A Prospective Randomized Comparison of Sublingual and Oral Misoprostol When Combined With Mifepristone for Medical Abortion at 12–20 Weeks Gestation

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A prospective randomized comparison of sublingual and oral misoprostol when combined with mifepristone for medical abortion at 12–20 weeks gestation

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BACKGROUND: Sublingual misoprostol has been shown to be effective in medical abortion. A prospective double-blinded placebo-controlled trial was done to compare the efficacy and side-effects of sublingual to oral misoprostol when used with mifepristone for medical abortion from 12 to 20 weeks gestation. METHODS: A total of 120 women at 12–20 weeks of gestation were randomized to receive 200 mg oral mifepristone followed by either sublingual or oral misoprostol 400 μg every 3 h for a maximum of five doses 36–48 h later. The course of misoprostol was repeated if the woman did not abort within 24 h. RESULTS: There was no significant difference (P = 0.43) in the success rate at 24 h [relative risk = 1.075; 95% confidence interval (CI): 0.94–1.19]. Abortion occurred in 91.4% in the sublingual group (95% CI: 81.0–96.7%) as compared to 85.0% (95% CI: 73.7–92.1%) in the oral group. The median induction-to-abortion interval was significantly shorter (P = 0.009) in the sublingual group (5.5 h) as compared to the oral group (7.5 h). The incidence of fever was higher in the sublingual group (P < 0.0001). The incidences of other side-effects were similar. CONCLUSION: Sublingual misoprostol, when combined with mifepristone, is effective for medical abortion in the second trimester. The induction-to-abortion interval is shorter when sublingual misoprostol is used when compared to oral misoprostol.

Key words: abortion/misoprostol/oral/second trimester/sublingual

Introduction

Medical abortion is becoming more popular nowadays as a method of termination of pregnancy in the second trimester because it is effective and technically less demanding when compared to surgical methods. Prostaglandin analogues are the mainstay of drugs used for this purpose. Among the prostaglandin analogues available, misoprostol is the most commonly used one, as it is cheap and stable at room temperature. It has been shown to be effective for second trimester termination of pregnancy with or without mifepristone (El-Rafaey et al., 1995; Ho et al., 1996; Wong et al., 2000). Although misoprostol is licensed for oral use, vaginal administration was used in most studies since it has been shown to be more effective. Recently, we have explored the use of sublingual misoprostol for medical abortion. A pharmacokinetic study has demonstrated that sublingual administration achieved the peak concentration in the shortest time and had the highest bioavailability (Tang et al., 2002). The time to peak concentration after oral administration was similar to the sublingual route but the plasma concentration achieved was lower. As a result, the bioavailability after oral administration was lower than sublingual administration. Previous studies have shown that sublingual misoprostol is effective in second trimester medical abortion (Tang and Ho, 2001). A study comparing a sublingual to a vaginal misoprostol-alone regimen has demonstrated that both sublingual and vaginal misoprostol are effective ways of giving the drug, but the success rate in 24 h is higher in the vaginal group. However, the same study also demonstrated that the sublingual route was more popular than the vaginal route because it was more convenient to use (Tang et al., 2004). Oral and sublingual routes would be the alternative for those women who do not like the vaginal route of administration. It was also proposed that pre-treatment with mifepristone would improve the performance of misoprostol and therefore routes of administration other than the vaginal route may still be effective. Therefore, it was the aim of this randomized study to compare the sublingual route to the oral route in administration of misoprostol for medical abortion in the second trimester after pretreatment with mifepristone.

Materials and methods

Women aged &gt;18 years requesting legal termination of pregnancy at 12–20 weeks of gestation from August 2002 to January 2004 at Queen Mary Hospital in Hong Kong were approached. Women who were using prescription drugs regularly, women with an intrauterine contraceptive...
device in utero, nursing mothers, multiple pregnancies and heavy smokers were excluded. An ultrasound examination was done to confirm the gestation of the pregnancy. An informed written consent was obtained. The study was approved by the ethics committee, The University of Hong Kong.

We used a computer-generated randomization sequence to assign participants to two treatment groups. All subjects were given 200 mg oral mifepristone 36–48 h before the administration of misoprostol. In group 1, they were given two tablets of 200 mg misoprostol (Cytotec; Searle, Crows Nest, NSW, Australia) sublingually and two tablets of placebo orally, whereas in group 2 they were given 2 tablets of 200 mg misoprostol orally and 2 tablets of placebo sublingually every 3 h for a maximum of five doses in 24 h. Allocation was concealed by the use of sealed, sequentially numbered treatment packs, which were filled and labelled in accordance with the list of randomization. This was a double-blinded placebo-controlled study and neither the investigators nor the subjects knew the routes that the women were assigned to. If the women did not abort after the first course, a second course of five doses of misoprostol and placebo was repeated. The blood pressure, pulse rate and temperature were monitored every 3 h. Side-effects were recorded every 3 h by the nursing staff. Pethidine hydrochloride 50 mg (Pethidine; Antigen Pharmaceuticals Limited, Roscrea, Ireland) was given for pain relief if necessary. After abortion, the products of conception were examined and, if it was incomplete, evacuation of the uterus was performed. The decision for evacuation of the uterus was based on the clinical findings and ultrasound examination of the uterus was not done. The woman was discharged 24 h after the abortion if there were no complications.

The primary outcome measure was the success rate at 24 h. Success rate was defined as abortion occurring without the need for further prostaglandin analogues or syntocinon. The induction-to-abortion interval and side-effects of the two regimens were also assessed. Differences in continuous variables were analysed with Student t-test for normally distributed data and the Mann–Whitney U-tests for skewed data. Differences in discontinuous variables were analysed by χ²-test and the Fisher’s exact test as appropriate.

The difference in success rate at 24 h was used to calculate the sample size required. According to previous studies, the use of oral misoprostol would achieve a success rate of 70% at 24 h (Ho et al., 1997; Ngai et al., 2000). A sample size of 120 has a power of 0.8 at 5% significance to detect a difference of 20% in success rate.

Results
A total of 229 women at 12–20 weeks of gestation who requested termination of pregnancy were interviewed during the study period. Twenty-three women did not want to join. Thirty-three women did not meet the inclusion criteria because the gestation was found to be <12 weeks. Fourteen women had history of current medical diseases. Five women had attempted to terminate the current pregnancy with other drugs. Thirty-five women were excluded because they had multiple pregnancies, could not give a valid consent because of language barrier or had history of taking other drugs in the current pregnancy. A total of 120 women were eligible and agreed to participate in the study (Figure 1). Two women from the sublingual group were excluded from the study after randomization. One of them had an abnormal liver function test which was discovered after the administration of mifepristone. The pregnancy was terminated by vaginal misoprostol. The other woman had allergic reaction after the administration of the first dose of misoprostol and the pregnancy was terminated surgically at 14 weeks of gestation. Therefore, there were 58 women in the sublingual group and 60 women in the oral group included in the final analysis. Table I shows the demographic characteristics of these 118 women. The success rate in 24 h was 91.4% [95% confidence interval (CI): 81.0–96.7%] in the sublingual group and 85% (95% CI: 73.7–92.1%) in the oral group (Table II). There was no significant difference between the two groups (relative risk = 1.075; 95% CI: 0.94–1.19). However, the induction-to-abortion interval in the sublingual group (5.5 h) was significantly shorter (P = 0.009) than that of the oral group.

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Sublingual group (n = 58)</th>
<th>Oral group (n = 60)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Age (years)</td>
<td>Weight (kg)</td>
</tr>
<tr>
<td>26.5 (7.6)</td>
<td>51.8 (7.6)</td>
<td>155.9 (6.5)</td>
</tr>
<tr>
<td>24.9 (6.8)</td>
<td>51.2 (9.9)</td>
<td>155.8 (6.5)</td>
</tr>
</tbody>
</table>

*Results are expressed as mean (SD).
Figure 2 shows the cumulative success rate of the two routes of administration of misoprostol. It showed that the majority of the successful subjects (87.9%) in the sublingual group aborted within 12 h of the start of misoprostol whereas only 66.7% of the subjects in the oral group aborted within that period of time. Table III compares the cumulative abortion rate of the two groups. Side-effect profile is shown in Table IV. Ten (17.2%) and seven (11.7%) subjects in the sublingual and oral groups required surgical evacuation for incomplete abortion respectively. The difference was not statistically significant ($P = 0.549$). The only side-effect that showed a significant difference was fever which was higher in the sublingual group ($P < 0.0001$). Eighteen women (31%) in the sublingual group and 17 women (28.3%) in the oral group required analgesia. The difference was not significant ($P = 0.549$). All the women attended the follow-up visit and no serious complication was reported.

**Discussion**

Many prostaglandin analogues with or without mifepristone have been investigated for medical abortion in the second trimester. Misoprostol has been studied extensively in this regard, as it is cheap and stable at room temperature. The use of oral mifepristone 36–48 h before prostaglandin administration can increase the success rate, shorten the induction-to-abortion interval and reduce the amount of prostaglandins required in second trimester abortion (Thong and Baird, 1992; Ho et al., 1995, 1997). The recommended dose of mifepristone is 600 mg but it has been shown in a randomized trial that the abortion rate and induction-to-abortion interval were the same even if the dose was reduced to 200 mg (Webster et al., 1996).

Although misoprostol was initially developed for oral administration, vaginal administration is very commonly used in medical abortion. For second trimester medical abortion, oral misoprostol is less effective than vaginal administration in terms of abortion rate and induction-to-abortion interval. In a
Table III. The cumulative abortion rate

<table>
<thead>
<tr>
<th>Women aborted within:</th>
<th>Sublingual (n = 58)</th>
<th>Oral (n = 60)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 h</td>
<td>19 (32.7)</td>
<td>9 (15)</td>
</tr>
<tr>
<td>6 h</td>
<td>34 (58.6)</td>
<td>23 (38.3)</td>
</tr>
<tr>
<td>12 h</td>
<td>51 (87.9)</td>
<td>40 (66.7)</td>
</tr>
<tr>
<td>18 h</td>
<td>53 (91.4)</td>
<td>50 (83.3)</td>
</tr>
<tr>
<td>24 h</td>
<td>53 (91.4)</td>
<td>51 (85.0)</td>
</tr>
<tr>
<td>48 h</td>
<td>57 (98.3)</td>
<td>55 (91.7)</td>
</tr>
</tbody>
</table>

*P < 0.05.

Table IV. Side-effects

<table>
<thead>
<tr>
<th></th>
<th>Sublingual group (n = 58)</th>
<th>Oral group (n = 60)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>22 (37.9)</td>
<td>26 (43.3)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>17 (29.3)</td>
<td>22 (36.7)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>20 (34.5)</td>
<td>28 (46.7)</td>
</tr>
<tr>
<td>Breast tenderness</td>
<td>6 (10.3)</td>
<td>9 (15.0)</td>
</tr>
<tr>
<td>Headache</td>
<td>13 (22.4)</td>
<td>14 (23.3)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>8 (13.8)</td>
<td>13 (21.7)</td>
</tr>
<tr>
<td>Chills and rigors</td>
<td>21 (36.2)</td>
<td>21 (35.0)</td>
</tr>
<tr>
<td>Need for analgesic</td>
<td>18 (31.0)</td>
<td>17 (28.3)</td>
</tr>
<tr>
<td>Fever</td>
<td>12 (20.7)*</td>
<td>0*</td>
</tr>
</tbody>
</table>

*aDiarrhoea more than three episodes.

*bTemperature >38°C.

randomized study using misoprostol 200 µg every 3 h, the oral route had been shown to give a lower abortion rate in 48 h (69%) and a longer induction to abortion interval (13 h) compared to vaginal route (abortion rate in 48 h: 93% and induction-to-abortion interval: 9 h) (Ho et al., 1997). The efficacy of oral misoprostol may be improved by increasing the dose to 400 µg. A study using 400 µg oral misoprostol every 3 h showed that the induction-to-abortion interval was 8.7 h and the abortion rate was 92% (Ho et al., 1996). This was comparable to 200 µg vaginal misoprostol. A randomized trial comparing 400 µg of oral misoprostol with 200 µg vaginal misoprostol demonstrated that there was no difference in the induction-to-abortion interval and the abortion rate (Ngai et al., 2000). The incidence of diarrhoea was higher with oral misoprostol. However, it was shown that women preferred oral to vaginal administration because it was less painful and more convenient and it gave more privacy (Ho et al., 1997). It would be an important factor affecting the acceptability of a regimen in second trimester abortion since more than one dose of misoprostol is usually required. Moreover, the absorption of vaginal misoprostol may be difficult to predict when the woman starts to bleed. Therefore, a regimen using a combination of vaginal and oral misoprostol was developed which involved the use of 600 µg vaginal misoprostol as the first dose followed by 400 µg oral misoprostol every 3 h. The abortion rate (97%) and the induction-to-abortion interval (6.5 h) were the same as using similar doses of vaginal misoprostol (El-Rafaey et al., 1995). The results were later confirmed by a larger series of patients using a slightly higher initial dose of vaginal misoprostol (800 µg). It was believed that the use of vaginal misoprostol as the first dose could lead to more effective cervical priming and there was no advantage in the vaginal administration of subsequent doses (Ashok and Templeton, 1999).

Recently, it has been shown that misoprostol can be administered sublingually. A pharmacokinetic study has shown that after a single dose of sublingual misoprostol, the peak concentration is achieved in a shorter time than with vaginal misoprostol. The peak concentration and bioavailability were also higher with sublingual administration. Therefore, it was postulated that sublingual route of administration might be the most effective route for administration of misoprostol (Tang et al., 2002). However, a previous study comparing sublingual and vaginal misoprostol when given without mifepristone has shown that vaginal route was slightly superior. The discrepancy of the clinical and pharmacokinetics findings might be due to the fact that the cumulative serum level of misoprostol is higher for vaginal administration when compared to sublingual administration. This effect will be more significant for misoprostol-alone regimens which require more repeated doses of misoprostol to achieve the clinical outcome. For regimens involving mifepristone pre-treatment, the doses of misoprostol required are usually less and therefore sublingual misoprostol may be superior. The current study has shown that sublingual misoprostol when combined with mifepristone is very effective for second trimester medical abortion and is superior to oral misoprostol. The success rate of 91.4% in 24 h is comparable to 200 microg every 3 h) and oral (400 microg every 3 h) misoprostol when combined with mifepristone is required to find out the best route of administration of misoprostol in second trimester medical abortion.

Acknowledgement

The study was supported by the Special Programme of Research, Development and Research Training in Human Reproduction, World Health Organization, Geneva, Switzerland.

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Ngai SW, Tang OS and Ho PC (2000) Randomized comparison of vaginal (200 microg every 3 h) and oral (400 microg every 3 h) misoprostol when combined with mifepristone in termination of second trimester pregnancy. Obstet Gynaecol 90,735–738.


Submitted on April 16, 2005; accepted on June 16, 2005