**ABSTRACT**

**Aim:** The aim of the present study was to compare the effectiveness and tolerability of 400 μg oral and 400 μg vaginal misoprostol administered 3 or 6 hours before surgical evacuation for termination of pregnancy before 10 weeks of gestation.

**Material and Method:** A total of 210 patients with mostly used four regimens in our department: oral 400 μg misoprostol 3 hours before evacuation (O3), oral 400 μg misoprostol 6 hours before evacuation (O6), vaginal 400 μg misoprostol 3 hours before evacuation (V3), vaginal 400 μg misoprostol 6 hours before evacuation (V6) were retrospectively analyzed.

**Results:** Misoprostol administration regardless to dosage, route and timing had significant effect on cervical dilatation. Dilatation requirement was significantly low in all misoprostol groups compared with control. 5.8% of subjects in control group had abundant blood loss significantly higher than other four groups. Postoperative evaluation showed that hematocrite decrease, endometrial thickness measurement and postoperative analgesic usage were similar in all groups. Preoperative VAS scores were higher in O6 and V6 groups. The most frequent side effect was nausea and it was especially seen in oral (O3, O6) groups.

**Conclusion:** The analyze showed that 400 μg vaginal misoprostol taken 3 hours before vacuum aspiration for voluntary termination of pregnancy before 10 weeks gestation seems as an ideal route and dosage.

**Key words:** Misoprostol; unplanned pregnancy;
AIM

Each year 46 million pregnancies are terminated voluntarily. Nearly 60% of these terminations carried out under safe conditions and the remaining are “unsafe abortions”. At the second half of the twentieth century, dilatation and curettage (D & C) was the most common method for safe termination of early pregnancy until 1960s when the vacuum aspiration gained greater acceptance and has become the standard of care (1,2).

Misoprostol (15-deoxy-16-hydroxy-16-methyl prostaglandin E1) is a synthetic prostaglandin E1 analogue. It was developed by Searle in 1973 for the treatment and prevention of peptic ulcer due to its inhibition of gastric acid secretion and its various mucosa-protective properties (3). Besides this action on the digestive tract, misoprostol is also a strong stimulator of uterine contractility, cervical ripening and dilatation (4). Misoprostol like agents, that have great importance for successful vacuum aspiration, seems to be needed for minimizing the risks related with inadequate cervical dilatation such as incomplete evacuation of the uterine cavity and excessive bleeding due to retained products and damage to the cervix in the form of cervical lacerations or cervical stenosis and incompetence with possible negative impacts on future pregnancies (5).

As a cervix-ripening agent, misoprostol has demonstrated usefulness by both oral and vaginal routes in a dose of 400 μg, as self-administered or as administered by a physician. The oral route mostly caused more side effects than the vaginal route. However there is no consensus about the timing of administration (6-8).

The aim of the present study was to compare the effectiveness and tolerability of 400 μg oral and 400 μg vaginal misoprostol administered 3 or 6 hours before surgical evacuation for termination of pregnancy before 10 weeks of gestation.

MATERIAL AND METHOD

A total of 312 patients complied with gestational age of up to 84 days of amenorrhea were retrospectively analyzed. The patients with systemic disease, history of cervical minor or major operations (electrocautery, conization, cervical cerclage, etc.), active genital infection, bleeding or spotting during the current pregnancy or threatened or missed abortion, multiple pregnancy and basal cervical dilatation greater than 4 mm were excluded from the study.

A total of 210 patients with mostly used four regimens in our department; oral 400 μg misoprostol 3 hours before evacuation, oral 400 μg misoprostol 6 hours before evacuation, vaginal 400 μg misoprostol 3 hours before evacuation and vaginal 400 μg misoprostol 6 hours before evacuation are retrospectively analyzed. Also 42 women without any medication were taken as the control group.

Four different protocols used in the department were assessed retrospectively.

Group 1, oral misoprostol (O3) 400 μg 3 hours before vacuum aspiration (n =48);
Group 2, oral misoprostol (O6) 400 μg 6 hours before vacuum aspiration (n =54);
Group 3, vaginal misoprostol (V3) 400 μg 3 hours before vacuum aspiration (n =56);
Group 4, vaginal misoprostol (V6) 400 μg 6 hours before vacuum aspiration (n =52);
Group 5, control without any medication (n =42);

All the patients were taken for manual vacuum aspiration (MVA) with Karman suction curette under general anesthesia. After the aspiration had ended, the uterine cavity was carefully checked with a curette. All uterine aspirations were performed with the assistance of direct abdominal ultrasound.

RESULTS

Table 1 shows baseline characteristics. The mean age of women was about 30-35 years, with mean gestational week of 6-7 weeks. The four study groups and the control group were similar in terms of demographic variables, gestational age in weeks at the time of surgical evacuation and obstetric history, (gravidity, parity, and number of primiparous and multiparous patients) (Table 1).

<table>
<thead>
<tr>
<th>Group</th>
<th>Age (years) (mean)</th>
<th>Gravidity (mean)</th>
<th>Parity (mean)</th>
<th>D&amp;C (mean)</th>
<th>Vaginal birth (mean)</th>
<th>Caeserean Section (mean)</th>
<th>Gestational week (mean)</th>
</tr>
</thead>
<tbody>
<tr>
<td>O3 (n=48)</td>
<td>31,62</td>
<td>2,62</td>
<td>1,06</td>
<td>0,44</td>
<td>0,62</td>
<td>0,44</td>
<td>6,06</td>
</tr>
<tr>
<td>O6 (n=54)</td>
<td>33,62</td>
<td>3,38</td>
<td>1,5</td>
<td>0,62</td>
<td>0,88</td>
<td>0,62</td>
<td>6,38</td>
</tr>
<tr>
<td>V3 (n=56)</td>
<td>35,21</td>
<td>3,07</td>
<td>1,43</td>
<td>1,36</td>
<td>0,93</td>
<td>0,50</td>
<td>6,43</td>
</tr>
<tr>
<td>V6 (n=52)</td>
<td>30,67</td>
<td>2,92</td>
<td>0,96</td>
<td>0,25</td>
<td>0,63</td>
<td>0,33</td>
<td>6,42</td>
</tr>
<tr>
<td>Control (n=42)</td>
<td>31,35</td>
<td>2,68</td>
<td>1</td>
<td>0,40</td>
<td>0,45</td>
<td>0,55</td>
<td>6,20</td>
</tr>
</tbody>
</table>
Operative outcome measures

In the operation room; the postmedication cervical dilatation before termination, duration of the procedure and intraoperative bleeding, need for dilatation were evaluated.

Before termination in the operating room, the size of the largest Hegar’s dilator that could be passed into the cervical os without resistance was recorded as the cervical dilatation achieved by medication. The mean dilatation recorded for all groups were 4.06, 5.25, 5.93, 6.07 and 2.95 respectively. Misoprostol administration regardless to dosage, route and timing had significant effect on cervical dilatation (Table 2).

The need for dilatation was also assessed in all groups. 62.5% of O3 group, 62.9% of O6 group, 67.8% of V3 group and 63.4% of V6 group didn’t need any intraoperative dilatation before evacuation. On the other side 73.9% patients without medication needed dilatation. Dilatation requirement was significantly low in all misoprostol groups compared with control, but no difference was found between the misoprostol groups (Table 2).

Surgical time was measured immediately from the speculum inserted after the general anesthesia had been administered until the speculum had been removed at the end of the procedure. The surgical timings were 9.56, 9.38, 9.00, 9.00 and 10.85 minutes in groups 1-5 respectively. The time spent for evacuation was less in group 1, 2, 3, 4 then group 5 but was not significant (Table 2). The surgical termination was unsuccessful in two of the control group subjects. The surgeon was unable to pass the Carmen cannula from the cervical os in both patients.

Intraoperative blood loss was subjectively measured by the surgeon as scarce, usual or abundant (Table 3). All misoprostol groups had similar results for intraoperative blood loss. 5.8% of subjects in control group had abundant blood loss significantly higher then other four groups.

Postoperative outcome measures

Postoperatively subjects were assessed 2 hours and 7 days after the surgical procedure. None of the subjects had serious postoperative complications. The vital signs were evaluated for 2 hours and all the patients were discharged 2 hours after the procedure. In the 7th day postoperative examination, the hematocrite levels, endometrial thickness and postoperative analgesic requirement were examined.

Preoperative hematocrite levels of the five groups were (O3:36.6% O6:34.3% V3:36.3% V6:34.5% Control:

<table>
<thead>
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<th>Table 2. Preoperative outcome measures</th>
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<tr>
<td>Cervical dilatation achieved by medication (mean)*</td>
</tr>
<tr>
<td>O3 (n=48)</td>
</tr>
<tr>
<td>O6 (n=54)</td>
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<tr>
<td>V3 (n=56)</td>
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<tr>
<td>V6 (n=52)</td>
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<tr>
<td>Control (n=42)</td>
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* The size of the largest Hegar’s dilator that could be passed into the cervical os without resistance was recorded as the cervical dilatation
¶ P<0.05 Control group compared with study groups

<table>
<thead>
<tr>
<th>Table 3. Intraoperative blood loss</th>
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<tr>
<td>Scarce</td>
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<tr>
<td>O3 (n=48)</td>
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<td>O6 (n=54)</td>
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<td>V3 (n=56)</td>
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<td>Control (n=42)</td>
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¶ P<0.05 Control group compared with study groups
36.4%) similar, and did not changed postoperatively at the seventh day (O3:36.1% O6:33.5% V3:35.7% V6:34% Control:35.6%). When postoperative follow-ups were evaluated, the number of days of spotting or bleeding after vacuum aspiration showed no difference between the groups (O3:4.1, O6:4.6, V3:4.3, V6:3.4, Control:5.1, in days).

Seven days after evacuation, mean endometrial thickness measured by transvaginal ultrasonography (General electric Logic 200) in the misoprostol groups were similar to each other and control group. (O3:3.31mm, O6:4.75mm, V3:3.79mm, V6:4.25, Control:4.55mm). Postoperative analgesic requirement which was assessed by the number of pills used during this period was similar for all groups.

Complications, side effects and pain scores

The pain scores and side effects of the medication just before the surgical procedure were analyzed. The degrees of the pain of the subjects were tested by VAS (visual analogue scale) which was a horizontal line, 10cm in length. The subjects marked on the line, the point that they felt, representing their pain perception of the current state. The pain score was determined by measuring in centimeters from the left hand end of the line to the point that the patient marked. The pain VAS scores were measured before evacuation, 2 hours after evacuation and seven days after evacuation.

The mean VAS score before evacuation were statistically high in O6 (4,38) and V6 (4,33) groups. O3 (1,88) and V3 (1,86) groups’ VAS scores were slightly higher then the control (0,92) but not statistically significant. The VAS scores at the 2nd hour and 7th day were also assessed and no difference was found (Table 5).

The side effects evaluated preoperatively were shown in Table 5. The mostly seen side effect of misoprostol was nausea. The other mostly seen side effects were; vomiting, fever and diarrhea. Nausea was significantly higher in oral groups rather then vaginal and control groups. Nearly 1/3 of the subjects in oral groups experienced nausea without vomiting. Vomiting, fever and diarrhea was similar in all groups.

The presence of vaginal bleeding before the surgical procedure was also assessed. The bleeding was seen in 25%, %25.9, 30.3%, 51.9% and 0.02% of subjects in group1-5 respectively. It was significantly high in V6 group then control and other study groups (Table 6).

DISCUSSION

There are many different protocols used for first
trimester pregnancy termination. Especially in developing countries, since the educated trained staff number is not enough, some non-surgical abortion techniques are provided as well. These medical techniques usually include mifepristone followed by prostaglandin analogue. But for many countries like Turkey, since mifepristone is not available, surgery still seems to be the first choice for voluntary termination. In this retrospective analyze we tried to find answer for three simple questions. Should misoprostol be given as a premedication before manual vacuum aspiration (MVA) with Karman suction curette under general anesthesia for pregnancy termination before 10 weeks of gestation? If yes, what should be the route of administration and when should be the ideal timing?

In the study we assessed two different routes (oral and vaginal) and two different timing (3 and 6 hour before procedure) and compared with a control group without any medication. Zieman et al.(9) performed the first pharmacokinetic study comparing the oral and vaginal routes of administration in 1997. They found out that the area under the plasma concentration-versus-time curve (AUC) which represents the bioavailability of misoprostol after vaginal administration was significantly greater than that following oral administration.

Postmedication cervical dilatation before termination & Need for dilatation & Preoperative bleeding

As we focused on the preoperative parameter analyze, in the analyze it’s obvious that regardless to timing, vaginal administration of misoprostol have greater effect on cervical dilatation. But the average dilatation for both vaginal and oral routes was lower then previously reported studies (10-12) but similar to one reported from Spain (13). Also the evacuation with prior vaginal premedication needed less dilatation. Both the oral and vaginal group needed statistically significant less dilatation then the control group (14).

Decreasing the need for cervical dilatation has the potential to decrease the number of uterine perforations that may complicate up to 2% of the first trimester surgical abortions (15). On the other hand, most of the uterine perforations are clinically unnoticed without causing serious complications and the incidence may be as low as 0.12% in the experienced hands of senior surgeons.

The strong actions of vaginal groups on cervix uteri brought out an unwanted problem. 51.9% of V6 group subjects had bleedings preoperatively which was higher then the oral and control group. This is an important side effect of the medication that may decrease the patients’ compliance to the procedure and the comfort of the subjects.

Intraoperative bleeding & Duration of the procedure

Intraoperative blood loss was less in the vaginal groups but statistically there were no difference between the five groups, however it’s not measured but the staff’s observations were considered. The loss was reported similar in recent studies, too (13).

Duration of the procedure did not differ between the groups, and it was longer to what has been reported by others (5) However, the terminations in our study were all done by second year trainees which may explain the long duration of the procedure (16,17).

VAS score

Regarding pain scores as assessed using the VAS, O3, V3 and control groups were nearly same prior to evacuation (Table 5). O6 and V6 groups had significantly higher scores preoperatively. Two hours and seven days after evacuation, pain scores were comparable for all the misoprostol and control groups. The total number of analgesic pills used between evacuation and the seventh day were high in O6 and control groups (O3:1.88, O6:2.50, V3:1.36, V6:1.00, Control:2.35).

The hematocrite levels & Mean endometrial thickness

Preoperative hematocrite levels of the groups were changed minimally and similarly in all groups without any significant differences. Also we evaluated the number of days of bleeding or spotting after the procedure, showing no significant differences between any groups. Prior
medication did not significantly effect the bleeding postoperatively as previously shown in other researches (5).

In the present study, the mean thickness of endometrial line was evaluated 7 days after evacuation finding no differences between the groups. As previously analyzed postoperative thickness is an important indicator for a successful termination procedure (18-20).

Although the endometrial line was thinner in O3 and V3 groups, all groups had lines lower than 5mm that indicated a successful termination without any rest tissue.

Complications and Side Effects

There were many conflicting results for side effects of misoprostol used at the first trimester. Except the nausea the side effects of misoprostol was minimal in our study. The oral group had higher incidence of nausea compared with the vaginal and control groups. We found no difference between oral, vaginal and control group when compared the other side effects like, vomiting, fever and diarrhea. Previously many other researches proved the higher gastrointestinal side effects after oral route (21-26).

The overall bioavailability is higher with vaginal misoprostol, but peak plasma concentration is higher with oral than with vaginal route and it is believed that this high peak plasma concentration may be the cause of the increased systemic adverse effects (27).

As a conclusion, the study showed that 400 μg vaginal misoprostol taken 3 hours before vacuum aspiration for voluntary termination of pregnancy before 10 weeks gestation seems as an ideal route and dosage by decreasing the need for cervical dilatation with higher cervical dilatation levels with fewer side effects. Vaginal misoprostol given 6 hours before the procedure have high preoperative bleeding ratio and pain scores which limits its usage.

REFERENCES


