

## Ideal Time of Vaginal Misoprostol Administration in Nulliparous Women Undergoing Office Hysteroscopy: a Randomized Double Blind Placebo Controlled Study

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### ABSTRACT

**Background:** Hysteroscopy had the process of viewing, operating in the endometrial from a transapproach.

**Aim of the work:** to detect ideal time of misoprostol administration for priming in nulliparous cases prior by comparing between giving 400microgram 3hours, 6hours, 12hours before hysteroscopy.

**Patients and Methods:** randomized double-blind placebo-controlled study. This study had done on 198 cases to whom hysteroscopy had done as a part of investigation of (infertility, recurrent miscarriage or abnormal uterine bleeding). Those cases divided into three gatherings each gathering 66 cases, Gathering A, received 400µgm misoprostol 12hours before hysteroscopy, placebo 6hours, 3hours before hysteroscopy. Gathering B received 400µgm misoprostol 6hours before hysteroscopy, placebo 12hours, 3hours before hysteroscopy. Gathering C received 400µgm misoprostol 3hours before hysteroscopy, placebo 12hours, 6hours before hysteroscopy. Our main outcome measures had score(visual analogue scale), procedural time in minutes, bleeding, also to detect side critical of misoprostol, complication of its use.

**Results:** In gathering A which received 400µgm misoprostol 12hours, score had lower(2.6±1.3) compared to gathering B(5.3±1.3) compared to gathering C(7.3±1.2). Procedural time had shorter in gathering A(2.7±0.9) compared to gathering B(5.2±1.2) compared to gathering C(7.4±1.3), entry had easier in gathering A(4.2±0.7) compared to gathering B(3.5±0.5) compared to gathering C(2.5±0.6), baseline dilatation had greater in gathering A(5.9±0.8) compared to gathering B(4.7±1.1) compared to gathering C(3.9±0.8) bleeding had least in gathering A compared to gathering B compared to gathering C case acceptability had higher in gathering A(4.2±0.7) compared to gathering B(3.5±0.5) compared to gathering C(2.5±0.6). No complication detected in both gatherings.

**Conclusion:** use of 400µgm misoprostol 12hours had better than using it 6hours, 3hours in facilitating ripening with minimal side critical without use of anesthesia. it decreases score, decrease procedure duration, increase ease of entry, higher case acceptability, with minimal side critical.

**Keywords:** hysteroscopy; misoprostol; primin

### INTRODUCTION

Hysteroscopy had the process of viewing, operating in the endometrial from a transapproach. It had the gold standard procedure for uterine exploration<sup>1</sup>.

Hysteroscopy allows direct visualization of the uterine, the endometrium, the canal. The examination might be practiced on an out-case basis, without anesthesia, using appropriate small-caliber instruments, irrigation with physiological saline<sup>2</sup>.

Hysteroscopy had associated with minimal case discomfort, excellent visualization, very low complication, failure rates<sup>3,4</sup>.

Taking into account that an efficient method to facilitate an easier uncomplicated entry during the hysteroscopic procedure could substantially minimize the risk of complications, several modalities for ripening prior had adopted<sup>5</sup>.

priming prior to diagnostic hysteroscopy softens the cervix, lessens the force needed for dilation, thereby potentially reducing the probability of procedural complication such as uterine perforation, laceration, failure to dilate, creation of a false track that could occur during entry<sup>6</sup>.

The synthetic analogue of prostaglandin E1, misoprostol, had the agent used most often for preparation prior<sup>7</sup>.

It could be given orally, vaginally, sublingually, buccally, or rectally<sup>8-10</sup>.

The route appears to be superior to the oral route<sup>11</sup>.

Based on the available evidence on the use of misoprostol prior, the optimal time of misoprostol administration prior to the hysteroscopy. So we tried in our study to test for appropriate time by comparing between 3hours, 6hours, 12hours administration prior.

## PATIENTS AND METHODS

Type of the study: Randomized double-blind placebo-controlled study.

Double blinded means that: neither participants nor operator know which intervention would be received.

Setting of the study: This study had conducted at El Sahel Teaching Hospital from October 2017 till October 2018.

Protocol approval by ethics committee: Before the beginning of the study, in accordance with the local regulation followed, the protocol, all corresponding documents had declared for Ethical, Research approval by the Council of Obstetrics, Gynecology Department, Al-Azhar University.

Sample size calculation: We had planning a study of a continuous response variable from 3equal study gatherings. We added 10% to each gathering to compensate for the dropped cases, so each gathering would be 66cases.

Case selection: One hundred ninety eight nulliparous cases had subjected with the following

Inclusion criteria: Age-childbearing period or postmenopause from 20-50years, Nulliparous cases, Indication for hysteroscopy; Infertile cases either primary or secondary infertility, Cases with history of recurrent miscarriage, Cases with history of abnormal uterine bleeding.

Exclusion criteria: Contraindications: Any uterine abnormality that would obviate passage of a catheter, marked stenosis, recent pelvic disease, uterine bleeding. Contraindications to prostaglandins.

After obtaining informed consent, all included cases had subjected to: thorough history taking, Full examination, Pelvic ultrasound, Laboratory investigations: Serum cases test: to exclude cases.

Interventions: The cases had divided into 3gatherings randomly, each gathering contained 66cases. Method of randomization: computerized randomization(covariate adaptive randomization) randomization.

First gathering (long interval misoprostol gathering): Two misoprostol (400micrograms) had given vaginally 12hours prior. Two placebo had given vaginally 6hours, 3hours prior.

Second gathering(intermediate interval misoprostol gathering): Two placebo had given vaginally 12hours prior. Two misoprostol had given vaginally 6hours prior. Two placebo had given vaginally 3hours prior.

Third gathering(short interval misoprostol gathering): Two placebo had given vaginally 12hours, 6hours prior. Two misoprostol had given vaginally 3hours prior. The placebo had folic acid 500mcg. The hysteroscopy had scheduled in the proliferative menstrual phase from the 5<sup>th</sup> day to the 14<sup>th</sup> day of the cycle. Informed written consent had signed by all the cases.

Technique: Case preparation had one of the most important aspects for successful hysteroscopy, thus the procedure had described to every case prior to the examination, each step had explained during the procedure so the cases had an active participants, this helped them to understand the experience, relieved anxiety. The hysteroscope used in this study had that of Karl Storz,(Germany 1996). It had a rigid continuous flow panoramic hysteroscopy 25cm in length, 4mm in diameter with an outer sheath of 5.5mm, a 30degree fibro optic lens. The light source used in this study had a metal halide automatic light source from Circon Acmi G71A/Germany with 150watt lamp. A fibro optic cable had connected to the light source. The technique used to provide constant uterine distention had by 3L volume saline bags to dual infusion tubing which had suspended one meter above the case level. Each bag had then wrapped in a pressure infusion cuff similar to that used in BP to reach a pressure of 150-200mmHg. The tubing had connected to the hysteroscope. It had helpful, more comfortable for the operator to sit on a low chair, to elevate the foot of the examination table to perform the procedure. After the case had installed in the lithotomy position then the gynecologist used sterile gloves, checking the flow of the distention medium, the hysteroscope had introduced under direct vision into the cervix without the use of anesthesia or analgesia, using a specific technique. No dilatation had done.

|  |
|--|
| No dilatation  |
| No blind insertion of the instruments                      |
| No use of portio tenaculum                                 |
| Atraumatic, sight-controlled insertion of the hysteroscope |
| Use non-irritating distension media (saline)               |
| No anesthesia or analgesia necessary                       |

**Table 1:** Technique of a traumatic diagnostic hysteroscopy:

The outcomes that had measured: The level of pelvic had rated according to a 10-point visual analogue

scale(VAS). The VAS had applied immediately after the procedure ended. Ease of entry of the cervix recorded on a 5-point Likert scale(Likert 1932): very difficult=1, difficult=2, fair=3, easy=4, very easy=5. Baseline width at the beginning of the procedure had assessed by the largest number of Hegar dilator that could be inserted into the cervix without resistance. The bleeding during the procedures had assessed whether if there had no or moderate or severe bleeding. The time from introduction through the external os, the visualization of the uterine had recorded in minutes. Any complications or side critical to perform hysteroscopy.

Statistical analysis: Data had then transferred to the IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp.

## RESULTS

| Demographic DATA      | Gathering A<br>(n=66) | Gathering B<br>(n=66) | Gathering C<br>(n=66) | P Value | A*B   | A*C   | B*C   |
|-----------------------|-----------------------|-----------------------|-----------------------|---------|-------|-------|-------|
| Age:                  |                       |                       |                       |         |       |       |       |
| <i>Mean±SD</i>        | 33.6±8.1              | 33.6±7.3              | 32.7±6.8              | 0.753   | 0.999 | 0.801 | 0.781 |
| Range                 | 20-49                 | 22-50                 | 22-50                 |         |       |       |       |
| Duration of marriage: |                       |                       |                       |         |       |       |       |
| <i>Mean±SD</i>        | 10.4±5.7              | 10.5±5.6              | 9.9±5.2               | 0.817   | 0.991 | 0.883 | 0.819 |
| Range                 | 2-25                  | 3-25                  | 4-25                  |         |       |       |       |
| Gravidity:            |                       |                       |                       |         |       |       |       |
| MG                    | 30(45.5%)             | 28(42.4%)             | 39(59.1%)             | 0.125   | 0.726 | 0.117 | 0.055 |
| NG                    | 36(54.5%)             | 38(57.6%)             | 27(40.9%)             |         |       |       |       |
| Prev. procedure:      |                       |                       |                       |         |       |       |       |
| Cerclage              | 15(22.7%)             | 18(27.3%)             | 19(28.8%)             | 0.533   | 0.559 | 0.273 | 0.571 |
| Cautery               | 14(21.2%)             | 10(15.2%)             | 6(9.1%)               |         |       |       |       |
| Biopsy                | 3(4.5%)               | 1(1.4%)               | 3(4.5%)               |         |       |       |       |
| No previous technique | 34(51.6%)             | 37(56.1%)             | 38(57.6%)             |         |       |       |       |
| Indications:          |                       |                       |                       |         |       |       |       |
| Infertility           | 26(39.4%)             | 26(39.4%)             | 31(47%)               | 0.455   | 0.975 | 0.207 | 0.281 |
| Abortion              | 18(27.3%)             | 19(28.8%)             | 22(33.3%)             |         |       |       |       |
| Bleeding              | 22(33.3%)             | 21(31.8%)             | 13(19.7%)             |         |       |       |       |

**Table 2:** Comparison between gatherings as regard demographic data.

| Outcome Measures  | Gathering A                     | Gathering B                       | Gathering C                         | P VALUE | A, B   | A, C   | B, C   |
|---|---------------------------------|-----------------------------------|-------------------------------------|---------|--------|--------|--------|
| Level of according to VAS:<br>Mean±SD<br>Range              | 2.6±1.3<br>1-5                  | 5.3±1.3<br>3-9                    | 7.3±1.2<br>5-10                     | <0.001  | <0.001 | <0.001 | <0.001 |
| Ease of entry according to LIKERT scale<br>Mean±SD<br>Range | 4.2±0.7<br>1-5                  | 3.5±0.5<br>3-4                    | 2.5±0.6<br>1-4                      | <0.001  | <0.001 | <0.001 | <0.001 |
| Baseline dilatation by Hegar dilator<br>Mean±SD<br>Range    | 5.9±0.8<br>5-7                  | 4.7±1.1<br>3-6                    | 3.9±0.8<br>3-5                      | <0.001  | <0.001 | <0.001 | <0.001 |
| Duration of procedure in minutes<br>Mean±SD<br>Range        | 2.7±0.9<br>1-4                  | 5.2±1.2<br>3-8                    | 7.4±1.3<br>5-10                     | <0.001  | <0.001 | <0.001 | <0.001 |
| bleeding:<br>Mild<br>Moderate<br>No                         | 3(4.6%)<br>1(1.5%)<br>62(93.9%) | 12(18.2%)<br>5(7.6%)<br>49(74.2%) | 30(45.5%)<br>10(15.2%)<br>26(39.3%) | <0.001  | 0.008  | <0.001 | <0.001 |
| Case acceptability:<br>Mean±SD<br>Range                     | 4.2±0.7<br>1-5                  | 3.5±0.5<br>3-4                    | 2.5±0.6<br>1-4                      | <0.001  | <0.001 | <0.001 | <0.001 |

**Table 3:** Comparison between gatherings as regard outcome measures: Data had expressed as number±standard deviation, percent(%)

F- ANOVA test;

| Misoprostol side critical | Gathering A (n=66) | Gathering B (n=66) | Gathering C (n=66) | P value | A*B   | A*C   | B*C   |
|---------------------------|--------------------|--------------------|--------------------|---------|-------|-------|-------|
| Pain                      | 5(7.6%)            | 10(15.2%)          | 12(18.2%)          | 0.125   | 0.217 | 0.054 | 0.717 |
| Nausea                    | 3(4.5%)            | 7(10.6%)           | 9(13.6%)           |         |       |       |       |
| Diarrhea                  | 2(3%)              | 3(4.5%)            | 5(7.6%)            |         |       |       |       |
| No Side critical          | 56(84.8%)          | 46(69.7%)          | 40(60.6%)          |         |       |       |       |

**Table 4:** Comparison between gatherings as regard side effect of misoprostol.

Data had expressed as number, percent(%)

## DISCUSSION

This study showed that giving 400microgram misoprostol 12hours prior (gathering A) had better than giving it 6hours(gathering B), 3hours(gathering C) prior as level of pelvic had lowest in gathering A followed by gathering B followed by gathering C, ease of pelvic entry had easier in gathering A followed by gathering B followed by gathering C, baseline dilatation had greater in gathering A followed by gathering B followed by gathering C, time of the procedure had shorter in gathering A followed by gathering B followed by gathering C, bleeding had least in gathering A, followed by gathering B, then gathering C. Misoprostol related side effect as fever, abdominal pain, nausea, diarrhea had minimal, there had no critical difference between the three gatherings.

Fouda et al., they compared 400mcg misoprostol 12h, 3h before hysteroscopy, they found that misoprostol administration 12hours before hysteroscopy<sup>12</sup>.

Bastu et al., they found that 200µg, 400µg, critical facilitated the procedure of OH compared to the controls as entry had easier; procedural time had shorter; baseline width had larger, scoring had lower<sup>13</sup>.

Bakas et al, administered 200µg oral misoprostol to one gathering(12hours before), 200µg misoprostol to another, 200µg misoprostol to a third gathering.

El-Mazny, Abou-Salem compared 200µg gathering in which placebo had not used; procedure time had shorter, case acceptability had higher, scoring had lower in the gathering, which had in line with our findings<sup>15</sup>.

Preutthipan, Herabutya, showed that misoprostol, resulted in critical priming before hysteroscopy in non cases. They reported greater dilation, decreased resistance, or curettage with oral or misoprostol<sup>16</sup>.

El Khayat et al. compared the critical of isosorbide mononitrate(I.M.N), misoprostol for priming before the hysteroscopy, there had a critical difference between I.M.N, misoprostol with regard to the baseline dilatation(5mm for I.M.N, 8mm for misoprostol), duration of dilatation(73s for I.M.N, 49s for misoprostol)<sup>17</sup>.

Mulayim et al. two gatherings of cases who received sublingual misoprostol or placebo before hysteroscopy had compared with each other. Dilatation time had higher in placebo gathering. Furthermore, tearing had occurred more often in placebo gathering than in misoprostol gathering<sup>18</sup>.

Batukan et al. reported that 400µg administration of misoprostol had more critical than the oral route with the same dose for preoperative ripening in premenopausal cases in terms of extent of initial width, percentage of cases requiring dilatation, procedural time as well as complications during procedure, associated side critical<sup>20</sup>.

Preutthipan & Herabutya compared the critical of misoprostol more critical technique, suggested to use misoprostol for priming instead of dinoprostone<sup>23</sup>.

Choksuchat et al. suggested that 400mg oral misoprostol had as critical as 200µg route for ripening<sup>24</sup>.

Preutthipan, Herabutya reported that 200µg misoprostol 9-10hours before the procedure lessens resistance, facilitates the procedures<sup>25</sup>.

Bahamondes et al. found that pretreatment with intra100mcg of misoprostol after IUD insertion failure in 104cases 4-10hours before 2<sup>nd</sup> attempt had critical better than placebo(RCT)<sup>26</sup>.

But this had not in agreement with a randomized controlled study which revealed that 400µg misoprostol administered vaginally 6hours before hysteroscopy had not critical in reducing experienced during hysteroscopy<sup>27</sup>.

In addition, sequential doses of 400mg of oral misoprostol at 12-24hours before technique did not demonstrate any advantage in so far as dilation<sup>28</sup>.

Fernandez et al. who gave cases three different doses of misoprostol in either 200, 400, or 800µg 4hours before OH, they found no critical difference<sup>29</sup>.

Bisharah et al. compared the effect of 100µg of sublingual misoprostol administered 12h prior to operative hysteroscopy in 20cases to placebo, found no difference in facilitation of dilatation. Similarly, demonstrated no difference in ease of dilatation following administration of 800µg of misoprostol administered at least 5h prior compared to placebo in postmenopausal cases<sup>30</sup>.

## CONCLUSION

Hysteroscopy had an essential tool for uterine environment assessment. Misoprostol had a good ripening agent, had critical in changing the character of the cervix from harder, softer. This study showed that giving 400microgram misoprostol 12hours prior had better than giving it 6hours, 3hours prior.

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