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Research Article

Clinical use of misoprostol for cervical ripening before transcervical procedures in non pregnant women: a randomized comparison of vaginal and sublingual administrations

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ABSTRACT

Background: Endometrial sampling techniques like endometrial biopsy, Fractional curettage, Dilatation & curettage and hysteroscopy are the common gynaecological outpatient transcervical diagnostic procedures for various clinical conditions. Complications encountered during these procedures are often due to difficulties in cervical dilatation. The incidence of these complications can be reduced if cervix is ripened before the procedures. The aim of the present study was to evaluate the efficacy of 400mcg of misoprostol administered vaginally or sublingually for cervical ripening before transcervical gynaecological diagnostic procedures in both pre and post-menopausal women.
Methods: Non pregnant pre and post-menopausal women scheduled for transcervical diagnostic procedures were assigned by computerized randomization to receive 400 mcg of misoprostol, administered either sublingually or vaginally 3-4 hours prior to the procedure. The primary outcome in this study was the pre procedural cervical width as measured by the largest number of Hegar dilators. The side effects related to misoprostol and complications associated with the procedure if any also noted.
Results: Patients were randomized to receive sublingual (50) or vaginal (50) misoprostol. The two groups were comparable in terms of age, BMI (body mass index), parity, menopausal status and indications for diagnostic procedures. The mean cervical dilatation in sublingual group was 7.28 ± 2.21 mm and it was 6.57 ± 2.24 mm in vaginal group which was statistically similar among the groups. There were no complications associated with the procedure. Side effects were also comparable among the groups.
Conclusion: Even though we found sublingual route is an effective alternate to vaginal administration of misoprostol for cervical ripening before transcervical diagnostic procedures like endometrial biopsy, fractional curettage and dilatational curettage in non pregnant pre and post-menopausal women especially when women feel uncomfortable with vaginal route. However, the optimal dose and time interval remains to be identified. It needs larger randomized control trials are required to prove clinical significance if any.

Keywords: Cervical ripening, Misoprostol, Postmenopausal, Sublingual, Transcervical, Vagina

INTRODUCTION

Endometrial sampling techniques like endometrial biopsy, Fractional curettage, Dilatation & curettage and hysteroscopy are the common gynaecological outpatient transcervical diagnostic procedures used in conditions like abnormal uterine bleeding, postmenopausal bleeding, amenorrhoea, infertility etc. Complications encountered

during these procedures are often due to difficulties in cervical dilatation. These include creation of false passage, difficulty in entering the internal os, cervical tear, hemorrhage, uterine perforation etc [1] The incidence of these complications can be reduced if cervix is ripened before the procedures.

Although the mechanisms are poorly understood, ripening of cervix involves various inflammatory reactions and the effect of misoprostol on cervical dilatation and softening in pregnant women is well established.[2] In pregnancy, it is recommended in first trimester before surgical abortion to facilitate cervical dilatation later on to induce labour. There are several methods both mechanical and pharmacological available for ripening of cervix but prostaglandins are the most commonly used agent for cervical ripening in both pregnant and non pregnant women.

Prostaglandins have been used for cervical priming prior to hysteroscopy since 1985. As misoprostol is inexpensive, easy to use, cheap and has a long shelf life it has been employed as a cervical ripening agent before certain gynaecological procedures in order to reduce the complications occurring during the dilatation procedure.[3] Endometrial biopsy sometimes fails in nulliparous women due to difficulty in dilation of internal os. In postmenopausal patients the cervix may be small and endometrial biopsy is again difficult. Such patients require anaesthesia to do the diagnostic procedures. Recently office endometrial biopsy and hysteroscopy has gained in popularity because of the increase in sensitivity for detection of uterine pathology when compared with endometrial aspiration alone. The great concern in such situations is cervical dilatation. Therefore there is a need for an effective cervical priming agent which can be used in non pregnant women in general gynaecological practice.

Misoprostol has been shown to be equally efficacious when compared with laminaria in inducing cervical ripening prior to transcervical diagnostic and hysteroscopic surgeries (procedures) with minimal time required for cervical dilatation, low cost, easy administration and increased patient convenience.[4]

The route of administration of misoprostol for cervical ripening and dilatation can be oral, vaginal and sublingual. However it is still unclear which route is more effective for cervical dilatation in non pregnant women before transcervical procedures. Batukan et al found that vaginal administration was more effective than the oral route for preoperative cervical ripening in non pregnant premenopausal women while the other studies have not found a difference between oral and vaginal routes.[3,5] Sublingual route was a better alternative for pregnancy termination however in non pregnant premenopausal women it was found that all three routes were comparable.[6]

Various studies in premenopausal women have shown misoprostol is a cheap alternative to laminaria tent whereas in post menopausal women it failed to show the similar benefit.[7] As far as the route is concerned both oral and vaginal has similar efficacy rate. Few studies have shown sublingual route is more effective when compared with vaginal and oral for pregnancy termination.[8,9] There are only few studies comparing sublingual, oral and vaginal misoprostol in non pregnant post menopausal women.[1,10,11] The present study was undertaken to evaluate the efficacy of 400mcg of misoprostol administered vaginally or sublingually for cervical ripening before transcervical gynaecological diagnostic procedures in both pre and post menopausal women.

METHODS

The study was a prospective randomized comparative study involving two groups. It was conducted in the department of Obstetrics and Gynaecology, JIPMER, Puducherry. The study was conducted over a period of 24 months from September 2011 to July 2013. 100 women requiring transcervical procedures were included in the study after informed consent and fulfilling inclusion and exclusion criteria (Figure 1).

All the participants underwent a detailed physical examination after obtaining thorough obstetric, medical and gynaecologic histories.

The study included all non pregnant women who requiring endometrial biopsy (EB), fractional curettage (FC) and dilatation curettage (DC) for various indications. Those who were pregnant, had active genital tract infections, bleeding disorders, seizure disorder, liver disease and women with history of allergy and contraindication to prostaglandins like bronchial asthma were excluded from the study. All the individuals who were scheduled for these procedures were randomized into two groups to receive either sublingual or vaginal misoprostol using computer generated random number table.

The sublingual group received 400mcg misoprostol 3-4 hours before the procedure and the other group received 400mcg misoprostol vaginally 3-4 hours before the procedure. Computerized randomization list was prepared by a statistician outside the department.

In each group patients were divided into premenopausal and postmenopausal. The observations were compared between the two groups and results were analyzed using SPSS software version 20.

The procedure was done by doctors who have similar experience in obstetrics and gynaecology in both groups. Before the procedure cervical dilatation was measured by passing Hegar dilators through the cervix in ascending order, starting with the size of No.2 Hegar dilator. The

largest Hegar dilator passed without resistance was recorded as mean cervical diameter.

Any complications during the procedure like false passage, uterine perforation and cervical tear were noted. The side effects of the drug and ability to get adequate sample were also recorded. The need for additional mechanical dilators with Hegar dilator was also recoded.

The primary outcome measured was preprocedural cervical dilatation in both the groups. The secondary outcomes were ability to do the procedure without the use of adjunctive measures like dilators, complications during cervical dilatation like cervical tear, creation of false passage, uterine perforation, failure to dilate, failure to get adequate sample, presence of medication side effects like nausea, diarrhea, abdominal cramping, vaginal spotting, skin rash, unpleasant taste in the mouth and to assess the degree of discomfort or pain associated with the procedure with '0' being no pain and '10' being worst imaginable pain.

The demographic characteristics and outcome variables were compared between the two groups. The quantitative variables were analyzed using independent t test and the qualitative variables using Chi- square test. The pain scores were compared with Mann- Whitney U test. The analyses were performed according to intention to treat basis. Difference between the two groups was considered statistically significant if P value ≤ 0.05. SPSS software version 20 was used for the statistical analysis.

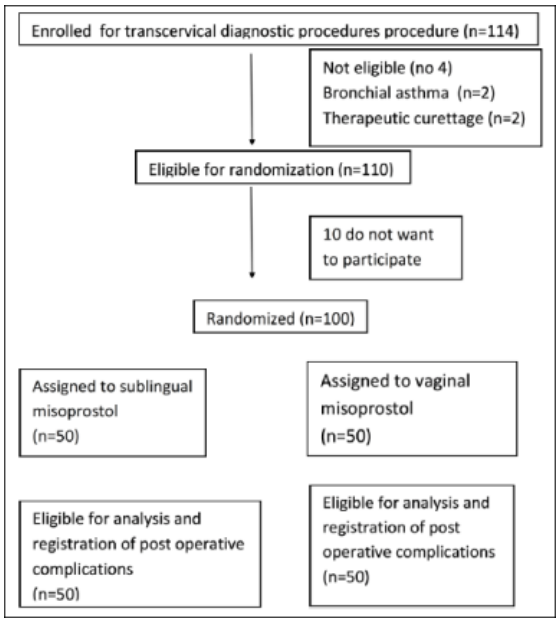

Figure 1: Study flow chart.

RESULTS

Of the 100 women who were enrolled in the current study were randomized to receive either sublingual (50) and vaginal (50) misoprostol (Figure 1). Both the groups were well balanced in terms of baseline demographics and surgical characteristics (Table 1). The commonest procedure was fractional curettage, 88% in sublingual misoprostol group and 80% in vaginal misoprostol group. The commonest indication was DUB in both the groups (60% in sublingual misoprostol group and 54% in vaginal misoprostol group) (Table 2).

Table 1: Comparison of demographic characteristics in sublingual and vaginal groups.

Demographic characteristics	Sublingual (n=50)		Vaginal (n=50)		P value
	n	%	n	%	
Age					0.897
20-40	12	24	14	28	
41-50	26	52	23	46	
>50	12	24	13	26	
Parity					0.182
Nullipara	3	6	7	14	
Primipara	4	8	1	2	
Multipara	43	86	42	84	
Menopausal status					0.334
Premenopausal	41	82	37	74	
Postmenopausal	9	18	13	26	

Table 2: Comparison of the indications for the diagnostic procedure in sublingual and vaginal groups.

Indications	Sublingual (n= 50)	Vaginal (n =50)	P value
DUB	30 (60%)	27 (54%)	0.647
Postmenopausal bleeding	9 (18%)	13 (26%)	
Fibroid	9 (18%)	6 (12%)	
Secondary amenorrhoea	1 (2%)	1 (2%)	
Primary infertility	1 (2%)	3 (6%)	

The mean cervical dilatation in multiparous women prior to the procedure in sublingual group was 7.53mm (SD ± 1.89mm) whereas in the vaginal group was 7.22mm (SD± 1.55mm). It was almost same in both the groups. The mean cervical dilatation before the procedure among the nulliparous women in sublingual group was 3.33mm (SD 3.5mm) whereas in the vaginal group was 2.57 (SD 1.5). The mean dilatation was less in both the groups. The sample size was too small in nulliparous women to find statistically significant difference between both the groups.

The mean cervical dilatation among premenopausal women in the sublingual group was 7.4mm and vaginal group was 6.54mm (SD 2.77) and among postmenopausal

women was 6.72mm (SD 2.2) and 6.65mm (SD 2.52mm) in both sublingual and vaginal group respectively. Though there was a difference of 0.9mm between the sublingual and vaginal groups in premenopausal women it was not statistically significant (Table 3).

Table 3: Mean cervical dilatation in both the groups.

Variable	Mean cervical dilatation (mm)		P value
	Sublingual group (n=50)	**Vaginal group (n=50)**	
Parity			
Nulliparous	3.33 ± 3.5 (n=3)	2.57 ± 1.5 (n=7)	0.628
Multiparous	7.53 ± 1.89 (n=47)	7.22 ± 1.55 (n=43)	0.4
Menopausal status			
Premenopausal	7.40 ± 2.22 (n=41)	6.54 ± 2.17 (n=37)	0.087
Post menopausal	6.72 ± 2.20 (n=9)	6.65 ± 2.52 (n=13)	0.948
Obesity			
Obese	5.71 ± 1.73 (n=12)	5.84 ±1.64 (n=22)	0.89
Non obese	7.77 ± 2.84 (n=38)	7.14 ± 2.68 (n=28)	0.14

The number of women who require adjunctive measures were 11 (22%) in sublingual group and 16 (32%) in vaginal group.

The difference was not statistically significant (P value : 0.26). Among the women who required additional measure like mechanical dilatation the mean dilatation time taken for dilatation upto Hegar No 8 in sublingual group was 1.36 minute and 1.69 minute in vaginal group (Figure 2).

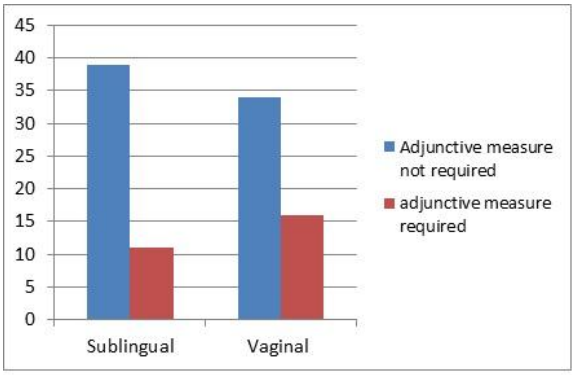

Figure 2: Requirement of adjunctive procedures in sublingual and vaginal groups.

58% of women in sublingual group and 82% in vaginal group did not experience any side effects. The most common side effect in both the groups was crampy lower abdominal pain. It was 14% in sublingual group and 8% in vaginal group. 14% in sublingual group experienced unpleasant taste (Figure 3).

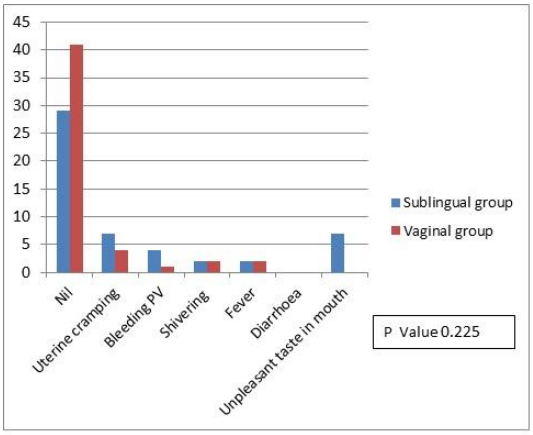

Figure 3: Adverse effects of misoprostol between both the groups.

DISCUSSION

Earlier studies compared the effects of preoperative oral and vaginal misoprostol on cervical ripening before hysteroscopic surgeries.[3,5,12] A study by Batukean et al found that vaginal administration was more effective than the oral route for cervical ripening in non pregnant premenopausal women while the others found no difference between both the routes.[5] In addition, sublingual route was more effective when compared with vaginal and oral routes for pregnancy termination [8]. Lee et al compared various routes of misoprostol in premenopausal non pregnant women. The efficacy of sublingual misoprostol was comparable to oral and vaginal routes.[12] Even these findings correspond well with the sublingual use of misoprostol in termination of pregnancy with the possible benefit of convenient administration. Compared to other studies which compared (studied) oral and vaginal misoprostol with placebo our study compared the sublingual and vaginal routes in both pre and post menopausal women.[5,6]

400 mcg of misoprostol has been studied widely for oral, vaginal and sublingual routes with good results. In the above studies the time interval varied from 4-24 hours for oral and vaginal routes.[3,5,6] Lee et al used relatively shorter time interval of 6-8 hours.[12] The sublingual misoprostol was administered with an interval of 2-4 hours. Most of the studies of pregnancy termination also used same time interval. But there was one study with sublingual misoprostol by Saav et al in which it was given 1 hour before IUCD insertion in premenopausal women, however the cervical widths were not assessed in that study.[13]

The effect of misoprostol is dependent on the route of administration. Clinical data suggests oral route is less effective with more side effects. However if it is administered vaginally the efficacy is increased and side

effects are decreased.[14] A possible explanation for the more pronounced effect of vaginal misoprostol could be a slower uptake and metabolism and a more prolonged elevated plasma concentration compared to oral route and associated with lesser side effects. Sublingual administration was also found to be more effective than oral as it results in more rapid elevation of plasma levels and development of uterine contractility similar to vaginal administration. Clinical data suggest that the efficacy of 200mcg of vaginal misoprostol to 400mcg oral misoprostol is comparable with laminaria and is more effective than dinoprostone for cervical ripening before hysteroscopy.[3] The present study compared the sublingual and vaginal misoprostol with a dose of 400mcg 3-4 hours before procedure to reduce side effects and minimize the discomfort.

The mean cervical dilatation in premenopausal women was 7.4mm ± 2.2mm in sublingual misoprostol group and 6.5mm ± 2.1 mm in vaginal misoprostol group. The mean cervical dilatation in post menopausal women was almost same in both sublingual (6.7mm ± 2mm) and vaginal group (6.6 ± 2.5mm). The rationale behind the subgroup analysis for premenopausal and post menopausal women was that menopausal status appears to correlate with the effect of misoprostol on cervix. 33% of postmenopausal women in sublingual group and 35% in vaginal group required additional dilatation whereas only 16% of premenopausal women in sublingual group and 22% in vaginal group required additional dilatation in the present study.

The effect of misoprostol on postmenopausal women is less studied. The present study also showed no difference in cervical dilatation between pre and post menopausal women in vaginal group but in sublingual group slightly lesser dilatation (7.4 mm Vs 6.7 mm) was observed in postmenopausal women but this was not statistically significant. Nulliparous and postmenopausal women showed less response to misoprostol than multiparous and premenopausal women.

The high efficacy observed in premenopausal women compared to postmenopausal women may be attributed to a different consistency of cervix. Owing to hypoestrogenic status, the tissues of postmenopausal women are more fibrotic and less elastic and the hormone receptor sensitivity in the cervix is also decreased. Consequently misoprostol which is a prostaglandin analogue successfully dilates the cervix in premenopausal but has no or little effect in postmenopausal women. In a RCT by Oppegard et al they found that addition of estrogen with misoprostol in postmenopausal significantly increases the cervical diameter prior to the procedure.[6]

Endogenous estrogen may be essential for the cervical priming induced by prostaglandin and therefore women in a hypoestrogenic state would show little response to prostaglandins and premenopausal women respond better than postmenopusal women. Similarly pregnant women with placental sulphatase deficiency do not show ripening of their cervices due to low circulating estrogen. The inflammatory cascade during the cervical ripening process involves leucocytes and the presence of estrogen receptors on cervical leucocytes suggests that estrogen may directly regulate leucocytes function in the cervix.[15]

There have been few published studies on the effect of misoprostol in the postmenopausal cervix and the results are inconclusive. These studies did not find a significant ripening effect of misoprostol compared with placebo.[1,11,16] Two earlier studies have suggested that misoprostol is effective for cervical ripening in postmenopausal women but both studies included postmenopausal women as a subgroup in their analysis.[10,11] Atmaca et al studied the ripening effect of misoprostol on estrogen pretreated cervix in postmenopausal women. It was concluded that misoprostol alone was ineffective for cervical ripening but it was effective in 22 women as they had used estriol vaginal cream for 14 days prior to dilatation.[7]

The types of side effects were comparable in both the groups, consistent with the findings of previous studies.[6] However the frequencies of side effects were slightly more in our study. The use of higher dosage and shorter time interval before the procedure may be associated with more side effects.

The complications related to the procedure were nil in both the groups in our study which is also comparable with earlier studies. Only one patient had perforation of fundus with resectoscope after dilatation in a study by Oppegard which may be related to the inherent complication associated with resectoscope.[6] Not only misoprostol increases cervical dilatation but also improves the ease of dilatation in those women who require additional mechanical cervical dilatation.

Overall side effects were less in both the groups. This may be because the dose of misoprostol was limited to 400mcg and to 3-4 hours before surgery. Unpleasant taste in mouth was observed in cases 14% of cases in sublingual group. There was significant difference in pain scores between the sublingual and vaginal groups.

CONCLUSION

This is the first study comparing the cervical diameter changes with sublingual and vaginal routes both in non pregnant pre and post menopausal women. 400mcg of both sublingual and vaginal misoprostol given at the dose of 400mcg lessens cervical resistance and increase the cervical diameter equally in both the groups. The adverse effects were almost equal in both the routes except for the unpleasant taste in mouth in sublingual group. Both the routes resulted in greater cervical dilatation, reduced cervical resistance and less need for mechanical dilatation before transcervical procedures.

Based on the results of our study sublingual route is an effective alternate to vaginal administration of

misoprostol for cervical ripening before transcervical diagnostic procedures like endometrial biopsy, fractional curettage and dilatation curettage in non pregnant pre and post menopausal women especially when they feel uncomfortable with vaginal route.

However the optimal dose and time interval remains to be defined. It needs larger randomized controlled trials involving pre and post menopausal women to prove statistical significance if any.

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Ethical approval: The study was approved by the Institute Ethical Committee for Research, JIPMER

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