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Intravaginal misoprostol versus sublingual misoprostol for second trimester pregnancy termination: a randomized controlled trial

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Objective: To compare the efficacy and adverse effects of 400 mcg misoprostol for second trimester pregnancy termination via the intravaginal or sublingual route. *Methods*: In this study, 170 women at GA 14-28 weeks underwent termination of pregnancy. They were randomized to receive either intravaginal or sublingual 400 mcg misoprostol at 6 hour intervals until fetal expulsion occurred or within 48 hours after the initiation of the first dose of misoprostol. The primary outcomes were median abortion time and percentage of failure. The secondary outcomes included rates of maternal adverse effects, oxytocin use and analgesia requirement. *Results*: Intravaginal misoprostol demonstrates significantly greater efficacy for pregnancy termination compared to sublingual misoprostol at the same dosage. The median time to abortion was 16.66 hours and 22.88 hours in the intravaginal group and sublingual group respectively. Maternal adverse effects, specifically rate of chill and diarrhea, were statistically higher in the sublingual group. *Conclusion*: Intravaginal misoprostol was superior to sublingual misoprostol in terms of shorter abortion time and fewer adverse effects. In addition the rate of oxytocin use was found to be higher in the sublingual group. In conclusion misoprostol via the intravaginal route should be considered for second trimester pregnancy termination rather than the sublingual route due to greater efficacy and fewer adverse maternal effects.

Keywords

Intravaginal; Sublingual; Second trimester; Pregnancy termination

1. Introduction

Several techniques have been used in termination of pregnancy (TOP) including both surgical and medical approaches. Dilation and evacuation (D&E) is one of the preferable methods for early second trimester TOP due to much shorter and predictable time for abortion, as well as lower rate of incomplete abortion in comparison to medical abortion [1, 2]. On the contrary, D&E is invasive, possibly resulting in birth canal injury, needs experienced personnel and more hospital facilities [2]. Therefore, medical abortion, especially with the range of prostaglandins available, is currently more popular due to its high level of effectiveness and the fact it is less invasive.

Misoprostol, a prostaglandin E1 analogue plays an important role in pregnancy termination in all trimesters. Even though the primary objective for misoprostol is prevention of gastric ulcer caused by NSAIDS use, it has a concomitant effect of cervical ripening and myometrial contraction. Currently, misoprostol has become widely accepted as an effective medication for TOP. Usefully it has the attractive properties of stability at room temperature and low cost.

Although various regimens and routes of misoprostol administration in second trimester TOP have been extensively explored, the most appropriate still need to be established. One accepted method is 400 mcg delivered intravaginally every 3-6 hours [3–5]. However the sublingual route has become increasingly popular for second trimester TOP because of its convenience in drug administration and higher levels of patient satisfaction than the vaginal route. The pharmacokinetics of sublingual misoprostol contribute to an outstanding profile due to a higher peak concentration and shorter time to peak drug concentration when compared to vaginal administration [6]. Nevertheless, few studies have aimed to compare the efficacy of the intravaginal and sublingual routes, therefore we conducted this study to increase knowledge surrounding this. The focus of the study was the efficacy in terms of induction of abortion time by misoprostol alone between the intravaginal route and sublingual route at the same dosage of 400 mcg for second trimester pregnancy termination in live fetuses.

2. Materials and methods

This study was undertaken at a tertiary teaching hospital (Department of Obstetrics and Gynecology, Chiang Mai University, Thailand). All subjects gave their informed consent for inclusion before they participated in the study and the protocol was approved by the Research Ethics Committee, Faculty of Medicine, Chiang Mai University (Reference No 3975).

The sample size was calculated based on previous data of the induction abortion time of the intravaginal misoprostol of the same regimen [3] and the prediction of the difference in abortion time between intravaginal route and sublingual route with 95% confidence interval, 80% power with a failure

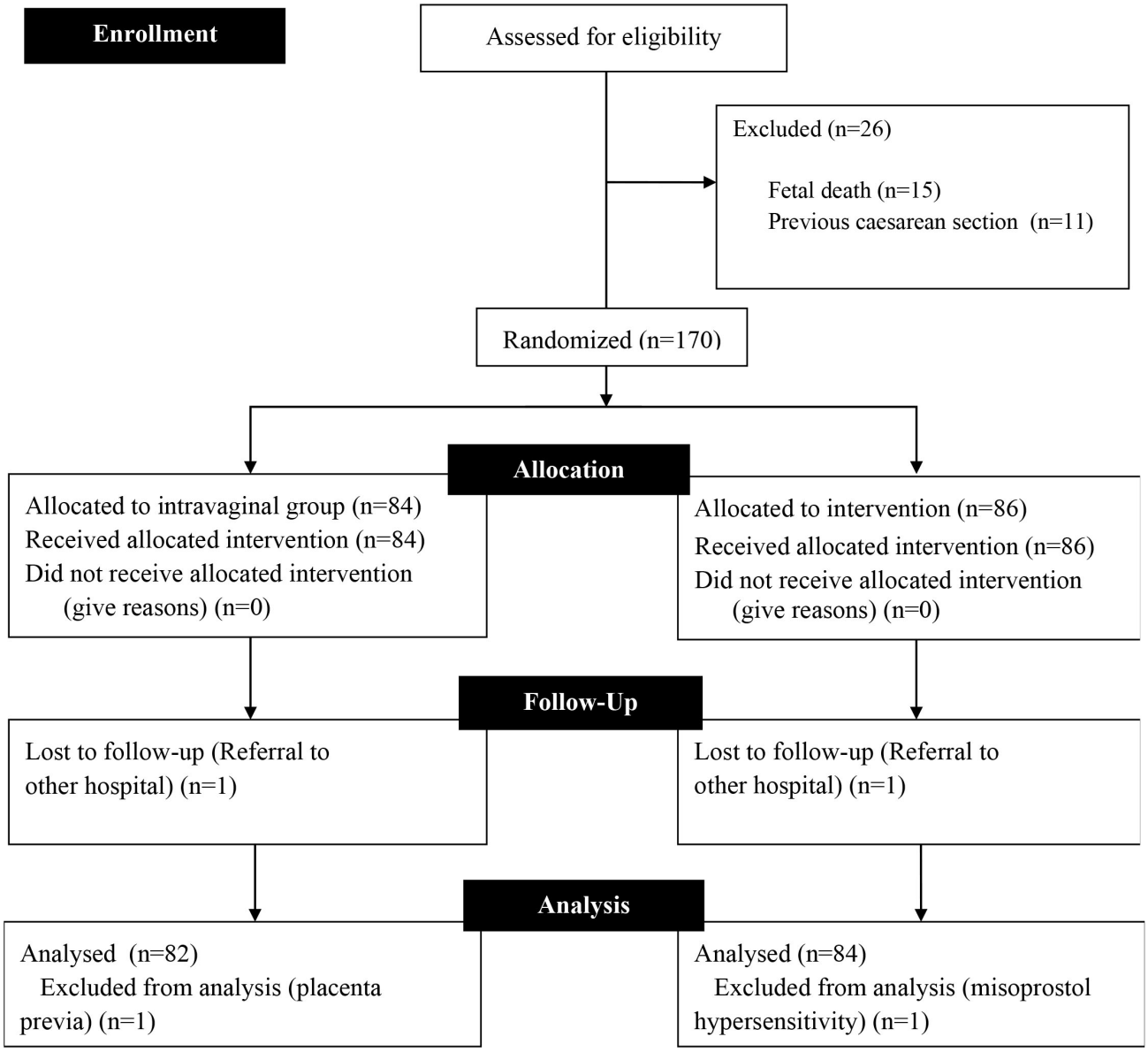

Fig. 1. CONSORT Diagram.

rate estimation of 10%. The recommended sample size was 56 subjects in each group.

The participants were pregnant women with indications for TOP including fetal lethal anomaly, severe fetal thalassemia or maternal indications. They were invited to participate in the study and following appropriate professional information gave their written consent. The inclusion criteria were as follows: 1) singleton pregnancies; 2) gestational age of 14-28 weeks based on reliable last menstrual history and fetal sonographic biometry in the first half of pregnancy; 3) live fetuses; 4) Bishop score of 4 or less; 5) no history of previous uterine surgery such as cesarean section or myomectomy; and 6) no contraindication for misoprostol use. Exclusion criteria included: 1) receiving other forms of TOP or undergoing feticide before or during the process of TOP; 2) spontaneous labor before starting misoprostol; 3) drug hypersensitivity occurring during TOP; and 4) incomplete data or unknown final outcomes.

The participants meeting the inclusion criteria were allocated by block computer-generated randomization to receive 400 mcg (2 tablets) of misoprostol by either the intravaginal or sublingual route at intervals of 6 hours (Fig. 1). The random numbers were sealed and provided to attending physicians at the time of recruitment in which the physicians did not know what regimen would be selected. However, all participants and all health care providers were finally unblinded to the regimens. In the intravaginal group, misoprostol was moistened with 1 ml of 5% acetic acid before vaginal insertion but in the sublingual group nothing was added. After the initial dose, misoprostol was then repeated at intervals of 6 hours if abortion did not occur, adequate uterine contraction was not established or no cervical progression was

found. In cases of adequate uterine contraction or significant cervical progression, the next dose was omitted as a precaution against uterine rupture. In some cases, repeat treatment with misoprostol may have been necessitated at the same time interval after previous omission due to slowing or inadequate uterine contraction and inadequate cervical progression or no cervical progression at all. Participants defined as skipped dose meant that they had received misoprostol again at any time in the dose schedule before fetal delivery. It is widely accepted procedure that misoprostol can be repeated until 48 hours after the initial dose. During the process of TOP in both groups, intravenous oxytocin was occasionally used after stopping misoprostol to promote adequate uterine contraction. Intravenous 50 mg meperidine was given for pain relief as needed. Adverse effects of misoprostol including fever (T $>$ 38.0 °C), chill, diarrhea, nausea, and vomiting were monitored and recorded.

Successful abortion was defined as fetal expulsion occurring within 48 hours of administration of the first dose of misoprostol. In cases of failure, a repeated course of misoprostol or other methods of TOP such as infusion of high concentration oxytocin, modified condom balloon technique or intra-amniotic hypertonic saline infusion were invoked following guidance from the attending physicians.

The primary outcomes were median abortion time and percentage of failure (no abortion within 48 hours after the initial dose). The secondary outcomes included rates of maternal adverse effects, oxytocin use and analgesia requirements.

Statistical analysis was performed using the statistical package for social sciences (SPSS), software version 21.0 (IBM SPSS Statistics for Windows, Released 2012. Armonk, NY: IBM Corp). Comparisons of the continuous variables were made using the Student T test or Mann-Whitney U-test as appropriate. The categorical data were compared using Chi square test or Fisher's exact test. A *P*-value of < 0.05 was considered statistically significant.

3. Results

During the study, 170 women meeting the inclusion criteria were enrolled. Four patients were excluded for the following reasons: the need for referral to other hospitals as a consequence of health insurance coverage (2 cases), suspected of drug hypersensitivity to misoprostol without any serious consequences (1 case), and heavy vaginal bleeding caused by placenta previa totalis necessitating a hysterotomy (1 case). Data from the remaining 166 women, 82 in the intravaginal group and 84 in the sublingual group, were available for analysis.

Baseline characteristics of the patients in terms of maternal age, gestational age at the time of recruitment, Bishop scores and indications for TOP are presented in Table 1. There were no significant differences between the two groups, with the exception that the percentage of nulliparous women was significantly higher in the intravaginal group. The most common indications for TOP were fetal chromosome abnormalities or fetal anomalies followed by severe fetal thalassemia.

The median abortion time was significantly shorter in the intravaginal group when compared to the sublingual group (16.66 vs 22.88 hours, respectively), as presented in Table 2. Likewise, the placental delivery time was also shorter in the intravaginal group (17.17 vs 23.82 hours, respectively). The percentage of cases with failures tended to be higher in the sublingual group but the difference was not statistically significant (7.32% vs 15.48%). The rate of oxytocin use and the total dose of misoprostol use were significantly higher in the sublingual group.

Adverse effects of misoprostol were found to be more common in the sublingual group as shown in Table 3. Chill and diarrhea were significantly higher in the sublingual group than those in the intravaginal group (73.8% vs 36.6% for chill and 39.3% vs 15.9% for diarrhea, in the sublingual group and the intravaginal group, respectively). There were no significant differences in other adverse effects between the two groups.

After exclusion of the failed cases, the median abortion time in the intravaginal group was still shorter than that in the sublingual group (15.3 vs 21.0 hours, respectively; *P*-value 0.044).

4. Discussion

The results of this study demonstrates the efficacy of misoprostol alone without the need for priming with mifepristone, even though the combination of two drugs may give a better outcome. The reason behind the use of misoprostol alone was the lack of availability of mifepristone in Thailand.

This study demonstrated that, at the same dosage, intravaginal misoprostol was superior to sublingual misoprostol in terms of median abortion time and fewer adverse effects.

Whereas most baseline characteristics were comparable, the percentage of nulliparous women was slightly higher in the intravaginal group. However, this was judged unlikely to change our conclusion since parity has little or even a negative effect on misoprostol efficacy. If the comparable percentage of nulliparous was included in the analysis the abortion time in the intravaginal group would be even shorter, i.e. the efficacy would be greater.

Various regimens for the use of misoprostol have been proposed for TOP. Each has its own advantages and disadvantages in terms of success rates and adverse effects. Some authors suggest the regimen of 400 mcg misoprostol every 3 hours rather than 6 hours because of the higher efficacy for abortion [7]. However, in our experience, we have found the higher rate of skipping dose at the 3 hour interval and the cervical assessment every 3 hours is more distressing for patients. Therefore, we chose a 6 hour interval in this study but we still found a high rate of skipping dose (40% and 60% for the intravaginal group and sublingual group respectively). We could not ascertain exactly why the sublingual group had

Table 1. Baseline characteristics and indications for TOP.

Characteristics	Intravaginal misoprostol group (n = 82)	Sublingual misoprostol group (n = 84)	*P*-value
Mean maternal age (years)	30.41 ± 6.83	29.87 ± 7.22	0.624
Mean gestational age (weeks)	20.39 ± 3.03	20.35 ± 2.43	0.916
Parity%			
Nulliparous	56.4	43.6	
Parous	40.3	59.7	0.043
Bishop scores	1.26 ± 0.88-9	1.35 ± 0.93	0.527
Indication for TOP%			
Severe fetal thalassemia	37.8	28.6	
Fetal chromosome abnormalities or fetal anomalies	54.9	66.7	
Maternal indication	0	1.2	0.254
Other indications	7.3	3.6	

Table 2. Abortion profiles and total dose of misoprostol.

Profiles	Intravaginal misoprostol (n = 82)	Sublingual misoprostol group (n = 84)	*P*-value
Median abortion time (hours)	16.66	22.88	0.007
Median placental delivery time (hours)	17.17	23.82	0.008
Failure to abort within 48 hours	7.32%	15.48%	0.099
Oxytocin use	7.3%	20.2%	0.023
Analgesia requirement	35.4%	38.1%	0.749
Total dose of misoprostol (mcg)	1039.02 ± 707.94	1300.00 ± 811.66	0.029
Estimated blood loss (ml)	143.05 ± 116.36	152.50 ± 161.21	0.666
Skipped dose of misoprostol	40%	60%	0.113

a higher rate of skipping dose (with no statistical significance). It might be due to the higher rate of chill which may interfere with the action of the drug leading to misinterpretation of the more potent intensity of uterine contractions. In addition the skipping dose was deemed to be necessary due to the level of patient dissatisfaction with adverse effects (chill and diarrhea) and it was imprudent to give the scheduled dose at that time.

Intravaginal misoprostol is the most well established route of administration in clinical practice due to long-term experience and familiarity of use. However, pharmacokinetic studies have demonstrated that the sublingual route of misoprostol results in a higher peak of blood concentration than the other routes of administration and takes shorter time to reach the peak level than the intravaginal route [6]. Accordingly, the sublingual route theoretically provides the greater efficacy than the intravaginal route. To our knowledge, the studies comparing the efficacy between intravaginal and sublingual misoprostol for second trimester TOP are limited, the results of such studies also being relatively conflicting. For instance, Milani *et al.* [8], Rahimi-Sharbaf *et al.* [9] and Cabrera *et al.* [10] showed the better results with sublingual routes whereas Dickinson *et al.* [11], Tanha *et al.* [12], Bhattacharjee *et al.* [13], and Tang *et al.* [14] found the efficacy between the two routes to be comparable. Cabrera *et al.* [10] performed meta-analysis and suggested that further research is required to determine the efficacy, safety and optimal doses of sublingual and vaginal misoprostol for second-trimester TOP. Therefore, we conducted this study to compare the efficacy of the two routes at the same dosage and interval of drug administration.

Most aforementioned studies used 400 mcg misoprostol with interval of 3-4 hours and also included intrauterine fetal death (IUFD) in such studies [8, 9]. However some studies did not record the status of fetal life or did not included dead fetuses in the exclusion criteria [10–14]. As already known, fetal death could be a potent confounder and strongly impacts on shortening abortion time interval. Thus, to assess the most accurate efficacy of misoprostol regimens, the status of fetal life must be specified and the rate of dead fetuses must be comparable in the two groups. This is the reason why we did not include IUFD in this study. Possibly, the difference in this baseline characteristic might explain the different results. Likewise, the longer abortion time interval in our study was probably associated with fetal live status since this study included only live fetuses while the others did not exclude IUFD.

Our study protocol was similar to that reported by Tanha *et al.* [12] but the conclusion was different. While Tanha *et al.* [12] observed the same efficacy of the two routes, we found that intravaginal route gave a better results as mentioned above. Whereas the reason of the difference was unclear, it was possible that the addition of acetic acid in the intravaginal route before application in our study might be

Table 3. Adverse maternal effects associated with misoprostol and other complications.

Adverse effects or complications	Intravaginal misoprostol (n = 82)	Sublingual misoprostol group (n = 84)	*P*-value
Fever	43.9%	36.9%	0.429
Chill	36.6%	73.8%	0.0000
Nausea	8.5%	13.1%	0.455
Vomiting	4.9%	7.1%	0.746
Diarrhea	15.9%	39.3%	0.001
Postpartum hemorrhage	0.0%	4.8%	0.063
Curettage for incomplete abortion	14.6%	17.9%	0.675
Uterine rupture	0%	0%	-

associated with the greater efficacy. This is due to the fact that the acidified environment can enhance the dissolution of misoprostol [15]. Concerning abortion interval ,Tanha *et al.* [12] reported a shorter abortion interval than that found in this study. This was most likely due to the fact that IUFD was not excluded in that study [12].

In our study we found that the sublingual route results in more adverse effects including chill and diarrhea than the intravaginal route. The explanation for these phenomena is not well understood, but it might from the more rapid onset of action and a higher peak of blood concentration in the sublingual route.

Based on the findings of this study, the 6 hour interval of intravaginal misoprostol application is the preferred and recommended route. If our study had used a 3-hour interval instead of a 6-hour interval the sublingual route may well have given a greater efficacy than the intravaginal route since the sublingual route provides more rapid onset but shorter action than the intravaginal route. In the case of the intravaginal route, at the end of 6 hours an active metabolite of misoprostol still exists in situ at a higher level than the sublingual route [6]. Accordingly, the different outcomes of this study from the others might probably be associated with the difference in the interval of drug administration and fetal live status as mentioned above.

The weaknesses of this study are as follows: 1) The study could not blindly conducted. 2) There was a high rate of skipped doses. The skipped doses represent the actual practice and reflect the high sensitivity of the uterus to misoprostol which is necessary to skip dose to prevent potential risk of uterine rupture. However this weakness is unlikely affect the interpretation of the efficacy of misoprostol at all.

In conclusion, this study showed different results from other the previous studies. Intravaginal misoprostol moistened with acetic acid provided a greater level of efficacy for second trimester TOP than the sublingual route with the same dosage at a 6-hour interval. Additionally, the need for oxytocin use and the dose of misoprostol requirements was lower in patients in the intravaginal cohort. This group also exhibited fewer maternal adverse effects such as chill and diarrhea. Therefore, in second trimester TOP with a misoprostol dosage of 400 mcg at 6-hour intervals the intravaginal route is recommended rather than the sublingual route.

Author contributions

Saipin Pongsatha designed the reasearch, wrote the manuscript. Theera Tongsong analysed data and provided help and advice on the manuscript. All authors read and approved the final manuscript.

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Conflict of interest

All authors declare that they have no conflict of interest.

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