# Comparison of Intracervical and Intravaginal Misoprostol for Cervical Ripening and Labour Induction in Patients with an Unfavourable Cervix

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**Abstract**

Objective : To compare the efficacy of intracervical *versus* intravaginal misoprostol for cervical ripening and labour induction at term in patients with an unfavourable cervix.

Method : A total of 100 pregnant women with indications for induction of labour and unfavourable cervix (Bishop score $\leq$ 4) were randomly assigned to receive either 100 ug misoprostol administered intracervically (50 cases) or intravaginally (50 cases).

Results : No significant differences were noted between intracervical and intravaginal misoprostol in terms of Bishop score change, (score 7.2 *vs* score 7.5), interval from gel insertion to vaginal delivery (17.0 hours *vs* 16.4 hours), meperidine as analgesic requirement (80% *vs* 76%), route of delivery and perinatal outcome. Uterine tachysystole occurred in 24 per cent and 32 per cent in the intracervical and intravaginal groups respectively which did not significantly differ, however, all could be rapidly resolved by terbutaline injection. No evidence of fetal distress was noted in these events. Spillage of gel out of the cervix was observed in 70 per cent of patients receiving intracervical misoprostol. Fever was observed in one patient of each group. No other serious side effects were found in both groups. One patient in the intravaginal group had postpartum hemorrhage due to delayed placental separation and uterine atony.

Conclusion : The two routes of misoprostol gel application appear to be safe and equally effective in ripening cervix and inducing labour, however, the intravaginal application is more convenient to administer practically compared with the intracervical.

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Local administration of prostaglandins (PGs) has been extensively used for cervical ripening and induction of labour in pregnant women at term with an unfavourable cervix[1-4]. A variety of PGs, dose, interval, and route of application have been described for this purpose, including the new prostaglandin E1 analogue, misoprostol which is effective, inexpensive and safe for preinduction cervical ripening and labour induction[3-6]. The major drawback of this agent is an unacceptable high frequency of uterine tachysystole which occurred in approximately 17-35 per cent depending on the dose and interval of intravaginal application[4,5,7]. A report comparing the route of prostaglandin administration found that the incidence of uterine hyperstimulation was more frequent in the intravaginal group than in the intracervical group[8].

In cases of highly unfavourable cervix, the intracervical application was significantly more effective than the intravaginal in priming cervix. But when studying the intrauterine pressure, it was found that the intravaginal route could induce more myometrial activity than the intracervical[9]. Therefore, this study was conducted to compare the efficacy and safety of these two routes of misoprostol application in ripening cervix and inducing labour in patients at term gestation with an unfavourable cervix.

## MATERIAL AND METHOD

The study was undertaken at the Department of Obstetrics and Gynaecology, Chiang Mai University Hospital, from August 1994 to September 1995. Inclusion criteria were (1) singleton pregnancy with parity of $\leq 3$, (2) vertex presentation of the fetus, (3) obstetric or medical indications for labour induction, (4) intact membranes with no prior stripping, (5) Bishop score $\leq 4$, (6) gestational age $> 35$ weeks, (7) absence of labor or fetal distress, (8) no previous caesarean delivery or other type of uterine surgery, (9) no evidence of cephalopelvic disproportion, (10) no placenta previa, forelying cord or vasa previa, and (11) no contraindication to the use of prostaglandins.

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

The subjects were allocated to receive misoprostol gel either intracervically or intravaginally by means of blocked randomization. Prior to gel application, transabdominal and transvaginal sonography were carried out to visualize the fetal presentation, location of the placenta and the umbilical cord. The Bishop score was later assessed according to the original article[10].

For preparation of misoprostol gel, 100 ug of misoprostol (one-half 200 ug tablet of Cytotec; Searle, Illinois, U.S.A.) was crushed to powder in a sterile container and mixed with 3 ml of sterile hydroxyethyl cellulose gel (K-Y Jelly, Johnson & Johnson, New Jersey, U.S.A.). The mixture was drawn up into a sterile 10 ml syringe which was connected with nylon feeding tube 8" 5 FR. After exposure of the cervix by vaginal speculum, misoprostol gel was instilled within the endocervical canal during the slow continuous withdrawal of the feeding tube, starting just below the internal os. For intravaginal application, the gel was squirted into the posterior fornix and a further 2 ml of air was pushed to empty the contents in the tube.

The patient was left in 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 patients. Oxytocin infusion and pelvic examination as well as amniotomy were strictly not employed within 12 hours of gel instillation.

Each patient was reexamined to evaluate the Bishop score 12 hours after dosing. A Bishop score of 13 was arbitrarily assigned for those patients who entered the active phase of labour or delivered within 12 hours. Those whose cervix remained unfavourable without labour were given a second dose of misoprostol gel. If the cervix became favourable (Bishop score $> 6$), an amniotomy was performed and oxytocin infusion was instituted if necessary. If labour 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. Oxytocin was infused for induction of labour if no cervical change or regular uterine contraction occurred after the second dose.

The CTG was assessed for frequency and duration of uterine tachysystole, hypertonus, and hyperstimulation syndrome[11]. Tachysystole was defined as more than 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 associated with fetal tachycardia > 160 beats per minute, late deceleration, and/or loss of short term variability. For treatment of hyperstimulation syndrome, the patients were positioned on their left side, given oxygen *via* nasal catheter, administered 250 ug of terbutaline intravenously or subcutaneously and monitored until the resolution of hyperstimulation.

The baseline data and outcome variables were collected and analyzed by microcomputer statistical program (SPSS PC +). Statistical analysis were conducted by using parametric (Student *t* test) or nonparametric (chi square or Fisher's exact tests) as appropriate to examine the differences between the two groups and were regarded as significant at $p < 0.05$.

## RESULTS

A total of 100 eligible patients requiring labour induction were randomly enrolled in the study to receive either intracervial (50 cases) or intravaginal misoprostol (50 cases). The two groups were comparable with respect to maternal age, parity and gestational age (Table 1). The indications for induction of labour were similar between groups (Table 2).

Table 3 compares the Bishop score before and 12 hours after gel insertion of each group. There was no significant difference in mean change of the Bishop score in both groups. However, vaginal speculum insertion in the patients for intracervical application was quite cumbersome and occasionally uncomfortable. Spillage of gel out of the cervix was observed in 35 patients (70%), causing the problem of exact dosing in this group. No problems of gel instillation were encountered in the intravaginal group.

The mean duration from shart of misoprostol insertion to vaginal delivery was not significantly different in both groups (Table 4). Approximately four-fifth of the patients achieved vaginal delivery within 24 hours. Uterine tachysystole occurred more frequently in the intravaginal group compared with the intracervical group, but the difference was not of statistical significance. All cases of uterine tachysystole manifested within 2 hours of gel administration. However, no patients showed signs of fetal distress while the remainder had no change in the fetal heart rate patterns. All

**Table 1. Demographic data of the study group ***

| | Intracervical | Intravaginal |
|---|---|---|
| Age (yr) | 25.8 ± 5.3 | 28.1 ± 5.8 |
| Parity | 1.3 ± 0.5 | 1.4 ± 0.5 |
| Nulliparous | 30 (60%) | 37 (74%) |
| Parous | 20 (40%) | 13 (26%) |
| Gestational age (wk) | 39.7 ± 2.2 | 39.2 ± 2.2 |

Data presented as mean ± SD or number and per cent,
* There was no significant difference in any of the data.

**Table 2. Indications for labour induction ***

| Indications | Intracervical | Intravaginal |
|---|---|---|
| PIH | 12 | 19 |
| IUGR | 13 | 13 |
| Postterm | 20 | 14 |
| Others | 5 | 4 |
| Total | 50 | 50 |

PIH = pregnancy-induced hypertension,
IUGR = intrauterine growth retardation,
Others = oligohydramnios, decreased fetal movement and diabetes
* There was no significant difference in any of the data.

**Table 3. Mean Bishop score before and 12 hours after gel insertion ***

| Bishop score | Intracervical | Intravaginal |
|---|---|---|
| Before insertion ± SD | 2.6 ± 0.8 | 2.6 ± 0.9 |
| After insertion ± SD | 9.9 ± 2.9 | 10.1 ± 2.7 |
| Mean change ± SD | 7.2 ± 2.9 | 7.5 ± 2.6 |

* There was no significant difference in any of the data.

**Table 4. Time intervals to delivery (hours) and intrapartum variables ***

| | Intracervical | Intravaginal |
|---|---|---|
| Insertion to RUC | 2.7 ± 3.5 | 2.1 ± 1.5 |
| RUC to vaginal delivery | 14.2 ± 9.0 | 14.4 ± 8.3 |
| Insertion to vaginal delivery | 17.0 ± 8.6 | 16.4 ± 8.6 |
| Vaginal delivery in 12 hour | 15/47 (32.0%) | 17/45 (37.8%) |
| Vaginal delivery in 24 hour | 37/47 (78.7%) | 38/45 (84.4%) |
| Uterine tachysystole | 12/50 (24%) | 16/50 (32%) |
| Oxytocin augmentation | 35/50 (70%) | 33/50 (66%) |
| Analgesia requirement | 38/50 (76%) | 40/50 (80%) |

Data presented as mean ± SD or number and per cent
RUC = regular uterine contraction
* There was no significant difference in any of the data.

patients with uterine tachysystole could be rapidly normalized by terbutaline injection. Oxytocin infusion was necessary for augmentation of uterine contraction in about two-thirds of the patients in both groups. No significant difference was noted in analgesia requirement between the study groups.

Fever was observed in one patient of each group. Other side effects including nausea, vomiting and diarrhea were not found in either group.

There was no significant difference in the mode of delivery and perinatal outcome between the study groups (Table 5). The indications for cesarean delivery in the intracervical group were cephalopelvic disproportion (CPD) in all 3 patients. For the intravaginal group, the indications were fetal distress and CPD in 4 and 1 patients respectively. One patient in the intravaginal group had postpartum hemorrhage caused by delayed placental separation and uterine atony which occurred after manual removal of the placenta. Such a complication could be resolved by manual uterine massage and methylergonovine injection.

**Table 5. Delivery method, maternal and fetal outcomes. ***

| | Intracervical | Intravaginal |
|---|---|---|
| Vaginal | | |
| Spontaneous | 37 | 31 |
| Forceps | 2 | 5 |
| Vacuum | 8 | 9 |
| Cesarean section | 3 | 5 |
| Apgar score < 7 | | |
| 1 minute | 3 | 0 |
| 5 minute | 0 | 0 |
| Birth weight (gram) | 2823 ± 426 | 2833 ± 505 |
| Postpartum hemorrhage | 0 | 1 |

Data presented as mean ± SD or number
* There was no significant difference in any of the data.

## DISCUSSION

This study has demonstrated that 100 ug misoprostol in the form of gel administered either intracervically or intravaginally is equally effective and safe in ripening the cervix and inducing labour in pregnant women at term with an unfavourable cervix. The mean time from intracervical or intravaginal application to vaginal delivery (17.0 hours and 16.4 hours respectively) was similar to that reported by Fletcher et al[12]. (15.6 hours) using the same dosing regimen. However, such a duration was shorter when compared with 100 ug of misoprostol used in tablet form (21.8 hours)[3]. Absorption of prostaglandin compound into the systemic circulation may be better in the form of gel compared with the tablet form. Vaginal delivery within 24 hours was achieved in 78.7 per cent and 84.4 per cent of the intracervical and intravaginal groups respectively, which was higher than that reported by Wing et al employing 25 ug - 50 ug every 3 hours[5,7].

Although unacceptably high and not significantly different between groups, the incidence of uterine tachysystole of the patients in the intracervical group was lower than that in the intravaginal (24% *vs* 37%) which was comparable to that observed by other investigators using different dosing regimens[4,5]. However, no abnormal FHR patterns associated with complications were noted in this study. All cases of uterine tachysystole could be rapidly resolved by terbutaline injection without interfering with the cervical ripening effect. The two studies by Wing et al showed that the frequency of uterine tachysystole was diminished with reduced dosage of misoprostol[5,7]. Such a complication was decreased from 36.7 per cent to 17.4 per cent when the dosage was reduced from 50 μg to 25 μg, while the success of achieving vaginal delivery within 24 hours remained unchanged.

In the intracervical group, a portion of the gel was found to frequently spill out of the cervical canal to the vagina. Despite this event, the cervical ripening and interval to vaginal delivery were still identical in both groups. The intravaginal gel had the advantage of ease in application in the posterior vaginal fornix without need of speculum insertion which was virtually required for intracervical application. Consequently, intravaginal misoprostol should be the most preferable route of drug administration.

At present, no pharmacodynamic and clinical data of intracervical and intravaginal misoprostol have been reported. The dosage and frequency of misoprostol administration still vary in each report. Future clinical trials should be focused on optimal dosing regimens satisfactorily effective

in ripening the cervix and inducing labour with acceptable incidence of uterine contraction abnormalities.

On the basis of these preliminary findings, misoprostol administered either intracervically or intravaginally appears to be safe and equally effective in ripening the cervix and inducing labour. The higher frequency of uterine tachysystole did not increase the risk of adverse intrapartum and neonatal outcomes. Practically, intravaginal application is more convenient to administer compared with intracervical. However, further studies are needed to determine the optimal dosing regimens of this agent.

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# การเปรียบเทียบระหว่างการสอด misoprostol ทางปากมดลูกกับทางช่องคลอด เพื่อทำให้ปากมดลูกนุ่ม และชักนำการเจ็บครรภ์ในผู้ป่วยที่ปากมดลูกไม่พร้อม

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จุดประสงค์ : เพื่อเปรียบเทียบประสิทธิภาพระหว่างการสอด misoprostol ทางปากมดลูกกับทางช่องคลอดเพื่อทำให้ปากมดลูกนุ่ม และชักนำการเจ็บครรภ์ในสตรีตั้งครรภ์ครบกำหนดที่มีปากมดลูกไม่พร้อม

วิธีการ : สตรีตั้งครรภ์ 100 คน ที่มีข้อบ่งชี้ในการชักนำให้เจ็บครรภ์คลอดและมีปากมดลูกไม่พร้อม (คะแนน Bishop $\leq$ 4) ได้รับการสอด misoprostol 100 ไมโครกรัม เข้าทางปากมดลูก (50 ราย) และเข้าทางช่องคลอด (50 ราย) โดยทำการแบ่งแบบสุ่ม

ผลการศึกษา : การสอดยา misoprostol เข้าทางปากมดลูกและทางช่องคลอดไม่มีความแตกต่างอย่างมีนัยสำคัญในแง่ของการเปลี่ยนแปลงคะแนน Bishop (คะแนน 7.2 กับ 7.5) ระยะเวลา ตั้งแต่สอดยาจนกระทั่งคลอดทางช่องคลอด (17.0 ชม. กับ 16.4 ชม.) ความต้องการยาแก้ปวด meperidine (80% กับ 76%) ช่องทางคลอดและผลลัพธ์ปริกำเนิด ภาวะมดลูกหดรัดตัวถี่พบ 24% และ 32% ในกลุ่มที่ได้รับการสอดยาทางปากมดลูกและทางช่องคลอดตามลำดับ ซึ่งไม่แตกต่างอย่างมีนัยสำคัญ ภาวะดังกล่าวสามารถแก้ไขได้ทุกรายด้วย การฉีด terbutaline ไม่พบว่ามีภาวะทารกเครียดในกรณีดังกล่าว ผู้ป่วยที่ได้รับยา misoprostol ทางปากมดลูกมีการไหลของยาออกมาจากปากมดลูกประมาณ 70% ผู้ป่วยมีไข้กลุ่มละ 1 ราย ไม่พบว่ามีผลข้างเคียงที่รุนแรงในผู้ป่วยทั้ง 2 กลุ่ม กลุ่มที่ได้รับยาทางช่องคลอดมีการตกเลือดหลังคลอด 1 ราย จากกรกลอกตัวช้าและมดลูกอ่อนล้า

สรุป : การให้ยา misoprostol ทั้ง 2 วิธี มีความปลอดภัยและมีประสิทธิภาพเท่ากันในการทำให้ปากมดลูกนุ่มและชักนำการเจ็บครรภ์ ในทางปฏิบัติแล้วการสอดยาทางช่องคลอดจะง่าย และสะดวกกว่าการสอดยาทางปากมดลูก

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