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# Comparative study of oral versus vaginal misoprostol for cervical ripening in gynaecological procedures

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***Abstract:****Office hysteroscopy and endometrial aspiration are the most common investigations in patients presenting with infertility or abnormal vaginal bleeding. Difficulty in cervical dilatation during these procedures may cause excessive pain, cervical tear or uterine perforation. These complications can be reduced by using a cervical priming agent like misoprostol prior to the procedure. In this study, Two hundred non-pregnant patients undergoing gynaecological procedure were randomized to oral or vaginal misoprostol groups. 400 µg misoprostol was administered 3 hours prior to procedure in each group. After 3 hours cervical dilatation, pain perceived (VAS score), side effects of misoprostol or complication of the procedure were noted. Further comparison were made between nulliparous versus multiparous women and premenopausal versus postmenopausal women.The difference in mean cervical dilatation between the two groups was not found to be statistically significant. Mean VAS score during the procedure was comparable between both the groups. Side-effects of misoprostol were seen more frequently in oral misoprostol group as compared to vaginal misoprostol group. Both oral and vaginal misoprostol were found to cause more cervical dilatation in multiparous women as compared to nulliparous women and in premenopausal women as compared to postmenopausal women.We conclude that misoprostol is effective in cervical ripening in non-pregnant women prior to gynaecological procedures. Both oral and vaginal route have similar efficacy. Side-effects are more common with oral route. Vaginal administration of misoprostol may be preferred prior to gynaecological procedures as it has minimal side-effects.*

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## I. Introduction

Office hysteroscopy, endometrial aspiration and therapeutic dilatation & curettage (D&C) are the most common investigations in patients presenting with infertility or abnormal vaginal bleed with suspected uterine pathology. These are done as outpatient procedures. In centres where office hysteroscopy is not available, endometrial aspiration is still popular because of the convenience of the procedure as well as its high sensitivity for the detection of endometrial pathology. Difficulty in cervical dilatation during a transcervical procedure may cause excessive pain, cervical tear, a false tract or uterine perforation.

Misoprostol is a stable, synthetic form of prostaglandin E1 analogue. It has uterotonic and cervical ripening action due to which it has become an important drug in obstetrics and gynaecology. In 1997, Zieman et al performed the first pharmacokinetic study comparing oral and vaginal routes of misoprostol administration and found that the absorption kinetics of misoprostol was similar in pregnant and non-pregnant women and following a single dose of 400µg misoprostol orally, the plasma misoprostol acid level increased rapidly and peaked at about 34 minutes, declined rapidly by 2 hour and remain low thereafter. In contrast, after vaginal administration, the plasma concentration increased gradually reaching its maximum level after 70-80 minutes before slowly declining with detectable drug level still present after 6 hour.[1]

In 1997, Ngai et al and Atay et al were the first to report that misoprostol was effective for preoperative cervical dilatation in non-pregnant women prior to diagnostic hysteroscopy.[2,3] Since then multiple studies have been done to use misoprostol prior to gynaecological procedures for cervical dilatation but results are equivocal. Considering the literature, route and dose of misoprostol in non-pregnant out-patient procedures is still controversial, therefore we conducted the present study to compare the efficacy of oral and vaginal misoprostol for cervical priming prior to gynaecological procedures.

## II. Material And Methods

This prospective study was conducted on two hundred non-pregnant patients who attended outpatient department in 2015-2016 and underwent gynaecological procedures such as endometrial aspiration, endometrial biopsy or therapeutic dilatation & curettage.

The patients were randomized into two groups by computer generated randomization with 100 patients in each group:

- Group A received 400µg oral misoprostol 3 hour prior to the procedure (2 tablets of 200µg each).
- Group B received 400µg misoprostol by vaginal route 3 hour prior to the procedure (2 tablets of 200µg each).

**Exclusion criteria**

Pregnant women, women with medical illness like heart disease, uncontrolled hypertension, uncontrolled diabetes, renal disease, asthma, allergy to the drug, active genital infections such as vaginitis or cervicitis or other high risk factors were excluded from the study.

**Procedure methodology**

A written informed consent was taken from the patients after explaining the surgical procedure, the drug, its effects and side-effects. A detailed history along with abdominal and vaginal examination was done. In vaginal examination, consistency of the cervix, position and the size of the uterus and any adnexal pathology was noted.After administering the drug in both groups, patients were observed for any side-effects like abdomen cramps, nausea, vomiting, shivering and fever until starting the procedure.

During the procedure, main outcome measure were ease to cervical dilatation, cervical consistency, pain perceived by the patient, any side effects of the drug or complication of the procedure. Ease to cervical dilatation prior to procedure was measured by passing Hegar dilators serially from smaller to larger size. Largest Hegar dilator passed easily was recorded as mean cervical diameter. Visual analog scale (VAS) was used to assess the pain perceived by the patient. Pain was graded from 0 to 10, 0 representing no pain at all and 10 worst possible pain imaginable. Patients having pain score 7 or more were given paracervical block as anaesthesia.

Any complication of the procedure like cervical injury, tear, excessive bleeding or uterine perforation or failure to obtain tissue for biopsy was noted. The patients were observed for one hour after the procedure for any complication. All the procedures were done by single investigator to avoid inter observer variation.

**Statistical analysis**

At the end of the study, the data was collected and analysed statistically. The observations were compared between the two groups and results analyzed using Chi-square test and Student t-test. A p-value less than 0.05 was considered as statistically significant.

## III. Result

In our study both the groups were comparable in age, parity, menstrual status, haemoglobin concentration and indication of gynaecological procedure. Abnormal uterine bleeding was the most common indication of gynaecological procedure followed by primary or secondary infertility and post-menopausal bleeding.

**Table no 1:**Age, Parity, Menstrual status, Haemoglobin distribution

| | Group A (n=100) n(%) | Group B (n=100) n(%) |
|---|---|---|
| Mean age (years) | 40.19±10.96 | 41.78±11.13 |
| Parity Nulliparous | 22(22%) | 18(18%) |
| Multiparous | 78(78%) | 82(82%) |
| Menstrual status | | |
| Pre-menopausal | 85(85%) | 83(83%) |
| Post-menopausal | 15(15%) | 17(17%) |
| Mean haemoglobin (g/dL) | 9.23±1.3 | 9.44±1.01 |

Mean cervical dilatation as measured by largest size Hegar dilator that was passed easily through cervix just before the procedure was 8.18±1.63mm in group A and 8.26±1.42mm in group B. 81% patients in group A and 87% patients in group B has cervical dilatation ≥ 7mm. The difference in cervical dilatation was not found to be statistically significant between the two groups (p value=0.712).

VAS score measured during the procedure was found to be comparable between the two groups. 73 % patients in group A and 66% patients in group B had VAS score 4-6 during the procedure while 14% patients in group A and 15 % patient in group B had VAS score 7-10.

In the present study abdominal cramps were the most common side-effect of misoprostol seen in 24% patients in group A as compared to 11% patients in group B. This difference was statistically significant (p value=0.01). Other less common side-effects were nausea, vomiting and shivering seen more frequently after oral misoprostol administration. Paracervical block was required as additional analgesia in 14% of patients in group A and 15% of patients in group B.

In the present study there were 22 nulliparous patients in group A and in 18 nulliparous patients in group B.

**Table 2:** Correlation of various parameters in nulliparous patients

| Variables | Group A (n=22) | Group B (n=18) | p value |
|---|---|---|---|
| Mean Hegar dilatation | 6.54±0.67 | 6.66±0.48 | 0.512 |
| Mean VAS during procedure | 5.68±1.35 | 5±1.13 | 0.09 |
| Time taken for procedure (minutes) | 5.81±1.55 | 5.71±1.82 | 0.807 |
| Side-effects of misoprostol<br>Abdominal cramps<br>Nausea<br>Vomiting | <br>10(45.5%)<br>4(18.1%)<br>1(4.5%) | <br>3(16.6%)<br>1(5.5%)<br>0 | <br>0.05<br>0.229<br>0.359 |
| Additional analgesia required (paracervical block) | 6(27.2%) | 2(11.1%) | 0.203 |

In this study there were 78 multiparous patients in group A and in 82 multiparous patients in group B.

**Table 3:**Correlation of various parameters in multiparous patients

| Variables | Group A(n=78) | Group B(n=82) | p value |
|---|---|---|---|
| Mean hegar dilatation | 8.64±1.52 | 8.60±1.32 | 0.890 |
| Mean VAS during procedure | 4.94±1.21 | 4.93±1.48 | 0.963 |
| Time taken | 7.45±1.59 | 7.56±1.41 | 0.642 |
| Side-effects of misoprostol<br>Abdominal cramps<br>Nausea<br>Vomiting<br>Shivering | <br>14(17.9%)<br>5(6.4%)<br>3(3.8%)<br>2(2.5%) | <br>8(9.7%)<br>2(2.4%)<br>0<br>0 | <br>0.132<br>0.219<br>0.07<br>0.144 |
| Additional analgesia required | 8(10.2%) | 13(15.8%) | 0.294 |

In our study there were 85 pre-menopausal patients in group A and in 83 pre-menopausal patients in group B.

**Table 4:** Correlation of various parameters in pre-menopausal patients

| Variables | Group A (n=85) | Group B (n=83) | p value |
|---|---|---|---|
| Mean Hegar dilatation | 8.41±1.58 | 8.44±1.37 | 0.881 |
| Mean VAS during procedure | 5±1.19 | 4.72±1.22 | 0.139 |
| Time taken for operative procedure | 6.89±1.68 | 6.93±1.26 | 0.849 |
| Side-effects of misoprostol<br>Abdominal cramps<br>Nausea<br>Vomiting<br>Shivering | <br>20(23.5%)<br>8(9.4%)<br>4(4.7%)<br>1(1.1%) | <br>11(13.2%)<br>3(3.6%)<br>0<br>0 | <br>0.08<br>0.128<br>0.04<br>0.321 |
| Analgesic required (Paracervical block) | 9(10.5%) | 7(8.4%) | 0.634 |

In the present study there were 15 post-menopausal patients in group A and in 17 post-menopausal patients in group B.

**Table 5:** Correlation of various parameters in post-menopausal patients

| Variables | Group A (n=15) | Group B (n=17) | p value |
|---|---|---|---|
| Mean Hegar dilatation | 6.86±1.30 | 7.35±1.36 | 0.311 |
| Mean VAS during procedure | 5.73±1.57 | 6.05±1.81 | 0.591 |
| Time taken for operative procedure | 8.21±1.50 | 8.66±1.76 | 0.441 |
| Side-effects of misoprostol<br>Abdominal cramps<br>Nausea<br>Shivering | <br>4(26.6%)<br>1(6.6%)<br>1(6.6%) | <br>0<br>0<br>0 | <br>0.02<br>0.279<br>0.279 |
| paracervical block required | 5(33.3%) | 8(47.0%) | 0.430 |

## IV. Discussion

Various investigators have studied the role of misoprostol as cervical priming agent before transcervical procedures in non-pregnant women. Choksuchat et al (2006) concluded that misoprostol is equally efficacious for cervical dilatation in non-pregnant women when given by either oral or vaginal route.[4] Lee Young et al (2010) and Song et al (2014) also concluded oral and vaginal misoprostol are equally efficacious in cervical dilatation when given before transcervical procedure.[5,6] Alternatively, Batukan et al (2008) concluded that the vaginal administration of misoprostol is more effective than the oral route for preoperative cervical ripening in premenopausal women.[7]Kalampokas et al (2012) concluded that the application of 200µg misoprostol vaginally 12 hour before hysteroscopy reduced cervical resistance and consequently the need for cervical dilatation with only mild side effects.[8]Saha et al (2015) concluded that misoprostol was effective in cervical ripening of non-pregnant pre-menopausal uterus to facilitate gynaecological procedures.[9] In a systematic review, Al-Fozan et al (2015) concluded that misoprostol is preferable to placebo for cervical ripening before operative hysteroscopy, however it is associated with treatment side effects including mild abdominal pain, nausea, diarrhoea and vaginal bleeding.[10]

400µg is the most commonly used dose of misoprostol for gynaecological procedures. Pharmacokinetic profile of misoprostol indicates that single oral dose of misoprostol might not remain effective after 4-6 hour of administration and after vaginal administration, peak concentration is reached in 1-2 hour. Hence, in the present study time interval of 3 hour was chosen between administration of misoprostol and transcervical procedure. In our study difference in the cervical dilatation between both the groups was not found to be statistically significant. Remnants of vaginal tablets were found in 53% of patients in group B which indicated that vaginal absorption is variable. Changing the preparation for vaginal administration may increase the efficacy of vaginal route.

In the present study mean pain score during procedure was 5.11±1.27 in group A and 4.95±1.42 in group B. This difference was not statistically significant (p value=0.46). Atay et al (1997) observed that mean dilatation pain scores for the misoprostol and placebo groups were 5.1 and 9.3 respectively which was found to be statistically significant (p value <0.05).[3] Saha et al (2015) found that only 3.61 % patients in misoprostol group had intolerable pain during procedure as compared to 48.74% patients in the control group.[9]

It was seen that side effects were more common in oral misoprostol group as compared to vaginal administration. Abdominal cramps was the most common side-effect seen in 24% patients in oral group as compared to 11% patients in vaginal misoprostol group. Pain was mild and did not preclude the patient from taking the drug. In our study no patient had any complication of procedure like cervical injury, excessive bleeding or uterine perforation. Thomas et al (2002) observed that adverse effects like diarrhoea (p value < .001), cramps (p value < .0001) and bleeding (p value < .001) were more common in the misoprostol group as compared to control group but were mild.[11]Choksuchat et al (2006) found that diarrhoea occurred in 23.3% patients in oral misoprostol group as compared to 3.3% in vaginal misoprostol group which was statistically significant (p value=0.05).[4]Saha et al (2015) concluded that nausea and vomiting occurred in 5.1% patients and mild abdominal cramps occurred in 20% patients in misoprostol group as compared to placebo group.[9]

In the present study there were 22 nulliparous patients in group A and in 18 nulliparous patients in group B. In both the groups, mean cervical dilatation after misoprostol administration was found to be significantly more in multiparous patients as compared to nulliparous patients (p value<0.001). This may be due to the fact that because of previous vaginal deliveries cervical width might be more in multiparous women even before misoprostol administration.

Mean VAS score during the procedure was 5.68±1.35 in nulliparous patients as compared to 4.94±1.21 in multiparous patients. This difference was found to be statistically significant (p value=0.02). In group A, side-effects of misoprostol occurred more frequently in nulliparous patients as compared to multiparous patients. Abdominal cramps occurred in 45.5% nulliparous patients as compared to 17.9% multiparous patients. This difference was found to be statistically significant (p value <0.001). Incidence of other side-effects was comparable between nulliparous and multiparous women. In group B incidence of side-effects was comparable between nulliparous and multiparous patients and was significantly less than that of group A. Hence it was found that oral misoprostol caused significantly more side-effects as compared to vaginal administration and side-effects occurred more frequently in nulliparous women as compared to multiparous women.

Ngai et al (2001) and Bunnasathiansri et al (2004) concluded that misoprostol was not effective in cervical dilatation in post-menopausal women.[12,13] Crane et al (2006) and Polyzos et al (2012) conducted systematic review and meta-analysis and concluded that misoprostol is effective for cervical ripening in non-pregnant pre-menopausal women but not effective in post-menopausal women.[14,15] In contrast Kant et al (2011) concluded that misoprostol is effective for cervical ripening in post-menopausal women.[16]

In our study there were 15 post-menopausal patients in group A and in 17 post-menopausal patients in group B. In both the groups, mean cervical dilatation after misoprostol administration was found to be significantly more in pre-menopausal patients as compared to post-menopausal patients (p value < 0.001). This may be due to the theory that due to hypoestrogenic status, the cervical tissue of post-menopausal women is

more fibrotic and less elastic and the hormone receptor sensitivity in the cervix is decreased. This is supported with studies by Atmaca et al (2005) and Oppegaard et al (2010) who concluded that combination of esterogen and misoprostol is effective for preoperative cervical ripening in post-menopausal women.[17,18]

In this study, mean VAS score during the procedure was 4.72±1.22 in pre-menopausal patients as compared to 6.05±1.81 in post-menopausal patients. This difference was found to be statistically significant (p value < 0.001). Hence due to lesser degree of cervical dilatation in post-menopausal patients, they perceived significantly more pain during the operative procedure as compared to pre-menopausal patients.

In both groups side-effects of misoprostol were comparable between pre-menopausal and post-menopausal women (p value >0.05).

Hence it was observed that multiparous patients had more cervical dilatation and less per-operative pain as compared to nulliparous patients. Nulliparous patients had significantly higher side-effects as compared to multiparous patients after misoprostol administration. Similarly, pre-menopausal women had more cervical dilatation, less per-operative pain and less requirement of additional analgesia as compared to post-menopausal women after oral or vaginal misoprostol administration.

## V. Conclusion

Misoprostol is effective in cervical ripening in non-pregnant women prior to gynaecological procedures. Both oral and vaginal route have similar efficacy. Side-effects are more common with oral route as compared to vaginal route but are mild and do not preclude the use of drug. Misoprostol is more effective for cervical ripening in multiparous women as compared to nulliparous women and in pre-menopausal women as compared to post-menopausal women. Vaginal administration of misoprostol may be preferred prior to gynaecological procedures as it has minimal side-effects.

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