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Sublingual misoprostol compared to artificial rupture of membranes plus oxytocin infusion for labour induction in nulliparous women with a favourable cervix at term

首次生產嬰兒而子宮頸成熟度合適的女性，以舌底米索前列醇藥物和以人工破膜結合催產藥兩種引產方法的比較

Objectives. To compare the efficacy of labour induction using sublingual misoprostol versus combined artificial rupture of membranes and oxytocin infusion for nulliparous women with a favourable cervix at term.

Design. Open randomised controlled trial.

Setting. Regional hospital, Hong Kong.

Patients. Fifty nulliparous women with a favourable cervix (Bishop score 6 or more) at term and indications for labour induction.

Interventions. With their informed consent, 100 eligible women were to be randomised to receive either sublingual misoprostol 50 µg every 4 hours for up to five doses or oxytocin infusion after artificial rupture of membranes. Interim analysis was planned at a sample size of 50.

Main outcome measures. Vaginal delivery within 24 hours of induction.

Results. The study was terminated when interim analysis of the first 50 recruits showed that a significantly smaller proportion of misoprostol-treated women delivered vaginally within 24 hours of induction than in the conventional treatment group (68% vs 100%; relative risk, 0.68; 95% confidence interval, 0.51-0.91; P=0.009), although comparable numbers of women eventually delivered vaginally. The mean induction to vaginal delivery interval was 4.5 hours longer in the misoprostol group (P=0.027). After misoprostol treatment, all women went into labour. Forty percent of them delivered without oxytocin. There was no significant difference in uterine hyperstimulation rate, operative delivery rate, and neonatal outcomes. Maternal satisfaction was higher in the misoprostol group (92% vs 60%; relative risk, 1.53; 95% confidence interval, 1.09-2.16; P=0.008).

Conclusions. Despite being well accepted by women, labour induction using this regimen of sublingual misoprostol is less effective in achieving vaginal delivery within 24 hours.

Key words:

Cervix uteri;
 Labor, induced;
 Misoprostol;
 Oxytocin

關鍵詞：

子宮頸；
 分娩，引導的；
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目的：對於首次生產嬰兒而子宮頸成熟度合適的女性，比較以舌底米索前列醇藥物和以人工破膜結合催產藥兩種引產方法的效果。

設計：開放式隨機對照測試。

安排：地區醫院，香港。

患者：50名首次生產嬰兒、子宮頸成熟度適宜（「Bishop 級數」6或以上）而且有引產訊號的孕婦。

治療：在獲得患者同意下，100名符合要求的孕婦被隨機安排接受舌底米索前列醇藥物（每4小時50 µg劑量，最多五次），或進行人工破膜然後注入催產藥。另為首50名孕婦進行中期分析。

主要結果測量：引產後24小時內陰道分娩。

結果：首50名孕婦的中期分析顯示，即使最終能陰道分娩，以舌底米索前列醇藥物引產的孕婦，可以在引產後24小時內陰道分娩的比率明顯低於以常規方法引產的對照組（68%對100%；相對風險為0.68；95%置信區間為0.51-0.91，P=0.009），因此研究被終止。由引產至陰道分娩所需時間，米索前列醇藥物方式平均多用

4.5 小時 ($P=0.027$)。所有孕婦在使用米索前列醇藥物後都能生產，其中 40% 孕婦毋須使用催產藥。在子宮過度反應、手術分娩比率和新生嬰兒情況各方面，兩個引產方法沒有明顯分別。母親的滿意度方面，則以米索前列醇藥物方式較高 (92% 對 60%；相對風險為 1.53；95% 置信區間為 1.09-2.16； $P=0.008$)。

結論：雖然舌底米索前列醇藥物引產廣受孕婦接受，但用於引產後 24 小時內陰道分娩則未及傳統引產方式有效。

Introduction

Artificial rupture of membranes followed by oxytocin infusion is the conventional means of inducing labour in women with a favourable cervix. The use of oxytocin requires intravenous infusion and the patient is confined to bed during the whole process. Treatment with prostaglandins (such as misoprostol) is an alternative means of inducing labour.^{1,2} Although the manufacturer of misoprostol does not list this obstetrical indication, the Food and Drug Administration of the United States has recognised its extensive off-label use in cervical priming and labour induction.³ Misoprostol has a number of theoretical advantages for clinical use: it has a long shelf life, is easy to administer and, unlike other prostaglandins used in obstetrics, is significantly cheaper and does not require refrigeration.⁴ Without the need for intravenous infusion, it offers women greater autonomy during labour induction.

Misoprostol can be administered orally, vaginally, and sublingually. Via the oral and sublingual routes it has a rapid onset of action.⁵ The vaginal and sublingual routes have the advantage of prolonged activity and greater bioavailability.⁵ Regular uterine contractions develop in all subjects following sublingual and vaginal dosing but not after oral administration.⁶ In clinical trials, vaginal misoprostol is more effective than the oral route for cervical priming and labour induction, but is also associated with a higher risk of uterine hyperstimulation.⁴ Although clinical data for sublingual dosing are limited, this route is expected to be as effective as vaginal administration, and by avoiding a direct (topical) effect on the cervix, it may reduce the risk of uterine hyperstimulation.⁴ In cases of vaginal bleeding, infection or ruptured membranes, it also avoids the inconvenience of the vaginal route.⁷

Sublingual misoprostol has been used for labour induction with an unfavourable cervix. Fifty-microgram misoprostol sublingually every 4 hours was reported to be effective, safe, and well accepted by women.^{5,8} Although 100 µg seems more effective, this dose may be associated with a higher incidence of uterine tachysystole and hyperstimulation syndrome.⁹

The current study is the first reported use of sublingual misoprostol for labour induction in women with a favourable cervix. A regimen of 50 µg doses every 4 hours was chosen, because of the favourable experience with 100 µg reported for labour induction in women having an unfavourable cervix,^{5,7,8} and was expected to be more effective when used with a favourable cervix. This regimen

was compared with the conventional treatment (artificial rupture of membranes followed by oxytocin infusion). We hypothesised that the two approaches were equally effective.

Methods

The study was approved by the Clinical Research Ethics Committee of the Kowloon West Cluster (KWC-CREC Reference Number KW/EX/04-068). It was also reviewed by the Research Committee of the Hong Kong College of Obstetricians and Gynaecologists (HKCOG) and approved by the Education Committee of HKCOG. It was carried out in the labour ward of the Kwong Wah Hospital from January to June 2005.

Women admitted with an obstetric or medical indication for labour induction and fulfilling the following criteria were included: (1) gestation of ≥ 37 weeks ascertained by dating scan before 20 weeks of gestation, (2) nulliparity, (3) having a live single conceptus in a cephalic presentation, (4) Bishop score >5 , and (5) normal 30-minute foetal heart tracing. Only nulliparous women were included to eliminate the confounding effect of parity and enhance patient safety. Rarely uterine rupture had been reported during labour induction in primiparous women without a previous uterine scar.¹⁰ Women with the following conditions were excluded: (1) known hypersensitivity or any contraindication to prostaglandins (eg glaucoma), (2) previous uterine scar, and (3) any confirmed or suspected membrane rupture.

It was our departmental policy to admit women scheduled for labour induction 1 day before the procedure. Written information and an oral explanation about the study were provided on admission. Eligible subjects giving written informed consent were randomised into the misoprostol or oxytocin treatment group, according to a computer-generated random number table. The allocation was concealed in sealed sequentially numbered envelopes prepared by an assistant not involved in the clinical care of patients. After randomisation, neither the patients nor the staff were blinded to the induction method.

Women randomised to misoprostol therapy were given 50 µg sublingual misoprostol every 4 hours for a maximum of five doses; each dose was prepared by dividing a 200 µg tablet (Cytotec, Pharmacia, Hong Kong) into four equal parts (by the same pharmacist). The midwife supervised administration of the doses. Before each dose, a 30-minute foetal heart rate (FHR) tracing was obtained. Repeat dosing was withheld at labour onset (three or more uterine contractions in 10 minutes associated with abdominal pain),

at entry into active labour (cervix 3 cm dilated and effaced), and when there was intolerance to the medication. Once misoprostol was stopped, membranes were ruptured artificially. Labour augmentation with intravenous oxytocin, if necessary, was allowed only after 2 hours had lapsed following the last dose of misoprostol. Cases of failed induction (not going into labour after exhausting five doses) were treated with oxytocin after artificial rupture of membranes.

The conventional (control) treatment involved artificial rupture of membranes followed by intravenous oxytocin infusion as per our departmental induction protocol. Four units of oxytocin were added to 500 mL normal saline. The infusion was started at two drops per minute (0.8 mu/min) and the rate doubled at 15-minute intervals until there were adequate contractions (three contractions every 10 minutes).

At the start of labour induction, women in both groups had blood sampling for haemoglobin level and cross-match and an intravenous cannula was inserted. For women in the misoprostol group, food was allowed until labour onset. In accordance with our departmental protocol, use of oxytocin infusion (either for labour induction or augmentation) required continuous FHR monitoring and the women were kept nil by mouth, irrespective of their study group. Two days after delivery, the haemoglobin was routinely determined. Before discharge from the postnatal ward, each participant in the trial was asked whether they were satisfied with the way labour was induced.

We collected and logged baseline data, including: maternal age, gestation, maternal height, maternal body mass index (BMI), indication for induction, and the initial Bishop score. The primary outcome measure was vaginal delivery within 24 hours of induction. Other outcome measures included induction-to-delivery interval, vaginal delivery within 12 hours of induction, requirement for oxytocin, uterine hyperstimulation rate and other side-effects, mode of delivery, blood loss during delivery, maternal satisfaction, and neonatal outcomes. Non-reassuring FHR pattern referred to suspicious or pathological FHR tracing (as per the guideline of the Royal College of Obstetricians and Gynaecologists).¹¹ Uterine hyperstimulation was defined as non-reassuring FHR pattern associated with six or more contractions in 10 minutes or a single contraction lasting longer than 2 minutes that required immediate delivery. The change in haemoglobin level from the start of induction to 2 days after delivery served as an objective estimation of blood loss.

When oxytocin was used for labour induction in nulliparous women with a favourable cervix, 90% of women who delivered vaginally did so within 24 hours.¹⁰ Using misoprostol, we considered any corresponding reduction to below 60% as clinically relevant. Assuming a type I error of 0.05 and a type II error of 0.2, a sample size of 38 subjects in each group was required using a two-tailed approach.

Allowing for a Caesarean section rate of 20%,¹⁰ 48 subjects were needed in each group. We therefore planned to recruit 100 patients.

Statistical analysis was performed using the Statistical Package for the Social Sciences (Windows version 10.0; SPSS Inc, Chicago [IL], US) and an intention to treat principle was adopted. Maternal age, gestation, height, BMI, induction-to-delivery interval, oxytocin dosage, drop in haemoglobin level, and birth weight were analysed using Student's *t* test. Differences in Bishop scores were analysed using the Mann-Whitney *U* test. The Chi squared test was used to detect differences between percentages. All tests were two-tailed. Statistical significance was set at $P < 0.05$.

For ethical reasons, an interim analysis was performed after recruitment of the first 50 women. An a priori decision was made to terminate the study should a statistically significant benefit or harm be associated with the misoprostol treatment, using a *P* value of < 0.01 (as recommended by Pocock for such an interim analysis).¹²

Results

Between January and June 2005, a total of 50 patients were recruited, of whom 25 were allocated to receive sublingual misoprostol and 25 oxytocin infusion (Fig). The baseline characteristics of the two groups were similar (Table 1).

The study was terminated after recruitment of the first 50 women according to the predetermined stopping rule based on the interim analysis. This revealed that among those delivered vaginally significantly fewer misoprostol-treated women did so within 24 hours of induction than those in the oxytocin group (68% vs 100%; relative risk [RR], 0.68; 95% confidence interval [CI], 0.51-0.91; $P = 0.009$). Nevertheless, eventually comparable numbers of women delivered vaginally (22 vs 21) [Table 2]. The 4.5-hour difference in induction-to-delivery interval was statistically significant ($P = 0.027$).

All women in the misoprostol group went into labour after receiving misoprostol alone (Table 3). Forty percent did so after just one dose of misoprostol. Oxytocin for labour augmentation was required subsequently by 60% of misoprostol-treated women (Table 4). Their oxytocin 'requirement' was significantly lower than that in the oxytocin group. The abdominal delivery rate in the two groups was similar. The only case of maternal fever was in the oxytocin group and was epidural-related. Septic workup was negative for both the mother and newborn, and placental histology did not show chorioamnionitis. The uterine hyperstimulation rate was low, and was zero in the misoprostol group.

Ninety-two percent of women in the misoprostol group were satisfied with the induction method (vs 60% in the oxytocin group; RR, 1.53; 95% CI, 1.09-2.16; $P = 0.008$).

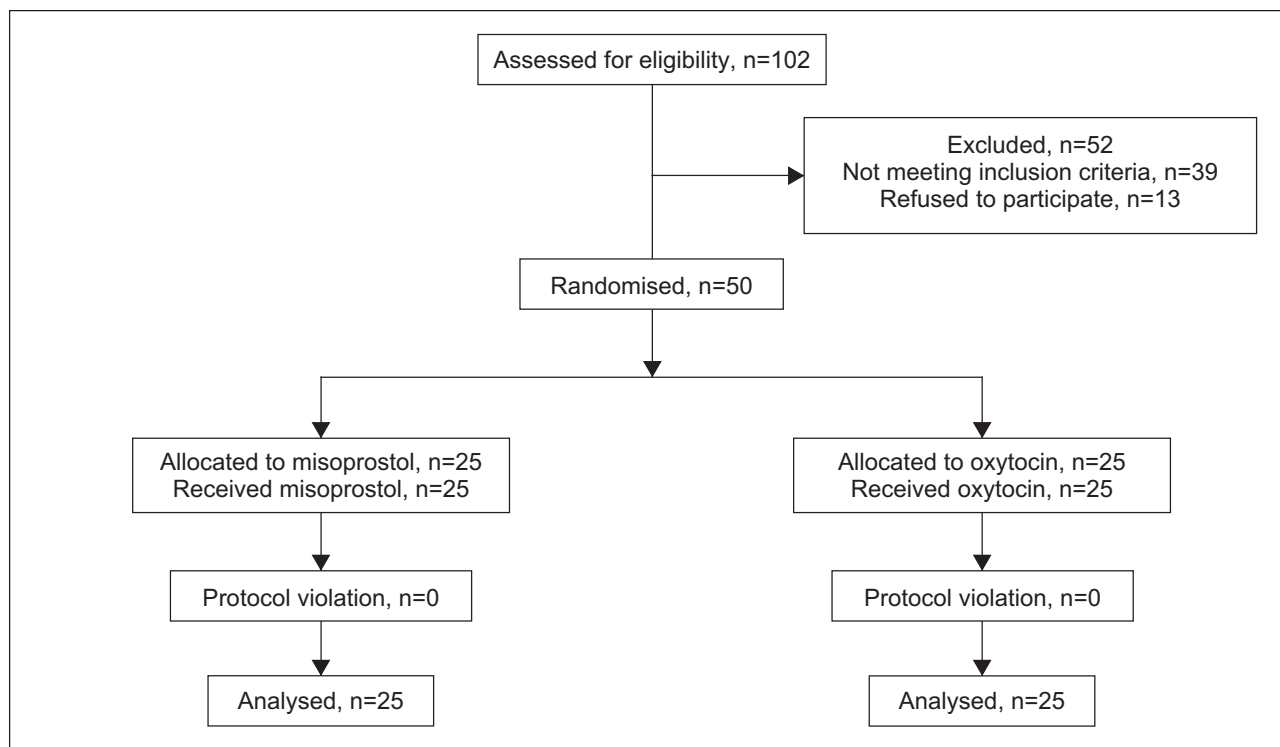


Fig. Flowchart of misoprostol trial

Table 1. Maternal characteristics

Characteristic	Misoprostol, n=25	Oxytocin, n=25
Mean age (SD) [years]	29.3 (5.3)	28.6 (4.0)
Mean gestation (SD) [days]	282 (12)	284 (11)
Mean height (SD) [cm]	158.6 (4.9)	158.4 (5.0)
Mean body mass index (SD) [kg/m ²]	20.3 (3.0)	20.0 (3.8)
Median Bishop score (range)	7 (6-8)	7 (6-8)
Indications for induction		
Past-date*	17 (68%)	17 (68%)
Hypertensive disorder	5 (20%)	4 (16%)
Small baby	1	1
Diabetes	1	1
Antepartum haemorrhage	1	2

* Gestation from 41 weeks to 41 weeks and 6 days

Table 3. Profile of misoprostol use

Use of misoprostol	No. of patients
Dosage	
1	10
2	9
3	4
4	1
5	1
Reason for stopping	
Onset of labour	17
Onset of active labour	7
Five doses completed	1*

* Onset of labour after the 5th dose of misoprostol

Two misoprostol-treated women delivering by Caesarean section for no progress in labour, were not satisfied with the induction. The seven women who delivered vaginally after

Table 2. Outcome of vaginal deliveries

	Misoprostol	Oxytocin	P value
No. of vaginal deliveries	22	21	
Delivery within 24 hours	15 (68%)	21 (100%)	0.009
Delivery within 12 hours	11 (50%)	15 (71%)	NS*
Mean induction-to-delivery interval (SD) [minutes]	864 (478)	598 (240)	0.027
Instrumental vaginal delivery	5 (23%)	4 (19%)	NS

* NS denotes not significant

24 hours of induction in the misoprostol group were all satisfied. In the oxytocin group, the four women who delivered abdominally showed dissatisfaction.

There was no significant difference in neonatal outcomes (Table 5). A trend towards higher rate of meconium passage in the misoprostol group was observed.

Discussion

Use of sublingual misoprostol for labour induction in women with a favourable cervix is novel. The vaginal delivery rate of 68% within 24 hours of induction for women treated with 50 µg sublingual misoprostol is consistent with other reports,^{5,8} which used the same dosage regimen on women with mixed parity and an unfavourable cervix. Sublingual misoprostol was expected to be more effective for women with a favourable cervix. Nevertheless, in the present study, nulliparity might have neutralised any gain in efficacy due to that reason.

Table 4. Labour outcome

Labour outcome	Misoprostol, n=25	Oxytocin, n=25	P value
Use of oxytocin	15 (60%)	25 (100%)	0.001
Mean total dose (SD) [mU]	1241 (1179)	2634 (2157)	0.007
Use of epidural analgesia	6 (24%)	5 (20%)	NS*
Foetal heart rate (FHR) abnormalities			
Non-reassuring FHR	4 (16%)	6 (24%)	NS
Uterine hyperstimulation	0	1	-
Mode of delivery			
Vaginal	22 (88%)	21 (84%)	NS
Abdominal	3 (12%)	4 (16%)	NS
For non-reassuring FHR pattern	0	1	-
For no progress in labour	3	3	-
Mean drop in haemoglobin (SD) [g/L]	13 (16)	16 (10)	NS
Side-effects			
Metoclopramide required for vomiting	1	1	-
Maternal fever (>38°C)	0	1	-
Maternal satisfaction	23 (92%)	15 (60%)	0.008

* NS denotes not significant

Table 5. Neonatal outcome

Neonatal outcome	Misoprostol, n=25	Oxytocin n=25	P value
Mean birth weight (SD) [g]	3364 (520)	3348 (437)	NS*
Meconium passage	4 (16%)	2 (8%)	NS
Apgar score <7 at 5th minute	0	0	-
Cord blood pH <7.0	0	1	-
Neonatal intensive care unit admission	0	0	-

* NS denotes not significant

We found that the rate of FHR abnormalities in the misoprostol group was not higher than that in the oxytocin group; it was actually one third lower, although the difference was not statistically significant. No case of uterine hyperstimulation was encountered with 50 µg sublingual misoprostol. This encouraging result is in line with the low hyperstimulation rates (2% and 1.6% respectively) reported in other studies using the same sublingual misoprostol dosing regimen.^{5,8}

Misoprostol for labour induction has been associated with a higher rate of meconium passage compared with oxytocin.^{1,13-16} In this study, meconium-stained liquor was seen in 16% of misoprostol-treated deliveries (double that in the oxytocin group), but the difference was not significant (possibly due to the small sample size). Another study reported a meconium passage rate of 21.6% for labour induced by 50 µg sublingual misoprostol.⁸ The higher meconium passage rate in the misoprostol than oxytocin group (16% vs 8%) is in contrast to the absence of hyperstimulation and a similar (likely lower) rate of FHR abnormalities (16% vs 24%). The reason for such differences in meconium passage rates is not known. Excessive uterine contractility may not be the only cause for increased meconium passage.⁴ It was found that oxytocin had no effect on rat ileum, while misoprostol had a stimulatory effect.¹⁶ Neonatal outcomes were not different between the two groups. It is likely that a higher

rate of meconium passage does not translate into worse neonatal outcome.¹⁵

Ninety-two percent of women in the misoprostol group were satisfied with the treatment, consistent with another study reporting that 92.6% of women found induction by sublingual misoprostol acceptable.⁸ Thus, sublingual misoprostol seems well accepted by women. The reasons underlying such satisfaction or dissatisfaction were not addressed in the study protocol. Nevertheless, it appeared that unexpected emergency abdominal delivery is a major reason for dissatisfaction; six of the seven women who delivered abdominally expressed dissatisfaction. We postulate that the higher satisfaction rate among misoprostol-treated women may be related to the better self-control they perceived. Forty percent of them were completely free of oxytocin infusion. Food was allowed before labour onset. Without the inconvenience of intravenous infusion and continuous foetal heart monitoring, they enjoyed freedom during labour induction. Among those who required oxytocin augmentation, the actual 'suffering' might have been limited to only the later part of labour, and they received significantly lower total doses. Ancillary measures in the misoprostol protocol, such as allowing food and avoiding an intravenous drip (although a heparin block was still in place), may have contributed to the satisfaction of those receiving misoprostol. It is the use of misoprostol tablet that makes these desirable measures possible. The use of other prostaglandins, such as prostaglandin E₂, may also provide comparable favourable effects. Nonetheless, misoprostol is cheaper and more convenient to store and administer.

The membranes were ruptured before oxytocin infusion as this is the recommended practice,¹⁷ which is also in accordance with our departmental protocol for this means of labour induction and augmentation. For patient convenience, the membranes were not ruptured before starting misoprostol. Artificial rupture of membranes before starting oral misoprostol in the presence of a

favourable cervix has been associated with a Caesarean section rate 3 times that of oxytocin controls (16.7% vs 6.5%, $P=0.13$).¹⁸ Thus, although we used sublingual misoprostol in the present study, for reasons of safety, prior artificial rupture of membranes was not contemplated.

The present study bears several potential weaknesses. First, neither the woman nor the staff were blinded to the induction strategy after randomisation, potentially introducing biases caused by differences in interventions other than those specified in the study protocol. It is reassuring that we observed no difference in the rates of major interventions (such as operative delivery and use of epidural anaesthesia) between the two groups. Second, the 50 µg doses were prepared by quartering a 200 µg misoprostol tablet; the dose in each fraction may not be exact. However, the 200 µg tablet (Cytotec) is the only registered preparation of misoprostol available locally. The practice of preparing 50 µg test doses by quartering a 200 µg misoprostol tablet was also adopted by other researchers.⁷ Third, the present study primarily answers the question on efficacy of labour induction by administering 50 µg sublingual misoprostol in the setting of a favourable cervix. It is underpowered for conclusions to be drawn on other aspects of sublingual misoprostol. Nevertheless, findings in the present study were consistent with those reported in the literature^{5,8} using the same dosage regimen of sublingual misoprostol for labour induction.

In conclusion, although labour induction by sublingual misoprostol is well accepted by women with a favourable cervix, the 50 µg regimen we used is less effective than artificial rupture of membranes followed by oxytocin infusion in achieving vaginal delivery within 24 hours.

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