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## Comparative study of early (24 hours) versus late (48 hours) misoprostol administration after mifepristone for termination of early pregnancy

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### Abstract

**Background:** Medical method of abortion – a combination of Mifepristone followed by prostaglandin analogue such as Misoprostol has been used up to 9 completed weeks since last menstrual period. Misoprostol is the prostaglandin of choice for most settings since it is cheap and does not require refrigeration.

The availability of safe and effective medical methods for inducing abortion remains limited at present. However, rapid development and ongoing research may lead to their wider introduction in the near future.

**Objectives:** The aim of the present study is to compare the efficacy of Mifepristone followed after 24 hours by Misoprostol with the standard protocol (Mifepristone followed by Misoprostol after 48 hours).

**Materials and Methods:** This prospective case control study was conducted in 120 patients up to 63 days period of gestation who was diagnosed with early pregnancy failure & suitable for medical abortion from a period of November 2018-July 2019.

- Subjects in study arm was given 200 mg oral Mifepristone followed by 800 mcg vaginal Misoprostol after 24 hours, whereas those in control arm was given 200 mg oral Mifepristone followed by 800 mcg of vaginal Misoprostol after 48 hours.
- Women who did not have bleeding in the first 8 hrs following 800 mcg Misoprostol were given subsequent 200 mcg of vaginal Misoprostol. Doses were repeated at 4th hourly interval to a maximum Misoprostol dose of 1200mcg.
- Sequential allocation was done in the ratio of 1:1.

**Statistical analysis:** It was done by using Student t test & chi-square test. Descriptive and inferential statistical analysis has been carried out in the present study.

**Summary of Results:** Out of 135 patients screened 15 patients were excluded as per exclusion criteria and 120 patients were taken for study. Mean induction to abortion interval in study group was in the range of 5-6 hrs versus 6-7 hrs in control group with P value of 0.772. The success rate in study group versus control group is 78.3 % versus 81.6% with P value of 0.29. 11/58 patients required curettage in study group compared to 6/55 in control group. Side effect profile between 24 vs 48 hour regimen was statistically insignificant.

**Conclusion:** Vaginal Misoprostol can be safely administered 24 hours following Mifepristone compared to 48 hours regimen with equal efficacy.

**Keywords:** Medical abortion, mifepristone, misoprostol, early pregnancy failure

### Introduction

Medical abortion is a safe, effective and non invasive alternative for early pregnancy termination. It holds great promise to access to safe abortion practices in developing countries like India. Drug control general of India approved 600 mg of Mifepristone coupled with 400 mcg of Misoprostol for early pregnancy termination up to 49 days period of gestation [1-4].

25-50% of pregnancies encounter spontaneous pregnancy loss which usually occurs up to 13 weeks of gestation. This spontaneous first trimester pregnancy loss can be described by various non standardized terminologies such as early pregnancy failure, blighted ovum, anembryonic gestation and missed abortion which are confusing but still commonly used terms. The total rate of pregnancy loss after implantation, including clinically recognized spontaneous abortions is 31 percent [5].

### Sonographic diagnostic criteria for early pregnancy failure [6]

- Crown-rump length (CRL) of  $\geq 7$  mm and no heartbeat on a transvaginal scan.

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- Mean sac diameter (MSD) of  $\geq 5$  mm and no embryo on a transvaginal scan.
- Absence of embryo with heartbeat  $\geq 6$  weeks after a scan that showed a gestational sac without a yolk sac.
- Absence of embryo with heartbeat  $\geq 11$  days after a scan that showed a gestational sac with a yolk sac.

### Non invasive management modalities for early pregnancy termination

The success rate of expectant management which is clearly an option for embryonic death or anembryonic gestation is influenced by various factors such as unpredictable expulsion, uncertainty, anxiety resulting from pregnancy loss, often makes expectant management less appealing to patients [7, 8].

### Characteristics of medical management [9]

Medical management with Misoprostol for early pregnancy failure appears to offer more prompt evacuation and has become an increasingly popular alternative with the following features,

- Avoids invasive procedure and anesthesia.
- Requires two or more visits.
- Takes days to weeks to complete the process.
- Available during early pregnancy with high success rate (Approx-95%).
- Moderate amount of bleeding which rarely becomes heavy.
- Requires follow-up to ensure completion of abortion.
- Requires patient participation throughout a multiple-step process.

### WHO recommendation for medical methods of abortion [10]

“The WHO multinational trial with respect to side effects and acceptability of medical methods have found that 85% of participants had successful outcome for the procedure. Significantly higher acceptability was found among parous women (Compared to nulliparous women).

In 2003, World Health Organization (WHO) recommended that oral/vaginal Misoprostol should be administered 36–48 hours after oral Mifepristone. However based on the studies conducted by Singh *et al.* and Schaff *et al.* it has been proved that the interval of 48 hours can be safely reduced to even 8 hours without compromising safety and efficacy [11].

In our study interval of 24 hours has been chosen based on the pharmacokinetics of Mifepristone, which exerts its response in the uterus by blocking the action of progesterone. It has also been reported that 40% of patients started to bleed prior to Misoprostol administration, indicating that the abortion process has already started [12].

Thus when the process of abortion starts even before administration of Misoprostol, the rationale behind waiting for 48 hours has to be questioned and this concept forms the baseline of our study.

### Aims and objectives of study

- The aim of the present study is to compare the efficacy of Mifepristone followed by Misoprostol after 24 hours with the standard protocol (Mifepristone followed by Misoprostol after 48 hours).
- To evaluate whether 24 hour interval regimen will be an alternative to standard 48 hour regimen without compromising its safety.

### Materials and Methods

This prospective case control study was conducted in 120

patients up to 63 days period of gestation who was diagnosed with early pregnancy failure & suitable for medical abortion from a period of November 2018-July 2019 at Dept. of OBGYN, KMC Hospital.

- Subjects in study arm was given 200 mg oral Mifepristone followed by 800 mcg vaginal Misoprostol after 24 hours, whereas those in control arm was given 200 mg oral Mifepristone followed by 800 mcg of vaginal Misoprostol after 48 hours.
- Women who did not have bleeding in the first 8 hrs following 800 mcg Misoprostol were given subsequent 200 mcg of vaginal Misoprostol. Doses were repeated at 4th hourly interval to a maximum Misoprostol dose of 1200mcg.
- Sequential allocation was done in the ratio of 1:1.

We conducted a Prospective case-control study in the Department of Obstetrics and Gynaecology, Adichunchanagiri institute of medical sciences, B.G. Nagara from the period November 2013 to October 2015. We included all pregnant women with gestational age of less than 9 weeks diagnosed with intrauterine pregnancy failure as confirmed by ultrasonogram and undergoing medical abortion and who are willing for follow up. Sample size was 120 (Among 135 patients screened, 120 fulfilled the inclusion criteria-60 in study group and 60 in control group). Study group includes women who were given Vaginal Misoprostol 24 hours following Mifepristone whereas 48 hour interval between Mifepristone and Misoprostol stands as control group.

### Exclusion criteria

1. Women in whom ectopic gestation is suspected (even clinically).
2. Women who are not willing for follow up protocols.
3. Breast feeding mothers.
4. Women with haemoglobin of less than 10 gm/dl.
5. Women with previous cervical surgery - scarred cervix.
6. Women with previous scar in the uterus.
7. Women with asthma/glaucoma/adrenal insufficiency/poorly controlled seizures/cardiovascular disease/coagulopathy.
8. Women on systemic corticosteroid therapy/anticoagulant therapy.
9. Pregnancy with IUCD in situ.

### Procedure

Informed written consent of the patient was taken after explaining the complete procedure in patients own understandable language.

### Preparation of the patient

- Complete history was taken and thorough general and systemic examination was carried out.
- Speculum and vaginal examination was done in all the patients.
- Patients were counselled about the method they were allocated and side effects of the drug.
- Sequential allocation was done in the ratio of 1:1.
- Subjects in study arm was given 200 mg oral Mifepristone followed by 800 mcg vaginal Misoprostol after 24 hours, where as those in control arm was given 200 mg oral Mifepristone followed by 800 mcg of vaginal Misoprostol after 48 hours.
- Women who did not have bleeding in the first 8 hours

following 800 mcg Misoprostol were given subsequent 200 mcg of vaginal Misoprostol. Doses were repeated at 4<sup>th</sup> hourly interval to a maximum Misoprostol dose of 1200mcg.

- All subjects were informed about the signs and symptoms of expulsion and need for follow-up.
- All women was given a 24 hour contact telephone number for any post treatment advice.
- They were asked to come for follow-up after 14 days when transvaginal ultrasound (TVS) was performed to confirm whether expulsion process was complete.
- If retained products of conception was documented on check scan, depending on the amount of retained products of conception and amount of bleeding, Curettage was performed and products sent for histopathological examination.

**Statistical Analysis**

- Statistical Methods: Descriptive and inferential statistical analysis has been carried out in the present study. Results on continuous measurements are presented on Mean □SD (Min-Max) and results on categorical measurements are presented in number (%). Significance is assessed at 5 % level of significance.
- Chi-square test/ Fishers exact test has been used to find the significance of study parameters on categorical scale between two groups.
- Student t test (Two tailed, independent) has been used to find the significance of study parameters on continuous scale between two groups (Inter group analysis).
- The P value was calculated and if P value of less than or equal to 0.05 was considered as statistically significant.

**Results**

In this Prospective case-control study conducted in the Department of Obstetrics and Gynaecology, Adichunchanagiri institute of medical sciences, from the period of November 2013 to October 2015, 135 pregnant women with gestational age of less than 9 weeks diagnosed with intrauterine pregnancy failure as confirmed by ultrasonogram and undergoing medical abortion were screened and 15 patients were excluded as per exclusion criteria.

Totally 120 patients who fulfilled the inclusion criteria was taken (60 in study group and 60 in control group). Study group includes women who were given 800 mcg of Vaginal Misoprostol 24 hours following Mifepristone whereas 48 hour interval between mifepristone and misoprostol stands as control group.

Majority of patients who underwent medical abortion (both in study as well as control group) were in the age group of 20-30 years contributing 80.8%, which was followed by patients in age group 31-40 years, constituting 12.5%.

**Table 1: Age distribution of patients studied**

Age in yrs	Study Group (n=60)	Control Group (n=60)	Total (n=120)
<20	5(8.3%)	3(5%)	8(6.6%)
20-30	46(76.7%)	51(85%)	97(80.8%)
31-40	9(15%)	6(10%)	15(12.5%)
Mean ± SD	25.35±3.84	24.89±3.74	25.1±3.73

Mean value for age in control group is 24.89 ±3.74 and in study group it is 25.35 ± 3.84 years.

10 % of women were in the elderly age group of 31-40 yrs in control group whereas 15 % of women were in the age group of 31-40 yrs in the study group.

5 % of women in control group and 8 % of women in study group belongs to teenage group.

Samples of age are matched with P = 0.507, Chi Square test

**Table 2: Obstetric Index**

Obstetric Index	Study Group (n=60)	Control Group (n=60)	Total (n=120)
Multigravida	40(66.6%)	44(73.3%)	84(70%)
Primigravida	20(33.3%)	16(26%)	36(30%)

73.3% of women who underwent 48 hour interval regimen and 66.6% of women who underwent 24 hour interval regimen were Multiparous with the P value of 0.425 which is not significant. 26 % of the patients who underwent 48 hour interval regimen and 33.3% of the patients who underwent 24hour interval regimen were Primigravida.

P=0.425, Not significant, Chi-Square test

**Table 3: Gestational age (weeks)**

Gestational age (weeks)	Study Group (n=60)	Control Group (n=60)	Total (n=120)
< 7	17(28.4%)	18(30%)	35(29.1%)
7 to < 8	14(23.3%)	15(25%)	29(24.1%)
8-9	29(48.3%)	27(45%)	56(46.6%)

The main indication for which medical abortion was done in our study is early pregnancy failure (Blighted ovum) and missed abortion. Majority of patients were in the gestational age between 8-9 weeks with 46.6 %.P value documented is 0.934 which is not significant. P=0.934, Not significant, Chi-Square test.

**Table 4: Misoprostol application to abortion interval (hours)**

Misoprostol application to abortion interval (hrs)	Study Group (n=60)	Control Group (n=60)	Total (n=120)
<8hrs	41(68.3%)	43(71.6%)	84(70%)
8-12 hrs	13(21.7%)	10(16.6%)	23(19.2%)
13-24 hrs	6(10%)	7(11.8%)	13(10.8%)

71.6 % of patients in control group and 68.3 % of patients in study group expelled the abortus in less than 8 hours following the vaginal administration of 800 mcg of Misoprostol. Whereas 16.6 % of patients in control group and 21.7 % in study group expelled in 8-12hrs. 11.8 % of women in 48 hour group and 10 % in 24 hour group required time interval of 13-24 hours for their expulsion with P value of 0.772 which is not significant.

P value of 0.772, Not significant, Chi-square test.

**Table 5: Number of doses of Misoprostol**

No of doses of Misoprostol	Study Group (n=60)	Control Group (n=60)	Total (n=120)
1(800 mcg)	42(70%)	37(61.6%)	79(65.8%)
2(800+200 mcg)	14(23.3%)	12(20%)	26(21.6%)
3(800+200+200 mcg)	4(6.6%)	11(18.3%)	15(12.5%)

61% of women in control group and 70 % of women in study group required a single dose of 800 mcg of Misoprostol for their expulsion. Whereas 20 % of patients in control group and 23.3%

in study group required an additional dose of 200 mcg of Misoprostol. 18.3 % of patients in control group and 6.6 % in study group required 3 doses of Misoprostol (Including the first dose of 800 mcg) and they expelled in 13-24 hrs. P=0.154, Not significant, Chi-Square test

**Table 6:** Success rate

USG	Study Group (n=60)	Control Group (n=60)	Total (n=120)
Complete Expulsion	47(78.3%)	49(81.6%)	96(80%)
Incomplete Expulsion	11(18.3%)	6(10%)	17(14.1%)
Lost follow up	2(3.3%)	5(8.3%)	7(5.8%)

Out of 120 patients who underwent medical abortion, 7 patients did not turn up for check scan, thus their expulsion status was

**Table 8:** Side effect profile

Side effects	Control Group (n=60)	Study Group (n=60)	Total (n=120)
Number of patients with side effects	20(33.3%)	25(41.6%)	45(37.5%)
▪ Diarrhea	4(6.6%)	13(21.6%)	17(14.1%)
▪ Fever with Chills	2(3.3%)	1(1.6%)	3(2.5%)
▪ Fever	2(3.3%)	7(11.6%)	9(7.5%)
▪ Vomiting	7(11.6%)	1(1.6%)	8(6.6%)
▪ Chills alone	5(8.3%)	3(5%)	8(6.6%)

Regarding side effect profile 21.6 %, 1.6%, 1.6 %, 11.6%, 5 % of women in study group had diarrhea, fever with chills, vomiting, fever and chills. Most common side effect which patients encountered in study group was diarrhoea.

In control group 6.6 %, 3.3 %, 11.6 %, 3.3 %, 8.3 % of women in had diarrhea, fever with chills, vomiting, fever alone and chills alone respectively. Most common side effect in control group was vomiting. Very few of the patients with side effects in both the groups required symptomatic treatment. Others had spontaneous relief of symptom followed by completion of procedure.

There was no statistically significant difference in the percentage of side effect profile between the study and control groups.

P=0.234, Not significant, Chi-Square test

**Summary**

The present study is a Prospective Case control study “Comparative study of early (24 hours) versus late (48 hours) Misoprostol administration after Mifepristone for termination of early pregnancy” was conducted at Adichunchanagiri Institute of medical sciences from November 2013- October 2015.

- All pregnant women of less than 9 weeks of gestation with early pregnancy failure such as blighted ovum, Missed abortion which was confirmed sonographically were included in this study (Provided they fulfill our inclusion criteria).
- Subjects in study arm was given 200 mg oral Mifepristone followed by 800 mcg vaginal Misoprostol after 24 hours, where as those in control arm was given 200 mg oral Mifepristone followed by 800 mcg of vaginal Misoprostol after 48 hours.
- 120 cases were studied.
- Mean value for age in control group is 24.89 ±3.74 and in study group it is 25.35± 3.84 years.
- 57% of patients in study group and 47% of patients in control group who underwent medical abortion belongs to lower middle class.
- 73.3% of women who underwent 48 hour interval regimen

not known. Out of 113 patients who underwent check scan 81% of women in control group and 78 % of women in study group had complete expulsion.

18 % of patients required curettage in study group, whereas 10 % of patients required curettage in control group. The P value obtained is 0.29 which is not significant.

P=0.2904, Not significant, Fishers exact test.

**Table 7:** Surgical evacuation

Curettage	Study Group (n=58) (60-2)	Control Group (n=55) (60-5)	Total
No	47(81%)	49(89%)	96(84.9%)
Yes	11(18.9%)	6(10.9%)	17(15%)

P=0.2959, not significant, Fishers exact test.

and 66.6% of women who underwent 24 hour interval regimen were Multiparous with the P value of 0.425 which is not significant.

- Majority of patients were in the gestational age between 8-9 weeks contributing 46.6 %.
- Mean Misoprostol application to abortion interval in study group was in the range of 5-6 hrs versus 6-7 hrs in control group with P value of 0.772.

**Conclusion**

- Vaginal Misoprostol can be safely administered 24 hours following Mifepristone instead of waiting for 48 hours.
- Efficacy in achieving complete abortion rate is almost equal to 48 hours regimen and most acceptable from patients side also.
- Reduces multiple outpatient visits, without increasing the rate of surgical evacuation.

Thus 24 hours regimen serves as an alternative to 48 hour regimen with equal efficacy and acceptable side effect profile thereby helping women to complete their abortion process in short span of time, with highest patient satisfaction and cost effectiveness by preventing multiple clinic visits.

- The Success rate in study group versus control group is 78.3 % versus 81.6 % with P value of 0.29.
- 11/58 patients required curettage in study group compared to 6/55 in control group.
- Side effect profile between 24 hour vs 48 hour regimen was statistically insignificant.
- 70% of women strongly agreed, 30% were neutral for 24 hr regimen.
- Thus vaginal Misoprostol can be safely administered 24 hours following Mifepristone compared to 48 hours regimen with equal efficacy.

**Recommendations**

1. Medical methods can be safely prescribed for women who undergoes abortion as it reduces the complications of surgical evacuation of uterus in untrained hands of rural

India.

2. Since most of the women encountered in this study belongs to lower middle class, who rely on daily wages for their life, instead of prolonging the abortion process for 48 hours, it can be safely reduced to 24 hours, thus saving their precious time.

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