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Original Research Article

A randomized study to compare the efficacy and side effects of misoprostol given either orally or vaginally for first trimester medical termination of pregnancy

Urmila Tripathi, Pratibha Garg*

Department of Obstetrics and Gynecology, Gajra Raja Medical College, Gwalior, Madhya Pradesh, India

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***Correspondence:**
Dr. Pratibha Garg,
E-mail: drgargpratibha@gmail.com

ABSTRACT

Background: Medical abortion represents an alternative to first trimester aspiration abortion and has been used by millions of women throughout the world. Numerous studies have study has demonstrated that combination of mifepristone and misporostol is highly efficacious with success rate of approximately 97%.
Methods: In the present randomized study 100 women who were requesting for first trimester medication abortion were included in the study. This randomized study was conducted for a period of one year in a tertiary health care centre. All these women were randomly assigned to receive either oral misoprostol (n=52) (group 1) or vaginal misoprostol (n=48) (group 2). We found that after the administration of mifepristone, vaginal misoprostol for the induction of abortion upto 49 days was more effective than oral misoprostol.
Results: In present study maximum number of patients were in the age group of 26-30 years. Multiparous women comprised of maximum number of patients in both 70% in group 1 and 83% in group 2. The gestational age at the time of inclusion in study was maximum upto 7 weeks or 49 days gestation in both groups. Acceptability of medical abortion is more in urban locality i.e. 73% in group 1 and 81% in group 2. 73% in group 1 and 79% in group 2 chose to have misoprostol at home. 92% patients in group 1 and 95% patients in group 2 initiated bleeding per vaginum within 4 hours. Side effects like nausea, vomiting and diarrhea were compared. 92.4% patients in group 1 and 97% patients in group 2 who had expulsion of conception without need of surgical intervention was comparable. Only 2 patients in group 1 had incomplete abortion and needed surgical aspiration.
Conclusions: The combination of mifepristone with misoprostol is inexpensive, simple, effective, noninvasive and is acceptable amongst the current regimens for medication abortion.

Keywords: Medical termination of pregnancy, Mifepristone, Misoprostol, Medication abortion

INTRODUCTION

Awareness of risk associated with surgical evacuation of uterine cavity during early pregnancy has prompted a search for alternative management strategies such as expectant management and medical treatment.[1-7] Medical abortion of pregnancy with a combination of mifepristone and prostaglandin is a relatively safe and effective alternative to manual vacuum aspiration or suction and evacuation upto 7 weeks of gestation. Medical abortion has the advantage of being less invasive, and more autonomous, self-directed, and discrete. It is preferable to users because it feels more natural as the drug induced the miscarriage.[8]

In September 2000, the US Food and Drug Administration (FDA) approved mifepristone in combination with misoprostol for early medical abortion.

In India, medical method of termination was approved only in 2002 for upto 49 days after last menstrual period. The drug controller has approved the use of combipack upto 63 days. EL Rafey et al, state that although misoprostol tablet is formulated for oral use, research has indicated that vaginal administration might be more effective.[9] A dose of 800 µg of vaginal misoprostol was found to be more effective than the same dose orally, in combination with 200 mg of mifepristone. The complete abortion rate was 95% and 87% respectively in pregnancies with <49 days of amenorrhea. The continuing live pregnancy rate was higher and vomiting, diarrhoea was more frequent with oral administration.

The progesterone receptor antagonist, mifepristone, increases the uterine contractility and sensitizes the myometrium to prostaglandin. The maximum effect is achieved when prostaglandins are administered 36-48 hours after mifepristone. Oral misoprostol leads to increased uterine tone without regular contraction while vaginal and sublingual administration lead to a longer lasting effect on the myometrium and subsequent development of regular contractions.

The present study was conducted to evaluate the efficacy and side effects of oral versus vaginal administration of misoprostol combined with the mifepristone in termination of pregnancy up to <49 days as amenorrhea.

METHODS

The study was conducted after approval from ethical committee.

Present study subjects were women requesting termination of early pregnancy at antenatal clinic of tertiary care centre, all of whom gave written informed consent to participate in the study. 100 women requesting for termination as pregnancy within 7 weeks from the onset of amenorrhea were taken for the study. In this study patient were divided into two groups:

Group 1

- Patient receiving mifepristone 200 mg orally on day 1 and Tab. misoprostol 800 µg orally after 48 hours (D3)

Group 2

- Patients receiving mifepristone 200 mg orally on day 1 and Tab. misoprostol 800 µg vaginally after 48 hours

After proper history, physical examination and per vaginum examination and routine investigation like blood group type and CBC and TVS to know the gestational age and for exclusion of ectopic pregnancy was advised followed by protocol as given below.

- Day 1: Mifepristone 200 mg orally, Inj Anti D to Rh -ve patient or any day prior to misoprostol administration was given.
- Day 3: Misoprostol 800 µg orally or vaginally.
- Day 14: Follow up visit to assess for complication of abortion by TVS.

The women were monitored for four hours after administration of misoprostol for initiation of bleeding and sudden severe bleeding if any.

The patient is asked to report if she does not bleed within 24 hours of using or if she had excessive bleeding or if she begins to feel very ill at any time during the medical abortion process.

If failure occurs surgical evacuation is performed to complete the abortion for any reason including incomplete abortion, continuing pregnancy or haemorrhage.

Inclusion criteria

- Good general health
- Older than the age of legal consent
- Requesting for termination of pregnancy
- Duration of pregnancy $\leq$ 7 weeks of duration (or $\leq$ 49 days of amenorrhea)
- Single intrauterine pregnancy
- Hb >10.0 gm%
- Willing to use contraception other than hormonal or intrauterine until the first menses after abortion.

Exclusion criteria

- Suspected ectopic pregnancy
- Contraindication of use of mifepristone including chronic systemic corticosteroid administration or adrenal disease
- Known coagulopathy or concurrent anticoagulant therapy
- Inherited porphyria

Statistical analysis

Statistical analysis was performed by student's 't' test and chi square or fisher's exact test.

RESULTS

Table 1 shows that group 1 - 2(3%) patient in age group <20 yrs, 12 (23%) were in age between 20-25 yrs, 22 (42%) were in age group 26-30 yrs, 10 (19%) were in age group 31-35 yrs and only 2(3%) patients were in > 35 yrs of age. In group 2 no patient in age group between 15-20 yrs of age group, there is 10(20%) patient were in 20-25 yrs of age group, 24(50%) patients were in age between 26-30 yrs, 12(25%) patients were in age group between

31-35 yrs and only 2(4%) patients were in age group > 35 yrs. This shows that maximum number of patients were in age group of an age in range of 26-30 yrs.

Table 1: Distribution of pregnant women according to age.

Age (yrs)	Oral misoprostol Group 1 (n=52)	Vaginal misoprostol Group 2 (n=48)
<20	2 (3%)	0 (0%)
20-25	12 (23%)	10 (20%)
26-30	22 (42%)	24 (50%)
31-35	10 (19%)	12 (25%)
>35	2 (3%)	2 (4%)

Table 2 shows the age distribution of 100 patients and the mean age in group 1 was 27.63±6.045 and in group 2 was 27.87±4.715. There was no significant difference in mean age of the patient in both groups (p=0.642).

Table 2: Mean age of patients.

Age (yrs)	Oral misoprostol Group 1 (n=52)	Vaginal misoprostol Group 2 (n=48)
Mean±SD	27.63±6.045	27.87±4.715

p value - 0.642

Table 3 shows parity distribution of patients in both groups, 16 (30%) patients from group 1 and 8 (16%) patients from group 2 were primigravidas. Multigravidas was contributed 36 (70%) in group 1 and 40 (83%) in group 2. This shows that maximum number of patients was multigravidas. Parity distribution among both groups were comparable (p value-0.099).

Table 3: Distribution of cases according to parity.

Parity	Oral misoprostol Group 1 (n=52)	Vaginal misoprostol Group 2 (n=48)
Primigravidas	16 (30%)	8 (16%)
Multigravaidas	36 (70%)	40 (83%)

p value - 0.099

Table 4: Distribution of cases according to literacy.

Education	Oral misoprostol Group 1 (n=52)	Vaginal misoprostol Group 2 (n=48)
Illiterate	0 (0%)	0 (0%)
Primary	0 (0%)	1 (2%)
High School	14 (26.91%)	10 (20.8%)
Graduation	38 (73%)	37 (77%)

Table 4 shows there was no patients was illiterate in both groups. 14 (26.91%) patients in group 1 was high school pass and 38 (73%) patients was graduate. In group 2, 1 (2%) was taken primary education, 10 (20.8%) was high school pass and 37 (77%) patients was graduate.

Table 5: Distribution of cases according to socioeconomic status.

Socioeconomic status (per capita income)	Oral misoprostol Group 1 (n=52)	Vaginal misoprostol Group 2 (n=48)
I: >1000	33 (63%)	20 (41%)
II: 994-500	17 (32%)	19 (39%)
III: 449-230	10 (19%)	08 (16%)
IV: 229-101	2 (3.8%)	0 (0%)
V: <100	0 (0%)	0 (0%)

p value - 0.62

Table 5 shows that in group 1 - according to modified B.J. Prasad classification of socioeconomic status updated by P. Kumar, 33(63%) cases belongs to class I, 17 (32%) cases to class II, 10 (19%) cases to class III and only 2 (3.8%) belongs to IV, there is not a single case belongs to class V in both groups. As compared to group 1 - 20 (41%), 19 (39%), 08(16%) and 0(0%) respectively in group 2. This shows that maximum number of patients commonly belongs to class I, II and III. There was no significant difference in both groups. Both groups are comparable (p value - 0.62).

Table 6: Distribution of cases according to area.

Area	Oral misoprostol Group 1 (n=52)	Vaginal misoprostol Group 2 (n=48)
Rural	14 (29.92%)	10 (20.8%)
Urban	38 (73%)	38 (81.25%)

p value - 0.047

Table 6 shows in group 1, 73% patients belongs to urban area and 81% in group 2 who belongs to rural area. 29% patients in group 1 belongs to rural area and 20% patients in group 2 belongs to rural area. This shows that maximum number of patients belongs to urban area and there is no significant difference in both group and both groups are comparable.

Table 7: Distribution of cases according to gestational age (in weeks).

Gestational age (weeks)	Oral misoprostol Group 1 (n=52)	Vaginal misoprostol Group 2 (n=48)
Upto 5	36 (70%)	33 (68%)
5-7	16 (30%)	15 (32%)

p value - 0.095

Table 7 shows 70% cases in group 1 and 68% cases in group 2, they had pregnancy upto5 weeks and 30% cases in group 1 and 32% cases in group 2 had pregnancy 5-7 weeks. The number of cases is maximum in pregnancy upto 5 weeks.

Table 8 shows the distribution of cases in relation of period of amenorrhoea in days. 57% cases in group 1 and 75% cases in group 2 had pregnancy upto 35 days and 43% cases in group 1 and 25% cases in group 2 they had pregnancy from 35-49 days. Number of cases is maximum in pregnancy upto 35 days of amenorrhea.

Table 8: Distribution of cases in relation to period of amenorhoea.

Amenorrhoea (days)	Oral misoprostol Group 1 (n=52)	Vaginal misoprostol Group 2 (n=48)
35	30 (57%)	36 (75%)
35-49	22 (43%)	12 (25%)

p value - 0.067

Table 9 shows that the maximum number of 73% patients in group I and 79% in group II have voluntarily taken misoprostol at home.

Table 9: Distribution of cases according to administration of misoprostol either at the clinic or at home.

	Oral misoprostol Group 1 (n=52)	Vaginal misoprostol Group 2 (n=48)
At the clinic	14 (26%)	10 (20%)
At the home	38 (73%)	38 (79%)

Table 10 shows that the maximum number of 48 patients in group I and 46% in group II had initiation of bleeding in four hours.

Table 10: Distribution of cases according to initiation of bleeding.

Initiation of bleeding (abortion process)	Oral misoprostol Group 1 (n=52)	Vaginal misoprostol Group 2 (n=48)
Within four hours	48 (92%)	46 (95%)
After four hours	4 (7%)	2 (4%)

Table 11 shows that two patient in group 1 had bleeding more than 2 days and she need aspiration for completion of abortion.

The difference in each of the group was not statistically significant in relation to period of amenorrhoea.

Table 12 shows that the total number of women in each group represents the number who reported on all the listed side effects. CI denotes the confidence interval for the difference between oral and vaginal misoprostol. Negative numbers indicate a higher rate in the vaginal misoprostol group and positive numbers a higher rate in the oral-misoprostol group.

Table 11: Bleeding pattern in relation to period of amenorrhoea.

Amenorrhoea in days		Bleeding pattern			P value
		<7 days	8-12 days	>12 days	
35	Group 1	13 (25%)	7 (13%)	0 (0%)	0.029
	Group 2	9 (18%)	9 (18%)	0 (0%)	
36-49	Group 1	20 (38%)	11 (21%)	1 (2%)	0.049
	Group 2	21 (43%)	9 (18%)	0 (0%)	

Table 12: Incidence of side effects as reported by the patients.

Side effect	Oral Misoprostol Group 1 (n=52)	Vaginal Misoprostol Group 2 (n=48)	Differences in incidence (95% CI)
Nausea	26 (50%)	19 (39.5%)	11
Vomiting	15 (28%)	9 (18.7%)	10
Diarrhoea	4 (7%)	1 (2%)	5
Tiredness	2 (3%)	2 (4.1%)	-1
Headache	4 (4.6%)	3 (6.25%)	1
Hot flushes	1 (1.9%)	2 (4.1%)	-3
Dizziness	2 (3.8%)	2 (4.1%)	-3

p value - 0.906

Table 13: Outcome of treatment with misoprostol administered orally or vaginally.

Gestational age (weeks)	Oral Misoprostol Group 1 (n=52)	Vaginal Misoprostol Group 2 (n=48)
Expulsion of the conceptus without need for surgery	48 (92.4%)	47 (97.91%)
Continued pregnancy	0 (0%)	0 (0%)
Missed abortion	2 (3.8%)	1 (2%)
Incomplete abortion	2 (3.8%)	0 (0%)

p value - 0.62

Table 13 shows that success rate of complete expulsion of concept or without need of surgical intervention is more with vaginal route (97.91%) incomplete abortion rate in higher in group receiving oral misoprostol.

DISCUSSION

The study was undertaken as the randomized study to compare the efficacy and side effects of misoprostol given either orally or vaginally. Randomization was done into either group 1 and group 2. All these 100 women who were requesting to terminate randomly assigned to receive either oral misoprostol (n=52) group 1 or vaginal misoprostol (n=48) group 2.

In the present study majority of women were in the age group of 26-38 years with the mean age of 27.63±6.045 in group 1 and 27.87±4.715 in group 2.

In relation to parity 70% in group 1 and 83% in group 2 were multigravidae and 30% in group 1 and 16% in group 2 patients were primigravidae. Maximum number of patients was multigravidae in both groups.

The Royal College of Obstetrician and Gynaecologists evidence based clinical guidelines state that medical abortion is an appropriate (Royal College of Obstetrician and Gynaecologist 2004). Mifepristone is an efficient abortificient in doses as low as 200 mg.[10]

Studies shows that regimen using mifepristone 200 mg are as effective as regime using mifepristone 600 mg. McKinley reported the result of a randomized trial of 220 women received single dose mifepristone 200 mg or 600 mg followed by misoprostol 600 µg orally 48 hours later in early pregnancy (<63 days of amenorrhoea).[11] No difference were found for clinical outcome, efficacy, bleeding or pain. Overall effectiveness was 97.5% at upto 49 days of gestation.

Ashok et al reported a retrospective evaluation of 2000 women who received mifepristone 200 mg followed by 36-48 hours later by misoprostol 800 µg vaginally in women upto 63 days gestation.[12] Complete abortion rate was 97.5% after administration of misoprostol vaginally. Same study was done by Schaff et al published two reports evaluating 200 mg dose of mifepirstone followed by either 2 doses of oral misoprostol 400 µg taken 2 hours apart or misoprostol vaginally.[13] Complete abortion rate was 97% upto 63 days of gestation.

In present study using mifepristone 200 mg followed by misoprostol 800 µg was given orally in group 1 (n=52), complete abortion rate was 92.4% in this group and in group 2 (n=48) complete abortion rate was 97.91%. Success rate was almost similar as in previous studies.

Schaff et al randomized women upto 8 weeks gestation self-administered misoprostol 800 µg vaginally at home.[14] 48 hours after taking mifepirstone 200 mg orally follow up occurred within 1-4 days after mifepirstone. Complete medical abortion occurred in 86% in 24 hours group, 98% in the 48 hours group.

In present study, we consider failure if bleeding continue more than 12 days and ultrasound shows retained product of conception with or without bleeding PV during follow-up.

El-Refaey et al used a clinical endpoint to define success (i.e. cesation of bleeding or normal findings on pelvic examination).[4] Lelaidier et al performed a vaginal ultrasound examination on day 5 and defined success as expulsion of pregnancy products.[15]

In present study 92% patients had started abortion process (initiation of bleeding) in group 1 within 4 hours and 95% patient in group 2. Only 7% patients in group 1 and 4% patient in group 2 had initiation of bleeding after 4 hours and need repeat dose of misoprostol 400 µg either orally or vaginally.

Schaff et al performed three largest studies using mifepristone 200 mg and misoprostol 800 µg vaginally with home administration of the misoprostol.[13,14] All studies demonstrates high efficacy through 63 days of gestation with the self-administration of the misoprostol at home. Approximately 90% of subjects in all studies found home use of misoprostol acceptable.

In present study 73% patient in group 1 and 79% in group 2 chosen voluntarily for home administration of misoprostol. Success rate was almost similar as in previous studies.

Reported median bleeding time ranges from 9-13 days the heaviest period of bleeding typically occurred when the abortion is occurring and persistent for 1-4 hours.

In a study done by Spitz et al pregnancy was terminated in 762 women pregnant for <49 days.[15] Termination occurred with 4 hours after administration of misoprostol in 495 of women and within 24 hours in 75%. The median day of bleeding or spotting was 13 days in the <49 days group and 15 days in another group. Bleeding was highest on day 3 and then decreased.

In present study result were almost similar, the mean duration of bleeding is 7-12 days. The range of bleeding is correlated to length gestation 63% patient in group 1 having bleeding 7 days and 34% patient having bleeding between 8-12 days. There is only one patient who reported bleeding >12 days and came with heavy bleeding need surgical aspiration and one unit blood transfusion. In group 2, 61% patient having bleeding <7 days and 36% patient bleeding between 8-12 days. No one patient in this group who had bleeding > 12 days.

Side effect can be managed with appropriate counseling and symptomatic treatment such as oral analgesic for pain. Side effects include nausea, vomiting, diarrhoea, fever and chills. Temperature elevation (defined as $>100.4^0$F or 38^0C). This is sustaining (>4 hours) or begin later than 6-8 hours after misoprostol administration women on clinical assessment. Most patient report that side effects are tolerable. The same study was done by Silvester et al in his randomized trial study.[7]

In present study, the patient having side effect of medication i.e. nausea, vomiting, diarrhea, were managed symptomatically. No other side effects noted in this study. 50% in group 1 and 39% in group 2 complaining vomiting. 28% in patients in group 1 and 18% in group 2 complaining of nausea, 7% patient in group 1 and 2% patient in group 2 complaining of diarrhoea. Spitz et al

found that nearly all patient had abdominal pain, the overall percentage of side effects were 3% for diarrhea, 10% for vomiting and 20% for nausea.[15]

CONCLUSION

This study concluded that after the administration of mifepristone, vaginal route of administration of misoprostol is more effective and better tolerated than oral route for the first trimester medication abortion. The combination of 200 mg of mifepristone and 800 µg of misoprostol is inexpensive, simple, effective, non-invasive and is most widely acceptable amongst the current regimens for the early first trimester medical abortion.

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