Vaginal Misoprostol for Cervical Priming before Gynaecological Procedures on Non Pregnant Women

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Abstract:

Background
Misoprostol has been extensively researched for its use in obstetrics and has proved to be a very effective cervical softening agent before termination of pregnancy. The beneficial effects on cervical ripening may make misoprostol a desirable agent for helping cervical dilatation on non pregnant women also. The objective is to study the efficacy of preoperative vaginal application of misoprostol as cervical priming agent before gynaecological procedures on non pregnant women.

Methods
***Design*:** A randomized controlled trial.
Setting: Department of Gynaecology and Obstetrics of two medical colleges.

Participants: 468 non pregnant pre-menopausal nulli-parous or parous women scheduled to have diagnostic D&C or diagnostic hysteroscopy operations.

Interventions: 400 mcg intravaginal misoprostol (229 women) in the study group and 400 mg intravaginal metronidazole as placebo (231women) in control group.
Outcome Measure: The main outcome measures were baseline cervical width at the beginning of the procedures, the number of women who required further cervical dilatation, time taken for dilatation, side effects and other complications.

Results : Base line cervical width in the study group was significantly higher than control group (4.6±0.8 mm vs. 3.8±0.7 mm, $p < 0.0001$). 141 (61.57%) cases required further cervical dilatation in the study group compared to 206 (89.18%) in the control group ($p < 0.0001$). Time taken for further cervical dilatation was significantly lower in the study group compared to control group (48.3±18.4 sec vs. 68.6±17.3 sec, $p < 0.0001$). Cervical injury and uterine perforation occurred in 12 and 3 women respectively in the control group compared to 1 and 0 women respectively in the misoprostol group. Two most common side effects of vaginal misoprostol were mild lower abdominal pain (21%) and slight vaginal bleeding (09.2%) which were within tolerable limit.

Conclusion: Preoperative vaginal application of misoprostol before gynaecological procedures on non pregnant women decreases the cervical resistance, facilitates the cervical dilatation and operative procedures minimizing cervical or uterine injuries.

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Introduction

Misoprostol, a synthetic prostaglandin E_1 analogue, was originally introduced for prevention and treatment of gastric ulcer diseases. Later, misoprostol has been found to be a useful drug with a wide range of applications in both obstetrics and gynaecology because of its effectiveness, low cost, stability in light and hot climate condition and ease of administration compared to its legalized counterpart such as dinoprostone and gemeprost. It has been shown that misoprostol increases myometrial contraction as well as decreases cervical resistance [1, 2].

Misoprostol has been extensively researched for its use in obstetrics and has proved to be a very effective cervical softening agent before termination of pregnancy [3, 4]. The beneficial effects on cervical ripening may make misoprostol a desirable agent for helping cervical dilatation on non pregnant women also. A few studies are available on the use of misoprostol as cervical priming agent before gynaecological procedures on non pregnant women. After oral administration, Misoprostol is rapidly absorbed and converted to its pharmacologically active metabolite – misoprostol acid. Plasma concentration of misoprostol acid reaches its peak in about 30 minutes and decline rapidly thereafter. Misoprostol is primarily metabolised in liver and less than 1% of its active metabolite is excreted in urine. Most common adverse effects of misoprostol after oral administration are nausea vomiting diarrhoea, abdominal cramps and fever which are dose dependent.

The effects of misoprostol on the reproductive tract are increased and gastro-intestinal side effects are decreased if the tablets are administered vaginally. After vaginal application the peak plasma concentration of misoprostol acid is reached in one to two hours and then declines slowly. Though vaginal application of misoprostol results in slower increase and lower peak plasma concentration as compared to oral administration, the overall exposure to the drug is increased.[5]

Methods

Settings: The study was conducted simultaneously in two medical colleges in the state of West Bengal, India, over a period of two and half years between July' 2004 and December' 2006, viz. North Bengal Medical College & Hospital, Darjeeling and R.G. Kar Medical College & Hospital, Kolkata.

Design: This is a randomized controlled trial. The study followed a double blind design for two parallel groups.

Participants: Participants in this study were 468 non pregnant pre-menopausal nulli-parous or parous women admitted for gynaecological procedures due to any of the following two indications - diagnostic dilatation & curettage (D&C) and diagnostic hysteroscopy. Exclusion criteria in our study were – post- menopausal women, presence of any contraindications for use of misoprostol like history of bronchial asthma, allergy to prostaglandins, irritable bowel syndrome and cardiovascular diseases.

Protocol: Initially 503 patients were enrolled for this study. 35 patients were excluded from the study either due to not meeting the inclusion criteria (n=30) or due to refusal subsequently (n=5). 468 patients were thus randomised into two groups having 234 patients in each arm. In the study group (Gr. A), five patients were removed from the study after randomisation due to onset of menstruation (n=3), and development of RTI or fever (n=2) before administration of the drug. In the control group (Gr. B) similarly three patients were removed from the study after randomization due to onset of menstruation (n=2), and development of UTI (n=1) before administration of the drug. Hence 229 patients in group A and 231 in group B completed the study and analysed (Figure-1). The study was blinded doubly till the final outcome.

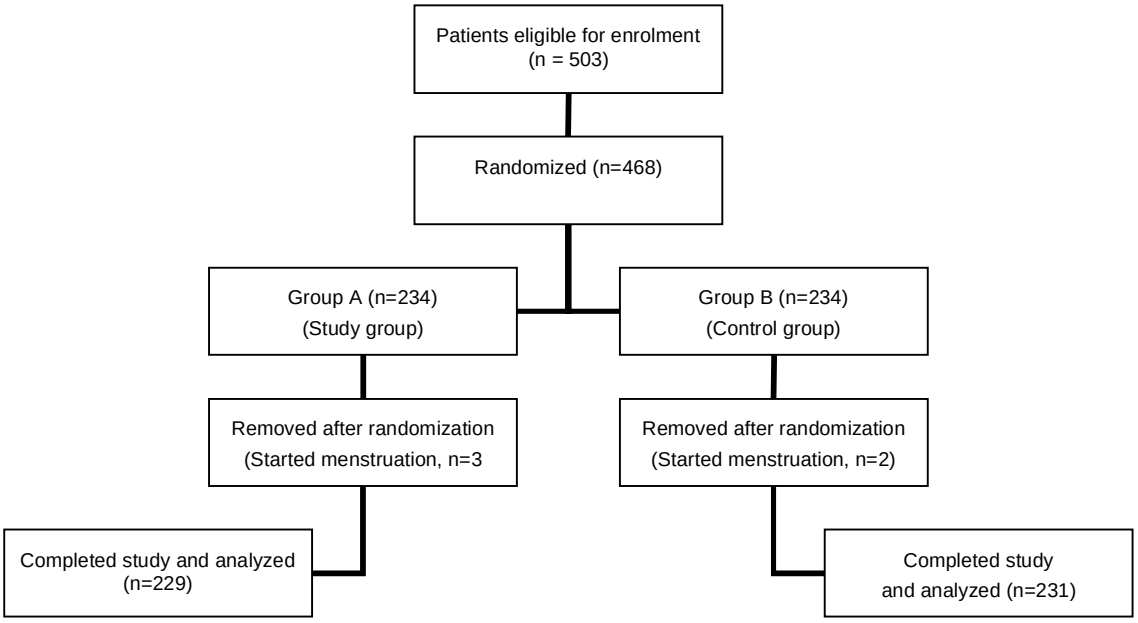

Fig. (1). Patient flow through the study.

Methods

Four hundred and sixty eight women scheduled to have diagnostic D & C or diagnostic hysteroscopy for various indications (described later) were included in this study after going through inclusion and exclusion criteria.

The patient were randomly allocated in to two parallel groups (A and B) having 234 patients in each of the two arms using computer generated randomization protocol.

All the patients were admitted on the day before operation and undergone detailed history taking and clinical examination. Routine baseline investigations were also performed.

The patients in the study group (Group A) received 400 microgram misoprostol (two 200 mcg misoprostol tablets) in posterior fornix of vagina 6 hours prior to the operative procedures and the patients in the control group (Group B) received 400 mg metronidazole (two 200 mg metronidazole uncoated tablets) in posterior fornix of vagina 6 hours prior to the operative procedures. Drugs were administered in all women by the resident doctors on duty.

We used metronidazole tablet as placebo because, firstly, it has no effects on cervical tissue or uterine musculature and secondly, a single intravaginal application of 400 mg metronidazole tablets produce no significant systemic effects, though some amount of drug is absorbed through vaginal epithelium.

We had used both the misoprostol and uncoated metronidazole tablets in round compressed shape (white in colour) which appeared to be almost identical with a difference of little bit larger size of metronidazole tablet.

To make the study double blinded, both the drugs were supplied to the admitting ward as per randomization schedule, on the day of admission in identical sealed envelop mentioning the registration number from our hospital pharmacy. On duty Resident doctor, just before application of the drugs, opened the sealed envelop and applied the same in posterior fornix of the patients without showing the tablets to the patients. Normal saline vaginal wash was given in both groups by on duty nursing staff just before sending the patients to Operation Theater to remove the remnants of drugs, had there been any, present within the vagina. The investigators did not have any kind of discussion regarding the procedures, with those persons who had supplied the drugs and who had applied the same till completion of this study.

The operative procedures were started without using any analgesia or anaesthesia.

Primary outcome measure was cervical response assessed by the largest size Hegars dilator that could be inserted without resistance at the beginning of the surgical procedures. The secondary outcome measures were - need for further cervical dilatation, ease of dilatation, time taken for dilatation (up to 8mm) and subjective assessment of pain during dilatation using Visual Analog Scale (VAS). Those patients who complained of moderate to severe pain (VAS score 5 or more) received either analgesia or anaesthesia during further cervical dilatation (up to Hegars 8).

Development of any pre-operative side effects like nausea, vomiting, abdominal cramp, vaginal bleeding, pyrexia of significance, loose motions etc. were also noted.

Per-operative complications, if any were also taken into consideration.

All data entries were visually double checked by an independent second investigator. The data were analyzed using MedCalc 9 statistical software (Publisher: MedCalc Software, Web site: http://www.medcalc.be). Statistical analysis included Chi-square test and '*t*' test to compare the outcomes between the study group and the control group. A *p*-value less than 0.05 was considered as statistically significant.

Ethical Consideration: The study was approved by "The Medical Ethical Committee for Human research", North Bengal Medical College & Hospital and "The Committee for Ethical Consideration and Approval for Human Research", R G Kar Medical College & Hospital, as required by Indian law. Before enrolments for the study entry, all women provided a written informed consent meeting all local institutional requirements.

Results

Patients of both the study and control groups were comparable in relation to age, parity and BMI Table (1).

Table (1). Patient profile.

Characteristics	Study Group (n= 229)	Control Group (n= 231)	p value
Age in Years			
20-29	72 (31.44%)	69 (29.87%)	
30-39	81 (35.37%)	85 (36.80%)	
40-49	69 (30.13%)	71 (30.74%)	
50 and above	07 (03.06%)	06 (02.59%)	
Mean age ± sd	35.4 ± 5.5	36.1 ± 5.2	0.1614
Parity			
Nulliparous	56 (24.45%)	61 (26.41%)	0.7072
Parous	173 (75.55%)	170 (73.59%)	0.7072
BMI (mean ± sd)	23.3 ± 0.96	23.4 ± 0.88	0.2447

Operative procedures undertaken in both groups were also comparable Table (2).

Infertility, either primary or secondary, was the main indication for hysteroscopy in both groups. The second most common indication for hysteroscopy was abnormal uterine bleeding. Abnormal menstrual bleeding was the only indication for Diagnostic D & C in both groups.

From the result it is evident that cervical status at the beginning of surgical procedures was superior in the study group in comparison to the control group (Table-3). Baseline cervical dilatation was 4.6 ± 0.8 (mm) in the study group compared to 3.8 ± 0.7 (mm) in the control group (p = < 0.0001; 95% CI = -0.94 to - 0.66). Requirement of further cervical dilatation and time required for that were also significantly less in the study group (p = < 0.0001; 95% CI = 17.03 to 23.57).

Table (2). Operative procedures and Indications.

Operative procedures	Study Group (n= 229)	Control Group (n= 231)	p value
Diagnostic D & C (For abnormal menstrual bleeding)	87 (37.99%)	95 (41.12%)	0.5545
Diagnostic hysteroscopy	142 (62.01%)	136 (58.88%)	0.5545
Indications for Hysteroscopy:			
Primary infertility*	41 (28.86%)	33 (24.26%)	0.4643
Secondary infertility*	25 (17.53%)	27 (19.85%)	0.7321
Recurrent abortion*	10 (07.22%)	09 (06.62%)	0.9686
Abnormal uterine Bleeding*	35 (24.74%)	31 (22.79%)	0.8097
Missed IUCD	13 (09.28%)	15 (11.03%)	0.7760
Secondary Amenorrhoea*	18 (12.37%)	21 (15.45%)	0.5693

** In case of suspected intrauterine pathology.*

Table (3). Results of misoprostol administration.

Results	Study Group (n= 229)	Control Group (n= 231)	p value & (95% CI)
Baseline Cervical dilatation [in mm] (mean ± sd)	4.6 ± 0.8	3.8 ± 0.7	< 0.0001 (-0.94 to -0.66)
Further cervical dilatation required	141(61.57%)	206 (89.18%) (66.346 to 78.874)	< 0.0001
Time taken for dilatation [in seconds] (mean ± sd)	48.3 ± 18.4	68.6 ± 17.3	< 0.0001 (17.03 to 23.57)

No patient in the study group complained of intolerable pain during dilatation procedure but in the control group a significant number of patients (49.03%) complained of such pain Table (4) for which analgesia or anaesthesia had to be given to expedite the procedures.

Most common side effects of vaginal misoprostol, were lower abdominal cramp (21.0%) and mild vaginal bleeding (09.2%) which were within tolerable limit Table (5).

Table (4). Subjective assessment of pain during cervical dilatation.

Pain (VAS score)	Study Group (n= 141)	Control Group (n= 206)	p value
No discomfort (0)	60 (42.55%)	0	< 0.0001
Mild discomfort (1-2)	59 (41.84%)	22 (10.68%)	< 0.0001
Mild pain (3-4)	17 (12.06%)	83 (40.29%)	< 0.0001
Moderate to severe pain requiring analgesia / anesthesia (5 or more)	05 (03.55%)	101 (49.03%)	< 0.0001

Table (5). Side effects (Pre-operatively) & Complications (Per-operatively).

	Study Group (n= 229)	Control Group (n= 231)	p value
Pre-operative Side effects			
No side effects	144 (62.9%)	231 (100%)	< 0.0001
Nausea & vomiting	12 (05.2%)	0	0.0013
Abdominal cramp (mild)	48 (21.0%)	0	< 0.0001
Pyrexia of significance	0	0	
Loose motion	04 (01.7%)	0	0.1386
Vaginal Bleeding (mild)	21 (09.2%)	0	< 0.0001
Per-operative Complications			
No complication	228 (99.56%)	216 (93.51%)	0.0010
Cervical injury	1 (0.44%)	12 (5.19%)	0.0052
Uterine perforation	0	3 (1.30%)	0.2493

Cervical injury and uterine perforation occurred in 12 and 3 patients respectively during operative procedure in the control group but in the study group only one woman had cervical injury.

Discussion

Procedure such as D & C, hysteroscopy are frequently performed for different gynaecological problems in both pre and post menopausal women either for diagnostic or for therapeutic purpose. Cervical dilatation is the most unpleasant part of these procedures. Cervical priming prior to operative procedures facilitates the operation and reduces the risk of cervical injury and uterine perforation that are often associated with mechanical cervical dilatation. Agents commonly used for this purpose includes laminaria tents and various prostaglandin preparations.

Discomfort and complications due to cervical dilatation despite local anaesthesia and precise technique are serious problems in those women. Cervical narrowing or stenosis that is a frequently encountered condition during these procedures is a major cause of these undesired effects. New techniques, premedications, analgesia and anaesthesia methods to solve this problem are always investigated.

Misoprostol, a prostaglandin E_1 analogue is now a day widely used in obstetrics for its strong uterotonic and cervical ripening effects. Different studies in this regard are showing misoprostol as a very good cervical ripening agent before induction of labour or abortion.[6-9]

The authors have been using various prostaglandin preparations for 1st and 2nd trimester termination of pregnancies over a long period of time. [10, 11]

Ngai et al. (1997) [12] had reported that oral misoprostol was effective for preoperative cervical dilatation in non pregnant women. Following this study, many reports supported this beneficial effect of misoprostol, used either vaginally or orally. [13-16]

However some studies reported that pre operative use of vaginal misoprostol did not reduce the cervical resistance particularly when used in post menopausal women. [17-19]

It might be due to hypo estrogenic state in postmenopausal women. Bisharah et al. in 2003 had reported that misoprostol did not produce cervical priming effect when used in hypo estrogenic state caused by using leuprolide aetate injection. [20]

We had used misoprostol as cervical priming agent before D & C and diagnostic hysteroscopy with the main objective to see the effectiveness of the drug in this regard. Though the diagnostic hysteroscopy could be performed using 4 mm scope without any prior cervical dilatation and without using any analgesia or anaesthesia in many cases, it was our observation from clinical experience that in number of cases we had to face difficulties during introduction of hysteroscope without prior dilatation of cervix particularly in nulliparous and elderly women. In this study we used operative hysteroscope for diagnostic purpose, introduction of which required prior cervical dilatation. We used larger size operative scope instead of using smaller size diagnostic scope with the idea that if minor operative procedures like removal of Cu T, endometrial biopsy etc. were required following diagnostic procedures, those could be done in the same sitting and if vaginal misoprostol was found to be effective as cervical priming agent in non-pregnant women, the same could be applied before operative hysteroscopy in future.

From our study in pre-menopausal women, it is evident that there is a significant difference between the study and control groups in terms of cervical softening and dilatation as determined by increased basal cervical width in misoprostol group.

Preoperative application of vaginal misoprostol decreased the need of further cervical dilatation in large number of cases. Cervical dilatation was also easier in the study group. Cervical priming by vaginal misoprostol decreased the discomfort of the patients during dilatation of the cervix and less time was required for desired dilatation.

Cervico-uterine injury during operation was very rare (only a single case of cervical injury out of 229 women) in the misoprostol group. Though vaginal use of misoprostol produced mild abdominal discomfort and slight vaginal bleeding in some women, those were not very serious side effects and well tolerated by the patients.

Use of misoprostol as cervical priming agents decreases the need of analgesia and anaesthesia during the operative procedures thereby minimising the hazards and cost, associated with analgesia and anaesthesia.

The only limitation of the use of misoprostol tablets vaginally is the requirement of prior hospitalisation of the patients. Sublingual route of misoprostol may be the solution in this regard, if found effective by well controlled randomised studies.

Conclusion

We conclude that vaginal misoprostol applied in non pregnant women, before gynaecological procedures like D & C and hysteroscopy, decreases the cervical resistance, reduces the need for further cervical dilatation, facilitates the cervical dilatation (if it is required) and operative procedures minimizing cervical or uterine injuries.

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