ORIGINAL ARTICLE

Effectiveness and Safety of Sublingual versus Vaginal Misoprostol for Induction of Labor for Full Term Pregnant Women in Cha-Am Hospital

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Objective: To study the effectiveness and safety of sublingual misoprostol compared with the same dose administered vaginally every four hours for induction of labor at term pregnancy within 24 hours.

Materials and Methods: One hundred seventy-six pregnant women of 37 to 42 gestational age fulfilling the study inclusion criteria were recruited and assigned by randomization into two groups. Each group was treated separately by 25-mcg misoprostol sublingually or vaginally every four hours within 24 hours.

Results: Mean age of sublingual and vaginal misoprostol group was 25.9±6.9 and 25.5±7.2 years old, respectively, while the mean parity of sublingual and vaginal group was 0.9±1.0 and 1.0±1.0, respectively, which most were first pregnant. Three out of four had no underlying diseases. The initial cervical diameter before receiving misoprostol was 1.7±1.0 and 1.7±0.9 mm, respectively. The total labor time between the two groups was not significantly different. The percentage of success in the sublingual group was more than in the vaginal group, at 79.3 and 74.7, respectively. The side effects of induction were more significantly found in the vaginal group ($p<0.05$). The pain score was not different, but the satisfactory score was better reported in the sublingual group than in the vaginal one ($p<0.05$). The Apgar score at 5 minutes of neonates between the two groups were not significantly different (9.8±0.4 and 9.9±0.2).

Conclusion: Twenty-five mcg misoprostol administered through sublingual for labor induction in full term pregnant women could not make the total labor time significantly shorter than in the vaginal group. The success rate in the sublingual group was not significantly better than in the vaginal group. The satisfaction was higher in the sublingual group but the pain scores and Apgar score at 5 minutes were not different between the groups.

Keywords: Induction of labor; 25-microgram misoprostol; Sublingual and vaginal route; Success; Crisis situation

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The induction of labor (IOL) is normally implemented in case of cervix unripening in a proper time[1]. Risks to the pregnant women or fetuses while giving birth may be caused by the medical and health service system, especially a shortage of the health care resources[2,3].

Health care provider shortage in Thailand was more serious during the COVID-19 pandemic[4]. When COVID-19 started, the disease precautions were unclear. The medical management for reducing infection for both clients and providers was urgently set. While the full-term pregnant women conveniently got services at a time, the providers had to be ready and have staff sufficiency. Moreover, prolonged prenatal stage may increase the risk of infection, thus, it should be shortened as much as possible. Therefore, a technique of cervical ripening was needed. The dosage and route recommended by the World Health Organization (WHO)[5] had to be considered.

The misoprostol tablet is soluble and can be dissolved within 20 minutes under the tongue. The absorption kinetics through sublingual has a shortest time to peak concentration[6]. Its acid is rapidly metabolized by the liver and excreted by the kidneys[7,8]. Using misoprostol for IOL fluctuated. A systematic review concluded that a 25-mcg starting dose may be good for balancing efficacy and safety[9]. Recently in Thailand, a 25-mcg oral dose every two hours until 50 mcg, then every four hours was applied[10], while in Brazil, they administrated 12.5-mcg sublingually or 25-mcg vaginally[11].

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The present study was to compare giving 25 mcg misoprostol doses sublingually or vaginally every four hours for IOL in full-term pregnancy for effectiveness and safety.

Materials and Methods

The present study was a double-blinded randomized controlled clinical trial (RCT)[12] conducted between October 2022 and June 2023 at the in-patient labor room of Cha-Am Hospital. The sample size calculated by G*Power version 3.1[13] at power of test 0.95 was 176. They were randomly divided into two groups of 88 cases each as sublingual misoprostol and vaginal misoprostol group. Term pregnancy women gestational aged 37 to 42 weeks with single viable fetus were the inclusion criteria for IOL. The exclusion criteria were previous uterine scar, non-vertex presentation, non-reassuring fetal status, fetal anomalies, fetal growth restriction, tumors, malformations and/or ulcers of vulva, perineum, or vagina, and allergy to misoprostol.

The participants received service at the first stage as normal routine procedure for assessing and recording the wellbeing of both pregnant women and fetuses. They were informed about the research process to make the decision to co-operate or discontinue. They gave informed consents prior to the start. A nurse permitted them to choose between the sublingual or vaginal group. This stage was cared for by a nurse, and the obstetrician was unaware of which medication was allocated to whom.

A modified Bishop's score[14], obtained through palpation, was immediately evaluated by the obstetrician before the induction. Then they received 25 mcg misoprostol in concealed envelope from the nurse, which was administrated sublingually or vaginally every four hours until giving birth or within 24 hours. At the first dose, and during first four hours, they were evaluated for the first stage of labor progression and cared for the effectiveness and safety of both pregnant women and their fetuses for vital sign, uterine contraction, hyper stimulation, fetal heart sound, and pain scale. Parenteral analgesia would be provided for the pregnant women with a pain score of more than 8. The Bishop score was assessed a second time when finishing the fourth hour. If the score was greater than 6 or the cervical ripening and cervix dilatation progressed well, a second dose was considered unnecessary. On the other hand, if the score was less than 6, another 25-mcg misoprostol dose was given. This was continued every 4 hours and both the pregnant women, and their fetuses were cared for effectiveness and safety. After twenty-fourth hour, the obstetricians would stop IOL, assessed the progression, signs, and symptoms, and share their with opinion with the pregnant women to decide about vaginal delivery. In those cases, other methods were considered for labor augmentation. These might be oxytocin infusion, amniotomy or both.

The total labor time and success rate of using 25 mcg misoprostol in those without any labor augmentation was evaluated. Side effects, complications in mother and fetus/newborn, pain and satisfactory scores were considered to answer the research questions. SPSS Statistics, version 13.0 (SPSS Inc., Chicago, IL, USA) was used for the statistical analysis. Means of dependent variables were compared between groups by using t-test as a parametric test while the chi-square was used to test the frequency of the categorical variables. The p-value of less than 0.05 was considered as significant. The percentage was also calculated for variables that could explain the main research results.

The research proposal was approved by Phetchaburi Provincial Public Health Office Ethics Review Committee (PBEC No. 06/2565).

Results

One hundred seventy-six term pregnancy gestational aged 37 to 42 weeks met the inclusion criteria and were induced to labor. They were randomly divided into two groups, each with eighty-eight persons but one of each person in each group discontinued the intervention (Figure 1). There were no statistical differences between the two groups regarding maternal and obstetrical characteristics such as mean age, mean body mass index (BMI), gravidity, parity, gestational age, mean age of the last child, education level, and economic status. Details are shown in Table 1.

The mean initial cervical diameters, at first admission of the sublingual and the vaginal group, were 1.8±1.0 and 1.7±0.9 cm, respectively. The cohort with the Bishop Score 6 or less was started for cervical ripening. The mean total time of labor was 8.7 hours while the longest was 13.8 and the shortest was 2.1 hours. The total time of labor between the two groups was not significantly different. The percentage of success in the sublingual group was more than in the vaginal group, at 79.3 and 74.7, respectively (Table 2, Figure 1). The patients who received augmentation by oxytocin infusion and amniotomy, which was 12% and 11% in the sublingual and in the vaginal group, respectively, were excluded from

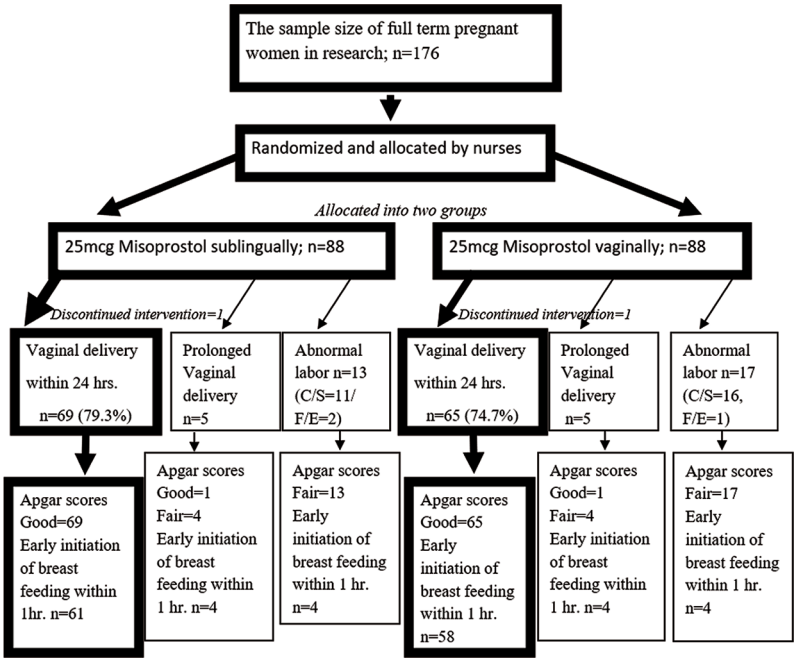

Figure 1. Research procedure and results.

Table 1. Pregnant women demographics data divided to the route of misoprostol administration

	Sublingual (n=87)	Vaginal (n=87)	p-value
Age (years); mean±SD	25.9±6.9	25.8±7.2	0.96
Education level; n (%)			0.09
Uneducated	4 (4.64)	5 (2.9)	
Primary school	11 (12.6)	26 (14.9)	
Secondary school	36 (41.4)	64 (36.8)	
High school	22 (25.3)	57 (32.8)	
Bachelor	14 (16.1)	22 (12.6)	
Occupation; n (%)			0.77
Non or housework	37 (42.5)	41 (47.1)	
Farmer	2 (2.3)	1 (1.1)	
Private business	10 (11.5)	8 (9.2)	
Employee	35 (40.2)	36 (41.4)	
Government office	3 (3.4)	1 (1.1)	
BMI (kg/m^2); mean±SD	29.2±5.4	33.6±5.1	0.28
Gravidity; mean±SD	1.9±1.1	2.0±1.1	0.41
Parity; mean±SD	0.9±1.0	1.0±1.0	0.60
Nulliparity; n (%)	35 (41.6)	32 (38.1)	
Multiparity; n (%)	49 (58.4)	52 (61.9)	
Gestational age (weeks); mean±SD	39.05±0.38	39.09±0.38	0.14
Age of last child (years); mean±SD	1.5±3.1	2.3±3.6	0.13
Underlying diseases; n (%)			
DM, HD, coagulopathy	4 (4.6)	1 (1.1)	
None	83 (95.4)	86 (98.9)	

SD=standard deviation; BMI=body mass index; DM=diabetes mellitus; HD=hemodialysis

Table 2. Cervical dilatation before induction, success of labor and total time of labor

	Sublingual (n=87)	Vaginal (n=87)	p-value
Cervical dilatation before induction (cm); mean±SD	1.8±1.0	1.7±0.9	0.87
Total time of labor (hours); mean±SD	11.7±6.7	10.6±7.0	0.30
Success of labor; n (%)			
Yes	69 (79.3)	65 (74.7)	0.47
No	18 (20.7)	22 (25.3)	

SD=standard deviation

the success group. In the cohort with unsuccessful delivery, some delivered by normal vaginal delivery but took longer than 24 hours. However, most delivered by caesarean section (CS). A few had forceps extractions (Figure 1).

The general and obstetrical variables that could explain the main research results in both groups were found as follows. The higher percentage of success in labor induction was on mothers aged 20 to 34 years old. Many unsuccessful cases were found in teenage mothers. The least success was found in obese mothers with a BMI of 30 kg/m² or above. Mothers that had previous pregnancies were more successful in labor induction than the newer mothers. However, the group comparison revealed no significance.

The side effects that occurred in all pregnant women of the two groups only involved abdominal

Table 3. Side effects, complications, pain scores, satisfactory scores, and Apgar scores between sublingual and vaginal group

	Sublingual (n=87)	Vaginal (n=87)	p-value
Side effect; n (%)			
Nausea	0 (0.0)	0 (0.0)	
Vomiting	0 (0.0)	0 (0.0)	
Fever	0 (0.0)	0 (0.0)	
Diarrhea	0 (0.0)	0 (0.0)	
Abdominal pain	87 (100)	87 (100)	
Headache	0 (0.0)	0 (0.0)	
No	0 (0.0)	0 (0.0)	
Complication; n (%)			
Pregnant women or mother			0.31
• Uterine hyper-stimulation	0 (0.0)	1 (1.1)	
• Uterine rupture	0 (0.0)	0 (0.0)	
• No complications	87 (100)	86 (98.8)	
Pain score; mean±SD	6.2±1.7	6.4±1.4	0.50
Satisfactory score; mean±SD	9.2±0.8	8.9±0.7	0.01
Apgar score at 5 minutes; mean±SD	9.8±0.4	9.9±0.2	0.30

SD=standard deviation

pain. However, there was one subject in the vaginal group who had a uterine hyper-stimulation during the induction but there was no uterine rupture or other complication in both mothers and fetuses and newborn infants. The mean pain score between induction of the sublingual and vaginal groups was 6.2±1.7 and 6.4±1.4, respectively. The side effects, complication, and pain scores that occurred during and post inductive process in both mother and child were not different. The only significant difference was found on the mean satisfactory score. The sublingual group was significantly more satisfied than the vaginal group at 9.2±0.8 and 8.9±0.7, respectively (Table 3). The early outcomes seen from the Apgar scores at five minutes of the success groups, in both the sublingual and vaginal groups, showed no difference and both groups were in good condition. In the unsuccessful group, with prolonged vaginal delivery and abnormal labor group, the Apgar scores of most were fair. The later outcome of mothers and infants saw an early initiation of breastfeeding within one hour in the two success groups of 88% and 89%, respectively. However, in the prolonged vaginal delivery, the success was lower, and in the abnormal labor group it was the lowest (Figure 1).

Discussion

The shortage of staff and medical resources occurred seriously during COVID-19 pandemic. It forced the obstetrics and gynecology department to provide care as in a crisis mode. The pregnant mothers and babies had to receive quality service under the highest strict prevention of disease transmission. Strategies had to be created in time of disease pandemic and for driving in the future. Therefore, intervention must be researched and redesigned to manage a service in crisis and to find the better choices.

The author, the only one obstetrician of a middle-size community hospital, needed to find a care process for the full-term pregnant women to have effective and safe procedure for them and their babies in all stages of labor, while the health care teams should be protected and safe from the infection. The IOL was performed by the health care team and health resources in all relevant sectors available in the community hospital during the COVID-19 outbreak. Marconi concluded from their review that IOL requires a range of human resources, services, monitoring, and interventions that all should be available for conducting elective IOL safely[15]. Therefore, the present finding could be applied to adjust a future rule and hospital's policy for the next disease outbreak.

The present study's pregnant women were divided into two groups, one who received 25 mcg misoprostol sublingually and the other who received 25 mcg misoprostol vaginally. This dosage was the lowest by WHO's recommendation and most used to induce labor[11]. This dosage was convenient. It could be done by dividing one tablet of 100 mcg, which is available in Thailand, into four parts, thus one fourth (1/4) of one tablet. However, the dosage and time found in the other research were varied, such as 12.5 mcg sublingually versus 25 mcg vaginally every six hours[11]. Researchers administrated 10 to 25 mcg or up to 50 mcg[10], and some administrated up to 800 mcg within 24 hours[16]. The systematic reviews showed that the dosages and frequency were varied. However, from most findings, it can be concluded that a starting dose of 25 mcg may offer a good balance of efficacy and safety[9].

The present research showed that the success of labor induction, within 24 hours after providing the first dose of misoprostol was better in the sublingual group than in the vaginal group, at 79.3% versus 74.7%, but did not reach statistical difference. The research of Chantrarangsan administrated the same dose and route but studied in post-term pregnant women. It was found that spontaneous vaginal delivery was at 75.0% and 78.1% sublingually and vaginally, respectively[17]. The success rate found in

the research of Ifarinola et al., which applied the same dose, period, and route, showed the vaginal delivery at 90% sublingually and 94% vaginally. However, these rates were with augmentation at 6.5±1.4 and 8.7±3.4 hours, respectively, from the starting dose to augmentation[16]. The study of Pradutchon et al., applying 25 mcg every two hours until 12 doses within 24 hours, then on the second day, 50 mcg every four hours, found lower achievement in vaginal delivery within 24 hours at 41.4% though the cervical ripening could be highly accomplished at 88.3%[10]. The same dose of 25 mcg, administrated constantly every two hours orally, studied by Wallstrom et al. found the success rate of vaginal delivery within 24 hours at 60%[18].

The mean gestational age of this cohort was 39 weeks, which the finding from systematic review and the meta-analysis by Anna Maria Marconi found no effect of elective IOL in gestational age between 39 and 41 weeks. However, in cases of shorter of longer gestation, the outcomes were worse[15]. Likewise, Wallstrom et al. found that in applying 25 mcg every two hours constantly orally, the CS was less in gestational age of 41 weeks than in over 41 weeks[18]. The present study found the success rate in more gravidity was higher than the less gravidity. Similarly to Wallstorm et al finding that the CS in primiparous women was higher than in multiparous[18].

Though the present study found that having a BMI of 30 kg/m² or above was not statistically significant, it was the less successful. The systematic review by Marconi showed that BMI was one factor that associated with the success of the induction, which the obese women took longer than the women with normal weight[15]. Similarly to the finding of Carlhäll et al. found that there was effect of maternal BMI on duration of induced labor that the women with BMI of 40 kg/m² or more had longer duration of labor and more CS[19]. Therefore, these factors that relate to the success of IOL with spontaneous vaginal delivery should be studied further.

The complication, uterine hyper-stimulation, found in the presented research was only one case in the vaginal group. In the study mentioned above, 98% and 94% of the sublingual and the vaginal group respectively did not have any complication[16]. Noteworthy consideration in the research that compare 12.5 mcg sublingually versus 25 mcg vaginally, it was found that the frequency of tachysystole was significantly lower in the sublingual group while the mean time between the first dose and delivery, and the caesarean rates were similar in both groups. A systematic review showed that the risk in the tachysystole was greater in the sublingual group that administrated a dosage of more than 12.5 mcg. The complication was on dose dependence, combining with the pharmacokinetic reason that oral and sublingual misoprostol are more rapidly absorbed than using the vaginal route[11,20].

The present study showed statistical significantly higher in satisfactory scores in the sublingual group than in the vaginal group, which complied to most research that showed that administrating sublingually was more convenient, and the patients had a higher satisfaction score than the administration via vagina, though, not statistically different[11,16,21]. Moreover, the women may reject the repeated vaginal examination[20].

The present study showed the newborn outcome condition by the Apgar score at 5 minutes of most of the success groups were on good condition. This score rate was similar to the study of Ifariola et al[16]. Then, the later outcome from the early initiation of breastfeeding within one hour, the present study saw a success rate of 90%. The finding by Andrew et al. found only in-labor CS was the strongest predictor of formula supplementation in hospital followed by pre-labor CS, epidural analgesia, and oxytocin infusion. There was no effect of IOL to breastfeeding in case of normal labor[22].

Conclusion

IOL with 25 mcg misoprostol for the pregnant women, gestational aged at 39 weeks, on the latent stage of labor or before the labor began spontaneously could be effective and safe for mothers and infants and the mothers' satisfaction.

What is already known on this topic?

The medical criterion of labor induction is mostly indicated on the first stage of labor with the Bishop score 6 or less with recommended dose of 25 mcg, orally or vaginally.

What does this study add?

Providing 25 mcg misoprostol at full term pregnancy before the labor onset can be an effective IOL in three out of four pregnant women promoting spontaneous vaginal delivery within 24 hours that is safe and effective for mother and infants.

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Conflicts of interest

The authors declare no conflict of interest.

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