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Misoprostol Alone or In Combination with Mifepristone: The Search for a Safe and Economical Option

Authors
Dr. K. Shail[1], Dr. Harleen Grover[2]
[1]Assistant Professor, Department of Obstetrics and Gynaecology
Punjab Institute of Medical Sciences, Jalandhar, India
[2]Senior resident, Dept. of Obs and Gynae, PIMS Jalandhar
Corresponding Author
Dr Shail Kaur
M.D
1126, Urban Estate Phase1, Jalandhar, Punjab India
Email: *shgrewal@yahoo.com*

ABSTRACT

Background: *Medical abortion provides women with a safe, less invasive method for termination of pregnancy. Regimens with mifepristone and misoprostol are expensive and not freely available throughout the world.*

Aims and objectives: *The objective of this study was to confirm the effectiveness, safety and cost efficacy of medical abortion up to 7 weeks (up to 49 days) using 2 different regimes.*

Materials and methods: *Hundred and twenty prospective patients attending our OPD for termination of pregnancy who fulfilled the inclusion criteria were included in the study after informed consent. The patients were randomly allotted to one of the following two groups: (1) group 1- mifepristone 200mg orally with 800mcg misoprostol vaginally after 48 hours; (2) group 2- 3 doses of vaginal misoprostol 1000mcg 24 hourly. Outcomes measured were (1) successful abortion (complete abortion without requiring additional procedure), (2) side effects, (3) mean time of onset of cramping, (4) mean time of onset of bleeding, (5) mean duration of bleeding, (6) mean decrease in haemoglobin and (7) mean time of menstruation returning.*

Results: *Medical abortion was successful in 55 of 60 (91.67%) patients in group 1 and in 54 of 60 (90%) patients in group 2 (p=1.00). The mean change in haemoglobin was 0.70+0.5g/dl in group 1 and 0.7+0.4g/dl in group 2 (p=0.713). Cramping began at 4.1 + 1.6 hours and lasted 5.2 + 3.7 hours in group 1. Cramping began at 5.1 + 3.4 hours and lasted 3.7 + 1.9 hours in group 2. Vaginal bleeding started at 3.43+1.2 hours after administration of misoprostol in group 1 and 6.46+ 1.6 hours after first dose of misoprostol in group 2. Mean duration of bleeding in group 1 was 6.23+5.3 days and 7.0+4.6 days in group 2. Time to return of menstruation was 36.9 +97.1 days in group 1 and 37 + 7.1 days in group 2.*

Conclusions: *The present study suggests that 1000mcg misoprostol administered vaginally at 24 hour intervals could be a more economical and viable option in situations where financial constraints restrict the use of mifepristone. Moreover the 24 hour interval improves patient compliance and allows out patient management.*

Key Words: *first trimester pregnancy, medical abortion, mifepristone, termination, vaginal misoprostol*

INTRODUCTION

Medical abortion has gained precedence over surgical methods as it is associated with less morbidity and mortality.[1-3] The search for a safe and effective method of abortion which can be provided to women in need can have a major impact on decreasing complications from unsafe abortions. It is likely that the numbers of unsafe abortions will continue to increase unless women's access to safe abortion and contraception – and support to empower women (including their freedom to decide whether and when to have a child) – are put in place and further strengthened. [1]

The mifepristone regimen and several variants have been found to be effective, feasible and acceptable method of induced abortion for women and providers in a variety of countries and health care settings.[2-6] The unavailability of mifepristone in many countries and restraints due to its costs led to a search for safe and effective alternatives.[7-9] Multiple modifications of the dose and interval in which misoprostol may be administered have provided additional options while improving acceptability and efficacy.[8-13]

The objective of the present study was to confirm the effectiveness and safety to achieve a complete abortion by misoprostol 800 mcg vaginally 48 hours after pre-treatment with mifespristone 200mg as compared to giving 3 doses of misoprostol 1000mcg at 24 hour intervals. This is more economical and the interval between doses ensures better compliance by not interfering in day to day activities. Not hospitalizing patients would allow better acceptability, increase confidentiality and lower the burden on health care facilities.

MATERIALS AND METHODS

This study was conducted in a teaching institution where 120 consecutive patients fulfilling the inclusion criteria were enrolled after written informed consent.

The patients were randomly allotted to one of the following two groups: (1) group 1 (n=60)- mifepristone 200mg orally with 800mcg misoprostol vaginally after 48 hours; (2) group 2(n=60)- misoprostol 1000mcg vaginally 24 hourly three doses

The inclusion criteria were: (1) women seeking MTP up to 49 days gestation as counted from the first day of the last menstrual period; (2) informed consent ; (3) access to a telephone; (4) residence within 1 hours distance from the hospital; (5) voluntary permission for surgical intervention if medically advised or in cases of failure.

Women were excluded from the study if they had (1) a known allergy to prostaglandins or mifepristone; (2) a history of cardiac, respiratory renal, hepatic or adrenal disease; (3) a history of thromboembolism, hypertension, coagulopathy and diabetes mellitus; (4) history or sonographic evidence of uterine pathology; (5) active genital infection; (6) previous uterine surgery; and (7) prior uterine bleeding.

The patients were informed of the nature of the study, risks benefits, visiting schedule and the possible requirement of suction and evacuation if incomplete abortion or failure occurred. The patient was instructed to report to the hospital immediately in case of excessive bleeding, cramps or any other side effects. The patient was advised to keep a diary of the symptoms experienced.

DRUG PROTOCOL

Group 1; on day 1 the patients were given mifepristone 200mg orally with a glass of water; on day 3 the patient reported back and was questioned about bleeding and side effects. Four tablets of misoprostol (200mcg each) were inserted in the posterior fornix. The patient was instructed to lie in the lateral position for half an hour.

Group 2; on day 1 the patient was given a tablet of paracetamol. After half an hour five tablets of misoprostol (200mcg each) were inserted in the posterior fornix. The patient was instructed to lie in the lateral position for half an hour; day 2 the patient was asked about bleeding and side effects experienced. Pulse and bp were noted and a p/s and p/v were done. The same dose of misoprostol was repeated. On day 3 the same procedure was carried out as on day 2

Patients of both groups were called for follow up on day 7 or earlier in case of excessive bleeding or severe side effects experienced. On day 7, an ultrasound examination was conducted for the presence of gestation sac, retained products of conception or increased endometrial thickness (>16mm significant)

The next follow up was scheduled for day 14 for assessment of amount and duration of bleeding, pelvic examination, repeat Hb and for S/E in case of incomplete abortion or failure. The patient was then advised to report back after the next menses or earlier in case she experienced bleeding, fever or abdominal pain.

The principal outcomes assessed were successful abortion, side effects, mean expulsion time and mean decrease in haemoglobin. Secondary outcomes assessed were mean duration of bleeding, mean time of onset of cramping, mean time of onset of bleeding and mean time of menstruation returning. Side effects assessed included chills, nausea, dizziness, fever, vomiting, diarrhoea and pelvic pain.

Success was defined as complete evacuation of the products of conception without the need for surgical intervention. Failure was defined as recourse to surgical abortion for decision to drop out, doctors decision as a result of complications (such as excessive bleeding, pain, intrauterine remains or infection) or failure due to inefficiency of the method itself that is when the gestational sac was not expelled.

Statistical analysis was performed using spss software. A paired t-test was used for comparisons and a probability (p) level of <0.05 was considered significant.

RESULTS

The trial included 120 women who requested a pregnancy termination and who complied with the inclusion criteria. The patient characteristics are mentioned in table 1.

Cramping began at 4.1 $\pm$ 1.6 hours and lasted 5.2 $\pm$ 3.7 hours in group 1. Cramping began at 5.1 $\pm$ 3.4 hours and lasted 3.7 $\pm$ 1.9 hours in group 2. The duration of cramping pain was$\leq$5 hours in 70% of patients in group 1 and $\leq$5 hours in 90% of patients in group 2 (P value equals 0.0110). 90% of patients in group 1 and 70% of patients in group 2 did not require any analgesics (P value equals 0.0110). Vaginal bleeding started at 6.46$\pm$ 1.6 hours and lasted 7.0$\pm$4.6 days. Onset of bleeding was after the first dose of misoprostol in

95% and after the second dose in 5% in patients of group 2. The duration of bleeding was ≤5 days in 56.7% of patients in group 1 and in 46.7% of patients in group 2 (P value equals 0.3611). The mean change in haemoglobin was 0.70±0.5g/dl in group 1 and 0.7±0.4g/dl in group 2 (p=0.713). The most common side effects noted were cramping pain (100% in both groups), nausea (70% in both groups), diarrhoea (33.3% vs. 46.7%, p=0.1919), chills (10% vs. 46.7%, p=0.0012) and fever (13.3% vs. 23.3%, p=0.238). Time to return of menstruation was 36.9 ±97.1 days in group 1 and 37 ± 7.1 days in group 2. Resumption of normal menses was within 45 days in 56.67% patients in group 1 and 63.33% patients in group 2, p=0.576. Medical abortion was successful in 55 of 60 (91.67%) patients in group 1 and in 54 of 60 (90%) patients in group 2 (p=1.00). In group 1, five women were classified as failure, according to protocol criteria. Of these, four patients (80% of failures) had excessive bleeding and one (20% of failures) had retained products of conception on ultrasound. There was no case of failure due to continuation of pregnancy. In group 2, six women were classified as failure, according to protocol criteria. Of these, four patients (66.7% of failures) had excessive bleeding and two (33.3% of failures) had retained products of conception on ultrasound. There was no case of failure due to continuation of pregnancy.

Table 1 Characteristics of the patients (n=120)*

	Group 1		Group 2	
	n	%	n	%
Age				
≤30	34	56.7	38	63.3
31-40	22	36.7	20	33.3
>40	4	6.6	2	3.3
Marital status				
Married	60	100	58	96.7
Single	0	0	2	3.3
Education				
Uneducated	0	0	0	0
Educated	60	100	60	100
Parity				
0	0	0	2	3.3
1	18	30	16	26.7

2	32	53.3	30	50
3	10	16.7	12	20
Previous abortions				
0	42	70	36	60
1	16	26.7	18	30
2	2	3.3	6	10
Residence				
Urban	48	80	52	86.7
Rural	12	20	8	3.3

DISCUSSION

Medical termination of pregnancy was liberalised in India through the MTP Act 1971.[14] Surgical procedures were the mainstay of termination of pregnancy, however, there was need for better methods since complications such as perforation, synechiae formation, cervical injury and infections associated with surgical methods were unacceptable.[1-3] Medical abortions are more acceptable to women since it provides a natural way of termination of pregnancy that is safe, effective and non invasive, and does not require hospitalization thus minimizes inference with day to day activities. [15] The 2003 amendment to the MTP act permitted medical abortions up to a gestation of 49 days [14]nevertheless, unsafe abortions take place.[16] Irrespective of legal conditions the consequences of unsafe abortion place great demands on the scarce clinical, material and financial resources of hospitals in many developing countries, compromising other maternity and emergency services.[17] Major physiological, financial and emotional costs are also incurred by the women who undergo unsafe abortion.

Mifepristone followed by misoprostol has become standard regime for medical termination of pregnancy [3, 8, 9, 14], however the non-availability of mifepristone in number of countries and high cost has limited its scope. Misoprostol alone is a valid alternative to this regime which is reported to be safe and effective [1, 4, 5, 7]. Various dosage schedules from 600, 800, 1000 microgram administered at 3 hours, 6 hours and 12 hours interval[6, 7] have been documented. Though outcomes improved at 3 hourly intervals from 6 hourly interval of misoprostol, no difference was noticed between 6 hourly and 12 hourly intervals.

This trial was conducted to compare the safety and efficacy of medical abortion with misoprostol alone at a dose of 1000mcg administered at 24 hourly intervals to the combined regimen of mifepristone with misoprostol.

Vaginal bleeding started at 3.43±1.2 hours after administration of misoprostol in group 1 and 6.46± 1.6 hours after first dose of misoprostol in

group 2. Mean duration of bleeding in group 1 was 6.23±5.3 days and 7.0±4.6 days in group 2. The duration of bleeding was ≤5 days in 56.7% of patients in group 1 and in 46.7% of patients in group 2 (P value equals 0.3611). The two groups were comparable (p=0.713) with regards mean change in haemoglobin (0.70±0.5g/dl in group 1 and 0.7±0.4g/dl in group 2). The two groups were comparable (p=0.576) with regards time to return of menstruation.

Cramping began at 4.1 ± 1.6 hours and lasted 5.2 ± 3.7 hours in group 1. Cramping began at 5.1 ± 3.4 hours and lasted 3.7 ± 1.9 hours in group 2. 90% of patients in group 1 and 70% of patients in group 2 did not require any analgesics (P value equals 0.0110).

Nearly 40% of all pregnancies worldwide are unplanned of which 40% end in abortion.[18] Providing these women all over the world who are highly likely to have an induced abortion when faced with an unplanned pregnancy with a safe, effective and economical option will have a major impact. The present study suggests that 1000mcg misoprostol administered vaginally at 24 hour intervals could be a more economical and viable option in situations where financial constraints restrict the use of mifepristone. Moreover the 24 hour interval improves patient compliance and allows out patient management.

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