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Oral Misoprostol for Cervical Ripening and Labour Induction: A Randomized Controlled Trial

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ABSTRACT

Objective To study the efficiency of oral misoprostol for cervical ripening and induction of labour, as compared to the conventional vaginal route of administration.

Design A prospective randomized controlled trial.

Setting A university hospital.

Subjects One hundred thirty-one pregnant women of greater than 34 weeks of gestation who consented and had fulfilled indications for induction of labour and had no contraindications.

Main outcome measures Induction-to-regular contraction, induction-to-full dilation and induction-to-delivery times. Peripartum maternal data and neonatal outcome were also recorded.

Results No statistically significant difference between the "oral" group (n=65) and the "vaginal" group (n=66) was obtained from all of the main outcome measures and other data records, except for the mean dosage and the number of spontaneous rupture of membranes. Although the induction-to-full dilation time between the two groups were comparable, the oral misoprostol was used with a mean of 2.86 doses, while vaginal route required only 1.69 doses (p=0.03). The difference in the number of cases with spontaneous rupture of membranes (SRM) (p=0.002) was also noted between oral (n=2) and vaginal (n=14) misoprostol. The causes of these differences were extensively discussed in the details.

Conclusion Oral administration of misoprostol (50 microgramme every 4 hours) is simple and very effective for cervical ripening and labour induction at term or near term pregnancy.

Key words: cervical ripening, labour induction, misoprostol, Cytotec®, prostaglandin E_1, prostaglandin E_2

Induction of labour near term is frequently necessary for a variety of obstetric and medical indications. Prostaglandins (PGs), particularly PGE series, have been proven to be effective in cervical ripening and labour induction. Originally, PGE_2 has been designed specifically for these purposes[2] with acceptable results. Because of the high cost and unstability at room temperature, PGE_2 has been decreasing in its popularity. Therefore, the other more stable and much cheaper PGE's have to be developed and PGE_1 was accidentally found to be one of them. Misoprostol (15-deoxy-16-hydroxy methyl PGE_1) is originally manufactured and marketed under the trade name "Cytotec"® for the treatment of peptic ulcer. Owing to its potent uterotonic properties and increasing risk of miscarriage, misoprostol is therefore contraindicated in pregnancy. On the other hand, it was utilized, for the first time in Latin America, to

terminate pregnancy with quite satisfactory results.[1] Since then, several studies on the effectiveness of misoprostol for cervical ripening and labour induction have been conducted and recently randomized controlled trials[2,3] have shown it to be a cheap and effective agent for these purposes.

In the early studies, vaginal administration of misoprostol tablets was shown to be effective for cervical ripening and induction of labour, without an increase in adverse maternal or neonatal outcome.[4,5] Furthermore, it has been shown in the very recent studies that oral route of misoprostol may be as effective as vaginal one.[6,7] Therefore, the aim of this study is to compare the above-mentioned effectiveness of oral and vaginal administration of misoprostol tablets in Thai women with respect to risks and benefits to mother and child.

Materials and methods

This study was conducted between August 1, 1997, and May 31, 1998, at Maharaj Hospital, Chiang Mai. The research proposal was approved by the Human Investigation Committee of the Faculty of Medicine, Chiang Mai University.

Patients were eligible for this study if they had an indication for induction of labour, a single live fetus, gestation greater than 34 complete weeks, and cephalic presentation, Exclusion criteria were nonreassuring fetal heart rate (FHR) tracings, previous uterine surgery, known hypersensitivity to misoprostol or other PGs, and contraindication to vaginal birth.

Continuous electronic FHR and uterine contraction monitoring were carried out in all cases. Baseline Bishop scores and progression of cervical ripening were closely followed up. Following the initial dose of misoprostol, 4-hour interval dosage could be repeated until one of the following occurred: progressive labour, contraction frequency of three per 10 minutes, membranes ruptured, nonreassuring FHR tracings, or delivery. All decision with regard to artificial membrane rupture, analgesia, epidural block, and oxytocin augmentation were made by the attending physician, who reassessed the patient before each administration of misoprostol.

One hundred thirty one eligible subjects, who had given informed consent, were randomly allocated into two groups using block-of-four randomization method. The study group (n=65) were given 50 ug of misoprotol orally (a 200-ug cut in quarter) while the same dose was administered vaginally in the control group (n=66). The primary outcome measures were the intervals from labour induction to cervical fully dilatation and from induction to vaginal delivery. Data were analyzed by parametric (Student-t) and nonparametric (Mann-Whitney-U and Fisher exact-X2) statistical tests, as appropriate. The outcome measures were considered significant if $P< 0.05$.

Results

The two groups were not statistically different in their demographic data including initial Bishop score and indications for induction of labour (Table 1). Primary outcome measures were presented in Table 2 in which no statistically significant difference between the two groups was shown. The reason why the number of cases in each category of Table 2 was not consistent was that a few of them could not achieve regular uterine contraction, failed to dilate progressively, developed fetal distress, or ended up with cesarean section.

Data concerning peripartum maternal interventions and neonatal outcomes were shown in Table 3 and Table 4 respectively. Except for the mean dosage and the number of spontaneous rupture of membranes, other parameters were not different between the two groups.

Table 1. Demographic data

	Oral Misoprostol (n=65)	Vaginal Misoprostol (n=66)	P
Maternal age	27.6 ± 6.2	26.3 ± 5.8	0.22
Gestational age	38.6 ± 2.2	39.1 ± 2.0	0.21
Gravidity	1.7 ± 1.0	1.5 ± 0.9	0.68
Parity	0.7 ± 0.7	0.6 ± 0.7	0.74
Initial Bishop score	2.4	2.2	0.66
Indications for labour induction			
Hypertension	13	9	0.35
IUGR	21	23	0.35
Postterm	24	31	0.35
Others*	7	3	0.35

* PIH with IUGR, oligo- or poly-hydramnios, and decreasing fetal movement.

Table 2. Primary outcome measures

	Oral Misoprostol	Vaginal Misoprostol	P
Induction to regular contraction	134 ± 189 (n=64)	88 ± 76 (n=62)	0.07
Induction to full dilation	998 ± 603 (n=61)	853 ± 465 (n=60)	0.14
Induction to birth	1020 ± 602 (n=60)	880 ± 471 (n=60)	0.16

Table 3. Peripartum maternal interventions

	Oral Misoprostol (n=65)	Vaginal Misoprostol (n=66)	P
Mean dosage	2.86	1.69	0.03*
Spontaneous rupture of membranes	2	14	0.002*
Oxytocin augmentation	39	37	0.21
Analgesic requirement	50	46	0.87
Assisted delivery (F/E or V/E)	14	15	0.15
Postpartum uterine atony	8	5	0.37
Tachysystole or hypertonus	5	2	0.55
Hyperstimulation	2	0	0.15

Table 4. Neonatal outcomes

	Oral Misoprostol (n=65)	Vaginal Misoprostol (n=66)	P
Birth weight	2681 ± 525	2847 ± 576	0.09
Male / female	37 / 28	36 / 30	0.78
Apgar score at 1 min (median)	10	9	0.19
Apgar score at 10 min (median)	10	10	0.09
Congenital anomaly	1*	0	0.31

* Gross anomalies: club-foot (right), Rocker-bottom feet, severe IUGR, karyotype: 47 XXX

Discussion

Prostaglandins and oxytocin are the agents of choice for induction of labour. In case of unfavorable cervix, prostaglandins are preferable to oxytocin because of their effectiveness in shortening induction-to-delivery time, decreasing cesarean section rate and less requirement for intrapartum analgesia.[8] Compared with other prostaglandins, misoprostol is more stable and much cheaper,[9] while keeping the same[9,10] or more[11,12] efficiency for induction of labour. Therefore, misoprostol was selected for this study.

For cervical ripening and labour induction, vaginal and/or oral routes of misoprostol administration have been studied, most of which were done with the former one. The result from a meta-analysis (n=966) confirmed the effectiveness of this agent for those purposes.[13] Since then, various dosages of vaginal misoprostol, from 25,[12,14] 50,[15,16] and 100[17,18] microgramme every 2,[12] 3,[14,16] 6,[14] and 12[15] hours have been studied. Most of the studies concerning vaginal misoprostol for induction of labour have concluded that the optimal dosage of 25-50 microgramme[15,16] every 3-6 hours [16,19] would take the induction-to-delivery time around 14-16 hours and have the least side-effects.[16,19] However, caution has to be taken since uterine rupture from such a small dose of vaginal misoprostol (2x25 microgramme) has recently been reported.[20]

Following the establishment of vaginal misoprostol for cervical ripening and labour induction, oral route of misoprostol administration has gained attention because it would then be more simple and would reduce the risk of intra-amniotic infection associated with multiple vaginal insertion of this agent.[21,22] From a previous study in our institute, it has shown that the optimal dosage of vaginal misoprostol for induction of labour for the northern Thai pregnant women is 50 microgramme every 4 hours.[23] We therefore decided to use this dosage in our study to compare the effectiveness between oral and vaginal misoprostol.

The results showed statistically comparable demographic data, primary outcome measures, neonatal outcomes and peripartum data except for the mean dosage and number of cases with spontaneous rupture of membranes, which were different between the two groups. The rationale of these two differences would be as following.

Although the induction-to-full dilation time between the two groups were comparable, the present study showed that oral misoprostol was used with a mean of 2.86 doses, while vaginal route required only 1.69 doses (p=0.03). This could be explained by the difference in absorption kinetics between oral and vaginal misoprostol as confirmed by a recent study.[24] With equal doses of misoprostol administered either orally or vaginally, it was shown that the peak level was higher (227±144 vs. 165±86 pg/ml) and the mean time to peak level of misorpostol acid was shorter (34±17 vs. 80±27 min; p=0.03) in the "oral" group compared

with the "vaginal" group. This implied that metabolism of oral misoprostol was much faster than that of vaginal one. Therefore, more doses of oral misoprostol were required in order to accomplish the same uterine effects as those of vaginal route.

Another explanation for the above finding was also from a recent study comparing oral and vaginal misoprostol.[25] In that study, greater oxytocic effect of vaginal misoprostol was explained by the mechanism that prolonged absorption of drug to the myometrium via counter-current transfer from the perivaginal venous plexus to uterine arterioles might be the cause of this different in dosage requirement between oral and vaginal misoprostol as found in our study.

The difference in the number of cases with spontaneous rupture of membranes (SRM) between oral and vaginal misoprostol (2 vs. 14; p=0.002) might be caused directly by multiple vaginal insertions of drug in the "vaginal" group, which unintentionally caused spontaneous rupture of membranes and consequently accelerated labour,[26] or it was just a coincidental episode. Since the number of such cases was too small in this study, more further studies are required before final conclusion can be drawn. However, majority (more than 80 per cent) of cases in both groups had the membranes ruptured artificially (ARM), the results, the primary outcome measures in particular, should have not been affected by the remainders (SRM). Besides, when all of the SRM-cases were excluded and only the ARM-cases were calculated statistically (data not shown), the final results had still been the same. Finally, there has also been a study confirming that rupture of membranes (PROM) alone had very little effect on progression of labour when compared with that from misoprostol administration.[21]

In conclusion, the present study has shown that oral administration of misoprostol (50 microgramme every 4 hours) is simple and very effective for cervical ripening and labour induction at term or near term pregnancy. Effectively comparable to vaginal misoprostol, the oral route of administration is also advantageous for PROM-cases and cases which multiple vaginal examinations may increase the risk of ascending infection. However, more study is needed before this optimum oral dosage of misoprostol for these purposes can be prescribed for general obstetric practice.

References

1. Paxman JM, Rizo A, Brown L, Benson J. The clandestine epidemic: the practice of unsafe abortion in Latin America. Stud Fam Plann 1993; 24: 205-26.
2. Kramer RL, Gilson GJ, Morrison DS. A randomized trial of misoprostol and oxytocin for induction of labor: safety and efficacy. Obstet Gynecol 1997; 89: 387-91.
3. Escudero F, Contreras H. A comparative trial of labor induction with misoprostol versus oxytocin. Int J Obstet.1997; 57: 139-43.
4. Keirse M JNC. Prostaglandins in preinduction of cervical ripening: meta-analysis of worldwide clinical experience. J Reprod med 1993; 38: 89-100.
5. Chuck FG, Huffaker BJ. Labor induction with intravaginal misoprostol versus intracervical prostaglandin E gel (Prepidil gel) : randomized comparison. Am J Obstet Gynecol 1995; 173: 1137-42.
6. Sanchez-Ramos L, Kaunitz A. Oral administration of misoprostol for labor induction : a randomized controlled trial (letter). Obstet Gynecol 1997; 90: 153-4.
7. Windrim R, Benntt K, Mundle W. Oral administration of misoprostol for labor induction : a randomized controlled trial. Obstet Gynecol 1997; 89: 392-7.
8. Bugalho A, Bigue C, Machungo F. A comparative study of vaginal misoprostol and intravenous oxytocin for induction of labor. Gynecol Obstet Invest 1995; 39: 252-6.
9. Wing DA, Rachell A, Goodwin TM. Misoprostol: an effective agent for cervical ripening and labor induction. Am J Obstet Gynecol 1995; 172: 1811-6.
10. Buser D, Mora G, Arias F. A randomized comparison between misoprostol and dinoprostone for cervical ripening and labor induction in patients with unfavorable cervix. Obstet Gynecol 1997; 89: 581-5.
11. Chuck FJ, Huffaker BJ. Labor induction with intravaginal misoprostol versus intracervical prostaglandin E gel (Prepidil gel) : randomized comparison. Am J Obstet Gynecol 1995; 173: 1137-42.
12. Veraklis K, Gumina R, Stubblefield PG. Randomized controlled trial of vaginal misoprostol and intracervical prostaglandin E gel for induction of labor at term. Obstet Gynecol 1995; 86: 541-4.
13. Sanchez-Ramos L, Kaunitz AM, Wears RL. Misoprostol for cervical ripening and labor induction : a meta-analysis. Obstet Gynecol 1997; 89: 633-42.
14. Wing DA, Paul RH. A comparison of differing dosing regimens of vaginally administered misoprostol for preinduction cervical ripening and labor induction. Am J Obstet Gynecol 1996; 175: 158-64.
15. Bugalho A, Bique C, Machungo F. Low dose vaginal misoprostol for induction of labor with a live fetus. Int J

Gynecol Obstet 1995; 49: 149-55.
16. Farah LA, Sanchez-Ramos L, Rosa C. Randomized trial of two doses of the prostaglandin E analog misoprostol for labor induction. Am J Obstet Gynecol 1997; 177: 369-71.
17. Fletcher HM, Mitchell S, Frederick J. Intravaginal misoprostol versus dinoprostone cervical ripening and labor-induction agents. Obstet Gynecol 1994; 83: 244-7.
18. Fletcher HM, Mitchell S, Simeon D, Fredrick J. Intravaginal misoprostol as a cervical ripening agent. Br J Obstet Gynecol 1993; 100: 641-4.
19. William R, David C. Vaginal misoprostol for induction of labor : a randomized controlled trial. Obstet Gynecol 1996; 88: 521-5.
20. Bennett BB. Uterine rupture during induction of labor at term with intravaginal misoprostol. Obstet Gynecol 1997; 89: 832-3.
21. Ngai SW, To WK, Lao T. Cervical ripening priming with oral misoprostol in pre-labor rupture of membranes at term. Obstet Gynecol 1996; 87: 923-6.
22. Hannesh ME, Ohalsson A, Wang EE. Maternal conization with group B streptococcus and pre labor rupture of membranes at term: the role of induction of labor. Term PROM Study Group. Am J Obstet Gynecol 1997; 177: 780-5.
23. Srisomboon J, Singchai S. A comparison between 25 ug and 50 ug of intravaginal misoprostol for labor induction. J Obstet Gynecol Res (in press).
24. Zieman M, Fong SK, Benowitz NL. Absorption kinetics of misoprostol with oral or vaginal administration. Obstet Gynecol 1997; 90: 88-92.
25. Toppozada MK, Anwar MY, Hassan HA. Oral or vaginal misoprostol for induction of labor. Int J Gynecol Obstet 1997; 56: 135-9.
26. Sanchez-Ramos L, Kaunitz A. Oral administration of misoprostol for labor induction : a randomized controlled trial (letter). Obstet Gynecol 1997; 90: 153-4.