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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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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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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.

Statistical analysis

Statistical calculations were performed using Microsoft Excel 2010 and SPSS computer programs. Chi-square test, Student *t* test, and Fisher's exact test were used as appropriate. A probability value (*p*-value) of less than 0.05 was considered statistically significant.

Results

Between January 2015 and March 2016, 76 postmenopausal patients were recruited to the study with 38 patients randomised to each arm of the study. The flow of the patients in the study is presented in Fig. 1.

Both groups were comparable with regard to age, body mass index, parity, gravidity, mode of delivery, state anxiety score, trait anxiety score, years of menopause, and indications of office hysteroscopy (Table 1). The waiting time before the procedure was comparable between both groups (36.45 ± 11.79 vs. 32.39 ± 10.63 min, $p = 0.12$).

Operative findings were similar in both groups. 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, $p = 0.379$) (Table 2).

Although the abdominal cramps, nausea, diarrhoea, vaginal bleeding, and fever were more frequent in the misoprostol group, the differences between the groups failed to reach statistical significance (Table 2). There were no operative complications in either group. In the bladder distension group, 47.37%, 18.42%, and 7.89% of the patients experienced mild, moderate, or severe discomfort, respectively.

Table 1
Patients characteristics.

	Misoprostol group ($n = 38$)	Bladder distension group ($n = 38$)	*p*-Value
Age (years)	60.13 ± 7.82	58.42 ± 7.9	0.346
Body mass index (Kg/m^2)	28.07 ± 4.13	27.08 ± 4.09	0.298
Gravidity	4.61 ± 2.14	5.05 ± 2.04	0.354
Parity	3.24 ± 1.44	3.58 ± 1.39	0.295
Mode of delivery			0.427
Any vaginal delivery	27 (71.05%)	30 (78.95%)	
Caesarean section only	11 (28.95%)	8 (21.05%)	
Years of menopause	9.87 ± 6.45	8.16 ± 7.88	0.304
State anxiety score	39.47 ± 10.59	42.45 ± 9.25	0.196
Trait anxiety score	37.58 ± 9.43	40.47 ± 8.15	0.156
Indications of examination			0.736
Postmenopausal bleeding	32 (84.21%)	34 (89.47%)	
Abnormal ultrasound findings	6 (15.79%)	4 (10.53%)	

Values are expressed as *n* (%) or mean ± SD.

Comment

The data presented in this study revealed that misoprostol given vaginally 12 h before diagnostic office hysteroscopy is more effective than uterine straightening by bladder distension in facilitating the passage of the hysteroscope through the cervical canal and in reducing VAS pain scores during the procedure. To our knowledge, this is the first randomised controlled trial that compared the efficacy of misoprostol with uterine straightening by bladder distension in relieving the pain experienced by postmenopausal patients during office hysteroscopy.

Several randomised controlled trials examined the use of vaginal misoprostol in postmenopausal patients undergoing office hysteroscopy. A randomised controlled trial including 120 postmenopausal patients reported that vaginal misoprostol (200 μg) administered 8 h before office hysteroscopy was more effective than placebo in minimising the experienced pain [6]. Waddell et al.

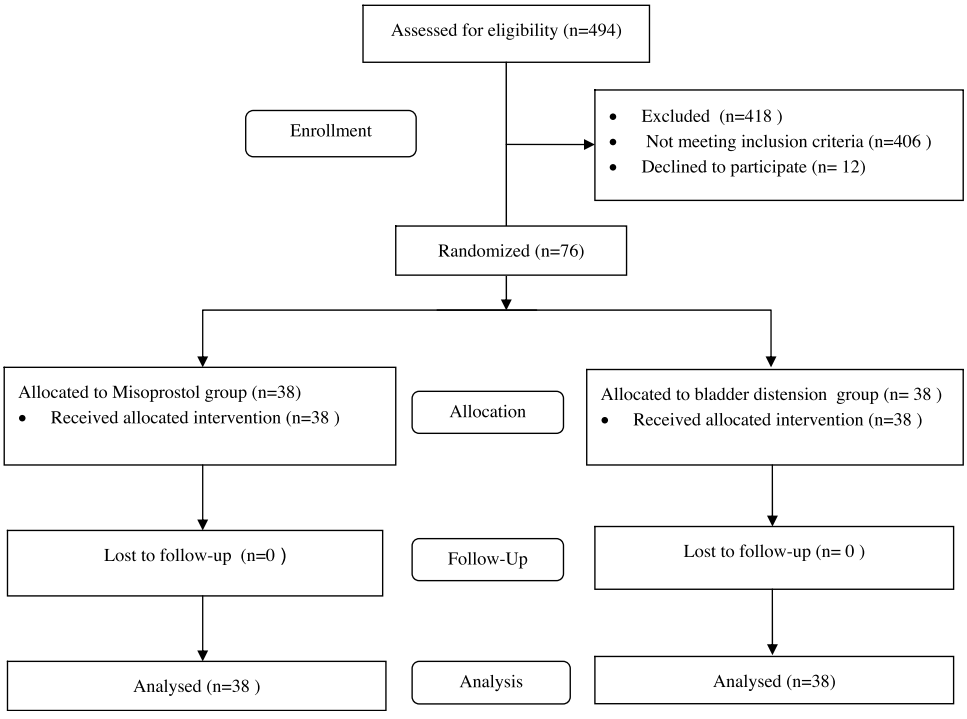

Fig. 1. The flow chart of the patients included in the study.

Table 2
Procedure details.

	Misoprostol group ($n=38$)	Bladder distension group ($n=38$)	p-Value
Operator			0.486
First hysteroscopist	15	12	
Second hysteroscopist	11	16	
Third hysteroscopist	12	10	
Procedure duration (s)	205.03 ± 49.39	219.08 ± 67.68	0.305
Need for cervical dilatation	0 (0%)	0 (0%)	>0.999
Intraoperative findings			
Endometrial polyp	11(28.95%)	9(23.68%)	0.602
Submucous myoma	1(2.63%)	0(0%)	>0.999
Pain estimated by the patient[a]			
During the procedure	39.47 ± 13.96	50.18 ± 15.44	0.002
Thirty minutes post-procedure	11.82 ± 3.71	12.61 ± 4.06	0.379
Ease of hysteroscope insertion[b]	60.37 ± 15.78	50.05 ± 19.88	0.015
Adverse effects			
Abdominal cramps	8 (21.05%)	2 (5.26%)	0.086
Nausea	4 (10.53%)	2 (5.26%)	0.675
Diarrhoea	3 (7.89%)	1 (2.63%)	0.615
Vaginal bleeding	6 (15.79%)	2 (5.26%)	0.262
Fever	2 (5.26%)	0 (0%)	0.493

Values are expressed as n (%), mean ± SD.
[a] Assessed by the patients using a 100-mm visual analogue scale (0 = no pain and 100 = worst imaginable pain).
[b] Assessed by the hysteroscopists using a 100-mm visual analogue scale (0 = most difficult passage of the hysteroscope through the cervical canal and 100 = easiest passage of the hysteroscope through the cervical canal).

examined the use of misoprostol (400 μg) given vaginally 12–24 h prior to office hysteroscopy in a series of 101 premenopausal and postmenopausal patients. The force needed to dilate the cervix to 6 mm and the pain scores during the procedure were significantly lower in the misoprostol group compared with the placebo group [7]. Singh et al. examined the use of misoprostol (400 μg) given vaginally 4 to 6 h prior to office hysteroscopy in a series of 100 premenopausal and postmenopausal patients. Misoprostol significantly reduced the pain scores at the end of procedure compared with no medication [15].

Studies evaluating the use of misoprostol in postmenopausal women for cervical ripening before inpatient operative hysteroscopy have inconclusive results. Two randomised controlled trials revealed that vaginal misoprostol significantly increased the cervical width and reduced the need for cervical dilatation compared with placebo [16,17]. Other studies failed to find any benefit of misoprostol administration. Several authors hypothesised that the hypoestrogenic state is the cause of the weak cervical priming effect of misoprostol in postmenopausal patients [18,19].

In 1984, Sundström et al. reported that the embryo transfer catheter passes smoothly into the uterine cavity in patients with distended bladder [20]. Subsequent studies confirmed that uterine straightening by bladder distension facilitates the passage of the embryo transfer catheter through the cervical canal and improves the outcomes of IVF-ET [21,22]. The results of these studies should be interpreted with caution. Embryo transfer catheters are more fine and flexible than conventional office hysteroscopes and, therefore, we think that the success of uterine straightening by bladder distension in facilitating the passage of the embryo transfer catheter through the cervical canal does not necessary confirm its efficacy in facilitating the passage of the hysteroscope through the cervical canal.

Two randomised controlled studies investigated the effectiveness of uterine straightening by bladder distension in facilitating office hysteroscopy examination and intrauterine device (IUD) insertion [13,23]. A randomised controlled trial evaluating the effect of uterine straightening by bladder distension on the provider's reported ease of IUD insertion and women's reported pain scores during IUD insertion revealed that bladder filling has no effect on the ease of IUD insertion or the reported pain scores [23]. Celik et al. reported that uterine straightening by bladder distension was associated with less pain experienced by the patients during office hysteroscopy. The results of above-mentioned study should be interpreted with caution as all the study participants were parous women of reproductive age [13].

Women with previous vaginal delivery have wider cervical canal diameter compared with nulliparous and postmenopausal women (7–8 mm vs. 4–5 mm) [24]. In nulliparous and postmenopausal patients, the outer sheath diameter of the conventional office hysteroscope (5 mm) is larger than the cervical canal diameter and therefore the passage of the hysteroscope through the cervical canal is often difficult and associated with severe pain [2,3]. We think that nulliparous and postmenopausal patients undergoing office hysteroscopy can benefit from misoprostol more than they can benefit from uterine straightening by bladder distension. Misoprostol can soften and widen the cervical canal and therefore facilitates the passage of the hysteroscope through the cervical canal and minimises the pain experienced during the procedure. In patients with previous vaginal delivery, the outer sheath diameter of the conventional office hysteroscope is less than the cervical canal diameter and therefore the passage of the hysteroscope through the cervical canal is easy and associated with mild pain or discomfort [2,3]. Bladder distension may be beneficial for this subgroup of patients because bladder distension causes alignment of the uterine cavity with the cervical canal and therefore facilitates the passage of the hysteroscope from the cervical canal to the uterine cavity.

The majority of the patients in the bladder distension group (73.68%) complained of mild to severe discomfort related to bladder distension. Bodri et al. reported that 63% of patients who had a full bladder during embryo transfer complained of discomfort related to bladder distension [25]. Patients in the misoprostol group complained of abdominal cramps (21.05%), nausea (10.53%), diarrhoea (7.89%), genital bleeding (15.79%), and fever (5.26%). The results of our study are in agreement with several studies that revealed that vaginal misoprostol administration prior to office or inpatient hysteroscopy is frequently associated with undesired side effects [7,8,12]. Waddell et al. reported the occurrence of abdominal cramps (45%), genital bleeding (14%), nausea (8%), diarrhoea (7%), and fever (7%) following the administration of vaginal misoprostol (400 μg) 12–24 h prior to office hysteroscopy examination [7].

The main strength of this study is the prospective randomised single blind design. The current study has two limitations. First, the patients were not blind to the received treatment. Second, three hysteroscopists performed the procedures. However, the even distribution of the hysteroscopists in the groups of the study and the comparable skill and experience of the hysteroscopists reduced the interobserver variability.

In conclusion, vaginal misoprostol is more effective than uterine straightening by bladder distension in relieving the pain experienced by postmenopausal patients during office hysteroscopy.

Conflict of interest

The authors declare that they have no conflict of interest.

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