

Misoprostol for Cervical Priming on Non-Pregnant Uterus

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Citation

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Abstract

INTRODUCTION

Effect of Misoprostol on cervical dilatation and softening in pregnant uterus is well documented now. But the effect on non-pregnant uterus is not well known. Most of the complications in gynaecological procedures requiring cervical dilatation like endometrial biopsy, Hysteroscopy, IUCD insertion, and fractional curettage occur during cervical dilatation.

Endometrial biopsy is often performed as outpatient procedure. Difficulty may be encountered in entering cervical os especially in nulliparous women. This may cause, complications, excessive pain and may even hinder performance of the procedure. The same problem may occur during hysteroscopy, dilatation & curettage, chromopertubation, IUCD insertion or fractional curettage. If cervical priming is done by some agent before the procedure, complications may be reduced. Most of the minor gynaecological procedures may be done as outpatient procedures, which may reduce anesthetic complications and decrease hospital stay and hence reduce the cost of the procedure. In addition, occasionally an endometrial biopsy cannot be easily obtained secondary to anatomic cervical stenosis, scarring, or atrophy. These are two areas of concern, and it would be beneficial to our patients if the biopsy could be less painful.

This issue is not new and has been approached previously with the use of either paracervical analgesic blocks or oral nonsteroidal anti-inflammatory drugs before biopsy attempt. Secondly, in difficult biopsy cases caused by cervical anatomic changes, it would be worthwhile if there was a way to intrinsically change the cervix to make the biopsy easier.

Currently, the mechanical means to overcome anatomic cervical stenosis, scarring, and atrophy during endometrial biopsy is by direct cervical traction with a tenaculum and/or the additional use of a probe, dilator, or spreading clamp.

These techniques usually are associated with increased pain and anxiety. They also do not always result in successful biopsies. Misoprostol is known to cause cervical priming in pregnant uterus but its effect in nonpregnant uterus is not well known.

We studied the effectiveness of 400 µg of misoprostol given vaginally for cervical priming before endometrial biopsy, hysteroscopy, D&C, chromopertubation & fractional curettage.

MATERIAL & METHODS

The study was conducted at Himalayan Institute of Medical Sciences, Jolly Grant, Dehradun for one year from January 2007 to December 2007. 100 women requiring endometrial biopsy, D&C, Hysteroscopy, fractional curettage or IUCD insertion for various indications were randomized to receive 400 µg misoprostol or placebo vaginally at night before the procedure. Those who were not admitted in the hospital were advised self administration at home. Women with medical illness like heart disease; hypertension, uncontrolled diabetes, renal disease, asthma, malignancy or other high risk factors were excluded from the study.

Detailed history & examination was done. Proforma was filled. Procedure; its indication and Gynaecological examination including consistency and length of cervix will be recorded. The resistance to cervical dilatation, mean cervical diameter, pain perceived by the patient, time taken for the procedure, amount of bleeding, any side effects or failure to do the procedure or failure to obtain adequate tissue for biopsy were recorded. The observations were compared between the two groups and results analyzed. Mean cervical dilation achieved before procedure were calculated by passing hegar dilator number 2 to 8 serially. Largest hegar dilator passed without resistance was recorded as mean cervical diameter. Number of women who achieved cervical dilatation more than 5 mm were calculated and

compared between two groups. Pain perceived was calculated by visual analogue score and were divided in to three groups ie mild, moderate and severe. All the procedures were done by one consultant to avoid inter observer variation. Acceptability of the procedure was assessed by direct questioning.

RESULTS

Out of total 150 women, 120 were premenopausal and 30 post menopausal. The procedures done were EB, D&C, fractional curettage, hysteroscopy, IUCD insertion and pyometra drainage. Most common indication of the procedure were infertility (53) and menstrual abnormality (n=48) (Table 1). Mean cervical diameter was 6.2 mm in premenopausal group (2.0 mm more than placebo group) where as in post menopausal group mean cervical diameter in misoprostol and placebo group were comparable (3.6mm Vs 3.4 mm). Resistant to cervical dilatation was also significantly reduced in misoprostol group (13.35 Vs 33.3%) but in post menopausal women 86.6% women had difficult cervical dilatation even in misoprostol group. Cervical dilatation ≥ 5 mm was achieved in 86.6% (Table 2). Premenopausal women in misoprostol group measuring there by office hysteroscopy (with 4 mm hysteroscopy) could be easily done in these women as OPD procedure. Failure to do the procedure or inadequate time for biopsy was comparable in both the groups. Vaginal misoprostol was acceptable in 79% women.

Complications were very few i.e. uterine perforation in 2 cases, cervical tear in 8 and false passage in 2 cases. There was no correlation with misoprostol in both pre and post menopausal women (Table -3). More side effects were seen in misoprostol group (38/75 Vs. 15/75, Table No. 4) but most of side effects were minor like slight bleeding P/V, vaginal discharge, lower abdominal pain or nausea. Distressing adverse effects like fever, shivering and diarrhoea were present only in 6 cases. Pain was of mild intensity and did not require medication. Only 3 patients require analgesic. Anti pyretic was given for fever in 3 patients.

Figure 1

Table 1: Indications of Procedure

Outcome	Premenopausal		Postmenopausal	
	Misoprostol N=60	Placebo N=60	Misoprostol N=15	Placebo N=15
Cervical resistance	8(13.3%)	20(33.3%)	13(86.6%)	12(80%)
Cervical dilatation required	22(36.6%)	39(65%)	14(93.3%)	15(100%)
Time required for cx dilatation	50 sec	70sec	90sec	85sec
Baseline cervical dilatation	6.2mm	4.2mm	3.6mm	3.4mm
Cervical dilatation ≥ 5 mm	52(86.6%)	38(63.3%)	2(13.3%)	1(6.6%)
Acceptability	79%		60%	
Failed procedure	2(3.3%)	3(5%)	1(6.6%)	1(6.6%)
Inadequate tissue	2(3.3%)	2(3.3%)	1(6.6%)	2(13.3%)

Figure 2

Table 2: Outcome Measures

Primary infertility	35
Secondary infertility	18
Menorrhagia	16
Polymenorrhoea	11
Metrorrhagia	13
Metropathia hemorrhagica	8
Endometrial polyp	7
Endometrial hyperplasia	12
Postmenopausal bleeding	20
IUCD insertion	06
Pyometra	04

Figure 3

Table 3: Complications

Adverse effects	Premenopausal (n=120)		Postmenopausal	
	Misoprostol (n=60)	Placebo (n=60)	Misoprostol (n=15)	Placebo (n=15)
Bleeding	6(10%)	2(3.3%)	1(6.6%)	1(6.6%)
Shivering	1 (1.8%)	0	1(6.6%)	0
Fever	2 (3.3%)	0	1(6.6%)	0
Diarrhoea	1(1.8%)	0	0	0
Pelvic pain	7(11.6%)	3(5%)	2(13.3%)	1(6.6%)
Uterine cramp	6(10.0%)	2(3.3%)	1(6.6%)	0
Nausea	2(3.3%)	2(3.3%)	2(13.6%)	2(13.6%)
Vaginal discharge	3(5%)	2(3.3%)	1(6.6%)	1(6.6%)

Figure 4

Table 4: Pre-Operative adverse effects

COMPLICATIONS	Premenopausal		Postmenopausal	
	misoprostol	placebo	misoprostol	placebo
Uterine perforation	1	1	0	0
Cervical tear	1	2	3	3
False passage	1	0	1	0

Figure 5

Table 5: Correlation with different studies

Study	Age group	No of women	Dose & route of misoprostol	Procedure	Outcome
Oppegaard K.S. 2008	Premenopausal	86	1000 µg vaginally 12 hrs. before	Hysteroscopy	Mean cervical diameter 6.4 mm.
Batukan et al 2008	Premenopausal	86	400 µg vaginally 12 hrs. before	Hysteroscopy	Mean cervical diameter 7.3 mm.
Our study	Premenopausal	120	400 µg vaginally 12 hrs. before	Gynecological procedures	Mean cervical diameter 6.2 mm
Preuthippan S, et al 2006	Nulliparous	310	400 µg Vaginally	Operative hysteroscopy	Mean cervical diameter 7.4 mm
Fernandez H, et al 2004	Premenopausal	48	200 - 800 µg Vaginally 4 hrs. before	Operative hysteroscopy	No effect
Perrone JF et al 2002	35-77 years	42	400 µg oral 3 hrs. before	Endometrial biopsy	No effect
Ngai SW et al 1997	Nulliparous	44	400 µg 12 hrs. before Orally	Endometrial biopsy + Diagnostic hysteroscopy	Mean cervical diameter 6 mm
Oppegaard K.S. 2008	Postmenopausal	86	1000 µg vaginally 12 hrs. before	Hysteroscopy	No effect
Fung et al 2002	Postmenopausal	96	400 µg vaginally 5 hrs. before	Hysteroscopy	No effect
Bar Caille E et al 2005	Peri & Postmenopausal	105	400 µg vaginally 12 hrs. before	Hysteroscopy	Mean cervical diameter 7.6 mm
Our study	Post menopausal	30	400 µg vaginally 12 hrs. before	Gynecological procedures	No effect

DISCUSSION

Misoprostol is a stable, synthetic prostaglandin estrone analogue available in 100-µg and 200-µg tablets. It has food and drug administration approval for preventing nonsteroidal anti-inflammatory drug-induced gastric ulcers in patients at high risk for complications resulting from gastric ulcers. In the specialty of obstetrics and gynecology, misoprostol has been used off-label for cervical priming or ripening in pregnant patients, induction of labor in gravid patients, pretreatment of the cervix before suction curettage for pregnancy terminations, missed and elective medical abortions, and for preventing and treating postpartum hemorrhage. The off-label use of misoprostol for gynecologic indications has received less attention. Many studies involving cervical priming before hysteroscopy in non pregnant women have been published, Three of these studies¹²³ reported that oral or vaginal misoprostol resulted in greater cervical dilatation, decreased cervical resistance, and less need for mechanical dilatation before hysteroscopy. In contrast, the other reported study did not demonstrate a cervical priming effect from misoprostol before hysteroscopy⁴. The results of different studies are controversial (table no. 5) thus, additional information is needed to further evaluate the clinical efficacy of misoprostol for gynecologic procedures.

In our study in premenopausal group the misoprostol-treated women had significantly increased baseline cervical dilatation 6.2 Vs. 4.2 mm in control group. Resistance to cervical dilatation was less in mesoprostol group (13.3% Vs. 33.3%). Patients in the placebo group had significantly ($P < .05$) fewer adverse side effects than those in the misoprostol group. Out of 60 women 28 (46.6%) women had side effects but most of the side effects were minor and the procedure was acceptable to 79% women. The studies that evaluated misoprostol for cervical priming before diagnostic and operative hysteroscopy reported different results. Oppegaard KS et al₅₆, Batukan et al₇ and Barcaite et al₈ showed that misoprostol significantly increased cervical dilatation and decreased both cervical resistance and the need for additional cervical dilatation before hysteroscopy. Conversely, Fernandez et al₄ found no significant difference in the cervical resistance between misoprostol and placebo when misoprostol was given as a 200-800 µg vaginally placed tablet 4 hours before operative hysteroscopy in women treated with goserelin for 5 weeks preoperatively. Thomas J et al₉ demonstrated a benefit in GnRh treated women also.

Endometrial biopsy is a simple gynaecological procedure and often done as an OPD procedure. Mesoprostol does not appear to reduce pain or side effects in parous women. Perrone JF₁₀ evaluated the effect of 400 µg oral mesoprostol in women more than 35 years, three hours before endometrial biopsy. There was no effect on cervical resistance, ease of performing biopsy, success rate of obtaining endometrial biopsy or adverse side effects. Misoprostol caused more pain and uterine cramping than placebo whereas in nulliparous women with long cervix mesoprostol significantly decreases operating time, need for cervical dilatation, difficult cervical dilatations and complications

like cervical tear, vaginal bleeding and pain during procedure. Preutthipan S et al₁₁ studied the effect of mesoprostol on 310 nulliparous women before operative hysteroscopy. Mean cervical diameter was 7.4 mm. However, significant differences in side effects of mild lower abdominal pain and slight vaginal bleeding, and low grade fever were also noted in the misoprostol group. Ngai SW et al also achieved a mean cervical diameter of 6mm compared to 3.3 mm in controls. No intra operative complications were reported. Saav I et al₁₂ used 400 µg misoprostol sublingually one hour prior to IUCD insertion in nulliparous women. Misoprostol reduced number of

difficult and failed attempts and hence another potential use of misoprostol is for cervical dilatation prior to IUCD insertion in nulliparous women, previous caesarean section or with long firm cervix.

Different studies have used misoprostol in different dose and route. Dose varies from 100-1000 micrograms and duration of insertion before procedure varies from 2-12 hours. Fiala C et al₁₃ concluded that single dose of 400-µg misoprostol given sublingually or vaginally 3 hrs before the intervention has given the best efficacy with least side effects. Higher doses or longer intervals do not improve the effect on cervix. Outcome measures of various studies are not same. Most of the studies are on use of misoprostol before operative and diagnostic hysteroscopy and only few studies on endometrial sampling and IUCD insertion.

Misoprostol has no effect on cervical dilatation in post menopausal women. In our study also mean cervical dilatation and resistance to cervical dilatation was similar in misoprostol treated and placebo group. Though number of women were less in our study. Adverse side effects were significantly more in Misoprostol group (60% Vs. 26.6%) but complication rate was similar. Mostly side effects were minor and misoprostol insertion at home was acceptable to 60% of post menopausal women. Fung et al₁₄ investigated the effectiveness of vaginal misoprostol in post menopausal women before hysteroscopy. Similar number of women required cervical dilatation, operative time and side effects were similar in both the groups. Thus misoprostol cannot convert diagnostic hysteroscopy from a hospital procedure into an office procedure. We speculate whether the lack of estrogen is the main reason why misoprostol does not have any significant effect. We therefore feel that further investigations as to whether a short course of local hormone therapy combine with misoprostol might have a positive cervical ripening effect on post menopausal women are warranted.

Though misoprostol 400 -µg inserted vaginally appears to be safe and effective before gynaecological procedures in premenopausal women but further long term multicentric trials are required to find out appropriate dose and route of administration of misoprostol and its use in postmenopausal women.

Therefore we recommend offering this inexpensive and easy to use regime to premenopausal women prior to gynecological procedures as it helps to reduce complications and facilitates cervical dilatation.

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