Misoprostol and Isosorbide Mononitrate for Cervical Ripening before Hysteroscopy: a Randomized Clinical Trial

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ABSTRACT

Background: Hysteroscopy is a diagnostic and therapeutic modality, while cervical ripening before hysteroscopy is an issue of concern and different agents have been used for this purpose. The goal of this study is to compare the effectiveness of misoprostol and isosorbide mononitrate (IMN) for cervical ripening before hysteroscopy.

Methods: In this randomized clinical trial, 56 women who were candidates for hysteroscopy were randomly assigned to misoprostol or isosorbide mononitrate groups. During the early follicular phase of the cycle, a gynecology expert performed the hysteroscopies. Cervical dilation was measured by insertion of Hegar dilators up to size 9 without force. Vaginal bleeding, headache, abdominal pain, nausea, and vital signs were recorded by a specialized nurse.

Results: There was no significant difference regarding age, systolic and diastolic blood pressure in the two groups. Heart rate was significantly higher in the IMN group. Bleeding rate was not significantly different between the two groups (25.8% in the misoprostol group and 24% in the isosorbide mononitrate group, p=0.8). Headache was significantly more frequent in the isosorbide group, while abdominal pain, nausea, vomiting were significantly prevalent in the misoprostol group. The mean Hegar number used in the misoprostol and IMN groups was 7.3±1.1 vs 6.7±0.8 (p=0.03).

Conclusion: Isosorbide mononitrate (IMN) is more effective than misoprostol for cervical ripening before hysteroscopy and complications are more frequent in the misoprostol group.

Keywords: misoprostol, cervical ripening, hysteroscopy, isosorbide mononitrate.
INTRODUCTION

In recent years, hysteroscopy is the most common method which is used for intrauterine pathologies such as myomas and endometrial polyps (1). Although hysteroscopy is considered as a less invasive method, complications such as abdominal cramping, uterine and cervical perforation could occur during the procedure (2). To reduce complications, cervical ripening before hysteroscopy is recommended (3).

Misoprostol, a E1 prostaglandin analog, is used for cervical ripening, labor induction, and pregnancy termination (4). By administration of misoprostol, the passage of hysteroscope can be easier, with fewer complications (5). Misoprostol had different routes and the vaginal route will cause longer and regular uterine contractions (6, 7). Administration of misoprostol is contraindicated in some cases.

Isosorbide mononitrate (IMN) is a nitric oxide (NO) donor which can be used for cervical ripening without uterine contractions but increasing uterine blood flow (8-10).

There is controversy regarding the effectiveness of vaginal IMN for cervical ripening (11-14). As there are little studies comparing the effectiveness of misoprostol and isosorbide mononitrate for cervical ripening, we designed this study to compare the effectiveness of these two therapeutic agents for cervical ripening before hysteroscopy.

METHODS

This randomized clinical trial was conducted in Amiralmomenin Hospital (affiliated hospital of Zabol University of Medical Sciences) between March 2018 and March 2019.

The inclusion criteria were: infertility, nulliparity, and candidate for hysteroscopy. The exclusion criteria were: glaucoma, hypertension, sickle cell anemia, mitral valve stenosis, and allergic reaction to misoprostol.

The study was approved by the Ethics Committee of Zabol University of Medical Sciences (IRCT20180826040879N1).

All patients filled the informed consent forms before enrollment.

By means of computer-generated randomization sequences, patients were assigned into two groups: group 1, who received 25-µg of vaginal misoprostol every four hours up to four doses, and group 2, treated with 40-µg of vaginal isosorbide mononitrate every six hours up to two doses.

Neither patients, nor physicians were blinded to the study groups.

During the early follicular phase of the cycle, a gynecology expert performed the hysteroscopies. Cervical dilation was measured by insertion of Hegar dilators up to size 9 without force. Vaginal bleeding, headache, abdominal pain, nausea, and vital signs were recorded by a specialized nurse.

Data analysis was done by means of SPSS version 22 (SPSS Inc., Chicago, IL, USA). Data were presented as mean± SD for continuous or frequencies for categorical variables. Comparison of continuous variables was made with the independent sample t-test and that of categorical variables by using the chi-squared test. A P-value less than 0.05 were considered as significant.

RESULTS

Sixty-six cases were randomly assigned to the two groups. Two cases from the misoprostol group and eight from the other one withdrew from the study before entrance.

There was no significant difference regarding age, systolic and diastolic blood pressure in the two groups. Heart rate was significantly higher in the IMN group (Table 1).

Bleeding rate was not significantly different between the two groups (25.8% in the misoprostol group and 24% in the isosorbide mononitrate group, p=0.8).

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group one n=31</th>
<th>Group two n=25</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>30.3±4.7</td>
<td>30.3±5.3</td>
<td>0.9</td>
</tr>
<tr>
<td>Respiratory rate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate</td>
<td>75.5±3.4</td>
<td>78.4±1.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Temperature</td>
<td>36.8±0.1</td>
<td>36.9±0.4</td>
<td>0.3</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>100.3±7.5</td>
<td>96.8±6.1</td>
<td>0.06</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>72.9±3.5</td>
<td>72±6.2</td>
<td>0.2</td>
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</table>

TABLE 1. Comparison of vital signs between the two groups.
Headache was significantly more frequent in the isosorbide group, while abdominal pain, nausea, and vomiting were significantly prevalent in the misoprostol group (Table 2).

The mean Hegar number used in the misoprostol group and the IMN group, respectively, was $7.3 \pm 1.1$ vs $6.7 \pm 0.8$ ($p=0.03$).

**DISCUSSION**

To our knowledge, this is the first study evaluation of IMN and misoprostol use for cervical ripening before hysteroscopy. The results of the current study showed that dilation was significantly better in the isosorbide group (a lower number of Hegar was used) and most complications were more prevalent in the misoprostol group.

El-Khayat et al. randomly assigned women who were candidates for hysteroscopy into vaginal IMN (40 mg) or vaginal misoprostol (200 µg) before hysteroscopy. Their findings revealed that the duration of dilation was significantly lower and the degree of dilation was significantly better in the misoprostol group than in the IMN group. Feasibility of dilation was also better in the misoprostol group, while abdominal pain was reported more frequently in the misoprostol group (15).

Li et al. randomly assigned women who were candidates for pregnancy termination into isosorbide mononitrate, misoprostol and control groups. They found that cervical dilation was significantly higher and blood loss significantly lower in the misoprostol group (16).

Thomson et administered 40 mg of IMN for three hours for term termination in 22 women and found that 15 of them were symptom-free at the time of the evaluation (17).

<table>
<thead>
<tr>
<th></th>
<th>Group 1</th>
<th>Group 2</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>5(16.1%)</td>
<td>19(76%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>21(67.7%)</td>
<td>4(16%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Nausea</td>
<td>8(25.8%)</td>
<td>_</td>
<td>0.006</td>
</tr>
<tr>
<td>Vomiting</td>
<td>3(9.7%)</td>
<td>_</td>
<td>0.2</td>
</tr>
</tbody>
</table>

**TABLE 2.** Frequency of complications in two groups

In a previous study, Zhuo et al. randomly assigned women into 600 µg oral or vaginal misoprostol and control groups (vitamin B6) before hysteroscopy. They found that the effect of cervical dilation was significantly higher in both misoprostol groups, while cervical dilation was needed in a higher extent in the oral misoprostol group. In their study, ease degree of cervical dilation and dilation time were similar in both misoprostol groups (3). In their study, nausea and vomiting was higher in oral group.

In another study, Singh et al. reported that administration of 400 mg vaginal misoprostol 3-4 hours before hysteroscopy was helpful for optimal cervical dilation before abortion (18).

Mulayim et al. found that sublingual misoprostol could reduce the dilation time before hysteroscopy in comparison with controls (19).

Hysteroscopy is a diagnostic/therapeutic modality which could be associated with complications. To reduce complications and ease the procedure, cervical ripening could be done before hysteroscopy.

We know that in women’s genital system, the nitric oxide-generating system exists, which has been tested in different studies in different situations, including cervical ripening during the first and third trimesters of pregnancy as well as pre-eclampsia (20).

Misoprostol is used for pregnancy termination and cervical ripening under different routes. A study was conducted previously showed that sublingual route is more effective than vaginal route before hysteroscopy.

This study had some limitation. First, it conducted in a single center. Second, the sample size was limited. Larger multi-centric studies are recommended.

**CONCLUSION**

isosorbide mononitrate is more effective than misoprostol for cervical ripening before hysteroscopy and complications are more frequent in the misoprostol group.

Conflicts of interest: none declared.

Financial support: none declared.
REFERENCES


