# Low Dose Mifepristone And Vaginal Misoprostol: A Safe Option For Termination Of Pregnancy Up To 63 Days

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**Citation**

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**Abstract**

Aim: To evaluate the efficacy and safety of low dose mifepristone (200mg) followed 48 hours later by 400µg of vaginal misoprostol to terminate pregnancy up to 63 days
Methods: This was a prospective study enrolling 72 healthy women, 37 with less than 49 days gestation (group A) and 35 with 50 to 63 days gestation (group B). They were given 200 mg of mifepristone orally followed by 400µg of misoprostol vaginally after 48 hours. Failure was defined as need for surgical intervention for any reason. Secondary outcome measures were side effects, complications and acceptability. Results were compared between the two groups.
Results: Both the groups were comparable with respect to age, parity and hemoglobin. Complete abortion occurred in 97.3% in <49days pregnancy group and 97.1% in 50 - 63 days group. In 19.4% subjects, bleeding started following mifepristone alone and in rest it started within 4 hrs of receiving misoprostol and lasted for 11.5 days. Mean duration of bleeding was longer in group B (13.15 vs. 9.97 days). Mean fall in hemoglobin was minimal (0.42 gm%) though it was more in group B (0.49gm%) than in group A (0.37gm%). Moderate amount of pain was reported by 71.4% and 37.8% subjects in group B and A respectively. Analgesics were required by 13.9% of subjects. Incidence of nausea, vomiting and diarrhea was 26.4%, 9.7% and 15.3% respectively and it was similar in either groups.
Conclusion: Medical abortion using low dose mifepristone and vaginal misoprostol is a safe and effective option for terminating pregnancy up to 9 weeks.

## INTRODUCTION

Surgical evacuation under some kind of anaesthesia is a commonly used method for termination of early pregnancy with success rate of more than 95% [1]. But it carries the risks of instrumentation and anaesthesia. It involves hospitalization and cost, the factors that are important, particularly in low-resource settings of developing countries. Considering these facts, there is an ever- growing need to explore into safe, efficacious and cost-effective methods of medical abortion.

Mifepristone, a norethindrone derivative, is a synthetic antiprogestin. Misoprostol is a methyl ester of prostaglandin $E_1$ that stimulates uterine contractions through $EP_2/EP_3$ receptors. Given 48 hours after mifepristone, it results in complete abortion in up to 95-99% of cases. Initially mifepristone was advocated in the dose of 600 mg for this purpose [2,3]. Studies regarding the pharmacokinetics of mifepristone suggest that after ingestion of doses higher than 100mg, there is no significant difference in plasma concentrations of the drug within the first 48 hrs[4] (peak serum concentration remains between 2.0-2.5µg/ml). Further trials have confirmed equal efficacy (93-97%) of low dose mifepristone as well[5,6,7] .

Misoprostol has been administered through oral, vaginal and sublingual route in various studies. Oral misoprostol in the dose 400µg is insufficient to cause abortion when length of pregnancy is more than 7 weeks[8,9,10]. As compared to oral route, overall exposure to misoprostol acid is increased after vaginal administration[11]. Uterine contractility is increased continuously for four hours and maximal contractility is higher after vaginal administration[12]. Sublingual route has maximum peak concentration and bioavailability and thus high efficacy but at the cost of increased gastrointestinal side-effects[13]. In their study, Hamoda et al[14] reported success rate of 98.9% with sublingual route but the incidence of side effects in the form of nausea, vomiting and diarrhea was 79%, 57% and 62% respectively. Further, there is no consensus on the dosage schedule of the drug by any route.

Considering the pharmacokinetics and the side-effect profile of the drug we tried to examine the efficacy of single and lowest dose of misoprostol by vaginal route following 200mg of mifepristone in terminating pregnancy. More importantly, we wished to determine whether the above regime is safe and effective up to 9 weeks.

## METHODS

This study was conducted at Maulana Azad Medical College and Lok Nayak Hospital, Delhi after obtaining approval from the ethical committee of the Maulana Azad Medical College and Lok Nayak Hospital,Delhi.

A total of 72 women between 18 and 35 years of age, with period of gestation ≤63 days who were willing for medical abortion after understanding the benefits and risks of the method were recruited to the study. Out of these, 37 women had gestational age of less than 49 days and 35 had period of gestation corresponding to 50 – 63 days.

Inclusion criteria were: Hemoglobin ≥ than 10 gm%, Singleton intrauterine pregnancy, no clinical evidence of active infection, and ready for surgical intervention in case of failure or excessive bleeding.

Exclusion criteria were: Any adnexal mass, history of long term steroid therapy, any medication taken that would affect the outcome, any contraindication to drugs like hypertension, cardiovascular disease etc. or allergy to drugs.

Written informed consent was obtained. After obtaining history, complete general physical examination and systemic examination was performed. Gestational age was confirmed by menstrual history, pelvic examination and by ultrasonography. Blood grouping and Rh typing was done. Urine analysis was done to look for sugar or proteins. Haemoglobin level was checked.

## TREATMENT PROTOCOL

On day one, 200mg of mifepristone was given. Anti- D was administered to Rh- negative women. Second visit was scheduled on day 3, i.e. after 48 hours, when after reviewing the symptoms and performing speculum examination, 400 µg (2 tablets of 200 µg each) of misoprostol moistened with a few drops of saline were inserted into the posterior fornix of vagina. Most of the cases were observed for 4 hours in the hospital but those with history of previous abortion or caesarean section were observed for longer duration. Pulse and blood pressure were monitored and side effects noted.

Opiate analgesia and antiemetics were given as per requirement. On follow up visit, on day 15, symptoms were reviewed, general physical examination and pelvic examination was performed. Ultrasonography was done in all cases to confirm the completeness of abortion. Haemoglobin level was checked again.

The women who had any evidence of retained products of conception on ultrasonography but not having heavy bleeding were allowed to wait for 1 week for spontaneous expulsion. Outcome was measured in terms of success (i.e. complete abortion with drugs without any surgical intervention) or failure (i.e. any need for surgical intervention). Secondary outcome measures were bleeding pattern, side effects, fall in Haemoglobin, pain and acceptability. Comparison was made between the two groups based on the gestational age with respect to all the outcome measures.

## STATISTICAL ANALYSIS

The data was presented as mean ± standard deviation. Statistical analysis was done using student's t test, chi-square test, Mann- Whitney U test, wherever required.

## RESULTS

A total of 72 women were recruited into the study out of which 37 had gestational age of less than or equal to 49 days (group A) and 35 had period of gestation corresponding to 50-63 days (group B).

## BASELINE CHARACTERISTICS (TABLE 1)

The mean age of the subjects was 26.5 ± 4.0 yrs. Four women were nullipara and all of them aborted successfully. Only 2 subjects had undergone induced abortion prior to this by suction curettage and both had complete abortion without any complications. Both of them expressed satisfaction with the method and compared it to be better than surgical abortion. Six women had a history of uterine scar in the form of previous one caesarean delivery. All of them had successful outcome. There was no significant difference in baseline characteristics like mean age (p value 0.599), parity (p value = 0.155), mean hemoglobin (p = 0.353) between either group.

**Figure 1**

Table 1: Demographic characteristics

| Characteristics | Group A (POG† ≤ 49 days) | Group B (POG 50-63 days) | P value |
|---|---|---|---|
| Mean age (yrs) | 26.7 ± 3.9 | 26.2 ± 4.1 | NS†† |
| Parity (%) | | | |
| 0 | 8.1 | 2.9 | |
| 1 | 32.4 | 54.3 | NS |
| 2 | 54.1 | 42.9 | |
| > 2 | 5.4 | 0 | |
| Previous cesarean delivery (no.) | 3 | 3 | NS |
| Baseline Hemoglobin (gm%) | 11.3 ± 0.4 | 11.1 ± 0.5 | NS |

†POG =period of gestation ††NS= Not- significant

## EFFICACY

Defining failure as the need to do surgical intervention for any reason, two subjects failed the medical abortion. One of them with period of gestation of 55 days required suction curettage because of excessive bleeding. Another one with 48 days pregnancy underwent surgical evacuation because of retained products of conception that despite being separate from uterine wall were not expelled even after waiting for one more week. Overall success rate was 97.2% and was similar in women with gestation of less than 49 days (97.3%) and 50- 63 days (97.1%).

## BLEEDING PATTERN (TABLE 2)

In 19.4% subjects, bleeding started with mifepristone alone. In rest of the subjects bleeding started within 4 hours of receiving misoprostol, average being 1.5 ± 0.13 hrs in group A and 1.18 ± 0.13 hrs in group B. Bleeding lasted for 7-14 days in over 70% of subjects, average being 11.5 ± 4.7 days. Mean duration of bleeding in group B was significantly longer than that in group A (13.15 vs 9.97 days). More number of women in group A reported the amount of bleeding to be comparable to normal menstruation. Bleeding was perceived to be heavier than menstruation by more number of subjects in group B and the difference was statistically significant. (p value 0.018). Mean fall in hemoglobin was 0.42 ± 0.04 gm%. There was a significantly greater mean fall in hemoglobin in women with higher period of gestation (p value 0.003) but the difference was otherwise minimal.

**Figure 2**

Table 2 : Bleeding pattern

| Parameters | Group A (POG† ≤ 49 days) | Group B (POG 50-63 days) | P value |
|---|---|---|---|
| Onset of bleeding with mifepristone alone (%) | 24.3 | 14.3 | NS†† |
| Onset of bleeding with misoprostol (hours) | 1.50± 0.13 | 1.18± 0.13 | NS |
| Duration of bleeding (days) | 9.97 | 13.15 | S††† |
| Amount of bleeding | | | |
| • Comparable to menses (%) | 40.5 | 11.4 | |
| | 51.4 | 80 | S |
| • Heavier than menses (%) | 8.1 | 8.6 | |
| • Excessive bleeding (%) | | | |
| Fall in hemoglobin (gm%) | 0.37 ± 0.05 | 0.49 ± 0.06 | S |

†POG =period of gestation ††NS= Not- significant †††S-Significant

## SIDE EFFECTS (TABLE 3)

Pain was the most commonly reported side effect. 54.2% had moderate amount of pain. Significantly more number of subjects in group B reported moderate amount of pain as compared to group A (71.4% vs. 37.8%). Overall, 13.9% subjects required opiate analgesia. Incidence of severe cramping pain and the analgesic requirement was similar in either group. No significant difference was observed in incidence of nausea (p value=0.345), vomiting (p= 0.635) and diarrhea (p value= 0.820) between either groups. Diarrhea was self-limiting, and no antidiarrheal agents were required by any subject. Overall 62 subjects (86.1%) were highly satisfied with this method and would recommend this to others.

**Figure 3**

Table 3: Comparison of side effects between two groups

| Side effects | Group A n (%) | Group B n (%) | p value |
|---|---|---|---|
| Pain | | | |
| Mild | 21 (56.8) | 5 (14.3) | S† |
| Moderate | 14 (37.8) | 25 (71.4) | S |
| Severe | 02 (5.4) | 5 (14.3) | NS†† |
| Analgesic Requirement | 03(8.1) | 07(20) | NS |
| Nausea | 8(21.6) | 11(31.4) | NS |
| Vomiting | 3(8.1) | 4(11.4) | NS |
| Diarrhea | 6(16.2) | 5(14.3) | NS |

†S-Significant ††NS= Not- significant

## DISCUSSION

This study was basically aimed at establishing the safety and efficacy of the regime comprising low dose mifepristone and single dose of misoprostol vaginally to terminate the pregnancy up to 9 weeks.

With above regime we attained success rate of 97.3% in < 49 days gestation group and 97.1% in 50 – 63 days gestation group. This confirms its efficacy in inducing abortion up to 63 days pregnancy. The method was acceptable to most women, with 86% of them being highly satisfied.

Some studies have reported complete abortion following mifepristone alone in a few subjects [2,3]. Though in present study, none of the subjects had complete abortion with mifepristone alone but bleeding started in 19.4% of them. This may be due to higher dose of mifepristone in those studies, but the overall complete abortion rate at the end was similar.

We examined the results of study by Spitz et al[2] who reported 92% success in less than or equal to 49 days, 83% in 50 to 63 days and 77% in 57 to 63 days of gestation. The low success rate in their study has been explained by the authors to be due to unnecessary surgical intervention done in all those subjects on day 15 in whom complete abortion had not occurred by then or out of women's request due to heavy bleeding. Learning from there experience, we allowed some time for spontaneous expulsion of retained products of conception if they were present on day 15 follow up visit. Finally 4 out of 5 women who had retained products on day 15 had complete abortion within the following week, thus accounting for higher success rate.

Bleeding is a component of natural abortion process. Significantly more number of subjects with gestation more than 49 days (80% vs. 51.4%) had heavier bleeding as compared to normal menstruation. Mean length of duration of bleeding in the entire study group was 11.5±4.7 days. Duration of bleeding was found to be significantly greater in subjects in higher gestational-age group (13.15 days in group B vs. 9.97 days in group A).

Haemoglobin level declined by 0.42± 0.04gm%. There was a significantly greater fall in haemoglobin in women with period of gestation of 50- 63 days (0.49gm%) than those with pregnancy of less than 49 days (0.37gm%) although the difference was actually minimal. None of the women had clinically significant fall in hemoglobin (≥2gm%) so as to affect their general health. None of them required blood transfusion whereas 0.7% of women in UK multi-centre trial[15] and 4 women in a study by Spitz et al[2] required it.

Pain is a natural component of abortion process and is unavoidable. Overall 54.2% subjects had moderate intensity of pain. Similarly, in a multi centre study[16] conducted in India, China and Cuba, pain was reported by 61.9% of Indian subjects. Analgesic requirement was lesser (13.4%) in the current study, due to proper counseling about the side effects and due to higher dose of misoprostol (800µg) used in other trials[2,7].

Incidence of nausea and vomiting (26.4% and 9.7 %) was lower than other studies [16], may be explained by lower dose and vaginal route for administering misoprostol in present study. Self-limiting diarrhea occurred in 15.3% of subjects. On comparing the side effects in our study with those reported by Hamoda et al[14] who compared sublingual route of administration with vaginal route, we found that nausea, vomiting and diarrhea were significantly more with sublingual route (79%, 57% and 62% respectively).

We included six women with a history of one cesarean delivery. All of these women aborted completely. This conclusion is consistent with the findings of Gautam et al[17] who reported successful abortion without complications in 66 women with ≤ 60 days pregnancy and with history of previous one or two cesarean sections.

Termination of pregnancy with low dose mifepristone and vaginal misoprostol is a safe and effective procedure after proper case selection. Low dose mifepristone (200mg) is as effective as 600 mg. Vaginal route for administration of misoprostol is efficacious and is better tolerated. Most importantly, we would like to emphasize that this regime can be safely given up to 9 weeks of pregnancy. Bleeding is generally heavier than normal menstruation but in properly selected cases, fall in haemoglobin is minimal and is not clinically significant. Pain is unavoidable component of abortion process, but proper counseling about pain and low doses of drugs reduces the severity of pain and analgesic requirement. If there is any evidence of retained products of conception in uterine cavity on Day 15 and the woman is not actively bleeding, then some time should be allowed for their spontaneous expulsion before attempting any surgical intervention.

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