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Different Time Schedules of Mifepristone and Misoprostol in Second Trimester Medical Abortion: A Comparative Study

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ABSTRACT

Background & aim: Recently, the use of mifepristone followed by misoprostol after 36-48 h has been demonstrated to be an effective and safe method for the second trimester medical abortion. However, this regimen entails long total abortion time, and consequently increases the financial burden and anxiety in the patients. We hypothesize that one day interval would be also effective and can be used to provide the abortion care. Regarding this, the present study aimed to compare the effectiveness and safety of 24- and 36-hour intervals between the administration of mifepristone and misoprstol for second trimester abortion.

Methods: This prospective comparative study was conducted on 70 females who opted for second trimester medical abortion between 12-20 weeks. Mifepristone (200 mg) was followed by sublingual misoprostol (800 mcg) after one and two days in the first and second groups, respectively. Four hours after the administration of 800 mcg misoprostol, all patients received 400 mcg sublingual misoprostol every 4 h (maximum of four doses in 24 h). For the purpose of the study, such parameters as the rate of successful abortion 24 h after the first dose of misoprostol, abortion duration, and the associated side effect profile were examined.

Results: According to the results of the present study, the two-day interval (100%) was more effective than the one-day interval (91.4%) (P=0.021). Furthermore, the mean induction abortion duration was significantly less in the two-day regimen. However, the side effect profiles were comparable in both groups.

Conclusion: As the findings of the present study indicated, both schedules of mifepristone and misoprostol were safe and effective in second trimester abortion. The 36-hour interval between mifepristone and misoprostol was more effective than the 24-hour interval. Furthermore, it had shorter abortion duration. We can individualize the patient care by offering a one-day interval regimen since it is more effective and has less duration for total abortion.

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Introduction

In spite of the availability of effective contraceptives, emergency contraceptives facilitate first trimester abortion. In clinical practice, clinician have to provide second trimester abortion. There may be various reasons for abortion, including the diagnosis of increased sex-linked disorders, metabolic disorders, and fetal anomaly. It may be also due to financial and logistics problems in obtaining abortion services (1, 2). According to the World health organization (WHO) and Royal College of Obstetricians and Gynecologists, mifepristone followed by misoprostol is considered as an effective and safe method for second trimester abortion (3, 4).

It has been demonstrated that not only the cervical ripening with mifepristone 36-48 h before misoprostol administration increases the rate of complete abortion, but also it decreases

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the induction abortion duration and the total dose of misoprostol required. Therefore, this method reduces the side effects in the second trimester abortion. Mifepristone is an antiprogesteron that competitively blocks the progesterone receptor and elicits a variety of effects that makes the uterus more susceptible to abortion. These effects include cervical dilatation, decidual necrosis, increased endogenous prostaglandin (PG) production, and increased uterine sensitivity to PG 24-48 hr after its administration.

A two-day interval has been reported to be more effective in various studies. Nevertheless, this regimen requires long total abortion time, and consequently increases the patients' anxiety and poses financial burden on them. We hypothesize that a one-day interval would be also effective and can be used to provide abortion care (5). With this background in mind, the present prospective comparative study aimed to compare the efficacy of different time intervals between the mifepristone and misoprostol administration in second trimester abortion. To this aim such parameters as the rate of successful abortion, abortion duration, and the associated side effect profile were examined to compare the two regimens.

Materials and Methods

This prospective comparative study was conducted on 70 females seeking second trimester abortion at a tertiary medical institute in the northeast India within 2014 January-2015 December. We compared the 24- and 36-hour time intervals between the administration of mifepristone and misoprostol in second trimester abortion. This study was approved and authorized by the Institutional Ethics Committee.

The females who referred to the Gynecology Department for second trimester abortion within the Medical Termination of Pregnancy MTPAct and those fulfilling the study criteria were enrolled in the study. The inclusion criteria were live pregnancy and having 12-20 weeks of gestation. The gestational age was confirmed by the menstrual history, clinical examination, and ultrasonography. The participants should have provided the informed consent and agreed to follow up.

The exclusion criteria included: 1) any known previous uterine surgery other than lower segment caesarean section (LSCS), 2) a history of two cesarean sections, 3) any contraindication to use misoprostol (e.g., allergy to prostaglandin) or mifepristone (e.g., taking anticoagulants and corticosteroid or suffering from adrenal insufficiency and porphyria).

The first 35 females were consecutively assigned into the first group, and the next 35 cases formed the second group. The two groups were comparable in terms of the demographic and obstetric variables. After admission to the Gynecology Ward, the participamts in the first group were orally administered a single tablet of mifepristone 200 mg (Mifegest, Zydus, India). Subsequently, 24 h after the mifepristone administration, misoprostol 800 mcg (cytotec, Pfizer India) was given sublingually. Afterwards, misoprostol 400 mcg was sublingually administered every 4 h (maximum of four doses in 24 h).

On the other hand, the females in the second group were orally administered a single tablet of mifepristone 200 mg followed by misoprostol 800 mcg given sublingually 36 h after the administration of the mifepristone. Subse-quently, misoprostol 400 mcg was administered sublingually every 4 h with the maximum of four doses in 24 h. After the administration of the first dose of misoprostol, the participants' vital signs (i.e., blood pressure and temperature) and other complaints (e.g., diarrhea, shivering, fever, and bleeding) were recorded every 4 h.

Analgesics (both oral and parenteral) were also provided if required. If the subjects aborted completely (both fetus and placenta) within 24 h of the first misoprostol dose, then no surgical intervention was performed. The uterine evacuation was carried out if there was retained placental tissue, or if the subjects had vaginal bleeding. In case of fetal expulsion and retained placenta, we administered another sublingual misoprostol 400 mcg to the respective patient and waited for the spontaneous expulsion of the placenta in the next 4 h. Successful termination was considered as the occurrence of abortion within 24 h of the first dose of misoprostol.

The participants were discharged one day after the abortion in case of not having any complaints or complications. The females were

called for the follow-up after 15 days. At the follow-up, they were interviewed and examined for any complication.

The demographic and obstetric variables were evaluated using the descriptive statistics (mean and standard deviation). Furthermore, the independent t-test was employed to compare the mean parameters between the two groups. A 95% confidence interval and 5% level of significance were adopted. The P-value less than 0.05 was considered statistically significant. The statistical analysis was performed using the SPSS version 16 (SPSS version 16, Chicago).

Results

A total of 70 females participated in the present study. The demographic and obstetric variables were similar in both groups (Table 1). According to the results of the study, the eugenic ground was the reason of pregnancy termination in nine (12.8%) women.

Table 1. Demographic and baseline parameters of the study groups

	Group 1 N=35	Group 2 N=35	P-value
Age (year)	25.6±4.76	25.68±3.833	0.934
Gravida	2.65±1.39	2.48±1.41	0.28
Gestational age (week)	15.82±1.70	15.85±1.682	0.943
Previous abortion	8(22.8%)	9(25.7%)	0.387
Nullipara	12(34.2%)	13(37.1%)	0.403
Previous lower segment caesarean section	6 (17.1 %)	5(14.2%)	0.746
Unmarried	7(20 %)	8(22.8%)	0.38

The rates of complete abortion were significantly different between the first and second groups, which were 100% and 91.4%, respectively (P=0.021) (Table 2). One woman in the second group aborted after the administration of mife-pristone; as a result, she was excluded from the statistical analysis.

Table 2. Various outcomes between the study groups

Variables	Group 1 N=35	Group 2 N=34	P-value
Completion rate	91.4%	100%	0. 021
Rate of surgical evacuation	2(5.7%)	0	0.000
Induction abortion duration (hour)	8.25±2.41	6.75±1.39	0.001
Misoprostol doses (mcg)	1405.714±280.69	1247.059±191.066	0.003

Two subjects of the first group required curettage due to incomplete abortion. In the first group, two women did not aborted with first course of medicine; i.e., the fetuses failed to expel in 24 h. Therefore, the second course of medicine was given to these female, which resulted in complete abortion. There was no case of emergency curettage in both groups. The mean induction abortion duration was lower in the second group (6.75 h) in comparison to the first group (8.25 h) (P<0.0018).

Moreover, regarding the first group, this value was higher in the females with gestational age of more than 16 weeks (10 h vs. 7.7 h; P<0.005) and those who had not have previous vaginal delivery (9.16 h vs. 7.92 h; P<0.025). The two groups were comparable in terms of the incidence of side effects (Table 3). The most common side effect was pain, and the analgesic requirement was higher in the nulliparae.

Table 3. Comparison of side effects between the study groups

Side Effect profile	Group 1 N=35	Group 2 N=34	P-value
Pain	18(51.4%)	11(32%)	0.11
Chills and rigors	5(14%)	3(8.82%)	0.48
Fever > 99.8 degree F	4(11.4%)	2(5.88%)	0.439
Nausea, vomiting	8(22.8%)	4(11.76%)	0.228
Diarrhoea	3(8.5%)	2(5.88%)	0.671

The incidence of such side effects as pain, fever, chills, and rigors were higher in the first group than that in the second group; however, it was not statistically significant (P>0.05). There was no case of infection, excessive vaginal bleeding, cervical injury, or uterine rupture in both groups. During the follow-up, no specific difference was noted between both the groups regarding the complaints. It should be noted that 27 (38.5%) women didn't turn up for the follow-up visit.

Discussion

This prospective comparative study compared the 24- and 36-hour intervals between the administration of mifepristone and misoprostol for second trimester abortion. As the findings indicated, the rates of complete abortion were 91.4% and 100% in the first and second groups, respectively. The rate of complete abortion was higher in the second group since the onset of mifepristone effect was above 24 h, which reached its peak at about 36-48 h (6). The findings of the present study were in line with those of the literature (1, 2, 7-9). However, one study reported similar rate of successful abortion for both regimens (5).

There was 1.5 h differences in the induction abortion duration between both regimens. Nevertheless, in the daily clinical practice, this difference was not significant (10-12). In contrast to a study reported a high rate of incomplete abortion rate for the two-day interval, the success rate of complete abortion was higher in the two-day regimen in the present study (12). This discrepancy might be due to the fact that in the mentioned study, they used 400 mcg vaginal misoprostol every 3 h. The higher initial dose of misoprostol (600-800 mcg) not only leads to higher complete abortion rate, but also decreases the induction abortion duration (2, 7, 8).

For the nullipara and higher gestational age (>16 week), the induction abortion interval was relatively high as compared to the multigravida and lower gestational age. Furthermore, for the nullipara and higher gestational age (>16week), the induction abortion interval was lower in the second group (P<0.05), which is consistent with the findings of the other studies (5, 7, 11, 12). One of the complications of second trimester abortion is uterine rupture (13). In the present study, no case of uterine rupture was observed.

One woman (multigravida of 15 weeks gestational age) in the second group aborted only with mifepristone 200 mg without the administration of misoprostol. This may happen in 0.2-0.4% of the cases (14). There was no excessive vaginal bleeding, and the females aborted completely. The limitations of the present study were its small sample size and not using the randomization. In addition, 38.5 % of the females missed the follow-up.

Conclusion

As the findings of the present study indicated, both schedules of mifepristone and misoprostol were safe and effective in the second trimester abortion. Furthermore, the 36-hour interval between mifepristone and misoprostol administration was more effective with shorter induction abortion duration than the one-day interval. Therefore, we can individualize patient care by offering a one-day interval regimen. Further well-designed and randomized studies with more sample size may be justified.

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Conflicts of interest

The authors declare no conflicts of interest.

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