Available online at: http://www.ijmtst.com/vol5issue04.html

International Journal for Modern Trends in Science and Technology

ISSN: 2455-3778 :: Volume: 05, Issue No: 04, April 2019

Vaginal Misoprostol Administration for Cervical Ripening and Labor Induction

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To Cite this Article

Saeedeh Shahali, "Vaginal Misoprostol Administration for Cervical Ripening and Labor Induction", *International Journal for Modern Trends in Science and Technology*, Vol. 05, Issue 04, April 2019, pp.-01-06.

Article Info

Received on 05-March-2019, Revised on 30-March-2019, Accepted on 05-April-2019.

ABSTRACT

Purpose: *favorable cervix and uterine contraction are two basic factors in delivery and are important to success in labor induction.Different treatments are used for laborinduction that one of them is misoprostol. Because of the importance of the subject and the lack of a similar study in Iran, the purpose of this study isto compare the effect of sublingual and vaginal misoprostolin theinduction of labor in term patients.*

Methodology: *This is a double-blind randomized clinical trial. 270 pregnant women in oneof thehospitals of Tehran during the years 2012 and 2013 were randomly divided into two groups. One group received 27mg vaginal misoprostol and oral placebo and other group received 27mg oral misoprostol and vaginal placebo. The embryonic and maternal complications and theBishop score, and the time of onset of pain and time interval between pain anddeliverywere evaluated in two groups.*

Results:*the mean of bishop score before and after misoprostol and the time of onset of pain and its interval until delivery and the number of doses of misoprostol were not different in the two groups (p>0.05). 60 women(6.34 %)had anatural childbirthin the sublingual method and 72 women (53.2 %) had anatural childbirth in the vaginal method, which did not show thestatistically significant difference. Also, the frequency of maternal and fetal complications was similar in the two groups (p>0.05).There is no difference between sublingual and vaginal misoprostol from the aspect of results of pregnancy and fetal and maternal complications.*

KEYWORDS: *Misoprostol, Labor induction, Term pregnancy.*

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I. INTRODUCTION

Softening,expanding and effacing the cervix are some results of ripening of cervix.An unripe cervix is mostly not soft and is expanded less than 2 cm and is less than 50 %effaced. In routine pregnancieswith an unripe cervix, some procedures are commonly used to ripen the cervix that this process is used before delivery and prolongs 41 weeks. For cervical ripeningand labor induction, misoprostol, which isa synthetic prostaglandin Eanalogue, is used.But the U.S. Food and Drug Administrationdoes not approve thatthe use of misoprostol is effective for ripening of cervix.

Favorable cervix or ripenedcervixrefers to shortness, effacement, and dilatation of the cervix, which normally begins at the end of the third trimester before the labor.The pharmaceutical method including oxytocin and prostaglandinprescription and mechanical method including use of Foley catheter and separating amniotomy and amniotic membranes are used to prepare cervix.Unfortunately, in many cases that there are indications for labor induction, the cervix is not favorable.As the favorable state or Bishop score decreases, the rate of unsuccessful labor induction alsoprogressively increases. According to the aims of researches, a Bishop score 4 or lessBishop Score is used to identify an unfavorable cervix, and this criterion may be an indication for cervical ripening. Different methods have been developed to prepare the cervix in cases that have indications inlaborinduction that one of these methods is apharmaceutical method. As previously mentioned, the use of prostaglandins is one of these methods.This can be done with different types of prostaglandins, most commonly either prostaglandin E2 (dinoprostone) in the form of gel or suppository or prostaglandin E1 (misoprostol) in the form oral or vaginal tablets. In the case of theunfavorable cervix, prostaglandins affectthe production of cervicalcollagenand increase matrix decomposition of cervical collagen which causes the cervix get soft and get ready. As mentioned above, different methods of prescription of misoprostol are oral, sublingual and vaginal, but among these methods, the misoprostolin compare to dinoprostoneis cheaper and has less complication. The use of misoprostol can reduce the need for oxytocin and causesthe increase in vaginal within 24 hours after induction and alsomisoprostol shortens the time between induction and delivery.Vaginal misoprostolisused in the cases that induction is needed for theunfavorable cervix.One of the risks and complications of vaginal misoprostolare excessive uterine stimulation, increase the uterine contractions, meconium excretion and meconium aspiration, which is seen in cases of misoprostol use, and the rate of cesarean delivery also increases due to excessive uterine stimulation. Previous studies have shown that oral and sublingualmisoprostol create ahigher concentration of plasma in compare with vaginal misoprostol, and the time between induction and delivery in thesublingual methodis less than other methods of prescription of misoprostol. In addition, the sublingual method, like the vaginal method, is effective in cervical ripening and may reduce the risk of excessive uterine stimulation due to the prevention of direct effects on the cervix. Also, the benefits of using sublingual misoprostol are its simple prescription,giving patients more freedom and less need for repeated vaginal examinations. In general, due to the importance of the subject and the lack of a similar study in Iran, this study compared the effects of vaginal and sublingualmisoprostol on labor induction in term pregnant women who were thecandidate of labor induction in Bu-Alihospital during 2012 and 2013.

II. Methodology

This study is a double-blind randomized clinical trial.Individuals in the study werenulliparaor multipara (women with less than five delivery), who were in Bu-Ali hospital in Tehran during the years 2012 and 2013and were thecandidatefor laborinduction.The sample size was 270 pregnant women.Inclusion criteria for participation in the study were singleton pregnancy, live fetus, gestational age greater than or equal to 37 weeks, embryo with weighing less than four kilograms, amniotic fluid index of greater than five, normal, Bishop score of less than seven, and lack of delivery pains (NST) in the mother.Exclusion criteria included stripping the membranes, fetal growth restriction, suspected fetal abnormality, previous uterine scar, need to immediate delivery, more than fivedeliveries, a fever above 38 degrees in the mother, chorioamnionitis, embryo with estimated weighing more than four kilograms,diagnosis of oligohydramnios or polyhydramnios, previous sensitivity to prostaglandins and gestational age less than 37 weeks.In this study, individuals, who received sufficient explanation andcompleted written consent and have inclusion criteria for participation in the study, were randomly divided into two groups by using the Random Number Generators in SPSS software.One group received 27mg vaginal misoprostol (cytotec, searle, England)with oral placebo and other group received 27mg oral misoprostol (cytotec, searle, England)with vaginal placebo and thefetal heartbeatwas recorded before and after and during uterine contractionsevery 15 minutes.

In addition, uterine contractions were evaluatedevery half hour and vital signs and digestive symptoms of the mother were also monitored every hour. In the cases that after 6 hours, the Bishop scores did not change or

appropriate uterine contractions(three contractions for more than 40 seconds within 10 minutes) did not occur, the second dose of misoprostol was repeated, and again all of the above cases were recorded and this process was continued until appropriate contractions were achieved, or four doses of misoprostol repeated at 6-hour intervals.If six hours after the last dose of misoprostol,appropriate uterine contractions did not occur or the Bishop score did not change, so it was considered as failed induction and acesarean was performed.

Side effects of the drug were evaluated in two groups, side effects such as uterine tachysystole (at least five uterine contractions in 10 minutes and excessive uterine stimulation)with changes in heart rate of the embryo in the form of bradycardia (fetal heartbeat which is less than 110, or late deceleration or the lack of variation in the beat-to-beat interval) and gastrointestinal complications including nausea, vomiting, diarrhea, fever and headache. Also, fetal heart rate, meconium excretion, fetal death, first and fifth minute Apgar scores, and the need to NICU were compared in two groups.After collecting the required data, the data were analyzed by using SPSS software version 13 and use of chi-square test and student's T-test. Consideredsignificant levelto theinterpretation of the results was 0.05.

III. Results and Discussion

The mean age, parity, gestational age and BMI were same in two groups (P> 0.05). Table 1 shows Bishop scoremeans before and after the intervention (P> 0.05). Of course, Bishop score was lessin thesublingual groupafter little intervention (table 2). There was no significant differencebetween the two groups in the number of doses of misoprostol (Table 2).

Table 1 Frequency distribution of demographic variables in two studied groups

Variable and group	Mean	Standard deviation	P*
Age(year)			
Vaginal	25.56	2.54	> 0.05
Sublingual	26.33	3.96	
Parity			
Vaginal	1.03	0.94	> 0.05
Sublingual	0.91	1.03	
Gestational age (week)			
Vaginal	40.21	1.32	> 0.05
Sublingual	39.92	1.63	
BMI (kg/m^2)			
Vaginal	28.35	3.98	> 0.05
Sublingual	27.86	2.05	

*T-test and p>0.05 is statistically significant.

Table 2 Frequency distribution of maternal complicationsin two studied groups

Variable and group	Mean	Standard deviation	P
Bishop score (at the time of admission)			
Vaginal	3.68	1.31	> 0.05*
Sublingual	3.87	0.75	
Bishop score (6 hours after misoprostol)			
Vaginal	5.67	2.07	> 0.05*
Sublingual	5	2.85	
The time of onset of pain (minute)			
Vaginal	42.06	23.62	> 0.05*
Sublingual	39.94	23.46	
The time interval between pain and delivery (hour)			
Vaginal	11.19	2.05	> 0.05*
Sublingual	11.06	3.6	
The types of delivery			
Vaginal	Natural childbirth	43.2%	> 0.05**
Sublingual	Natural childbirth	34.4%	
The most common complication			
Vaginal	Headache	6.4%	> 0.05**
Sublingual	Headache	4.8%	
Tachysystole			
Vaginal	0	-	-
Sublingual	0	-	

*t-test and p>0.05 is statistically significant.

**Chi-square test (x^2) and p>0.05 is statisticallysignificant.

Table 3 Frequency distribution of doses of misoprostolin two studied groups

Doses	Sublingual misoprostol	Vaginal misoprostol
	Number (percentage)	Number (percentage)
25 microgram (1 dose)	28 (22.4%)	30 (24%)
50 microgram (2 dose)	27 (21.6%)	31 (24.8%)
75 microgram (3 dose)	24 (19.2%)	22 (17.6%)
100 microgram (4 dose)	46 (36.8%)	42 (33.6%)
	125	125

Table 4 showsthe average Apgar scores at the first and fifth minutes and fetal weightat the onset of the pain and the interval between the beginning of labor in the two groups were the same in the two groups (Table 4) (P> 0.05). There was aneed to NICU for 15 newborn babies (12.4%) in vaginal method and for 20newborn babies (16.4%) in thesublingual method so there was no significant differencebetween the two groups (P>0.05).Complications such as headache, nausea,and bleeding were seen in 22 women (86.4%) in vaginal method and 20 women (18%) in thesublingual method. There was notstillbirth and

meconium excretion by embryo in the two groups. In both groups, the frequency of death and fetal distress was zero and the most common side effects were headache and nausea.

Table 4 Frequency distribution of the average Apgar scores at the first and fifth minutes in two studied groups

Variable and group	Mean	Standard deviation	P
Fetal weight (gram)			
Vaginal	3449.53	332.19	> 0.05*
Sublingual	3387.58	424.6	
Apgar scores at the first minutes			
Vaginal	9.17	0.37	> 0.05*
Sublingual	9.15	0.64	
Apgar scores at the fifth minutes			
Vaginal	9.61	0.49	> 0.05*
Sublingual	9.66	0.47	
Fetal distress			
Vaginal	0	-	> 0.05**
Sublingual	0	-	
Meconium excretion			
Vaginal	0	-	> 0.05**
Sublingual	0	-	
Stillbirth			
Vaginal	0	-	> 0.05**
Sublingual	0	-	
Need to NICU			
Vaginal	10.4%	-	> 0.05**
Sublingual	14.4%	-	

*t-test and p>0.05 is statistically significant.

**Chi-square test (x^2) and p>0.05 is statisticallysignificant.

Our study was carried out on pregnant womenwho were labor induction in Bu-Ali hospital in Tehran during the years 2012-2013 that results showed that there was no significant difference between the two groups in terms of efficacy and maternal and fetal complications (P> 0/05). In addition, there was notstillbirth and meconium excretion by embryo in the two groups.

A study was conducted in the United States in 2010 by Schaff, 14 women were prescribed 800 mg ofsublingual misoprostol or buccal, and the plasma concentration of the drug, its half-life and the time to reach the peak of concentration were measured. The results show that two women ofthepatients, whoused sublingual misoprostol, got severe cramps. Also, plasma concentrations in the sublingual method were higher than the buccal method. In general, thebuccal method was more acceptable in patients. However, in our study, none of the patientsdidnot haveabdominal cramps, which was probably due tousing a low dose in compare withScoff's research.In a study which was conducted by Wolf in the United States in 2010, 220 women were randomly prescribed either of 55 or 100mgof sunlingual misoprostal to labor induction. In this study, tachysystole was more in the group who used 100mg of this drug and there was aneed to induction in 61 percents of pregnants that used 100mg of the drug and in 82 percents of pregnants that used 55mg of the drug.But tachystrophy was not observed in our study,the possible reason for that wastheuse a low dose in compare with Wolf's research.In Elhassan's research in Sudan in 2007, 150 pregnants were selected and subdivided into 3 groups. The first group took 55 mg dose of sublingual misoprostol, thesecond group took 55 mg dose of oral misoprostol and the last group took 55 mg dose of vaginal misoprostol. Then the need to cesarean, the need to NICU for the newborn, and the meconium excretion in the three groups were compared. The need for cesarean in vaginal method was 64.5%, in oral method was 29.3% and in sublingual method was 18.2%. The need for NICU in our study was less than this study. In Bartusevicius's research, vaginal and sublingual misoprostolfor labor induction was compared.86 percent of pregnant women in thesublingual method havenatural childbirth and 78percent of pregnantwomen in thevaginal methodhave anatural childbirth.The prevalence of tachysystole in the sublingual method was three times higher than vaginal method, but there was no significant difference. In addition, the time interval between induction and delivery in the sublingual method was shorter than vaginal method, and also the fetal complicationsdidnot differ between the two groups, the results of this study are quite similar to our study.

In Feitosa's study, 155 pregnants in two groups were compared that one group received 25 mg of sublingual misoprostol and vaginal placebo and othergroup received 25 mg ofvaginalmisoprostol and sublingual placebo that 57% of sublingual misoprostol group and 69% of vaginal misoprostol group have anatural childbirth. There was fetal distress in 15 percent of thesublingual group and 5 percent of thevaginal group, but there was not asignificant difference between the time interval betweenfirst does and delivery and these results were similar to our study. In Shetty's research, 270 pregnant were divided in two groups that one group took 55 mg sublingual misoprostol and another group received 100 mg oral misoprostol that 62.7% of sunlingual method and 59% of oral method have natural childbirth and the time

interval between induction and delivery in subligual and oral method were 23.8 and 24.1 hours, in respect. There was not excessive stimulation of the uterus in two groups. In the other study, Caliskan divided 85 pregnant womeninto two groups and one group received 55 mg vaginal misoprostol and another group took 55 mg sublingual misoprostol that during 24 hours, 92.5% of sublingual method and 94.3% of vaginal have natural childbirthand the time interval between induction and delivery in subligual and oral method were 711 and 748 minutes and 17.5% of women in the sublingual method and 3.8%. of women in the vaginal method experienced tachysystole. But in our study, the number of natural delivery was less than the mentioned research. In Zahran's study, 500 pregnants were divided in two groups that one group took 55 mg sublingual misoprostol and another group received 55 mg vaginal misoprostol that during 24 hours, 72.4% of sublingual group and 69.7% of vaginal method have natural childbirth andmeconium excretion was reported in13.8% of sublingual group and 17.3% of vaginal group. In Karsidag's study, 51 women were divided into two groups: one subgroup took 200mg subgroup misoprostol and one group received 200mg vaginal misoprostol. The interval between the beginning of labor and induction in the sublingual misoprostol group was shorter than vaginal misoprostol but this difference was not statistically significant.However in our study, the interval between the beginning of labor and induction in the sublingual misoprostol group was shorter than vaginal misoprostol, but this difference was not statistically significant. In another study in Lebanon in 2009, Nassar divided 180 women into two groups, one group of them took 55 mg sublingual misoprostol and another group recieved 55 mg vaginal misoprostol, during 24hours,natural childbirth, and maternal and fetal complications were same in both groups. The most important point was that women had the lower pain during the pelvic exam. Of course, in our study similar to the mentioned study, maternal and fetal complications were same in both groups. In Marzouk's study, 29 women were divided into two groups, one group took 55 mg sublingual misoprostol and another group received 55 mg vaginal misoprostol group, during 24 hours, natural childbirth and maternal and fetal complications were same in both groups. Of course, in our study similar tothe mentioned study, maternal and fetal complications were similar in both groups. In the study of Zein, 45 pregnants in one group took 100 mg sublingual misoprostol and in another group 100 mg vaginal misoprostol that during 48 hours, maternal and fetal complications were similar in both groups.In our study of the mentioned study, maternal and fetal complications were similar in both groups.

Overall, based on the results of this study, it is concluded that there is no difference between the two sublingual and vaginal misoprostol in the aspects maternal and fetal complications. Therefore, each of them can be used according to the condition of the pregnant andthe doctor's opinion.

IV. Conclusion

Various therapies are used forlabor induction, including misoprostol.Because of the importance of the subject and the lack of a similar study in Iran, the effect of sublingual and vaginal misoprostolin theinduction of labor in term was compared.This is a double-blind randomized clinical trial. 270 pregnant in a hospital in Tehran during the years 2012-2013 were randomly divided into two groups. One group received 27mg vaginal misoprostol and oral placebo and other group received 27mg oral misoprostol and vaginal placebo. The embryonic and maternal complications and the bishop score, and the time of onset of pain and the time between labor pain and delivery were evaluated in two groups.

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