in the vaginal group vs. 13.1 ± 3.46 h in the sublingual group).

The rate of tachysystole and uterine hyperstimulation as well as the need for oxytocin augmentation was similar in the two groups. The mean dose of misoprostol applied was significantly lower in the sublingual group than in the vaginal group (38.5 ± 14 vs. 84.9 ± 33; $P = 0.001$). Five cases in the vaginal group and two cases in the sublingual group required emergency cesarean section for fetal distress (Tables 2 and 3)

Table 4 illustrates the neonatal outcomes in these two groups.

There were no significant differences in unfavorable neonatal outcomes such as low birth weight, 1-min and 5-min Apgar score less than 7, meconium passage and admission to NICU in the two groups.

Discussion

Based on our results, there was no statistically significant difference between the 25-µg sublingual misoprostol (every 4 h) and the 50-µg intravaginal misoprostol for cervical ripening and induction of labor in primiparous women. According to our findings, the confidence interval of difference between two methods was -1.05 h and 1.25 h. The lower and upper bound of the presented confidence interval as a difference are not clinically significant. This effect can be related to higher peak of serum concentration of misoprostol with the sublingual method in comparison to the vaginal route. Some studies on the pharmacokinetics of misoprostol have indicated that the sublingual route of misoprosl results in higher serum peak concentrations and shorter time to peak concentrations of misoprostol compared to the vaginal route.[8,9]

Some studies showed that sublingual administration of misoprostol has faster onset of action and higher plasma concentration in comparison with the vaginal route. This may be explained by the good blood supply under the tongue and neutral pH in the buccal cavity.[7,8,11,12]

Also, it must be noted that one reason for the prolonged activity and greater bioavailability of the misoprostol tablet administered sublingually is the fact that it dissolves in only 10-15 min, while it takes several hours with the vaginal route.[8] The vaginal route of misoprostol administration may not be the optimal way, because women prefer to take the misoprostol tablet in their mouth in order to avoid uncomfortable vaginal examination.[8]

While the use of vaginal misoprostol for cervical ripening and labor induction is growing, the sublingual use of misoprostol is still limited and in spite of being an effective route of administration, the use of sublingual misoprostol needs more clinical trials to establish its optimal dose, effectiveness and safety.[13]

Since there is a narrow range between safe and dangerous doses of misoprostol, especially in women with a uterine scar, researches are needed to determine safe guidelines and the optimal doses of misoprostol for cervical ripening and induction of labor.[14]

There has been no previous report in the literature to compare 25 µg of sublingual misoprostol with 50 µg of vaginal misoprostol used every 4 h for labor induction at term.

This is the first randomized, double blind, controlled clinical trial on these two routes of misoprostol administration that compared 25 µg sublingual misoprostol with 50 µg vaginal misoprostol. With respect to the safety of the sublingual administration of misoprostol, there is still insufficient data in literature for this route of administration to be recommended in clinical practice.

Bartusevicius, et al., (2006) compared the efficacy and safety of 50 µg of sublingual misoprostol with 25 µg of vaginal misoprostol for cervical ripening. In their study, 58 women (83%) in the sublingual misoprostol group and 53 (76%) in the vaginal group delivered vaginally within 24 h and the induction to vaginal delivery time was significantly shorter in the sublingual group (15 ± 3.7 h) compared with the vaginal group (16.7 ± 4.1 h, $P = 0.03$). The incidence of tachysystole was more than threefold higher in the sublingual than in the vaginal group. They concluded that 50 µg dose of sublingual misoprostol (every 4 h) for labor induction at term has similar efficacy as 25 µg of vaginal misoprostol.[15]

We compared a lower sublingual dose (25 µg) with an accepted dose of vaginal misoprostol (50 µg), because data from previous studies suggested that 50 µg sublingual misoprostol might be the optimal dose that maintains the balance between efficacy and safety.[12,16]

Different routes and doses of misoprostol administration for labor induction necessitate balancing the benefits (success of indication and shorter time of delivery) against the risks (uterine hyper stimulation, adverse neonatal and maternal outcomes).

Vaginal misoprostol in 50 µg dosage is associated with 3-fold higher rate of uterine hyper- stimulation,[17] and a higher rate of meconium stained amniotic fluid because the direct effects of vaginal misoprostol on the cervix can increase uterine activity.[18]

The higher rates of tachysystole with vaginal misoprostol in comparison to sublingual misoprostol suggest that avoidance of a direct effect on the cervix reduces the risk of excessive uterine activity.

Feitosa, et al., determined the effectiveness and safety of 25-µg sublingual misoprostol, given every 6 h up to a maximum of 4, for induction of labor in 40 women with high risk pregnancy. The active phase occurred in 100% of cases. The mean (±SD) induction to labor interval was 4.8 (±3.8 h). The interval from induction to delivery varied from 8 to 37 hours with 95% of deliveries occurring in the first 24 h. The frequency of vaginal delivery was 75% and the rate of tachysystole was 12.5%. They concluded that 25-µg of sublingual misoprostol is effective and safe for induction of labor in high-risk pregnancy and its efficacy and safety should be compared to the vaginal route.[19]

In another study, the efficacy and safety of 25-µg sublingual misoprostol was compared with 25-µg vaginal misoprostol for cervical ripening and there were no significant differences between the number of women with vaginal delivery between the two groups (65.5 vs. 75.8%, $P < 0.02$), or in the interval between the induction onset and delivery, rate of uterine hyperstimulation, meconium passage and other adverse effects.[20] These results are comparable with our study.

Feitosa, et al., compared 25-µg sublingual misoprostol with the same dose of vaginal misoprostol for induction of labor and concluded that these two routes of administration of misoprostol are not significantly different with respect to delivery end points,[21] and maternal and neonatal outcomes. There are some limitations associated with the current study. Because of the small sample size, this study had inadequate statistical power to evaluate the safety of sublingual misoprostol and because of excessive exclusion criteria, the results of this study may not be generalized to high-risk populations.

The results of this study revealed that administration of 25-µg sublingual misoprostol every 4 hours is as efficacious and safe as 50-µg intravaginal misoprostol for cervical ripening and labor induction in term pregnancies. Further studies with larger number of women are needed to establish the safety and effectiveness of 25-µg sublingual misoprostol before we advocate 25-µg sublingual misoprostol using for labor induction.

Conflict of interest

The authors report no conflict of interest related to this study.

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