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Determination of the Effect of Vaginal Misoprostol in Cervical Ripening Before the Operative Hysteroscopy in Premenopausal Women without History of Normal Vaginal Delivery

Mansoureh Vahdat [1], Abolfazl Mehdizadeh Kashi [1, *], Mahboubeh Saberifard [1], Shahla Chaichian [1]

[1] Minimally Invasive Surgery Research Center, Iran University of Medical Sciences. Tehran, IR Iran

*Corresponding author: Abolfazl Mehdizadeh Kashi, Minimally Invasive Surgery Research Center, Iran University of Medical Sciences. Tehran, IR Iran. Tel: +98-2166509283, Fax: +98-9121176057, E-mail: amehdizadehkashi@yahoo.com.

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Background: With the advent of hystroscopic surgery, abnormalities confined to the uterine cavity such as endometrial polyps, submucous myomas, uterine septae and synechia, were supposed to be treated effectively. Diagnostic hysteroscopy is the gold standard for investigating the intrauterine diseases as it allows for biopsy and removal of lesions.

Objectives: Forty premenopausal women without the history of normal vaginal delivery eligible for operative hysteroscopy were recruited. Patients were randomly assigned to receive 400 microgram vaginal misoprostol or no treatment, 10-12 hours before operative hysteroscopy. Main outcome measures were cervical width and duration of cervical dilatation.

Patients and Methods: Forty premenopausal women without the history of normal vaginal delivery eligible for operative hysteroscopy were recruited. Patients were randomly assigned to receive 400 microgram vaginal misoprostol or no treatment, 10-12 hours before operative hysteroscopy. Main outcome measures were cervical width and duration of cervical dilatation.

Results: Patients using vaginal misoprostol in treatment group had significantly greater cervical width compared with control group patients (mean: 7.85 vs. 5.80, P = 0.024).

Conclusions: The mean duration of cervical dilatation in misoprostol group was significantly lower than that of control group (30.50 s vs. 52.75 s, P = 0.030). The frequency of complications was similar in treatment and control groups.

Keywords: Misoprostol; Cervical Ripening; Hysteroscopy

1. Background

With the advent of hystroscopic surgery, abnormalities confined to the uterine cavity, such as endometrial polyps, submucous myomas, and uterine septae and synechia, were supposed to be treated effectively (1). Diagnostic hysteroscopy is the gold standard for investigating the intrauterine diseases as it allows for biopsy and removal of lesions. The method revealed a sensitivity ranging from 84% to 97% and specificity ranging from 88% to 93% in order to detect the intrauterine lesion (2). One of the major problems of operative hysteroscopy is the difficultly to enter the internal cervical os with an operative hysteroscope, especially a resectoscope. Accessing to the uterine cavity requires insertion of the resectoscope through the internal cervical os, which necessitates the cervical dilatation exceeding up to hegar 8-10 (1). The common complications encountered during the operative hysteroscopy are mainly related to the difficulty of cervical dilatation and entering the internal cervical os (3, 4). These complications include cervical injury, creation of flash tract, and uterine perforation. In the past, laminaria and prostaglandins of the E series have been proven to be effective for dilating and softening the cervix. However, laminaria may not be suitable for women who have marked cervical stenosis or shellfish allergy, and prostaglandins such as sulprostone and dinoprostone are expensive and require special storage condition (1). Misoprostal is a synthetic PGE1 analog that has been approved for the treatment and prevention of peptic ulcer that is caused by nonsteroidal anti- inflammatoty drugs. Currently, misoprostol is widely used in obstetrics and gynecology for medical abortion in the first and second trimesters of pregnancy and cervical priming before vacuum aspiration or dilation and treatment of postpartum hemorrhage (2, 5-7). The advantage of misoprostol over other prostaglandin analogues is that it is cheaper, stable at room temperature, and also available in oral-

Implication for health policy/practice/research/medical education:
This study aims to access the effectiveness of vaginal misoprostol in cervical ripening before the operative hysteroscopy in premenopausal women without history of normal vaginal delivery.

tablet form (1, 4, 8). Various studies have shown that misoprostol also has a beneficial effect on pre-operative cervical ripening in women who require hysteroscopic surgery (8-12). Vaginal misoprostol had been proved to be more effective than dinoprostone for cervical priming in nulliparous women before hysteroscopic surgery (4). The use of vaginal misoprostol before hysteroscopy reduces the pain and the force needed to dilate the cervix (6), cervical resistance, the need for cervical dilation (9) and also reduced pain severity during hysteroscopy (10). But two meta-analysis of misoprostol in the operative hysteroscopy concluded that in spite of beneficial effect of misoprostol on cervical dilatation or surgical complications, current evidence does not support routine use of misoprostol before the operative hysteroscopy (11, 12). Although misoprostol is made for oral administration, several pharmacokinetic studies have shown that the plasma concentration of the active metabolites is sustained for a longer period after vaginal administration. From these studies, it is expected that vaginally administered misoprostol should be more effective for achieving a favorable cervical consistency (13).

2. Objectives

The aim of the present study is to evaluate the efficacy of vaginal misoprostol on cervical ripening before the operative hysteroscopic procedure.

3. Patients and Methods

This study was performed as a single-blinded clinical trial study with easy sampling in Hazrat Rasol Hospital of Tehran with patients referring to the Gynecology clinic, they were candidate for the operative hysteroscopy and had inclusion criteria of the study, and were categorized into two groups. There were 20 patients in each group. A medical, obstetrical, and gynecological history was taken from the patients with uterine pathologies who were candidate for the operative hysteroscopy and then complete physical examination was done one day before surgery. The inclusion criteria were being premenopausal with no previous NVD (normal vaginal delivery); having a definite indication for hysteroscopy ;and being in good general health . Exclusion criteria were contraindications to prostaglandin treatment (server Asthma, glaucoma, cardiac disease,hypertension, or renal failuse),server uterovainal prolapse, and previous history of cervical operation or cervical incompetence. The patients were assigned to two groups randomly. In the study group (n = 20), 400 mg of misoprostol was inserted in the posterior vaginal fornix at least 10-12 h before hysteroscopy. No patient received any agent before the surgery in the control group (n = 20). The hysteroscopists were blinded to the priming method and grouping patients. Patients were asked about adverse effects such as nausea, vomiting, vaginal bleeding, diarrhea, and uterine cramps prior to general anesthesia. The hysteroscopy and indicated procedure were performed under general anesthesia by two surgeons in all patients. Operative hysteroscopies were performed using Endomat resectoscope with an 11 mm outer sheath diameter and 30 ° forward oblique lenses. Primary outcome measures in this study were postoperative cervical width and dilatation time. Cervical width was assessed by performing cervical dilatation, starting with four Hegar dilator and subsequently inserting larger hegar dilator through internal os, until resistance was felt. The hegar dilator that was one size smaller (i.e., the largest one that could be passed without resistance) was taken as the initial cervical width. Dilatation time was the time from the beginning of dilatation till inserting the hysteroscope. Other outcome measures include the number and percentage of patients who require cervical dilatation to allow for passage of the resectoscope, complications during dilatation and the operative hysteroscopy (creation of a false tract, uterine perforation, and cervical tears), and associated side effects. Finally, the mean of this variable were compared in two groups to determine the efficacy of vaginal misoprostol for cervical ripening. Before the beginning of the study; all patients were informed about study aims, methods, and treatment advantages and adverse effects,, and a written consent was obtained in order to agree to participate in the study.

3.1. Statistical Analysis

Data analysis was performed by using the statistical package for the Social sciences (SPSS, Version 20). Mean cervical width and dilatation time of both groups were compared by using the independent t-test and chi square test used for comparing secondary outcome measures in two groups. $P < 0.05$ was considered statistically significant.

4. Results

A total of 40 patients scheduled for the operative hysteroscopy were divided two groups: 20 patients in the treatment group and 20 patients in the control group. Comparison of quantitative variables between two groups was as follows (Table1)The mean age in the vaginal misoprostol and control group was 39.8 years and 39.3 years respectively; that this difference was not statistically significant (P = 0.89). The mean parity of both groups was similar (2.2 in misoprostol group vs. 2.1 in control group, P = 0.87). Patients using vaginal misoprostol in the treatment group had significantly greater cervical width compared with control group patients (mean: 7.85 vs. 5.80, P = 0.024). The mean duration of cervical dilatation in misoprostol group was significantly lower than control group (30.50 s vs. 52.75 s, P = 0.030). There was statistically significant difference between two groups regarding the need for cervical dilatation (P = 0.019). The prevalence of hysteroscopically found anomalies in both groups is shown in Table 2. Four patients (20%) in the misoprostol

group and three patients (15%) in the control group had endometrial polyp. Four patients (20%) in each group had endometrial hyperplasia. In each group, one patient (5%) had submucosal myoma. No patient in the misoprostol group and four patients (20%) in the control group had uterine septum. Adhesions were found in two patients (10%) of the misoprostol group and not found in patients of the control group. One patient (5%) in the misoprostol group and no patients of the control group had bicornuate uterus. More than one anomaly was found in two patients (10%) of each group. Six patients (30%) in each group were found to have no anomaly. The frequency of complications was similar in both the treatment and control groups: six patients developed vaginal bleeding. One had uterine cramping, one had nausea, and one had diarrhea after procedure in treatment group whereas only two patients of the control group developed vaginal bleeding and there was no other complications (Table 3).

Table 1. Comparison of Calculated Variables in two Groups

Treatment group	Misoprostol, Mean ± SD	Control, Mean ± SD	P value
Age, y	39.89 ± 3.04	39.30 ± 2.42	0.89
Parity	2.2 ± 0.48	2.1± 0.42	0.87
Cervical width	7.85 ± 0.62	5.80 ± 0.60	0.02
Dilatation time	30.50 ± 6.67	52.75 ± 7.24	0.03

Table 2. Prevalence of Different Anomalies in two Groups

Anomaly type	Misoprostol, No. (%)	Control, No. (%)
No anomaly	6 (30)	6 (30)
Polyp	4 (20)	3 (15)
Hyperplasia	4 (20)	4 (20)
Myoma	1 (5)	1 (5)
Septum	0	4 (20)
Adhesion	2 (10)	0
Bicornuate uterus	1 (5)	0
More than one anomaly	2 (10)	2 (10)

Table 3. Comparison of Treatment Side Effects in two Groups

	Misoprostol, No.	Control, No.	P value
Vaginal bleeding	6	2	0.11
Nausea	1	0	0.31
Vomitting	0	0	
Diarhea	1	0	0.31
Uterine cramp	1	0	0.31

5. Discussion

Various studies have evaluated the beneficial effect of misoprostol on pre-operative cervical ripening in women who require hysteroscopic surgery: El_khayat et al. compared the efficacy of isosorbide mononitrate (IMN) and misoprostal for cervical priming before the hysteroscopy, and concluded that there was no significant difference between IMN and misoprostol with regard to the duration of application or difficult dilatation ;but there was a significant difference between IMN and misoprostol with regard to the baseline cervical dilatation (5mm for IMN and 8 mm for misoprostol)and duration of dilatation (73s for IMN and 49s for misoprostol) (5). Preutthipam et al. compared the efficacy of vaginal priming before the operative hysteroscopy in nulliparous women and concluded that vaginal misoprostol is more effective than dinoprostone for cervical priming in nulliparous women before hysteroscopic surgery and suggested to use vaginal misoprostol for cervical priming instead of dinoprostone (4). Waddell et al. found that the use of vaginal misoprostol before hysteroscopy reduces the pain and the force needed to dilate the cervix (6). Barcaite et al. evaluated the effectiveness of vaginal misoprostol for cervical priming before hysteroscopy in perimenopausal and postmenopausal women and concluded that vaginal misoprostol applied before hysteroscopy reduces cervical resistance and the need for cervical dilation in this women (9) da Costa et al.

studied the effect of misoprostol for cervical priming before hysteroscopy in postmenopausal women and found that previous use of misoprostol reduced the pain severity during hysteroscopy (10). Uckuyu et al. in a randomized controlled study found that administration of vaginal misoprostol before hysteroscopy proved to be effective in cervical ripening and reducing complication and failure rates (8). Selk et al. in a meta-analysis of misoprostol in the operative hysteroscopy concluded that despite the beneficial effect of misoprostol on cervical dilatation or surgical complications, current evidence does not support routine use of misoprostol before the operative hysteroscopy (12). In another systematic review and meta-analysis of randomized studies, with regard to comparing misoprostol versus placebo for cervical ripening prior to hysteroscopy, and according to its results after vaginal misoprostol administration, the need for cervical dilatation in the whole pre- and postmenopausal population, prior to either any type of hysteroscopy or only operative hysteroscopy, was decreased to a statistically significant degree. When premenopausal and postmenopausal women were studied separately, there was no significance, although for the postmenopausal women this was marginal. There was no difference in the duration of the procedure after the administration of misoprostol except in the operative hysteroscopy subgroup. Hysteroscopy complications such as perforation and cervical tears were not significantly less frequent after misoprostol, with the exception of cervical tears in the operative hysteroscopy subgroup. Therefore a beneficial effect of misoprostol cannot be clearly demonstrated in all women, but mainly in postmenopausal women undergoing operative hysteroscopy. Gkrozou et al. discussed that there is insufficient evidence to recommend the routine use of misoprostol before every hysteroscopy (11). The present study showed that before the operative hysteroscopy in premenopausal women, vaginally administered misoprostol is effective in cervical ripening, in terms of shorter cervical dilatation time and the need for cervical dilatation to Hegar number nine, and fewer women requiring dilatation .We observed that the number of patients who needed further cervical dilatation was significantly lower in those who were treated with vaginal misoprostol. The post-treatment cervical width was significantly greater after vaginal application of misoprostol that is an indicator of more cervical ripening. We had no more complication rates during cervical dilatation in vaginal misoprostol group in comparison with control group and the drug related adverse effects rates were not significantly higher in treatment group. Therefore, administration of vaginal misoprostol is effective in cervical ripening. We suggest to use vaginal misoprostol for cervical priming, as it is effective, easy to use, inexpensive, and low risk.

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Authors' Contribution

The first author and corresponding author contributed 80% and the others 50%.

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