A Comparison Between 50 mcg Oral Misoprostol Every 4 Hours and 6 Hours for Labor Induction : A Prospective Randomized Controlled Trial

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Abstract

Objective : To compare the effectiveness and safety between 50 mcg oral misoprostol every 4 hours and 6 hours for labor induction.

Design : A prospective randomized controlled trial.

Setting : Department of Obstetrics & Gynecology, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand.

Subjects : Eighty nine pregnant women of at least 34 weeks' gestation with indications for labor induction in the condition of unfavourable cervix (Bishop score $\leq$ 4) and no contraindication to prostaglandin therapy.

Interventions : All pregnant women were randomized to receive either 50 mcg misoprostol orally every 4 hours or 6 hours.

Main Outcome Measures : Treatment interval from induction to vaginal delivery, maternal and neonatal complication.

Results : The mean treatment intervals from induction to vaginal delivery were 22.10 $\pm$ 18.49 hours and 20.91 $\pm$ 11.98 hours in the misoprostol group every 4 hours and 6 hours, respectively. The treatment intervals between the two groups were not statistically significant. There was also no significant difference between both groups with regard to maternal and neonatal complications.

Conclusion : The effectiveness in terms of treatment interval from induction to vaginal delivery were comparable between the two groups, but administration of misoprostol every 6 hours was found to have a slightly shorter interval, although it did not reach statistical significance. No serious maternal and neonatal complication was demonstrated in both groups. Either regimen in this study can be an alternative for labor induction.

Key word : Misoprostol, Labor, Unfavorable Cervix

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Various prostaglandin preparations either in the form of intravaginal tablets or gel have been extensively used for cervical ripening and labor induction in pregnant women with an unfavourable cervix[1-4]. The most commonly used agent is dinoprostone, a prostaglandin E_2 analog which has been approved for the ripening the cervix and inducing labor in many countries. Currently, the new prostaglandin E_1 analog, misoprostol has also been successfully used for labor induction and is widely used because of its effectiveness, low cost, and stability in room temperature[5-8]. Based on meta-analysis by Sanchez-Ramos[6], misoprostol seems to be more effective than prostaglandin E_2 and has resulted in a lower cesarean section rate. The effectiveness of intravaginal misoprostol has been established. However, to date there are only a few studies regarding oral misoprostol for induction of labor. Initially, oral administration of misoprostol was mainly used for prevention and treatment of nonsteroidal anti-inflammatory drug-induced gastric and duodenal ulcers. The preliminary reports showed that misoprostol can be used orally for labor induction which was found to be effective and well tolerated[9-11], however, the optimal interval for any administration has not been established.

The purpose of this study was to compare the effectiveness and safety between 50 mcg oral misoprostol every 4 hours and 6 hours for labor induction in pregnant women with an unfavourable cervix.

MATERIAL AND METHOD

The study was undertaken at the Department of Obstetrics and Gynecology, Maharaj Nakorn Chiang Mai Hospital, Faculty of Medicine, Chiang Mai University. Pregnant women with indications for labor induction were recruited into the study. The inclusion criteria included singleton pregnancy, vertex presentation of the fetus, obstetric or medical indications for labor induction, Bishop score of ≤ 4, gestational age of ≥ 34 weeks, intact membranes with no previous stripping, absence of labor or fetal distress, no previous cesarean delivery or other type of uterine surgery, no definite cephalopelvic disproportion and no contraindication to the use of prostaglandins. The pregnant women meeting these criteria were enrolled with written informed consent.

The subjects were allocated to receive 50 mcg misoprostol (Cytotec®) orally every 4 hours or 6 hours by means of blocked randomization. 50 mcg misoprostol (one fourth 200 mcg tablet) was ingested with 30 cc of water. After drug administration in both groups, vital signs and side effects were monitored hourly and continuous external cardiotocography (CTG) was performed in all cases. The medication was repeated every 4 hours or 6 hours until adequate uterine contraction (≥ 3 contractions in 10 minutes), favourable change of cervix, or spontaneous rupture of the membranes occurred. The maximum dosing of misoprostol was limited to 48 hours. When labor had not been achieved with the maximum dosage, it was considered to be failure of induction.

If the cervix became favourable, amniotomy was carried out and oxytocin was infused as needed. Oxytocin was started at 1-2 milliunits/minute and was gradually adjusted in a dose increment of 1-2 milliunits/minute. The CTG was evaluated for frequency and duration of uterine tachysystole, hypertonus and hyperstimulation syndrome. Tachysystole was defined as > 5 contractions per 10-minute period. Hypertonus was defined as a contraction exceeding 90-seconds' duration. Hyperstimulation syndrome was defined as the presence of tachysystole or hypertonus accompanied by fetal tachycardia (> 160 beats per minute), late deceleration, and/or loss of short term variability. In cases of hyperstimulation syndrome, the pregnant women were positioned on their left side, given oxygen *via* nasal catheter, intravenously injected with 250 mcg of terbutaline and closely monitored until resolution of hyperstimulation. The difference between both groups with regard to baseline data and outcome variables were tested with student *t* test, or Chi square as appropriate, and was regarded as significant at $P < 0.05$.

RESULTS

A total of 89 pregnant women meeting the inclusion criteria were randomly allocated into each group, 43 for 50 mcg oral misoprostol every 4 hours and 46 for 50 mcg oral misoprostol every 6 hours. There was no significant difference in the baseline characteristics such as maternal age, gestational age and initial Bishop score. But difference was found in the percentage of nulliparous between the two groups. The percentage of nulliparous was nearly double in the misoprostol group every 6 hours when compared with the another group (Table 1).

Table 1. Baseline characteristics of the pregnant women.

Characteristics	misoprostol 50 mcg oral q 4 h (N = 43)	misoprostol 50 mcg oral q 6 h (N = 46)	P value
Age (years) mean ± SD	28.0 ± 6.1	25.9 ± 6.2	0.105*
Gestational weeks mean ± SD	39.3 ± 2.1	39.0 ± 2.3	0.553*
Initial Bishop score mean ± SD	2.45 ± 0.98	2.56 ± 0.83	0.233#
Nulliparous (%)	46.5	82.6	0.001#

* Student's *t* test
# Chi-square test

Table 2. Indications for labor induction.

Indications	misoprostol 50 mcg oral q 4 h (N = 43)	misoprostol 50 mcg oral q 6 h (N = 46)	P value
IUGR	16	21	> 0.05#
Postterm	16	18	> 0.05#
PIH	7	3	> 0.05#
Oligohydramnios	4	4	> 0.05#

IUGR = Intrauterine growth retardation
PIH = Pregnancy-induced hypertension
# Chi-square test

There was no significant difference in the indications for labor induction between both groups. Intrauterine growth retardation was the most common indication (Table 2).

Treatment interval (induction to vaginal delivery, not including cases of cesarean section) was slightly longer but not statistically different in the misoprostol group of 4 hours. However, the number of doses required (misoprostol) and the other peripartum variables were no significantly different (Table 3).

Mode of delivery and fetal outcomes were not significantly different between the two groups as shown in Table 4. No postpartum complication was detected in both groups.

DISCUSSION

Many high-risk pregnancies require labor induction to achieve the best outcome of pregnancy. However, oxytocin infusion, the conventional technique, has a high failure rate, especially in cases of unfavourable cervix. Currently, of several methods, prostaglandin E_2 administration is the most popular because of its high efficacy for cervical ripening and induction of labor. The main problem encountered with prostaglandin E_2 use is its high cost.

Therefore, a simple, inexpensive and more practical technique should be sought for. To overcome these problems, the new prostaglandin E_1 analog, misoprostol, has been studied and proved to have high efficacy, low cost and stability in room temperature. It has been established that misoprostol is as effective as, or even more effective than prostaglandin E_2 analog in labor induction[4,6,12-14]. Therefore, misoprostol has been widely used in a short period of its development. The appropriate dose and time interval in administration to avoid complications and giving high efficacy of misoprostol has been widely studied in the last few years.

The effects of vaginal misoprostol on the pregnant uterus have been reported by several authors, whereas, there are only a few reports on the effects of the oral route, especially in the third trimester. In a double blind RCT with a single dose of 200 mcg oral misoprostol *versus* placebo for cervical priming in term PROM, Ngai[9] found that the treatment interval from induction to delivery was shorter in the misoprostol group. Windrim[10] showed that 50 mcg oral misoprostol every 4 hours was effective in labor induction and the pregnant women tolerated it well, suggesting that oral miso-

Table 3. Treatment interval and peripartum variables.

	misoprostol 50 mcg oral q 4 h	misoprostol 50 mcg oral q 6 h	P value
Induction to vaginal delivery (hours)	22.10 ± 18.49 (N = 37)	20.91 ± 11.98 (N = 42)	0.734#
Number of doses of misoprostol			
1	20	22	0.160#
2	7	14	
3	7	2	
≥ 4	9	8	
mean ± SD	2.46 ± 1.96	2.19 ± 1.76	0.306#
Uterine hyperstimulation sydrome	1 (2.3%)	6 (13%)	0.061*
Nausea and vomiting	0	1	0.167*
Diarrhea	0	1	0.167*
Amniotomy	40 (93%)	42 (91%)	0.763*
Meconium stained amniotic fluid	1 (2.3%)	0	0.298*
Oxytocin augmentation	15 (35%)	14 (31%)	0.132*
Analgesia requirement	26 (60%)	31 (67%)	0.495*

Data presented as mean ± SD or number and per cent
* Student' *t* test
# Chi-square test

Table 4. Mode of delivery, fetal and maternal outcomes.

	misoprostol 50 mcg oral q 4 h	misoprostol 50 mcg oral q 6 h	P value
Spontaneous normal delivery	34	37	0.629#
Vacuum extraction	3	5	
Cesarean section	6	4	
Median and range of Apgar score			
1 minute	9 (6-10)	9 (3-10)	0.628*
5 minutes	10 (6-10)	10 (7-10)	0.515*
Birth weight (gram) (mean ± SD)	2658.3 ± 479.9	2744.0 ± 489.4	0.662*
Postpartum complication	0	0	-

* Student' *t* test
# Chi-square test

prostol be a new option for labor induction. However, the optimal interval was not known.

The effectiveness of 50 mcg oral misoprostol every 4 hours and 6 hours was comparable. The effectiveness in terms of treatment interval was slightly longer in the first group, eventhough the percentage of nulliparous was nearly double. So the number of parity may not influence the duration of the first stage of labor. The effectiveness in terms of induction-delivery time was comparable between both groups, although the percentage of nulliparous women was nearly double in the first group. Notably, the number of nulliparous women was significantly higher in the group of 4-hour-interval. This may be due to random error, occurring by chance. However, based on several previous reports, the parity was unlikely to influence the effectiveness of misoprostol. Therefore, we believe that, inspite of the different baseline characteristics, we can conclude that the effectiveness and safety of 50 mcg oral misoprostol between 4-hour-interval and 6-hour-interval of administration was the same.

Whereas the number of required doses (misoprostol), and peripartum variables were not different between the two groups, we found only 2 cases with maternal side effects (1 case with nausea and vomiting, 1 case with diarrhea), indicating that the dosage of 50 mcg is well tolerated.

To achieve better efficacy, a higher dose is necessary for further studies.

In summary, 50 mcg oral misoprostol every 4 hours and 6 hours demonstrated the same effi-

cacy in terms of treatment interval and number of required doses. Both groups also showed that misoprostol was safe for labor induction. However, further studies should be carried out to find out the appropriate dose, interval and route of administration.

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การศึกษาเปรียบเทียบประสิทธิภาพระหว่าง 50 ไมโครกรัม มีโสพรอสตอล รับประทานทุก 4 ชั่วโมง กับ 6 ชั่วโมง เพื่อชักนำให้เจ็บครรภ์คลอด

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วัตถุประสงค์ : เพื่อศึกษาประสิทธิภาพและความปลอดภัยของการชักนำให้เจ็บครรภ์คลอดโดยการรับประทาน misoprostol 50 ไมโครกรัม ทุก 4 ชั่วโมง เปรียบเทียบกับการรับประทานทุก 6 ชั่วโมง

รูปแบบการวิจัย : การศึกษาแบบ randomized controlled trial

สถานที่ศึกษา : ภาควิชาสูติศาสตร์และนรีเวชวิทยา คณะแพทยศาสตร์ มหาวิทยาลัยเชียงใหม่

ตัวอย่างการวิจัย : สตรีตั้งครรภ์ทั้งหมด 89 ราย ที่มีอายุครรภ์อย่างน้อย 34 สัปดาห์ ที่มีข้อบ่งชี้ให้ยุติการตั้งครรภ์ โดยมีคะแนน Bishop ของปากมดลูกไม่เกิน 4 และไม่มีข้อบ่งห้ามของการให้พรอสตาแกลนดินส์

การดำเนินการวิจัย : สตรีตั้งครรภ์ทั้งหมดถูกแบ่งโดยวิธีสุ่มออกเป็น 2 กลุ่ม ได้แก่ กลุ่มแรกจำนวน 43 ราย ได้รับประทาน misoprostol 50 ไมโครกรัมทุก 4 ชั่วโมง และกลุ่มที่สองจำนวน 46 ราย ได้รับประทาน misoprostol 50 ไมโครกรัม ทุก 6 ชั่วโมง เพื่อชักนำให้เจ็บครรภ์คลอด

ตัววัดที่สำคัญ : ค่าเฉลี่ยระยะเวลาตั้งแต่เริ่มรับประทานจนกระทั่งคลอดทางช่องคลอด ภาวะแทรกซ้อนในสตรีตั้งครรภ์และทารก

ผลการศึกษา : ระยะเวลาเฉลี่ยตั้งแต่รับประทานยาจนกระทั่งคลอดทางช่องคลอด เท่ากับ 22.10 $\pm$ 18.49 ชั่วโมง และ 20.91 $\pm$ 11.98 ชั่วโมง ในกลุ่มที่ 1 และ 2 ตามลำดับ ซึ่งไม่มีความแตกต่างอย่างมีนัยสำคัญทางสถิติ รวมถึงไม่มีความแตกต่างในภาวะแทรกซ้อนทั้งในสตรีตั้งครรภ์และทารก

สรุป : แม้ว่าระยะเวลาเฉลี่ยตั้งแต่รับประทานยาจนกระทั่งทารกคลอดทางช่องคลอดจะยาวกว่าเล็กน้อยในสตรีที่ได้รับประทาน misoprostol 50 ไมโครกรัม ทุก 4 ชั่วโมงก็ตาม แต่ก็ไม่มีความแตกต่างอย่างมีนัยสำคัญทางสถิติ อีกทั้งไม่พบภาวะแทรกซ้อนที่รุนแรงทั้งในสตรีตั้งครรภ์และทารกแต่อย่างใด

ดังนั้นการเลือกรับประทาน misoprostol 50 ไมโครกรัมทุก 4 หรือ 6 ชั่วโมงน่าจะเป็นทางเลือกของการชักนำให้เจ็บครรภ์คลอดได้ เพราะประสิทธิภาพไม่แตกต่างกัน

คำสำคัญ : มีโสพรอสตอล, การชักนำให้เจ็บครรภ์คลอด

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