Gynecol Surg (2012) 9:169–173
DOI 10.1007/s10397-011-0715-3

ORIGINAL ARTICLE

Prostaglandins prior to hysteroscopy

A randomized controlled trial

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Received: 17 September 2011 / Accepted: 22 October 2011 / Published online: 18 November 2011

Abstract This prospective randomized controlled study was conducted to assess the role of misoprostol, given sublingually or rectally, on the outcome of hysteroscopic procedures. A total of 212 premenopausal patients undergoing hysteroscopic procedures were randomly allocated into three groups: group 1 (n=71), sublingual misoprostal given 2 h before the procedure; group 2 (n=71) rectal misoprostal 2 h before the procedure; group 3 (n=70), control group, no medications were given. Main outcome measures were ease of cervical dilatation, dilatation time to Hegar 6, complications as cervical laceration and postoperative cramps, bleeding and pyrexia. The cervical canal at the start was significantly wider misoprostol groups (P= 0.038). Cervical dilatation was significantly easier in the rectal misoprostol group over control (P=0.035). Misoprostol groups showed significant reduction in the mean time needed to dilate to Hegar 6 (P=0.021). Postoperative pain and cramps were significantly higher in misoprostol groups (P=0.002). Misoprostol before hysteroscopy demonstrates a benefit in the ease of cervical dilatation, cervical width at the start and time for dilatation with low risk of cervical tears. Rectal misoprostol appears advantageous than sublingual one. However, postoperative adverse effects are more common with misoprostol groups.

Keywords Sublingual · Rectal · Misoprostol · Hysteroscopy

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Introduction

Advances in endoscopic instrumentations and fiber optics made hysteroscopy an important diagnostic and therapeutic tool for patients with intrauterine diseases. Hysteroscopy provides detailed observation and optional management of intrauterine lesions, thus constituting a valuable gynecologic procedure [1].Many patients require cervical dilatation prior to hysteroscopy, which might lead to considerable traumatization of tissues especially in women with firmly closed rigid cervix. Furthermore, complicated cervical dilatation is attended by the risk of lacerations caused by the tenaculum, the creation of false passages and an increased risk of uterine perforation especially in nulliparous and postmenopausal women [2–4].

Ripening or softening of the uterine cervical tissue is a complex process recommended before procedures where intrauterine manipulations either for diagnostic or therapeutic purposes are needed [5]. Cervical ripening can be achieved in various ways, mechanically and biologically with agents such as prostaglandins, antiprogestins or nitric oxide donors, although prostaglandins are the most commonly used agent for cervical ripening [6]. Misoprostol, a prostaglandin E1 analogue (PGE1) was first approved in 1988 by the US Food and Drug Administration for prevention and treatment of gastric ulcer induced by nonsteroidal anti-inflammatory drugs, and because of its cervical ripening and uterotonic activity effects, it has been used prior to hysteroscopy in order to reduce the complications occurring during the dilatation procedures [7, 8]. The routes of administration can be oral, vaginal or sublingual. However, it is still unclear which route is more effective for cervical dilatation before transcervical procedures in non pregnant premenopausal women [9]. This study evaluated

the effect of misoprostol, given preoperatively sublingually or rectally, on intraoperative and postoperative outcomes during hysteroscopic procedures in premenstmal non-pregnant women.

Subjects and methods

The approval of the official ethical committee of the faculty of medicine was granted before the research commenced. From October 2009 until September 2010, 212 premenopausal patients scheduled for hysteroscopic procedures were recruited from the outpatient Gynecology clinic of our university hospital by two senior staff physicians. Indications for hysteroscopy were: infertility work-up (n=98), abnormal uterine bleeding (n=102) and uterine abnormality (uterine septum, n=7) and endometrial polyp (n=5). All eligible subjects were non-pregnant, who had their last menstrual period within the last 2 months. However, those with untreated genital infection, allergy to prostaglandins or ongoing pregnancy were excluded. A fully informed consent was obtained from all participants.

All participants underwent a physical examination and detailed medical obstetric and gynecologic histories were obtained. Women were randomly allocated into three groups by another senior staff researcher using the online researcher randomizer software (www.randomizer.org/form.htm]: group 1 (n=71), sublingual misoprostol (400 μg) (two tablets, cytotec 200 μg/tablet, a synthetic prostaglandin E_1 analog; Searle, England) was given 2 h before the procedure. In group 2 (n=71), rectal misoprostol 400 μg was given 2 h before the procedure. In group 3 (n=70; control group), no medications were given. There were no dropouts.

The primary outcome measures were the ease of cervical dilatation recorded on a 5-point Likert scale [10] by the subjective assessment of the performing surgeon and Hegar size that could be first inserted with feeling of resistance. Secondary outcome measures included the duration of cervical dilatation up to Hegar 6, potential intraoperative complications as cervical laceration and postoperative complications as pain (cramps), vomiting, diarrhea, bleeding and pyrexia.

Surgical procedure

All hysteroscopic procedures were performed by the first author. All patients were in the proliferative phase of the menstrual cycle. General anesthesia was used. A standard, rigid, 9-mm hysteroscope with a 30° forward-oblique lens was used (Karl Storz GmbH, Tuttlingen, Germany). Serial cervical dilatation was done starting from Hegar 1 dilator. For diagnostic purposes, if the endocervical canal was tight, the cervix was dilated to Hegar 6. If the operative sheath was required, the cervix was dilated to Hegar 9. Normal saline solution was used as a distention medium for diagnostic procedures, whereas 1.5% Glycine was used with the monopolar energy.

Statistical methodology

Using a one-tailed test with an alpha level of 0.50 and a 90% power, the sample size was calculated to be a total of 195 patients, i.e., 65 patient per group. Data were collected, coded and entered into IBM compatible computer, using SPSS version 12 for windows. Qualitative variables were expressed as the number and percentage, while the quantitative variables were expressed as the mean and standard deviation. Comparison of means was performed using the one-way ANOVA as a parametric test or Kruskal–Wallis test as a non-parametric test. Frequency distributions between categorical variables among the three groups were compared using the χ^2 test. The 5% level of significance was chosen.

Findings

Patients' characteristics were comparable in terms of age, parity, body mass index (BMI) and the number of patients with previous cervical dilatation (Table 1). Different hysteroscopic procedures were done as indicated to the three random groups. The difference between the studied groups in terms of the primary and secondary outcome measures is shown in Table 2 and Fig. 1. The adverse effects in the present study were abdominal pain due to cramp and bleeding that were significantly greater in the misoprostol groups compared to control group (P=0.002 and P=0.003, respectively). Other adverse effects in the form of vomiting, diarrhea and pyrexia occurred only in misoprostol groups and were significant in sublingual misoprostol group compared to rectal one (P=0.003, P=0.003 and P=0.023, respectively; Table 3). Mean time of surgery was 32.55±11.42, 32.89±12.65, and 33.25±15.55 min in groups 1, 2 and 3, respectively, which showed no significant difference.

Discussion

Prostaglandins had been shown to be effective for cervical ripening in non-pregnant women undergoing hysteroscopic procedures being administered orally or vaginally [11–13]. However, misoprostol use via rectal or sublingual route for the same indication was not thoroughly studied and there is scarce evidence to support or decline such role. Hence it was considered worthwhile to investigate such role in this work.

Table 1 Patients' characteristics

	GI (n=71)	G2 (n=71)	G3 (n=70)	F or χ^2	P	LSD
Age (years)						
Mean ± SD	29±4.3	29±4.21	29.9±5.05	F=1.03	0.22	N.S.
Range	22–37	22–37	22–44			
Parity						
Mean ± SD	0.90±1.21	0.9±1.43	0.79±1.16	F=2.22	0.109	N.S.
Range	0–4	0–5	0–5			
BMI (kg/m^2)						
Mean ± SD	27.35±2.76	25.7±2.91	25.6±3.14	F=2.66	0.101	N.S.
Range	23.5–36	19–31	19–33.5			
Previous surgery						
No. (%)	18 (25.35)	15 (21.27)	17 (24.29)	χ^2=1.036	0.411	N.S.

N.S. not significant, *SD* standard deviation, *LSD* least significant difference

In the present study, sublingual and rectal misoprostol groups were associated with easy cervical dilatation as well as, significantly shorter time to dilate to Hegar 6. We used 400 μg misoprostol rectally or sublingually 2 h before hysteroscopy based on the studies of pregnancy termination [14, 15]. The plasma concentration of misoprostol biologically active metabolite peaks less than 30 min after oral or sublingual administration and 1 h after the vaginal one, then it gradually decreases [16]. The systemic bioavailability of sublingually administered misoprostol is significantly better than oral or vaginal routes [16]. Rectally administered misoprostol is associated with a qualitatively similar absorption curve as that vaginally administered but with lower bioavailability [17]. Also, studies have found that higher doses of misoprostol did not provide greater cervical response than lower dosages [15]. Ngai et al. [18] studied the effect of 400 μg oral misoprostol on premenopausal women undergoing hysteroscopy for infertility and demonstrated that the cumulative forces required to dilate the cervix were 61% lower in misoprostol group compared to placebo and the mean baseline cervical width was significantly greater in the misoprostol group. The same was also observed by Batukan et al. [19]. Similarly, Preutthipan and Herabutya [20] evaluated the effectiveness of 200 μg vaginal misoprostol on cervical dilatation in non-pregnant premenopausal women undergoing hysteroscopy and found that the mean baseline cervical width was significantly greater and the mean time of cervical dilatation to Hegar 9 was significantly shorter after misoprostol compared to placebo. They also mentioned more cervical tears in the control group. Similar results were reported by Singh et al. [12] and Choksuchat et al. [13]. Only a few studies evaluated the effectiveness of sublingual misoprostol for cervical ripening in non-pregnant premenopausal women undergoing hysteroscopy. In agreement, Mulayim et al. [21] compared the effectiveness of 200 μg sublingual misoprostol vs. placebo and found that less patients needed cervical dilatation in the misoprostol group whereas, the duration of dilatation was longer in the placebo group. Also, Lee et al. [22] compared sublingual to oral/vaginal misoprostol

Table 2 Main outcome measures

	GI (n=71)	G2 (n=71)	G3 (n=70)	F or χ^2	P	LSD
Primary outcome measures						
Ease of cervical dilatation						
Mean ± SD	2.63±0.95	2.03±0.74	2.97±0.81	F=4.65	0.035*	2#3
Range	1–5	1–3	2–5			
Baseline cervical width						
Mean ± SD	4.25±0.98	4.27±0.79	3.22±1.03	F=4.05	0.038*	1,2#3
Range	2.5–6.5	2–5.5	1–5			
Secondary outcome measures						
Time to Hegar 6 (s)						
Mean ± SD	63.77±9.69	63.24±9.03	73.24±11.15	F=6.98	0.021*	1,2#3
Range	45–85	45–85	55–95			
Cervical lacerations						
n (%)	3 (4.23)	1 (1.4)	9 (12.85)	χ^2=5.38	0.02*	2#3

Ease of cervical dilatation is scored from 1 to 5 on a Likert scale, with 1 being easier than normal and 5 more difficult than normal

SD standard deviation

*Significant at P<0.05

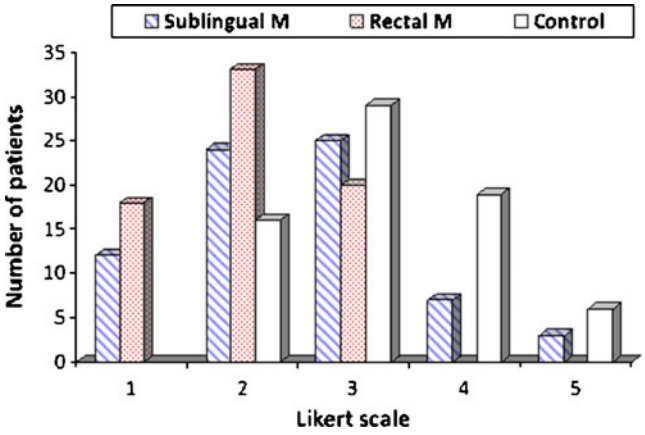

Fig. 1 Ease of cervical dilatation in the studied groups on a Likert Scale

before hysteroscopic procedures in non-pregnant premenopausal women. They concluded that the preoperative cervical width and time to Hegar 10 were comparable among the three groups. In addition, the sublingual route was effective when compared with the vaginal and the oral routes for pregnancy termination [23, 24]. However, to our knowledge, there have been no published studies comparing sublingual to other routes (including rectal) in non-pregnant premenopausal women undergoing hysteroscopy.

In the present study, rectally administered misoprostol was as effective as sublingual misoprostol in producing cervical ripening during hysteroscopy with ease cervical dilatation and shorter time to dilatation to Hegar 6. Since the rectal misoprostol has similar absorption curve as the vaginal one, therefore, it is expected to behave in a similar manner as the vaginally administered misoprostol with the added advantage of shorter time of administration before hysteroscopic procedures (2 vs. 6–12 h) and avoidance of instrument interferences with tablet residue. In contrast to the present results, Bisharah et al. [25] tested sublingual misoprostol (100 μg) 12 h before hysteroscopy against placebo in a cohort of 40 patients, they pointed no difference between the two groups in terms of cervical width and time to dilate to Hegar 9. This might be attributed to leuprolide's hypoestrogenic effect, to which patients were subjected 4 weeks before the procedures. Also, Healey et al. [26] studied 64 premenopausal women and found no improvement in baseline cervical width and time required to dilate the cervix with oral misoprostol 12 h before diagnostic hysteroscopy compared to placebo. This might be explained by a long interval between drug intake and hysteroscopic procedure.

In the present study, the incidence of cervical lacerations was significantly lower in misoprostol groups, unlike the adverse effects, namely; pain and bleeding, which were significantly more severe with misoprostol. The occurrence of abdominal pain after misoprostol might be attributed to the uterotonic activity of prostaglandins inducing uterine contractions. The reduction in the incidence of cervical laceration after misoprostol was also confirmed by Preutthipan and Herabutya [20]. Also, some authors believed that the severity of the adverse effect after misoprostol varies considerably and are often not correlated with dosage, interval of use or route of administration [27]. Lee et al. [22] reported adverse effects in the form of cramp (10.6%), bleeding (4.3%), nausea (4.3%) and shivering (2.1%) after 400 μg sublingual misoprostol 2–4 h prior to hysteroscopy. Also, Bisharah et al. [25] found mild abdominal cramp (20%) and vaginal bleeding (20%) after 100 μg sublingual misoprostol 12 h prior to hysteroscopy.

Conclusion

In premenopausal non-pregnant women, misoprostol appears to be a promising cervical ripening agent prior to hysteroscopy, being safe, effective and cheap. Its use led to ease of cervical dilatation, with a short time of dilatation to Hegar 6 and with minimal cervical laceration. Rectal misoprostol (400 μg) was as effective as the 400 μg sublingual one when given 2 h before hysteroscopy with the added advantage over oral or vaginal misoprostol of being administered shortly before hysteroscopy and avoidance of instrument interference

Table 3 Adverse effects of sublingual and rectal misoprostol groups vs. control group

	G1		G2		G3		χ^2	*P*	LSD
	n	%	*n*	%	*n*	%			
Pain (cramps)	27	38.03	30	42.25	3	4.29	15.98	0.002*	1,2#3
Bleeding	10	14.08	9	12.68	2	2.86	8.98	0.003*	1,2#3
Vomiting	18	25.35	6	8.45	0	0.00	8.25	0.003*	2,3#1 2#1
Diarrhea	18	25.35	6	8.45	0	0.00	8.25	0.003*	2,3#1 2#1
Pyrexia	6	8.45	0	0.00	0	0.00	5.65	0.023*	1#2.3

*Significant at $P<0.05$ level

with tablet residue. The adverse effects after rectal misoprostol appear to be less when compared with the sublingual route. Further studies are required on a large number of women to reassess the use of sublingual and rectal misoprostol on non-pregnant premenopausal women undergoing hysteroscopy.

Acknowledgements The authors thank the University of Alexandria for funding most of the stages of this study. The study was entirely funded by Alexandria University-administered research funds, together with the Obstetrics and Gynecology Department's own funds.

Authors' contribution F. Moiety designed the study, operated on all the patients, supervised the analysis and interpreted the results. A. Azzam performed the statistical analysis and contributed to study design and interpretation. All authors have approved the final version.

Ethics approval The study was formally approved by the Ethical Committee of the Faculty of Medicine, Alexandria University.

Conflicts of interest The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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