

Pilot study on the use of repeated doses of sublingual misoprostol in termination of pregnancy up to 12 weeks gestation: efficacy and acceptability

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BACKGROUND: A sublingual misoprostol-alone regimen was used in 50 women requesting medical abortion at up to 12 weeks gestation. The efficacy and acceptability of this regimen were studied. **METHODS:** The women were given 600 µg misoprostol sublingually every 3 h for a maximum of 5 doses. **RESULTS:** The overall complete abortion rate was 86% (95% confidence interval: 74–93). The mean number of doses of misoprostol required was 4.1 ± 1.1 . There was no significant change in haemoglobin concentration and the median duration of vaginal bleeding was 15 days (range: 7–56). Diarrhoea, fever and chills were the most common side-effects. The acceptability of this regimen of misoprostol was good: 97.7% of the women who had a complete abortion would choose this method again and 88.4% would recommend it to others. They preferred sublingual misoprostol as it is convenient to take, avoids the painful vaginal administration and gives more privacy during the abortion process. **CONCLUSION:** This regimen of sublingual misoprostol is an effective and acceptable method of medical abortion. Randomized controlled trials are required to compare the efficacy of various misoprostol-alone regimens of medical abortion. Pharmacokinetic studies and clinical trials are needed to find out the most appropriate dose, dosing interval and route of administration of misoprostol.

Key words: medical abortion/misoprostol/sublingual

Introduction

Unplanned pregnancy is a major problem in many parts of the world. Surgical evacuation is currently the standard management for termination of pregnancies <12 weeks gestation in many countries. It is an effective method with a success rate of >95% (Child *et al.*, 2001a). However, it is associated with major morbidity in up to 1% of women and minor morbidity in 10% (Joint Study of the Royal College of General Practitioners and the Royal College of Obstetricians and Gynaecologists, 1985). In some developing countries, the complications of unsafe surgical abortion, including incomplete abortion, sepsis, haemorrhage and intra-abdominal injury, cause the majority of maternal deaths. Medical abortion using mifepristone and a prostaglandin has been shown to be an effective method of abortion in up to 63 days gestation (El-Refaey *et al.*, 1995). Ashok *et al.* showed that medical abortion is feasible between 9–13 weeks gestation by a combination of mifepristone and repeated doses of misoprostol (Ashok *et al.*, 1998). They were able to achieve an overall complete abortion rate of 95%.

Many of the complications of surgical abortion can be avoided by medical abortion and this is especially important in developing countries where surgical evacuation is unsafe

(Child *et al.*, 2001b). Although misoprostol is not licensed for medical abortion, it is the prostaglandin of choice in developing countries as it is cheap, easily available and stable at room temperature. Mifepristone, however, is expensive and only available in a limited number of countries, including China, France, Sweden, UK and USA. Therefore, it is very important to develop a regimen of medical abortion without mifepristone so that women in other countries can benefit from the advantages of medical abortion. In many studies, repeated doses of misoprostol were used for medical abortion in the first trimester. Most of the regimens were either inconvenient to administer or ineffective (Koopersmith and Mishell, 1996; Carbonell *et al.*, 1998; Tang *et al.*, 1999a).

Recently, we have explored the use of sublingual misoprostol in medical abortion. Misoprostol is absorbed through the vaginal mucosa in vaginal administration. The buccal mucosa, being very vascular, should be able to serve the same purpose. Sublingual administration of misoprostol avoids the first pass effect through the liver as in oral administration. It avoids the painful vaginal administration, is more convenient to take and offers more privacy during the abortion process. Therefore, it is the aim of this pilot study to investigate the efficacy and acceptability of sublingual misoprostol alone in first trimester medical abortion up to 12 weeks gestation.

Materials and methods

This is an open, single arm, observational study. Fifty pregnant women up to 12 weeks gestation were recruited from among women requesting legal termination of pregnancy from October 2000 to January 2001. The study was carried out at the Department of Obstetrics and Gynaecology, University of Hong Kong. All subjects were counselled on both surgical and medical methods for abortion. The gestational age was confirmed by pelvic ultrasonography.

All subjects were admitted to the hospital on day 1 of the treatment and were given 600 µg of sublingual misoprostol (Cytotec; Searle Pharmaceutical, Skokie, IL, USA) every 3 h for 3 doses. Two more doses of 600 µg sublingual misoprostol every 3 h were given if the subject did not abort after the first 3 doses. The blood pressure, pulse rate and side-effects were monitored hourly. The subject's temperature was taken every 3 h after the administration of misoprostol. Vaginal examination was performed when the subjects passed the products of gestation. They were discharged from the hospital the next morning if bleeding and abdominal pain were not severe. A diary card was given to them to record the duration of bleeding and side-effects. They were reminded to return to the hospital at any time if there was heavy bleeding or abdominal pain.

All subjects were followed-up on days 7 and 43 after misoprostol. An ultrasound examination of the pelvis was performed in all subjects on day 7. Vacuum aspiration was arranged if the ultrasound examination showed live pregnancy. Women with missed abortion were allowed to opt for continuing observation for some time or to undergo vacuum aspiration immediately. Subjects with missed abortion who opted for conservative management were followed up 2 weeks later and vacuum aspiration was performed if there was no passage of product of gestation within 2 weeks. The other subjects were seen again on day 43 if the bleeding was not heavy. Extra follow-up visits were arranged for subjects who did not have their periods by day 43. If no emergency or elective curettage was required during the interval up to the first menstruation, the outcome was classified as a complete abortion. Venous blood was taken on days 1, 7 and 43 to check the haemoglobin concentration. The subjects were seen by one of the investigators in the hospital and surgical evacuation was done in the same hospital if required. At the last follow-up visit, women were asked a series of questions about their comments on the treatment they had received. They were also asked about their preference for medical abortion versus vacuum aspiration. The study protocol was approved by the Ethics Committee, Faculty of Medicine, University of Hong Kong.

The primary outcome measure was the complete abortion rate. The change in haemoglobin concentration, side-effects and duration of vaginal bleeding after abortion were also noted. Comparisons were made by Fisher's exact test or χ^2 test for categorical data. Paired data were compared using Wilcoxon signed ranks test. *P*-values (two-tailed) of < 0.05 were considered statistically significant.

Results

Table I summarizes the demographic characteristics of the 50 women who underwent medical abortion with sublingual misoprostol. The mean gestational age was 8.5 weeks and 14 women were pregnant for >9 weeks. Table II describes the abortion characteristics of the 50 women. The mean overall number of doses of misoprostol required was 4.1 and 40% of the subjects required ≤ 3 doses of misoprostol. The overall complete abortion rate was 86% and the complete abortion rate for women with gestational age ≤ 9 weeks was 88.9%. All women (9/9) with a gestational age of ≤ 7 weeks had a

Table I. Demographic characteristics of the 50 women who underwent medical abortion with sublingual misoprostol (mean \pm SD)

Characteristic	
Age in years (range)	23.3 \pm 6.0 (18–45)
Weight in kg (range)	48.7 \pm 5.7 (37–63)
Height in cm (range)	158.2 \pm 5.2 (150–170)
Gestational age in weeks (range)	8.5 \pm 1.6 (5.6–11.9)
Number of women <7 weeks	9
Number of women 7–9 weeks	27
Number of women >9 weeks	14
Number (%) of parous women	6 (12)
Number (%) of women with history of abortion	14 (28)

complete abortion. Two (4%) women had a missed abortion and two (4%) had an on-going pregnancy that required vacuum evacuation. All of them had elective operation.

It is worthwhile to discuss in detail the three women who had an outcome classified as undetermined, as they defaulted the day 43 follow-up visit. The first woman had a complete abortion as diagnosed by ultrasound examination on day 7 and histological examination of the tissue mass passed on the day of misoprostol revealed products of conception. The second woman returned to the hospital on day 6 because of abdominal pain and ultrasound examination showed missed abortion. She was observed for another 2 weeks and repeated ultrasound examination revealed a complete abortion. The third woman had an ultrasound diagnosis of incomplete abortion on day 7 and vacuum evacuation was not required, as the vaginal bleeding was not heavy. These three women did not return for follow-up on day 43 and the return of menstruation could not be ascertained and therefore, the outcome was classified as undetermined.

In 34 subjects, products of conception could be identified either in hospital or after discharge. Twenty-six subjects had passage of tissue mass on day 1 in the hospital. The median induction-to-abortion interval for this group of subjects was 7.7 h (range: 3.3–13). Another eight subjects passed the tissue mass after discharge and the median induction-to-abortion interval was 108.1 h (range: 58.8–140). The median duration of vaginal bleeding was 15 (range: 7–56). There was no significant change in haemoglobin concentration before and after abortion. There was a significant increase in the incidence of diarrhoea, fatigue, lower abdominal pain, headache, chills and fever on the day of sublingual misoprostol treatment compared with that which occurred before the administration of misoprostol (Table III). All subjects who had a final outcome classified as complete abortion were followed-up until the return of menstruation. The median duration for return of menstruation was 39 days (range: 26–72) from the day of misoprostol administration.

The 43 women who attended the day 43 follow-up visit and had complete abortion were asked to complete a questionnaire concerning the acceptability of this method of medical abortion (Table IV). Thirteen (30.2%) women had a history of vacuum aspiration for termination of pregnancy or miscarriages in the past. One woman had used misoprostol for medical abortion before. The most common reasons for choosing medical rather

Table II. The characteristics of the abortion process of the 50 women who underwent medical abortion with repeated doses of sublingual misoprostol

	<7 weeks (n = 9)	7–9 weeks (n = 27)	>9 weeks (n = 14)	Total (n = 50)
Mean (\pm SD) number of doses of misoprostol	4.8 \pm 0.7	4.0 \pm 1.2	3.7 \pm 3.5	4.1 \pm 1.1
Number (%) of women requiring \leq 3 doses of misoprostol	1 (11.1)	11 (40.7)	8 (57.1)	20 (40)
Mean haemoglobin concentration (g/dl)				
Day 1	12.5 \pm 0.6	12.1 \pm 0.8	12.1 \pm 0.6	12.2 \pm 0.7
Day 7	12.1 \pm 0.5	12.1 \pm 0.8	12.0 \pm 0.7	12.1 \pm 0.7 ^b
Day 43	12.1 \pm 2.2	12.7 \pm 0.8	12.7 \pm 0.8	12.6 \pm 1.2 ^c
Outcome				
Complete abortion (%)	9/9 (100)	23/27 (85.2)	11/14 (78.6)	43/50 (86)
95% CI	70–100	67–94	53–93	74–93
Missed abortion (%)	0/9 (0)	1/27 (3.7)	1/14 (7.1)	2/50 (4)
95% CI	0–30	1–19	1–31	1–13
Ongoing pregnancy (%)	0/9 (0)	1/27 (3.7)	1/14 (7.1)	2/50 (4)
95% CI	0–30	1–19	1–31	1–13
Undetermined ^a (%)	0/9 (0)	2/27 (7.4)	1/14 (7.1)	3/50 (6)
95% CI	0–30	3–18	3–18	2–16
Median days of vaginal bleeding (range)	10 (7–48)	19 (9–55)	11 (7–56)	15 (7–56)

^aSubjects defaulted the day 43 follow-up and outcome was classified as undetermined.

^{b,c}No significant change in haemoglobin level by Wilcoxon signed ranks test.

Table III. Side-effects of repeated doses of sublingual misoprostol in the 50 women who underwent medical abortion

	Before administration of misoprostol n = 50 (%)	Day of misoprostol administration n = 50 (%)	Day 7 follow-up n = 50 (%)	Day 43 follow-up n = 47 (%)
Nausea	35 (70)	34 (68)	3 (6)	–
Vomiting	8 (16)	17 (34)	2 (4)	1 (2)
Diarrhoea	3 (6)	36 (72) ^b	14 (28)	3 (6)
Dizziness	14 (28)	22 (44)	8 (16)	2 (4)
Fainting	2 (4)	–	–	–
Fatigue	17 (34)	35 (70) ^b	27 (54)	4 (8)
Lower abdominal pain	17 (34)	50 (100) ^b	41 (82)	8 (16)
Breast tenderness	18 (36)	12 (24)	11 (22)	1 (2)
Headache	12 (24)	26 (52) ^b	18 (36)	5 (10)
Chills	–	41 (82) ^b	–	–
Fever ^a	–	36 (72) ^b	–	–

^aDefined as temperature $>38^{\circ}\text{C}$.

^bSignificant increase ($P < 0.05$) in incidence compared with that occurring during pregnancy by χ^2 or Fisher's exact test, as appropriate.

than surgical abortion this time were that they were worried about the risks of surgery (65%) and its effect on future pregnancy (37%) and 23% of them were confident in the medical method. Most of the subjects thought that the degree of pain was tolerable, expected or slight (93%) and the duration of vaginal bleeding was acceptable, expected or short (76%). Most of the subjects (97.7%) would choose medical abortion again next time and 88.4% of the women would recommend medical abortion to other people. All of our subjects would choose medical abortion if medical and surgical methods were equally effective. Eighty percent of the women preferred the sublingual route of administration, as they thought that it was more convenient (79.4%), avoided the uncomfortable vaginal examination (23.5%), was more effective (14.7%) and provided more privacy (14.7%). The unpleasant taste of drug was the

main reason given by the 19% of women who preferred the other route of administration.

Discussion

The results of this study have demonstrated that the use of repeated doses of sublingual misoprostol alone is an effective and acceptable method of medical abortion up to 12 weeks gestation. The complete abortion rate of this regimen was 86% and it increased to 90% if the two women who were diagnosed to have complete abortion on ultrasound examination were included. The complete abortion rate was 100% for women with a gestational age of ≤ 7 weeks.

The combination of mifepristone and misoprostol is a more effective regimen for medical abortion. However, mifepristone

Table IV. Acceptability study of sublingual misoprostol ($n = 43$)^a

Characteristic	n (%)
History of abortion/miscarriage by	
Vacuum aspiration	13 (30.2)
Medical method	1 (2.3)
Reasons for choosing medical method this time	
Worried about risks of surgery	28 (65.1)
Worried about the effect of surgery on future pregnancy	16 (37.2)
Confident in new medical method	10 (23.3)
Worried about anaesthetic complications	3 (7.0)
Surgery is painful	1 (2.3)
Medical method is convenient	1 (2.3)
Degree of pain	
Severe, not tolerable	3 (7.0)
Tolerable	34 (79.1)
Expected	1 (2.3)
Little pain	5 (11.6)
Duration of vaginal bleeding	
Too long	10 (23.3)
Long but acceptable	21 (48.8)
Expected	8 (18.6)
Less than expected	3 (7.0)
Very little	1 (2.3)
Preference on medical abortion versus surgery	
No. of women who prefer surgery if allowed to choose again this time	1 (2.3)
No. of women who prefer sublingual misoprostol if allowed to choose again this time	42 (97.7)
No. of women who prefer sublingual misoprostol if both surgery and medical treatment are equally effective	43 (100)
No. of women who prefer surgery if both surgery and medical treatment are equally effective	0 (0)
No. of women who prefer sublingual misoprostol next time	42 (97.7)
No. of women prefer surgery next time	1 (2.3)
No. of women who will recommend medical method to other people	38 (88.4)
Preference on the route of administration of misoprostol ^b	
No. of women who prefer sublingual misoprostol ^c	34 (79.1)
More convenient	27 (79.4)
Avoid discomfort during vaginal administration	8 (23.5)
Think that route of absorption more effective	5 (14.7)
More privacy as no vaginal examination is required	5 (14.7)
No. of women who prefer other route of administration	8 (18.6)
Taste of drug not pleasant	6 (75)
Think that other route of absorption more effective	1 (12.5)
Not convenient	1 (12.5)

^aOnly women who had a complete abortion and had attended the day 43 follow-up were included in the acceptability study.

^bOne woman refused to choose her preference on the route of administration as she had no experience on the other route of administration before.

^cMore than one answer could be given.

is expensive and is not available in many developing countries. Therefore, an effective misoprostol-alone regimen is important for women who want the medical method for abortion in these countries. A misoprostol-alone regimen will be considered clinically applicable if it is effective, convenient to use, safe, acceptable to women and gives the least side-effects.

Most regimens of medical abortion using a combination of mifepristone and a prostaglandin have yielded a complete abortion rate ranging from 90–95% (Grimes, 1997), whereas the success rate of surgical abortion was reported to be 95% (Child *et al.*, 2001b). A misoprostol-alone regimen will be considered effective if the complete abortion rate reaches 90%. Different

misoprostol-alone regimens have been reported in the literature for medical abortion in the first trimester (Bugalho *et al.*, 1996; Koopersmith and Mishell, 1996; Carbonell *et al.*, 1997a,b, 1998, 1999; Tang *et al.*, 1999a; Ngai *et al.*, 2000). These studies are difficult to compare as different regimens of misoprostol were used and the waiting time to diagnose complete abortion was also different. The regimen used by Carbonell yielded the highest overall success rate (87–94%), whereas the success rate in the other studies ranged from 47–70% (Bugalho *et al.*, 1996; Koopersmith *et al.*, 1996; Tang *et al.*, 1999a).

The women in Carbonell's studies received 800 µg of vaginal misoprostol every 24–48 h up to a maximum of 3 doses. The women were asked to administer the drug themselves at home. They had to perform vaginal cleansing with water, sterilized by boiling, on the night before the insertion. The women were instructed to manually insert the four misoprostol tablets, after dampening them with 2–3 drops of water, and remain in a supine position for 3 h. The follow-up of the subjects was quite intense and demanding as they had to return to hospital for an ultrasound scan to confirm abortion after each dose of misoprostol and undergo another ultrasound scan 3 weeks afterwards to confirm complete abortion.

Ngai *et al.* repeated the study using a similar regimen to Carbonell and yielded a lower complete abortion rate of 94% in women <7 weeks pregnant and 77% in women 7–9 weeks pregnant (Ngai *et al.*, 2000). Moreover, 40% of the women who had used this regimen indicated that they preferred the surgical method in future. The complexity of this regimen raised concern about its incorporation into existing programmes or services in developing countries, where there is the greatest need for medical methods of abortion (Blanchard *et al.*, 1999). It is unlikely that women would return repeatedly to the clinic and the demand for repeated ultrasound examinations also posed an additional cost to the abortion service. The regimens using repeated doses of misoprostol alone that can be finished within 1 day have the advantage of requiring less hospital visits and ultrasound examinations.

Only two studies used regimens that could be finished within 1 day. Koopersmith reported a complete abortion rate of 60% using 200–400 µg of vaginal misoprostol every 4–8 h for 4–5 doses in women <10 weeks pregnant (Koopersmith and Mishell, 1996). Another study using a higher dose and more frequent dosing interval of vaginal misoprostol (800 µg initial dose followed by 400 µg every 3 h for a maximum of 4 doses) achieved 70% complete abortion in women <9 weeks pregnant (Tang *et al.*, 1999a). It appears that increasing the dose and shortening the dosing interval of vaginal misoprostol does not improve the complete abortion rate.

By changing the route of administration to sublingual, a complete abortion rate of almost 90% was achieved using a regimen of 600 µg misoprostol every 3 h for a maximum of 5 doses. This regimen is convenient to use as it can be completed within 12 h and the frequency of follow-up visits is similar to regimen using a combination of mifepristone and a prostaglandin. Sublingual misoprostol is easier to administer when compared with vaginal administration and it has the potential to be developed as a self-administered regimen.

The misoprostol-alone regimen appeared to be a safe method of medical abortion. Oral misoprostol is a safe drug for the treatment of peptic ulcer. There is no reported serious complication associated with various vaginal misoprostol-alone regimens. We did not encounter any serious complication in this study. There was no significant decrease in haemoglobin concentration and no women required a blood transfusion in this study using sublingual misoprostol. However, more studies are required to confirm the safety of sublingual misoprostol.

The side-effects of various misoprostol-alone regimens are another important factor determining their usefulness and acceptability. The duration of vaginal bleeding was 15 days and this is comparable with regimens using a combination of mifepristone and misoprostol (Tang *et al.*, 1999b). Diarrhoea, fever and chills are the three most important side-effects associated with this regimen of sublingual misoprostol. Seventy-two percent of the women complained of diarrhoea on the day of treatment and 70–80% of them had a fever and chills. The incidences of diarrhoea, fever and chills were higher compared with other studies using repeated doses of vaginal misoprostol only (Tang *et al.*, 1999a; Wong *et al.*, 2000).

However, it is difficult to compare the side-effects among different studies because of differences in the characteristics of the subjects and regimens used. Furthermore, these side-effects did not affect the acceptability of this regimen to the women in this study. If allowed to choose, >90% of the women would use sublingual misoprostol again and will choose this method in the future. Eighty-eight percent of the women will recommend this method to others. Most of the women thought that the duration of bleeding and pain were acceptable and expected. The women who preferred sublingual misoprostol as compared with other routes of administration commented that it was more convenient (79.4%) and could avoid the discomfort associated with vaginal administration (23.5%). They also thought that this route of administration was more effective (14.7%) and gave more privacy during the abortion (14.7%). It appears that the effectiveness is the most important factor affecting the acceptability of medical abortion. All of these women would choose medical abortion if medical and surgical methods were equally effective.

The results of this study show that sublingual misoprostol is a promising method of administration and it has the potential to develop into a self-administered misoprostol-only regimen for medical abortion. Misoprostol is designed for oral rather than vaginal administration. It is not uncommon to identify remnants of the tablets hours after its administration, indicating that absorption is variable and incomplete (Zieman *et al.*, 1997; Singh *et al.*, 1999). It has been suggested that absorption through the vaginal route is inconsistent and absorption could be improved by adding water to the misoprostol tablets (Carbonell *et al.*, 1997b, 1999). A pharmacokinetic study also showed that there was a larger individual variation in the absorption of vaginal when compared with oral misoprostol. Misoprostol is very soluble in water. It was observed that it could be dissolved under the tongue within 10–15 min. Therefore, the absorption may be more reliable than vaginal administration. In addition, sublingual misoprostol can avoid the first-pass effect by the liver when compared with oral administration. As a result, the systemic absorption of sublingual misoprostol may be the best among

these three different routes of administration. This was reflected by the high complete abortion rate and incidences of side-effects in this study. The dosing regimen used was empirical and the incidences of side-effects may be reduced with adjustment of the dosage and dosing interval.

In conclusion, this regimen of sublingual misoprostol is an effective and acceptable method of medical abortion. Randomized controlled trials are required to compare various misoprostol-alone regimens of medical abortion and a pharmacokinetic study is required to find the most appropriate dose, dosing interval and route of administration of misoprostol.

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