

## Comparison of oral versus vaginal misoprostol & continued use of misoprostol after mifepristone for early medical abortion

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**Background & objectives:** Medical abortion though legalized in India, is still not very popular. A disadvantage of medical abortion is the longer duration of bleeding compared with surgical abortion which may reduce acceptability. Due consideration needs to be given to the issues related to medical abortion for improving the reproductive health status of women suffering from consequences of unsafe and illegal surgical abortion. The present study compared the efficacy of oral and vaginal administration of misoprostol after a single dose of 200 mg of mifepristone and evaluated the influence of continuing misoprostol for one week on efficacy and side effects.

**Methods:** A double-blind randomized controlled trial with 150 healthy pregnant women requesting medical abortion with < 63 days of amenorrhoea was conducted in the gynecological and family planning clinic at All India Institute of Medical Sciences, New Delhi. Mifepristone (200 mg) was administered orally on day one, followed by 0.8 mg misoprostol either orally or vaginally on day three. Women in the oral group and one of the two vaginal groups continued 0.4 mg of oral misoprostol twice daily for seven days.

**Results:** Complete abortion rate in each of the groups was 96-100 per cent. The addition of misoprostol 0.4 mg twice a day from day 4-10 did not help in increasing successful outcome or shortening of duration or amount of bleeding.

**Interpretation & conclusion:** Medical abortion for pregnancy up to 63 days using misoprostol 0.8 mg vaginal/oral after pretreatment with mifepristone 200 mg is a safe and successful procedure. No differences in efficacy or duration of bleeding were observed with addition of oral misoprostol for 1 wk after abortion.

**Key words** Abortifacient efficacy - duration of bleeding - medical abortion - misoprostol

In India, 6.7 million induced abortions are performed a year, with ratio of 452 abortions per 1000 live births or 60 induced abortions per 1000 women of child bearing age<sup>1</sup>. Although abortion was legalized in India in 1972, illegal abortion is still three (urban) to five (rural) times more common than legal abortion<sup>2</sup>.

Medical abortion offers great potential for improving abortion access and safety, as it requires a less extensive infrastructure than surgical abortion.

Research has been continued to improve the medical abortion regimen since its inception. It has

also been demonstrated that the oral misoprostol dose of 0.4 mg was insufficient when the length of pregnancy was more than seven weeks<sup>3,4</sup>. Studies have also shown that vaginal administration of misoprostol after pre-treatment with mifepristone resulted in higher complete abortion compared to oral dose<sup>5</sup>. A disadvantage of medical abortion is the longer duration of bleeding compared with surgical abortion which may reduce acceptability. The present study was planned to find a safe, simple and optimally effective regimen of mifepristone and misoprostol for abortion of pregnancy up to 63 days. Three different regimens were tested and abortifacient efficacy, side effects and the duration of bleeding of the three treatment regimens differing in the route of administration and in the duration of treatment with misoprostol were compared.

### Material & Methods

The study has been carried out in the Department of Obstetrics & Gynaecology, All India Institute of Medical Sciences, New Delhi, as a part of WHO multicentric, double-blind, randomized controlled trial from November 1998 to March 2000. The trial included 150 healthy pregnant women requesting legal termination of pregnancy up to 9 wk or < 63 days of amenorrhoea or ultrasound showing crown rump length up to 21 mm. Exclusion criteria included adrenal disease, hypertension, heart disease, bronchial asthma, glaucoma, sickle cell anaemia, haemoglobin < 100 g/l, history or evidence of thromboembolism, liver disease, previous surgery on uterine cervix and suspected or proven ectopic pregnancy. Each woman signed an informed consent and had a medical and gynaecological examination and haemoglobin estimation.

Computer generated random number sequence was used for randomization of women to one of the three groups. Mifepristone 200 mg orally was administered on day one of study. On day three (36-48 h later) the group 1 women (oral/oral) received 0.8 mg of misoprostol orally and placebo vaginally, group 2 (vaginal/oral) and group 3 (vaginal only) women received 0.8 mg of misoprostol vaginally and placebo tablets orally. After administration of misoprostol, women were observed for 3 h for pulse, temperature and blood pressure, and side effects and onset of bleeding recorded. Those in groups 1 and 2 received

0.4 mg misoprostol twice daily for seven days, starting on day four of study, while women in group 3 took placebo tablets. Pelvic examination was done at the end of 3 h observation. Participants were requested to maintain a diary card to record days of bleeding and occurrence of side effects. The subjects returned for follow up evaluations on days 15 and 43 after beginning the treatment. All had haemoglobin estimation, record of the diary card, pelvic examination and ultrasonography, if necessary. Double blinding was maintained throughout the study and drugs were provided by the World Health Organisation.

The three regimens were compared in their efficacy to induce complete abortion, frequency of side effects, and duration of bleeding. Complete abortion was confirmed by passage of products of conception and by clinical findings at pelvic examination and on curettage during the period up to the first menstruation. Missed abortion included a non-viable pregnancy on ultrasonography. Failure was a continuing pregnancy. Incomplete abortion included those requiring curettage for completion. Those women who had vacuum aspiration before the outcome was known and who were lost to follow up were classified as undetermined.

Statistical analysis was done using the SAS software to calculate percentages of women with various outcome measures and  $X^2$  test was used for comparison of outcome.  $P < 0.05$  was considered significant.

Our study group of 150 patients formed a subgroup of the entire WHO multicentric trial and these were analysed separately in relation to the compiled data from all centers to assess the efficacy and acceptability of these medical abortion regimens in the Indian population.

### Results

The three groups of 50 women each were comparable in various demographic characters such as age, ethnicity, parity, and duration of amenorrhoea (Table I). Mifepristone (200 mg) was administered orally to all women on day 1. Predominant side effect was nausea in about 33 per cent of patients. One woman in group 2 expelled products of conception on

**Table I.** Demographic profile of pregnant women

Parameter	Group 1	Group 2	Group 3
Age (yr)	27.6 ± 4.8	27.2 ± 3.9	27.1 ± 2.9
<i>Parity no. (%):</i>			
Primi	5 (10)	5 (12)	8 (16)
Multi	45 (90)	45 (90)	42 (84)
Weight (kg)	54.72 ± 3.42	51.70 ± 4.78	52.62 ± 4.86
Duration of pregnancy (days)	51.68 ± 6.98	49.98±5.54	51.46 ± 5.98
Ultrasonography			
CRL (mm)	9.38 ± 1.88	10.06 ± 2.02	10.5 ± 2.12
Values are mean ± SD CRL, Crown rump length			

**Table II.** Side effects after misoprostol administration

Parameters	Group 1	Group 2	Group 3
Nausea	9 (18)	15 (30)	14 (28)
Vomiting	1 (2)	0	0
Diarrhoea	0	1 (2)	0
Dizziness	1 (2)	2 (4)	0
Headache	1 (2)	2 (4)	0
Fainting	0	1 (2)	0
Breast tenderness	2 (4)	3 (6)	2 (4)
Lower abdominal pain	10 (20)	7 (14)	13 (26)
Rash	1 (2)	0	0
n=50 in each group Values are given as no. (%)			

day 2. Vaginal bleeding in the form of spotting started in about 30 per cent women on day 2-3. On day 3 after misoprostol administration the women were monitored hourly for vitals, side effects and onset of bleeding. The blood pressure, pulse rate and temperature of the women showed no significant difference at the end of 3 h observation in each group. Gastrointestinal and other side effects did not show significant difference in the three treatment regimens (Table II). At the end of 3 h observation period bleeding started in 92 per cent women in the oral misoprostol group (group1) and 89 per cent women in the vaginal misoprostol groups (groups 2 & 3). Products of conception were expelled in about 36 per cent women in each of the group.

#### Outcome of treatment

All women in oral group (group 1) had successful complete abortion. In group 2, 49 women (98%) had successful outcome, only one had trial interruption as

**Table III.** Bleeding pattern in relation to period of amenorrhoea

Amenorrhoea	Group 1 (n=50)	Group 2 (n=49)	Group 3 (n=46)
< 50 days	8.62 ± 1.22	8.41 ± 1.42	9.55 ± 1.86
50-57 days	9.00 ± 1.86	8.53 ± 1.42	8.64 ± 1.82
> 58 days	9.00 ± 1.66	8.23 ± 1.24	9.19 ± 1.69
Values are mean ± SD			

she got surgical evacuation done due to acute pain abdomen. In group 3, success rate was 96 per cent, 2 women were lost to follow up, 2 had vacuum aspiration - 1 for continuing pregnancy and 1 for incomplete abortion. This woman with incomplete abortion also required 2 units blood transfusion.

#### Bleeding pattern

*Duration:* The mean duration of bleeding for women with a successful outcome in relation to period of amenorrhoea was compared. Duration of bleeding varied from 7-12 days. The difference in each of the groups was not statistically significant in relation to period of amenorrhoea (Table III).

Bleeding more than that for their normal menstrual period was reported by 70 per cent in group 1, 68 per cent in group 2 and 60 per cent in group 3, the difference being statistically non significant.

*Resumption of menstruation:* In about 92-94 per cent women bleeding had stopped by the day 15 visit. Majority of women who had complete abortion had their menstruation by day 43 of follow up. The remaining resumed menses in the following two week period.

The study subjects were also interviewed regarding their acceptability of medical abortion; 97 per cent women reported it to be safe and thus would prefer medical to surgical abortion in future. However, 86 per cent of women felt that the procedure should be conducted at a health facility under strict medical supervision to avoid complications.

#### Discussion

The antiprogesterone mifepristone followed by a prostaglandin analogue two days later has been in clinical use for over a decade. Multi centre trials with

different prostaglandin analogues have shown that the same effectiveness as seen with 600 mg dose can be achieved by 200 mg of mifepristone<sup>3,4</sup>. It has also been demonstrated that the oral misoprostol dose of 0.4 mg is insufficient when the length of pregnancy is more than seven weeks<sup>3,4</sup>. A clinical study on 263 women with up to 63 days of amenorrhoea showed that vaginal administration of misoprostol (0.8 mg) after pretreatment with mifepristone resulted in a higher complete abortion rate (95%) than with oral route (87%)<sup>4</sup>.

In our study the results were not statistically significantly different in the three study groups. The better efficacy after vaginal administration of misoprostol could be explained by different contractility patterns. Vaginal administration of misoprostol caused long lasting and continuously increasing uterine contractility, while no regular contractility could be seen after oral administration<sup>6</sup>. The efficacy in our study was very high (96-100%) with only 2 failures. Schaff *et al*<sup>7</sup> in their trial in 933 women with pregnancy up to 8 wk have shown 97 per cent complete abortion rate with 0.8 mg misoprostol self-administered vaginally at home after pretreatment with 200 mg mifepristone. The success rates in our study are consistent with other reports indicating both oral and vaginal routes to be equally effective. There were marginal differences in the side effects, with no statistical significance.

A disadvantage of medical abortion is the longer duration of bleeding compared with surgical abortion<sup>8</sup>. In the three WHO multicentre studies<sup>3,4,9</sup>, the median duration of bleeding for medical abortion was 11-12 days. Because long duration of bleeding reduces acceptability of medical abortion, there have been attempts to shorten the bleeding. Continuation of misoprostol after day 3 for seven days was tested to shorten the duration of bleeding as well as improve efficacy. The three groups in our study had mean duration of bleeding 7-12 days and no benefit was seen with continuation of misoprostol. Another multicentre trial from China, Cuba and India<sup>10</sup> showed medical abortion clients perceived their bleeding to be heavier than did the surgical patients and few statistically significant differences in clinical measures of blood loss were noted. In order for women to know

what to expect with medical abortion, they must be counselled prior to the procedure about duration and amount of bleeding versus excessive bleeding that would signal a clinical problem.

The compilation of data from all centres in this study showed vaginal misoprostol to be more effective than oral for pregnancy >57 days when continued with 0.4 mg oral misoprostol twice daily for seven days. However, continued misoprostol till days 4-10 did not shorten the duration of bleeding and no differences in efficacy were observed when amenorrhoea length was <57 days<sup>11</sup>. In our study women showed 97 per cent acceptability for medical abortion in future, however, 86 per cent were against home administration of drugs. Coyaji in his study on 1162 women has extensively compared medical abortion in urban research centre, urban family planning clinic, and rural health station and found it to be effective, acceptable, feasible and safe in all three setting<sup>12</sup>. It has been suggested that medical abortion could now be safely phased into the existing health care infrastructure in India. Due consideration needs to be given to the service delivery issues of medical abortion for improving the reproductive health status of millions of women suffering consequences of unsafe and illegal surgical abortion in developing countries including India.

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