

A Randomized Trial of Oral Misoprostol in Premenopausal Women Before Hysteroscopy

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Abstract

Objective: To determine if the use of oral misoprostol in premenopausal women undergoing diagnostic hysteroscopy produces a clinically important difference in pre-procedural cervical dilatation.

Methods: At a tertiary care hospital, premenopausal women undergoing diagnostic hysteroscopy were randomized to receive either 400 µg of misoprostol or a vitamin B6 placebo orally 12 hours before the procedure. Patients were stratified on the basis of parity. The primary outcome was the pre-procedural dilatation of the cervix. Secondary outcomes included the need to further dilate the cervix, the time required to further dilate the cervix, and side effects.

Results: Sixty-four women (11 nulliparous and 53 parous) undergoing diagnostic hysteroscopy consented to participate in the study. Thirty-three women received misoprostol and 31 received placebo. Baseline demographics showed no difference in age and parity between the two groups. There were no significant differences in pre-procedural dilatation (5.0 mm vs. 4.7 mm, $P = 0.52$), need to further dilate the cervix (56.7% vs. 63.0%, $P = 0.63$), and time required to further dilate the cervix (12.7 seconds vs. 25.7 seconds, $P = 0.27$). Significantly more women in the misoprostol group experienced menstrual-like cramping (24.2% vs. 3.3%, $P = 0.03$) and vaginal spotting (21.2% vs. 3.3%, $P = 0.05$).

Conclusion: In premenopausal women, there is no improvement in pre-procedural cervical dilatation with administration of oral misoprostol 12 hours before diagnostic hysteroscopy. Further research is required in both nulliparous and parous premenopausal women to determine whether oral misoprostol improves cervical dilatation and, if so, the ideal dose, route and timing.

Résumé

Objectif : Déterminer si l'administration de misoprostol par voie orale aux femmes préménopausées subissant une hystérocopie diagnostique génère une différence importante sur le plan clinique en matière de dilatation cervicale préintervention.

Key Words: Hysteroscopy, misoprostol, cervical dilatation, cervical ripening, randomized controlled trial

Competing Interests: None declared.

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Méthodes : Au sein d'un hôpital de soins tertiaires, les femmes préménopausées subissant une hystérocopie diagnostique ont été affectées, au hasard, à un groupe se voyant administrer 400 µg de misoprostol ou à un groupe se voyant administrer un placebo de vitamine B6 (l'administration se déroulant par voie orale, 12 heures avant l'intervention, dans chacun de ces groupes). Les patientes ont été stratifiées en fonction de la parité. La dilatation préintervention du col utérin constituait le critère d'évaluation principal. Parmi les critères d'évaluation secondaires, on trouvait la nécessité de dilater davantage le col utérin, le délai requis pour dilater davantage le col utérin et les effets indésirables.

Résultats : Soixante-quatre femmes (11 nullipares et 53 pares) subissant une hystérocopie diagnostique ont consenti à participer à l'étude. Trente-trois femmes se sont vu administrer du misoprostol et 31, un placebo. Les données démographiques de départ n'indiquaient aucune différence en matière d'âge et de parité entre les deux groupes. Aucune différence significative n'a été constatée en matière de dilatation préintervention (5,0 mm, par comparaison avec 4,7 mm, $P = 0,52$), de nécessité de dilater davantage le col utérin (56,7 %, par comparaison avec 63,0 %, $P = 0,63$) et de délai requis pour dilater davantage le col utérin (12,7 secondes, par comparaison avec 25,7 secondes, $P = 0,27$). Un nombre considérablement plus élevé de femmes du groupe « Misoprostol » ont connu des crampes de type menstruel (24,2 %, par comparaison avec 3,3 %, $P = 0,03$) et une microrragie (21,2 %, par comparaison avec 3,3 %, $P = 0,05$).

Conclusion : Chez les femmes préménopausées, aucune amélioration de la dilatation cervicale préintervention n'est constatée à la suite de l'administration de misoprostol par voie orale 12 heures avant la tenue de l'hystérocopie diagnostique. D'autres recherches s'avèrent nécessaires, tant chez les femmes préménopausées nullipares que pares, afin de déterminer si le misoprostol administré par voie orale améliore la dilatation cervicale et, si tel est le cas, d'en identifier la posologie idéale.

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INTRODUCTION

As minimally invasive procedures become the standard surgical approach and as minimizing operating time becomes critical, the ability to perform procedures under local anaesthesia carries an advantage. Before making hysteroscopy under local anaesthesia the standard of care in our centre, we sought to identify techniques to improve patient acceptance and to simplify the procedure.

Misoprostol, a prostaglandin E₁ analogue used for treatment of gastric ulcers induced by nonsteroidal anti-inflammatory drugs, has been shown to be effective in priming the cervix for induction of labour and before curettage for surgical abortion.¹⁻⁶ However, reports of its effectiveness in non-pregnant women to reduce complications of hysteroscopy related to cervical dilatation have described conflicting results.^{2,7-16} A systematic review by our group concluded that misoprostol appears to be promising as a cervical ripening agent prior to hysteroscopy, but further research is needed to identify the ideal dose, route, and timing.¹⁶

The purpose of this double-blind randomized controlled trial was to determine if oral misoprostol would improve pre-procedural cervical dilatation in premenopausal women and avoid the need to dilate the cervix before a diagnostic hysteroscopy.

MATERIAL AND METHODS

This study was performed between January 2001 and January 2003 in the Department of Obstetrics and Gynecology, Health Sciences Centre, Eastern Health, Memorial University of Newfoundland, St. John's, Newfoundland, a tertiary care centre. The study was approved by the Human Investigation Committee of Memorial University and the Ethics Board of the hospital. Patients were recruited from gynaecology clinics by their attending physicians, and written consent was obtained.

Subjects eligible for the study were healthy premenopausal women, 19 years and over, who were scheduled for diagnostic hysteroscopy. The exclusion criteria were known hypersensitivity or allergy to prostaglandins, seizure disorder, or liver disease with abnormal liver function tests.

Consenting women were randomized using a computer-generated list of random numbers to receive either 400 µg of misoprostol or 50 mg vitamin B6 (used as placebo) orally 12 hours prior to the procedure. The oral route was chosen as it would be easy and convenient for women to self-administer. The hospital pharmacy dispensed the medication according to the random assignment. The women and health care providers were blinded to the treatment allocation. Women were stratified based on parity; a parous woman was defined as a woman who had had a delivery after 20 weeks' gestation.

The primary outcome was the pre-procedural measured dilatation of the cervix. The need to further dilate the cervix, the time required to further dilate the cervix, and side effects including nausea, vomiting, diarrhea, abdominal cramping, vaginal bleeding/spotting, and headache were recorded as secondary outcomes.

To help ensure compliance, patients were contacted by telephone on the night before surgery to remind them to take the medication. All but one woman took the assigned medication. On arrival at the day surgery unit, the women were asked to complete a questionnaire regarding any side effects experienced. They were also asked if they would take the medication if they required hysteroscopy again.

The patients were taken to the operating room and underwent general anaesthesia using a standard protocol. They were placed in lithotomy position and prepared and draped in the standard surgical fashion. A weighted speculum was placed into the vagina to allow visualization of the cervix. We then attempted to insert Hegar dilators into the cervical canal, beginning with the largest (#9) and continuing with progressively smaller dilators until the dilator passed easily, in order to determine the pre-procedural diameter. If the diameter of the cervical canal measured less than the diameter of the diagnostic hysteroscope (6 mm), the time required to dilate the cervix was recorded in seconds. The remaining procedure was completed according to standard protocol for hysteroscopy.

The required sample size was calculated based on the mean pre-procedural dilatation. A standard deviation of 1.3 mm was used from previous research,² and the clinically important difference of 1 mm was chosen on the basis of interviews with gynaecologists. A difference of 1 mm was felt to be clinically important as it may mean the difference between requiring and not requiring additional cervical dilatation. As any additional dilatation can be associated with potential complications, even a 1 mm difference was therefore felt to be clinically significant. The number of women required to demonstrate this difference, with a power of 80% and a significance level of 5%, was 28 per group, or 56 in total.

The data were analyzed on the basis of intent to treat, using SPSS 14.0 (Analytical Software, Tallahassee, FL). Shapiro-Wilks test was used to determine normality of the data. Continuous data were analyzed with the Student *t* test. The Fisher exact test and chi-squared test were used to analyze proportions. Significance was set at $P < 0.05$. The CONSORT criteria for randomized clinical trials was followed.¹⁷

ABBREVIATIONS

CI	confidence intervals
NSAID	nonsteroidal anti-inflammatory drugs

Figure. Flow diagram of study enrolment

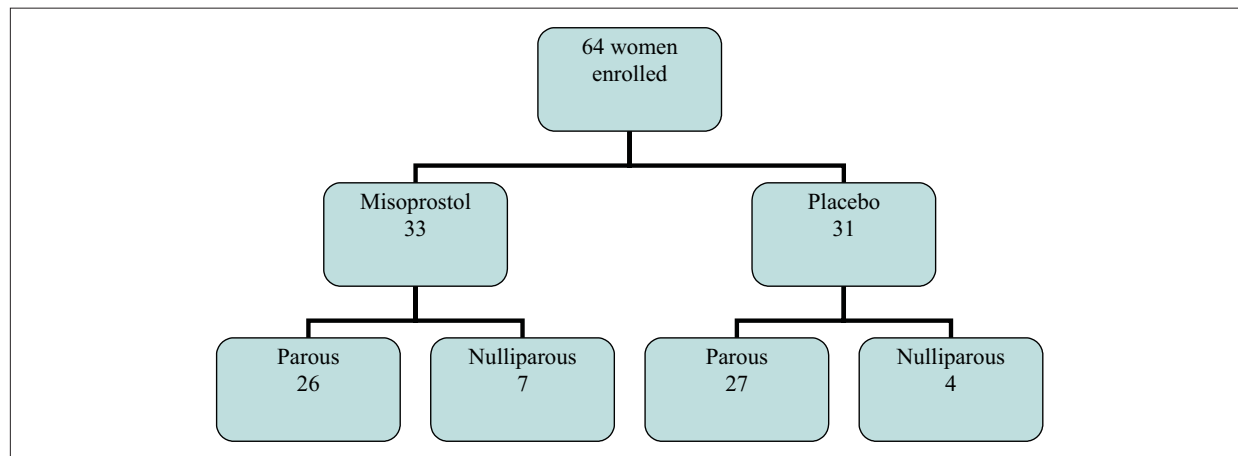


Table 1. Demographics and cervical dilatation

	Misoprostol n = 33	Placebo n = 31	P
Age (years)	39.9	40.7	0.67*
Parous	26 (78.8%)	27 (87.1%)	0.51†
Nulliparous	7 (21.2%)	4 (12.9%)	0.51†
Need to further dilate the cervix	17/30 (56.7%)	17/27 (63.0%)	0.63†
Pre-procedural dilatation (mm)	5.0 (n = 30)	4.7 (n = 28)	0.52*
Time required to further dilate cervix (seconds)	12.7 (n = 30)	25.7 (n = 27)	0.27*
Post-procedural dilatation (mm)	6.5 (n = 30)	6.6 (n = 29)	0.83*

*Mean and student *t* test; †n (%) and chi-square test.

RESULTS

Sixty-four premenopausal women were enrolled and underwent diagnostic hysteroscopy, 33 women receiving misoprostol and 31 receiving placebo. Fifty-three women were parous and 11 were nulliparous (Figure). Data were missing on pre-procedural dilatation for three women in the misoprostol group and three women in the placebo group; on post-procedural dilatation for three women in the misoprostol group and two women in the placebo group; on time required to further dilate the cervix for three women in the misoprostol group and two women in the placebo group; and on side effects for one woman in the placebo group.

There were no differences between the misoprostol and placebo groups in the need for further cervical dilatation (relative risk 0.88; 95% CI 0.54–1.45), pre-procedural dilatation (mean difference 0.32, 95% CI 0.66–1.30), or time required to further dilate the cervix (mean difference 13 seconds, 95% CI 36.5–10.5) (Table 1). No complications of

cervical laceration or uterine perforation were reported. When subgroup analysis was performed for parous and nulliparous women, there were no significant differences between the groups in these outcomes (Table 2). From the questionnaire, more patients in the misoprostol group experienced menstrual-like cramping and vaginal spotting (Table 3). Despite the higher rates of these side effects, only one woman in the misoprostol group indicated she would not take the medication again for this procedure.

DISCUSSION

The utility of diagnostic hysteroscopy could be improved by facilitating its use in an office setting. One limiting factor is cervical dilatation. If misoprostol could decrease or eliminate the need for the cervical dilatation, hysteroscopy could be accomplished more easily. We undertook this study to determine if the use of misoprostol would improve baseline cervical dilatation before diagnostic hysteroscopy and obviate the need for dilatation.

Table 2. Subgroup analysis of parous versus nulliparous women

	Misoprostol	Placebo	P
Need to further dilate the cervix			
Parous	15/25 (60.0%)	14/24 (58.3%)	0.91*
Nulliparous	2/5 (40%)	3/3 (100%)	0.20†
Pre-procedural dilatation (mm)			
Parous	5.1 (n = 25)	5.1 (n = 24)	0.99‡
Nulliparous	4.8 (n = 5)	2.5 (n = 4)	0.16‡
Time required to further dilate the cervix (seconds)			
Parous	12.5 (n = 25)	21.6 (n = 24)	0.34‡
Nulliparous	14 (n = 5)	28 (n = 3)	0.49‡
Post-procedural dilatation (mm)			
Parous	6.5 (n = 25)	6.5 (n = 25)	0.99‡
Nulliparous	6.4 (n = 5)	6.8 (n = 4)	0.58‡

*chi-square test (%); †Fisher exact test; ‡Student *t* test**Table 3. Side effects and satisfaction survey results**

Side Effect	Misoprostol n = 33 (%)	Placebo n = 30 (%)	P*
Nausea	1 (3.0)	1 (3.3)	0.99
Vomiting	0 (0)	0 (0)	
Diarrhea	2 (6.1)	1 (3.3)	0.99
Abdominal pain	3 (9.1)	0 (0)	0.24
Menstrual cramps	8 (24.2)	1 (3.3)	0.03
Vaginal bleeding	1 (3.0)	0 (0)	0.99
Vaginal spotting	7 (21.2)	1 (3.3)	0.05
Headache	1 (3.0)	3 (10.0)	0.34

*Fisher exact test

The research to date using misoprostol clearly demonstrates its effectiveness in cervical ripening on a well-estrogenized cervix in pregnant women, both early and late in pregnancy.¹⁻⁶ As we continue to learn about the pharmacodynamics of misoprostol, it appears that it may not be as effective in hypoestrogenic women; studies have shown no effect on pre-procedural dilatation of the cervix in women who were postmenopausal or taking GnRH agonists.^{10-14,16}

A clinically significant outcome in this context is to eliminate the need for cervical dilatation. In a study by Preuthippan et al., only 6.5% women in the vaginal misoprostol group needed pre-procedural dilatation compared with 31% in the placebo group, but all patients in this study were nulliparous.⁷ This result was echoed in a second study on operative hysteroscopy by the same group in 2000, showing 75% of women in the misoprostol group required cervical dilatation compared with 95% of women in the

placebo group; again most patients were nulliparous.⁸ The proportion of parous patients in our study was much higher (82.8%) and may account for the difference in our findings. Other studies not finding a benefit with use of misoprostol before hysteroscopy involve hypoestrogenic women.¹⁰⁻¹⁴

Unlike previous studies, our study failed to show a benefit from use of oral misoprostol before hysteroscopy in premenopausal women. The timing of administration of misoprostol (12 hours prior to hysteroscopy) is similar to other studies.^{2, 7,8,10} However, some of the previous studies used misoprostol administered vaginally,^{7,9} whereas we used oral administration. Studies of the pharmacokinetics of misoprostol show vaginal administration is associated with a longer time to peak serum misoprostol levels than oral administration, but with longer bioavailability.^{18,19} Because the single dose of misoprostol was given 12 hours before the procedure, this may explain the difference

between our findings and others. Perhaps a better effect on cervical ripening may be seen if the hysteroscopy is performed sooner after the oral dose of misoprostol.

On review of the side effects and reported satisfaction, all but one woman reported they would take the drug again. This appeared to indicate that despite a significant increase in the rates of spotting and cramping, these side effects were not bothersome enough to prohibit its use.

It is important that the limitations of the study be addressed. Several different surgeons performed the hysteroscopies, but over 80% of the procedures were performed by a single surgeon. We did not attempt to measure the force required to dilate the cervix, as has been done by some investigators^{10,12}; however, we feel that the actual cervical dilatation and the need to dilate the cervix further are more important clinical outcomes. Unfortunately, we do not have information on women who were eligible for the study but were not approached or declined to participate. Nevertheless, the age and parity of the women in the study are reflective of the population of premenopausal women undergoing diagnostic hysteroscopy at our centre. Although we performed secondary analyses based on parity, we did not have adequate statistical power to evaluate the primary outcome in these subgroups, particularly in the nulliparous group. Perhaps it is in this group that misoprostol has the most beneficial effect. We recognize that the diameter of the hysteroscope used in our centre during the study (6 mm) is larger than that of currently available office hysteroscopes (1–5 mm). Use of smaller hysteroscopes is less likely to require additional dilatation, and this may explain the number of women requiring additional cervical dilatation in our study (59.6%). Finally, women in the study had diagnostic hysteroscopy performed in the operating room under general anaesthetic because there was no space available at that time in our outpatient clinics. We acknowledge that in many centres, hysteroscopy is performed in an office setting, but this was not the standard practice at the time of the study. We wanted to determine if misoprostol would help facilitate the procedure before beginning to do the procedure in an office setting.

CONCLUSION

In contrast to previous reports, we did not find that oral misoprostol given 12 hours prior to hysteroscopy improved cervical dilatation. Further research is required, in both nulliparous and parous premenopausal women, to determine if there is indeed a beneficial effect and, if so, the ideal dose, route, and timing.

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