Vaginal misoprostol for cervical ripening before operative hysteroscopy in pre-menopausal women: a double-blind, placebo-controlled trial with three dose regimens

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BACKGROUND: To evaluate the effects of vaginal misoprostol on cervical dilatation before operative hysteroscopy in pre-menopausal women. METHODS: Four groups of 12 women were randomly assigned to receive either placebo or vaginal misoprostol in doses of 200, 400 or 800 μg 4 h before the surgical procedure. The number of patients was calculated with an α = 0.01 and β =0.20 for a difference of 50%. The primary outcome measure was cervical width, assessed by the largest size of Hegar dilator that could be inserted without resistance. The secondary outcomes were subjective assessments of the ease of dilatation and pre-operative pain, as well as adverse effects and complications. RESULTS: There was no difference in the baseline diameter of the cervical opening between the placebo group (6.1 ± 1.4 cm) and the misoprostol groups (6.3 ± 2.1 cm). The groups did not differ significantly in the time required for dilatation, ease of dilation, or the number of adverse effects. Pre-operative pain, evaluated by a pain scale, was greater in the treatment groups and was rated at 2.5 ± 2.3 (P = 0.015), 2.4 ± 1.2 (P = 0.073) and 2.8 ± 2.9 (P = 0.012) respectively for each increasing dose group. CONCLUSIONS: Vaginal misoprostol applied 4 h before operative hysteroscopy at three different doses did not reduce the need for cervical dilatation, did not facilitate hysteroscopic surgery, and increased pre-operative pain.

Key words: cervical ripening/misoprostol/operative hysteroscopy/pre-menopausal women/vaginal route

Introduction

Operative hysteroscopy is an important tool for the management of intrauterine abnormalities. Complications encountered during the procedure are partly related to difficulties in cervical dilatation. These include cervical tears, creation of a false track, haemorrhaging, uterine perforation requiring laparoscopy, or simply difficulty in entering the internal cervical os with the resectoscope (Loffer et al., 1989; Cooper et al., 1996). The incidence of these complications can be reduced if the cervix is ripened before the procedure by inserting laminaria into the cervical canal the night before surgery (Ostrzenski, 1994) or by using Sulprostone gel (Rath et al., 1985).

Misoprostol, a synthetic prostaglandin E1 analogue widely prescribed for prevention and treatment of gastric ulcers, has been shown to have cervical ripening effects in both pregnant and non-pregnant patients when administered either orally or vaginally (Ngai et al., 1997; Preutthipan et al., 2000). The systemic bioavailability of misoprostol is three times greater when it is administered vaginally than orally (Zieman et al., 1997) and suggests that vaginal administration could be dosed at longer intervals than oral. The purpose of this randomized, placebo-controlled study was to evaluate the effectiveness of vaginal misoprostol in facilitating cervical dilatation in non-menopausal women before operative hysteroscopy and to identify the best dose.

Materials and methods

Between January 1 and March 30, 2001, 48 of 56 women (eight patients refused to participate) of reproductive age who required operative hysteroscopy for submucous myoma (n = 36) or polyps (n = 12) were randomly allocated by a computer-generated randomization table to receive either four placebo tablets or three placebo tablets and 200 μg misoprostol or two placebo tablets and 400 or 800 μg misoprostol (Cytotec®; Laboratories Searle, France), given vaginally 4 h before surgery. The placebos were identical to misoprostol in appearance. Four hours before the procedure, the dry tablets were placed by a nurse in the posterior vaginal fornix.

Surgeons and operating theatre nurses who removed the tablets which were not totally disintegrated after 4 h were blinded to patient
allocation. The study was approved by the institutional review board before it began. The study was set in one centre.

Patients who were considered medically fit were scheduled for operative hysteroscopy under general anaesthesia with a 10 mm hysteroscope during the follicular phase of their cycles.

The primary outcome measure in this study was cervical width, which was assessed by the subjective force required to enter the cervical os without resistance with successive Hegar dilators from 3–8 mm. Surgery was performed by two investigators (Drs Fernandez or Chauveaud-Lambling) to reduce individual variability. Secondary outcome measurements included the subjective ease of cervical dilatation, the time required for dilatation up to Hegar 10, pre-operative pain, and the adverse effects and complications of the procedure (cervical injuries, uterine perforation, false track, bleeding). Pain tolerance evaluated by a visual analogue scale (VAS) and side-effects were noted by the surgical nurses before the procedure.

The exclusion criteria were: contraindication to prostaglandins (asthma, glaucoma, hypertension), history of cervical surgery or of cervical incompetence, and treatment with GnRH agonists.

Sample size was calculated with a test that had an \( \alpha \) of 0.01 and a \( \beta \) of 0.20. The study had the power to detect a 50% difference between the treatment and control groups, as shown by Preutthipan et al. (1999).

**Statistical analysis**

Results are presented as the mean ± SD (range) for quantitative variables and frequency (percentage) for qualitative variables. Analysis of the trial was performed according to the intention-to-treat principle and the patients’ number was calculated to find a difference in the efficacy of the treatment. Groups were compared at inclusion with the Kruskal–Wallis test. For the principal and secondary endpoints, each treatment group was compared with the placebo group. Experimental groups that differed significantly from the placebo group were also compared with one another. Wilcoxon rank sum tests were used for the quantitative variables, since the distribution of the variables was obviously not Gaussian. Fisher’s exact tests were used for qualitative variables.

To take multiple testing into account in the assessment of the subjective outcome criteria, the significance level was set at 0.01. For the other global group comparisons, the significance level was \( P < 0.05 \).

All analyses were performed with S-Plus 2000 software (MathSoft Inc., USA).

**Results**

**Description of the sample**

Forty-eight patients were randomized. One patient withdrew her consent during the study and was therefore excluded from this analysis. The flow chart is presented in Figure 1. The time interval between insertion and the operative hysteroscopy was 4 h and 5 min (range: 3 h 50 min to 4 h 20 min).

The study therefore assessed 47 patients divided into four groups: placebo group \((n = 13)\), a group receiving 200 \( \mu \)g misoprostol \((n = 12)\), a group receiving 400 \( \mu \)g of misoprostol \((n = 12)\), and another group receiving 800 \( \mu \)g of misoprostol \((n = 10)\).

All inclusion and exclusion criteria in the study were met. Nonetheless one patient had to withdraw from the study because she was found during surgery to be pregnant. The data for this patient were included in the analysis, in compliance with the study protocol.

<table>
<thead>
<tr>
<th>Group</th>
<th>( P^a )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td><strong>0.87</strong></td>
</tr>
<tr>
<td>Misoprostol 200 ( \mu )g</td>
<td><strong>0.83</strong></td>
</tr>
<tr>
<td>Misoprostol 400 ( \mu )g</td>
<td><strong>0.95</strong></td>
</tr>
<tr>
<td>Misoprostol 800 ( \mu )g</td>
<td><strong>0.57</strong></td>
</tr>
</tbody>
</table>

Mean ± SD (range).

\( ^a \)Kruskal–Wallis test: overall comparison of the different groups for each variable.
with the principle of intention-to-treat analysis. Similarly, one patient received a different treatment than that to which she was randomly allocated. Indeed, she received placebo tablets instead of 800 μg of misoprostol. So, the analysis considered her to be in the group to which she was allocated, that is, group 1 (Table I).

Analysis of the outcome measures
At a risk of 1%, the results reported in Table II and Table III do not enable us to conclude that misoprostol had any effect on spontaneous cervical dilatation at any dose (Figure 3). Nor do they allow us to judge the efficacy of the treatment or the effect on the duration of dilatation (Figure 2).

Discussion
We administered misoprostol vaginally at three different doses 4 h before operative hysteroscopy and compared the results with placebo: misoprostol was not associated significantly with better baseline cervical opening, it did not decrease the time to cervical dilatation, or affect the degree of difficulty in

![Figure 2. Effect of misoprostol on the spontaneous dilatation.](image)

![Figure 3. Effect of misoprostol on the time required for cervical dilatation.](image)

**Table II.** Outcome measures

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Misoprostol 200 μg</th>
<th>Misoprostol 400 μg</th>
<th>Misoprostol 800 μg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spontaneous dilatation (cm)</td>
<td>6.1 ± 1.4 (3–8)</td>
<td>6.3 ± 1.4 (4.5–9)</td>
<td>5.7 ± 2.0 (3–10)</td>
<td>6.8 ± 2.1 (4–10)</td>
</tr>
<tr>
<td>Pre-operative painb</td>
<td>0.7 ± 0.5 (0–1)</td>
<td>2.5 ± 2.3 (0–7)</td>
<td>1.4 ± 1.2 (0–4)</td>
<td>2.8 ± 2.9 (1–9)</td>
</tr>
<tr>
<td>Duration of dilatation (s)</td>
<td>45 ± 30 (16–128)</td>
<td>35 ± 27 (15–105)</td>
<td>59 ± 50 (0–160)</td>
<td>30 ± 31 (3–105)</td>
</tr>
</tbody>
</table>

Values are mean ± SD (range).

*aWilcoxon’s test: comparison of each experimental group with placebo.

*bVisual analogue scale.

**Table III.** Complications

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Misoprostol 200 μg</th>
<th>Misoprostol 400 μg</th>
<th>Misoprostol 800 μg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dilatation difficult</td>
<td>2 (15.4)</td>
<td>1 (9.1)</td>
<td>1 (8.3)</td>
<td>1 (11.1)</td>
</tr>
<tr>
<td>Complications</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perforation</td>
<td>0</td>
<td>1 (8.3)</td>
<td>1 (8.3)</td>
<td>0</td>
</tr>
<tr>
<td>Cervical laceration</td>
<td>1 (7.7)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>False track</td>
<td>1 (9.1)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Values are n (%).

*aFisher’s exact test comparing each group with the placebo.

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dilatating the cervix regardless of dose. However, in the placebo group, we observed two difficult dilatations (2/13) against three among 34 patients treated by misoprostol whatever the dose regimen. In addition, misoprostol was associated with more pre-operative pain. In this study, we evaluated only subjectively the force required to enter the cervical os. Ngai (1999) used a force-sensing handle and baseline dilatation was defined as the first dilator requiring a peak force of 5 N and the cumulative force was calculated by adding the peak forces needed for each dilator up to 8 mm. Obviously, this objective evaluation would be better but this cervical tonometer was not available in our centre. However, we would like initially to evaluate the surgeon’s reaction in intention-to-treat.

To limit the bias due to dilatation, we excluded menopausal women and the women treated with GnRH agonists and we always operated during the follicular phase. Cooper et al. (1996) showed that the lack of estrogen induced by agonists may explain the inefficacy of misoprostol.

The route of administration and the delay separating misoprostol administration from the surgery were justified by the study on misoprostol absorption kinetics (Zieman et al., 1997). The comparative analysis of the serum levels of the principal metabolite of misoprostol revealed that bioavailability was best following vaginal administration ($T_{\text{max}} = 80 \pm 27$ min), followed by a plateau phase lasting several hours. Moreover, since all our patients underwent outpatient surgery, this facilitated the organization of the study and seemed to ensure that we were in compliance with prescriptions and could monitor possible side-effects during hospitalization.

The lack of efficacy of misoprostol, at three successive doses, may therefore be related to the time period separating its administration (vaginal or oral) from the surgery. Indeed, in our series the tablets were never disintegrated totally at the time of surgery. Thomas et al. (2002) and Preuthiphan et al. (1999) reported in larger series that administration respectively of 400 $\mu$g oral misoprostol 12 or 24 h before surgery or 200 $\mu$g vaginal misoprostol 9–10 h before surgery demonstrated an increased ease of cervical dilatation, but at the price of mild side-effects such as diarrhoea, cramps and vaginal bleeding, which were reported in an average of 25% of cases.

Nonetheless, no placebo-controlled trials so far have shown a significant diminution in the rate of severe complications such as cervical laceration or perforation. Does the surgeon’s subjective assessment that dilatation is facilitated, when combined with a side-effect rate of 25%, justify the prescription of misoprostol before operative hysteroscopy? We must answer that no benefit was demonstrated when misoprostol is given 4 h before the intervention, since our study confirmed the inefficacy of this protocol. Twelve hours earlier, that is, at home, the night before the procedure, without the ability to treat the side-effects, the answer could be positive, but the risk:benefit ratio needs more thorough assessment. The sublingual administration of 100 $\mu$g of misoprostol 12 h before surgery is not efficacious (Bisharah et al., 2003), even though Tang et al. (2002) found a peak of high concentration after sublingual administration.

In conclusion, administration of misoprostol up to 800 $\mu$g 4 h before operative hysteroscopy showed no evidence of promoting cervical dilatation. Other studies assessing the efficacy and optimizing the dose of misoprostol are necessary to learn whether there is any real effect of this product on the cervix or only the surgeon’s subjective assessment.

Acknowledgements

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References


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