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Sublingual misoprostol plus laminaria for cervical preparation before surgical management of late first trimester missed abortions, a randomized controlled trial

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Abstract

Objective: Comparing the efficacy of low-dose sublingual misoprostol plus laminaria to medium-dose sublingual misoprostol alone for cervical dilation before surgical management of late first trimester missed abortions.

Methods: Randomized, controlled trial evaluated 70 women with missed abortion, admitted for surgical termination of pregnancy. The patients were randomly assigned to receive 200 μg sublingual misoprostol with cervical laminaria (intervention group) or 400 μg sublingual misoprostol without laminaria (control group), four hours before surgical process. The study is registered at www.irct.ir (IRCT2014070711020N4).

Results: More patients in the intervention group achieved the desired cervical dilation (Hegar7) before surgical process than the control group (91.4% versus 17.1%, p < 0.001). Patients in the intervention group experienced less pain during the waiting period (mean Visual Analog Scale scores: 30.8 ± 3.7 versus 43.7 ± 5.9, p < 0.001), and had higher satisfaction level (highly satisfied: 97.1% versus 77.1%, p = 0.02). Four patients in the intervention group and none in the control group had spontaneous expulsion of pregnancy products (p = 0.11).

Conclusions: Compared to medium-dose sublingual misoprostol alone, using a combination of cervical laminaria plus low-dose sublingual misoprostol before surgical process is associated with significantly more effective and rapid cervical dilation, lower requirement for mechanical dilation, lower abdominal pain and discomfort during the waiting period and higher patients’ satisfaction.

Keywords

Cervix, dilation, prostaglandin, ripening, termination

Introduction

Missed abortion is a condition when a pregnant woman has an ultrasound examination that shows either anembryonic pregnancy or embryonic demise while having a closed cervix, which complicates around 2.8% of pregnancies [1,2]. Expectant, medical, and surgical managements are reasonable options for the management of missed abortions [3,4]. However, most women choose medical or surgical managements at the time of diagnosis [3]. Cervical preparation before surgical management is an important step which could reduce the complications of cervical injury and uterine perforation, and makes the procedure shorter and easier [5,6].

Cervical ripening can be achieved with pharmacological agents or with osmotic dilators [5,6]; misoprostol is the most commonly used pharmacologic agent for cervical ripening and can be administered through vaginal, rectal, oral, sublingual and buccal routes [3,5,6]. Although some studies indicate that misoprostol can achieve equal cervical dilation as laminaria [7], most studies document that laminaria is a more effective cervical dilator than misoprostol [4,8,9]. Compared to laminaria, misoprostol might be associated with more vaginal bleeding [4,7], more gastrointestinal side effects [4,9], and more pain before and after the surgical process [7,10]. On the other hand laminaria is associated with more pain at insertion [4,7,8,10], and because of its slow action it requires significantly longer time to dilate the cervix and since there are some concerns that laminaria might facilitate ascending infection into the uterine cavity, the longer presence of laminaria in the cervix could increase the risk of bacteremia [6].

To overcome these limitations of misoprostol and laminaria some researchers assessed their combination for cervical ripening and/or medical abortion [11–16]. These studies had conflicting results; some concluded that using a
combined method was more effective with less side effects of using either methods alone [11–13]; while some other studies showed no superiority for the combined method over misoprostol alone [14–16]. However most these studies were conducted in the second gestational trimester [12–16], when the uterus is more sensitive and responsive to misoprostol [17].

We could not find studies evaluating the combined method for cervical ripening during the first gestational trimester. This period is especially important because due to the lower uterine sensitivity to misoprostol, higher doses of misoprostol are required for cervical ripening in this period which could cause higher adverse effects [17]. Additionally, all the available studies used laminaria in combination with vaginal, buccal or oral misoprostol [11–16], while the sublingual administration of misoprostol, which has not been assessed in combined treatment, is believed to have superior cervical effects than other routes [5,6]. Finally, based on the world health organization (WHO) the efficacy, methods and adverse effects of cervical preparation before late first trimester surgical abortion require further investigation [18].

We postulate that the combination of laminaria and sublingual misoprostol in the first gestational trimester might cause more effective and rapid cervical dilation with lower doses of misoprostol and lower side effects than using misoprostol alone. Therefore, we conducted this study on pregnant women who underwent surgical management for first trimester missed abortions, to assess the efficacy, adverse effects and patients’ satisfaction of using the combined administration of laminaria plus low-dose sublingual misoprostol versus medium-dose sublingual misoprostol for cervical ripening before surgical process.

Methods

Study population and study design

This randomized, open label, prospective clinical trial was conducted on 70 pregnant women who had a confirmed diagnosis of missed abortion and were admitted for surgical termination of pregnancy from July 2015 through November 2015. The inclusion criteria were: documented missed abortion on serial ultrasound imaging, a closed cervix and a gestational age between 9 and 14 weeks, in which cervical preparation is recommended before surgical process [5,6,18]. Exclusion criteria were: vaginal bleeding upon admission, uterine anomaly, multiple pregnancy, allergy to prostaglandins, any contraindication to prostaglandin (including coronary artery stenosis, glaucoma, sickle cell anemia, and asthma), any history of urinary tract infection within the previous month, history of prior cone biopsy or loop electrosurgical excision procedure, a history of more than one Cesarean Sections, using other drugs for termination of pregnancy, uterine contractions and any medical illness including hypertension, diabetes, and cardiac diseases.

The diagnosis of missed abortion was confirmed using ultrasound imaging by the absence of a cardiac activity when the crown–rump length was >6 mm and of an anembryonic pregnancy by an absent fetal pole in a gestational sac >25 mm in diameter [19].

After explaining the whole procedure an informed written consent was obtained from the participants, the women then were randomly allocated in two groups; the control group to receive 400 μg sublingual misoprostol 4 h before procedure, and the intervention group to receive cervical laminaria plus 200 μg sublingual misoprostol 4 h before procedure (Figure 1).

M.S. performed the simple randomization using computerized random number generator for sequence generation. N.Y. performed the allocation concealment using consecutive opaque envelopes. The envelopes were opened sequentially only after the participant’s name and other details were written on the appropriate envelope. M.K carried out the implementation of assignments.

The primary outcome of our study was achieving the desired cervical dilation as ≥ Hegar7 during the waiting period before surgical process. Secondary outcomes were spontaneous expulsion of pregnancy products, pain intensity during waiting period, adverse effects of the ripening methods including nausea/vomiting, diarrhea, flashing and fever, post abortive infection and finally the patients’ satisfaction at discharge.

This study was approved by the Research Deputy and the Ethics Committee of Tehran University of Medical Sciences (Reference ID: 9111290040–144511). This study is registered at the Iranian Registry of Clinical Trials (www.irct.ir) which is a Primary Registry in the WHO Registry Network (Registration Number: IRCT2014070711020N4).

Although the study was submitted to www.irct.ir before the expected recruitment start date, the approval process took a long time and the date of confirming the registration passed the submitted starting date, therefore, the registration timing appeared as registration while recruiting. However, officially recruiting the patients was started after the registration approval on 26th June 2014.

The protocol

Upon enrollment a standardized questionnaire was completed for all the participants through interviews and investigating their medical records. The questionnaire contained demographic, medical, gynecological, and obstetrical history. All the participants underwent physical and pelvic examinations.

In the control group the dose and route of misoprostol administration was chosen based on previous studies and the WHO recommendation [5,6,18]. After the required interviews and examinations the participants in the control group received 400 μg misoprostol sublingually four hours before the surgical process. For the participants in the intervention group the vagina was cleaned using aqueous betadine solution, then the cervix was exposed with speculum. A tenaculum was applied to anterior cervix lip and a 3 mm laminaria tent was inserted. Simultaneously 200 μg misoprostol was administered sublingually four hours before the surgical process. In the intervention group the dose was chosen based on previous studies that showed 200 μg sublingual misoprostol is associated with significantly lower adverse effects and patients discomfort compared to the usual dose of 400 μg sublingual misoprostol [5,6,20]. The time point was chosen four hours because cervical preparation
using laminaria requires at least four hours to be effective [18].

The patients’ pulse, blood pressure, temperature and systemic symptoms were monitored hourly for possible detection of fever, flashing, nausea/vomiting and diarrhea. In this study Visual Analog Scale (VAS) was used to determine the pain intensity. VAS is a continuous scale comprised of a horizontal line, 10 cm (100 mm) in length. The scale ranges from 0 (no pain) to 100 (worst imaginable pain). The following cut points on the pain VAS were used: no pain (0–4 mm), mild pain (5–44 mm), moderate pain (45–74 mm), and severe pain (75–100 mm). The patients were educated on how to use and interpret the pain VAS, they were also asked to place a cross line on the unmarked horizontal scale at the required times. VAS pain score was checked every 2 h. If the products of conception were passed within 4 h and was complete based on ultrasound imaging, the women were observed for a further 4 h and then were discharged. After four hours the patients were taken for vacuum aspiration. At the operating room using Hegar’s dilators the degree of cervical dilation before surgical process was measured. Cervical dilation before surgery was considered successful if the degree of cervical dilation had reached $\geq$ Hegar7. If cervical dilation was not achieved within four hours with either methods, mechanical dilation was performed in the operating room using Hegar’s dilators. Upon discharge patients’ satisfaction was assessed as high, moderate or low satisfaction level. The patients were followed for two weeks to detect the following symptoms of possible post-abortive infections: weakness, nausea, vomiting, diarrhea, fever that lasts more than 24 h or is $>38^\circ C$, abdominal pain, heavy vaginal bleeding, and foul smelling vaginal discharge.

**Statistical analysis**

Sample size was calculated for a power of 80%, $\alpha = 0.05$, $\beta = 20\%$, and a standard effect size of 0.84. All the statistical analyses were performed using SPSS statistical software (version 18.0.0: PASW, Chicago, IL). Data were displayed using Mean, Standard Deviation (SD), Median and Range. The t-test, Chi-squared analysis, Fisher’s exact test and multivariate logistic regression were used for the analysis when appropriate. The level of statistical significance was set at $p$ values $< 0.05$. 

Figure 1. Flow chart of the study showing patients randomization.
Results
This study was conducted on 70 pregnant women with late first trimester missed abortion who were admitted for surgical termination of pregnancy. Eighty-three women agreed to participate in the study, 13 of whom were excluded due to having one or more of the exclusion criteria; 35 women were randomly assigned to receive 400 μg sublingual misoprostol (control group), and 35 women were randomly allocated to receive cervical laminaria plus 200 μg sublingual misoprostol (intervention group), four hours before surgical procedure (Figure 1).

The mean ± standard deviation (SD) for participants’ age was 28.2 ± 4.2 years; gestational age was 10.5 ± 1.1 weeks; participants’ BMI was 24.6 ± 3.5; VAS pain score was 37.2 ± 8.1. Thirty-seven women (54.3%) were nulliparous, 38 (54.3%) achieved the desired cervical dilation before surgical procedure, 4 women (5.7%) had spontaneous expulsion of pregnancy products before surgical intervention; 5 (6.6%) had nausea/vomiting, 3 (4.2%) had diarrhea, 6 (8.6%) experienced flashing; 2 (2.9%) developed fever; 61 women were highly satisfied with the received treatment (87.1%), post-abortive infection did not develop in any of the participants. There were no statistically significant differences in the demographics between the intervention and the control groups (Table 1).

However, compared to 17.1% of the patients in the control group (p < 0.001), 91.4% of the patients in the intervention group achieved the desired cervical dilation before the surgical process (Table 2). Patients in the intervention group experienced significantly less pain during the waiting period and required more mechanical cervical dilation compared to the patients in the control group (both p < 0.001) (Table 2). Four patients in the intervention group had spontaneous expulsion of pregnancy products without requiring surgical intervention while none in the control group had spontaneous expulsion of pregnancy products (p = 0.11). Patients in the intervention group experienced lower rates of systemic side effects including nausea/vomiting, diarrhea, flashing and fever compared to the patients in the control group, although none were statistically significant (p = 0.35, p = 0.23, p = 0.67, p = 0.49, respectively) (Table 2). Finally at discharge women in the intervention group had significantly higher satisfaction level from the received treatment than the mothers in the control group (p = 0.02).

Discussion
In this randomized controlled trial, combined administration of 200 μg sublingual misoprostol plus laminaria was significantly more effective than 400 μg sublingual misoprostol alone for cervical dilation when administered 4h prior to surgical management of late first trimester missed abortions. The combined treatment resulted in significantly more rapid and effective cervical dilation with lower misoprostol requirement, lower requirement for mechanical dilation in the operating room, less pain during the waiting period, and higher patients’ satisfaction at discharge compared to using misoprostol alone for cervical dilation.

We could not find studies comparing the combination of laminaria and misoprostol to misoprostol alone for cervical dilation before first trimester surgical process. In the current study using the combined method was associated with significantly more effective and rapid cervical dilation than using misoprostol alone before surgical process and decreased the requirement for mechanical dilation in the operating room. Two other studies compared the combined method to laminaria alone for cervical dilation before second trimester dilation and evacuation (D&E) [12,13]; they showed that the use of the combined method resulted in greater cervical dilation before surgical process, and shorter duration of D&E compared to laminaria alone [12,13]. Four other studies compared the combined method to prostaglandins alone for first or second trimester medical abortions [11,14–16]; the combined method was significantly more effective than prostaglandins alone during the first trimester [11], while the combined treatment was not superior to misoprostol alone during the second trimester [14–16]. Our results supported by the results of other studies [11–16], show that the combination of laminaria plus misoprostol is more effective when used for cervical dilation before surgical termination of pregnancy, especially during the first gestational trimester when the uterus is less sensitive and responsive to prostaglandins [17], however, the use of the combined method for medical termination requires further investigations.

In this study we showed that more effective cervical dilation could be achieved by adding lower misoprostol dose (200 μg) to laminaria than the usual recommended dose of 400 μg for first trimester cervical ripening [5,6,18]. Insertion of laminaria significantly reduces the requirement for misoprostol administration because after insertion in the cervix laminaria swells to 3–4 times its dry diameter applying radial forces to the walls of the cervical canal, these radial forces induce the endogenous production of prostaglandins, thus decrease the requirement for further exogenous administration of prostaglandins [6,20,21]. The produced endogenous prostaglandins promote further cervical dilation and induce painless uterine contractions [6,21,22].

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Control group (Misoprostol alone)</th>
<th>Intervention Group (Laminaria + Misoprostol)</th>
<th>p values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age (years) (Mean ± SD)</td>
<td>27.8 ± 4.3</td>
<td>28.6 ± 4.2</td>
<td>0.4 (N.S)</td>
</tr>
<tr>
<td>Gestational age (weeks) (Mean ± SD)</td>
<td>10.4 ± 1.1</td>
<td>11.1 ± 0.6</td>
<td>0.31 (N.S)</td>
</tr>
<tr>
<td>BMI (Mean ± SD)</td>
<td>24.7 ± 3.7</td>
<td>24.2 ± 3.5</td>
<td>0.2 (N.S)</td>
</tr>
<tr>
<td>Nulliparity [Number (%)]</td>
<td>19 (54.3%)</td>
<td>19 (54.3%)</td>
<td>1 (N.S)</td>
</tr>
<tr>
<td>History of one C/S [Number (%)]</td>
<td>6 (17.1%)</td>
<td>6 (17.1%)</td>
<td>1 (N.S)</td>
</tr>
</tbody>
</table>

SD: Standard deviation, N.S: nonsignificant, BMI: body mass index.
Table 2. Comparison of the outcomes between the intervention versus control groups.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Control group (Misoprostol alone)</th>
<th>Intervention group (Laminaria + Misoprostol)</th>
<th>p values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Achieved the desired cervical dilation before surgical process</td>
<td>6 (17.1%)</td>
<td>32 (91.4%)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Required mechanical dilation during the surgical process</td>
<td>29 (82.8%)</td>
<td>3 (8.5%)</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>VAS pain score during the waiting period</td>
<td>43.7 ± 5.9</td>
<td>30.8 ± 3.7</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Spontaneous expulsion of pregnancy products</td>
<td>0</td>
<td>4 (11.4%)</td>
<td>0.11 (N.S)</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>4 (11.4%)</td>
<td>1 (2.9%)</td>
<td>0.35 (N.S)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>3 (8.6%)</td>
<td>0</td>
<td>0.23 (N.S)</td>
</tr>
<tr>
<td>Flashing</td>
<td>4 (11.4%)</td>
<td>2 (5.7%)</td>
<td>0.67 (N.S)</td>
</tr>
<tr>
<td>Fever</td>
<td>2 (5.7%)</td>
<td>0</td>
<td>0.49 (N.S)</td>
</tr>
<tr>
<td>Patient satisfaction</td>
<td></td>
<td></td>
<td>0.02*</td>
</tr>
<tr>
<td>- High</td>
<td>27 (77.1%)</td>
<td>34 (97.1%)</td>
<td></td>
</tr>
<tr>
<td>- Moderate</td>
<td>7 (20%)</td>
<td>1 (2.9%)</td>
<td></td>
</tr>
<tr>
<td>- Poor</td>
<td>1 (2.9%)</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

SD: Standard deviation, VAS: visual analog scale, N.S: nonsignificant.
*Statistically significant.
†Cervical dilation ≥ Hegar7.

In our study sublingual route was used for misoprostol administration; adding 200 μg sublingual misoprostol to laminaria resulted in effective cervical dilation in 91.4% and spontaneous expulsion of pregnancy products in 11.4% of patients within four hours of administration, while in three other studies that showed the superiority of combined treatment over either misoprostol or laminaria alone, higher misoprostol dose (400 μg) was added to laminaria through oral or buccal routes [11–13]. On the other hand the studies that showed no superiority for the combined method, several doses of 200 μg misoprostol were administered through vaginal route [14–16]. These results indicate that in the combined method sublingual administration of misoprostol might be the most effective route of misoprostol administration requiring lower dose and duration for cervical dilation. It is documented that the sublingual route of misoprostol administration has more rapid absorption and higher peak levels than vaginal, oral or buccal administration [6,23].

In the current study using the combination of misoprostol plus laminaria for cervical dilation in late first trimester missed abortions was associated with less pain and systemic adverse effects during the waiting period than using misoprostol alone. Additionally at discharge women who received the combined treatment were more satisfied from the received treatment than women who received misoprostol alone. The increased abdominal pain and systemic adverse effects in the control group seem to be due to the higher doses of misoprostol received in this group than the intervention group; misoprostol causes pain through initiating uterine contractures that increase pressure in the lower uterine segment while softening the cervix [12]. It has been shown that when the dose of misoprostol reaches 400 μg and over abdominal cramps and pain increase in all administration routes [13,23]. In the studies of Chen et al. and Jain et al. that compared prostaglandins plus laminaria versus prostaglandins alone, no differences were observed in the pain scores between the two groups, which seem to be due to the equivalent doses of prostaglandins used in both the groups [11,16]. In the study of Drey et al. that compared laminaria alone versus laminaria and misoprostol, after laminaria insertion abdominal pain was significantly higher during the waiting period in patients who received misoprostol [12].

The strengths of our study were comparing for the first time the efficacy of misoprostol plus laminaria to misoprostol alone for cervical dilation in the first trimester, using the sublingual route of misoprostol administration in the combined treatment and comparing two different doses of misoprostol for first trimester cervical dilation. This study however had several limitations; the main ones are that this study was neither placebo-controlled nor blinded. Another limitation was that we did not evaluate the effect of combined treatment on surgical procedure time. Additionally some serious side-effects such as maternal hemorrhage need to be evaluated in further studies with larger sample sizes.

Conclusions

Using a combination of cervical laminaria plus 200 μg sublingual misoprostol four hours prior to surgical process is an effective and rapid method for cervical dilation before surgical management of late first trimester missed abortions. This combined method significantly decreases the requirement for mechanical dilation during surgical process and reduces the required misoprostol dose, and therefore is associated with lower abdominal pain and systemic side effects during the waiting period and higher patients satisfaction at discharge compared to using the recommended 400 μg misoprostol alone for cervical ripening. However, these results need to be confirmed by larger double-blind placebo-controlled studies. Furthermore, the studies are required for comparing the cost-benefit analysis between using the combination method versus using laminaria or misoprostol alone for cervical dilation before surgical management of missed abortions.

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Declaration of interest

The authors report no declarations of interest.

References