European Journal of Obstetrics & Gynecology and Reproductive Biology 203 (2016) 326–330

Contents lists available at ScienceDirect

European Journal of Obstetrics & Gynecology and Reproductive Biology

journal homepage: www.elsevier.com/locate/ejogrb

Misoprostol versus uterine straightening by bladder distension for pain relief in postmenopausal patients undergoing diagnostic office hysteroscopy: a randomised controlled non-inferiority trial

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ARTICLE INFO

Article history:
Received 5 May 2016
Received in revised form 3 June 2016
Accepted 24 June 2016

Keywords:
Bladder distension
Misoprostol
Office hysteroscopy
Pain
Uterine straightening

ABSTRACT

Objective: To compare the effectiveness of misoprostol with uterine straightening by bladder distension in minimising the pain experienced by postmenopausal patients during diagnostic office hysteroscopy.
Study design: Seventy-six postmenopausal patients were randomly allocated in a 1:1 ratio to the misoprostol group or to the bladder distension group. Patients in the misoprostol group were instructed to insert two misoprostol tablets (400 μg) in the vagina 12 h before office hysteroscopy. Patients in the bladder distension group were instructed to drink one litre of water and to avoid urination during a period of 2 h before office hysteroscopy. The severity of pain experienced by the patients during and at 30 min after the procedure was measured using a 100-mm visual analogue scale (VAS). The ease of passing the hysteroscope through the cervical canal was assessed by the hysteroscopists using a 100-mm VAS.
Results: The passage of the hysteroscope through the cervical canal was easier in the misoprostol group [60.37 ± 15.78 vs. 50.05 ± 19.88, $p = 0.015$]. The mean VAS pain score during the procedure was significantly lower in the misoprostol group [39.47 ± 13.96 vs. 50.18 ± 15.44, $p = 0.002$]. The mean VAS pain score 30 min post-procedure was comparable between both groups [11.82 ± 3.71 vs. 12.61 ± 4.06, $p = 0.379$].
Conclusion: Vaginal misoprostol is more effective than uterine straightening by bladder distension in relieving the pain experienced by postmenopausal patients during office hysteroscopy.
Trial registration: Clinicaltrials.gov [NCT02328495]. https://clinicaltrials.gov/ct2/show/NCT02328495.

Introduction

Outpatient or office hysteroscopy is an important tool for diagnosis and treatment of intrauterine lesions. Office hysteroscopy requires no operation theatre facilities or general anaesthesia and therefore it is more convenient to the patients and more cost effective than inpatient hysteroscopy. During office hysteroscopy, mild pain is experienced by the majority of the patients and severe pain is experienced by few patients [1]. Menopausal status, absence of vaginal delivery, and history of previous Caesarean section are the main risk factors for severe or intolerable pain during office hysteroscopy [2,3].

There is no consensus on the most effective method for pain relief during office hysteroscopy. The use of small-calibre hysteroscopes, flexible hysteroscopes, vaginoscopic technique, analgesics (opioids and non-opioids), local anaesthetics, misoprostol, and osmotic dilators have been advocated by several authors to minimise the pain experienced during office hysteroscopy [4,5].

Menopausal status is associated with a narrowing of the cervical canal and internal os and therefore the passage of the hysteroscope through the cervical canal is frequently associated with severe pain. Several authors suggested that cervical ripening with misoprostol could soften and widen the cervical canal and therefore facilitates the passage of the hysteroscope through the cervical canal [1,4]. Several studies revealed that cervical ripening with misoprostol is effective in reducing pain in postmenopausal patients [6,7]. Other randomised controlled trials including nulliparous women or women of reproductive age have shown mixed results [8–11]. A recent meta-analysis revealed that misoprostol is effective in minimising the pain experienced by

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http://dx.doi.org/10.1016/j.ejogrb.2016.06.024
0301-2115/

postmenopausal patients during office hysteroscopy [12]. The main disadvantage of misoprostol administration prior to office hysteroscopy is the frequent occurrence of undesired side effects such as abdominal cramps, nausea, diarrhoea, vaginal bleeding, and fever [7,8,12].

Celik et al. reported that patients who underwent office hysteroscopy with a full bladder experienced less pain compared with patients who underwent office hysteroscopy with an empty bladder. The authors suggested that bladder distension can align the cervical canal with uterine cavity and therefore minimises the trauma caused by the passage of the hysteroscope through the cervical canal and internal os [13].

We thought that this new treatment (bladder distension) might offer important advantages over currently available treatment (misoprostol), in terms of better convenience, compliance, and cost-effectiveness. The aim of this study was to compare the effectiveness of misoprostol with uterine straightening by bladder distension in minimising the pain experienced by postmenopausal patients during diagnostic office hysteroscopy.

Materials and methods

This prospective randomised controlled trial (No. NCT02328495: clinicaltrials.gov.org) was conducted at the Obstetrics and Gynecology Department of Cairo University, Egypt from January 2015 to March 2016. The protocol of this study was approved by the institution research ethics committee. The patients were counselled and written informed consent was obtained before inclusion in the study.

Menopausal patients with an indication for office hysteroscopy (postmenopausal bleeding or abnormal ultrasound findings) were recruited to the study. Nulliparous patients and patients with cervical pathology, retroverted uterus (detected by transvaginal ultrasound), and previous cervical surgery were excluded from the study. Moreover, patients with severe vaginal bleeding, allergy to misoprostol, and contraindications to misoprostol therapy (asthma, liver, kidney, or heart disease) were excluded from the study.

A total of seventy-six patients were randomly assigned to the misoprostol group ($n = 38$) or the bladder distension group ($n = 38$). Randomisation was carried out by using a computer-generated randomisation table (obtained from http://graphpad.com/quickcalcs/randomize1) and sequentially numbered sealed opaque envelopes. The sealed envelopes contained allocation information written on a card. A statistician was responsible for preparation of the randomisation table and the sealed envelopes. The hysteroscopists were blind to the received treatment.

Office hysteroscopy was scheduled at a subsequent visit. Patients in the misoprostol group were instructed to insert two misoprostol tablets (each tablet 200 μg) (Cytotec, Pfizer, New York, USA) as deep as possible in the vagina 12 h before the scheduled procedure. Patients in the bladder distension group were instructed to drink one litre of water and to avoid urination during a period of 2 h before the scheduled procedure.

Immediately before the procedure, the patients in the misoprostol group were instructed to empty the bladder and the patients in the bladder distension group were asked to rank the degree of discomfort related to bladder distension on a 4-point Likert scale (no discomfort = 1, mild discomfort = 2, moderate discomfort = 3, and severe discomfort = 4). Moreover, a colleague performed transabdominal ultrasonography to confirm that the bladder was empty in patients in the misoprostol group and to confirm that uterine straightening (angle between the cervix and uterine cavity more than 120°) occurred in patients in the bladder distension group. If the angle between the cervix and uterine cavity was less than 120°, the patients were asked to wait for 30–60 min before repeating the ultrasound examination. The study nurse washed the vagina to remove any remnants of misoprostol tablets inserted into the vagina and the adverse effects of misoprostol (nausea, vomiting, fever, abdominal cramps, and diarrhoea) were recorded. The patients were asked to fill out the Arabic version of State-Trait anxiety inventory to evaluate the current state of anxiety and the trait of anxiety.

Three hysteroscopists (UF, HE, and KE) with comparable skill and experience performed all the procedures using the vaginoscopic technique [14]. A rigid 2.9-mm hysteroscope with a 30° lens and a 5-mm outer sheath (Karl Storz GmbH, Tuttlingen, Germany) was used in all procedures. The uterine cavity was expanded with normal saline at a pressure of 60- to 100-mmHg. If a uterine lesion (polyp or myoma) was detected, the patient was admitted to the hospital and operative hysteroscopy was performed under general or regional anaesthesia.

Waiting time before the procedure and the procedure duration were measured. The severity of pain experienced by the patients during and at 30 min after the procedure was measured using a 100-mm visual analogue scale (VAS) (0 = no pain, and 100 = worst imaginable pain). After the end of the procedure, the ease of passing the hysteroscope through the cervical canal was assessed by the hysteroscopists using a 100-mm VAS (0 = most difficult passage of the hysteroscope through the cervical canal, and 100 = easiest passage of the hysteroscope through the cervical canal). Moreover, operative complications (cervical tears, false passage, and uterine perforation) were recorded.

The primary outcome of interest was the severity of pain during the procedure. Secondary outcomes were the severity of pain at 30 min post-procedure, the ease of the passage of the hysteroscope through the cervical canal, surgical complications, and adverse effects of misoprostol.

Sample size calculation

This study aimed to reveal that uterine straightening by bladder distension was not inferior to misoprostol in relieving the pain experienced by postmenopausal patients during office hysteroscopy. At the time of the study design, there were no studies in literature that reported the use of vaginal misoprostol (400 μg) 12 h before office hysteroscopy in postmenopausal patients. Available studies either included a heterogeneous population of patients (postmenopausal patients and patients of reproductive age) or investigated different regimens of misoprostol administration in postmenopausal patients undergoing office hysteroscopy [6,7,15].

Before starting the present study, we conducted a pilot study to compare the effectiveness of vaginal misoprostol (400 μg) administered 12 h before office hysteroscopy with placebo in reducing the pain experienced by postmenopausal patients during diagnostic office hysteroscopy. The pilot study included 30 consecutive postmenopausal patients. The patients were randomised alternatively either to the misoprostol group or to the placebo group. The mean VAS pain score was significantly lower in the misoprostol group (32.56 ± 14.91 vs. 50.34 ± 18.01, $p = 0.006$).

We considered a 9-mm difference in the mean VAS pain score between the experimental treatment (bladder distension) and the conventional treatment (misoprostol) to be the critical threshold for noninferiority. Power calculation (calculated on sealedenvelope.com/power/continuous-noninferior) indicated that 34 patients should be recruited to each arm of the study to be 80% sure that the upper limit of a one-sided 95% confidence interval could exclude a difference in favour of the misoprostol group of more than 9 mm, if there is truly no difference between the misoprostol group and the bladder distension group in mean VAS pain score. We expected that the drop out incidence would be 10% and therefore 76 patients were recruited to the study.