Oral Versus Vaginal Misoprostol for Labor Induction

Richard Hall, MD, Maria Duarte-Gardea, PhD, and Frederick Harlass, MD

OBJECTIVE: To compare the safety and effectiveness of vaginal with oral misoprostol for induction of labor.

METHODS: A total of 107 women with clinical indication for induction were randomly assigned to receive oral or vaginal misoprostol. Doses of 100 μg of oral or 25 μg of vaginal misoprostol were given every 3–4 hours. If cervical ripening or active labor did not occur, repeated doses of oral (100–200 μg) or vaginal (25–50 μg) were given until labor was established.

RESULTS: Fifty-nine women received oral misoprostol, and 48 received vaginal administration. Delivery time was similar for the vaginal and oral arms (1074 ± 488 minutes versus 930 ± 454 minutes, $P = .11$). Parity was significantly different ($P = .04$) for the vaginal and oral groups. The cesarean delivery rate was similar for the vaginal and oral arms (17% versus 15%, $P = .72$). The number of medication administrations was consistent between groups. Birth weight was not different for patients in the control and treatment groups (vaginal 3281 ± 507 g versus oral 3359 ± 541 g, $P = .44$). Chorioamnionitis and tachysystole were comparable for the oral and vaginal groups. There was no statistical difference in neonatal outcomes. Similar proportions of infants were admitted to the well baby nursery and intermediate care nursery.

CONCLUSION: These findings indicate that, in a closely supervised hospital setting with adequate monitoring, oral misoprostol has the potential to induce labor as safely and effectively as its vaginal analogue. (Obstet Gynecol 2002; 99:1044–8. © 2002 by the American College of Obstetricians and Gynecologists.)

The search for the ideal agent, timing, and dosage interval to convert an unfavorable cervix to one receptive to delivery is an ongoing process. Attention has focused on prostaglandins as effective pharmacologic adjuncts to induction. Prostaglandin estradiol (PGE_2) is an agent that has been shown to have utility in promoting cervical ripening and labor initiation. Dinosprone is currently the only medication specifically approved by the Food and Drug Administration for this purpose. Although effective, these agents are expensive and require refrigeration. Because of these issues, the search for alternatives of more cost-effective cervical ripening has continued. One agent that has become intensely investigated is misoprostol, a PGE_1 analogue. Misoprostol has been approved for the treatment of pepetic ulcers. Initial studies attested to misoprostol's uterotonic abilities, and intravaginal application was successfully used to terminate first- and second-trimester pregnancies.[1,2] The first investigations using misoprostol in cervical ripening and cervical induction came from South America. Subsequent studies showed intravaginal misoprostol comparing favorably with other commonly used induction agents, including prostaglandins and oxytocin.[3–13] Misoprostol compares favorably with the currently approved agent dinoprostone in expense and storage requirements. The optimal dosing regimen, timing, and route of administration remain the focus of ongoing research.[14–16] Although vaginal application of misoprostol has been validated as a reasonable means of induction, there is patient resistance to the digital exams necessary for placement of the agent. We designed this randomized trial to compare the safety and effectiveness of vaginal misoprostol with oral misoprostol for induction of labor.

From the Department of Obstetrics and Gynecology, Texas Tech University Health Sciences Center at El Paso, El Paso, Texas; and School of Allied Health, The University of Texas at El Paso, El Paso, Texas.

MATERIALS AND METHODS

The study was conducted between June 1998 and June 1999 at R.E. Thomason General Hospital in El Paso, Texas. Institutional Review Board approval was obtained, and each participant signed an informed consent form. Annually, the hospital performs an average of 5000 deliveries of predominantly Hispanic women living in this border city. El Paso is located in the western tip of Texas, bordering on Mexico and New Mexico. El Paso and Ciudad Juarez form the largest border community on the US-Mexico border. The current population for the binational metropolitan area is estimated to be about 2 million. The Hispanic population for El Paso county was reported to be 73.5% in 1996.

Patients were eligible for inclusion if they presented with indications for induction and a single live fetus older than 37 weeks' gestation in cephalic presentation and no contraindication to vaginal delivery. Patients with previous uterine surgery, known prostaglandin hypersensitiv-

0029-7844/02/$22.00
PII S0029-7844(02)01995-6

ity, three or more contractions per 10 minutes, nonreassuring fetal heart tracings, and those with vaginal birth contraindications were excluded from participation.

Before the initiation of the study, computer randomization was performed. A series of consecutively numbered opaque envelopes with each envelope containing an even or odd number was generated. Even numbers indicated oral treatment, and odd numbers indicated vaginal assignment. Sealed envelopes were available to the attending physician at the labor and delivery unit. After the rationale for induction was reviewed and approved and cervical examination confirmed a Bishop score of less than 5,[17] consent was obtained. The sealed envelope in turn indicating oral or vaginal treatment was then opened. Patients in the oral group were initially given 100 μg of misoprostol orally. This was repeated every 3–4 hours until the occurrence of progressive labor (as evidenced by a Bishop score of 7 or more), a contraction pattern of three every 10 minutes, and evidence of fetal intolerance or delivery. If an insufficient response was noted with the first application, the physician managing labor had the discretion to increase subsequent doses to 200 μg. The physician made decisions regarding pain amelioration, rupture of membranes, and the need for oxytocin augmentation once active labor was achieved. All study inductions were done with continuous monitoring of uterine contractility and fetal heart rate. Fetal heart rate tracing was according to the caregiver's interpretation. Patients in the vaginal group received 25 μg of misoprostol placed at the posterior fornix using water as a lubricant. The need for repeated dosing in this group was managed by the same considerations as with the study group. The physician managing labor had the option of increasing subsequent vaginal doses to 50 μg.

The primary outcome measurement was the time from induction initiation to vaginal delivery. Secondary outcome variables included fetal status (as evidenced by Apgar scores, presence of meconium, or admission to a neonatal intensive care unit) and the mode of delivery. Cord artery acid-base values were not measured. Data were analyzed using SPSS-PC+ (Statistical Package for the Social Sciences, Chicago, IL) programs. Differences for continuous and categoric variables were analyzed using the t and χ^2 tests. Because parity was different between groups, the Mantel-Haenszel χ^2 test was conducted. Assuming an induction interval mean from onset to delivery of 12 ± 4 hours, 45 women were required in each arm to detect with 80% power a 20% difference in means between groups given a significance level of 0.05.[10]

Table 1. Induction Indication

Indication	Vaginal (n = 48)	Oral (n = 59)
Postdates	18 (49)	19 (51)
Rupture of membranes	14 (50)	14 (50)
Preeclampsia	6 (37)	10 (63)
Oligohydramnios	6 (46)	7 (54)
Nonreactive fetal heart tracing	1 (17)	5 (83)
Intrauterine growth retardation	1 (33)	2 (67)
Diabetes	1 (50)	1 (50)
Other	1 (50)	1 (50)

Data are presented as n (%).

RESULTS

A total of 107 women were enrolled in the study. Fifty-nine women were assigned to oral misoprostol and 48 to vaginal administration. Table 1 displays induction indication for the oral and vaginal groups. Parity was significantly different (P = .04) for the vaginal and oral groups. After adjusting for parity, no significant difference between groups was found in mode of delivery (Table 2). The cesarean delivery rate for the vaginal and oral arms (17% versus 15%, P = .72) was consistent with the institutional rate of 17%.

Nulliparous women receiving oral misoprostol were twice as likely to need assistance in delivery. Of the 33 nulliparous participants undergoing oral induction, four of 33 (13%) required forceps or vacuum, whereas seven (21%) underwent cesarean delivery. Five cesarean deliveries were needed for arrest of labor in the active phase and two were for nonreassuring fetal heart tracings. One infant (in the arrest of labor in the active phase) went to the intermediate care nursery for neonatal depression but subsequently did well. All the others had normal Apgar scores and newborn evaluations. Nulliparous participants who received vaginal misoprostol demonstrated less need for obstetric intervention. Of the 36

Table 2. Parity and Mode of Delivery in the Vaginal and Oral Misoprostol Groups

	Vaginal (n = 48)	Oral (n = 59)	P
Parity			.04*
Nulliparous	36 (75)	33 (56)	
Multiparous	12 (25)	26 (44)	
Mode of delivery			.72†
Spontaneous vaginal	37 (77)	43 (73)	
Vacuum	3 (6)	5 (8)	
Forceps	0	2 (3)	
Cesarean	8 (17)	9 (15)	

Data are presented as n (%)
* χ^2.
† Mantel-Haenszel χ^2.

Table 3. Outcome of Labor in the Vaginal and Oral Misoprostol Groups

	Vaginal (n = 48)	Oral (n = 59)	P
Induction initiation to vaginal delivery (min)	1074 ± 488	930 ± 454	.11*
Number of administrations	1.8 ± 1.0	1.5 ± 0.9	.17*
Use of pitocin to augment labor	43 (89)	47 (79)	.31†
Postpartum maternal complications	2 (4)	1 (2)	.30†
Meconium	3 (6)	9 (15)	.07†
Choriamnionitis	4 (8)	3 (5)	.66†

Data are presented as mean ± standard deviation or n (%).
* Student t test.
† Mantel-Haenszel χ^2.

participants, one (3%) required instrumental delivery, and five (14%) required cesarean delivery. Three cesarean deliveries were for nonreassuring fetal heart tracings and two were for arrest of labor in the active phase. Although one of the infants initially went to the intermediate care nursery for respiratory insufficiency, all subsequently did well.

A reversal pattern was seen when multiparous patients were evaluated: a vaginal birth was three times more likely with the oral study arm of the investigation. Outcomes of labor including the number of administrations did not show a significant difference. The number of medication administration was similar in the vaginal and oral groups (1.8 ± 1.0 versus 1.5 ± 1.5, P = .17); however, multiple doses of misoprostol to produce desired effects in cervical ripening were used in some patients. A cumulative maximum of 225 μg intravaginally and 800 μg orally was used in patients who were especially refractory to labor induction. Although greater levels of misoprostol demonstrated an increased tendency to uterine tachysystole, no difference was seen between the oral and vaginal study arms. Meconium was reported to be higher in the oral arm when compared with the vaginal treatment (15% versus 6%, P = .07). However, this difference did not approach statistical significance (Table 3). Other neonatal outcomes including Apgar scores, birth weight, and neonatal infection did not show a significant difference. Similar proportions of infants in both groups were admitted to the well baby nursery and intermediate care nursery (Table 4). The study was well tolerated by the maternal participants.

In the oral arm, one woman had an atonic uterus that responded to methergine administration, whereas another had a retained placenta. In the vaginal group, one woman had a wound seroma at the cesarean incision site. None of these sequelae can be attributed to the use of misoprostol. Two infants in the control arm had Apgar scores less than 7 at 5 minutes. Both were unassisted vaginal deliveries: the first had an Apgar score of 5 at 5 minutes, which improved to 7 at 10 minutes. The infant went to the intermediate nursery for respiratory distress and did well. The second was diagnosed with neonatal depression and had an Apgar score of 6 at 5 minutes and 8 by 10 minutes. This infant was also initially admitted to the intermediate care nursery and subsequently did well. Of the two infants in the vaginal group who went to the intensive care nursery, one was for observation after a difficult shoulder dystocia and the other was for respiratory distress. Both had uneventful courses and were discharged in stable condition.

Table 4. Neonatal Outcome in the Vaginal and Oral Misoprostol Groups

	Vaginal (n = 48)	Oral (n = 59)	P
Apgar <7 at 5 min	2 (4)	0	.08*
Birth weight (g)	3281 ± 507	3359 ± 541	.44†
Neonatal infection	8 (17)	5 (8)	.32*
Fetal intolerance of labor/tachysystole	4 (8)	4 (7)	.85*
Admission to special care neonatal unit			.34*
Well baby nursery	34 (71)	45 (76)	
Intermediate care nursery	11 (23)	14 (23)	
Intensive care nursery	3 (6)	0	

Data are presented as mean ± standard deviation or n (%).
* Mantel-Haenszel χ^2.
† Student t test.

DISCUSSION

Previous studies on the efficacy of oral misoprostol have used different dosing regimens with varying degrees of effectiveness. The results obtained in this study indicate that an initial oral application of 100 μg of oral misoprostol is similar in terms of efficacy and safety to an initial vaginal dose of 25 μg. The consensus of researchers' initial dose of 50 μg of oral misoprostol indicates less effective and longer induction time, presumably because of the previously mentioned "first-pass effects." Kwon et al,[18] Bennett et al,[19] and Wing et al[20] reported less effective inductions, whereas Windrim et al[21] found a 50-μg oral dose to be equally as effective in inducing labor as a 50-μg vaginal dose. In a study that used an initial dose of 200 μg of oral misoprostol, Carlan et al[22] reported similar efficacy with an initial 50-μg intravaginal application. Although there were no differences in outcomes, Carlan et al[22] reported that the initial dose of 200 μg is associated with a higher frequency of excessive uterine contractility and intervention. As in our study, Toppozada et al[23] used an initial oral misoprostol dosage of 100 μg although the vaginal arm differed in that 100 μg was used here as well. Inductions were more rapid with the vaginal approach, presumably because of the comparatively large intravaginal dose. Although there were similar clinical outcomes between the two arms, the vaginal approach was associated with more tachysystole and abnormal fetal heart tracings. Oral misoprostol appears to be a valid addition to the induction therapeutic armamentarium.

Because of the documented differences in bioavailability in oral versus vaginal misoprostol, a larger dose was used to compensate for the first-pass effects. It may be that an initial 100-μg dose of oral misoprostol effectively skirts the Scylla of ineffective induction and the Charybdis of tachysystole. Unlike other studies using smaller oral doses, the time from induction initiation to vaginal delivery was not prolonged compared with controls. This regimen detected no tendency towards the uterine tachysystole associated with larger misoprostol doses. There were no significant differences in outcomes between the oral and vaginal arms of the study. The perceived difference in delivery modes between nulliparous and multiparous participants in the respective arms was mentioned for the sake of completeness, and after statistical analyses the proportions in question did not approach statistical significance. Potential differences in rates of choriamnionitis were not seen in this study, presumably because of the relatively small numbers. Our findings indicate that, in a closely supervised hospital setting with adequate monitoring, oral misoprostol has the potential to induce labor as safely and effectively as its vaginal analogue. Additional research is needed to categorically determine the most effective dosing regimens and intervals.

REFERENCES

1. Jain JK, Mishell DR. A comparison of intravaginal misoprostol with prostaglandin E2 for termination of second trimester pregnancy. N Engl J Med 1994;331:290–3.
2. El-Rafaey H, Templeton A. Early induction of abortion by a combination of oral mifepristone and misoprostol administered by the vaginal route. Contraception 1994;49: 111–4.
3. Sanchez-Ramos L, Kaunitz AM, Del Valle GO, Delke I, Schroeder PA, Briones DK. Labor induction with the prostaglandin E1 methyl analogue misoprostol versus oxytocin: A randomized trial. Obstet Gynecol 1993;81: 332–6.
4. Fletcher H, Mitchell S, Simeon D, Frederick J, Brown D. Intravaginal misoprostol versus dinoprostone as cervical ripening and labor-inducing agents. Obstet Gynecol 1994; 83:244–7.
5. Varaklis K, Gumina R, Stubblefield PG. Randomized controlled trial of vaginal misoprostol and intracervical prostaglandin E2 gel for induction of labor at term. Obstet Gynecol 1995;86:541–4.
6. Chuck FJ, Huffaker BJ. Labor induction with intravaginal misoprostol versus intracervical prostaglandin E2 gel (Prepidil gel): Randomized comparison. Am J Obstet Gynecol 1995;86:541–4.
7. Mundle WR, Young DC. Vaginal misoprostol for induction of labor: A randomized controlled trial. Obstet Gynecol 1996;88:521–5.
8. Surbeck DV, Boesinger H, Hoesli I, Pavid N, Holzgreve W. A double blinded comparison of the safety and efficacy of intravaginal misoprostol and prostaglandin E2 to induce labor. Am J Obstet Gynecol 1997;177:1018–23.
9. Gottschall DS, Borgida AF, Mihalek JJ, Sauer F, Rodis JF. A randomized clinical trial comparing misoprostol with prostaglandin E2 gel for preinduction cervical ripening. Am J Obstet Gynecol 1997;177:1067–70.
10. Kramer RL, Gilson GJ, Morrison DS, Martin D, Gonzales JL, Qualls CR. A randomized trial of misoprostol and oxytocin for induction of labor: Safety and efficacy. Obstet Gynecol 1997;89:387–91.
11. Wing DA, Rahall A, Jones MM, Goodwin TM, Paul RH. Misoprostol: An effective agent for cervical ripening and labor induction. Am J Obstet Gynecol 1995;172:1811–6.
12. Wing DA, Ortiz-Omphroy G, Paul RH. A comparison of intermittent vaginal administration of misoprostol with continuous dinoprostone for cervical ripening and labor induction. Am J Obstet Gynecol 1997;177:612–8.
13. Sanchez-Ramos L, Peterson DE, Delke I, Gaudier FL, Kaunitz AM. Labor induction with prostaglandin E1 miso-

prostol compared with dinoprostone vaginal insert: A randomized trial. Obstet Gynecol 1998;91:401–5.

14. Wing DA, Paul RH. A comparison of different dosing regimens of vaginally administered misoprostol for preinduction cervical ripening and labor induction. Am J Obstet Gynecol 1996;175:158–64.
15. Sanchez-Ramos L, Kaunitz AM, Wears RL, Delke I, Gaudier FL. Misoprostol for cervical ripening and labor induction: A meta-analysis. Obstet Gynecol 1997;89: 633–42.
16. Farah LA, Sanchez-Ramos L, Rosa C, Del Valle GO, Gaudier FL, Delke I, et al. Randomized trial of two doses of the prostaglandin E_1 analog misoprostol for labor induction. Am J Obstet Gynecol 1997;177:364–71.
17. Bishop EH. Pelvic scoring for elective induction. Obstet Gynecol 1964;24:266–8.
18. Kwon JS, Mackenzie VP, Davies GA. A comparison of oral and vaginal misoprostol for induction of labour at term: A randomized trial. Am J Obstet Gynecol 1999;180: S128.
19. Bennett KA, Butt K, Crane JM, Hutchens D, Young DC. A masked randomized comparison of oral and vaginal administration of misoprostol for labor induction. Obstet Gynecol 1998;92:481–6.
20. Wing DA, Ham D, Paul RH. A comparison of orally administered misoprostol to vaginally administered misoprostol for cervical ripening and labour induction. Am J Obstet Gynecol 1999;180:1155–60.
21. Windrim R, Bennett K, Mundle W, Young D. Oral administration of misoprostol for labor induction: A randomized controlled trial. Obstet Gynecol 1997;89:92–7.
22. Carlan SJ, Bouldin S, Blust D, O'Brian WF. Safety and efficacy of misoprostol orally and vaginally: A randomized trial. Obstet Gynecol 2001;98:107–12.
23. Toppozada MK, Anwar MY, Hassan HA, el-Gazaerly WS. Oral or vaginal misoprostol for induction of labor. Int J Gynaecol Obstet 1997;56:135–9.

Address reprint requests to: Frederick Harlass, MD, Texas Tech University Health Sciences Center, Department of Obstetrics and Gynecology, 4800 Alberta Avenue, El Paso, TX 79905; E-mail: fharlass@ttmcelp.ttuhsc.edu.

Received August 7, 2001. Received in revised form December 12, 2001. Accepted January 17, 2002.