

## COMPARATIVE STUDY AND EVALUATION OF EFFICACY AND ACCEPTABILITY OF TWO REGIMENS WITH DIFFERENT TIME INTERVALS BETWEEN MIFEPRISTONE AND MISOPROSTOL FOR FIRST TRIMESTER MTP

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### ABSTRACT

#### BACKGROUND

Unsafe abortions are a major cause of maternal morbidity and mortality. Medical abortion, which is preferred over surgical abortion by most women may provide excellent alternative to unsafe abortion and their attendant risks. The primary aim of this research is to compare the efficacy and acceptability of two regimens with different time interval between mifepristone and misoprostol for first trimester MTP.

#### MATERIALS AND METHODS

The study was carried out in 150 pregnant women opting for MTP during first trimester by medical method. Pelvic ultrasound was done before giving drugs to assess the correct gestational age, intrauterine location of pregnancy and to exclude any obvious pelvic pathology. Women enrolled in the study were randomized to one of the two groups which differ in the time of administration of misoprostol. All 150 women were given Mifepristone 200mg on Day 1. However, 75 women in the study group were given misoprostol 600mcg on Day 2 and remaining 75 women in the control group were given misoprostol 600mcg on Day 3. The effects regarding efficacy, induction abortion interval, side effects and acceptability of two regimens were noted.

#### RESULTS

1) 98.66% cases in study group and 94.66% in control group had successful abortions (p value>0.05) 2) 94% of cases preferred 24 hours study protocol rather than established protocol of 48 hours for any future MTP (p value < 0.02).

#### CONCLUSION

The research work helps to derive a conclusion that medical abortion using misoprostol administration 24 hours after mifepristone appears to be equally efficacious and more acceptable than that of the established protocol of 48 hours.

#### KEYWORDS

MTP, Mifepristone, Misoprostol, Efficacy, Acceptability.

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#### BACKGROUND

Safe abortion has been defined by the WHO as "Abortion provided through approved facilities and/or persons". It is impossible to lower maternal mortality without safe abortion, and access to safe abortion is the most immediate and achievable step on the global road towards safe motherhood. In India, there are 15,000 to 20,000 abortion related deaths each year.<sup>1</sup> Unsafe abortions are a major cause of maternal morbidity and mortality. Medical abortion which is preferred over surgical abortion by most women,

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may provide excellent alternative to unsafe abortions and their attendant risks. In the last decade medical abortion has emerged as a realistic alternative to surgical abortion. The combination of Mifepristone (an antiprogesterin) and Misoprostol (a prostaglandin E1 analog) have emerged as one of the best options for medical termination of pregnancy with efficacy of 97% complete abortion rates among women with no more than 49 days pregnant. Recently large number of studies are being done using various permutations and combinations regarding dosage, route and timing of these two drugs to prove their efficacy at the best. The half-life of Mifepristone is approximately 24 to 29 hours. Misoprostol given any time after 24 hours of Mifepristone ingestion, is the most practical and effective method as Mifepristone reaches peak plasma concentration in 1-2 hours and its half-life is 24 hours, so its binding with progesterone receptors is almost complete by 24 hours and prostaglandins like Misoprostol then can increase uterine contractions and cause abortion effectively.

*Aims and Objectives*

Primary aim of this research is to compare the efficacy & acceptability of two different regimens for 1<sup>st</sup> Trimester MTP. In the present study the time interval between Mifepristone and Misoprostol is being reduced in an attempt to achieve maximum efficacy of the combination with maximum convenience i.e. acceptability to the women. When a longer interval is kept between the two doses patient remains anxious and on tenterhooks because for her the procedure has begun but the results in the form of bleeding is not yet there.

**MATERIALS AND METHODS**

This study was carried out in 150 pregnant women opting for MTP during first trimester by medical method, visiting the O.P.D. of Obstetrics and Gynaecology department, Fortis Escorts Hospital and Research centre, Faridabad between February 2005 and January 2006.

*Inclusion Criteria*

1. Pregnant woman willing for early termination of pregnancy by taking medicines.
2. Period of gestation should be less than or equal to 49 days by LMP (confirmed on ultrasound).
3. Woman should be ready to return to OPD for follow ups as and when necessary (upto 4 visits)
4. Woman should understand that once she takes Mifepristone she has to undergo termination and cannot change her mind and continue the pregnancy as Mifepristone can be teratogenic.
5. Woman should be willing to have a surgical procedure, in case the medical method fails or results in incomplete abortion.
6. Woman should have access to a telephone and emergency medical treatment in case of excessive bleeding or pain etc.

*Exclusion Criteria*

1. Intrauterine pregnancy over 49 days.
2. Confirmed or suspected ectopic pregnancy.
3. Known allergy to Mifepristone or prostaglandin analogue or known hypersensitivity.
4. Concurrent long-term use of corticosteroids therapy.
5. Patient on anticoagulants.
6. Known haemorrhagic disorder.
7. Chronic renal insufficiency.
8. Severe anaemia.
9. Women smokers over the age of 35 years (the risk of thromboembolism is more).
10. Undiagnosed adnexal mass.
11. IUCD in situ.
12. Chronic adrenal insufficiency.
13. Inherited porphyrias.
14. Epilepsy.
15. Breast feeding women.

After taking an informed written consent, women satisfying criteria for inclusion after careful consideration of

situation likely to render them unsuitable for the study described under exclusion criteria were entered into the study protocol. Such women were numbered in the order of their presence in the outpatient department.

*Group 1*

All odd numbered women were examined and evaluated as per the study schedule of Mifepristone 200mg on day 1 and Misoprostol 600mcg on day 2 (i.e. after 24hrs.) and labelled as Group 1.

*Group 2*

All even numbered women were examined and evaluated as per the established schedule of Mifepristone 200mg on day 1 and Misoprostol 600mcg on day 3 (i.e. after 48hrs.) and labelled as Group 2.

Patients were monitored similarly in both the groups. Patients were called for follow-up on 14<sup>th</sup> day (visit 3) from the first dose of the drug or earlier if there was any problem.

*Following things were noted on follow up-*

- Repeat pelvic ultrasound was done to check the completeness of abortion.
- Amount of bleeding.
- Severity of pain.
- Presence of GI symptoms (Nausea and vomiting).
- Requirement of blood transfusion.
- Requirement for any additional drug.
- Requirement of D & E.

Quantitative variables were compared using independent T test between the two groups and qualitative variables were compared using chi-square test. A p value of less than 0.05 was considered statistically significant.

**RESULTS**

This one-year prospective study had 150 pregnant women who opted for medical termination of pregnancy. In the present study the mean age of the patients was  $28 \pm 4.9$  years with a range of 19-38 years. Majority of the women in both groups were between 21-30 years. The mean period of gestation in group 1 was  $42.65 \pm 5.86$  days and that in the group 2 was  $43.39 \pm 5.97$  days. The range of period of gestation was 31-48 days in both groups. The two groups did not differ significantly with respect to baseline characteristics like age parity and gestational age.

*Induction Abortion Interval*

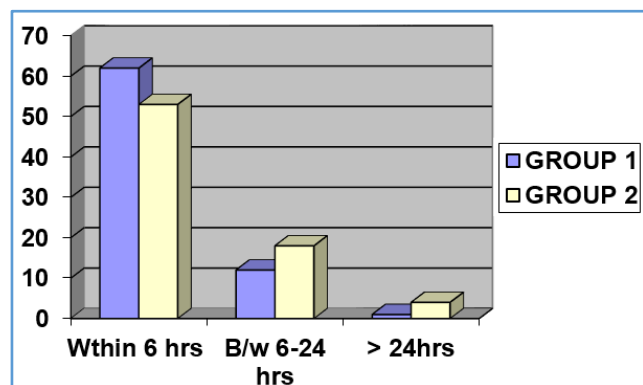
In the present study the mean induction abortion interval in the study group 1 was  $5.03 \pm 1.79$  hours and that in the control group 2 was  $8.03 \pm 1.79$  hours.

*Group 1*

98.66% patients reported bleeding within 24 hours of Misoprostol administration with majority (82.66%) having onset of bleeding within 6 hours. The only case in Group 1 with unsuccessful abortion reported delayed onset of bleeding i.e. after 32 hours.

*Group 2*

94.66% patients reported bleeding within 24 hours of Misoprostol administration with majority (70.66%) having onset of bleeding within 6 hours. There were 4 cases with unsuccessful abortion who reported delayed onset of bleeding i.e. after 24 hours.



**Comparative Bar Chart 1. Comparison of the time of onset of bleeding after Misoprostol administration in the 2 groups: Group 1 and Group 2.**

It is important observation that all five patients (1 in group 1 and 4 in group 2) who had unsuccessful abortion had induction – abortion interval of more than 24 hours.

*Efficacy of Two Different Regimes*

Group 1 After the administration of Mifepristone and Misoprostol as per the study protocol of Mifepristone 200mg on day 1 and Misoprostol 600mcg on day 2 (i.e. after 24hrs), 98.66% of the cases aborted successfully while 1.34% cases had incomplete abortion with retained products of conception on follow-up day 14. The only patient in Group 1 with incomplete abortion underwent suction evacuation on follow-up day 14. There were no ongoing pregnancies and missed abortion in our series of seventy-five cases in Group 1. None of the patients had heavy bleeding and no emergency surgical intervention was required.

Group 2 After the administration of Mifepristone and Misoprostol as per the already established protocol of Mifepristone 200mg on day 1 and Misoprostol 600mcg on day 3 (i.e. after 48 hrs.), 94.66% of the cases aborted successfully while 5.34% cases had incomplete abortion with retained products of conception on follow-up day 14. The four patients in Group 2 with incomplete abortion underwent suction evacuation on follow-up day 14. There were no ongoing pregnancies and missed abortion in our series of seventy-five cases in Group 2. None of the patients had heavy bleeding and no emergency surgical intervention was required. It was noted that one patient in group 1 and three patients (out of 4) in group 2 who required surgical evacuation had period of gestation of >= 45 days.

Results	Group-1 (n=75)	Group-2 (n=75)
Complete Abortion	74 (98.6%)	71 (94.6%)
Incomplete Abortion	1 (1.34%)	4 (5.34 %)

**Table 1. Results of Medical Abortion Regimen**

$\chi^2 = 2.1, df = 1, P > 0.05$ , not significant.

The two groups were compared using Chi square test and by applying Null hypothesis, it is concluded that there is no significant difference in efficacy of two regimens ( $P > 0.05$ ).

*Acceptability*

The response of the women, who participated in the study, when asked about their preference for the method of abortion in future, it was observed that out of total 150 patients under study, 9 patients (1 in group 1 and 8 in group 2) did not accept medical method as their preference in future abortions. Of these 9 patients (1 in group 1 and 8 in group 2) did not accept the method due to failure of medical method under study. The remaining 4 patients from Group 2 found the method unacceptable because of the side effects experienced by them during the procedure, however this does not appear to be the drawback of group 2 alone per se. When asked about their preference for a 24 hrs. Schedule under study as compared to the established protocol of 48 hrs, 94% (141/150) women under study preferred 24 hrs study protocol as a method of future abortion.

Acceptance	Group-1 (n=75)	Group-2 (n=75)
Yes	74 (98.6%)	67 (84.3%)
No	1 (1.34%)	8 (10.67 %)

**Table 2. Acceptability of Medical Method**

$\chi^2 = 5.78, df = 1, P < 0.02$ , Significant.

Two regimens were compared regarding acceptability by applying chi square test ( $\chi^2 = 5.786$ ) and calculating the degree of freedom and using the reference probability tables and it is inferred that the difference in acceptability is significant between two regimens  $p < 0.02$ . The acceptability in group 1 is better than group 2.

**DISCUSSION**

Medical abortion offers a novel approach to pregnancy termination by non-invasive methods, with minimal side effects and efficacy as high as 95%. It permits greater privacy and a degree of personal control by women. The method involves use of pharmacological agents capable of inducing abortion by causing uterine contractions. Several agents are used for early medical abortion, the common ones include Mifepristone and Misoprostol and their combination regimens. Large number of studies are still under trial using various permutation and combinations regarding dosage, route and timing of these two drugs to prove their efficacy at the best. The present study was done to evaluate the efficacy and acceptability of different regimens with variation in time interval between Mifepristone and Misoprostol administration for first trimester induced abortions. The analysis of 150 cases is presented in this study. 75 cases received the drugs i.e. Mifepristone followed by Misoprostol 24 hours apart which formed the study group and 75 cases received them 48 hours apart as in standard protocol which formed the control

group. The two groups did not differ significantly with respect to baseline characteristics like age, parity, gravidity and gestational age.

The exact induction abortion interval could be determined in the studies that included an observation period of 4-6 hours after Misoprostol administration e.g. the study by El-Rafaey et al<sup>2</sup> and Ashok et al.<sup>3</sup> In the present study the mean induction abortion interval in the study group 1 was  $5.03 \pm 1.79$  hours and that in the control group 2 was  $8.03 \pm 1.79$  hours. This data proves that the induction abortion interval is significantly decreased in the study group not only in terms of "mean" time but also because the study group received Misoprostol 24 hours prior to the control group and the time of onset of bleeding after Misoprostol administration is considered as the time of abortion. The above regimen under study is based on the criteria that the half-life of Mifepristone is approximately 24-29 hours. In the present study the time interval between Mifepristone and Misoprostol is being reduced in an attempt to achieve maximum efficacy of the combination with maximum convenience to the woman. When a longer interval is kept between the two doses, patient remains anxious and, on her tenterhooks, because for her, the procedure has begun but the results in the form of bleeding is not yet there.

The conventional timing of Misoprostol administration after Mifepristone for medical abortion is 2 days. In the study by Schaff, et al<sup>4</sup> it says that more flexible intervals would make these regimens substantially more convenient for the clients and clinicians in which Misoprostol was administered on day 1, 2 and 3 after Mifepristone.

In the present study, 98.66% women aborted successfully in the study protocol group while 1.34% women had incomplete abortion with retained products of conception on follow up visit for which suction evacuation was done. However, 94.66% cases aborted successfully in the established protocol group while 5.34% cases had incomplete abortion with retained products of conception on follow up visit for which suction evacuation was done. There were no ongoing pregnancies and missed abortion in both the groups. None of the patients had heavy bleeding and no emergency surgical intervention or blood transfusion was required. The results are similar to the studies mentioned below. The proportion of women who had complete abortion in group 1 and group 2 did not differ significantly ( $p > 0.05$ ).

The overall acceptance rate among women participating in the present study group 1 was 98.66% and that in group 2 was 90.66%. All the 5 patients who had incomplete abortion (1 in gr.1 and 4 in gr.2) found the method unacceptable. Four patients in group 2 who had successful abortion but still found the method unacceptable was due to side effects of misoprostol. However, when asked about their preference for a 24-hour schedule under study as compared to the established protocol of 48 hours, hundred percent of the women under study (all 150) preferred 24 hours study protocol reason being reduced induction abortion interval and the fact that the delay between two doses only build up the anxiety in the mind of patient and husband.

Similar results have been observed in the study of Schaff, et al.<sup>4</sup>

The high rate of acceptability for medical abortion with Mifepristone and Misoprostol regimens in the present study is in concordance with those recorded in earlier studies.

Similarly, a few studies<sup>5,6,7</sup> dedicated to Mifepristone – Misoprostol acceptability from a woman's perspective showed this method was highly acceptable to women and some other studies<sup>8,9</sup> reported that women were confident enough to use the method at home.

## CONCLUSION

The present study indicates that medical abortion using misoprostol administration 24 hours after mifepristone appears to be the most appropriate in terms of acceptability and efficacy. This study also associates the 24 hours regimen with a short abortion process in totality, which appears to be safe, highly efficacious and acceptable.

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