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A randomized clinical trial comparing the short-term side effects of sublingual and buccal routes of misoprostol administration for medical abortions up to 63 days' gestation☆,☆☆,★

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Abstract

Background: Buccal misoprostol 800 mcg and sublingual misoprostol 800 mcg show high efficacy when used with 200 mg mifepristone for early pregnancy termination but have different side effect profiles. This is the first double-blind randomized trial comparing the side effect profiles of these two routes of administration of misoprostol when used with mifepristone for termination of pregnancies up to 63 days' gestation.
Study Design: Eligible women (n=90) who requested legal termination of pregnancy up to 63 days' gestation were randomized to two groups and given 200 mg of oral mifepristone followed 48 h later by 800 mcg of either sublingual (n=45) or buccal (n=45) misoprostol.
Results: Most of the side effects including fever were more common in the sublingual group, but only the incidence of chills was significantly higher in the sublingual group (55.6% vs 91.1%, p=.0001). Complete abortion occurred in 95.4% [95% confidence interval (CI): 84.9–99.5] of women in the buccal group and 97.8% (95% CI: 88.2–99.9) in the sublingual group.
Conclusions: When combined with mifepristone for termination of pregnancy up to 63 days, both the buccal and sublingual routes are effective routes of administration. The sublingual route tended to be associated with more side effects.
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Keywords: Sublingual; Buccal; Misoprostol; Abortions

1. Introduction

After mifepristone was approved by the United States Food and Drug Administration in 2000, the combination of oral mifepristone 200 mg and vaginal administration of misoprostol 800 mcg became almost a standard of care in early medical abortion up to 63 days of gestation [1,2]. When combined with mifepristone for medical abortion in the first trimester, the vaginal administration of misoprostol is more effective than oral administration, with a lower rate of ongoing pregnancy and fewer gastrointestinal side effects than oral misoprostol [3,4]. However, vaginal administration is less acceptable for many women because it is more painful and less convenient [5]. Serious fatal bacterial infections have been reported after medical abortion with mifepristone and vaginal misoprostol [6]. Given these concerns, the alternative administration via sublingual (under the tongue) and buccal (in the cheek) routes was selected.

A pharmacokinetic study showed that sublingual administration of misoprostol resulted in the greatest bioavailability when compared with oral or vaginal administration [7]. A randomized, crossover pharmacokinetic study found that the mean misoprostol plasma concentration-time and the maximum concentration were significantly higher for sublingual administration than the buccal route. However, buccal administration resulted in few symptoms and was found to be more acceptable by women [8].

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Several studies have independently examined sublingual and buccal misoprostol regimens after mifepristone. When used for abortion through 56 days of gestation, buccal administration of misoprostol 1–2 days following mifepristone appears to be a highly effective and acceptable alternative compared with vaginal administration with similar side effect profiles [9].

Sublingual misoprostol 800 mcg 48 h after mifepristone 200 mg for medical abortions of less than 9 weeks' gestation has achieved complete abortion rate of 98% but is associated with more side effects when compared with the vaginal route [10]. A study by Winikoff et al. [11] demonstrated a higher success rate with buccal misoprostol 800 mcg 24–36 h after mifepristone 200 mg for terminating pregnancy through 63 days of gestation when compared with oral misoprostol. The side effect profiles were similar, although fever and chills were reported more often among women who took buccal misoprostol.

Both buccal administration and sublingual administration of misoprostol following mifepristone have been shown to be effective in inducing first-trimester medical abortions, but with different side effects profile. Most side effects are subjective, and the incidence of side effects varies among studies using the same dosage and same route of administration of misoprostol [10,12]. There is a need for a direct comparison of these two routes of administration before any definitive conclusions can be drawn. There is only one randomized clinical trial which directly compared the side effect profiles between 400 mcg sublingual and 400 mcg buccal misoprostol, although the patients were not blinded to their intervention [13]. The purpose of the present double-blind study is to compare the incidence of side effects of buccal and sublingual misoprostol when combined with mifepristone.

2. Materials and methods

The study was a double-blind randomized trial conducted at the Family Planning Association in Hong Kong. It was approved by the Institutional Review Board of the University of Hong Kong. The trial was registered with ClinicalTrials.gov (NCT01156688). Written consent was obtained from all participants before participation in the study. Women requesting termination of pregnancy were assessed by a gynecologist. The medical history was reviewed, and a clinical examination was performed. The research nurse recruited women at the clinic if the women were found to be suitable after assessment by the gynecologist. We recruited healthy women aged 18 years or older who requested termination of pregnancy of up to 63 days' gestation and were willing to comply with the schedule of follow-up visits. Following recruitment at the clinic, blood was taken for hemoglobin level. A transvaginal ultrasound examination was performed to verify the duration of pregnancy and to determine the gestational age. Exclusion criteria included (a) any contraindications or allergies to mifepristone or misoprostol, (b) an intrauterine contraceptive device in utero, (c) a hemoglobin level <100 g/L, (d) breastfeeding or (e) multiple pregnancies.

Randomization assignment was made by the research nurse using a computer program to allocate the study subjects into two groups: sublingual and buccal. We used placebo tablets so that both the study subjects and the investigators were blind to the allocation to avoid reporting and observation bias. We chose to administer 800 mcg misoprostol following 200 mg mifepristone as the dosage recommended by Royal College of Obstetricians and Gynaecologists for early medical abortion [2]. Based on the randomization schedule, the concealed packages of misoprostol and placebo tablets were prepared by the pharmacy. The placebo tablets were identical in appearance to the misoprostol tablets. For the buccal misoprostol group, the package contained four placebo tablets (Labatec-Pharma SA, Switzerland) to be given sublingually and four misoprostol tablets (Cytotec; Pfizer, New York, NY, USA) to be given buccally. For the sublingual misoprostol group, the package contained four misoprostol tablets to be given sublingually and four placebo tablets to be given buccally.

After admission into the study, all women were given 200 mg of mifepristone (Hua Lian Pharmaceutical Co., Shanghai, China) in the presence of medical or nursing staff. This was designated as day 1 of the study. Forty-eight hours after mifepristone administration, the women were given the packages of misoprostol and look-alike placebo tablets according to their randomization. They were instructed to put four tablets of misoprostol or placebo first under the tongue, which would dissolve in 10–15 min, and then hold two tablets of misoprostol or placebo in each cheek pouch for 30 min and then to swallow any remnants at the end of 30 min. The nurse who was not aware of the randomization supervised the procedure of administration throughout. Women stayed in the observation ward at the Family Planning Association of Hong Kong for 4 h, and temperature, blood pressure and pulse rate were recorded hourly by a nurse. Women were interviewed by a nurse at the end of 4 h regarding the side effects experienced. Vaginal examination was done at the end of 4 h. If a woman did not have heavy bleeding or severe pain, she was allowed to go home with a diary card to record the days of vaginal bleeding. The women came back on day 15 for clinical assessment, ultrasound examination of the pelvis and blood sampling for hemoglobin level. The intention was to determine whether the abortion was complete and to review the bleeding pattern. If the pelvic ultrasound examination showed the presence of ongoing pregnancy, vacuum aspiration would be arranged without further attempt with misoprostol. If the pelvic ultrasound examination showed that there was incomplete abortion or missed abortion, the women would be observed unless there was heavy bleeding. The women were followed up again on day 43 for return of menses.

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