Original Article

Effectiveness of Misoprostol in Office Hysteroscopy in Premenopausal Nulliparous Women: A Prospective Randomized Double-Blind Placebo-Controlled Trial

Vinod G. Nair, Kallol Kumar Roy, Rakhi Rai, Anamika Das, Juhi Bharti, Rinchen Zangmo

Department of Obstetrics and Gynaecology, Division of Minimally Invasive Gynaecological Surgery, All India Institute of Medical Sciences, New Delhi, India

Abstract

Study Objective: The objective of this was to evaluate the effectiveness of misoprostol in premenopausal nulliparous women with 200-mcg single vaginal dose 4 h before the procedure. **Design:** This was a prospective randomized double-blind placebo-controlled trial. **Setting:** This study was conducted in a tertiary care and academic research center. **Patients:** One hundred patients were included in the study: 50 in misoprostol group and 50 in placebo. **Interventions:** Patients underwent office hysteroscopy 4 h after vaginal application of misoprostol or placebo. **Measurements and Main Results:** Ease of doing hysteroscopy was significantly better in the misoprostol group (difficulty score: 2.74 ± 1.20) as compared to placebo (difficulty score: 4.20 ± 1.10), $P = 0.001$. The time taken for negotiating the internal os (cervical passage time) was found to be significantly shorter in the misoprostol group (6.20 ± 5.21 s) as compared to placebo (14.78 ± 11.84 s), $P = 0.001$. The overall Visual Analog Scale (VAS) score was significantly lower in the intervention group (2.64 ± 1.62) as compared to placebo (4.90 ± 1.90), $P = 0.001$. Moreover, the VAS score at the point of passing internal os was significantly lower in the misoprostol group (2.82 ± 1.39) as compared to placebo (4.94 ± 1.96), $P = 0.001$. Misoprostol had a significant positive effect on satisfaction level of patients; 76% ($n = 38$) of women in the misoprostol group expressed their willingness to undergo the procedure again if required versus 18% ($n = 9$) in placebo, $P = 0.001$. Furthermore, 78% ($n = 39$) of women in the misoprostol group would recommend the procedure to their friends and relatives versus 36% ($n = 18$) in placebo, $P = 0.001$. **Conclusion:** Preoperative cervical preparation with 200 mcg of misoprostol vaginal application 4 h before office hysteroscopy in premenopausal nulliparous women significantly reduces the difficulty encountered in negotiating the cervical canal. Further, it significantly reduces the pain experienced by the patient at the point of passage through internal os as well as throughout the entire procedure.

Keywords: *Difficulty, misoprostol, office hysteroscopy, Visual Analog Scale score*

Introduction

Office hysteroscopy has gained popularity as an outpatient procedure for diagnostic as well as operative purpose. It is an effective and safe procedure that can be performed in an outpatient setting without the need for

Address for correspondence: Dr. Vinod G. Nair, Department of Obstetrics and Gynaecology, Division of Minimally Invasive Gynaecological Surgery, All India Institute of Medical Sciences, New Delhi - 110 029, India.
E-mail: nair.vinod19@gmail.com

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operating theater facility.[1] Although office hysteroscopy is well tolerated, some patients complain of severe pain, especially nulliparous and postmenopausal women. The cervical os is generally less elastic and less dilated in these unfavorable cases for office hysteroscopy. Routine cervical preparation is not recommended in office hysteroscopy.[2]

Misoprostol is a methyl analog of prostaglandin E1 and is commonly used for cervical ripening in pregnant women for termination of pregnancy or for evacuation of retained products of conception. Applying the same principle, it appears that there is a beneficial effect of misoprostol in office hysteroscopy, although the evidences are conflicting. It can be administered either sublingually, orally, vaginally, or rectally. Plasma concentration reaches the maximum after 70–80 min of vaginal administration, with slowly declining levels till 6 h.[3] In most of the studies, misoprostol was administered either orally or vaginally, 12–24 h before the procedure. The basic purpose of office hysteroscopy is to avoid multiple visits and multiple investigations. However, if misoprostol has to be administered 12–24 h before the procedure, one more visit of the patient becomes essential. Moreover, the clinical effectiveness of the drug after 12–24 h of time lapse is questionable. Hence, evaluating the effectiveness of misoprostol application for a short duration, i.e. 4 h before the procedure becomes a need of the hour. The aim of our study was to evaluate the benefit of vaginal administration of misoprostol versus placebo 4 h before office hysteroscopy in premenopausal nulliparous women.

Materials and Methods

Trial design and sample size estimation

Our study is a prospective double-blind placebo-controlled trial which was conducted at a tertiary care center from March 2019 to August 2019. The study was approved by the Institute Ethics Committee and was registered under the Clinical Trial Registry-India (CTRI), number CTRI/2019/04/018458, registered on April 8, 2019. Any premenopausal nulliparous woman in the age group of 18–45 years undergoing office hysteroscopy for any indication as deemed necessary upon clinical evaluation was included in the study. Those who were having active genital infection, on-going vaginal bleeding, previous cervical surgery, or allergy to misoprostol or clotrimazole (placebo) were excluded from the study.

In an earlier similar type of study, Tesma *et.al*. (2017) had shown that the mean Visual Analog Scale (VAS) score for the misoprostol group was 2.9 ± 3.2 and corresponding placebo group 5.5 ± 3.1.[4] Assuming that similar results could be obtained in our study, a minimum number of 35 patients in each arm was considered sufficient enough to deduct statistically significant difference at 5% level of significance with 90% power. However, in order to bring out more statistical significance, it was decided to recruit fifty patients in each group.

Randomization, blinding, and intervention

Patients were enrolled into the study as per the inclusion criteria. Written informed consent was taken from each patient. Each patient was instructed to pick up an envelope at random from a box containing 100 opaque envelopes annotated on the inside as “test” in fifty and “control” in the other fifty. Furthermore, each envelope had a unique patient identification number endorsed. Each “test envelope” contained one tablet of 200 mcg misoprostol, and each “control envelope” had clotrimazole vaginal pessary 100 mg which is commonly used for treating vaginal candidiasis. Clotrimazole is not known to have any action on cervical ripening. Both these tablets are similar in appearance, size, shape, and color. In order to ensure uniformity, the same brand of test medicine was used in all fifty patients and likewise in the control group. The tablet was inserted 4 h before the procedure into the posterior vaginal fornix by the patient herself. Patients were instructed to wet the tablet with a few drops of tap water before insertion. Necessary assistance was provided by the nurse in charge of the front desk. The patient and the surgeon were blind about which arm the patient belonged to. All office hysteroscopies were done by a single surgeon using 3.2-mm compact hysteroscope [Figure 1] employing vaginoscopy technique with normal saline as distension medium. Hysteroscopic findings of each patient were recorded with the unique patient identification number which was disclosed to him by the nurse.

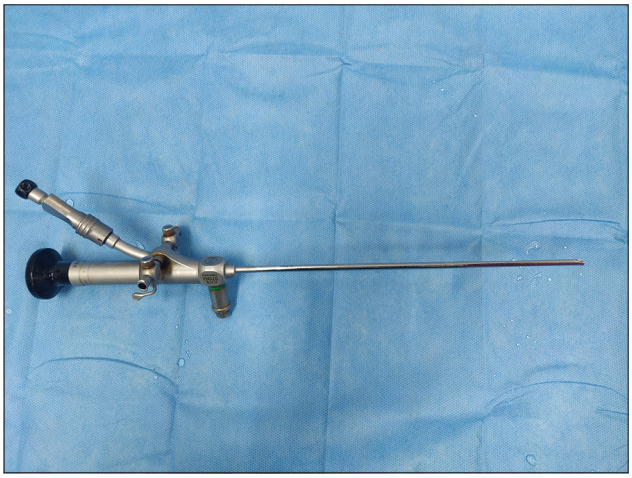

Figure 1: A 3.2-mm compact hysteroscope

Ease of doing the procedure was judged by the surgeon as a numerical score ranging from "0" to "5" on a Likert scale where "0" represented "very easy" and "5" represented "very difficult." The entire procedure was timed with a stopwatch, and four-time points were noted: T0 = beginning of the procedure when the hysteroscope touched the labia, T1 = when the hysteroscope touched the external os, T2 = when the scope left the cervix at the point of passing the internal os and entering uterine cavity, and T3 = when the scope was withdrawn from the vaginal canal after completion of the procedure. Duration of cervical passage and total time taken for the procedure were noted down. The procedure was considered as "failed" if uterine cavity could not be entered, if assistance with speculum and tenaculum was found necessary, or if additional cervical dilatation was required. Pain during the procedure was recorded as per VAS of 0 to 10, where a VAS score of 4 or less was considered as comfortable, 5 to 7 was considered as moderately painful, and 8 to 10 was considered as intolerable pain. Pain at the point of negotiation of internal os (T2) was recorded separately. Any requirement of additional analgesia during the procedure was noted. Intraoperative complications such as laceration of the cervix, creation of false passage, uterine perforation, and syncope were recorded. The patient was reassessed after 30 min, and any adverse effect such as vaginal bleeding, nausea, vomiting, fever, or abdominal pain (VAS score) was noted. In order to assess the patient's satisfaction level, she was asked whether she would undergo the same procedure again if needed and whether she would recommend this procedure to any of her friends or relatives. Answers to this questionnaire were noted down in the proforma for data collection. All these patients were assessed at 1 h after the procedure for fitness for discharge. Just before leaving the operating room, the patient would hand over the empty envelope at the front desk and the surgeon would mark the already filled up pro forma as "test" or "placebo" while matching the patient identification number.

Statistical analysis

Data analysis was carried out using statistical software (Software STATA version 12.0 by StataCorp, Texas, USA) Continuous variables were tested for normality assumption using the Kolmogorov–Smirnov test. Descriptive statistics such as mean, standard deviation, and range values were calculated for normally distributed data, and a comparison of mean values was done using Student's "*t*" independent test. For nonnormal data, median values and interquartile range values were computed and compared using nonparametric Mann–Whitney test. Categorical variables were presented as frequency and percentage values. A comparison of categorical variables was carried out using the Chi-square or Fisher's exact test as appropriate. For all statistical tests, a two-tailed probability of <0.05 was considered statistically significant.

Results

A total of 100 patients were enrolled in the study as per the inclusion criteria. After randomization and blinding, patients were allotted to either misoprostol group (n = 50) or placebo group (n = 50), as depicted in the flowchart [Figure 2]. Baseline characteristics of study participants and indications for hysteroscopy were comparable in both the groups [Table 1].

Ease of doing hysteroscopy was significantly better in the misoprostol group (difficulty score: 2.74 ± 1.20) as compared to placebo (difficulty score: 4.20 ± 1.10), P = 0.001. The time taken for negotiating the internal os (cervical passage time) was found to be significantly shorter in the misoprostol group (6.20 ± 5.21 s) as compared with placebo (14.78 ± 11.84 s), P = 0.001. However, there was no significant difference in the total time taken for the procedure: 1.80 ± 1.20 min in placebo and 1.40 ± 0.70 min in the misoprostol group, P = 0.121.

The overall VAS score was significantly lower in the misoprostol group (2.64 ± 1.62) as compared to placebo (4.90 ± 1.90), P = 0.001. Moreover, the VAS score at the point of passing internal os was significantly lower in the misoprostol group (2.82 ± 1.39) as compared to placebo (4.94 ± 1.96), P = 0.001.

Misoprostol had a significant positive effect on satisfaction level of patients. Majority of the women in the misoprostol group, 76% (n = 38), expressed their willingness to undergo the procedure again, if required, versus 18% (n = 9) in placebo, P = 0.001. Furthermore, 78% (n = 39) of women in the misoprostol group would recommend the procedure to their friends and relatives versus 36% (n = 18) in placebo, P = 0.001 [Table 2].

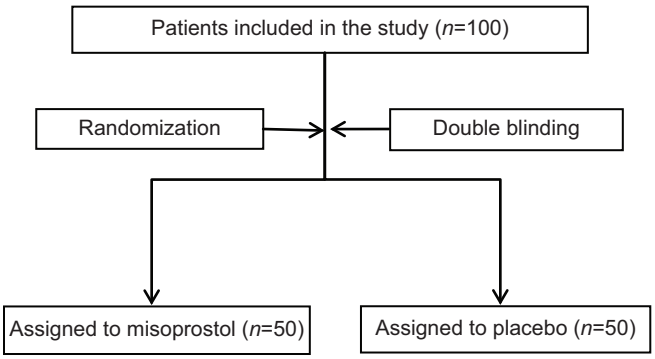

Figure 2: Flowchart depicting patient enrollment

There was no significant complication in either of the groups. Only one patient in the misoprostol group complained of abdominal cramps and nausea in the immediate postoperative period, and two patients in the placebo group had mild lower abdominal pain which was statistically not significant.

Discussion

Office hysteroscopy is a very useful diagnostic tool in the management of many frequent problems seen in gynecology such as infertility, recurrent pregnancy loss, and menstrual irregularities. The procedure is relatively simple and can be quite easily done without anesthesia in a day-care setting for most women. Ease of doing office hysteroscopy without anesthesia and at the same time causing no or minimal discomfort to the patient is the major point of attraction. However, a frequent problem encountered is a difficult entry into the endometrial cavity due to a resistant cervix, especially in premenopausal nulliparous and postmenopausal women. Although it is possible to dilate the canal mechanically, the patient may experience pain, thus making it difficult to proceed without analgesia or anesthesia. The resistant cervix also represents a recognized risk for its laceration or uterine perforation.[5] In order to overcome this issue, a narrow diameter hysteroscope can be used where the operator can perform an adequate examination without cervical preparation or analgesia. In office hysteroscopy, miniature hysteroscope with a diameter of 2.7 mm with 3–3.5-mm outer sheath is recommended without routine cervical preparation.[2] A systematic review by Paulo *et al*. of 8 studies including more than 2000 patients who underwent office hysteroscopy without anesthesia concluded that 3.5-mm rigid mini-hysteroscopes are associated with significantly less pain than conventional 5-mm hysteroscope.[6] There are various other studies which compared efficacy, acceptability, and diagnostic accuracy of smaller diameter hysteroscopes versus conventional one with a similar outcome.[7,8] In our study, we used a 3.2-mm compact hysteroscope, and there was no procedure failure in either of the study groups.

Even after using a smaller diameter hysteroscope, patients may perceive pain and discomfort if vaginal speculum and tenaculum are used to hold the cervix. Employing a "vaginoscopic" technique is one such method described by Bettochi and Selvaggi in 1997 to reduce pain and discomfort to the patient during hysteroscopy.[9] A randomized control trial by Sagiv *et al*. compared the vaginoscopic approach with traditional hysteroscopy and found that there was significantly reduced pain scores in vaginoscopic approach.[10] In our study, all the hysteroscopies were done with vaginoscopic approach.

Table 1: Baseline characteristics of patients and indications for hysteroscopy

Characteristic	Test (*n*=50)	Placebo (*n*=50)
Age, mean (SD)	28.96 (4.3)	29.86 (4.6)
BMI, mean (SD)	23.02 (1.8)	23.6 (2.0)
Indication of hysteroscopy, *n* (%)		
Infertility	39 (78)	40 (80)
Recurrent pregnancy loss	7 (14)	8 (16)
Menstrual irregularities	4 (8)	2 (4)

SD: Standard deviation, BMI: Body mass index

Table 2: Outcome measures comparison in both groups, expressed as mean (standard deviation) unless specified

Evaluation criteria	Test (*n*=50)	Placebo (*n*=50)	*P*
Difficulty score	2.74 (1.20)	4.20 (1.10)	0.001
Cervical passage time (sec)	6.20 (5.21)	14.78 (11.84)	0.001
Overall time (min)	1.40 (0.70)	1.80 (1.20)	0.121
VAS at T2 (internal os)	2.82 (1.39)	4.94 (1.96)	0.001
Overall VAS	2.64 (1.62)	4.90 (1.90)	0.001
Side effects, *n* (%)	1 (2)	2 (4)	Insignificant
Complications	Nil	Nil	Insignificant
Would undergo the procedure again if required, *n* (%)	38 (76)	9 (18)	0.001
Would recommend the procedure to friend or relative, *n* (%)	39 (78)	18 (36)	0.001

VAS: Visual Analog Scale

Difficulty in negotiating the internal os is a frequently encountered problem in hysteroscopy. There seems to be a useful effect of misoprostol on cervical ripening in nulliparous premenopausal women, although the evidence is conflicting. Many authors have evaluated the use of misoprostol for cervical preparation before hysteroscopy. One meta-analysis of 10 studies concluded that misoprostol leads to greater cervical dilatation and decreased need for additional dilatation.[11] Waddel *et al*. in their randomized double-blind trial concluded that vaginal application of misoprostol significantly reduced the force required to dilate the cervix.[12] In our study, we found that the ease of doing hysteroscopy was significantly better in the misoprostol group as compared to placebo ($P = 0.001$).

Pain relief in office hysteroscopy has been extensively studied. A few studies have examined the effectiveness of misoprostol in reducing pain experienced during office as well as operative hysteroscopy. In premenopausal nulliparous women, studies have found either 200, 400, or 1000 mcg of vaginal misoprostol or 400 mcg of oral misoprostol given at least 9 to 12 h preoperatively to be superior to placebo.[13-19] Even though a positive effect

of misoprostol on pain relief was established in most of these studies, the studied populations were diverse and sample sizes were small. In many of these studies, 400 mg of misoprostol was administered 12–24 h before the procedure, and there was a significant pain relief. In our study, 200-mcg misoprostol was self-administered vaginally by the patient 4 h before the procedure, and there was significantly reduced pain at the point of negotiation of internal os as well as during the entire procedure.

Ji Young Hwang *et al*., in their randomized double-blind trial, found that misoprostol-related adverse effects were more with 400 mcg cohort as compared to 200 mcg.[20] Ying Hua *et al*. in their systematic review and analysis of 14 randomized control trials showed that the use of misoprostol before hysteroscopy resulted in a statistically significant decrease in the rate of cervical lacerations and creation of false passage compared to placebo or no medication.[21] In the same review, pooled analysis revealed that side effects of misoprostol such as mild abdominal pain, bleeding, nausea, diarrhea, and fever were significantly more frequent in the misoprostol group compared with placebo or no medication. In our study, we used 200-mcg misoprostol single application in the test group, and there was no significant side effect or complications including cervical laceration or creation of false passage.

Conclusion

This double-blind randomized control trial demonstrates the effectiveness of misoprostol in cervical preparation for office hysteroscopy after a short application time of 4 h. Preoperative cervical preparation with 200 mcg of misoprostol vaginal application 4 h before office hysteroscopy in premenopausal nulliparous women significantly reduces the difficulty encountered in negotiating the cervical canal. Further, it significantly reduces the pain experienced by the patient at the point of passage through internal os as well as throughout the procedure. There are no significant side effects with 200-mcg vaginal application of misoprostol. Hence, we conclude that in order to facilitate office hysteroscopy with a 3.2-mm compact hysteroscope, 200-mcg vaginal misoprostol just 4 h before hysteroscopy is sufficient for the ease of doing hysteroscopy and for reducing the pain. However, we suggest further studies on larger cohorts to gather concrete evidence on the subject matter.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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