The use of misoprostol prior to hysteroscopy in postmenopausal women

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BACKGROUND: This study examined whether oral misoprostol exerted a cervical priming effect in postmenopausal women prior to hysteroscopy. METHOD: Thirty-seven patients were randomized to receive either oral misoprostol (400 µg) or placebo (vitamin B6) 12 h prior to hysteroscopy. The resistance of the cervix to dilatation was objectively assessed by a cervical tonometer. RESULTS: The mean baseline cervical dilatation (4.2 mm in misoprostol group versus 4.4 mm in placebo group) was similar between the two groups. The mean cumulative force measured (27.7 N in misoprostol group versus 21.8 N in placebo group) was also comparable. None of the patients suffered from any significant side-effects. CONCLUSIONS: These data showed that there were no significant benefits from giving misoprostol pre-operatively in postmenopausal women, and it was concluded that oral misoprostol had no significant cervical priming effect in postmenopausal women.

Key words: cervical priming/misoprostol/oestrogen/postmenopausal women

Introduction

Postmenopausal bleeding is a common gynaecological problem. Endometrial biopsy is often necessary to exclude endometrial carcinoma. The procedure is sometimes difficult because of the small and tight cervical os in postmenopausal women. Sometimes the patients need to undergo hysteroscopy and endometrial sampling for a formal assessment.

Difficulty in negotiating through the cervical os is not uncommon. The procedure may be abandoned even when it is performed under general anaesthesia. Cervical injuries, uterine perforation, creation of a false tract or haemorrhage may occur. Unfortunately, data concerning the effectiveness of cervical priming agent in postmenopausal women are lacking. This is of particular importance, especially if office hysteroscopy is to be used.

The synthetic prostaglandin E1 analogue misoprostol (Cytotec; Searle, High Wycombe, UK) has been used successfully in the management of peptic ulcer. It is an effective cervical priming agent prior to suction evacuation (Ngai et al., 1995; Ngai et al., 1999). A previous study showed that it was also effective in pre-menopausal non-pregnant patients (Ngai et al., 1997). It is safe, well tolerated and inexpensive. As data for the use of this drug in postmenopausal women were lacking, a randomized study was performed to investigate the cervical priming effect of misoprostol in this group.

Materials and methods

Ethical approval for the study was granted by the Ethics Committee, Queen Mary Hospital. A total of 37 women admitted for hysteroscopy and endometrial sampling were recruited for this double-blind, randomized trial in Queen Mary Hospital. Subjects participating in this trial were recruited from women who had a definite indication for hysteroscopy and endometrial sampling. The inclusion criteria included: (i) good general health; (ii) menopause (amenorrhoea for >12 months); and (iii) willingness to participate after the study had been explained. Women with a history of past ill health were excluded from the recruitment. None of the recruited patients was on hormonal replacement therapy.

Women who were recruited underwent a full medical, obstetrical and gynaecological history and physical examination. Subjects were admitted 1 day before the operation. The oral tablet (either misoprostol or vitamin B6) was given 12 h before the operation. All hysteroscopy and endometrial sampling was carried out under general anaesthesia by one of the two investigators (S.W.N or Y.M.C). The randomization schedule was unknown to the surgeon. A cervical tonometer (West of Scotland Health Board, Department of Clinical Physics and Bioengineering, UK) was used to measure the peak force required to enter the cervical os with successive dilators from 2–6 mm. The resistance of cervix to dilatation was objectively assessed using a series of tapered dilators attached to a force-sensing handle as described previously (El-Rafaey et al., 1994). Baseline dilatation was defined as the first dilator, which required a peak force >5 N to enter the internal os. The cumulative force required to dilate the cervix was calculated by summing the peak forces produced by each dilator.
The calculation of the sample size was based on the following assumptions: (i) type 1 error of 0.05 and power of 0.8 were acceptable and (ii) it was assumed that the baseline cervical dilatation was 1 mm in the postmenopausal women and a change of 2 mm in baseline dilatation would be significant in clinical management. The ideal sample size in each group was calculated as 17, and to allow for ~10% of the data being unusable, the number in each group was set at 19. Therefore, the total sample size was 38.

The characteristics of the subjects, the indication for dilatation and curettage, the incidence of side-effects and the baseline cervical dilatation between the two groups were compared. The difference in discontinuous variables was analysed by $\chi^2$ test and Fisher’s exact test. The difference of continuous variables was analysed by the Student’s t-test for normally distributed data and Mann–Whitney U-tests for skewed data.

**Results**

There was a change in treatment policy in our department after recruitment of 37 women and nearly all the hysteroscopy procedures were performed under local anaesthesia. Therefore, the project was terminated when a total of 37 postmenopausal women had been recruited. Three women did not have cumulative force and baseline cervical dilatation recorded because (i) there was no difference in baseline dilatation and duration of the procedure. The blood loss during the operation was assessed by subjective visual assessment. After hysteroscopy, women were observed for a further 6 h. The blood pressure and pulse rate were measured hourly. These observations were only recorded on the data forms if complications occurred. All women were followed up 6 weeks later.

The age of subjects in the misoprostol group was significantly older ($P < 0.05$).

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**Table I. Patients’ characteristics, mean ± SD**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Misoprostol n = 18</th>
<th>Placebo n = 16</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>56.1 ± 4.9</td>
<td>66.9 ± 12.7</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>54.1 ± 9.7</td>
<td>54.0 ± 8.0</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>153.6 ± 4.9</td>
<td>150.8 ± 6.2</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>23.0 ± 41.1</td>
<td>24.2 ± 4.0</td>
</tr>
</tbody>
</table>

*$P < 0.05$.

**Table II. Intra-operative findings in misoprostol and placebo groups**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Misoprostol n = 18</th>
<th>Placebo n = 16</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline cervical dilatation (mm)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>4.2 (1.7)</td>
<td>4.4 (1.6)</td>
</tr>
<tr>
<td>Median</td>
<td>5.0</td>
<td>5.0</td>
</tr>
<tr>
<td>Range</td>
<td>0–6</td>
<td>0–6</td>
</tr>
<tr>
<td>Cumulative force (N)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>27.7 (23.3)</td>
<td>21.8 (11.8)</td>
</tr>
<tr>
<td>Median</td>
<td>24.0</td>
<td>19.0</td>
</tr>
<tr>
<td>Range</td>
<td>2–101</td>
<td>8–50</td>
</tr>
<tr>
<td>Duration of operation (min)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>11.7 (10.8)</td>
<td>6.4 (4.2)</td>
</tr>
<tr>
<td>Median</td>
<td>7.0</td>
<td>5.0</td>
</tr>
<tr>
<td>Range</td>
<td>4–41</td>
<td>2–15</td>
</tr>
<tr>
<td>Blood loss (ml)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>21.7 (50.0)</td>
<td>6.9 (12.3)</td>
</tr>
<tr>
<td>Median</td>
<td>5.0</td>
<td>3.0</td>
</tr>
<tr>
<td>Range</td>
<td>0–20</td>
<td>0–50</td>
</tr>
</tbody>
</table>

**Table III. Pre-operative side-effects in misoprostol and placebo groups. Values are shown as number (%)**

<table>
<thead>
<tr>
<th>Side-effect</th>
<th>Misoprostol n = 18</th>
<th>Placebo n = 16</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>1 (5.6)</td>
<td>0</td>
</tr>
<tr>
<td>Dizziness</td>
<td>0</td>
<td>2 (12.5)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>3 (16.7)</td>
<td>1 (6.3)</td>
</tr>
<tr>
<td>Lower abdominal pain</td>
<td>1 (5.6)</td>
<td>0</td>
</tr>
<tr>
<td>Vaginal bleeding</td>
<td>5 (27.8)</td>
<td>6 (37.5)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

required for the procedure was also comparable (27.7 N in misoprostol group versus 21.8 N in placebo group).

As the patients in the placebo group were significantly older when compared with the misoprostol group, we have compared the cumulative force within the former group. There was no significant difference in cumulative force between those whose age was ≤65 years (median age) versus >65 years within the placebo group (26.9 N versus 19.2 N respectively). Similarly, there was no difference in baseline dilatation and duration of the operation between the two groups. Therefore, age differences between the misoprostol and placebo groups probably would not affect the ease of dilatation. The duration of the procedure as well as the blood loss was comparable between the two groups. No operative complications were encountered in any subjects. The pre-operative side-effects are shown in Table III. Gastrointestinal symptoms were uncommon and mild in both groups. The incidence was low and comparable between the two groups.

**Discussion**

Cervical ripening is a complicated process, being mediated by hormones, cytokines, growth factors and other biochemical compounds (Barclay _et al._, 1993; Norman _et al._, 1993). Misoprostol had been shown to be effective for cervical
Information on the use of prostaglandins in non-pregnant cervix
was scanty. With the introduction of various hysteroscopic
procedures, it was considered worthwhile to explore the role
of cervical priming in this group of women.

We have previously demonstrated that 400 µg oral misopros-
tol, when given 12 h prior to hysteroscopy, reduced cervical
resistance significantly when compared with placebo (Ngai
et al., 1997). In that study, subjects suffered from infertility
and were admitted for laparoscopy and hysteroscopy.

In the present study, using the same dosage and route of
administration as our prior study (Ngai et al., 1997), we failed
to demonstrate any beneficial effect. The only difference
between the two studies was that we recruited postmenopausal
women in this study, whereas women of reproductive age were
recruited in the previous study. Endogenous oestrogen may be
essential for the cervical priming induced by prostaglandin,
and therefore women in a hypo-oestrogenic state would show
no response to prostaglandins.

This theory is supported by findings from laboratory and
animal studies on cervical priming. The final, rapid cervical
softening that occurs just before the onset of labour corresponds
to the connective tissue remodelling characterized by an
increased turnover of both collagen and proteoglycans (Norman
et al., 1993). Several hormones, such as prostaglandins, gonadal
steroids and relaxin, are involved in the process. Administration
of oestrogen promotes, and of progesterone at high concentra-
tions inhibits, neutrophil migration into rodent uterine tissue
(Stites and Siiteri, 1983). Human studies have further demon-
strated that there is an upregulation of gene expression as well
as protein concentrations of interleukin-8, interleukin-6 and
granulocyte colony-stimulating factor during the final cervical
priming process, which is similar to an inflammatory process
(Sennstrom et al., 2000). The effect of hormones on cervical
priming may be related to the regulation of pro-inflammatory
cytokines.

Our knowledge of the molecular basis for the ripening of
the human cervix has increased substantially since the pioneering
reports by Danforth 40 years ago (Danforth, 1960). Expanded
knowledge of the biochemistry and ultrastructure of the human
cervix will most likely be of practical importance in the
near future. Further laboratory basic research on the local
concentration, action and interaction of gonadal steroids and
prostaglandins, and their effects on collagenase and non-
collagenolytic proteases in the cervical ripening process are
awaited to confirm or refute the speculation stated above.

Acknowledgement
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