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Original Research Article

Use of vaginal misoprostol before endometrial biopsy in premenopausal women: an observational study

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ABSTRACT

Background: It is well-known since long time the beneficial effects of misoprostol particularly as a cervical softening agent in obstetric practice. Keep in view, study aimed to evaluate the efficacy of vaginal misoprostol 400 mcg before endometrial biopsy in premenopausal women.

Methods: All the 200 patients were classified into two groups viz. study group (Group I) with 100 patients and control group (Group II) with 100 patients. To Group I patients, 400 mcg of misoprostol was given vaginally, 4 hours prior to the commencement of endometrial biopsy whereas no medication was received by Group II patients.

Results: In the present study, the base line cervical dilatation is found to be 5.8 ± 1.3 mm in Group I patients whereas 3.8 ± 0.92 mm in Group II patients which is significantly higher ($p < 0.05$). Only 32 patients in Group I required further dilatation whereas 88 patients in Group II underwent further dilatation. The mean time required for further dilatation in Group I and Group II patients was 42.6 ± 17.4 , 64.6 ± 16.8 sec respectively and was significantly higher in Group II patients ($p < 0.05$). Out of 100 patients in Group I, only 2% of patients complained severe pain whereas in Group II 48% of patients experienced intolerable pain and required anesthesia.

Conclusions: Vaginal administration of 400 mcg misoprostol 4 hours prior to endometrial biopsy in premenopausal women had a significant effect on cervical resistance and cervical dilatation.

Keywords: Cervical injury, Cervical ripening, Endometrial biopsy, Prostaglandin E1, Visual analog scale score

INTRODUCTION

Endometrial biopsy is a routine day care procedure used to assess the abnormal uterine bleeding, postmenopausal bleeding, recurrent pregnancy loss, infertility.^{1,2} Sometimes, it is very difficult to pass the endometrial curette through the cervix into the uterine cavity. In addition, the complications such as cramping pain, vasovagal reaction, bleeding and cervical/ uterine injuries are commonly encountered during the procedure.

Misoprostol, a prostaglandin E1 analogue has been found to be effective in cervical ripening /softening agent in obstetric practice.³⁻⁶ The same effectiveness of

misoprostol has been observed in gynaecological procedures such as hysteroscopy, endometrial biopsy to soften the cervix and also to treat submucosal fibroids, polyps etc. Misoprostol can be administered oral, vaginal and sublingual routes and the ideal recommended dose is 400 mcg 3-4 hours prior to gynaecological procedures such as endometrial biopsy, hysteroscopy and fractional curettage. The sublingual route is more effective than oral and vaginal routes of administration, but with more side effects.⁷ Similarly, vaginal administration has been found to be more effective than oral route with fewer side effects.⁸⁻¹⁰ The peak plasma misoprostol concentration is reached in 1-2 hours following vaginal application. The side effects such as nausea, vomiting, diarrhoea,

abdominal cramps, fever etc are the most common and are dose dependent. However, these side effects can be reduced by administration of drug vaginally rather than oral route.^{11,12} Although the beneficial effects of misoprostol have been successfully studied in obstetrics, the studies related beneficial effects in gynaecological operations are lacking. Hence, the present study was aimed to evaluate the efficacy of vaginal misoprostol 400 mcg administration before endometrial biopsy in nonpregnant, premenopausal women.

METHODS

This study was conducted in out-patient department of obstetrics and gynecology in NRI Institute of Medical Sciences, a tertiary care teaching hospital during May 2019 and October 2019. Two hundred non-pregnant premenopausal women between the age group of 30-50 years with abnormal uterine bleeding were included in the study after taking written informed consent. The pregnant and post-menopausal women, patients with a H/o bronchial asthma, abnormal liver function tests, medical disorders were excluded from the study. The study was approved by the Institutional Ethics Committee, NRIIMS.

By using computer generated randomization protocol, all the recruited patients with abnormal uterine bleeding were classified into two groups: study group (Group I) with 100 patients, and control group (Group II) with 100 patients. To Group I patients 400 mcg of misoprostol was given vaginally, 4 hours prior to the commencement of endometrial biopsy whereas no medication was received by Group II patients. Before sending the patients to operation theatre, vaginal wash with normal saline was given to all the patients particularly to Group I patients to remove any traces of the drug. The operative procedure was initiated without using any analgesics and anesthesia.

Using the large size (no. 8) Hegar's dilator, the primary outcome measure was assessed whether that could be inserted without resistance at the beginning of the procedure. The secondary outcomes such as;

- Need for further dilatation
- Ease of dilatation
- Anesthesia/ analgesia usage
- Cervical consistency
- Pain assessment by VAS score

were also studied in all the patients of Group I and Group II. The subjective assessment of pain during the procedure was divided into four groups viz. no discomfort (0), mild discomfort (1-2), mild to moderate pain (3-4) and moderate to severe pain (5 and >5). The patients who have experienced moderate to severe pain (VAS 5 or more) were given either analgesia or anaesthesia to continue the procedure. The side effects of misoprostol such as nausea, vomiting, diarrhea, abdominal pain, cramps, vaginal spotting, vaginal bleeding, shivering and pyrexia of significance were recorded. Pre-operative complications like cervical injury, uterine perforation was also noted.

Statistical analysis

Data were analysed using OpenEpi 2.3. Primary and secondary outcome between both the groups were compared by chi-square and t-test analysis and p-value <0.05 was considered statistically significant.

RESULTS

The demographic features such as age, parity and body mass index (BMI) were depicted in Table 1. The primary and secondary outcomes of misoprostol administration were presented in Table 2.

Table 1: Demographics of patients.

Characteristics	Study group (Group I)	Control group (Group II)	Chi-square	p-value
Age in years (mean±SD)	37.9±6.65	39.3±5.67	2.49	0.11
BMI (Mean±SD)	23.1±1.42	22.9±1.67	2.58	0.36
Parity				
Nulliparous, n (%)	34 (34%)	38 (38%)	0.35	0.5
Parous, n (%)	66 (66%)	62 (62%)	0.34	0.5

Note: *p<0.05 is significant.

The mean cervical dilatation is found to be 5.8±1.3 mm in Group I patients whereas 3.8±0.92 mm in Group II patients which is significantly higher (p<0.05). Out of 100 patients of Group I, 32 patients required further dilatation whereas 88 patients in Group II underwent further dilatation. The time required for cervical dilatation was very short in Group I patients whereas significantly prolonged in Group II patients (p<0.05) as compared to Group I. In Group II, 56.8% of patients

experienced significant resistance for dilatation but only 6.3% of patients in Group I. The side-effects of misoprostol were not significant in Group I patients as compared to Group II patients although very few patients complained side effects such as nausea, diarrhoea, cramping and vaginal spotting (Table 3). The subjective assessment of pain during cervical dilatation was done using VAS score. Out of 100 patients in Group I, only 2% of patients complained severe pain whereas in Group

II 48% of patients experienced intolerable pain and required anaesthesia (Table 4).

Table 2: Effectiveness of misoprostol before commencement of procedure.

Results	Group I	Group II	Chi-square	p-value
Base line cervical dilatation Mean±SD (mm)	5.8±1.3	3.8±0.92	11.54	<0.001*
Further dilatation required	32/100 (32%)	88/100 (88%)	65.01	<0.001*
Mean time for further dilatation Mean±SD (Sec)	42.6±12.1	67.9±16.9	10.79	0.001*
Ease of dilatation				
Easy, n (%)	25/32 (78.1%)	10/88 (31.8%)	50.2	<0.001*
Mild to moderate resistance, n (%)	5/32 (15.6%)	28/88 (31.8%)	3.06	0.04*
Significant resistance, n (%)	2/32 (6.3%)	50/88 (56.8%)	24.23	<0.001*

Note: *p-value <0.05 is significant.

Table 3: Side effects of misoprostol.

Side effect	Group I	Group II	Chi-square	p-value
No side effects	82/100	84/100	0.14	0.35
Nausea	3	1	0.85	0.17
Vomiting	0	0	-	-
Diarrhoea	3	0	2.83	0.04*
Cramping	3	2	0.11	0.36
Abdominal pain	4	5	0.34	0.27
Vaginal spotting	4	7	1.74	0.09
Vaginal bleeding	0	1	1.12	0.14
Shivering	1	0	-	-
Fever	0	0	-	-
No complications	100/100	91/100	-	-
Cervical injury	0	7/100	9.15	0.001*
Uterine perforation	0	2/100	2.14	0.06

Note: *p<0.05 is significant.

Table 4: Subjective assessment of pain during dilatation.

Pain (VAS score)	Group I	Group II	Chi square	p-value
No discomfort (0)	38 (38%)	0 (0%)	46.68	<0.001*
Mild discomfort (1-2)	52 (52%)	12 (12%)	36.58	<0.001*
Mild pain (3-4)	8 (8%)	40 (40%)	27.93	<0.001*
Moderate to severe pain required analgesia/ anaesthesia (5 or more)	2 (2%)	48 (48%)	56.14	<0.001*

Note: VAS: visual analogue scale; *p<0.05 is significant.

DISCUSSION

Misoprostol is a synthetic prostaglandin E1 analogue most commonly used for cervical priming and pain reduction before gynecological procedures because of its low cost and scientific evidence. The use of misoprostol before the endometrial biopsy helps in the cervical dilatation and thereby minimizes the cervical trauma. Misoprostol has been found to be useful particularly in premenopausal women for cervical ripening before gynecological procedures such as hysteroscopy, endometrial biopsy etc. to reduce the need for further dilatation and to minimize the rate of cervical lacerations.¹³ However, the usage and benefits of misoprostol in postmenopausal women is not yet clear

despite very few studies have suggested an improvement in cervical dilatation.^{13,14}

In the present study, the misoprostol received women had significantly increased base line cervical dilatation and time required for cervical dilatation was less as compared to Group II patients who did not receive any drug. In fact, the role of misoprostol has been studied in different dose format from 100 to 1000 mcg and routes of administration such as oral, vaginal, sublingual and duration of insertion of drug before the procedure (2 hours to 12 hours). However, no studies focussed on a clear dosing regimen for cervical priming in endometrial biopsy. In the present study, a single dose of 400 mcg given 4 hours before the start of procedure was adopted,

and it is found to be effective with minimal side effects such as nausea, vomiting, abdominal cramping pain, diarrhea and vaginal bleeding. However, Lee et al. did not find any significant difference between oral, vaginal and sublingual application of misoprostol in such cases.¹⁵

In the present study, 400 mcg single dose of misoprostol vaginally was given as a priming agent 4 hours prior to the procedure in premenopausal women and found to have promising results with the usage. However, Dam et al, and Perrone et al, did not find any promising effect in pre-menopausal women, rather it has caused more pain and uterine cramping.^{16,17} Similarly in another study, post-menopausal women also didn't benefit from misoprostol usage.¹⁸

Misoprostol can be administered oral, vaginal, sublingual, buccal or rectal for effective cervical dilatation and ripening.¹⁹ It is unclear that which route is effective for cervical dilatation before transvaginal procedures. However, vaginal misoprostol is similar to an extended release preparation due to its slower absorption, lower peak plasma levels and slower clearance and so that acts on cervix and uterus effectively for longer period.¹⁹ In the present study, we preferred to vaginal route as pharmaco-kinetic studies of misoprostol suggest more prolonged and sustained level of misoprostol with vaginal administration and found to be effective in terms of cervical ripening and reduction in pain. Similarly, Batukan et al, also claimed that vaginal administration was more effective than oral route of administration, whereas in another study no difference was observed between the two routes.^{20,21} In addition, on the contrary, Esteve C et al. stated that sublingual route is more effective than vaginal and oral routes. However, no specific studies were conducted to know the efficacy of sublingual administration of misoprostol in gynecological procedures.²²

A significant reduction in pain during dilatation for endometrial biopsy was observed in Group I patients as compared to Group II patients as evidenced by VAS score. About 38% of the patients in Group I have experienced no pain, 52% mild pain and 2% severe pain in the present study whereas in Group II, 48% of patients have suffered from severe pain and 40% of patients experienced mild pain suggesting the beneficial effects as well as efficacy of misoprostol on cervical ripening. But, on the contrary Perrona et al, stated that patients experienced more pain with oral 400 mcg when given 3 hours prior to endometrial biopsy.²⁰ However, the study had many pitfalls such as small sample size, inclusion of both premenopausal and postmenopausal women etc.

CONCLUSION

Vaginal administration of 400 mcg misoprostol 4 hours prior to endometrial biopsy in premenopausal women had a significant effect on cervical resistance and cervical dilatation. Further studies are required in large number of

populations to confirm the dosage and route of administration of misoprostol in endometrial biopsy.

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