A Comparison Between 25 Micrograms and 50 Micrograms of Intravaginal Misoprostol for Labor Induction

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Abstract

Our purpose was to compare the efficacy 25 μg and 50 ug dosage of intravaginal misoprostol for labor induction in patients with an unfavorable cervix. Fifty pregnant women were randomly assigned to receive either 25 μg (24 cases) or 50 μg (26 cases) of intravaginal misoprostol every 6 hours. The mean interval from induction to vaginal delivery was significantly shorter in the 50 μg group (13.8 ± 6.6 hours) when compared with the 25 μg group (20.9 ± 9.5 hours) (P = 004). The average number of misoprostol doses needed per patient was significantly fewer in the 50 μg group (1.6 ± 0.7 *versus* 2.3 ± 1.2, P = 0.018). The frequencies of uterine tachysystole were 4.2 per cent and 7.7 per cent in the 25 μg and 50 μg groups respectively which did not significantly differ. Requirement for oxytocin infusion in the 25 μg group was significantly more than in the 50 μg group (66.6 % *versus* 23.1 % respectively, P = 0.004). Analgesia requirement, delivery method, and perinatal outcomes were comparable in both groups. In summary, intravaginal application of 50 μg misoprostol at 6-hour interval is comparable in safety but more effective for labor induction than the 25 μg dosage.

Labor induction with prostaglandins offers the advantage of stimulating both cervical ripening and uterine contraction. Various prostaglandins have been used to induce labor in the presence of an unfavorable cervix including prostaglandin E_2 (dinoprostone), the currently approved agent and prostaglandin E_1 (misoprostol), the newly investigated one[1-3]. Intravaginal misoprostol is effective, cheap and safe in ripening the cervix and inducing labor. However, the major drawback of such a regimen is its high frequency of uterine tachysystole. We have previously reported our experience with intravaginal misoprostol at a dosage of 100 μg for cervical ripening and labor induction. The frequency of uterine tachysystole was unacceptably as high as 38 per cent[4].

Consequently, in this prospective randomized study, we decreased the dose of misoprostol to 25 μg and 50 μg administered intravaginally to

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compare the safety and efficacy in cervical ripening and labor induction.

SUBJECTS AND METHOD

The study was carried out between November 1, 1995 and May 31, 1996 at the Department of Obstetrics and Gynecology, Chiang Mai University Hospital and constituted 50 pregnant women eligible for induction of labor. Criteria for recruitment included the following : singleton pregnancy with parity ≤ 3, vertex presentation of the fetus, obstetric or medical indication for labor induction, intact membranes with no previous stripping, Bishop score ≤ 4, gestational age > 35 weeks, absence of labor or fetal distress, no previous caesarean delivery or other type of uterine surgery, no definite cephalopelvic disproportion, and no contraindication to the use of prostaglandins.

The patients who fulfilled these criteria were approached for participation and those who gave informed written consent were enrolled. The study was performed under the ethical approval of the Research Ethical Committee of Chiang Mai University Hospital.

The subjects were allocated to receive either 25 μg or 50 μg of misoprostol (Cytotec; Searle, Illinois, U.S.A.) by means of blocked randomization. The Bishop cervical score was assessed according to the original article[5].

For preparation of misoprostol gel, 50 μg (one half of 100 μg tablet) or 25 μg of misoprostol (one fourth 100 μg tablet) was crushed to powder and mixed with 2 ml of sterile 1 per cent carboxymethyl cellulose gel (prepared by the pharmacist). The mixture was squirted into the posterior vaginal fornix.

The patient was left in the supine position for at least 1 hour. Vital signs and side effects were monitored every 2 hours. Continuous external cardiotocography (CTG) was performed in all fetuses. Oxytocin infusion and pelvic examination were strictly not employed within 6 hours of gel insertion. The medication was repeated every 6 hours until adequate uterine contraction (≥ 3 contractions in 10 minutes), cervical ripening (Bishop score > 6 or dilatation ≥ 3 cm), or spontaneous rupture of membranes occurred. The maximum dosing of misoprostol was limited to 4 times or 24 hours.

If the cervix became favorable, an amniotomy was carried out and oxytocin was infused if deemed necessary. If uterine contraction was not adequate or did not occur, oxytocin was started at 1-2 mU/minute and was gradually increased in dose increments of 1-2 mU/minute at 30-minute intervals as needed.

The CTG was evaluated for frequency and duration of uterine tachysystole, hypertonus, and hyperstimulation syndrome[6]. Tachysystole was defined as > 5 contractions per 10-minute period. Hypertonus was defined as a contraction exceeding a 90-second duration. Hyperstimulation syndrome was defined as the presence of tachysystole or hypertonus accompanied with fetal tachycardia (> 160 beats per minute), late deceleration, and/or loss of short-term variability. In case of hyperstimulation syndrome, the patients were positioned on their left side, given oxygen *via* nasal catheter, intravenously injected 250 μg of terbutaline, and closely monitored until the resolution of hyperstimulation.

Sample size calculations were based on the pilot study using 25 μg and 50 μg of misoprostol for achieving successful labor induction with a type I error of 0.05 and a power of 95 per cent. On the basis of these assumptions, 23 patients were required in each study group.

The baseline data and outcome variables were installed in the microcomputer program Epi Info 6 for analysis. Statistical analyses were conducted by using parametric (Student *t* test) or nonparametric (Chi square or Fisher's exact test) as appropriate to examine the differences between the two groups and were regarded as significant at $P < 0.05$.

RESULTS

A total of 50 eligible pregnant women requiring labor induction were randomly enrolled in the study to receive either 25 μg (24 cases) or 50 μg (26 cases) of intravaginal misoprostol. There were no significant differences between the two groups in terms of maternal age, parity and gestational age (Table 1). Indications for labor induction did not differ significantly between the two groups as shown in Table 2.

Although the interval from the start of induction to regular uterine contraction was not significantly different in both groups, the mean duration to complete vaginal delivery was approximately 7 hours shorter in the 50 μg group. This difference was statistically significant. The average number of misoprostol doses needed per patient

and requirement for oxytocin infusion were significantly fewer in the 50 μg group (Table 3).

The frequency of uterine tachysystole was comparable in both groups. Tachysystole of the 2 patients in the 50 μg group occurred 3.5 hours and 2.5 hours respectively after receiving their first dose of misoprostol. One patient in the 25 μg group exhibited tachysystole 1.5 hours after the fourth dose. No changes in fetal heart rate patterns were noted in these patients. Such a complication spontaneously resolved within 1 hour without any intervention. No significant difference was observed in analgesia requirement between the study groups.

There were no significant differences in delivery method and perinatal outcomes in both groups (Table 4). No maternal side effects of misoprostol were noted. The postpartum courses were uneventful.

Table 1. Demographic data of patients in the two groups.

	25 μg (N = 24)	50 μg (N = 26)	P-value
Age (yr)	26.8 ± 5.7	28.1 ± 6.9	0.526
Parity			
Nulliparous	14 (58.3 %)	17 (65.4 %)	0.825
Parous	10 (41.7 %)	9 (34.6 %)	
Gestational age (wk)	39.2 ± 2.2	38.8 ± 2.4	0.554

Data presented as mean ± SD or number and per cent

DISCUSSION

This study has shown that intravaginal application of 50 μg misoprostol at 6-hour interval is more effective than 25 μg for labor induction in pregnant women at term with an unfavorable cervix. The average time from start of induction to vaginal delivery was significantly shorter in the 50 μg group (13.8 hours) when compared with the

Table 2. Indications for labor induction.

Indications	25 μg (N = 24)	50 μg (N = 26)
IUGR	12	14
Postterm	7	8
PIH	3	4
Others	2	-

IUGR = Intrauterine growth retardation
PIH = Pregnancy - induced hypertension
Others = Diabetes and decreased fetal movement
P value = 0.515

Table 4. Delivery method and fetal outcomes.

	25 μg	50 μg	P-value
Vaginal delivery			
Spontaneous	19 (79 %)	23 (88 %)	0.456
Instrumental	5 (21 %)	3 (12 %)	
Mean Apgar score ± SD			
1 minute	8.5 ± 1.7	8.7 ± 1.0	0.816
5 minute	9.9 ± 0.2	10.0 ± 0.0	0.298
Birth weight (gram)	2960 ± 484	2805 ± 439	0.238

Table 3. Time interval to delivery (hours) and intrapartum variables.

	25 μg	50 μg	P-value
Insertion to RUC	1.9 ± 0.9	1.5 ± 0.6	0.092
Insertion to vaginal delivery	20.9 ± 9.5	13.8 ± 6.6	0.004
Number of doses	2.3 ± 1.2	1.6 ± 0.7	0.018
Uterine tachysystole	1/24 (4.2 %)	2/26 (7.7 %)	0.531
Oxytocin augmentation	16/24 (66.6 %)	6/26 (23.1 %)	0.004
Analgesia requirement	18/24 (75 %)	13/26 (50 %)	0.147
Amniotomy	18/24 (75 %)	19/26 (73 %)	0.867
Meconium passage	0	2/50 (8 %)	0.491

Data presented as mean ± SD or number and per cent
RUC = Regular uterine contraction

25 μg (20.9 hours). These intervals were comparable with the two studies by Wing et al using the same dosages of misoprostol but in the form of tablet and applied every 3 hours. Such intervals were 15 hours and 22 hours in the 50 μg and 25 μg respectively[7,8]. The absorption of prostaglandin compound into the systemic circulation may be more readily in the form of gel compared with the tablet form. The induction time appears to depend on various factors including dosage, interval and form of intravaginal application. The mean time from dosing to vaginal delivery was longer than that (12 hours) of our previous study employing 100 μg of misoprostol gel inserted only once in the posterior vaginal fornix[4]. Furthermore, this study also demonstrated that the higher the dosage of misoprostol, the fewer the number of application. The average number of dosages utilized per patient as well as the need for oxytocin infusion was significantly lower in the 50 μg than the 25 μg.

Interestingly, the incidences of uterine tachysystole did not significantly differ in both groups and were much lower than those reported by Wing et al which were 36.7 per cent and 17.4 per cent in the 50 μg and 25 μg respectively[7,8]. This is possibly due to the difference in interval of dosing. The accumulative effect of frequent dosing may play a role in inducing uterine contractile abnormalities despite lower dosage. Our previous investigation using 100 μg of misoprostol, the occurrence of uterine tachysystole was as high as 38 per cent[4]. The frequency of such event is directly related to the dosage of misoprostol as shown in the study by Wing et al in which the incidence of tachysystole was reduced by 50 per cent when the dosage was decreased from 50 μg to 25 μg[7,8]. However, no changes of fetal heart rate pattern were observed with such complication in the present study. Regular uterine contraction resumed within 1 hour without any treatment. Nevertheless, uterine tachysystole may cause meconium passage and fetal distress especially in the compromised fetus i.e., growth retarded or post-term fetus, and pregnancy with oligohydramnios or uteroplacental insufficiency. Thus, uterine activity and fetal heart rate must be closely monitored during misoprostol application. Evaluation of fetal health should be performed prior to labor induction in pregnant women at risk to fetal jeopardy.

Although various techniques including vaginal irrigation had been mentioned to treat the uterine hyperactivity, the administration of intravenous tocolytic e.g., ritodrine or terbutaline was the most commonly reported[9-11]. Uterine tachysystole usually disappeared within a few minutes after tocolytic therapy and any fetal heart rate abnormality was always reversed[11]. However, such intervention may retard progression of labor but the action on cervical ripening is still maintained.

In summary, intravaginal application of 50 μg misoprostol at 6-hour interval is comparable in safety but more effective for labor induction than the 25 μg dosage.

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การเปรียบเทียบระหว่างมิโซโปรซอล ขนาด 25 ไมโครกรัม และ 50 ไมโครกรัม ที่สอดทางช่องคลอด เพื่อชักนำการเจ็บครรภ์

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เพื่อเปรียบเทียบประสิทธิภาพในการชักนำการเจ็บครรภ์ระหว่างการใช้ misoprostol สอดทางช่องคลอดในขนาด 25 ไมโครกรัม กับขนาด 50 ไมโครกรัม ในสตรีครรภ์ครบกำหนดที่ปากมดลูกยังไม่พร้อม โดยแบ่งสตรีตั้งครรภ์ 50 คน ที่มีข้อบ่งชี้ในการชักนำการเจ็บครรภ์และปากมดลูกยังไม่พร้อมออกเป็น 2 กลุ่ม เพื่อสอดยา misoprostol ทางช่องคลอด ในขนาด 25 ไมโครกรัม (24 ราย) และ 50 ไมโครกรัม (26 ราย) ทุก 6 ชั่วโมง ระยะเวลาเฉลี่ยตั้งแต่สอดยาจนกระทั่งคลอดทารกทางช่องคลอดในกลุ่มที่ได้รับ misoprostol 50 ไมโครกรัม (13.8 ± 6.7 ชั่วโมง) สั้นกว่าอย่างมีนัยสำคัญ เมื่อเปรียบเทียบกับกลุ่มที่ได้รับยาขนาด 25 ไมโครกรัม (20.9 ± 9.5 ชั่วโมง) (P = 0.004). จำนวนครั้งของการสอดยาในกลุ่มที่ได้รับยาขนาด 50 ไมโครกรัม (1.6 ± 0.7 ครั้ง) น้อยกว่าในกลุ่มที่ได้รับยาขนาด 25 ไมโครกรัม (2.3 ± 1.2 ครั้ง) อย่างมีนัยสำคัญทางสถิติ (= 0.018) การหดรัดตัวของมดลูกแบบ tachysystole พบประมาณ 4.2 % และ 7.7 % ในกลุ่มที่ได้รับยาขนาด 25 และ 50 ไมโครกรัม ตามลำดับ ซึ่งไม่แตกต่างอย่างมีนัยสำคัญทางสถิติ กลุ่มที่ใช้ยาในขนาด 25 ไมโครกรัมมีความจำเป็นในการใช้ oxytocin เพื่อเสริมการหดรัดตัวของมดลูกมากกว่าในกลุ่ม 50 ไมโครกรัม (66.6 % และ 23.1 % ตามลำดับ, P = 0.004). ความต้องการยาระงับปวด วิธีการคลอด ผลการคลอด และทารก ไม่แตกต่างในผู้ป่วยทั้ง 2 กลุ่ม โดยสรุปแล้วการสอด misoprostol ขนาด 50 ไมโครกรัม ทางช่องคลอดทุก 6 ชั่วโมง มีความปลอดภัยทัดเทียมกันแต่มีประสิทธิภาพในการชักนำการเจ็บครรภ์สูงกว่าการสอด misoprostol ขนาด 25 ไมโครกรัม ทางช่องคลอดทุก 6 ชั่วโมง

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