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A Comparative Study of Vaginal, Sublingual, and Buccal Misoprostol in Induction of Labor in Term Pregnancy

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ABSTRACT

Background & Objective: The purpose of this study was to compare the effectiveness of Buccal, Vaginal, and Sublingual misoprostol for induction of labor in term pregnancy.

Materials & Methods: The research was done as an RCT from 2017 to 2018. About 300 participants were randomly allocated to obtain 50 µg Buccal, 25 µg Vaginal, and 50 µg Sublingual misoprostol in Kosar Hospital, Qazvin, Iran. The maternal and fetal complications, Bishop score hour 1, and hour 6 were observed.

Results: There were no differences between fetal complications (P>0.05) and maternal complications (P>0.05) among the three groups. Bishop score hour 1 (P = 0.146), Bishop Score hour 6 (P = 0.704), and total dose (P = 0.15) also were no differences among these groups. Our study found a difference between the three groups (P = 0.015) in achieving standard vaginal delivery within 24 hours, as Buccal, Sublingual and Vaginal groups were performed respectively. The use of Oxytocin in the Buccal group was higher than that of other groups (P = 0.022).

Conclusion: This study found that there is no difference in terms of fetal complications and maternal complications in the three groups, but there was a significant difference in Oxytocin use and vaginal delivery within 24 h from the start of induction.

Keywords: Buccal, Sublingual, Vaginal, Misoprostol

Introduction

Induction of labor (IOL) is one of the common actions that are being taken because of maternal or fetal indication for termination of pregnancy. The induction of labor for pregnant women is widely spread in both developed and underdeveloped countries. IOL aims to stimulate uterine contractions before it starts automatically **(1, 2)**. Different types of prostaglandins can be used, but the most common types are as follows: 1. prostaglandin E2 (dinoprostone), which is in gel or suppository form; 2. prostaglandin E1 (misoprostol), which is used orally, rectally, or vaginally **(3)**. Because oxytocin only affects uterine contractions and does not soften the cervix, prostaglandins are a better solution for inducing labor due to their local effect on the cervix that only causes the cervix to dilate and contract.

Prostaglandin E1 (misoprostol) had been known as an inexpensive and cost-effective peptic ulcer medicine used for labor induction. Prostaglandin E1 should be kept at room temperature, and the side effects of taking a high dose of this drug include diarrhea, nausea, vomiting, and fever, which are temporary side effects **(4)**.

Side effects of misoprostol include fever, chills, bradycardia, uterine hyper-stimulation, and rarely uterine rupture **(5-7)**. The serum peak of misoprostol is 34 minutes after its usage and its half-life is about 20-40 minutes, while the serum peak of vaginal misoprostol is about 60-80 minutes and remains for four hours **(8)**. Usually, vaginal misoprostol is used at 25mg every four hours **(9)**.

Several studies have been done on the usage of vaginal and sublingual misoprostol and results show that in equal dosage, vaginal misoprostol causes more uterine contractions and shortens the labor duration. The better potency of the vaginal type is due to the pharmacokinetic effect of the drug. Although it is stated that the vaginal type has a better effect on the preparation of the cervix, an oral type of the drug has

better effects on uterine contractions control because of its shorter half-life **(3, 4, 10)**.

Misoprostol pharmacokinetic shows the immediate oral absorption of the medicine and reaches the highest serum level after 15 minutes of its oral usage (density of tmax=0.309 µ/L). After 20-40 minutes of oral usage, its half-life and its serum density reach the minimum level after 120 minutes. Some researchers believe that the better effect of the vaginal type is due to the absence of the first passage effect (liver effect) **(8-10)**.

Previous research shows that sublingual and oral misoprostol administration methods have higher plasma concentrations than vaginal types, and the duration of induction of labor in sublingual methods is shorter than in other misoprostol administration methods. Sublingual methods also affect the preparation of the cervix the same as vaginal methods and since it prevents direct effect on the cervix, the risk of uterine hyper-stimulation would decrease. The sublingual method has some advantages, such as its simple prescription, more comfort for the patient, and less need for vaginal examination **(2-12)**. The buccal area of the mouth is full of vessels that help the immediate absorption of medicines (drugs). Using buccal misoprostol for induction of labor is so effective, but it increases nausea. Patients' reception for buccal and sublingual methods is more than vaginal type **(13)**.

This study compares the effects of buccal, sublingual, and vaginal methods on the induction of labor for term pregnancies.

Methods

This study was conducted as a clinical trial. All the patients of Kosar Hospital in Qazvin Province (March-February) were included in the study after obtaining informed consent. Inclusion criteria were: induced live single pregnancy with an occipital presentation, gestational age more than 37 weeks, Bishop scores less than five, reassuring fetal heart rate pattern, less than four kg weight of the fetus, and the amniotic fluid greater than five.

But those patients with previous uterine surgery or cesarean section severe preeclampsia (urine protein more than 300 mg/dl, blood pressure more than 160/100, and abnormal liver tests) parity more than two, presence of uterine contractions, cardiovascular, renal, and liver diseases, rupture of the membrane, fetal growth restriction, and suspected fetal malformations could not enter the study (exclusion criteria).

All participants were divided into groups A, B, and C based on simple random sampling with random numbers and entered the randomized clinical trial. The research tool was a researcher-made questionnaire based on previous studies, whose validity was confirmed by experts and its reliability was confirmed by previous research **(2-4)**.

Maternal age gestational age, maternal BMI, and primary Bishop Score were recorded in their first time of admission. Gestational age was determined based on the last menstrual date that was verified by the primary sonography **(13)**. The fetal heart rate in all the pregnant women that entered the study was monitored continuously one hour before, one hour after the induction of labor, and after the beginning of uterine contractions. It was monitored constantly until the delivery. The first group received 50 mg misoprostol sublingual every six hours for 24 hours, the second group received 50 mg misoprostol buccal (between the tooth and cheek mucosa) every six hours for 24 hours, and the third group received 25 mg vaginal misoprostol for induction of labor (without repetition). In an appropriate dilatation when the fetal head was fixed, amniotomy was done by an Obstetrics-Gynecology resident.

Proper contraction occurs when a uterine contraction appears every 3-5 minutes and last for 40 seconds (three contractions in 10 minutes on average) in each of the three groups. The oxytocin induction would be started four hours after the last dosage of misoprostol. Fail induction is defined as not reaching the active phase (regular uterine contractions with four cm cervical dilatation) six hours after the last dosage of misoprostol. In the case of failed induction or prolonged active phase, a cesarean section was prescribed for patients. The primary results were vaginal delivery within the first 24 hours after the beginning of labor induction. The secondary results were the rate of cesarean section, the indication of cesarean, time for reaching the active phase, need for oxytocin for augmentation of labor, total dosages of misoprostol usage, fetal complications, such as abnormal heart rate pattern during labor which include; late deceleration, severe variable deceleration, prolonged deceleration, tachycardia, or reduced FHR variability **(14)**. Meconium excretion and Apgar score at one and five minutes after the delivery and confinement in NICU were recorded in the questionnaire. Maternal complications, such as fever, chills, nausea, vomiting, uterine tachysystole, and uterine hyperstimulation were monitored and recorded for the three groups. Tachysystole means six contractions in 10 minutes. Hyperstimulation means any contraction that lasts more than two minutes or a kind of tachysystole that leads to heart rate deceleration, which necessitates rapid intervention (tocolytic or delivery). In the case of hyperstimulation, 4gr intravenous magnesium sulfate was prescribed for 30 minutes.

SPSS software, version 21 (IBM, USA) was used for data analysis with ANOVA and chi-square tests and the significant level was $P<0.05$.

Results

In this research, 300 patients were studied and divided equally into three groups. None of the patients

were excluded from the study and for all three groups, the use of misoprostol continued until the necessary delivery. None of the procedures were discontinued because of drug side effects. The results show that the average age (P = 0.941), body mass index (P = 0.464), total dose (P = 0.80), Bishop score in the first hour (p = 0.07), and Bishop score in hour six (P = 0.185) were not significantly different between the three groups. However, there was a significant difference between oxytocin in the three groups (P = 0.022) (Table 1).

Causes for termination of pregnancy and induction of labor in three groups of buccal, sublingual, and vaginal methods respectively include 61.3, 50, 73% for postdate, 12, 18, 11% for rupture of membrane, 9.3, 23, 10% for labor pain, 5.3, 1, 3% for gestational diabetes, and 12, 7, 3% for gestational hypertension. Vaginal delivery within 24 h from the beginning of induction was 89, 87, and 83 respectively for three groups of buccal, sublingual, and vaginal, which is significantly different (P < 0.005).

Indication of cesarean section in three groups of buccal, sublingual, and vaginal respectively include the first reason was meconium with 49, 41, and 56%; the second reason was non-reassuring FHR pattern with 36, 43, and 44%, and the third reason was no-response to induction of labor. Furthermore, in the sublingual group, arrest in dilatation occurs in 11%. Oxytocin needs in the buccal, sublingual, and vaginal groups were 39, 22, and 21% respectively, which show differences among groups (P = 0.220).

Maternal complications, such as fever, chills, nausea, and vomiting were not signed in all groups, but uterine tachysystole was observed in 3% of participants who received sublingual misoprostol. Uterine hyperstimulation was nearly equal for all groups.

Neonatal complications, such as Apgar less than 7 in the first minute, Apgar less than 7 in five minutes, and admission to the NICU were not observed in any group, such as Non-reassuring FHR patterns were 20, 16, and 18 respectively, not significantly different (P = 0.79). Meconium excretion was 23, 16, and 23 respectively, which are not significantly different, too (P = 0.45).

Frequencies of non-reassuring FHR patterns for buccal, sublingual, and vaginal groups respectively were 20, 22, and 9% for tachycardia; 13, 33, and 9% for prolonged deceleration; 67, 40, and 82% for variable deceleration; and 5% of late deceleration in the sublingual group.

Table 1. Demographic variables among groups

Variable	Group	Mean	SD	P
Age/ Year	Buccal	25.25	5.22	0.941
	Sublingual	25.02	5.49	
	Vaginal	25.30	6.45	
BMI (Kg/M^2)	Buccal	28.16	3.17	0.464
	Sublingual	28.40	4.33	
	Vaginal	29.02	4.85	
Total Dose (µg)	Buccal	1.14	0.425	0.804
	Sublingual	1.18	0.386	
	Vaginal	1.14	0.355	
Bishop 1	Buccal	0.54	0.72	0.070
	Sublingual	0.65	0.80	
	Vaginal	0.87	0.96	
Bishop 6	Buccal	4.7	1.86	0.185
	Sublingual	5.54	3.34	
	Vaginal	5.2	2.46	
Oxytocin	Buccal	1.61	0.490	0.022*
	Sublingual	1.78	0.416	
	Vaginal	1.79	0.410	

Discussion

Misoprostol is safe and operative for the induction of labor **(15)** and has gained popularity as an IOL agent in recent years since it was developed and marketed in the United States in the 1980s **(16, 17)**. Evidence from meta-analyses, Canadian guidelines, and RCT proposes that misoprostol is likely safe for induction of labor and cervical ripening **(18)**. Oral misoprostol may make little difference in cesarean section rates **(19)**. Oral and buccal medications are recommended for induction of labor, wherever favorable cervical maturity is achieved with considerable patient comfort **(20)**.

Tachysystole in a sublingual misoprostol group was greater than in the buccal group, which does not verify the results of Carlan, Blust and O'Brien **(13)** findings. In their study, Carlan et al. investigated the effect of buccal and vaginal misoprostol on the induction of labor among 157 pregnant women. Their findings show that 63% of the vaginal group compares to 67% of the Buccal group reached vaginal delivery in 24 hours. Tachysystole for the buccal group was 38% which was greater than 19% in the vaginal group. But the findings of Bartusevicius, Barcaite **(21)** show that tachysystole was greater in the Sublingual group, but it was not significant **(21)**. Previous research **(21, 22)** indicated that participants who were treated with misoprostol were suffering from gastrointestinal experiences, tachysystole, and hyperstimulation which was the result of misoprostol dosage.

Neonatal complications, such as Apgar scores less than seven in the first minutes, Apgar score less than seven in five minutes and admitted to the NICU department and maternal complications, such as fever, chills, nausea, and vomiting did not observe in each group and other complications were not significantly different. The results also support the findings of Bartusevicius, which showed no significant difference between neonatal complications, type of delivery, and uterine hyperstimulation **(21)**. The results of Niroomanesh, Talebzadeh Nori and Hossain Pour **(4)** show a significant difference between maternal and neonatal complications in two groups (oral and sublingual). Nausea was higher in the oral than the sublingual group, and meconium excretion was higher in the sublingual than the oral group **(4)**. Results of Zahran, Shahin **(14)** also show that there was no difference between the time of reaching vaginal delivery, duration of labor, and maternal and infant complications **(14)**. Scacff et al. stated that buccal prescription shows fewer side effects (such as fever, chills, vomiting, and abdominal cramp), thus it has more acceptance **(23)**. Meconium excretion was 23% for the buccal and vaginal group and 16% for the sublingual group. Zahran et al. show 13.8% of meconium excretion results for the sublingual group and 16.3% for the vaginal group **(14)**.

Time of reaching delivery in less than 24 hours was 89% for the buccal group, 87% for the sublingual group, and 83% for the vaginal group, which is consistent with the results of Bartusevicius, Barcaite **(21)** study which show 83% for the sublingual group, 76% for vaginal group, and this period was significantly shortened in sublingual group **(21)**. Their study shows no significant difference in the induction of labor in term pregnancy based on pregnancy outcomes, pregnancy complications, and fetal complications in the misoprostol buccal and sublingual groups. Like our findings, the results of Beigi, Kazemipour and Tabarestani **(2)** show that there was no significant difference in the average score of a Bishop before and after the prescription of misoprostol the interval between the beginning of the pain and delivery, and the amount of used dosage **(2)**. Dadashaliha, Fallah and Mirzadeh **(24)** found the sublingual and intravaginal routes of administration, intracervical misoprostol at a single dose of 50µgm appears to be an effective method for induction of labor in women with an unfavorable cervix.

Conclusion

The purpose of this study was to compare the effectiveness of Buccal, Vaginal, and Sublingual misoprostol for induction of labor in term pregnancy. This study found that there is no difference in terms of fetal complications and maternal complications in the three groups, but there was a significant difference in Oxytocin use and vaginal delivery within 24 h from the start of induction. However, there needs much work with bigger samples to obtain the effectiveness of these misoprostol for induction of labor.

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Conflict of Interest

The authors declared no conflict of interest.

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