Original Article

Effect of misoprostol for cervical priming before gynecological procedures on nonpregnant premenopausal women

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Abstract

Background: Misoprostol is very effective in cervical ripening and is used for termination of pregnancy. A similar effect on the nonpregnant uterus will facilitate gynecological operations, and hence we assessed the effect of misoprostol on the nonpregnant uterus of premenopausal women. **Materials and Methods:** In a prospective double-blinded randomized controlled trial, 280 women were randomly allocated into two groups (12 women did not complete the intervention). Study (A) and control (B) group received 400 μg of misoprostol or 400 mg of metronidazole tablets (as a placebo) respectively in the posterior vaginal wall 6 h prior to gynecological procedures. **Results:** The mean cervical dilatation was significantly higher ($P < 0.0001$) in misoprostol compared to placebo group (4.6 ± 0.96 mm vs. 3.6 ± 0.82 mm), benefit were also observed on secondary outcome measures which were need for further dilatation, time taken for further dilatation, ease of dilatation, subjective assessment of pain by visual analog scale. Only 3.61% patients complained of intolerable pain during dilatation in the study group while in control group 48.74% complained of intolerable pain and required anesthesia. Most common side effects of misoprostol were abdominal pain and mild vaginal bleeding. **Conclusion:** Misoprostol was effective in cervical ripening of nonpregnant premenopausal uterus to facilitate gynecological procedures.

Key words: Cervical dilatation, misoprostol, nonpregnant

INTRODUCTION

Misoprostol is extensively used in obstetrics and has proved to be very effective cervical softening agent necessary intermination of pregnancy.[1-4] However, a similar beneficial effect of misoprostol on the nonpregnant uterus, will facilitate gynecological procedures that require cervical dilation such as endometrial biopsy, hysteroscopy, chromotubation, etc. Further the complications related to these procedures such as excessive pain, cervical injury may be reduced. Thus, most of the minor gynecological procedures may be performed without general anesthesia, which will lead to decreased hospital stay and hence reduce the cost of the procedure.

Access this article online	
Quick Response Code:	Website: www.jnsbm.org
	DOI: 10.4103/0976-9668.166116

How to cite this article: Saha M, Chakraborty A, Chattopadhyay S, Saha S, Paul J, Das A. Effect of misoprostol for cervical priming before gynecological procedures on nonpregnant premenopausal women. J Nat Sc Biol Med 2015;6:S123-7.

To facilitate cervical dilatation paracervical analgesia block or nonsteroidal anti-inflammatory drugs are commonly used before the procedure. Secondly in a difficult situation caused by cervical anatomic changes it would be worthwhile if there were a way to change intrinsically the cervix to make the dilatation easier. Misoprostol, a synthetic prostaglandin analog is found to be a very useful drug in obstetrics and gynecology. Following the vaginal application peak plasma concentration of misoprostol is reached in 1-2 h. The most common side effects of misoprostol are nausea, vomiting, diarrhea, abdominal cramps and fever, which are, dose-dependent. These side effects are, however, reduced if tablets are given vaginally compared to oral administration. Misoprostol causes strong myometrial contraction and cervical softening and dilatation.[5,6] Although the beneficial effects of misoprostol can be hypothesized on the nonpregnant uterus as well, only a few studies have tested this. Hence, this study was designed to evaluate the beneficial effects of misoprostol on nonpregnant premenopausal uterine cervix prior to some gynecological procedures that is, to decrease the cervical resistance and facilitate the mechanical cervical dilation, to minimize the cervical or uterine injury and to decrease the pain of dilatation procedure.

MATERIALS AND METHODS

This randomized controlled trial was conducted from April 2009 to March 2010 in a tertiary care hospital. Following Ethical Committee approval, written and informed consent was obtained from all patients. Patients aged 20-55 years and American Society of Anesthesiologists Physical Status I, II scheduled to have diagnostic D and C or hysteroscopy for different indications, were included in the study. Exclusion criteria included postmenopausal woman, H/O bronchial asthma, allergy to prostaglandin E1, irritable bowel disease, cardiovascular diseases, patient refusal, known allergy or hypersensitivity or contraindication to prostaglandins, impaired liver function (transaminases > twice upper limit), renal dysfunction (creatinine >2.0 mg/dl), uncontrolled chronic diseases, known or suspected history of drug abuse. Proper history regarding chief complains detailed clinical examination, including general and systemic examinations and routine baseline investigations were performed. Preoperative fasting of minimum 6 h was ensured before the operation, and all patients were admitted on the day before the operation in all day care cases. Patients received oral premedication, 10 mg diazepam on the night before surgery and tablet ranitidine 150 mg in the previous night and in the morning of operation with sips of water.

The patients were randomly allocated into two parallel Groups A and B with 135 patients in the study group (Group A) and 133 patients in the control group (Group B) using computer generated randomization protocol. The patients in the study group received 400 μg of misoprostol (two 200 μg misoprostol tablets) while control group received 400 mg of metronidazole (two 200 mg of metronidazole uncoated tablet) 6 h prior to operative procedure. Drugs were administered in all women by on-duty resident doctor without showing the drugs to the patients. Drugs were supplied to the ward as per randomization schedule on the day of admission in the identical sealed envelope mentioning the registration number of the patient.

Normal saline vaginal wash was given in all patients by the on-duty nursing staff to remove any remnant of the drug before sending the patient to the operation theater. There was no discussion regarding the procedure with those persons who had supplied the drug and those resident doctors who had applied the same till completion of the study. The operative procedure was started without using any analgesia or anesthesia. Primary outcome measure was assessed by the largest size Hegar's dilators that could be inserted without resistance at the beginning of the surgical procedure. Secondary outcome were:

(1) Need for further dilatation,
(2) Ease of dilatation,
(3) Subjective assessment of pain during dilatation using visual analog scale (VAS).

They were divided into four groups that are, no discomfort, mild discomfort, mild pain, moderate to severe pain. Those who had moderate to severe pain (VAS 5 or more) received either analgesia or anesthesia during further dilatation (up to Hegar's 8). Development of preoperative side effects such as nausea, vomiting, abdominal cramp, vaginal bleeding, pyrexia of significance, and loose motion was noted. Peroperative complications (cervical injury and uterine perforations) were also recorded.

Statistical analysis

The data were analyzed using Medcalc 11.3.3.0 statistical software (MedCalc Software bvba, Acacialaan22, Ostend, Belgium) (http://www.medcalc.be). Statistical analysis included Chi-square test and *t*-test to compare the primary and secondary outcome between the study and control group. $P < 0.05$ were considered statistically significant.

RESULTS

At the beginning of the study, 312 patients were eligible for enrollment. 32 women not meeting the inclusion criteria or refusal to consent were excluded. A total of 280 women were randomized to Group A (study group) and Group B

(control group) having 140 patients in each group. During follow-up, 5 in the study group and 7 in the control group were removed for not completing the intervention. 135 in the study group and 133 in the control group completed the study and were analyzed.

Patients in both the group were comparable in relation to age, parity and body mass index [Table 1]. Different operative procedures and indications of hysteroscopy were comparable between the two groups [Table 2a and b]. The primary outcome of misoprostol administration is presented in Table 3. Baseline cervical dilatation of 4.6 ± 0.96 mm in the study group was significantly ($P < 0.0001$) higher than the control group (3.6 ± 0.82 mm). Meantime needed for further cervical dilatation was significantly ($P < 0.0001$) delayed in the control group (study: 46.6 ± 14.57 s vs. control: 68.6 ± 14.3 s). Pain on cervical dilatation was significantly less in the study group ($P < 0.05$) [Table 4 and Figure 1]. Perioperative side effects of which preoperative abdominal cramp and nausea vomiting were significantly higher in study group although these effects did not lead to any prolonged hospital stay [Table 5].

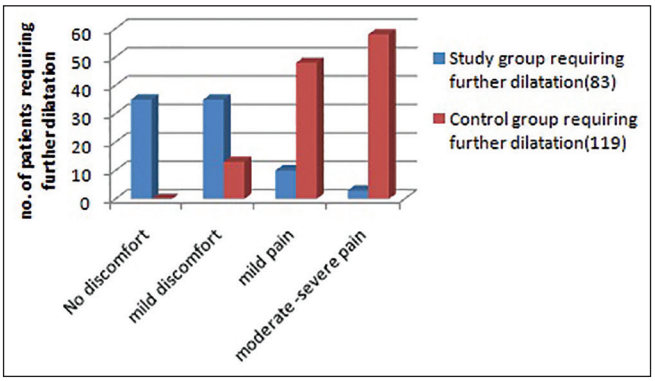

Figure 1: Assessment of pain during cervical dilatation

Table 1: Patient profile (age, parity, BMI)

Characteristics (age in year)	Study Group A (*n* = 135) (%)	Control Group B (*n* = 133) (%)	*P*	95% CI %
20-29	42/135 (31.11)	40/133 (30.07)	0.9584	10.457-12.495
30-39	48/135 (35.56)	49/133 (36.84)	0.9276	10.667-13.199
40-49	41/135 (30.37)	41/133 (30.83)	0.9594	11.017-11.939
50 and above	4/135 (2.96)	3/133 (2.26)	0.9810	−4.015-5.495
Parity				
Nulliparous	33/135 (24.44)	35/133 (26.32)	0.8311	9.019-12.754
Parous	102/135 (75.56)	98/133 (73.68)	0.8311	9.019-12.754
BMI (mean±SD)	22.55±1.67	22.58±1.7	0.884	−0.375-0.43

BMI: Body mass index, CI: Confidence interval, SD: Standard deviation

Table 2a: Operative procedures and indications

Operative procedures	Group A (*n* = 135) (%)	Group B (*n* = 133) (%)	*P*	95% CI %
Diagnostic D and C (for abnormal menstrual bleeding)	84/135 (62.22)	78/133 (58.65)	0.6364	−8.601-15.64
Diagnostic hysteroscopy	51/135 (37.78)	55/133 (41.35)	0.6364	−8.601-15.64

CI: Confidence interval

Table 2b: Indications for hysteroscopy

Hysteroscopy indications	Group A (*n* = 51) (%)	Group B (*n* = 55) (%)	*P*	95% CI %
Primary infertility	15/51 (29.41)	13/55 (23.64)	0.6507	12.154-23.552
Secondary infertility	9/51 (17.65)	11/55 (20)	0.9517	13.975-18.281
Recurrent abortions	4/51 (7.84)	4/55 (7.27)	0.7972	11.196-12.793
Abnormal uterine bleeding	12/51 (23.53)	13/55 (23.64)	0.8293	17.307-17.269
Missed IUCD	5/51 (9.81)	6/55 (10.91)	0.8941	12.356-14.192
Secondary amenorrhea	6/51 (11.76)	8/55 (14.54)	0.8924	11.754-16.937

IUCD: Intrauterine contraceptive device, CI: Confidence interval

Table 3: Results of misoprostol administration

Results	Group A (135) (%)	Group B (133) (%)	*P*	95% CI and OR %
Baseline cervical dilatation (mm)*	4.6±0.96	3.6±0.82	<0.0001	−1.215-−0.785
Further dilatation required	83/135 (61.48)	119/133 (89.47)	<0.0001	0.098-0.361
Time for further dilatation (s)*	46.6±14.57	68.6±14.3	<0.0001	17.94-26.06
Ease of dilation				
Easy	66/83 (79.52)	15/119 (12.6)	<0.0001	54.3-76.6
Mild to moderate resistance	14/83 (16.87)	46/119 (38.66)	0.0015	8.62-33.68
Significant resistance	3/83 (3.61)	58/119 (48.74)	<0.0001	33.76-54.9

*Values are (mean±SD). SD: Standard deviation, CI: Confidence interval, OR: Odds ratio

Table 4: Subjective assessment of pain during cervical dilatation

Pain (VAS score)	Group A (*n* = 83) (%)	Group B (*n* = 119) (%)	*P*	95% CI %
No discomfort (0)	35/83 (42.17)	0	<0.0001	30.98-53.51
Mild discomfort (1-2)	35/83 (42.17)	13/119 (10.92)	<0.0001	18.39-43.64
Mild pain (3-4)	10/83 (12.05)	48/119 (40.34)	<0.0001	15.64-39.49
Moderate to severe pain requiring analgesic or anesthesia (5 or more)	3/83 (3.61)	58/119 (48.74)	<0.0001	33.76-54.89

CI: Confidence interval, VAS: Visual analog scale

Table 5: Perioperative side effect

Side effect	Group A (135) (%)	Group B (133) (%)	*P*	95% CI %
No side effect	83/135 (63.7)	133/133 (100)	<0.0001	27.75-45.01
Nausea and vomiting	7/135 (5.19)	0	0.023	1.07-10.39
Mild abdominal cramps	28/135 (20.74)	0	<0.0001	13.69-28.56
Pyrexia of significance	0	0	—	—
Loose motion	2/135 (1.48)	0	0.485	−1.55-52.23
No complications	134/135 (99.26)	124/133 (93.23)	9.72	0.032
Cervical injury	1/135	7/133	0.134	0.062
Uterine perforations	0	2/133	0.194	0.29

CI: Confidence interval

DISCUSSION

Cervical priming prior to gynecological procedures facilitates the operation and decreases the risk of cervical, uterine injury that are often associated with the mechanical dilatation. Various prostaglandin preparations, laminaria tents are commonly used for cervical priming. Cervical injury, uterine perforations, pain due to cervical dilatation despite local anesthesia and precise technique are the major problem associated with these procedures.

The off-label use of misoprostol for gynecological indications has received less attention, despite reports of its effectiveness in inducing cervical dilatation.[7-9] Indeed oral or vaginal misoprostol application before hysteroscopy resulted in greater cervical dilatation, decreased cervical resistance and less need for further dilatation.[10-13] In the present study, as well misoprostol treated women had significantly increased baseline cervical dilatation. Resistance to cervical dilatation and mean time taken for dilatation was less in misoprostol group when compared with control group. Which is in contrast to Dan *et al.*[14] and Perrone *et al.*[15] reporting no priming effect of misoprostol on premenopausal cervix and rather misoprostol use causing more pain, uterine cramping, and vaginal bleeding. Likewise, Bunnasathiansri *et al.*,[16] Fung *et al.*[17] also did not observe any significant benefit from applying misoprostol in postmenopausal women. This might however, be due to hypo estrogenic state as pretreatment with estrogen facilitated misoprostol-induced cervical priming in postmenopausal women.[18,19]

Different studies had used misoprostol in different dose and routes of administration. The dose varied from 100 to 1000 μg and duration of insertion before procedures varied from 2 to 12 h. A single dose 400 μg misoprostol given vaginally 3 h prior to intervention seems to given the best efficacy with least side effects, however this is contradicted by study reporting similar effects achieved by all three routes of misoprostol application (i.e., oral, vaginal and sublingual).[20] In our study, we used 400 μg single dose of misoprostol by vaginal route 6 h prior to the procedures as a cervical priming agent. Our aim was to see the effectiveness of misoprostol by this approach. Though diagnostic hysteroscopy could be done using 4 mm scope without anesthesia in many cases. However, in nulliparous and elderly women introduction of hysteroscope without prior dilatation may cause difficulties. In this study, we have used larger size hysteroscope with an intention to perform minor operative procedures such as removal of Copper T, endometrial biopsy etc., if required, at the same sitting. As vaginal misoprostol was found to be effective as a cervical priming agent in nonpregnant premenopausal women in our study, this approach could be applied before operative hysteroscopy procedures. Moreover, the use of misoprostol as cervical priming agent reduces the requirement of analgesia or anesthesia during the hysteroscopy procedures thereby minimizing the complications and cost associated with treatment. Nevertheless, prior hospitalization was required to apply vaginal misoprostol, and this was the only limitation of this study. Self-vaginal application or sublingual route may be the solution of address this problem, which needs further evaluation. We conclude that misoprostol is effective in increasing cervical dilatation, decreasing both cervical resistance and need for additional dilatation before hysteroscopy in premenopausal women.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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