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Randomized controlled trial comparing efficacy between a vaginal misoprostol loading and non-loading dose regimen for second-trimester pregnancy termination

Saipin Pongsatha and Theera Tongsong

Department of Obstetrics and Gynecology, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand

Abstract

Aim: The aim of this study was to compare the efficacy of vaginal misoprostol loading dose regimen with non-loading dose regimen for termination of second-trimester pregnancy with live fetuses.

Material and Methods: A randomized controlled trial was conducted on pregnant women with a live fetus at 14–28 weeks. The patients were randomly allocated to receive either the vaginal misoprostol loading dose regimen (600 mcg, then 400 mcg every 6 h) or the non-loading dose regimen (400 mcg every 6 h). Failure to abort within 48 h was considered to be a failure.

Results: Of 157 recruited women, 77 were assigned to be in group 1 (loading group) and 80 were in group 2 (non-loading group). The median abortion time was not statistically different between the groups (14.08; 95% confidence interval: 12.45–17.77 h and 14.58; 95% confidence interval: 12.8–17.27 h, $P > 0.05$). The rates of abortion within 24 h and 48 h were also comparable between the groups. Fever and chills were more common in the loading group. No other serious complications, such as postpartum hemorrhage and uterine rupture, were found.

Conclusion: Vaginal misoprostol in the loading dose regimen had a similar efficacy to the non-loading dose regimen but was associated with more adverse maternal effects.

Key words: live fetus, loading dose, pregnancy termination, second trimester, vaginal misoprostol.

Introduction

Termination of a second-trimester pregnancy with a live fetus is a challenging procedure. Various methods,[1,2] either invasive or non-invasive, have been introduced to manage this issue. Several techniques for termination of second-trimester pregnancy have been used, including dilation and evacuation[3] and medical abortion. Medical abortion is the method of choice because most diagnoses are performed late in the second trimester and trained personnel capable of carrying out dilation and evacuation in late pregnancy are limited. Consequently, at the present time, prostaglandins (especially misoprostol) are the drugs of choice because of their efficacy, ease of administration and non-invasiveness.[4,5]

Various regimens of misoprostol use in terms of route, dosage, interval or combination of mifepristone have been tested to determine the optimal application in enhancing the efficacy of pregnancy termination. Some non-randomized controlled trials suggest that the combination of mifepristone with misoprostol have a very high efficacy for pregnancy termination.[6–9] Although there are some randomized control trials (RCT) in the recent literature showing that the combination of mifepristone and misoprostol is more

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Reprint request to: Professor Theera Tongsong, Department of Obstetrics and Gynecology, Faculty of Medicine, Chiang Mai University, Chiang Mai 50200, Thailand. Email: ttongson@mail.med.cmu.ac.th

effective,[10] mifepristone is illegal in Thailand and thus unavailable. Misoprostol is the most widely used medication for medical abortion in Thailand. Nevertheless, despite many studies on the most effective dose and timing interval, no consensus has been reached. The authors questioned whether the loading dose regimen promoted cervical change and facilitated uterine contractions better than the non-loading dose. Loading dose may have theoretical benefit, as the initial contraction may need a higher dosage than that in late labor. However, very few reports have explored this aspect. To the best of our knowledge, only a study reported by Dickinson and Evans[11] compared the abortion interval between a loading dose regimen and a non-loading one. The objective of this study was to compare the efficacy of the loading and non-loading regimen. However, the maintenance dose of misoprostol in this study was 400 mcg, which is more widely used, rather than 200 mcg, which was used in the study reported by Dickinson and Evans.[11]

Methods

This study was prospectively conducted with approval of the institutional review board (the Ethics Committee), at Maharaj Nakorn Chiang Mai Hospital, Chiang Mai University, Chiang Mai, Thailand between August 2009 and May 2012. Inclusion criteria were as follows: (i) singleton pregnancies with a live fetus; (ii) indicated for pregnancy termination due to either maternal or fetal conditions, such as lethal anomalies; (iii) gestational age of 14–28 weeks; (iv) no history of uterine scar, such as previous cesarean section, hysterotomy or myomectomy; (v) Bishop score of 4 or less; and (vi) no regular spontaneous uterine contraction before drug administration. The pregnant women were randomly allocated into two groups by block randomization (loading group vs non-loading group). Participants in the loading group first received a single dose of 600 mcg vaginal misoprostol as a loading dose, followed by administration of 400 mcg vaginal misoprostol every 6 h. Participants in the non-loading group received a fixed dose of 400-mcg vaginal misoprostol every 6 h. Each dose of misoprostol in both regimens was mixed with 1 ml of 5% acetic acid to facilitate drug dissolution leading to enhancement of the efficacy as described elsewhere.[12] The cervical Bishop score status was assessed by the authors before the initiation of misoprostol. Misoprostol was repeated if adequate uterine contractions were not achieved and the cervix was still unfavorable (Bishop score of 4 or less). If a favorable cervix was achieved but inadequate uterine contractions were found, then intravenous (i.v.) oxytocin was infused by automatic infusion pump starting from a low dose with no longer misoprostol administration. Oxytocin was started at 2 mU/min and increased as needed every 15 min to 4, 8, 12, 16, 20, 25, and 30 mU/min (maximum). Skipping a dose was defined by an omission of the next dose of misoprostol at the scheduled time interval and resuming misoprostol use at 12 h or 18 h after the previous dose. This might be used in cases of adequate contraction after 6 h of drug administration but becoming inadequate later.

Intravenous meperidine 50 mg for painful uterine contraction was given depending on the patient's need. Adverse effects of misoprostol were prospectively monitored and recorded, including fever (temperature > 38°C), chills, nausea, vomiting and diarrhea.

Successful treatment was defined as complete abortion or delivery of the fetus within 48 h after initiation of the first dose of misoprostol. In cases of failure, the next step of management depended on the cervical status, uterine contractions, physician and patient preference. Some women received only continuing i.v. oxytocin to further promote adequate uterine contraction. Some women received some additional doses of vaginal misoprostol, whereas the remainders needed more invasive procedures, such as the modified condom balloon technique or intra-amniotic hypertonic saline infusion in rare cases.

The main outcome measure included percentage of successful termination in 24 h and 48 h and median abortion/delivery time among the successful cases. The abortion/delivery time was defined as the interval from the initiation of the first dose of misoprostol to complete abortion or delivery of the fetus. According to a previous study that administered 400 mcg vaginal misoprostol every 6 h,[13] the mean abortion time was 20 h with a standard deviation of 10 h. The authors proposed that the loading dose regimen could shorten the abortion time by 4 h. Seventy-eight women were needed in each group to gain a power of 80% and alpha error of 0.05 (two sides).

SPSS 17.0 was used for statistical analysis. The difference in the mean continuous variables was analyzed using the Student's *t*-test for normally distributed data. Differences in proportions were analyzed using the χ^2-test or Fisher's exact test as appropriate. Mann–Whitney *U*-tests were used for determination of statistical significance of differences in non-normally

distributed variables between groups. A *P*-value of <0.05 was considered statistically significant.

Results

During the study period, a total of 175 pregnant women were eligible for the study. Of them, 18 were excluded due to various reasons, such as spontaneous contraction before allocation or refusing to join the study. Finally, 157 were available for allocation and analysis, as presented in Figure 1. Seventy-seven received the loading dose regimen (loading group) and 80 received the non-loading dose regimen (non-loading group). The baseline characteristics of the participants and indications for pregnancy termination were similar between the groups as presented in Table 1. The mean maternal age was 29 years and the mean gestational age was 20 weeks. The most common indications for pregnancy termination were fetal chromosomal abnormalities and major fetal anomaly followed by severe fetal thalassemia.

The adverse effects of misoprostol are shown in Table 2. The two most common adverse effects were fever, followed by chills. Of note, the common adverse

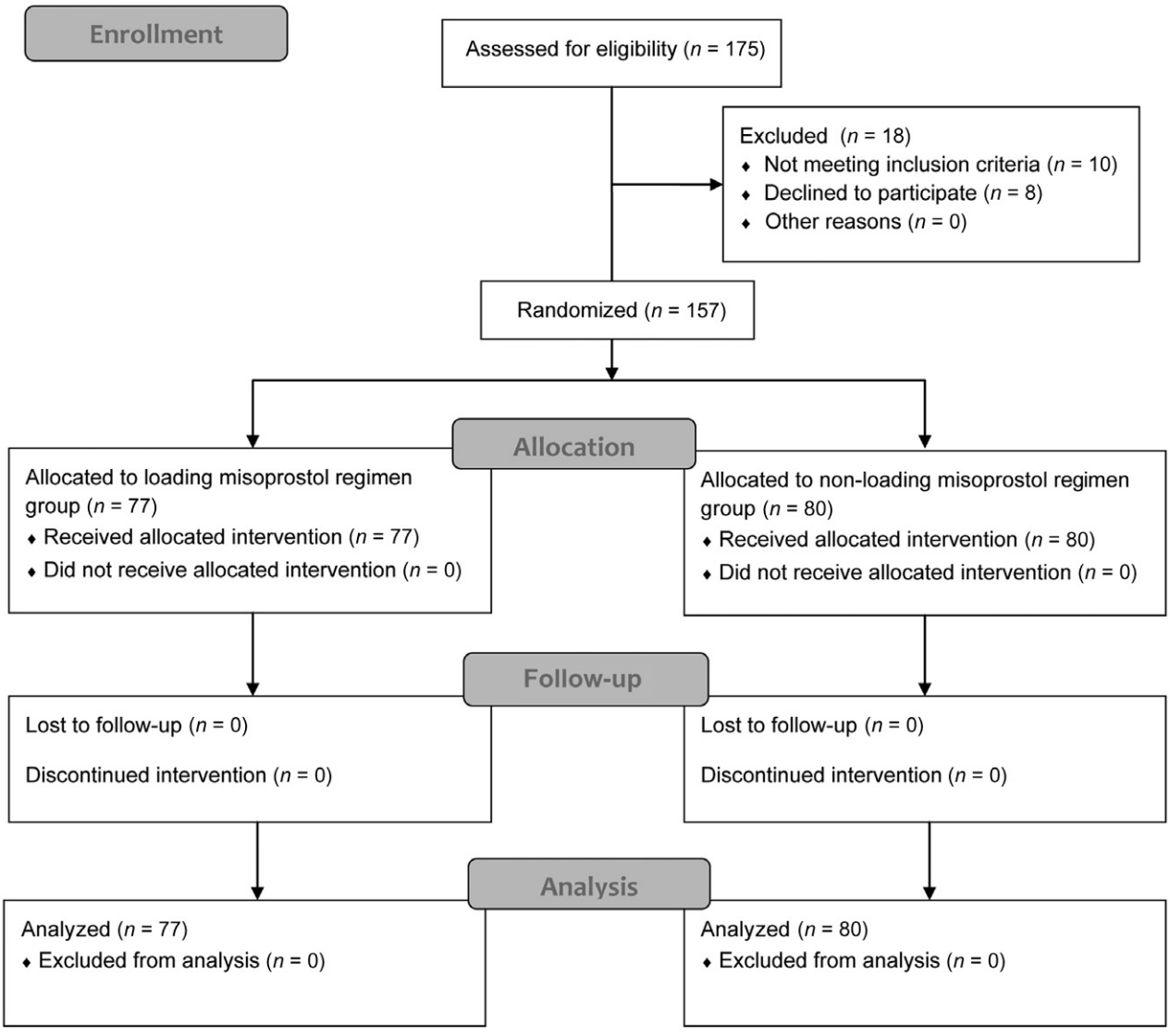

Figure 1 Flow diagram of the participants.

Table 1 Baseline characteristics and indication for pregnancy termination

Characteristics	Loading dose regimen ($n = 77$)	Non-loading dose regimen ($n = 80$)	*P*-value
Mean maternal age (years)	29.7 ± 7.0	29.2 ± 7.7	0.67
Mean gestational age (weeks)	20.6 ± 2.9	20.9 ± 3.1	0.55
Indications			
Fetal chromosomal abnormalities and major fetal anomaly	59.7%	51.3%	—
Severe fetal thalassemia	32.5%	38.7%	—
Maternal indications	3.9%	5.0%	—
Others	3.9%	5.0%	—

Table 2 Adverse effects of misoprostol

Adverse effects	Loading dose regimen ($n = 77$)	Non-loading dose regimen ($n = 80$)	*P*-value
Fever	25.5%	17.8%	0.03
Chills	24.8%	17.2%	0.03
Diarrhea	15.9%	9.6%	<0.05
Nausea	5.7%	3.2%	0.23
Vomiting	5.1%	1.9%	0.10
Postpartum hemorrhage	0%	0%	—
Uterine rupture	0%	0%	—
Other postpartum complications	0%	0%	—

Table 3 Comparison of the abortion/delivery outcomes between the groups

Abortion profile	Loading dose regimen ($n = 77$)	Non-loading dose regimen ($n = 80$)	*P*-value
Median abortion time (h)†	14.1 95%CI: 12. 5–17.8	14.6 95%CI: 12.8–17.3	0.78
Median abortion time (h)†			
Nulliparous ($n = 95$)	14.6 95%CI: 12.5–19. 9	16.6 95%CI: 13.35–19.2	0.93
Parous ($n = 62$)	12.9 95%CI: 10.1–15.9	13.9 95%CI: 11.2–20.2	0.81
Abortion			
Within 24 h	77.9%	76.3%	0.87
Within 48 h	93.5%	91.3%	0.87
Mean total dose of misoprostol (mcg)	1070.1 ± 611.1	1105 ± 785.3	0.76
Skipped dose of misoprostol	10.2%	13.4%	0.42
Single dose of misoprostol required	37.7%	23.8%	0.04
Oxytocin requirement	7.0%	10.8%	0.25
Intravenous analgesia requirement	20.4%	17.8%	0.40
Curettage	8.9%	7.0%	0.45
Estimated blood loss (mL)	100.1 ± 60.9	134.0 ± 95.4	0.01
Other method use after failure	0.6%	0.6%	0.98

†Mann–Whitney *U*-test. CI, confidence interval.

effects of misoprostol, including fever, chills and diarrhea, were significantly higher in the loading group (25.5% vs 17.8%; 24.8% vs 17.2%; and 15.9% vs 9.6%, respectively).

Table 3 presents abortion characteristics and other profiles. Median (95% confidence interval [CI]) abortion/delivery times were similar between the groups (14.08; 95%CI: 12.45–17.77 h and 14.58; 95%CI:

12.8–17.27 h, $P > 0.05$). In subgroup analysis, when separating the nulliparous and parous women, the median abortion/delivery times were also not significantly different between the regimens. Nevertheless the abortion/delivery time seemed to be shorter in parous women than that in nulliparous women, irrespective of regimen, but this was not significant. More than 90% of women aborted or delivered within 48 h after the initiation of misoprostol in both groups ($P > 0.05$).

Rates of oxytocin and analgesia requirement as well as curettage for incomplete abortion were not significantly different between the two groups. However, the estimated blood loss was significantly less in the loading group. Interestingly, the number of participants requiring a single dose of misoprostol was significantly higher in the loading group. Finally, the skipping dose rates were not significantly different.

Discussion

Our results indicate that a loading dose regimen was significantly associated with higher rates of adverse effects while the success rate was not significantly different. Nevertheless, the higher success rate with single dose and less blood loss was observed in the loading group, signifying that the loading regimen had a tendency to be more effective. However, such a high efficacy, if truly existed, would be only minimal and significance of such an outcome might only be shown with a larger sample size, and this would be unlikely to have clinical significance. Moreover, the difference in blood loss of only 30 mL in the loading group was also unlikely to have clinical impact. Therefore, our results did not support the advantage of loading dosage. In addition, there were similar rates of i.v. oxytocin use and analgesia requirements. While serious complications, such as postpartum hemorrhage or uterine rupture, were not found in the two groups, maternal side-effects, such as fever and chills, were significantly higher in the loading dose regimen. This finding is informative and may help clinicians make a decision on a regimen of choice. Though patients' satisfaction was not directly assessed in this study, the non-loading regimen with lower side-effects would certainly be a regimen of preference, while the efficacy was comparable.

Our results were contradictory to those reported by Dickinson and Evans,[11] who showed that the loading dose regimen (600 mcg vaginal dose followed by vaginal 200 mcg every 6 h) yielded a higher efficacy than the non-loading regimen (200 mcg vaginal every 6 h) in terms of shorter abortion time. Based on the two studies, it may be presumed that abortion/delivery time may be shorter with a loading dose of misoprostol in case of a maintenance dose of 200 mcg, but it seems unlikely to be helpful when a 400-mcg maintenance dose is used, whereas more adverse effects are significantly associated with a loading dose regimen. However, the two studies could not be compared because of the difference in gestational age, fetal viability and misoprostol maintenance dosage as mentioned above (200 vs 400 mcg). Gestational age in our study was strictly confined to 14–28 weeks of gestation but that in the study by Dickinson and Evans was extended to 30 weeks of gestation. Importantly, our study included only live fetuses while the study by Dickinson and Evans included both live and dead fetuses. As already known, higher gestational age and dead fetuses are independently associated with a higher success rate of termination of pregnancy with misoprostol.

The strengths of this study include: (i) the homogeneity of the participants in terms of gestational age and fetal viability as mentioned above; (ii) randomized controlled trial; and (iii) adequate sample size. The weakness of this study may be associated with its non-blinded nature. The assessors knew to which group the participants were allocated; however, blindness might not affect the main results as they were objectively measured. In addition, some outcomes were relatively subjective, especially blood loss estimation, which was based on the clinician's impression, not objectively measured in this study. Therefore, interpretation of such results may be less reliable. Moreover, patients' satisfaction was not assessed in this study. This study included only live fetuses in the second trimester and no obvious advantage was observed in loading regimen. However, loading regimen with lower dose for induction of labor in the last trimester should be further studied.

In conclusion, misoprostol in a dose of 400 mcg every 6 h, either with a loading dose or non-loading dose, was comparable in terms of abortion/delivery time. Higher maternal effects, such as fever and chills, were found in the loading dose regimen. Therefore, based on the present study, we recommend the non-loading dose regimen for second-trimester pregnancy termination.

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Disclosure

None.

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