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Pilot study on the use of sublingual misoprostol with mifepristone in termination of first trimester pregnancy up to 9 weeks gestation

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BACKGROUND: A combination of mifepristone and misoprostol provides an effective method of medical abortion for early pregnancy. A new route of administration of misoprostol, the sublingual route, was investigated in this study. METHODS: One hundred women who requested legal termination of pregnancy up to 63 days were given 200 mg of oral mifepristone followed 48 h later by 800 μg (4 × 200 μg tablets) of sublingual misoprostol. RESULTS: Ninety-four women (94%) had a complete abortion with this regimen. There was one ongoing pregnancy. The median duration of vaginal bleeding was 15 days. There were no serious complications. However, lower abdominal pain, diarrhoea, chills and fever were the commonest side-effects with incidences of 89, 42, 38 and 79% respectively. CONCLUSIONS: The combination of mifepristone and sublingual misoprostol is effective for medical abortion up to 63 days gestation. Randomized trials are required to compare its efficacy and side-effect profile with vaginal misoprostol.

Key words: medical abortion/mifepristone/misoprostol/sublingual

Introduction

The combination of mifepristone and a prostaglandin analogue is an effective and safe method of termination of pregnancy up to 63 days gestation (UK Multicentre Trial, 1990; World Health Organization, 1993; Baird *et al.*, 1995). Misoprostol, a synthetic analogue of naturally occurring prostaglandin E1, is the prostaglandin of choice because it is cheap, orally active and stable at room temperature. Misoprostol, originally designed to be taken by mouth, has been used extensively by vaginal administration. Vaginal misoprostol is more effective than oral misoprostol. The complete abortion rate has been previously found to be 95% for vaginal compared with 87% for oral misoprostol (El-Refaey, 1995).

A pharmacokinetic study has also shown that the systemic bioavailability of vaginally administered misoprostol is three times higher than that of orally administered misoprostol when determined by the area under the plasma concentration–time curve (AUC) for 360 min (Zieman *et al.*, 1997). The marked difference in AUC between oral and vaginal administration is likely the result of presystemic gastrointestinal or hepatic metabolism that occurs with oral but not with vaginal misoprostol. The same study also showed that the absorption of misoprostol by the vaginal route was variable and it was not uncommon to find that the majority of the misoprostol tablet was still not completely dissolved several hours after vaginal administration (Ziemen *et al.*, 1997; Singh *et al.*, 1999).

Recently, we have developed a new sublingual route of administration of misoprostol. Misoprostol, being very soluble in water, was put under the tongue; it was observed that the tablet took ~10–15 min to dissolve. It is given by mouth and therefore can avoid the uncomfortable vaginal examination during the administration of vaginal misoprostol. The aim of this pilot study was to determine the complete abortion rate of sublingual misoprostol when given with mifepristone for termination of first trimester pregnancy up to 9 weeks gestation.

Materials and methods

A total of 100 pregnant women with a menstrual delay of ⩽35 days were recruited in Hong Kong and Shanghai from among women requesting legal termination of pregnancy. There were 50 subjects from both Hong Kong and Shanghai. The study was approved by the ethics committees of the participating institutions. The gestational age was confirmed in all women by ultrasound examination.

All women were given 200 mg of mifepristone (Mifegyne; Roussel UCLAF, Romainville, France) in the presence of the medical or nursing staff. Forty-eight hours after mifepristone administration, the women were admitted to the hospital and 800 μg sublingual misoprostol (Cytotec; Searle Pharmaceutical, Skokie, IL, USA) was given. They were instructed to put four tablets of 200 μg misoprostol under the tongue and allow them to dissolve. The misoprostol took ~10–15 min to dissolve and during this period of time the subjects were told not to swallow the tablets. They stayed in the hospital for 4 h,

Table I. Demographic characteristics of the 100 women who underwent medical abortion with sublingual misoprostol (mean ± SD)

Characteristic	
Age (years)	25.2 ± 4.9
Weight (kg)	52.0 ± 6.4
Height (cm)	161.1 ± 5.7
Gestational age (weeks)	7.87 ± 1.1
Number (%) of parous women	29 (29)
Number (%) of women with history of abortion	45 (45)

and blood pressure and pulse rates were recorded hourly. A vaginal examination was performed at the end of the 4 h observation. The women were given a diary card to record the days and the amount of vaginal bleeding (in comparison with their usual menstrual periods) and any other side-effects.

The women returned to the hospital on day 15 (after mifepristone) and vaginal examination, measurement of blood pressure, pulse and haemoglobin level, and ultrasound of pelvis were carried out. If pelvic ultrasound showed the presence of an ongoing pregnancy, vacuum aspiration was arranged. If pelvic ultrasound examination showed that there was an incomplete or missed abortion, the women would be observed unless there was heavy bleeding.

The women were followed-up again on day 43. The examination and investigations on day 15 were repeated except the ultrasound examination of pelvis, which was only performed when it was clinically indicated. The side-effects and duration of bleeding as recorded in the diary card were checked during the follow-up visits. An extra follow-up visit was arranged if bleeding persisted or menstruation had not yet returned by 67 days after mifepristone. If no emergency or elective curettage was required during the interval up to the first menstruation, the outcome was classified as a complete abortion. All women were asked to use the barrier method for contraception.

The primary outcome was the complete abortion rate. The haemoglobin level, duration of vaginal bleeding and side-effects of the treatment were also studied.

Statistics for Social Sciences 10.0 for Windows was used for statistical analysis. Repeated measurements in haemoglobin levels were compared by Wilcoxon signed ranks test. *P*-values (two-tailed) of < 0.05 were considered as statistically significant.

Results

Table I shows the demographic data of the 100 women who underwent medical abortion with mifepristone and sublingual misoprostol. The mean gestational age was 7.87 weeks and 62 women (62%) were at a gestational age of <7 weeks. The complete abortion rate was 94% (95% confidence interval: 88–97) (Table II). There was only one woman who had an ongoing pregnancy, diagnosed on day 15 after mifepristone. One woman had a missed abortion. Three women required vacuum evacuation for an incomplete abortion. Three subjects defaulted the day 43 follow-up. Two of these three subjects had a complete abortion diagnosed on day 15 by ultrasound scan and the other subject had an incomplete abortion. The outcome of the last subject was classified as undetermined as she did not attend the day 43 follow-up.

There was no significant change in haemoglobin level on days 15 and 43 compared with the baseline on day 1. Passage of tissue mass was identified in 67 subjects; in 62 within the first 24 h after the administration of misoprostol. The median induction to abortion interval was 2.7 h (range 0.5–6.5) in these subjects. The median duration of vaginal bleeding after abortion was 15 days (range 5–83). Table III lists the side-effects of sublingual misoprostol. Lower abdominal pain, diarrhoea, chills and fever were the far commonest side-effects with incidences of 89, 42, 38 and 79% respectively.

Table II. The characteristics of the abortion process of the 100 women who underwent medical abortion with mifepristone and sublingual misoprostol

Characteristic	
Mean haemoglobin concentration (g/dl)	
Day 1	12.2 ± 0.9
Day 15	11.9 ± 1.1[b]
Day 43	11.9 ± 1.0[b]
Outcome	
Complete abortion (%)	94/100 (94)
Incomplete abortion (%)	3/100 (3)
Missed abortion (%)	1/100 (1)
Ongoing pregnancy (%)	1/100 (1)
Undetermined[a] (%)	1/100 (1)
Median days of vaginal bleeding (range)	15 (5–83)

[a]Subject defaulted the day 43 follow-up and outcome was classified as undetermined.
[b]No significant change in haemoglobin level by Wilcoxon signed ranks test.

Discussion

The combination of mifepristone and a prostaglandin has been shown to be effective for medical abortion in pregnancy up to 63 days. However, the optimal regimen still needs to be established. The use of 200 mg oral mifepristone followed 36–48 h later by 800 μg of vaginal misoprostol is the commonest regimen with a complete abortion rate of 90–95% (McKinley *et al.*, 1993; Ashok *et al.*, 1998; Child *et al.*, 2001). Vaginal misoprostol is not licensed for medical abortion, but it is still widely used off-label for medical abortion as it is effective, cheap and stable in room temperature. However, the misoprostol tablet was not manufactured and developed for use by routes other than oral administration.

Oral misoprostol has been shown to be less effective and to result in more side-effects than vaginal administration in randomized trials (El-Refaey *et al.*, 1995). Additionally, a pharmacokinetic study showed that the systemic bioavailability of vaginal administration, as indicated by the area under the serum level of misoprostol concentration versus time curve, was higher than oral misoprostol (Zieman *et al.*, 1997). However, the same study showed that there is a wide variation in the absorption of vaginal misoprostol, as shown by the large coefficients of variation of the AUC for vaginal misoprostol between individuals. Clinically, it was not uncommon to find that the majority of the misoprostol tablet was still not completely dissolved several hours after vaginal administration (Zieman *et al.*, 1997; Singh *et al.*, 1999). The action of vaginal misoprostol may be difficult to predict in individual patients. It has been suggested that adding water to the tablets may improve absorption (Carbonell *et al.*, 1997, 1999). This,

Table III. Side-effects of repeated doses of sublingual misoprostol in the 100 women who underwent medical abortion

Side-effect	During pregnancy $n = 100$ (%)	Day of misoprostol $n = 100$ (%)	Day 15 follow-up $n = 96$ (%)	Day 43 follow-up $n = 92$ (%)
Nausea	44 (44)	37 (37)	12 (12.5)	1 (1.1)
Vomiting	14 (14)	24 (24)	6 (6.3)	1 (1.1)
Diarrhoea	8 (8)	42 (42)	19 (19.8)	1 (1.1)
Dizziness	15 (15)	19 (19)	17 (17.7)	3 (3.3)
Fainting	2 (2)	1 (1)	2 (2.1)	–
Fatigue	16 (16)	32 (32)	22 (22.9)	4 (4.3)
Lower abdominal pain	22 (22)	89 (89)	47 (49)	7 (7.6)
Breast tenderness	26 (26)	11 (11)	12 (12.5)	1 (1.1)
Headache	5 (5)	7 (7)	5 (10)	4 (4.3)
Chills	–	38 (38)	–	–
Fever[a]	–	38 (79.2)	–	–

[a]Defined as temperature >38°C; data available for the 48 women in the Hong Kong centre only.

however, was not supported by a randomized trial (Ngai *et al.*, 2000).

Recently, we have investigated a new route of sublingual administration of misoprostol. The current study represents the first report on the use of sublingual misoprostol with mifepristone for medical abortion up to 63 days gestation. Misoprostol, being very soluble in water, was administered by putting the tablet under the tongue and allowing it to dissolve. It was observed that it could dissolve in 15–20 min. It is convenient to administer and avoids the uncomfortable vaginal administration. Sublingual misoprostol is taken by mouth but it can avoid the first-pass effect through the liver as in the oral route and therefore, may result in a higher complete abortion rate. Absorption of misoprostol tablets may be easier to ascertain as the dissolution of the tablets can be easily observed during sublingual compared with vaginal administration. It has been shown that some women find vaginal administration painful and uncomfortable and would like drugs that can be taken by mouth (Ho *et al.*, 1997). Sublingual misoprostol also has the potential of developing into an outpatient medical abortion regimen. This is especially convenient if repeated doses are required.

It was shown in this study that the complete abortion rate was 94% and this is similar to a previous study using vaginal misoprostol (El-Rafaey *et al.*, 1995). The onset of action with sublingual administration may be faster as the induction to abortion interval was only 2.7 h, shorter than the 4 h reported in the other study using vaginal misoprostol (Ashok *et al.*, 1998). However, the incidences of side-effects were higher in the present study with a relatively high percentage of women complaining of lower abdominal pain, diarrhoea and fever. Randomized studies are required to compare the efficacy of sublingual misoprostol with other routes of administration and work out the dosage of sublingual misoprostol that can give the highest complete abortion rate and lowest incidence of side-effects.

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