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Optimal timing of misoprostol administration in nulliparous women undergoing office hysteroscopy: a randomized double-blind placebo-controlled study

Usama M. Fouda, M.D., Ph.D., Sherine H. Gad Allah, M.D., Ph.D., and Hesham S. Elshaer, M.D., Ph.D.

Department of Obstetrics and Gynecology, Faculty of Medicine, Cairo University, Cairo, Egypt

Objective: To determine the optimal timing of vaginal misoprostol administration in nulliparous women undergoing office hysteroscopy.
Design: Randomized double-blind placebo-controlled study.
Setting: University teaching hospital.
Patient(s): One hundred twenty nulliparous patients were randomly allocated in a 1:1 ratio to the long-interval misoprostol group or the short-interval misoprostol group.
Intervention(s): In the long-interval misoprostol group, two misoprostol tablets (400 μg) and two placebo tablets were administered vaginally at 12 and 3 hours, respectively, before office hysteroscopy. In the short-interval misoprostol group, two placebo tablets and two misoprostol tablets (400 μg) were administered vaginally 12 and 3 hours, respectively, before office hysteroscopy.
Main Outcome Measure(s): The severity of pain was assessed by the patients with the use of a 100-mm visual analog scale (VAS). The operators assessed the ease of the passage of the hysteroscope through the cervical canal with the use of a 100-mm VAS as well.
Result(s): Pain scores during the procedure were significantly lower in the long-interval misoprostol group (37.98 $\pm$ 13.13 vs. 51.98 $\pm$ 20.68). In contrast, the pain scores 30 minutes after the procedure were similar between the two groups (11.92 $\pm$ 7.22 vs. 13.3 $\pm$ 6.73). Moreover, the passage of the hysteroscope through the cervical canal was easier in the long-interval misoprostol group (48.9 $\pm$ 17.79 vs. 58.28 $\pm$ 21.85).
Conclusion(s): Vaginal misoprostol administration 12 hours before office hysteroscopy was more effective than vaginal misoprostol administration 3 hours before office hysteroscopy in relieving pain experienced by nulliparous patients undergoing office hysteroscopy.
Clinical Trial Registration Number: NCT02316301. (Fertil Steril® 2016;■:■–■. ©2016 by American Society for Reproductive Medicine.)
Key Words: Pain, office hysteroscopy, misoprostol

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Office hysteroscopy has become the method of choice for evaluation of the cervical canal and uterine cavity. Because of the miniaturization of scopes and instruments, hysteroscopy can be performed in an outpatient setting without the need for general or regional anesthesia or operation theatre facilities. Consequently, office hysteroscopy is more time saving, cost effective and preferable to patients compared with inpatient hysteroscopy (1, 2).

Office hysteroscopy performed by an experienced hysteroscopist with the use of the vaginoscopic approach (without tenaculum and speculum) is usually associated with mild pain and discomfort (3). Sometimes, the introduction of the hysteroscope into the uterine cavity is difficult and associated with severe pain and vasovagal reaction. Several studies revealed that the subgroups of patients with a narrow cervical canal (nulliparous and

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Reprint requests: Usama M. Fouda, M.D., Ph.D., Department of Obstetrics and Gynecology, Faculty of Medicine, Cairo University, Kasr Al-Ainy Hospital, Al-Saraya Street, Cairo, Egypt (E-mail: umfrfouda@yahoo.com).

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menopausal patients) are at high risk for experiencing severe pain during office hysteroscopy (4, 5).

Several pharmacologic agents have been used to suppress pain associated with office hysteroscopy: opioid and nonopioid analgesics, paracervical block, intracervical instillation of anesthetics, and intrauterine injection of anesthetics. Moreover, easier and less painful passage of the hysteroscope through the cervical canal can be achieved with the use of prostaglandins and osmotic dilators, which soften the cervix and increase the cervical canal width (6). However, studies evaluating the effectiveness of various pharmacologic agents in relieving pain during office hysteroscopy have produced conflicting results. Consequently, there is no consensus regarding the safest and most effective method for pain relief during office hysteroscopy (1).

Few studies have examined the effectiveness of misoprostol (a methyl analogue of natural prostaglandins) in reducing pain experienced during office hysteroscopy. However, the studies varied in dose, route, and timing of misoprostol administration. Moreover, the studied populations were diverse and sample sizes were small (7–11). Consequently, there are no solid guidelines regarding the efficacy, dose, timing, and route of misoprostol administration before office hysteroscopy.

Studies evaluating the use of misoprostol before inpatient hysteroscopy revealed that the efficacy of misoprostol in cervical ripening was time dependent. Fernandez et al. reported that the administration of misoprostol via the vaginal route 4 hours before operative hysteroscopy was not effective in facilitating cervical dilation (12). However, other studies found that the administration of misoprostol 8–12 hours before operative hysteroscopy led to a significantly greater cervical width compared with placebo (13–15). Based on these studies, we think that it is better to wait for 8–12 hours after intravaginal misoprostol administration before performing office hysteroscopy.

The aim of the present study was to determine the optimal timing of vaginal misoprostol administration in nulliparous women undergoing office hysteroscopy.

MATERIALS AND METHODS

From February 2015 to December 2015, this double-blind, placebo-controlled, randomized, controlled study was conducted at the Obstetrics and Gynecology Department of Cairo University, Egypt. The study protocol was approved by the institutional Ethics Committee (ref. no. N–7–2015), and all of the patients gave informed consent before randomization.

Nulliparous women of reproductive age with an indication for office hysteroscopy were recruited for the study. The exclusion criteria included contraindication to misoprostol (asthma, glaucoma, renal failure, hypertension, and severe heart disease), allergy to misoprostol, severe vaginal bleeding, pelvic inflammatory disease, history of cervical operation, pregnancy, lesions of the endocervical canal, and treatment with GnRH agonists.

A total of 120 patients were randomly allocated to either the long-interval misoprostol group (n = 60) or the short-interval misoprostol group (n = 60) with the use of a computer-generated randomization list and sequentially numbered sealed envelopes. The randomization list and sealed envelopes were prepared by a college not directly involved in the study. Each sequentially numbered sealed envelope contained two labeled plastic bags (A and B), and each bag contained either two misoprostol tablets (each tablet 200 μg; Cytotec; Pfizer) or two placebo tablets of identical appearance. In the long-interval misoprostol group, bag A contained misoprostol tablets and bag B contained placebo tablets. In the short-interval misoprostol group, bag A contained placebo tablets and bag B contained misoprostol tablets. After informed consents were signed, the sealed envelopes were opened sequentially by the study nurse. Patients were instructed to insert the tablets in the bags A and B as deeply as possible inside the vagina. Tablets in bag A were inserted 12 hours before the scheduled office hysteroscopy, and tablets in bag B were inserted 3 hours before scheduled the office hysteroscopy. The doctors and patients were blinded to the treatment received.

On the day of scheduled office hysteroscopy, the Arabic version of State-Trait Anxiety Inventory (form Y) was used to assess the state of anxiety and the trait of anxiety. The vagina was washed with saline solution, and any remaining fragments of placebo or misoprostol tablets were removed by the study nurse. The time interval between the arrival of the patients at the clinic and the performance of office hysteroscopy (waiting time) was measured.

All of the procedures were performed during the proliferative phase of the menstrual cycle by three experienced operators. We used a rigid 2.9-mm hysteroscope with a 30° forward oblique lens and an outer sheath diameter of 5 mm in this study. Normal saline solution was used to distend the uterine cavity. The pressure of the distension media was maintained between 60 and 100 mm Hg. Hysteroscopy was performed with the use of the nontouch technique (vaginoscopic approach) as described by Bettocchi and Selvaggi (16). All of the procedures were diagnostic.

Procedure duration (from the introduction of hysteroscope into the vagina until completing hysteroscopy examination) was measured. The intensity of pain was assessed with the use of a 100-mm visual analog scale (VAS; 0 = the absence of pain; 100 = the worst experienced pain). The patients were asked to record the intensity of pain during and 30 minutes after the procedure.

After the end of the procedure, the operators assessed the ease of the passage of the hysteroscope through the cervical canal with the use of a 100-mm VAS (0 = the easiest insertion of the hysteroscope into the uterine cavity; 100 = the most difficult insertion of the hysteroscope into the uterine cavity). Any operative complications, such as uterine perforation, creation of false tract, and cervical lacerations, were recorded. Patients were contacted by telephone 24 hours after the office hysteroscopy to detect occurrences of the adverse effects of misoprostol, such as nausea, vomiting, fever (temperature >37.8°C), shivering, abdominal cramps, and diarrhea.

The primary outcome was the intensity of pain during the procedure, and secondary outcomes included the intensity of pain 30 minutes after the procedure, the ease of passing the hysteroscope through the cervical canal, surgical complications, and any surgical complications and adverse drug effects.