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Original Article

Cervical Priming by Vaginal or Oral Misoprostol Before Operative Hysteroscopy: A Double-Blind, Randomized Controlled Trial

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ABSTRACT **Study Objective:** To evaluate whether misoprostol oral is as effective as vaginal tablets for cervical ripening.
Design: Randomized controlled trial involving a parallel, double-blinded study (Canadian Task Force Classification XXX).
Setting: Department of Obstetrics and Gynecology, Cairo University Hospital, between January 2014 and January 2016.
Patients: Patients undergoing operative hysteroscopy for various indications.
Interventions: At 12 hours before hysteroscopy, the oral group received a 400-μg misoprostol tablet and 2 vaginal starch tablets. The vaginal group received 400 μg of misoprostol and 2 oral starch tablets. The control group received 2 oral starch and 2 vaginal starch tablets as placebo. Preoperative preparation was the same in all patients.
Measurements and Main Results: The main outcome measures were width of the endocervical canal, ease of dilatation, time to dilatation, and adverse effects. All subjects eligible for operative hysteroscopy (n = 430) were invited to participate. Twenty subjects refused, and 10 subjects were excluded. The enrolled subjects (n = 390) were randomized to oral misoprostol, vaginal misoprostol, or placebo. The differences in mean width of the endocervical canal between the oral and the control groups (4.79 ± 1.07 mm vs 3.92 ± 0.92 mm), and also between the vaginal and the control groups (4.25 ± 0.71 mm vs 3.92 ± 0.92 mm) were significant ($p < .001$ for both). Moreover, the difference in mean width of the endocervical canal between the oral and the vaginal groups was significant (4.79 ± 1.07 mm vs 4.25 ± 0.71 mm; $p = .009$). Cervical entry was easier in the oral and vaginal groups compared with the control group (mean Likert score, 4.25 ± 0.64 vs 4.22 ± 0.74 vs 2.55 ± 0.87; $p < .001$). In addition, the ease of cervical entry did not differ significantly between the oral and vaginal groups ($p = .998$). The mean time to dilatation was shorter in the oral group and the vaginal group (compared with the control group (48.98 ± 12.6 seconds vs 46.55 ± 15.32 seconds vs 178.05 ± 74.18 seconds; $p < .001$), but the difference between the oral and vaginal groups was not significant ($p = .987$). Adverse effects were comparable between groups ($p > .05$).
Conclusion: We found no statistically significant difference in the efficacy of cervical priming between oral misoprostol and vaginal misoprostol. Journal of Minimally Invasive Gynecology (2016) ■, ■–■

Keywords: Cervical ripening; Misoprostol; Operative hysteroscopy

Despite the widespread recognition of hysteroscopy as a tool for diagnosing as well as managing intrauterine abnormalities, difficulty in dilating the cervix limits its acceptability [1,2]. Difficult or inadequate cervical dilatation leads to approximately one-half of the complications associated with hysteroscopy [3], which include painful entry, false passage, bleeding, cervical tears, and uterine perforation [4].

Cervical priming or ripening before operative hysteroscopy can reduce these complications significantly. Numerous studies have evaluated methods of cervical ripening to minimize the risk of difficult cervical entry and thereby decrease the rate of complications due to hysteroscopy [2,5–7].

Since the introduction of misoprostol as an effective agent for medical termination of second trimester abortions, it has become widely used as a cervical ripening agent in obstetric indications [8]. There are many studies supporting its

The authors declare that they have no conflicts of interest.
Clinical Trial Registration: Pan African Clinical Trials Registry, http://www.pactr.org/ATMWeb/appmanager/atm/atmregistry?dar=true&tNo=PACTR201502001022393, PACTR201502001022393.

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Submitted May 2, 2016. Accepted for publication August 4, 2016.
Available at www.sciencedirect.com and www.jmig.org

1553-4650/$ - see front matter
http://dx.doi.org/10.1016/j.jmig.2016.08.002

use before gynecologic procedures involving insertion of intrauterine devices and hysteroscopy [9,10]. Clinical trials of different routes of misoprostol administration have yielded variable results however [8,11–13]. In addition, in our community, the vaginal route for misoprostol administration necessitates the aid of a gynecologist or a nurse, which makes the oral route more preferable than the vaginal route for patients.

This parallel randomized controlled study was conducted to compare the effectiveness and safety of misoprostol administration via the oral route and the vaginal route. Because vaginal is the standard route according to our institutional protocol, the shift from the vaginal route to the oral route can be evidence-based in our population of patients.

Patients and Methods

This study was conducted in the Department of Obstetrics and Gynecology, Cairo University Hospital, between January 2014 and January 2016. The study was conducted in accordance with the principles of the Declaration of Helsinki and the Medical Research Involving Human Subjects Act, and was approved by the Medical Ethical Review Committee of Cairo University. The purpose of this study was clearly explained in Arabic language to all subjects before enrollment to the study, and each subject enrolled provided written informed consent.

We recruited all patients admitted for different indications who had operative hysteroscopy as the first planned line of treatment. All patients underwent a full history, physical examination, and preoperative evaluation including random blood glucose levels and complete blood count. Documentation of intrauterine pathology was accomplished preoperatively by transvaginal ultrasound, followed by either hysterosalpingography or office hysteroscopy.

Exclusion criteria included pregnancy, profuse uterine bleeding, patients with marked cervical stenosis, known cervical malignancy, previous cervical surgery, recent or current pelvic inflammatory disease, and recent uterine perforation. In addition, patients with any contraindications to prostaglandins, severe cardiovascular disease, hypertension, severe bronchial asthma, or renal failure were excluded.

Randomization and Blinding

Starch tablets were prepared to be identical in appearance to oral and vaginal misoprostol tablets. A computer-generated list of random numbers was used to allocate the subjects to the 3 study groups: oral group, vaginal group, and placebo (control) group. Block randomization with a block size of 12 was used, with a 1:1:1 ratio of the 3 groups. The vaginal and oral tablets (active or placebo) were prepared in containers and consecutively numbered for each subject according to the randomization list for each block. The allocation sequence was concealed from the researchers who enrolled and assessed subjects.

Subjects were allocated at random to oral misoprostol (Cytotec; Pfizer, New York, NY) plus vaginal starch tablets (oral group), vaginal misoprostol and oral starch tablets (vaginal group), or oral and vaginal starch tablets (placebo control group). Neither the researcher allocating the subjects nor the researcher assessing the subjects was aware of the relationship between the numbers on the containers and the allocation sequence.

In one center, 10 surgeons with long experience in hysteroscopic surgery were assigned for operative hysteroscopy and were blinded to the study group allocation. Spinal anesthesia was achieved using a 20-gauge spinal needle for injection of 0.25 μg fentanyl and 12 mL of 0.5% bupivacaine.

The subjects oral group received a 400-μg misoprostol oral tablet and 2 vaginal starch tablets at 12 hours before undergoing hysteroscopy. The subjects in the vaginal group received 400 μg misoprostol (the standard dose used at Cairo University Hospital) inserted vaginally and 2 oral starch tablets at 12 hours before the operation. The subjects in the control group received 2 oral starch tablets and 2 vaginal starch tablets as placebo. Repeat dosages were considered when necessary.

Procedures

All patients were fasted for 10 hours before the procedure. With the patient under spinal anesthesia, the cervix was grasped with a tenaculum, and the initial endocervical diameter was confirmed with a Hegar dilator (10, 9, 8, 7, 6, 5, 4, or 3 mm). The dilator that passed without resistance was taken as the initial diameter. Then, we used the Hegar dilators (3–10 mm) to dilate the cervix to 10 mm. Time elapsed between the start and the end of dilation was measured by the circulating nurse with a stopwatch. Ease of dilatation was assessed by the surgeon using a 5-point Likert scale [14].

Complications occurring before the procedure (owing to the side effects of misoprostol), during dilatation, during hysteroscope entry, or after the operation were recorded. Postoperative bleeding is defined as bleeding necessitating more than 3 pad changes per day or bleeding continuing for 1 week or longer postoperatively. A 3-week follow-up included history and physical examination.

Outcome Measures

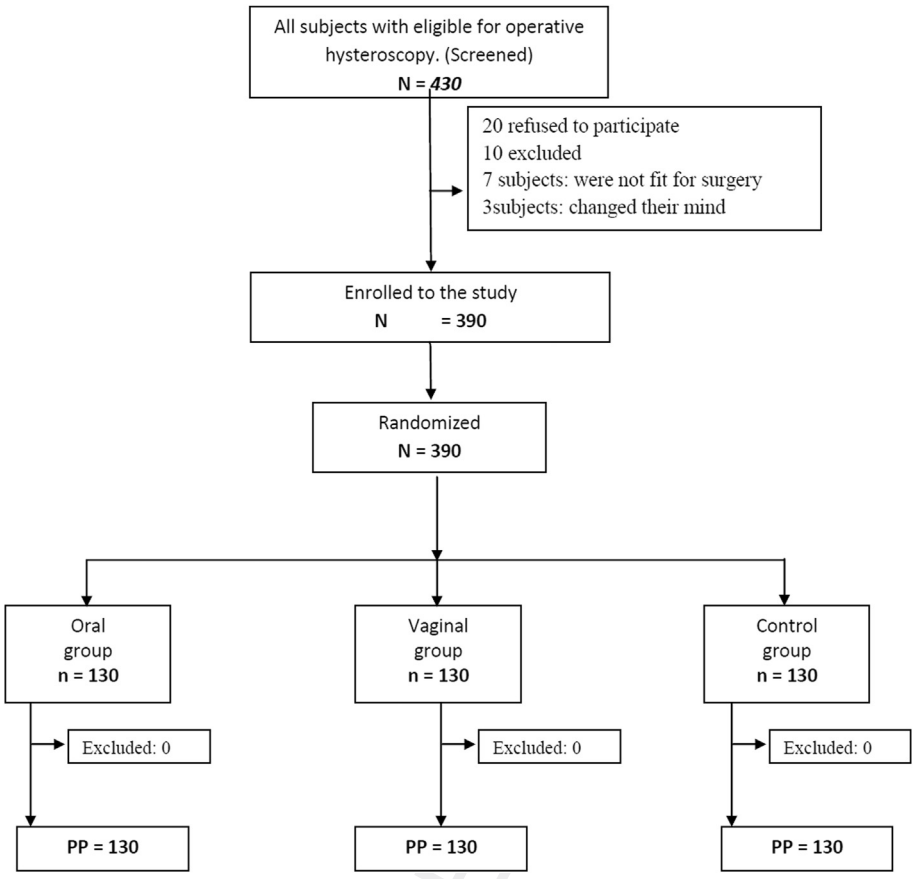
The primary outcome measures were width of the endocervical canal at the start of dilation, ease of dilatation on a 5-point Likert scale, and time for dilatation from the start of the procedure to final dilatation to Hegar 10 mm. Secondary outcome measures were preprocedure complications of misoprostol and intraoperative and postoperative complications of hysteroscopy.

Statistical Analysis

A sample size calculation was done to determine the number of subjects needed in each group. Previously

Fig

CONSORT flow diagram.



reported mean endocervical canal width following oral and vaginal misoprostol is 3.10 and 3.23 mm, respectively (p = .05 with 80% power) [15]. With a significance value of 0.05 and 80% power, detecting a difference of 0.65 mm requires at least 240 patients (120 patients per group) with a control group of 120. Thus, we needed a total sample size of 390, to account for any dropouts.

All statistical tests were conducted using a significance level of 95%. A p value $< .05$ was considered statistically significant. SPSS version 20.0 (IBM, Armonk, NY) was used for all statistical analyses. Data are presented as (mean ± SD) or median (range) for continuous variables and as frequency and percentage for categorical variables. Comparisons between groups were done using the phi and Cramer's test for categorical variables and analysis of variance and Bonferroni's post hoc test for continuous variables.

Results

All subjects who came to the centers and were eligible for operative hysteroscopy (n = 430) were invited to participate in the study. Twenty subjects refused participation, and 10 subjects were excluded before randomization for various reasons, leaving 390 subjects for randomization, with 120 assigned to each of the 3 groups. No subject was excluded

Table 1

Characteristics of the study groups

Characteristic	Oral group	Vaginal group	Control	p value
Age, years, mean ± (SD)	33.80 ± 6.80	33.20 ± 6.00	32.81 ± 5.72	.623
Gravidity, median (range)	3 (0–5)	3 (0–5)	3 (0–5)	.921
Parity, median (range)	2 (0–5)	2 (0–5)	2 (0–5)	.756
History of vaginal delivery, n (%)	83 (64)	67 (52)	67 (52)	.079
History of cesarean delivery, n (%)	23 (18)	18 (14)	12 (9)	.211

Table 2

Indications for hysteroscopy

Indication	Oral group, n (%)	Vaginal group, n (%)	Control, n (%)	p value
Endometrial hyperplasia	12 (9)	5 (4)	14 (11)	.059
Myoma	18 (14)	17 (13)	20 (15)	.152
Polyp	68 (52)	86 (66)	65 (50)	.231
Septate uterus	18 (14)	16 (12)	25 (19)	.563
Subseptate uterus	14 (11)	6 (5)	6 (5)	.091

after randomization. The dispositions of the subjects are shown in a CONSORT diagram in Fig.

Baseline Characteristics

Only 390 subjects were included in the analysis, 130 in each group. There was no statistically significant difference ($p > .05$) among the 3 groups regarding age, gravidity, parity, history of vaginal delivery, and history of cesarean section delivery, as shown in Table 1. All patients were premenopausal.

The 3 groups were comparable ($p > .05$) in terms of the indication for hysteroscopy. The most frequent indication in the 3 groups was endometrial polyps, found in 68% of the cases in the oral group, 86% of cases in the vaginal group, and 65% of cases in the control group. Other indications included septate uterus, subseptate uterus, myoma, and endometrial hyperplasia (Table 2).

Width of Endocervical Canal and Dilatation

The mean predilatation endocervical canal width was 4.79 ± 1.07 mm in the oral group, 4.25 ± 0.71 mm in the vaginal group, and 3.92 ± 0.92 mm in the placebo control group. There were statistically significant differences in endocervical canal width between the oral and the control groups and between the vaginal and the control groups ($p < .001$ for both), as well as between the oral and vaginal groups ($p = .009$; Table 3).

Cervical entry was easier in the oral group and vaginal groups than in the control group (mean Likert score, 4.25 ± 0.64 vs 4.22 ± 0.74 vs 2.55 ± 0.87). The difference in ease of cervical entry was significant between the oral and the control groups and between the vaginal and the control groups ($p < .001$ for both), but not between the oral and vaginal groups ($p = .998$), as shown in Table 3.

The mean time to dilatation was 48.98 ± 12.6 seconds in the oral group, 46.55 ± 15.32 seconds ion the vaginal group, and 178.05 ± 74.18 seconds in the control group ($p < .001$). The difference in time between the oral and vaginal groups was not significant, ($p = .987$), as shown in Table 3.

Misoprostol Safety

Adverse effects occurring during the study were comparable in the 3 groups ($p > .05$). Cervical laceration occurred in 5 cases in the oral group, 3 cases in the vaginal group, and 5 cases in the control group. Postoperative bleeding occurred in 0 cases in the oral group, 4 cases in the vaginal group, and 3 cases in the control group. Other side effects were cramps, diarrhea, nausea, vomiting, and fever (Table 4).

Discussion

In this randomized controlled study, we compared the most accepted route of misoprostol administration (oral) with the most common route used in our gynecologic practice (vaginal). Our findings indicate that both routes are effective and safe for cervical priming before operative hysteroscopy. Compared with placebo, misoprostol delivered either orally or vaginally resulted in greater initial

Table 3

Effects on the width of endocervical canal, ease of dilatation, and time needed for dilatation

Variable	Oral group, mean ± SD	Vaginal group, mean ± SD	Control, mean ± SD	p values: Oral vs control	p values: Vaginal vs control	p values: Oral vs vaginal
Width of the endocervical canal, mm	4.79 ± 1.07	4.25 ± 0.71	3.92 ± 0.92	.000	.000	.009
Ease of dilatation	4.25 ± 0.64	4.22 ± 0.74	2.55 ± 0.87	.000	.000	.998
Time needed for dilatation up to 10 mm, seconds	48.98 ± 12.6	46.55 ± 15.32	178.05 ± 74.18	.000	.000	.987

Table 4

Preoperative and postoperative adverse events and complications

Event/complication	Oral group, n (%)	Vaginal group, n (%)	Control group, n (%)	p value
Cervical lacerations	5 (4)	3 (2)	10 (8)	.057
Postoperative bleeding	4 (3)	4 (3)	6 (4)	.151
Preoperative cramps	5 (4)	5 (4)	5 (4)	1.000
Preoperative diarrhea	6 (5)	2 (2)	2 (2)	.194
Preoperative nausea	7 (5)	6 (5)	2 (2)	.946
Preoperative vomiting	7 (5)	2 (2)	5 (4)	.063
Preoperative fever	4 (3)	3 (2)	5 (4)	.773

endocervical canal diameter and subsequent cervical dilation in a significantly shorter time.

Our results are in accordance with a 2012 systematic review that strongly supported the effectiveness of misoprostol delivered via different routes as a cervical priming agent [16]. That review concluded that misoprostol appears to facilitate an easier and uncomplicated hysteroscopy in premenopausal women, but not in postmenopausal women.

Another randomized controlled trial conducted to compare the effectiveness and patient preference of different routes of misoprostol administration before operative hysteroscopy in premenopausal women published in 2014 [17]. The authors concluded that orally, sublingually, and vaginally administrated misoprostol are equally effective in inducing proper cervical priming before operative hysteroscopy. That study enrolled 40 patients in each group, with a total sample size of 160 patients. In our present study, we compared only the vaginal route and the oral route with a placebo control. Our sample size of 390 patients, 130 in each group, increased the power of our study.

Nonetheless, a 2015 Cochrane review [18] concluded that the quality of evidence that misoprostol aids preoperative ripening of the cervix before hysteroscopy with fewer complications is only moderate. Moreover, it concluded that misoprostol is associated with significant adverse effects, including preoperative pain and vaginal bleeding.

The initial design of misoprostol was as an oral agent, and clinical trials of different routes have reported extremely variable results [8,11–13]. It seems logical that the oral route would be the most desirable in clinical trials of misoprostol, and indeed this was the case [11–13,19].

With the use of misoprostol 400 μg as a single dose, both the oral and vaginal routes are medically safe regarding preoperative nausea, cramps, diarrhea, and fever. In addition, complications of the procedure itself, such as cervical lacerations, false passage, uterine perforation, and postoperative bleeding were comparable in the 3 groups. However, in other studies misoprostol was found to effectively reduce the incidence of cervical lacerations and postoperative bleeding compared with controls [2,4–7,17].

The strengths of this study include its design as a double-blinded, sufficiently powered trial with a large sample size. Moreover, it provided a head-to-head comparison of administration routes and adequate placebo with a various metrics measured as objectively as possible. Limitations of the study include the inability to define the exact of amount of bleeding considered significant, and variability on the assessment of ease of dilatation among surgeons, with the interrater variability possibly leading to assessment bias given the subjective nature of assessing ease of dilation. However, to our knowledge, no objective approach has been published in the literature until now. Finally, all of the study subjects were premenopausal.

Conclusion

Based on our findings reported here, we conclude that there are no statistically significant differences between oral misoprostol and vaginal misoprostol in the effectiveness and safety of cervical priming. Thus, the shift from the vaginal route to the oral route can be undertaken without incurring any risk or jeopardizing the clinical efficacy. In addition, we recommend search for objective test for ease of cervical dilatation.

Acknowledgments

We thank Dr. Emad R. H. Issak (ClinAmygate) for his assistance with statistical analysis and editing the manuscript.

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