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Original Research Article

Comparative study of the effectiveness of two different dosage of sublingual misoprostal for cervical ripening before hysteroscopy

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ABSTRACT

Background: Hysteroscopy a minimally invasive approach for evaluating uterine cavity, and has become an indispensable diagnostic and therapeutic procedure. The main limiting factor while performing office hysteroscopy is the level of pain or discomfort encountered during the procedure. The pain is attributed mainly to the difficulty in entering the internal cervical os with the hysteroscope and while distending uterine cavity. It could be reduced if cervix is ripened before the procedure. The purpose of this prospective observational study was to compare the effectiveness, adverse effects and surgery-related complications associated with two different doses of sublingual Misoprostol (100 and 200 µg) given 2-4 hours before hysteroscopy.

Methods: A randomised comparative study was conducted in the department of Obstetrics and Gynaecology of ABVIMS and Dr. RML hospital New Delhi, from 1st November, 2018 to 31st March, 2020. One hundred and twenty women, fulfilling inclusion criteria were subjected to hysteroscopy. Women received either 100 µg (Group I) or 200 µg (Group II) of sublingual Misoprostol 2-4 hours prior to hysteroscopy. The primary outcome of the study was cervical dilatation as measured by the largest number of Hegar dilator that could be inserted without resistance at the beginning of procedure. The largest dilator that negotiated cervical canal without resistance at the beginning of procedure was recorded as the baseline cervical width. The secondary outcomes were subjective assessment of the surgeon of the ease of dilatation of cervix and adverse effects of drug (i.e. vaginal bleeding, shivering, fever and pain as measured on visual analog scale).

Results: The mean baseline cervical width as measured by first Hegar dilator that could be passed through the cervical canal without resistance was 6.6±0.62 mm in group I and 6.94±1.21 mm in group II respectively (p value=0.016). Adverse effects like vaginal bleeding, shivering was more in group II compared to group I. No statistically significant difference was found between group I and II with regards to visual analog scale.

Conclusions: 100 µg Misoprostol can be used for cervical ripening prior to hysteroscopy with minimal adverse effects.

Keywords: Cervical ripening, Hysteroscopy, Misoprostol, Sublingual

INTRODUCTION

Hysteroscopy is a minimally invasive approach for evaluating uterine cavity for various gynaecological conditions, and has become an indispensable diagnostic and therapeutic procedure. Hysteroscopy has evolved as a standard procedure for diagnosis and treatment of intrauterine pathologies such as polyps, fibroids, septae, adhesions, evaluation of abnormal uterine bleeding, evaluation and treatment of infertility, removal of an intrauterine device or foreign body. The diameter of diagnostic hysteroscope ranges from 1 to 5 mm and operative hysteroscope can be as large as 8-10 mm. The main limiting factor while performing hysteroscopy is the

level of pain or discomfort a patient feels during or soon after the procedure. The pain encountered during the procedure are related to the difficulty in negotiating the internal cervical os with the hysteroscope especially in nulliparous and postmenopausal women. Other complications include cervical tear, creation of false passage and uterine perforation.[1] Jansen et al. reported that uterine perforation was the most frequent surgical complication with a rate of 0.76%; 54.5% of those occurred during entry.[2] Half of the complications were entry-related, so attention has to be paid to the method of entry with hysteroscope.[3] The incidence of these complications could be reduced if the cervix is ripened before the procedure.[4]

Cervical priming prior to hysteroscopy lessens the need of further cervical dilation pre-operatively, lessens the complications associated with the entry of the hysteroscope into the cervical os and offer minimal side effects and minimise the chances of failure to complete the procedure.[5] Various options available for cervical priming before hysteroscopy include osmotic dilators (i.e. laminaria), prostaglandins (PGs) and mifepristone.

Misoprostol, PGE1 analogue has emerged as best suited PG as it has a short half-life (T1/2 of 20-40 minutes), fewer side effects, stable at room temperature and economical. Different doses of Misoprostol 100, 200, 400, and 800 µg have been used for cervical ripening prior to hysteroscopy. It can be administered by various routes i.e. oral or sublingual or rectal or vaginal route. Sublingual route for administration of Misoprostol has been found to have the shortest time to peak concentration, the highest peak concentration and the greatest bioavailability when compared to other routes. It has been shown to be more effective for cervical priming compared with oral administration and equally effective as vaginal administration.[6]

Hence, the purpose of this prospective observational study was to compare the effectiveness, adverse effects and surgery-related complications associated with two different doses of sublingual Misoprostol (100 and 200 µg) given 2-4 hours before hysteroscopy.

METHODS

This randomised comparative study was conducted in the department of Obstetrics and Gynaecology of ABVIMS and Dr. RML hospital New Delhi, from 1st November, 2018 to 31st March, 2020. The study was approved by the institutional ethical committee (TP (MD/MS) (92/2018)/IEC/PGIMER/RMLH 1926) and the research review board. One hundred and twenty premenopausal women were selected according to inclusion criteria and were divided into 2 study groups, 60 women in each group. Group I received tab. misoprostol 100 µg sublingually for cervical ripening 2-4 hours before hysteroscopy and group II received Tab. Misoprostol 200 µg given sublingually for cervical ripening 2-4 hours before hysteroscopy. Women with any possible contraindications to use of prostaglandins (i.e. cardiovascular disease, renal failure, bronchial Asthma), postmenopausal women, women with previous cervical surgery or using other products that could affect the consistency of the cervix such as local estrogen, GnRH were excluded from the study. Misoprostol was administered by the investigator sublingually 2-4 hours before starting the hysteroscopy. Before starting the hysteroscopy, blood pressure and pulse were recorded and records were made of any other complaints i.e bleeding, shivering and fever. All the procedures were performed under paracervical block and tab. meftal spas was given half an hour before the procedure.

Single surgeon (IC) fully trained and experienced in the field of hysteroscopy performed the procedure in both groups to reduce individual variability. Surgeon performing the hysteroscopy was unaware of the dose of Misoprostol that had been given to the patient to reduce the bias.

Hysteroscopy was performed with HOPKINS II straight forward 5 mm, 0 degree/30-degree telescope (KARL STORZ, GERMANY). The hysteroscope was attached with light source and distending media source. An attempt was made to pass the hysteroscope directly through the cervix, if the surgeon found any difficulty while inserting the hysteroscope serial dilatation was performed using Hegar dilators.

The primary outcome of the study was cervical dilatation as measured by the largest number of Hegar dilator that could be inserted without resistance at the beginning of procedure. The largest dilator that negotiated cervical canal without resistance was recorded as the baseline cervical width. The secondary outcomes were subjective assessment of the surgeon of the ease of dilatation of cervix and adverse effect of drug. Ease to dilate the cervix was estimated by the surgeon and was recorded on 5-point Likert scale (1=very difficult, 2=difficult, 3=fair, 4=easy, 5=very easy). After completion of procedure patient was assessed on pain analogue score to determine the level of pain experienced with a score of zero to 10 (Figure 1). Note was made of other adverse effects of misoprostol i.e. vaginal bleeding, pain, shivering and fever which were recorded.

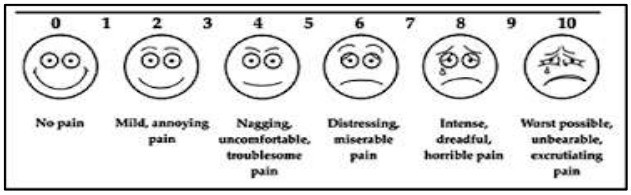

Figure 1: Pain analogue score pictogram.

The data was entered in MS EXCEL spreadsheet and analysis was done using Statistical package for Social Sciences (SPSS) version 21.0.

Statistical analysis

Categorical variables were presented in number and percentage (%) and continuous variables were presented as mean±SD and median. Normality of data was tested by Kolmogorov-Smirnov test. If the normality was rejected then non parametric test was used. Statistical tests were applied on both variables: quantitative variables were compared using Mann-Whitney test (as the data sets were not normally distributed) between the two groups. Qualitative variables were compared using Chi-Square test/Fisher's Exact test.

A p value of<0.05 was considered statistically significant. The data was entered in MS EXCEL spreadsheet and analysis was done using Statistical Package for Social Sciences (SPSS) version 21.0.

RESULTS

Baseline characters including age, parity and BMI, Co-morbidities and mode of delivery were compared in both groups (Table 1). Mean age of women who underwent hysteroscopic procedure was 32.28±6.03 years. in both group I and II (p value=1). There was no statistically significant difference regarding parity of women between group I and II (p=0.666). There was no statistically significant difference between group I and II regarding indication of hysteroscopy (p value=0.278). In group I, 44 patients (73.33%) had AUB, 14 patients (23.33%) had infertility and 2 patients (3.33%) had misplaced IUCD as an indication for hysteroscopy. In group II, 46 patients (76.67%) had AUB, 10 patients (16.67%) had infertility, 1 patient (1.67%) had misplaced IUCD and 3 patients (5%) had RPL as an indication for hysteroscopy.

Mean baseline cervical width as measured by largest no. of Hegar dilator that could be inserted in the cervical canal without resistance was 6.6 ±0.62 mm in group I and 6.94±1.21 mm in group II respectively. There is statistically significant difference present between group I and II regarding mean baseline cervical width after cervical ripening with two different doses (p value=0.016) (Table 2).

Table 1: Comparison of baseline characteristics between group I and II.

Variables	Group I	Group II	P value	Test performed
Mean age ±SD	32.28±6.03	32.28±6.03	1	Mann Whitney test;1800
Nulliparous	15 (25%)	13 (21.67%)	0.666	Chi square test,0.186
Multiparous	45 (75%)	47 (78.33%)	0.666	Chi square test,0.186
Mean BMI±SD	23.08±1.89	23.08±1.4	0.845	Mann Whitney test;1763

Table 2: Comparison of mean baseline cervical width between group I and II.

First Hegar No.	Group I (n=60)	Group II (n=60)	Total	P value	Test performed
Mean±SD	6.6±0.62	6.94±1.21	6.77±0.97	0.016	Mann Whitney test;1352.5
Median (IQR)	6.5 (6.5-7)	7 (6-8)	7 (6-7.5)		
Range	5-8	3-10	3-10		

Table 3: Comparison of adverse effects of Misoprostol between group I and II.

Adverse effects	Group I (n=60)	Group II (n=60)	Total	P value	Test performed
Bleeding	17 (28.33%)	47 (78.33%)	64 (53.33%)	<0.0001	Chi square test,30.134
Shivering	0 (0%)	19 (31.67%)	19 (15.83%)	<0.0001	Fisher Exact test
Fever	0 (0%)	2 (3.33%)	2 (1.67%)	0.496	Fisher Exact test

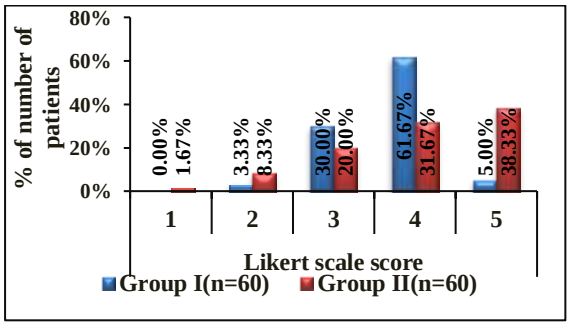

Figure 2: Comparison of ease of dilatation of cervix on 5-point Likert scale score between group I and II.

In group I, none of the patient had very difficult entry, 2 patients (3.33%) had difficult entry, 18 patients (30%) had fair entry, 37 patients (61.67%) had easy entry and 3 patients (5%) had very easy entry. In group II, 1 patient (1.67%) had very difficult entry, 5 patients (8.33%) had difficult entry, 12 patients (20%) had fair entry, 19 patients (31.67%) had easy entry and 23 patients (38.33%) had very easy entry. Results were statistically significant for Likert scale score 4 (easy) (p value=0.0019) and 5 (very easy) (p value<0.0001) (Figure 2). In group I majority of patients i.e. 37 patients (61.67%) had easy entry compared to 19 patients (31.67%) in group II and in group II, majority had very

easy entry i.e. 23 patients (38.33%) compared to 3 patients (5%) in group I. 5 patients (8.33%) in group I had distention leakage while 22 patients (36.67%) in group II had distention leakage. There was statistically significant difference between group I and II regarding distention leakage (p value=0.0002). This distention leakage is due to over-dilatation of cervix. In our study vaginal bleeding was experienced by significantly higher number of patients in group II (78.33%) compared to only 28.33% in group I (p<0.0001). Among 60 patients in group I, 17 patients (28.33%) experienced vaginal bleeding and none of the patient had experienced shivering and fever. Among 60 patients in group II, 47 patients (78.33%) experienced vaginal bleeding, 19 patients (31.67%) had experienced shivering and 2 (3.33%) had fever (Table 3).

Shivering was experienced by 31.67% patients in group II while none of the patients experienced shivering in group I (p<0.0001). Fever was experienced by 2 patients in group II and none in group I had such complaint (p=0.496). Statistically significant difference was present between group I and II regarding vaginal bleeding and shivering (p value <0.0001). There was no statistically significant difference present for fever between group I and II.

Mean visual analog score of group I was 2.7±1.09 and of group II was 2.77±1.28 (p value=0.997). No statistically significant difference was found between group I and II with regards to visual analog score (Figure 3).

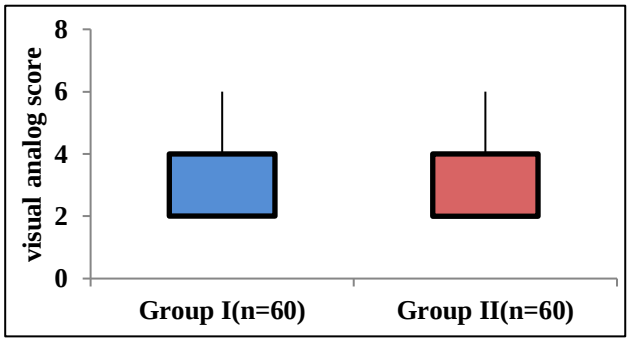

Figure 3: Comparison of pain score between group I and II (non-parametric variable, Box-whisker plot).

There was no statistically significant difference regarding cervical perforation, creation of false passage and abandoning of procedure between group I and II.

DISCUSSION

Hysteroscopy is a minimally invasive approach that can be used for both diagnostic and operative purposes. With the emergence of minimally invasive gynaecology surgery as a key benefit to patient care, operative hysteroscopy has earned an important role. Acceptability and feasibility are limited by difficulty in cervical dilatation; it represents a real challenge during operative as well as office hysteroscopy. In present study, 120 patients who required hysteroscopy were selected according to inclusion criteria and divided into group I and II, 60 patients in each group. In group I, patients received sublingual Misoprostol 100 µg 2-4 hours prior to procedure and in group II, patients received 200 µg sublingual Misoprostol 2-4 hours prior to procedure. The same surgeon had performed all the procedures to avoid inter-observer variation.

In present study, maximum patients had AUB as indication for hysteroscopy (73.33% in group I and 76.67% in group II) followed by infertility (28.33% in group I and 16.67% in group II) and rest had misplaced intrauterine contraceptive device (3.33% vs 1.67%) or recurrent pregnancy loss (0 vs 5%) as indication. Kesrouani et al reported in their study abnormal vaginal bleeding (40%) as most common indication followed by polyps (33%), myoma (13%), endometrial thickening (10%).[7] Study done by Ayyad et al had primary infertility (80%) as main indication for hysteroscopy.[8] Similarly study conducted by Al Hilli et al documented irregular vaginal bleeding (48.9%) followed by infertility (22.7%) as an indication of hysteroscopy.[9]

In our study mean baseline cervical width as measured by largest Hegar dilator to pass the cervical canal without resistance was 6.6±0.62 mm in group I and 6.94±1.21 mm in group II respectively. There is statistically significant difference present between group I and II regarding mean baseline cervical width (p value=0.016).

Study conducted by Bisharah et al who randomised 40 patients in two groups, one who received 100 µg Misoprostol sublingually and other received placebo 12 hours before operative hysteroscopy, found no difference in baseline diameter of the cervical opening between the Misoprostol group (4.0±0.1mm) and the control group (4.2±0.2 mm). This may be related to Leuprolide's hypoestrogenic effect given in this study 4 weeks prior to hysteroscopy.[12] Similarly a randomized controlled trial performed by Ayyad et al compared 200 µg sublingual Misoprostol with placebo. They found no statistical difference between both groups in number of patients requiring cervical dilatation and ease of introduction of the hysteroscope.[8]

Similar results were obtained in the study conducted by Gupta et al comparing 200 µg Misoprostol with 400 µg by vaginal route and found the mean base line cervical width in group 1(200 µg) was 6.41±0.29 mm while in group 2 (400 µg) was 6.43±0.21mm (p=0.084). No statistically significant difference found in mean baseline cervical width between group I and II.[10] Similarly, Hua et al conducted a meta-analysis to assess the effect of Misoprostol for cervical ripening prior to hysteroscopy. They found that the mean cervical dilatation was significantly more in the Misoprostol group compared to placebo or no medication (mean dilatation=1.34 mm; 95% CI:0.55-2.14) irrespective of the route of

administration. While comparing different doses by sublingual route, they concluded that in the 200 µg subgroup (MD 2.20 mm; 95% CI 1.21–3.19; I2=94%) or the 400 µg subgroup (MD 2.20 mm; 95% CI 1.14–3.26; I2=92%), the cervical width was significantly greater than that in the placebo or no medication group.[11]

In present study, in group I, 37 patients had easy entry (61.67%) as compared to 19 patients (31.67%) in group II. Ease of cervical entry as measured on 5- point Likert scale score showed statistically significant difference between group I and II (p value=0.0019). In group II, 23 patients (38.33) had very easy entry as compared to 3 patients (5%) in group I. Ease of cervical entry as measured on Likert scale score showed statistically significant difference between group I and II (p value<0.0001). Study conducted by Gupta et al demonstrated in group 1 (200 µg) 26.6% had very easy entry, 53.4% had easy entry while in group 2 (400 µg), 30% had very easy entry, 43.4% had easy entry.[10] In the study conducted by Khayat et al, 200 µg (group I) vaginal Misoprostol was compared with 400 µg (group II) for cervical priming prior to hysteroscopy. They found use of 400 µg vaginal misoprostol significantly facilitated the procedure of office hysteroscopy. Cervical entry (Likert scale) was easier in group II (4.02±0.832) than in group I (2.98±0.540) (p<0.001). Patient acceptability (Likert scale) was higher in group II (3.53±0.638) than in group I (3.03±0.495) (p<0.001).[13]

In the present study, among 60 patients in group I, 17 patients (28.33%) experienced vaginal bleeding and none of the patient had experienced shivering and fever. Among 60 patients in group II, 47 patients (78.33%) experienced vaginal bleeding and 19 patients (31.67%) had experienced shivering and 2 (3.33%) had fever. Statistically significant difference was present between group I and II regarding vaginal bleeding and shivering (p-value<0.0001). There was no statistically significant difference regarding fever between group I and II. Mulayim et al reported 2 patients (7.45%) in the placebo group and 3 patients (12%) in the Misoprostol group had nausea. Cramping was seen only in 4 patients; although statistically this difference was not significant.[14] Study conducted by Gupta et al route to be meant concluded that adverse effects like abdominal pain, vaginal bleeding, shivering and fever were observed more often in group 2 (400 µg) compared to group 1(200 µg) (p=0.038).[10] Similar results were obtained in the study conducted by Kesrouani et al. They found that increasing the dose of misoprostol from 200 to 400 µg doubled the rate of side effects while no clinical benefit was noted.[7]

In present study pain score as measured on visual analog score for group I was 2.7±1.09 and of group II was 2.77±1.28. No statistically significant difference was found between group I and II with regards to pain score (p-value=0.997). Similar results were obtained in the study conducted by Hilli et al on effect of different doses of sublingual misoprostol on pain experience during office hysteroscopy. Pain score was significantly higher in patients who did not receive misoprostol 4.09 compared with those who received (2.36 and 2.13 for the 200 µg and 100 µg groups respectively). No statistical difference was found between the two doses of misoprostol regarding pain score.[9] Ayyad et al revealed that visual analog score was significantly lower in study group (200 µg) compared to control group (placebo) (3.67±2.36 vs 6.23±1.62 respectively).[8] Similarly, study conducted by Saha et al compared 400 µg vaginal Misoprostol with placebo. They found Only 3.61% patients complained of intolerable pain during dilatation in the study group while in control group 48.74% complained of intolerable pain and required anesthesia.[15]

CONCLUSION

On the basis of present study, 100 µg Misoprostol can be used for cervical ripening prior to hysteroscopy with minimal adverse effects. Future prospective, large, randomized controlled, multicenter studies are required to establish this observation.

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Ethical approval: The study was approved by the Institutional Ethics Committee

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