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A Prospective, Randomized Comparison of Intramuscular Phloroglucinol Versus Oral Misoprostol for Cervix Pretreatment Before Diagnostic Hysteroscopy

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The aim of this study was to compare the effectiveness and safety of intramuscular phloroglucinol and oral misoprostol for cervix pretreatment before diagnostic hysteroscopy. Several modalities for cervical priming and pain reduction have been adopted to reduce the complications related to cervical dilatation before hysteroscopy. Among them, the prostaglandin analog misoprostol is the most frequently used agent. Phloroglucinol, a spasmolytic, has also been showed to have an effect in inducing cervical dilatation but is rarely used before hysteroscopy. One hundred twenty outpatients undergoing anesthesia-free diagnostic hysteroscopy were randomly assigned to receive 80 mg intramuscular phloroglucinol and 400 mg oral misoprostol before diagnostic hysteroscopy. The main outcome measures were preoperative cervical width, visual analog scales (VAS) for pain, cervical passage time, and adverse reactions. Intramuscular phloroglucinol resulted in a significantly wider cervical width, lower VAS pain score, shorter cervical passage time, and a lower adverse effects rate compared with oral misoprostol. Intramuscular phloroglucinol is more effective and safer than oral misoprostol in inducing proper cervical priming and may be the optimal choice for cervical pretreatment before diagnostic hysteroscopy.

Key words: Cervical priming – Phloroglucinol – Misoprostol – Hysteroscopy

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Diagnostic hysteroscopy is the gold standard in the study of uterine cavity morphology and in diagnosis of endocavitary pathologies. Most diagnostic hysteroscopies in China are performed in an outpatient setting without anesthesia. Access to the uterine cavity requires insertion of a resectoscope through the internal cervical os, which necessitates cervical dilatation. However, almost half of the complications of hysteroscopy, including pain, cervical tears, creation of a false tract, and uterine perforation, occur during cervical passage.[1–3]

Several modalities such as misoprostol, ketoprofen, lidocaine, laminaria, and so on for cervical priming and pain reduction before hysteroscopy have been adopted to reduce the complications related to cervical dilatation.[4–6] Among them, the prostaglandin analog misoprostol is the most frequently used agent for cervical preparation before hysteroscopy because of its low cost and previous testing in many randomized, controlled trials.[7–10] Phloroglucinol, a spasmolytic, is primarily used for gastrointestinal tract colic. It has been shown to have an effect in inducing cervical dilatation and promoting the progression of labor.[11] However, the effect of phloroglucinol in cervical pretreatment before hysteroscopy has rarely been reported. The objective of the present study was to compare the effectiveness and safety of intramuscular phloroglucinol and oral misoprostol in cervix pretreatment before anesthesia-free diagnostic hysteroscopy in premenopausal women.

Material and Methods

Patients

This study was conducted prospectively between January 2014 and November 2014 at the Department of Obstetrics and Gynecology at the Women's Hospital of Zhejiang University School of Medicine. Symptomatic patients who were suspected of having intrauterine pathology based on transvaginal ultrasound were enrolled. All the patients were scheduled for elective diagnostic hysteroscopic surgery at the Day Surgery Center. The hospital ethics committee reviewed and approved this study protocol. All subjects provided written informed consent before participation.

The inclusion criteria were as follows: premenopausal women with sexual history; patients who gave informed consent and voluntarily agreed to be enrolled in the study; patients with indications for diagnostic hysteroscopy; patients without cardiovascular, liver, kidney, or hematopoietic system and other medical diseases; patients with no contraindications to use prostaglandins; and patients who had not used steroids within 3 months.

The exclusion criteria included pregnancy and lactation; patients who had a previous history of cervical incompetence or diseases that can lead to dilatation of the cervix such as cervical myoma, cervical polyp prolapsed to internal cervical os, and type 0 submucous myoma; patients who had cold knife conization surgery; patients who had uterine perforation or had a history of intrauterine operation for cervical dilatation in the prior 3 months; patients who were forbidden to use prostaglandin such as those with asthma, cardiovascular diseases, glaucoma, and serious allergies, or those who had prostaglandin inhibitor intake recently; patients who had a body temperature >37.5°C, a large amount of prolonged uterine bleeding, reproductive tract infections, genital tuberculosis, or cervical cancer; patients with cardiovascular or cerebrovascular, liver, kidney, or hematopoietic system and other serious diseases, or mental illness; patients who did not sign the informed consent; patients who had shown poor compliance; and patients who could not go on with the examination or treatment.

Study protocol

Patients were randomly assigned to the phloroglucinol or misoprostol at a 1:1 ratio using the random numbers table. In the phloroglucinol group, 80 mg phloroglucinol was administered via intramuscular injection in the hip 30 minutes before surgery. In the misoprostol group, 400 mg oral misoprostol tablet was administered 2 hours before hysteroscopy.

The diagnostic hysteroscopy was performed without anesthesia, employing a 7-mm hysteroscope (exterior shaft) with a 30° optic lens (Richard Wolf Gmbh, Knittlingen, Germany). The hysteroscope was advanced into the uterine cavity, and the cavity was distended with normal saline at a pressure of 80 to 100 mmHg. The cavity and tubal ostia were visualized. If any lesions were present, biopsy samples were obtained. All the surgeries were performed by one surgeon in this study.

Outcome measures

Outcome measures include the following.

1. Cervical dilatation: The cervical width was assessed by performing cervical dilatation, beginning with a No. 10 Hegar dilator (East China

Medical Device Industry Co, Ltd, Yangzhou, China) and subsequently inserting smaller Hegar dilators until the dilator could pass through the internal os without resistance. The largest one that could be passed through was recorded as the initial cervical width.

2. Pain degree: The patients' pain scores during the operation were measured by visual analog scales (VAS) with 0 being no pain, 1 to 3 being mild pain, 4 to 7 being moderate pain, and 8 to 10 being severe pain.
3. Cervical passage time: The time from the entrance to the cervix to the cavity and tubal ostia were visualized.
4. Adverse reaction: Gastrointestinal symptoms such as diarrhea, nausea or vomiting, heart rate and blood pressure changes, as well as other side effects were observed.

Statistical analysis

SPSS 17.0 (SPSS) was used for the statistical analysis. Data are presented as the mean ± SD for quantitative variables and frequency for qualitative variables. Comparisons of quantitative variables were performed using a *t* test. Frequency distributions between categorical variables between the 2 groups were compared using the χ^2 test. A *P* value <0.05 was considered statistically significant.

Results

A total of 120 patients finally enrolled in this study and underwent randomization. The subjects were randomly assigned to the phloroglucinol group or misoprostol group. None of the study subjects changed groups or stopped participating in the study after randomization or before surgery. No cases of failed surgery or follow-up loss at 3 days after surgery were noted. The baseline demographic characteristics of the study subjects are listed in Table 1. The 2 groups were comparable in age, body weight, parity, and indication for hysteroscopy.

The main outcomes are summarized in Table 2. The mean preoperative cervical widths for the phloroglucinol and misoprostol groups were 8.03 ± 0.74 mm and 6.59 ± 1.50 mm, respectively. The mean cervical width in the phloroglucinol group was significantly wider than that in the misoprostol group ($P = 0.000$).

The mean patient pain scores evaluated by VAS for the phloroglucinol and misoprostol groups were 0.48 ± 0.85 and 2.57 ± 2.12, respectively. The score in the phloroglucinol group was significantly lower than that of the misoprostol group ($P = 0.000$).

The mean cervical passage time was 18.50 ± 7.66 seconds in the phloroglucinol group and 23.50 ± 7.86 seconds in the misoprostol group. The mean cervical passage time in the phloroglucinol group was significantly shorter than in the misoprostol group ($P = 0.001$).

No adverse effects were observed in the phloroglucinol group. The rate of adverse effects in the misoprostol group was 36.67%, but there was no case in which the surgery had to be delayed because of adverse effects, all of which were tolerable.

Table 1 Baseline characteristics[a]

Characteristic	Phloroglucinol (n = 60)	Misoprostol (n = 60)	*P* value
Age, y	38.00 ± 7.86	40.03 ± 6.58	0.127
Body weight, kg	53.00 ± 7.02	52.00 ± 5.70	0.393
Parity			0.850
Nulliparous	22 (36.67)	23 (38.33)	
History of vaginal delivery	30 (50)	27 (45)	
History of abortion	8 (13.33)	10 (16.67)	
Indications for hysteroscopy			0.827
Endometrial polyp	46 (76.67)	47(78.33)	
Intrauterine adhesions	14 (23.33)	13 (21.67)	

[a]Data are expressed as mean ± SD, median (range), or number (percentage) if appropriate.

Discussion

The present study used a prospective, randomized protocol to compare the effectiveness and safety of

Table 2 Summary of outcome measures[a]

Parameter	Phloroglucinol (n = 60)	Misoprostol (n = 60)	*P* value
Cervical width, mm	8.03 ± 0.74	6.59 ± 1.50	0.000
VAS pain score	0.48 ± 0.85	2.57 ± 2.12	0.000
Cervical entry time, s	18.5 ± 7.66	23.50 ± 7.86	0.001
Adverse effects (%)	0 (0)	22 (36.67)	0.000
Uterine cramping	0	6	
Gastrointestinal symptoms[b]	0	11	
HR/BP changes	0	5	

HR, heart rate; BP, blood pressure.

[a]Data are expressed as mean ± SD, median (range), or number (percentage) if appropriate.

[b]Gastrointestinal symptoms include diarrhea, nausea, vomiting.

intramuscular phloroglucinol and oral misoprostol for cervical priming before diagnosis hysteroscopy.

It has been well documented in many randomized, controlled trials that misoprostol, a synthetic prostaglandin E1 analog, has cervical ripening effects.[7–10] Several administration routes, including oral, sublingual, and vaginal misoprostol, are equally effective in inducing cervical priming before operative hysteroscopy. Considering patients' preference, Song *et al*[7] recommended oral administration as the optimal route for misoprostol administration. However, oral administration also induces some side effects, such as diarrhea, nausea, and vomiting. Moreover, it is limited to glaucoma, asthma, hypertension, and prostaglandin-allergic patients. Phloroglucinol, a spasmolytic, is primarily used for gastrointestinal tract colic. It can inhibit the contraction of uterine smooth muscle and relieve pain without the anticholinergic side effects seen in this class of agents. No toxicity has been observed even at high doses, and it provides remarkable pain relief.[12]

In this study, we demonstrated that intramuscular phloroglucinol was more effective than oral misoprostol in inducing cervical priming. With regard to the width of the cervical canal as evaluated by means of a Hegar dilator, we found that the cervical dilatation was greater in the phloroglucinol group than in the misoprostol group. The difference was statistically significant. Pain is one of the most common side effects of hysteroscopy and occurs during cervical dilatation. Thus, phloroglucinol, the foregoing drug having better effect in cervical dilation, also had better effect in pain reduction. The findings in our study also suggested that phloroglucinol was more effective in pain reduction than misoprostol as evaluated by VAS method. In addition, the cervical passage time in the phloroglucinol group was significantly shorter than in the misoprostol group, suggesting that cervical smooth muscle relaxation induced by phloroglucinol is better than that induced by misoprostol.

No side effects, such as nausea, vomiting, or hypotension, were noted in the phloroglucinol group. Meanwhile, the misoprostol group showed different adverse effects related to prostaglandin analog effect. These were largely gastrointestinal symptoms. The side effects experienced by the patients in both groups are shown in Table 2. However, the side effects were mild and tolerable.

Weaknesses of the study include the observational design, especially given the pain during the hysteroscopy influenced by many factors including the surgical technique, the surgical instrument, the distension medium, and the characteristics of the patients such as parity or the cervix condition.[13] We attempted to control for as many factors related to pain during the procedure as possible. In this study, all the surgeries were performed by one surgeon using the same instrument, and there was also no difference in the baseline characteristics of the patients in the 2 groups. There are always, however, variables that cannot be measured accurately and factors that may be unknown.

In conclusion, this study demonstrated that intramuscular injection of 80 mg phloroglucinol is more effective than oral administration of 400 mg misoprostol in cervical priming and pain reduction before hysteroscopy. In addition, considering the shorter cervical passage time and no adverse reaction compared with misoprostol, we recommend that intramuscular phloroglucinol be used for optimal cervical pretreatment before anesthesia-free diagnostic hysteroscopy.

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