Different routes of misoprostol for same-day cervical priming prior to hysteroscopy: a randomized controlled single-blinded trial

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Introduction Hysteroscopic surgery, with prior cervical ripening by misoprostol (a synthetic analog of prostaglandin E1), has been widely used to treat gynecological diseases, including submucosal myoma, endometrial polyps, and uterine synechia in nonpregnant women. The route of administration of misoprostol for cervical dilatation can be oral, vaginal, or sublingual.

Aims The aim of the present study was to evaluate the efficacy of 400 μg misoprostol administered orally, vaginally, or sublingually on cervical ripening before hysteroscopy

Patients and methods Study setting: Sayed Galal Hospital. Study duration: April 2017–April 2018. Number of patients: 300 patients. A prospective randomized controlled single-blinded trial. Nonpregnant women scheduled for hysteroscopy were divided randomly into four groups using sealed opaque envelopes to receive 400 mg of misoprostol, administered either orally (n=75) or vaginally (n=75) 6–8 h prior to surgery or 400 mg sublingually (n=75) 2–4 h prior to surgery or the control group (n=75) that received nothing. The primary outcome in this study was the preoperative cervical width as measured by the largest number of Hegar dilators. Duration of cervical dilatation was also recorded along with side effects related to misoprostol and complications during surgery for each group.

Results The mean±SD cervical widths for oral, sublingual, vaginal, and control groups were 7.60±1.76, 7.56±1.64, 7.57 ±2.06, and 5.65±2.17 mm, respectively, which was statistically significant. Time to cervical dilatation was also significantly longer in the control group than in the other three groups. Misoprostol-related adverse effects and hysteroscopy-related complications were comparable among the four study groups.

Conclusion All routes (oral, sublingual, vaginal) of administrations of misoprostol are equally effective in inducing proper cervical priming before hysteroscopy.

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Introduction

Hysteroscopic surgery, with prior cervical ripening by misoprostol [analog prostaglandins E1 (PGE1)], has been widely used to treat gynecological diseases including submucosal myoma, endometrial polyps, and uterine synechia in nonpregnant women [1,2]. Misoprostol has been shown to be equally effective when compared with laminaria in inducing cervical priming prior to hysteroscopic surgery with minimal time required for cervical dilatation, easy administration, reduced costs, and increased patient convenience [3].

Hysteroscopy is a minimally invasive intervention that can be used to diagnose and treat many intrauterine and endocervical problems. Hysteroscopic polypectomy, myomectomy, and endometrial ablation are just a few of the commonly performed procedures. Given their safety and efficacy, diagnostic and operative hysteroscopy have become standards in gynecologic practice [4].

Complications encountered during the procedure are partly related to difficulties in cervical dilatation. These include cervical tears, creation of a false track, hemorrhage, uterine perforation requiring laparoscopy, or simply difficulty in entering the internal cervical os with the resectoscope [5].

The incidence of these complications can be reduced if the cervix is ripened before the procedure by inserting laminaria into the cervical canal the night before surgery [6] or by using sulprostone gel [7].

Misoprostol, a synthetic PGE1 analog widely prescribed for prevention and treatment of gastric ulcers, has been shown to have cervical ripening effects in both pregnant and nonpregnant patients when administered either orally or vaginally [8,9].

The systemic bioavailability of misoprostol is three times greater when it is administered vaginally than orally [10].

The common side effects include diarrhea and abdominal pain. It is pregnancy category X meaning that it is known to result in negative outcomes for the baby if taken during pregnancy like Möbius syndrome (a child with oromandibular-limb hypogenesis and expressionless face due to bilateral facial nerve palsies and missing fingers). Uterine rupture may occur [11].

The route of administration of misoprostol for cervical dilatation can be oral, vaginal, or sublingual. However, it is still unclear which route is more effective for cervical dilation before transcervical procedures in nonpregnant women [12]. Cervical ripening is required to prevent complications during the transcervical procedure [12].

Previous studies have shown that misoprostol was effective when compared with placebo for cervical ripening whether the route of administration was oral or vaginal [1,2,8,9,13–16].

Two prior reports compared the effects of preoperative oral and vaginal misoprostol on cervical ripening before hysteroscopic surgery. One study has found that vaginal administration was more effective than the oral route for preoperative cervical ripening in nonpregnant premenopausal women [17], while the other found no difference between the two routes [18].

The aim of the present study was to evaluate the efficacy and side effects of 400 μg misoprostol administered orally, vaginally, or sublingually on cervical ripening before hysteroscopy.

Patients and methods

This study was conducted prospectively between April 2017 and April 2018 at the Department of Obstetrics and Gynecology at Sayed Galal Hospital. Symptomatic patients that were suspected as having intrauterine pathology, such as submucosal myoma, endometrial polyps, or other endometrial pathological findings based on the transvaginal ultrasound, were enrolled. All patients were scheduled for elective hysteroscopy.

Ethics committee was obtained before the beginning of the study, and informed consent was obtained prior to participation in the study.

All included women were subjected to the following:

(1) History taking: Important elements of the history include menstrual history, sexual history, illnesses and infections, surgeries, medications used and exposure to certain environmental agents (alcohol, radiation, steroids, chemotherapy, and toxic chemicals).
(2) Transvaginal ultrasound: ultrasound evaluation was used to identify intrauterine pathology, such as submucosal myoma, endometrial polyps, and congenital cavitary anomalies such as a septate uterus.
(3) Routine laboratory investigations including complete blood picture, hematocrit, coagulation profile, virology, and liver and kidney function tests.
(4) Preoperative senior anesthetist assessment.

Exclusion criteria included:

(1) Patients with any evidence of a contraindication or allergy to PGs (asthma, glaucoma, and hypertension).
(2) Patients with any sign of genital infection, history of cervical surgery, endometrial lesions with suspected endocervical, or exocervical lesions that could affect the cervical resistance.

All patients were randomly allocated at the outpatient department to the oral, sublingual, vaginal, or control groups at a 1:1:1:1 ratio using sealed opaque envelopes that were prepared by the study doctor and each contained a folded slip of paper with the treatment route (orally, sublingually, vaginally, or no medication) written on it. When the patients agreed to participate in this study at the outpatient clinic, the envelopes were opened by the study doctor, and the randomization took place. All misoprostol tablets were identical.

The study was conducted in a single-blinded manner; the drug administered was unknown (blinded) to the surgeon. Vaginal and oral groups received 400 μg of misoprostol, and the patients self-administered the medication vaginally or orally 6–8 h before surgery. The sublingual group received the same dose of misoprostol and took the tablets sublingually 2–4 h before surgery. In the control group, hysteroscopy was performed without misoprostol administration. To prevent bias, in all cases the vagina was cleaned, and any remnant of the misoprostol tablets was removed by the resident or physician assistant in charge before the operating surgeon began the procedure. Additionally, the patients were asked about pain, other misoprostol-associated side effects, and the acceptability of the self-administration of medications through a self-reported question before entrance into the operating room. The operator

performing the procedure was blinded to the group allocation.

The patients were given general intravenous anesthesia after the resident or physician assistant in charge prepared the patients for surgery by disinfecting the vulva and vaginal area with a betadine solution. After performing cervical dilatation with Hegar dilators, hysteroscopy was done and the uterine cavity was distended with normal saline at an insufflation pressure of 100–150 mmHg, with careful monitoring of the fluid balance. After hysteroscopy, the patients were monitored in the postanesthesia care unit for a minimum of 2 h and returned for follow-up visits 1 day and 1 week after surgery.

The primary outcome measure in this study was the preoperative cervical width at the time of surgery after misoprostol administration. The cervical width was assessed by performing cervical dilation, beginning with a number 10 Hegar dilator and subsequently inserting smaller Hegar dilators until the dilator could pass through the internal os without resistance. The largest one that could be passed was recorded as the initial cervical width. Secondary outcome measurements included: first, the duration of cervical dilatation; second, self-reported misoprostol-associated adverse effects before the procedure, such as uterine cramping, uterine bleeding, diarrhea, nausea, and vomiting; third, and complications during cervical dilatation and hysteroscopy. The patients were asked about possible side effects of misoprostol before induction of general anesthesia.

The sample size was calculated on the basis of a previous study, in which the cervical widths, after 400 μg oral misoprostol or placebo, were 8.2±2.3 and 7.5±2.2 mm, respectively [13].

We assumed that equivalence was of clinical significance if the difference in the initial cervical width was less than 1.5 mm among groups with an SD of the initial cervical width of 2.3 mm. Setting the type 1 error and power to 5 and 80%, respectively, and allowing a 7% dropout rate, the estimated sample size required was 75 patients in each group.

SPSS 20 (SPSS) (IBM Corp. Released 2011, IBM SPSS Statistics for Windows, Version 20.0, Armonk, NY: IBM Corp.) was used for the statistical analysis. Data are presented as the mean±SD or median (range) for quantitative variables and frequency (percentage) for qualitative variables. All analyses were performed according to the intention-to-treat principle. Comparisons of quantitative variables were performed using a one-way analysis of variance as a parametric test or a Kruskal–Wallis test as a nonparametric test and adjusted by Bonferroni's correction for multiple comparisons. Frequency distributions between categoric variables among the four groups were compared using the χ^2 test or Fisher's exact test. A P value of less than 0.05 was statistically significant.

Results

This study was conducted at the Department of Obstetrics and Gynecology at Sayed Galal Hospital during the period between April 2017 and April 2018, and follow-up visits were concluded in May 2018.

A total of 300 women who were scheduled for elective hysteroscopy.

All patients were randomly allocated at the outpatient department to the oral, sublingual, vaginal, or control group using sealed opaque envelopes.

None of the study participants changed groups or stopped participating in the study after randomization or before surgery. There were no cases of failed surgery or follow-up loss for 1 week after surgery.

The four groups were comparable in age, body mass index, parity and history of vaginal or cesarean section delivery (Table 1).

Table 1 Baseline characteristics of all groups

Characteristics	Oral (n=75)	Sublingual (n=75)	Vaginal (n=75)	Control (n=75)	P value
Age (years)	34.03±5.09 (19–47)	28.92±5.96 (20–45)	29.91±5.39 (22–43)	27.57±5.66 (20–48)	0.546
BMI (kg/m^2)	23.89±2.46 (20–33)	20.35±2.57 (15–26)	20.01±2.42 (17–26)	20.60±2.06 (17–26)	0.573
Parity					
Nulliparous	49 (65.3)	53 (70.7)	43 (57.3)	52 (69.3)	0.627
Parous	26 (34.7)	22 (29.3)	32 (42.7)	23 (30.7)	
History of vaginal delivery	15)20)	19 (25.3)	20 (26.7)	15 (20)	0.709
History of CS	11 (14.7)	3 (4)	12 (16)	8 (10.7)	0.716

All data are not statistically significant. Data are expressed as mean±SD, median (range), or number (percentage) if appropriate. CS, cesarean section. Misoprostol, 400 μg doses.

The mean preoperative cervical widths for the oral, sublingual, vaginal, and control groups were 7.60±1.76, 7.56±1.64, 7.57±2.06, and 5.65±2.17 mm, respectively.

These cervical widths were similar among the oral, sublingual, and vaginal groups, but the cervical width in the control group was significantly narrower than those in the three misoprostol groups ($P<0.001$), indicating that the use of misoprostol (regardless of administration route) before hysteroscopy reduced the difficulty in cervical dilation.

The time to cervical dilatation was 47.78±20.12 s in the oral group, 48.03±18.71 s in the sublingual group, 46.33±20.98 s in the vaginal group, and 84.18 ±39.49 s in the control group.

It took a significantly longer time to dilate the cervix in the control group than in the other three groups ($P<0.002$).

The rate of adverse effects in the control group was lower than that in the other three groups (oral, sublingual, and vaginal) (5.3 vs 21.3% −18.7–24.0%), but this difference did not reach statistical significance ($P<0.052$).

The rates of adverse effects were similar among the three misoprostol groups (oral, sublingual, and vaginal), and there was no case in which the surgery had to be delayed because of misoprostol adverse effects, all of which were tolerable (Table 2).

Complications during cervical dilation occurred in two participants

A cervical tear occurred in one participant in the oral group, one participant in the vaginal group and two participants in the control group; however, the length of the cervical tear was less than 10 mm in all cases, which did not require suturing.

Creation of a false tract during cervical dilation occurred in one participant in the oral group, one participant in the sublingual group, one participant in the vaginal group, and one participant in the control group but the participants were managed conservatively without any surgical, endoscopic, or radiologic intervention. One participant in the oral group was admitted for close observation of profuse uterine bleeding after hysteroscopic myomectomy.

The remaining participants were discharged after 2 h of observation, and no complications occurred during this period.

Discussion

The route of administration of misoprostol for cervical dilatation can be oral, sublingual, or vaginal. However, no solid conclusions have been reached as to which route is most effective for cervical dilation before hysteroscopy.

The aim of this study was to evaluate the efficacy and side effects of 400 μg misoprostol administered orally, vaginally, or sublingually on cervical ripening before hysteroscopy.

The current study was conducted at Sayed Galal Hospital during the period between April 2017 and April 2018. The study was conducted on patients who were scheduled for elective hysteroscopy.

The mean age of included women were 34.03±5.09 years (range: 19–47 years) of the oral group, 28.92±5.96 (range: 20–45 years) of the sublingual group, 29.91

Table 2 Outcome and adverse effects of cervical priming of all groups

Characteristics	Oral (n=75)	Sublingual (n=75)	Vaginal (n=75)	Control (n=75)	P value
Preoperative cervical width (mm)	7.60±1.76 (4.5–15)	7.56±1.64 (2.5–15)	7.57±2.06 (2–16)	5.65±2.17 (2–15)	<0.001
Duration of cervical dilatation (s)	47.48±20.12 (20–130)	48.03±18.71 (20–130)	46.33±20.98 (20–145)	84.18±39.49 (24–225)	<0.002
Complications during cervical dilatation and hysteroscopy	2 (2.7)	1 (1.3)	2 (2.7)	3 (4)	<0.999
Adverse effects related to misoprostol					
Cramping	16 (21.3)	14 (18.7)	18 (24)	4 (5.3)	0.052
Bleeding	7 (9.3)	5 (6.7)	7 (9.3)	2 (2.7)	0.406
Diarrhea	4 (5.3)	5 (6.7)	7 (9.3)	2 (2.7)	0.599
Nausea	1 (1.3)	2 (2.7)	2 (2.7)	0	0.999
Vomiting	2 (2.7)	1 (1.3)	1 (1.3)	0	0.999

Data are expressed as mean±SD, median (range), or number (percentage) if appropriate. Misoprostol, 400 μg doses.

±5.39 (range: 22–43 years) of the vaginal group, and 27.57±5.66 (range: 20–48 years) of the control group.

The main finding of this study was that outcomes with regard to cervical priming with misoprostol by oral, sublingual, and vaginal administration were comparable, and all adverse effects were similar among all groups and were tolerable.

Our results indicate that misoprostol, regardless of the route of administration, play a role as a cervical priming agent before hysteroscopy.

This finding is consistent with a recent meta-analysis [19] that analyzed 21 randomized, controlled trials involving 1786 participants and evaluated the effects of misoprostol before hysteroscopy for cervical dilatation. The mean cervical width before hysteroscopy was significantly wider in premenopausal women treated with misoprostol compared with the placebo group [mean difference, 95% confidence interval (CI): 2.47 mm (1.81–3.13 mm)]. Furthermore, cervical laceration was significantly lower in participants treated with misoprostol than in participants treated with placebo [relative risk (95% CI): 0.22 (0.09–0.54)]. These authors concluded that misoprostol before hysteroscopy facilitates an easier and uncomplicated procedure in premenopausal women.

The frequencies and types of adverse effects were similar among the three misoprostol groups, consistent with findings from previous studies [18]. However, the frequency of adverse effects was lower than in previous studies.

This discrepancy might be due to a relatively short time between medication and hysteroscopy, because the symptoms related to adverse effects could be masked during surgery under general anesthesia and after the procedure. Furthermore, similar to previous studies, there was no delay in the planned procedure based on misoprostol use, and all adverse effects were tolerable without the need for additional treatment. Although the difference did not reach statistical significance ($P<0.052$), the rates of adverse effects in the three misoprostol groups were higher than that in the control group (21.3% −18.7%–24.0 vs 5.3%).

This result is in line with a recent meta-analysis that analyzed seven randomized, controlled trials involving 568 participants and evaluated the use of misoprostol in operative hysteroscopy [20]. Compared with the placebo group, there was an increase in side effects (cramps, vaginal bleeding, nausea, vomiting, and diarrhea) in the misoprostol group [relative risk (95% CI): 4.28 (1.43–12.85)]. The researchers concluded that current evidence does not support the routine use of preoperative misoprostol in operative hysteroscopy [20].

A potential weakness of this study is that the same surgeon did not perform all the procedures and that the resistance during cervical dilatation was assessed subjectively. This may introduce the potential for bias because each clinician may have a different perception of cervical resistance. It has been suggested that the force applied during cervical dilatation can be measured by a tensiometer to overcome this drawback [8].

Our study had several limitations. First, the measurement of cervical width was not objective. It has been suggested that the forced applied during cervical dilation can be measured by a tensiometer to overcome this drawback [8]. However, measurements by a Hegar dilator have been acceptable and used in many previous studies [3,17,19,21].

Second, the control group was not given a ‘placebo’ intervention, which might have led to a reduction of adverse effects related to misoprostol medication. Meanwhile, the strength of this study is that it was conducted in a single blinded manner with a control group.

A previous study has shown that the routes of misoprostol at the same dose given sublingually, orally, and vaginally, before hysteroscopic surgery in the premenopausal nonpregnant women, were statistically equal with regard to the postmedication cervical width without any difference in cervical dilatation time to Hegar number 10, complications during cervical dilatation or drug side effects [22].

Cervical ripening is required to prevent complications during the transcervical procedure [12,23].

Previous studies have shown that misoprostol was effective when compared with placebo for cervical ripening [1,2,8] whether the route of administration was oral [8,13] or vaginal [9,14–16].

However, there are only two studies that have compared the oral and vaginal routes of administration, with different results [17,18]. The different outcomes between the two studies can be attributed to two possible factors. The first aspect is

the difference in dosage (200 vs 400 μg) for the vaginal route and the second factor is that both the studies assessed cervical force based on the ease of passage of the Hegar dilator, which is dependent on the individual surgeon.

Even in the current study, all procedures were assessed subjectively; however, surgeons with similar surgical skill and the relatively even distribution of surgeons in each route of misoprostol administration make this bias less likely.

There was one study comparing sublingual misoprostol and placebo in women with GnRH (gonadotropin-releasing hormone) agonist [24] which showed negative results, similar to the findings in oral and vaginal routes [14,25–27] and in contrast with other reports [8,16]. However, the efficacy of sublingual misoprostol in women with normal estrogen status has been unknown and our results demonstrated the equal efficacy of sublingual misoprostol with oral and vaginal routes.

These findings correspond well with the sublingual use of misoprostol in pregnancy termination [28,29] with the possible benefit of convenient administration [28].

In addition to the route of administration, the optimal dose and time interval from medication to surgery remain to be determined. On the basis of recent studies, 400 μg has been most widely used dose for oral [13,18,25,30], vaginal [15,16,31,32], and sublingual [33] administrations with good results. In the above-cited studies, the time interval varied from 4 to 24 h for the oral and vaginal routes.This study used a time interval of 6–8 h, a relatively short interval, because of patient convenience. Sublingual misoprostol 400 μg with an interval of 2–4 h, in this study, was based on the studies of pregnancy termination [28,29,34,35].

There was one prior study with sublingual administration 1 h before intrauterine device insertion in premenopausal women [33]; however, the cervical widths were not assessed in that study.

The frequencies and types of side effects were comparable among the three groups, consistent with the findings of previous studies [17,18]. However, the frequency of side effects was lower than in prior studies. This might be due to a relatively short time period between medication and operation because the symptoms related to side effects could be masked during surgery under general anesthesia and postoperation status. Also, similar to prior studies, there was no delay in the planned procedure based on misoprostol use, and all side effects were tolerable without the need for further treatment.

This study was performed in a single-blinded manner with a control group, which could be a potential strength. Because it has been proven there are more complications during procedures without cervical ripening compared with cases with cervical ripening [2,12,23,30], there should not be an ethical problem with a control group.

From the results of previous studies that had a control group [8,9,14,15], the average cervical widths after misoprostol administration were between 6 and 7.3 mm, which were similar to our results.

Because all women undergoing hysteroscopy might have not required cervical ripening in practice, it would be helpful to identify a population at higher risk for complication of cervical dilation.

In this study, we could not find any significant difference in cervical width and time to cervical dilatation based on parity. However, among the study population, about 65.6% (197/300) were nulliparous women. This is another limitation of this study. Further study for higher risk patients for complication of cervical dilation such as patients with nulliparity, cervical stenosis, or hypestrogen status should be warranted.

We sought to determine the efficacy of 400 μg misoprostol administered orally, vaginally, or sublingually on cervical ripening before hysteroscopy using a randomized, single-blinded controlled trial. Despite the need for cervical dilatation and the fact that the duration of dilatation was considerably lower in the misoprostol groups than in the control group, a statistically significant difference was not found. Also, although the need for cervical dilatation and duration of dilatation were considerably lower in the misoprostol groups than in the control group, a statistically significant difference was not found in this case. However, the results are clinically important and promising as well.

Conclusion

We found that cervical widths and adverse effects were comparable, regardless of the route of misoprostol administration. Additional randomized, controlled trials are required to confirm or reject the results of this study.

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Conflicts of interest
There are no conflicts of interest.

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