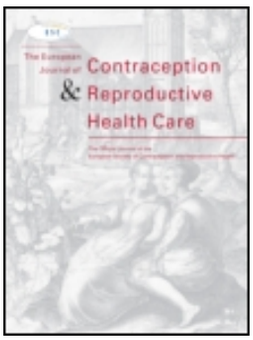

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Sublingual versus vaginal misoprostol for cervical ripening PRIOR TO manual vacuum aspiration under local anaesthesia: A randomized study

E. Caliskan, T. Filiz, G. Yucesoy, E. Coskun, B. Vural and A. Corakci

Department of Obstetrics and Gynaecology, Kocaeli University, School of Medicine, Kocaeli, Turkey

ABSTRACT

Objective To compare the effectiveness of sublingual and vaginal misoprostol application for cervical ripening prior to manual vacuum aspiration (MVA) under local anaesthesia for voluntary termination of pregnancy between 7 and 10 weeks of gestation.

Materials and methods Prospective randomized study in which 72 women were randomly assigned to administration of either 400 μg vaginal misoprostol 3 hours prior to or 200 μg sublingual misoprostol 2 hours prior to the surgical procedure. We took the pre-operative cervical dilatation that was achieved as the main outcome measure. The duration of the procedure, intra-operative blood loss, pain perception before and during the operation, patients' satisfaction, side effects and duration of post-operative bleeding were secondary outcome measures.

Results A similar pre-operative cervical dilatation was achieved in the sublingual and the vaginal groups (6.9 $\pm$ 1.6 mm and 6.6 $\pm$ 1.1 mm, respectively; $p = 0.3$). The duration of the operation, intra-operative blood loss, and patients' satisfaction did not differ between the two groups. Pain scores were significantly higher in the sublingual group than in the vaginal group, both after administration of misoprostol ($p = 0.02$) and during the procedure ($p = 0.02$). Nausea and vaginal spotting were significantly more frequent ($p = 0.01$ and $p = 0.003$, respectively), but post-operative bleeding significantly shorter ($p = 0.003$) in the sublingual group.

Conclusion Administration of 200 μg sublingual misoprostol 2 hours before suction curettage under local anaesthesia was as effective as 400 μg vaginal misoprostol 3 hours before that procedure with regard to achieving cervical dilatation. It resulted in higher pre-operative and intra-operative pain scores without changing patients' satisfaction.

KEY WORDS Cervical dilatation, Misoprostol, Manual vacuum aspiration, Termination of first trimester pregnancy, Induced abortion, Pre-operative ripening of the cervix

Correspondence: Eray Caliskan, Adnan Kahveci cd. Menekse sok. No: 37, Madenler Yapi Koop A2 Blok D:9, 41900 Yenikent, Derince, Kocaeli, Turkey. Tel: 0090-262-2331242. Fax: 0090-262-2335488. E-mail: eray68@hotmail.com

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INTRODUCTION

Manual vacuum aspiration (MVA), as an out-patient procedure, is currently, in many countries, the standard modality of induced abortion up to 12 weeks of gestation. Its success rate exceeds 95%[1]. Complications include excessive bleeding, incomplete abortion, cervical tear, stenosis or incompetence, and uterine perforation[2]. Cervical dilatation is the most critical step in vacuum aspiration as cervical and uterine injuries are often due to forceful dilatation of the cervix.

The advantages of pharmacological over mechanical cervical dilatation are well established[3]. Misoprostol, a synthetic 15 deoxy-16 hydroxyl 16-methyl analogue of naturally occurring prostaglandin E_1, has been administered orally, sublingually, rectally, and vaginally[4]. Oral and vaginal misoprostol are equally effective in achieving cervical dilatation and shortening the duration of the procedure[5]. A recent pharmacokinetic study has shown that sublingual misoprostol has a higher systemic bioavailability and requires less time to reach peak concentration in the serum than equal doses given via the oral or the vaginal routes[6]. Patients prefer oral to vaginal administration of misoprostol because it avoids vaginal manipulation[7]. Moreover, the serum concentrations following vaginal misoprostol being maintained longer, but remaining lower up to 240 minutes, a longer time is required to achieve maximum effect[8].

In the present study, we compared the preoperative cervical dilatation achieved with 200 μg sublingual misoprostol 2 hours prior, with that effected by 400 μg vaginal misoprostol administered 3 hours prior to MVA.

MATERIALS AND METHODS

We recruited women booked for voluntary termination of pregnancy (TOP) at 7–10 weeks of gestation. The local ethics committee approved the study. The exclusion criteria were systemic disease, a contraindication to misoprostol use, and a history of minor or major operations on the cervix (cauterization, cone biopsy, cerclage, etc.). Bleeding or spotting during the current pregnancy, threatened or missed abortion, pregnancy of less than 7 weeks duration, multiple pregnancy and basal cervical dilatation of more than 4 mm were also reasons for exclusion. All eligible patients were informed about the study protocol and those willing to participate signed an informed consent form. One of the consultants (GY) performed a vaginal examination on all participants. While patients were in the lithotomy position, the basal cervical dilatation and length were measured by ultrasound using a Siemens Versa plus® machine equipped with a 5 MHz transvaginal probe. The probe was placed in the vagina at approximately 3 cm from the cervix to avoid any cervical distortion and a sagittal view of the cervix, with the echogenic endocervical mucosa along the length of the canal, was obtained. We used calipers to measure the length of the cervical canal, being the distance between the furthest points at which the cervical walls were juxtaposed[9]. The diameter of the endocervical canal at the nearest point to the external cervical os was recorded as the cervical dilatation. Gestational age was confirmed by the measurement of crown–rump length.

After the initial evaluation, we enrolled 72 women in the study. Figure 1 presents the flow chart of the study. The study was conducted as a randomized trial; patients randomly allocated to group 1 were to receive 200 μg misoprostol sublingually ($n = 36$), those allocated to group 2 were given 400 μg misoprostol vaginally ($n = 36$). A computer-based restricted

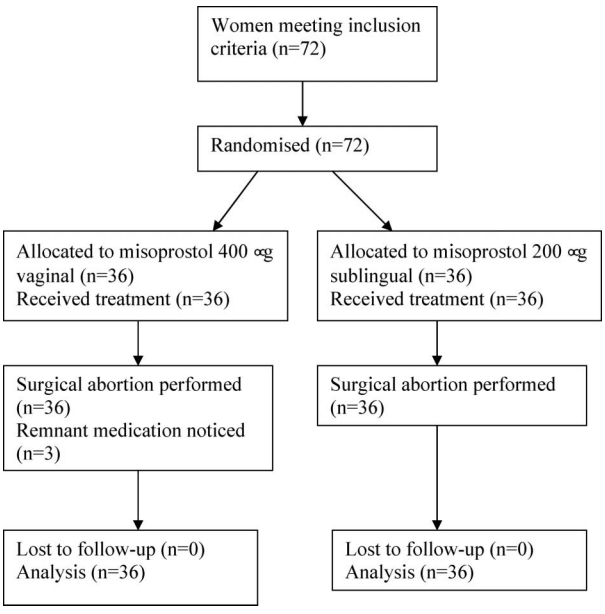

Figure 1 Flow chart of the study

stratified randomization was generated by a member of the staff (TF) who was not involved in the surgical procedure. The midwives administered the medications after initial examination and concealed the randomization code in a sealed envelope until completion of the study. The study was 'intention to treat', but no protocol deviations occurred after randomization. The procedures were performed by the same doctor (EC).

On the morning of the surgical procedure two misoprostol tablets (Cytotec®, Ali Raif Co, Turkey) were inserted into the posterior vaginal fornix 3 hours prior to the surgical procedure or one misoprostol tablet was placed under the tongue 2 hours before surgery, the patient having been warned not to swallow the tablet. All patients received 75 mg diclofenac sodium (Diclomec®, Abdi İbrahim Co, Turkey) 3 hours before the suction curettage; they were told that analgesics and anti-emetics were available if required. Their blood pressure, pulse rate and temperature were measured just before the surgical procedure. We informed about side effects of misoprostol, such as nausea, vomiting, abdominal pain, vaginal bleeding, headache and feverishness.

Remnants of vaginal medications were noticed in three (8.3%) patients of group 2 during MVA. Given the low frequency of vaginal remnants noticed, interpretation of the findings is not likely to be biased. 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 post-medication cervical dilatation achieved. No further mechanical dilatation was performed when the cervix was dilated to 7 mm or more, and the products of conception were evacuated with a 7-mm diameter Karman cannula. A paracervical block with 10 mL of 1% lidocaine was applied in all patients after the pre-operative cervical dilatation had been assessed and recorded. If this latter amounted to less than 7 mm, the cervix was instrumentally dilated to 7 mm before MVA. The duration of the procedure, the amount of intra-operative bleeding, the pain and other complications, if any, were recorded. The duration of the procedure included the time required for instrumental dilatation in cases where this latter was necessary. The intra-operative blood loss (IBL) was measured after removal of the products of conception from the uterine aspirate. The patients were asked to evaluate the pain they experienced by means of a 100 mm visual analogue scale (VAS) immediately before treatment with misoprostol, then again before insertion of the speculum prior to the procedure, and once more just before completion of the curettage. We asked the participants to indicate their degree of satisfaction on a five-point scale: 1, strongly dissatisfied; 2, dissatisfied; 3, neutral; 4, satisfied; 5, very satisfied.

We observed the patients for 2 hours after the operation for the possible occurrence of early complications. Paracetamol (3×500 mg) was given to all women for post-operative analgesia. We asked patients to record post-operative bleeding on a calendar and to come for follow-up after 7–10 days. At the follow-up visit, we inquired about the duration of post-operative bleeding and side effects, and performed a transvaginal ultrasound. No patient was lost to follow-up.

The primary outcome measure, namely pre-operative cervical dilatation achieved, was used to calculate the sample size. In a previous study, Ngai *et al.*[10] showed that a mean cervical dilatation of 7.2 ± 1.4 mm was achieved 3 hours after vaginal administration of 400 μg misoprostol. Considering a difference of 1 mm as being clinically significant, and using 0.05 types 1 error and 0.80 powers, 36 patients were needed in each group.

All data were recorded using standard forms. We used SPSS 11.5 (Statistical Package for Social Sciences) for Windows for statistical analysis. We expressed results as means $\pm$ SD, and as percents. We analysed continuous variables with Student's *t*-test for normally distributed data, and Mann–Whitney *U*-test for skewed data. We carried out Kruskal–Wallis test to compare duration of post-operative bleeding as this was not normally distributed. We made comparisons by chi-square test for the categorical data. For all comparisons $p < 0.05$ was considered statistically significant.

RESULTS

The study groups were similar in terms of demographic variables, gestational age, and obstetric history (Table 1). All 36 women in each group completed the study. The patients' ages ranged between 21 and 44 years, and gestational ages between 49 and 69 days.

Table 1 Patients' characteristics

Variables	*Misoprostol 200 μg sublingual (n = 36)*	*Misoprostol 400 μg vaginal (n = 36)*	*p*
Age (years)	29.3 ± 5	31.3 ± 5.3	0.1*
Education (years)	6.1 ± 4.4	6.5 ± 4.1	0.6*
Ever used contraception (%)	28 (77.8)	31 (86.1)	0.3**
Periodic abstinence and withdrawal (%)	17 (47.2)	17 (47.2)	1**
Body Mass Index (kg/m^2)	25 ± 3.5	26.2 ± 5.1	0.2*
Gestational age (days)	57.9 ± 6.5	56.8 ± 5.6	0.4*
Gravidity	3.6 ± 1.7	4.2 ± 1.2	0.1*
Parity	2.1 ± 1.4	2.3 ± 0.9	0.5*
Nulliparity (%)	4 (11.1)	2 (5.6)	0.3**
Spontaneous abortions (≥1)	7 (19.4)	12 (33.3)	0.1**
Surgical abortions (≥1)	12 (33.3)	15 (41.7)	0.4**

*Not statistically significant ($p > 0.05$), independent samples *t*-test.
**Not statistically significant ($p > 0.05$), Chi-square test.

Table 2 Distribution of transvaginal ultrasound and operative findings among the study groups

Variables	*Misoprostol 200 μg sublingual (n = 36)*	*Misoprostol 400 μg vaginal (n = 36)*	*p*
Cervical opening (mm)	2.4 ± 1.3	2.3 ± 1.5	0.7
Cervical length (mm)	33 ± 4.2	32.8 ± 3.8	0.8
Pre-operative cervical dilatation achieved	6.9 ± 1.6	6.6 ± 1.1	0.3
Number of patients requiring further dilatation (%)	13 (36.1)	13 (36.1)	1
Duration of operation (minutes)	4.6 ± 2.6	4.1 ± 1.7	0.3
Pain before misoprostol (0–100 mm)	1.8 ± 4.6	0.4 ± 1.8	0.1
Pain after misoprostol (0–100 mm)	15.7 ± 24.6	5.3 ± 12.2	0.02*
Intra-operative pain (0–100 mm)	58 ± 22	46.6 ± 20.8	0.02*

*Statistically significant ($p < 0.05$), independent samples *t*-test.

No patient aborted during the interval between drug administration and the MVA. Table 2 presents operative findings. Basal cervical length and dilatation were nearly identical in the two groups. A pre-operative cervical dilatation of 6.9 ± 1.6 mm was achieved in group 1 (sublingual misoprostol) and a dilatation of 6.6 ± 1.1 mm in group 2 (vaginal misoprostol; $p = 0.3$). The requirement for additional cervical dilatation, the duration of the operation and the amount of intra-operative blood loss were similar in the two groups.

The mean visual analogue pain scores of the groups were similar before misoprostol application but sublingual misoprostol was associated with more pain perception before and during the operation (Table 2). The mean patients' satisfaction score was 2.3 ± 1.2 among women given sublingual misoprostol and 2.8 ± 1 in those given the drug via the vaginal route ($p = 0.08$). The numbers of patients in both groups who were satisfied or very satisfied with the procedure were comparable (group 1: 16.7%, group 2: 19.4%; $p = 0.7$).

Table 3 summarizes the side effects. Most patients (group 1: 88.9%, group 2: 83.3%) experienced at least one side effect caused by the drug, but in no case was intervention or interruption of the procedure required. Nausea and vaginal spotting were significantly more frequent in group 1 than in group 2, but no patient in either group vomited. There were no intra- or post-operative complications. Post-operative bleeding was significantly shorter after treatment with sublingual misoprostol (3 ± 1.3 days) than following vaginal administration of the drug (3.7 ± 1.3 days, $p = 0.03$).

DISCUSSION

Reducing complications (such as retention of products of conception, excessive bleeding, and infection) and shortening operating time are major requirements with regard to the improvement of abortion services. As in our study, most surgical abortions are nowadays carried out in ambulatory settings under local anaesthesia and the World Health Organization

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

Variables	*Misoprostol 200 μg sublingual (n = 36)*	*Misoprostol 400 μg vaginal (n = 36)*	*p*
Any side effect	32 (88.9)	30 (83.3)	0.4
Nausea	20 (55.6)	10 (27.8)	0.01*
Abdominal pain	29 (80.6)	27 (75)	0.5
Diarrhoea	1 (2.8)	–	0.3
Fever	1 (2.8)	–	0.3
Vaginal spotting	19 (52.8)	7 (19.4)	0.003*
Headache	–	3 (8.3)	0.07

*Statistically significant ($p < 0.05$), Chi-square test.

(WHO) recommends the use of manual and electronic vacuum aspiration[11]. Using a cervical priming agent with minimal side effects and maximum efficacy and patient acceptance has been a subject for investigation for over 30 years.

The ideal drug should be administered via the most acceptable route, in the lowest possible dose, for the shortest possible period of time. Sublingual administration of misoprostol has some advantages over other routes; it is easy, it avoids a first passage through the liver and can be self-applied, avoiding an uncomfortable pelvic examination, which is objected to by many women[7]. It also has the advantage of avoiding fluid intake, which may be of some importance if one must perform the suction curettage under general anaesthesia. Tang *et al.*[6] reported that sublingual misoprostol achieves a serum peak concentration twice higher than when given orally and nearly five times higher than when used vaginally. The time needed to reach its peak concentration was significantly shorter when misoprostol was given via the sublingual route (26 ± 11.5 minutes) than after oral or vaginal administration. Although the high serum levels of sublingual misoprostol declined steeply to basal levels at 120 minutes, the lower serum concentrations of vaginal misoprostol declined to basal levels at 240 minutes[8].

The WHO recommends to prime the cervix before surgical abortion procedures if the pregnancy is over 9 weeks of gestation and the women have not previously borne children, for those under 18 years of age, and for all pregnancies exceeding 12 weeks[12]. Although not the standard of care in the first trimester of pregnancy, the need for cervical priming has not been tested by a sufficient number of randomized studies. We have previously shown that the cervical dilatation of parous women before MVA in the first trimester of pregnancy augments significantly after oral or vaginal administration of 400 μg misoprostol[5]. We conducted this study to find a more convenient route of misoprostol application that would also allow the cervix to ripen in a shorter time.

The recommended dose for cervical ripening by means of misoprostol given orally or vaginally 3 hours prior to vacuum aspiration is 400 μg[13,14]. Our study is different from those reported in the literature as we administered a lower dose (200 μg) of sublingual misoprostol only 2 hours prior to surgery. We found this regimen to have an efficacy similar to that of the vaginal administration of 400 μg misoprostol 3 hours before suction curettage in terms of pre-operative cervical dilatation achieved, operating time and intra-operative blood loss.

The percentages of patients who were satisfied or very satisfied with the procedure were 16.7% in group 1 and 19.4% in group 2. These percentages were lower than those (61%) reported by Ashok *et al.*[15]. In addition, we used VAS to evaluate pain scores before and after administration of misoprostol, and during the surgical procedure, which other investigators had not addressed properly in their studies. Although we performed a paracervical block in all cases, post-medication and intra-operative pain scores were significantly higher in the group given sulingual misoprostol. The reason for this is unclear, as cervical dilatation achieved by sublingual misoprostol was of the same order as that noted after oral administration of the prostaglandin analogue.

Higher pain scores in the sublingual group and pelvic examination in the vaginal group might have lowered satisfaction in our patients. In addition, patients spent two or 3 hours in the clinic waiting for the surgical intervention, which may have increased the psychological stress and decreased the satisfaction scores. Nausea experienced by many of the patients, particularly those treated with sublingual misoprostol, may have contributed to the low satisfaction scores.

Reducing the need for cervical dilatation is likely to decrease the number of uterine perforations, which may complicate up to 2% of first trimester surgical

abortions. It may also be associated with a lesser frequency of incomplete abortions and continuing pregnancies, which together complicate around 5% of surgical abortions[16]. On the other hand, most uterine perforations are clinically unnoticed and do not cause serious complications; the incidence of perforation may be as low as 0.12% in the hands of experienced surgeons[16]. Child *et al.*[1] found that the only significant factor affecting the outcome of surgical abortion was the seniority of the operating surgeon.

In our study, nausea was significantly more frequent after sublingual administration of misoprostol, which is consistent with the findings of Vimala *et al.*[4]. The incidence of nausea also after oral use is higher than after vaginal administration[15]. None of the side effects reported by our patients necessitated medical intervention.

We conclude that, a lower dose of sublingual misoprostol 2 hours before first trimester suction curettage under local anaesthesia is as effective as vaginal misoprostol applied 3 hours before this procedure with regard to achieving pre-operative cervical dilatation. It results in higher pre-operative and intra-operative pain scores but does not affect patients' satisfaction.

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