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A randomized comparison of three early medical abortion regimes: Mifepristone and misoprostol, misoprostol alone and methotrexate and misoprostol

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ABSTRACT

Background: Abortion is defined as the spontaneous or induced termination of pregnancy before fetal viability. It is extremely likely that couples will experience at least one unwanted pregnancy at some time during their reproductive years. Majority of abortions are performed in the first trimester. **Aims and Objectives:** The aim of the study was to evaluate and compare the efficacy and adverse effect profile of three regimes for medical abortion up to 56 days of gestation, that is, mifepristone and misoprostol, misoprostol alone and methotrexate and misoprostol. **Materials and Methods:** Ninety women attending the outpatient department for the purpose of medical abortion up to 56 days of pregnancy were enrolled for the study and divided into three groups. Group I received mifepristone and misoprostol. Group II received misoprostol alone and Group III received methotrexate and misoprostol. All women were followed up on day 14 and day 28 and assessed for completeness of abortion, side effects and complications, if any. **Results:** Four women (13.33%) in Group I, seven (23.33%) in Group II and 16 (53.33%) in Group III needed surgical evacuation as medical termination was unsuccessful. Nausea, vomiting and fever were the most common side effects in the study. **Conclusion:** The regime of mifepristone and misoprostol was found to be the most efficacious of the three regimes studied. All the regimes were safe as they did not result in any major complication.

Key words: Medical abortion regimes; Methotrexate; Mifepristone; Misoprostol

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INTRODUCTION

Abortion is defined as the spontaneous or induced termination of pregnancy before fetal viability.[1] It is extremely likely that couples will experience at least one unwanted pregnancy at some time during their reproductive years.[2] In India in 2015–2019, there were a total of 48,500,000 pregnancies annually, of these 21,500,000 pregnancies were unintended and 16,600,000 ended in abortions.[3] Majority of abortions are performed in the first trimester. Surgical abortion by vacuum aspiration or dilatation and curettage has been the method of choice for early pregnancy termination since 1960's.[4] As these procedures are painful and require anesthesia/analgesia, hospitalization, and have a risk of perforation, there has been growing interest in the medical methods of termination of pregnancy.[5] Medical abortion refers to an abortion induced by a pharmaceutical agent. The most widely used agents are prostaglandins, mifepristone, methotrexate and combinations of mifepristone and prostaglandins and of methotrexate with prostaglandins. Mifepristone is a 19-norsteroid agent which induces abortion by blocking

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the action of progesterone and increasing sensitivity to both endogenous and exogenous prostaglandins.[6] Misoprostol; a synthetic analog of prostaglandin E_1 (PGE_1) apart from being used in the prevention and treatment of gastro-duodenal ulcer worldwide, has strong utero-contractile properties.[7,8] Methotrexate is an antimetabolite which causes inhibition of dihydrofolate reductase and interferes with the cytotrophoblastic action and implantation of pregnancy.[9] The success of medical management for first-trimester abortion is dependent on the medication regime.[10] The present study was designed with the aim of comparing three first-trimester abortifacient regimes in terms of efficacy, adverse effects and complications, if any.

Aims and objectives

To evaluate and compare the efficacy and adverse effect profile of three regimes of medical abortion upto 56 days of gestation i.e. mifepristone & misoprostol, misoprostol alone and methotrexate & misoprostol.

MATERIALS AND METHODS

The present study was conducted prospectively after taking institutional ethical approval; the study included 90 women who attended the Out Patient Department of Obstetrics and Gynecology at Pandit Bhagwat Dayal Sharma Post Graduate Institute of Medical Sciences, Rohtak, Haryana, India for medical abortion up to 56 days of gestation. A detailed history including period of amenorrhea, menstrual cycles, obstetric history and any history of systemic medical disorders was taken. General physical and systemic examination was carried out. Pelvic examination was carried out to know the size and consistency of the uterus. Routine blood investigations and an ultrasound scan of the pelvis were also done. The enrolled women were divided into three groups by computer-generated randomization. Group I consisted of 30 women who received tablet mifepristone on day 1 and tablet misoprostol 800 mcg on Day 3 per vaginum. Group II included 30 women who received tablet misoprostol 800μg per vaginum on day 1 followed by 800 mcg misoprostol by the same route after 24 h if needed (if she failed to abort by 24 h). Group III constituted 30 women who received tablet methotrexate 50 mg orally on day 1 and tablet misoprostol 800μg per vaginum on day 3. All women were followed up on day 14 for the amount and duration of bleeding and their hemoglobin status. Women with spotting were graded as mild bleeding, those who experienced menstruation-like bleeding were considered to have moderate bleeding while all women with more blood loss or clots were graded as having severe bleeding. Pain was assessed on visual analog score (VAS) of 0–10. Transabdominal ultrasonography was carried out to check for completeness of abortion. Women in whom incomplete abortion or undisturbed pregnancy was detected on ultrasonography were offered manual vacuum aspiration. All the women were also called for follow-up visit on day 28 to look for complication, if any.

Inclusion criteria

Women with a single intrauterine pregnancy of ≤56 days were willing to undergo medical termination of pregnancy.

Exclusion criteria

Women with previous two or more cesarean sections, myomectomy or any other uterine reconstructive surgery, known allergy to drugs used in the study, any coagulopathy, severe anemia, renal and or hepatic disease, multiple pregnancies, and inherited porphyria were excluded from the study.

Statistical analysis

Continuous variables were expressed as mean±standard deviation; categorical variables were defined as percentages. Continuous variables were compared by One-way analysis of variance test (analysis of variance) (multi-group comparison) and the Chi-square test was used for the categorical variables between three groups. A $P<0.05$ was considered as statistically significant.

RESULTS

In the present study, the age ranged between 22 and 41 years in Group I, 22–42 years in Group II, and 20–35 years in Group III with mean ages being 28.53, 27.60, and 26.46 years in Groups I, II and III, respectively. The difference in the mean ages in the various groups of the study was not statistically significant (P=0.201). The parity ranged between 1 and 5 in our study. Most women (76.66% women each from Group I and Group II and 83.33% from Group III) being para 2 or more. There was no statistical difference in parity distribution among study groups (P=0.627). The mean gestational ages in Group I, II, and III were 6.4, 6.3, and 6.36 weeks, respectively (P=0.943). Table 1 shows the day of onset of bleeding in the present study. Twenty-nine women (96.66%) of Group I, 26 (86.66%) of Group II, and 16 (53.33%) of Group III started bleeding per vaginum within 3 days of administration of the abortifacient drugs. A total of 19 women (1 [3.33%] of Group I, 4 [13.33%] of Group II, and 14 [46.66%] of Group III) did not have any bleeding per vaginum. There was a statistically significant difference when the values were compared between Group II and Group III on day 0 (P=0.01), between Group I and III on day 1 (P=0.005), between Group I and II (P=0.02) and Group II and III (P=0.04) on day 2 and between Group II

Table 1: Day of onset of bleeding

Day of onset of bleeding	Group I (n=30) (%)	Group II (n=30) (%)	Group III (n=30) (%)	P-value	I/II	II/III	I/III
D0	9 (30)	11 (36.66)	3 (10)	χ^2=4.71; df=2; P=0.09 N.S.	χ^2=0.300; df=1; P=0.583 N.S.	χ^2=5.96; df=1; P=0.01 Sig.	χ^2=3.75; df=1; P=0.052 N.S.
D1	9 (30)	4 (13.33)	1 (3.33)	χ^2=10.43; df=2; P=0.005 Sig.	χ^2=2.45; df=1; P=0.11 N.S.	χ^2=1.96; df=1; P=0.16 N.S.	χ^2=7.68; df=1; P=0.005 Sig.
D2	1 (3.33)	7 (23.33)	0	χ^2=11.79; df=2; P=0.002 Sig.	χ^2=5.19; df=1; P=0.02 Sig.	χ^2=7.92; df=1; P=0.04 Sig.	χ^2=1.01; df=1; P=0.31 N.S.
D3	10 (33.33)	4 (13.33)	11 (36.66)	χ^2=4.76; df=2; P=0.09 N.S.	χ^2=3.35; df=1; P=0.06 N.S.	χ^2=4.35; df=1; P=0.03 Sig.	χ^2=0.07; df=1; P=0.78 N.S.
D4	0	0	1 (3.33)	χ^2=2.02; df=2; P=0.363 N.S	-	χ^2=1.01; df=1; P=0.31 N.S.	χ 2=1.01; df=1; P=0.31 N.S.
No bleeding	1 (3.33)	4 (13.33)	14 (46.66)	χ^2=18.54; df=2; P=0.0001 Sig.	χ^2=1.96; df=1; P=0.16 N.S.	χ^2=7.93; df=1; P=0.004 Sig.	χ^2=15.02; df=1; P=0.0001 Sig.

N.S.: Not significant; Sig.: Significant

and Group III (P=0.03) on day 3. Furthermore, there was a statistically significant difference in the amount of total blood lost per vaginum between Groups I and III (P<0.001) and Group II and III (P<0.05) (Table 2). Four women (13.33%) of Group I, 7 (23.33%) of Group II, and 14 (46.66%) in Group III needed surgical evacuation as medical termination was unsuccessful (Tables 3 and 4). Nausea was the most frequent side effect affecting 3 (10%) women of Group I and Group II each and 2 (6.66%) women from Group III. This was followed by vomiting which was observed in one woman each from Group I and Group II and two women of Group III (Table 5). A total of 89 women in the study, that is, 29 (96.66%) from Group I and 30 (100%) from each Group II and III had pain score of up to 6 on VAS. Only one patient from Group I experienced pain score of 8 on VAS. Hemoglobin on day 14 was 10.29±0.936 g/dL in Group I, 10.01±0.724 g/dL in Group II, and 9.85±0.85 g/dL in Group III. On statistical analysis, no significant difference was found in the hemoglobin between the groups. A total of 19 women were lost to follow-up on day 28 of the study and those who came for follow-up had no complaints/complications.

DISCUSSION

The first-trimester abortion may be performed either medically or surgically. Medical abortion is one of the important advances in reproductive health technology. In settings where abortion is legal, medical abortion has expanded the array of effective options available, thus improving abortion experience for those who wish to avoid surgery. Medical termination regimes have lower average costs and may allow for more privacy during the termination.[11] The drugs used for medical termination of pregnancy may be divided into three broad categories: Uterotonics (prostaglandins), antiprogesterone (mifepristone), and antimetabolites (methotrexate). Most available studies have reported results of either mifepristone and misoprostol combination or methotrexate and misoprostol or misoprostol alone. Given the unclear picture as to the best regime for medical termination of pregnancy in the first trimester, the present study was designed to compare mifepristone and vaginal misoprostol to vaginal misoprostol alone and combination of methotrexate and vaginal misoprostol for elective termination of early pregnancy.

In the present study, the three groups were comparable in terms of age with mean age being 28.53 years, 27.60 years, and 26.46 years in Group I, Group II, and Group III, respectively. No significant differences in mean ages of patients were reported by Jain et al., (compared mifepristone and misoprostol to misoprostol alone),

Table 2: Amount of bleeding per vaginum in the study

Amount of blood loss	Group I (n=30) (%)	Group II (n=30) (%)	Group III (n=30) (%)	I versus II	II versus III	I versus III
Mild	19 (63.33)	12 (40)	8 (26.22)	χ^2=4.18; df=3; P=0.242 not significant	χ^2=8.35; df=3; P<0.05 Significant	χ^2=16.03; df=3; P<0.001 Significant
Moderate	8 (26.66)	12 (40)	6 (20)			
Severe	2 (6.66)	2 (6.66)	2 (6.66)			
None	1 (3.33)	4 (13.33)	14 (46.66)			
Statistical analysis	χ^2=24.19; df=6; P=0.0005 significant					

Table 3: Finding of USG on day 14 follow-up

USG on day 14	Group I (n=30)	Group II (n=30)	Group III (n=30)	P-value
Empty uterus	26 (86.66)	23 (76.66)	14 (46.66)	χ^2=12.38; df=2; P=0.002 Significant
Retained products	3 (10)	4 (13.33)	1 (3.33)	χ^2=1.92; df=2; P=0.382 Not significant
Gestational sac with intact fetal node/cardiac activity	1 (3.33)	3 (10)	15 (50)	χ^2=22.95; df=2; P<0.001 Highly significant

USG: Ultrasound

Table 4: Need for surgical evacuation

Need for MVA (Surgical evacuation)	Group I (n=30) (%)	Group II (n=30) (%)	Group III (n=30) (%)
Yes	4 (13.33)	7 (23.33)	16 (53.33)
No	26 (86.66)	23 (76.66)	14 (46.66)
Statistical analysis group I versus group II	χ^2=1; df=1; P=0.316 Not significant		
Statistical analysis Group II versus Group III	χ^2=5.71; df=1; P=0.01 Significant		
Statistical analysis Group I VERSUS Group III	χ^2=10.80; df=1; P=0.001 Very high significant		
Overall statistical analysis	χ^2=12.38; df=1; P=0.002 Significant		

MVA: Manual vacuum aspiration

Table 5: Adverse effects of the various therapeutic agents used in the study

Adverse effects	Group I (n=30) (%)	Group II (n=30) (%)	Group III (n=30) (%)
Nausea	3 (10)	3 (10)	2 (6.66)
Vomiting	1 (3.33)	1 (3.33)	2 (6.66)
Fever	0	2 (6.66)	0
None	26 (86.66)	24 (80)	26 (86.66)
Statistical analysis	χ^2=4.85; df=6; P=0.562 Not significant		

Weibe et al., (compared mifepristone and misoprostol to methotrexate and misoprostol) and Ngoc et al., (compared mifepristone and misoprostol to misoprostol alone).[12-14] In the present study, the parity ranged between 1 and 5. The results were comparable with the study of Weibe et al., Sangwan et al., and Roudsari et al.[13,15,16]

The present study included women up to 56 days of amenorrhea with mean gestational age in Groups I, II, and III was 49.4 days, 49.30 days, and 49.36 days, respectively. The mean gestational age in studies by Jain et al., Weibe et al., Sangwan et al., and Bartley et al., was comparable to that of the present study.[12,13,15,17]

In the study by Weibe et al., bleeding per vaginum started after taking misoprostol on day 3 in both groups (mifepristone and misoprostol versus methotrexate and misoprostol) with mean period of 3 h after administration of misoprostol in mifepristone group and 4.6 h in methotrexate group. The mean day of abortion was 7.1 in methotrexate group as compared to 3.3 in mifepristone group.[13] In the present study, most of the women, that is, 29 (96.66%) women of Group I, 26 (86.66%) women of Group II, and 16 (53.33%) women of Group III started bleeding within 3 days of administration of abortifacient drugs, but 11 (36.66%) women of Group II started bleeding per vaginum on the 1st day itself as misoprostol has uterotonic activity and it was given on day 1 in Group II while on day 3 in Group II and III. Regarding the mean duration of bleeding after administration of abortifacient agents, most of the available studies have reported bleeding per vaginum for a period of 8.53–14.58 days.[12,13,18] In the present study, the bleeding per vaginum lasted for 10.58 days, 9.11 days, and 9.46 days in Groups I, II, and III, respectively, which is comparable to available literature.

In the present study, 26 (86.66%) women in mifepristone and misoprostol group aborted successfully. In misoprostol alone, group 23 (76.66%) women had complete abortion. However, in methotrexate and misoprostol group, only 14 (46.33%) women aborted completely. Hence, mifepristone and misoprostol were the most efficacious regime accounting for the successful termination of pregnancy in 86.66%

Table 6: Comparison of failure of medical abortion in different studies

Study	Mifepristone + misoprostol (%)	Misoprostol alone (%)	Methotrexate + misoprostol (%)	Significance
Carbonell et al. (1997)	-	9 (n=141) (6.38)	-	-
Jain et al. (2002)	5 (n=119) (4.20)	15 (n=125) (12)	-	Significant (P<0.05)
Wiebe et al. (2002)	22 (n=534) (4.19)	-	21 (n=518) (4.05)	NS
Sangwan et al. (2002)	-	-	21 (n=50) (42)	-
Roudsari et al. (2010)	-	17 (n=100) (17)	19 (n=100) (19)	NS (P=0.713)
Ngoc et al. (2010)	3 (n=202) (1.48)	32 (n=198) (16.16)	-	Significant (P<0.05)
Present study	4 (13.33)	7 (23.33)	16 (53.33)	P=0.002 Significant

of women. Mifepristone an antiprogesterone agent binds to progesterone receptors and causes the conceptus to detach from uterine wall due to withdrawal of progesterone support, hence rendering the uterus more susceptible to contractile activity, both spontaneous and induced.[19] The subsequent addition of misoprostol initiates the contractions in the already primed uterus. This may account for the highest success rate of termination of pregnancy with these agents. Jain et al., and Ngoc et al., compared the efficacy of mifepristone and misoprostol combination versus misoprostol alone and reported mifepristone and misoprostol regimen to be more effective for termination of pregnancy.[12,14] In the present study, 14 women of methotrexate group had ongoing pregnancy or undisturbed gestational sac with fetal node or cardiac activity. However, in the studies conducted by Weibe et al., Roudsari et al., methotrexate group was found to be equally efficacious to the mifepristone group and misoprostol alone[13,16] (Table 6).

Nausea, vomiting, and fever were the only adverse effects observed. Fever was observed in misoprostol group only. The variation in the side effects profile of the patients in all the three groups of our study was not found to be statistically significant (P=0.562). In studies conducted by Jain et al., and Weibe et al., nausea and vomiting were the most common side effects, while in the study by Ngoc et al., diarrhea was the most common side effect, followed by nausea, vomiting and fever in both the groups.[12-14] In the present study, using Visual Analog Score (VAS), most of the women had pain score of 6. A total of 48 patients (out of 90) had a VAS score suggesting mild pain only. Among the three groups, misoprostol alone group had least pain score thus making it a more patient-friendly option in comparison to other two regimes.

Limitations of the study

The limitation of our study include relatively small sample size and single cente study both of which may reduce generalizability of the data.

CONCLUSION

All three regimes studied were effective abortifacient regimes for termination of pregnancy in the first trimester. Of these, the one using mifepristone and misoprostol was the most efficacious (86.66%) regime followed by misoprostol alone regime (76.66%), and lastly methotrexate and misoprostol combination (46.66%). All the regimes were safe and did not result in major side effect or complication.

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RB- Definition of intellectual content, literature survey, prepared first draft of manuscript, implementation of study protocol, data collection, data analysis; **ND**- Concept, design, clinical protocol, manuscript preparation; **PB**- Manuscript preparation, editing, manuscript revision and submission of article.

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