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Comparison of oral and vaginal misoprostol for cervical ripening before manual vacuum aspiration of first trimester pregnancy under local anesthesia: a randomized placebo-controlled study

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Abstract

The objective of this prospective randomized placebo-controlled study was to determine the effectiveness of 400 μg oral and 400 μg vaginal misoprostol administration for cervical priming 3 h prior to manual vacuum aspiration (MVA) under local anesthesia for voluntary termination of pregnancy before 10 weeks of gestation in comparison with placebo oral or placebo vaginal administration ($n=40$ in each group). Postmedication cervical dilatation was similar in the oral (mean, 6.6±1.5) and vaginal (mean, 7.2±0.8) misoprostol groups but significantly higher compared with the oral (mean, 3.4±0.2) and vaginal (mean, 3.6±1.9) placebo groups. Duration of the procedure was also significantly shorter in the misoprostol groups in comparison with their placebo counterparts. Preoperative bleeding and side effects were more common in the misoprostol groups, but none required medical intervention. Intraoperative bleeding was less in the vaginal misoprostol group compared with the placebo groups. There was no significant difference in terms of visual analogue scores during the procedure, patient satisfaction, days of postoperative bleeding and rate of postoperative complications among the groups. Cervical priming with misoprostol administered orally or vaginally 3 h before MVA for termination of pregnancy under local anesthesia facilitates the procedure by decreasing the need for cervical dilatation and by shortening its duration without improving patients' pain perception and satisfaction mainly due to side effects.

Keywords: Cervical dilatation; Misoprostol; Manual vacuum aspiration

1. Introduction

Termination of pregnancy up to 10 weeks of gestation on voluntary basis has been legal in Turkey since 1983. As the rate of induced abortion is remarkably high (20 per 100 live births), improving the quality of abortion services is a major concern [1]. Manual vacuum aspiration (MVA) is a widely accepted safe method for termination of early pregnancies and is usually performed as an outpatient procedure [2].

Cervical dilatation is a critical step in MVA since several complications have been found associated with forceful mechanical dilatation [3]. Agents that induce cervical priming are proposed 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. Misoprostol is an orally active, synthetic 15-deoxy-16-hydroxy 16-methyl analogue of naturally occurring prostaglandin E1 currently used for prevention and treatment of peptic ulcers. Previous studies have shown that its oral, vaginal and sublingual routes are effective in cervical priming [4–6]. The optimal treatment regimen of misoprostol for this purpose is described as 400 μg administered at least 3 h before vacuum aspiration in most studies [7,8] and the procedures were carried out under general anesthesia or conscious sedation [5–8].

In the present study, we aimed to evaluate the effectiveness of oral and vaginal 400-μg misoprostol administrations in comparison with placebo in cervical priming prior to MVA performed under local anesthesia.

2. Materials and methods

Women who applied to our Family Planning Clinic between April and September 2003 for voluntary termina-

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tion of pregnancies of 7 to 10 weeks' duration, which is the upper limit for legal termination in Turkey, were included in the study. The local ethics committee approved the study. The exclusion criteria were presence of systemic disease, contraindication to misoprostol use, history of cervical minor or major operations (electrocautery, conization, cervical cerclage, etc.), bleeding or spotting during the current pregnancy or threatened or missed abortion, pregnancy less than 7 weeks' duration, multiple pregnancy and basal cervical dilatation greater than 4 mm. Patients were informed about the study and women who volunteered to participate in the study were asked to sign an informed consent form. All the patients had a vaginal examination and evaluation of basal cervical dilatation using Hegar's dilator in a descending order starting with Hegar No. 5 without using a teneculum and those with a cervical dilatation of 4 mm or greater were excluded from the study.

Medical and obstetric history and gestational age calculated via last menstrual period and confirmed by transvaginal ultrasonography were recorded. Preoperative hemoglobin values were measured and patients with a hemoglobin level less than 10 g/dl were not included in the study.

After the initial evaluation, 160 women were recruited in the study. A flowchart of the study is presented in Fig. 1. The study was conducted as a double-blind randomized trial and the patients were randomly allocated to one of the following: Group 1, oral placebo ($n=40$); Group 2, vaginal placebo ($n=40$); Group 3, oral misoprostol 400 μg ($n=40$); and Group 4, vaginal misoprostol 400 μg ($n=40$). A computer-based restricted stratified randomization was generated by a member of the staff (EC) who was not involved in the surgical procedure. The midwives applied the medications after initial examination and concealed the randomization code until study completion in a sealed envelope. The study was an intention-to-treat analysis but no protocol deviations occurred after randomization. The physician (LC) responsible for the initial examination and operative procedure was blinded to the study groups. All women who fasted overnight were admitted on the morning

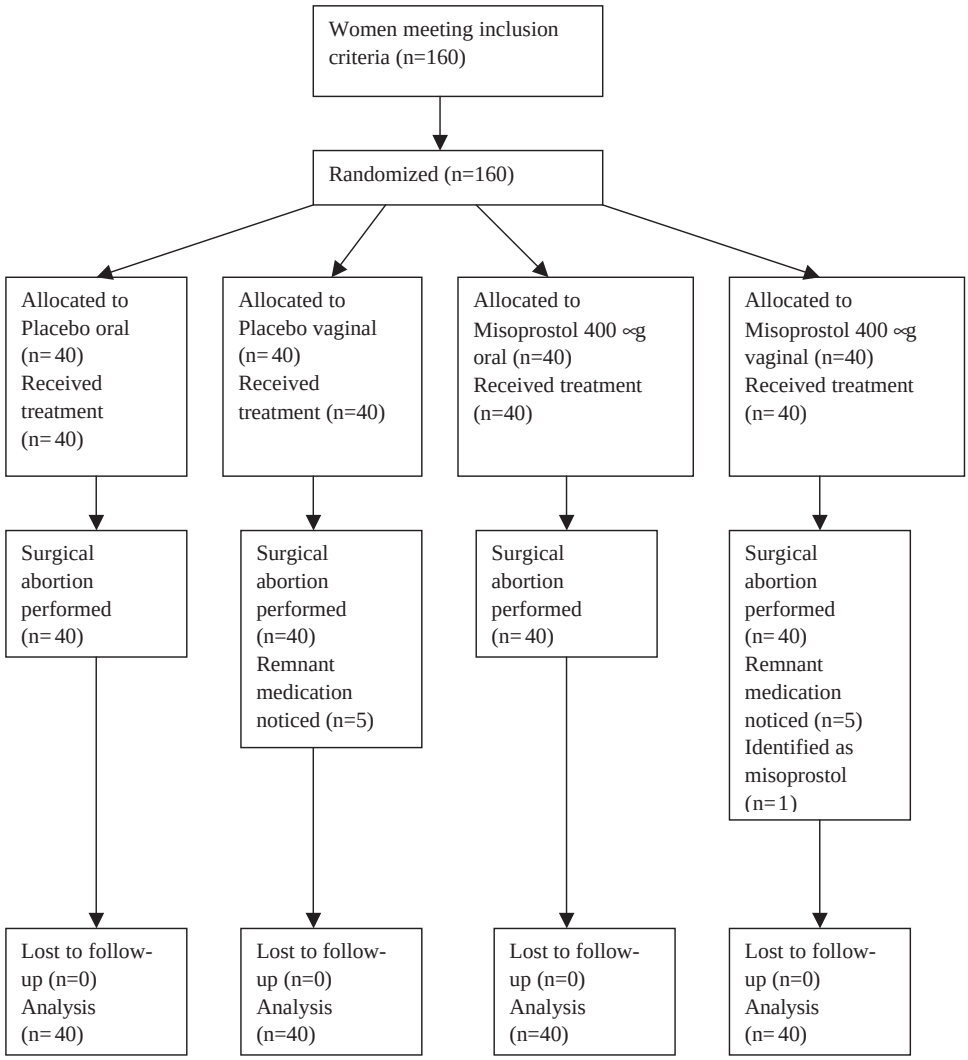

Fig. 1. Flowchart of the study.

of the surgical procedure and either 2 placebo tablets (Placebo, Plantafarma, Turkey) or 2 misoprostol tablets (Cytotec, Ali Raif, Turkey) were either placed into the posterior vaginal fornix or given to the patients for oral use. The patients were observed for 3 h, no premedication was given, but it was mentioned that analgesics and antiemetics were available if required. Their blood pressure, pulse rate and body temperature were measured just before the surgical procedure. Side effects related to misoprostol such as nausea, vomiting, abdominal pain, vaginal bleeding, headache and elevation of body temperature were recorded.

All the patients were taken for MVA with Karman suction curette 3 h after the administration of the tablets. The operations were performed by the same surgeon (LC) blinded to the randomization schedule in order to reduce individual variation. Remnants of vaginal medications were noticed in five (12.5%) patients of Group 2 and six (15%) patients of Group 4 but the tablet was identified to be misoprostol in only one patient by the surgeon. Given the low percentage of vaginal remnants noticed, outcome measures are not likely to be biased. A pad placed after the medication was weighed. The difference in — after and before — weight was calculated. A 1-g increase in weight was considered to be equivalent to 1 ml of blood (i.e., specific gravity, 1 g/ml). Blood collected in the vagina was drained into a glass jar and was added to the measurement of the preoperative blood loss. The degree of cervical dilatation before the operation was measured by passing Hegar's dilators in a descending order starting with Hegar No. 10. The size of the largest Hegar's dilator that could pass through the cervical os without resistance was recorded as the postmedication cervical dilatation (PMCD) achieved. No further dilatation was performed when the cervix was dilated to 7 mm or greater and the pregnancy was evacuated with a 7-mm diameter aspiration cannula. Paracervical block (1% lidocaine) was performed in all patients after assessment and recording of preoperative cervical dilatation. In case of dilatation less than 7 mm, the cervix was dilated up to 7 mm for MVA. The change in cervical dilatation was calculated by subtracting basal cervical dilatation from the PMCD achieved. Duration of the procedure, intraoperative bleeding and pain and other complications that occurred were recorded. Duration of the procedure included the time required for dilatation in cases where additional dilatation was necessary. Intraoperative blood loss was taken as the volume of blood measured after sieving away the products of conception from the uterine aspirate. Intraoperative pain was measured by asking each patient to evaluate the pain using a 100-mm visual analogue scale. Patient satisfaction was assessed by asking the subjects to indicate their degree of satisfaction on a five-point scale: 1=*strongly dissatisfied*; 2=*dissatisfied*; 3=*neutral*; 4=*satisfied*; 5=*very satisfied*.

The patients were observed for 2 h after the operation and doxycycline (2×100 mg) and paracetamol (3×500 mg) were prescribed before discharge. Patients were asked to come back for follow-up 7 to 10 days later and to record the postoperative bleeding days on a calendar. In the follow-up visit, duration of postoperative bleeding and side effects were questioned and recorded. None of the patients were lost to follow-up. Blood samples were taken for measurement of postoperative hemoglobin levels. Patients with a query of retained products of conception had a transvaginal ultrasonographic examination and management in due course.

In the calculation of the sample size, the difference in cervical dilatation was taken as the main outcome measure. A difference of 2 mm or greater between the pretreatment and posttreatment cervical dilatation was considered as meaningful and the number of patients in each group was calculated as 37 using 0.05 Type 1 error and 0.90 power. Estimating some 10% loss to follow-up, the sample size for each group was determined as 40.

All data were recorded using standard forms. SPSS (Statistical Package for Social Sciences) for Windows was used for statistical analysis. The results were given as mean±SD and as percents. Continuous variables were analyzed by analysis of variance (ANOVA) and Tukey tests; for the nonparametric tests, Kruskal–Wallis was

Table 1
Patient characteristics of four study groups

Variables	Placebo oral (n=40)	Placebo vaginal (n=40)	Misoprostol oral (n=40)	Misoprostol vaginal (n=40)	p
Age	31.4±5.8	30.3±5.7	29.9±6.4	30.9±6.09	.7[a]
BMI (kg/m^2)	24.1±3.3	23.9±3.6	24.2±3.9	25.1±4.1	.7[a]
Gestational age (days)	54.5±4.7	55±4.6	55.5±5.4	55.5±5.3	.8[a]
Gravida	4.5±1.8	4±1.7	4.1±1.8	4±1.4	.4[a]
Parity	2.5±1.2	2.3±1.1	2.3±1.2	2.1±0.8	.4[a]
Nulliparous	–	1 (2.5)	1 (2.5)	–	
Primaparous	7 (17.5)	10 (25)	9 (22.5)	8 (20)	
Multiparous	33 (82.5)	29 (72.5)	30 (75)	32 (80)	
Spontaneous abortion (≥1)	5 (12.5)	6 (15)	9 (22.5)	10 (25)	.6[b]
TOP (≥1)	13 (32.5)	12 (30)	12 (30)	14 (35)	.4[b]

Data are given as mean±SD or as n (%). BMI indicates body mass index (weight/height^2); TOP, termination of pregnancy.

[a] Not statistically significant (p>.05), ANOVA, Tukey test.

[b] Not statistically significant (p>.05), χ^2 test.

used. Comparisons were made by χ^2 test for the categorical data. For all comparisons, p<.05 was considered statistically significant.

3. Results

The four study groups were similar in terms of demographic variables, gestational age and obstetric history (Table 1). There were 40 women in each group. The maternal and gestational age ranges were 17–41 years and 49–68 days, respectively.

None of the patients aborted during the interval between drug administration and the MVA procedure. Operative findings are presented in Table 2. Basal cervical dilatation was uniform in all groups. Postmedication cervical dilatation achieved was significantly higher in the oral and vaginal misoprostol groups (Group 3, 6.6±1.5 mm; Group 4, 7.2±0.8 mm) compared with the placebo groups (Group 1, 3.4±2 mm; Group 2, 3.6±1.9 mm; p<.001). The change in cervical dilatation was significantly lower, the requirement for additional cervical dilatation was thus more frequent, in the placebo groups compared with the misoprostol groups.

The preoperative blood loss was significantly higher in the misoprostol groups while the duration of the operation was significantly shorter when compared with the placebo groups (Table 2). Only vaginal misoprostol caused significantly less intraoperative blood loss when compared with the placebo groups while the mean intraoperative blood loss of the oral misoprostol group was not significantly different from the placebo groups or the vaginal misoprostol group.

The mean visual analogue scores of the groups were similar (Table 2). The mean patient satisfaction score was 3.4±1 for oral placebo, 3.3±1.1 for vaginal placebo, 3.6±1 for oral misoprostol and 3.8±0.9 for vaginal misoprostol (p=.1). Also, the rate of patients indicating that they were satisfied or very satisfied with the procedure was comparable among Groups 1, 2, 3 and 4 (52.5%, 50%, 67.5% and 65%, respectively; p=.2).

Table 3
Side effects in the study groups [*n* (%)]

	Placebo oral (*n*=40)	Placebo vaginal (*n*=40)	Misoprostol oral (*n*=40)	Misoprostol vaginal (n=40)	p
Any side effect	11 (27.5)	14 (35)	37 (92.5)	35 (87.5)	<.001[a]
Nausea	7 (17.5)	11 (27.5)	23 (57.5)	19 (47.5)	.003[a]
Vomiting	2 (5)	–	4 (10)	2 (5)	.1[a]
Abdominal pain	6 (15)	10 (25)	28 (70)	30 (75)	<.001[a]
Diarrhea	1 (2.5)	–	2 (5)	1 (2.5)	.5[b]
Headache	3 (7.5)	–	–	2 (5)	.1[b]
Fever	–	–	2 (5)	–	.4[b]
Vaginal bleeding	1 (2.5)	2 (5)	21 (52.5)	23 (57.5)	<.001[a]

[a] χ^2 Test, Groups 1 and 2 are statistically different from Groups 3 and 4. No difference between Group 1 and Group 2 and Group 3 and Group 4.
[b] χ^2 Test, no statistically significant difference between the groups.

Side effects are summarized in Table 3. Most of the patients in the misoprostol groups (92.5% in Group 3 and 87.5% in Group 4) experienced any one of the side effects related with the drug, but none of them needed an intervention or interruption of the procedure. None of the patients had intraoperative or postoperative complications. Postoperative vital signs were stable and all the patients were sent home uneventfully.

Preoperative hemoglobin values of the groups were 12.4±0.8, 12.1±0.9, 12.3±0.6 and 12.2±0.9 g/dL, respectively, and they changed minimally and similarly in all groups. When postoperative follow-ups were evaluated, the number of days of bleeding after MVA showed no difference between the groups (in days: Group 1, 4.6±1.2; Group 2, 4.8±1.3; Group 3, 4.4±1.5; Group 4, 4.3±1.2; p=.6), and change in hemoglobin levels by the 10th postoperative day was similar (in g/dL: Group 1,

Table 2
Distribution of operative findings among the study groups

Variables	Placebo oral (*n*=40)	Placebo vaginal (*n*=40)	Misoprostol oral (*n*=40)	Misoprostol vaginal (*n*=40)	p
Basal cervical dilatation (mm)	2±1.8	2.3±1.5	2.2±1.5	2.3±1.5	.2[a]
PMCD achieved	3.4±2	3.6±1.9	6.6±1.5	7.2±0.8	<.001[b]
Change in cervical dilatation[c]	1.4±0.5	1.3±0.7	4.4±1.2	4.9±1.4	<.001[b]
No. of patients requiring dilatation	36 (90)	34 (85)	4 (10)	2 (5)	<.001[d]
Preoperative blood loss (mL)	0.1±0.2	0.2±0.3	3.2±0.7	3.1±0.9	<.001[b]
Intraoperative blood loss (mL)	73±17	70±14	66±16	57±14	<.05[e]
Duration of operation (min)	5.1±1	4.8±1.7	3.9±1	3.8±0.9	<.001[b]
Intraoperative pain (0–100 mm)	62±12	64±16	59±12	61±12	.6[a]

Data are given as mean±SD or *n* (%).
[a] Not statistically significant (p>.05), ANOVA, Tukey test.
[b] Groups 3 and 4 are significantly different from Groups 1 and 2, ANOVA, Tukey test.
[c] Postmedication minus basal cervical dilatation.
[d] Groups 3 and 4 are statistically significantly different from Groups 1 and 2, χ^2 test.
[e] Group 4 is statistically significantly different from Groups 1 (p=.03) and 2 (p=.04), no difference between Group 4 and Group 3, ANOVA, Tukey test.

0.3±0.2; Group 2, 0.2±0.3; Group 3, 0.3±0.3; Group 4, 0.3±0.2; p=.8).

4. Discussion

Induced abortions may lead to severe morbidity and mortality if not managed appropriately [9]. As in our study, most surgical abortions are carried out in ambulatory settings under local anesthesia and the World Health Organization recommends the use of manual and electronic vacuum aspiration as a safer alternative to dilatation and curettage [10,11].

Since termination of pregnancy is performed as an outpatient procedure or day case in most of the facilities, it is important to determine the time of misoprostol application prior to surgery as the patients will be waiting at the clinic for the surgery. Although misoprostol might well be administered the night before the operation without supervision, there is a major concern about a patient changing her mind after drug administration as misoprostol is known to have teratogenic effects [12]. An evacuation time interval of 3 to 4 h seems to be the most preferred choice since increasing the time interval does not appear to provide any positive effect on the degree of cervical dilatation but may cause some unwanted complications such as bleeding from incomplete abortion [13]. None of the patients in the current study aborted in the 3-h interval after misoprostol administration.

We found that vaginal and oral applications of misoprostol were equally effective in achieving cervical dilatation and have similar operating times and intraoperative blood loss as reported by Ashok et al. [14]. Our study is different from other trials on misoprostol use for cervical priming [4–8,12–15] in that we included placebo groups for both routes to evaluate clinical outcomes objectively. Misoprostol use caused an average of 3 ml more preoperative blood loss and about 13–16 ml less intraoperative blood loss without a significant change in postoperative bleeding days and hemoglobin levels by postoperative Day 10. Although the number of patients requiring additional cervical dilatation was less frequent in the misoprostol groups, this led to only a 2-min decrease in the duration of the operation.

None of these significant differences have the potential to cause profound clinical improvements except the decrease in the number of patients requiring additional cervical dilatation. 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 [16]. 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 [16,17]. Also, misoprostol has the potential to decrease the frequency of incomplete abortions and a continuing pregnancy that may complicate 5.4% of the surgical abortions [16]. As a consultant gynecologist performed all the procedures in our study, we did not observe any of these complications.

Analgesia during induced abortion is usually provided with paracervical block and backed up with nonsteroid analgesics and continuous sedation augmentation [18]. In a study, 50% of the patients undergoing surgical abortion in the first trimester under local anesthesia described the pain during the procedure as mild or moderate [19]. Preoperative treatment of the cervix with prostaglandin E1 was reported to increase pain intensity [20]. We found similar intraoperative pain scores in the misoprostol and placebo groups. Although the placebo groups more frequently required additional cervical dilatation, no increase in pain scores may be attributed to the efficacy of paracervical block performed in all procedures. Also, the most common side effect of the misoprostol groups was abdominal pain due to uterine contractions that may have negated the possible decrease in pain scores expected due to the lower rate of cervical dilatation needed.

Although oral misoprostol use was related with a higher incidence of nausea than the vaginal route [16], the difference was not statistically significant in our study. Obviously, drug-related side effects were more frequent in the misoprostol groups compared with the placebo groups. The unexpectedly high incidence of side effects in the placebo groups may have resulted from vaginal examination and evaluation of basal cervical dilatation. Also, the fact that all the patients had to spend 3 h in the clinic waiting for a surgical intervention may have contributed to the rate of side effects via increasing psychological stress. These possible confounders and similar pain scores resulted in similar patient satisfaction scores in the misoprostol and placebo groups.

We conclude that cervical priming with misoprostol administered at a dose of 400 μg po or vaginally 3 h before MVA for termination of pregnancy under local anesthesia facilitates the procedure by decreasing the need for cervical dilatation and by shortening its duration without improving pain perception and patient satisfaction mainly due to the side effects.

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