Original Article

Side effects and efficacy of oral mifepristone plus sublingual misoprostol regimen in early medical abortion (gestation up to 63 days)

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Abstract

Introduction: Medical abortion with mifepristone and misoprostol has few side effects that cannot be avoided. Efficacy of medical abortion varies with the routes of administration and the doses of mifepristone and misoprostol. This study aimed to investigate the side effects and abortifacient efficacy of 200 mg oral mifepristone and 800 mcg sublingual misoprostol regimen in termination of early pregnancy.

Methods: A descriptive cross-sectional study was carried out at Marie Stopes Clinic, Gongabu, Kathmandu. Altogether 103 women with a period of gestation (POG) up to 63 days were selected by purposive sampling technique and were interviewed using two sets of the semi-structured questionnaire. Each woman received 200 mg mifepristone at the clinic. Then 800 mcg misoprostol was taken sublingually at home after 48 hours. Confirmation of abortion was done by ultrasonography. Association between efficacy and POG was calculated by using Chi-square and/or Fisher's exact test.

Results: Side effects reported were nausea, vomiting, diarrhoea, dizziness, fever, chills/shivering, headache, lower abdominal pain, anorexia, lower back pain. The overall efficacy of the regimen was 98.1%. Rates of complete abortion were 98.8% in ≤49 days' POG and 95.0% in >49days' POG. The differences were not statistically significant (p-value >0.05).

Conclusion: Medical abortion done by using this regimen had few side effects, but no serious side effects or complications were reported. Efficacy of this regimen was high. This study will help to estimate the possible side effects, complications and effectiveness of the given regimen required for proper counselling to the women who opt for medical abortion.

Keywords: Efficacy, Medical abortion, Mifepristone, Misoprostol, Side effects, Sublingual

Introduction

Before the invention of prostaglandin analogues and mifepristone, surgical abortion was the only method of choice for termination of pregnancy. The arrival of these drugs has offered a new alternative method of abortion.[1] According to the World Health Organization (WHO), medical methods of abortion is the 'use of pharmacological drugs to terminate pregnancy'.[2] Many studies have already confirmed that the combined regimen of mifepristone and misoprostol is an effective and safe method for termination of pregnancy up to 63 days' gestation.[1,3,4] In 2012, WHO further developed an effective evidence-based regimen for termination of pregnancy of gestational age up to 63 days which consists 200 mg mifepristone taken orally followed by 800 mcg misoprostol taken through vaginal, buccal or sublingual routes after 24 to 48 hours ingestion of mifepristone. For gestation below 49 days, an alternative regimen of

400 mcg misoprostol may be given orally after 200 mg mifepristone.[2]

Mifepristone is always taken orally but misoprostol can be taken through various routes: oral, vaginal, sublingual, buccal and rectal. Among these, the sublingual administration can achieve the highest peak concentration (C_{max} = 574.8±250.7 pg/ml) in the shortest time (T_{max} = 26.0±11.5 min) and provides greater systemic bioavailability than other routes.[5] Additionally, sublingual route avoids the problems related to the vaginal route such as uncomfortable administration and incomplete dissolution of the vaginal tablet.[6,7]

The combined regimen of mifepristone and misoprostol shows prostaglandin-related side effects which include gastrointestinal disturbances (nausea, vomiting, and diarrhoea) and thermoregulatory changes (fever, chills and hot flushes).[8] Studies have shown that misoprostol taken through sublingual route shows more incidence of side effects (especially nausea, vomiting, diarrhoea, chills, and fever were significantly more common) than other routes of administration which may be attributed to the high bioavailability of misoprostol provided by sublingual route.[9–12] Some side effects such as vaginal bleeding and abdominal cramp are anticipated because these are the part of abortion process itself; but, the severe condition that is heavy bleeding (which requires a blood transfusion) and extreme lower abdominal cramping represent the complications of medical abortion.[8] However, these complications are rare; only <1% cases have reported excessive bleeding that requires a blood transfusion.[3,13,14] Various studies that followed 200 mg mifepristone and 800 mcg sublingual misoprostol regimen have confirmed the success rate ranging from 93.9 to 98.2%.[9,12,14,15] It is also reported that the efficacy of regimen decreases with increasing gestation.[9,12,14]

Medical abortion can be performed safely and effectively even in low-resource settings where surgical abortion services are not available.[16] So, it plays a crucial role in improving access to abortion services particularly in the rural areas of low-income countries like Nepal.[17] The primary objective of this study was to find out the frequency of side effects and abortifacient efficacy of a combined regimen of 200 mg oral mifepristone and 800 mcg sublingual misoprostol for termination of pregnancy up to 63 days' gestation.

Methods

A cross-sectional descriptive study was conducted at Marie Stopes Centre Gongabu, Kathmandu, a clinic of Sunaulo Parivar Nepal (a local affiliate of Marie Stopes International) from June to September 2013. Purposive sampling technique was used to select the subjects for the study. A total of 103 women with a period of gestation (POG) up to 63 days were included in this study. Participants who lost to follow up, who were having an intrauterine device, history of bronchial asthma, severe anaemia, chronic adrenal failure, and current long-term systemic corticosteroid therapy were excluded from the study.

The study was approved by the Institutional Review Board of Institute of Medicine, Tribhuvan University. The objective of the study was shared among the study participants and written informed consent was taken from them. There were two sets of questionnaires, one was administered by the investigator after interviewing with the participants on the first clinical visit and another self-administered questionnaire in the Nepali language was provided to be filled by the participants in which the side effects observed in between the period of first visit and follow-up visit were filled up.

At the first clinical visit (Day 1), the gestational age was confirmed on the basis of last menstrual period (LMP), bimanual examination and ultrasonography (if necessary). When the participants agreed to the medical abortion, then it was performed according to the WHO prescribed regimen. At first, 200 mg of mifepristone was given orally on the same day (Day 1). Later, she was advised to take misoprostol sublingually at home after 48 hours ingestion of mifepristone (on Day 3).[2] A self-administered questionnaire was provided to the participants to keep the record of observed side effects, amount of bleeding and abdominal pain in between the period of first visit and follow-up visit (on Day 14). On the follow-up visit, the self-administered questionnaire filled by the participants were collected and they were asked about various side effects observed in details. Completion of abortion was confirmed by ultrasonography. In case of incomplete abortion, manual vacuum aspiration (MVA) was performed. The outcomes of medical abortion were categorized as:

Complete abortion: Complete expulsion of the entire product of conception (POC) with the given regimen and no further procedure (like MVA or an additional dose of misoprostol) was required.

Incomplete abortion: Incomplete expulsion of the entire product of conception with some retained in the uterine cavity.

Pregnancy continued: Continuation of viable or nonviable pregnancy.

Efficacy of the regimen was defined as the percentage of cases in which complete abortion was confirmed. Serious side effects or complications were defined as the condition in which heavy bleeding (which required a blood transfusion or intravenous fluids) and extreme lower abdominal cramping (which required parenteral analgesics for their pain relief) occurred.

Data entry and analysis was done by using Statistical Package for Social Science (SPSS version 20.0). A graph illustrating the types of bleeding was generated by using Microsoft Excel 2013. Association between the efficacy of regimen and POG was tested by using Chi-square test and/or Fisher's exact test at 95% confidence interval. A p-value less than 0.05 were considered statistically significant.

Results

The majority (34.0%) of women were in between 25-29 years. The mean age of women was 27.2 years (SD±4.9). Most of the participants were multigravida (78.6%), multiparous (39.8%) and the majority (56.3%) of them had not done abortion before. Most of the respondents (80.6%) had POG up to 49 days. The mean POG was 42.98 days (SD±8.05) and the range was 21 to 63 days (Table 1).

Table 1 Demographic characteristics of the study participants

Characteristics	Frequency (n = 103)	Percentage (%)
Age		
<20	7	6.8%
20-24	26	25.2%
25-29	35	34.0%
30-34	23	22.3%
≥35	12	11.7%
Gravida		
1	22	21.4%
≥2	81	78.6%
Parity		
0	28	27.2%
1	34	33.0%
≥2	41	39.8%
Previous abortion	58	56.3%
POG (in days)		
≤49	83	80.6%
50-56	13	12.6%
57-63	7	6.8%

Incidence of side effects reported

Among 103 women, 27 (26.2%) had not experienced any side effect in between the period of mifepristone and misoprostol ingestion, while all the women had experienced at least one side effect after the use of misoprostol. Side effects reported were nausea, vomiting, diarrhoea, dizziness, fever, chills/shivering, headache, lower abdominal pain, anorexia, lower back pain. The incidence of all side effects (especially fever and chills) were seen more common after taking misoprostol. All the women experienced bleeding and lower abdominal pain after taking misoprostol (Table 2).

Table 2 Incidence of side effects self-reported by participants

Side effects	After mifepristone, before misoprostol (n = 103)	After misoprostol (n = 103)
	Number of participants (%)	
None	27 (26.2%)	0 (0%)
Nausea	43 (41.7%)	58 (56.3%)
Vomiting	19 (18.4%)	26 (25.2%)
Diarrhoea	9 (8.7%)	42 (40.8%)
Dizziness	33 (32.0%)	38 (36.9%)
Fever	2 (1.9%)	43 (41.7%)
Chills/Shivering	0 (0%)	44 (42.7%)
Headache	28 (27.2%)	46 (44.7%)
Lower abdominal pain	42 (40.8%)	103 (100.0%)
Anorexia	11 (10.7%)	25 (24.3%)
Lower back pain	3 (2.9%)	5 (4.9%)

Vaginal bleeding

Of total respondents, vaginal bleeding occurred in 37 (35.9%) women after using mifepristone before misoprostol. All of the women experienced vaginal bleeding after the use of misoprostol; among them, the majority (50.5%) of the women had bleeding less than 1 week (Table 3).

Table 3 Duration of bleeding after taking misoprostol

Duration (in days)	Frequency (n = 103)	Percentage (%)
<7	52	50.5%
7-14	37	35.9%
>14	14	13.6%

Types of vaginal bleeding

Assuming the day of administration of mifepristone at the clinic as Day 1, Figure 1 illustrates the types of vaginal bleeding in each day up to the Day 14 (follow-up day). All the women had vaginal bleeding on the same day of administration of misoprostol (Day 3); among them, most of the women (71%) bled 'more than menstrual' type, and the heavy bleeding constantly decreased until Day 9 and finally stopped on Day 10. A total number of bleeding women was almost same from Day 3 to 6, after that, it was also decreased. Fourteen women (13.6%) still reported bleeding on their follow-up day (Day 14). There was no serious complication observed in this study; not a single woman required a blood transfusion or intravenous fluids.

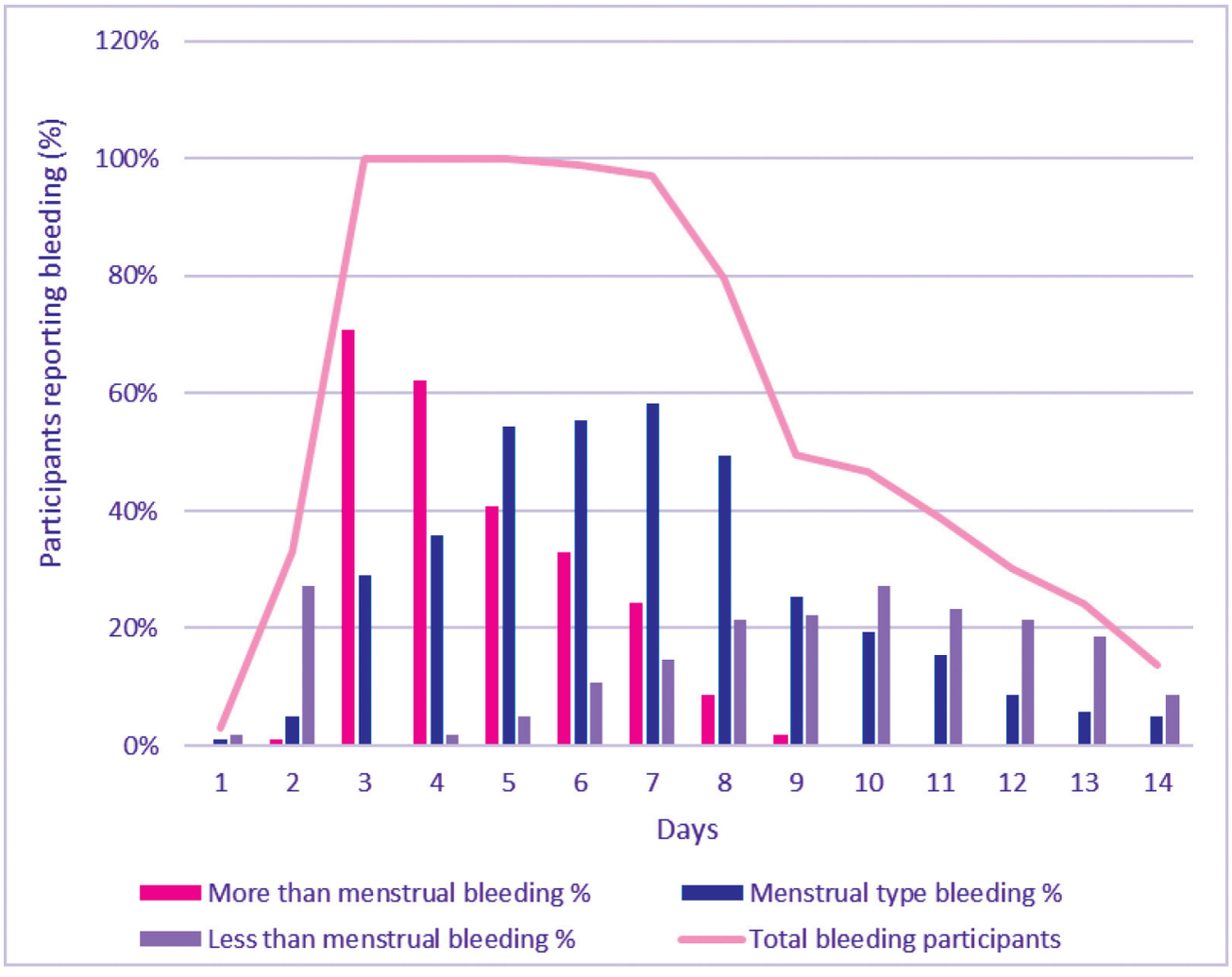

Figure 1 Vaginal bleeding recorded by participants from Day 1 (first visit) to Day 14 (follow-up day).

Lower abdominal pain

Out of total 103 women, the lower abdominal pain was experienced by 42 (40.8%) women after taking mifepristone before misoprostol. Among them, most of the women (78.6%) experienced pain as 'less than dysmenorrhoea' and no one needed analgesics for pain relief.

All the women experienced lower abdominal pain after the use of misoprostol. Among them, most of the women (66.0%) experienced pain as 'more than dysmenorrhoea' but did not require analgesics for pain relief, only 17.5% participants experienced extreme pain and needed analgesics (oral NSAIDs) for their pain relief (Table 4).

Table 4: Severity of abdominal pain experienced

Severity of pain	After mifepristone, before misoprostol (n = 42)	After misoprostol (n = 103)
	Number of participants (%)	
Less than dysmenorrhoea	33 (78.6%)	2 (1.9%)
Same as dysmenorrhoea	5 (11.9%)	15 (14.6%)
More than dysmenorrhoea	4 (9.5%)	68 (66.0%)
Need of analgesics for pain relief	0 (0%)	18 (17.5%)

Efficacy of the regimen

Out of total 103 participants who visited for the medical termination of pregnancy, most of them (98.1%) had complete abortion and only two women (1.9%) had an incomplete abortion. No one had an ongoing pregnancy. The overall efficacy of the given regimen was 98.1% (Table 5).

Table 5: Outcome of medical termination of pregnancy

Outcome	Frequency (n = 103)	Percentage (%)
Complete	101	98.1%
Incomplete	2	1.9%
Ongoing pregnancy	0	0%

The rates of pregnancy termination were 98.8% in ≤49 days group and 95.0% in >49days group. The differences were not statistically significant (p-value >0.05). There was no significant association between the period of gestation and the outcome of medical termination of pregnancy (Table 6).

Table 6 : Outcome of medical termination of pregnancy according to Period of Gestation

Outcome	Period of Gestation		Total (n=103)	p-value
	≤49 days (n=83)	>49 days (n=20)		
	Number of participants (%)			
Complete	82 (98.8%)	19 (95.0%)	101 (98.1%)	0.352
Incomplete	1 (1.2%)	1 (5.0%)	2 (1.9%)	

Fisher's exact test at 95% CI

Discussion

As observed in this study, the majority of women were in between 25-29 years and the mean age was 27.2 years (SD±4.9). The majority of the women were multigravida, multiparous, and with POG ≤49 days. The mean POG was 42.98 days (SD±8.05). These findings are almost similar to many studies[18–22] on medical abortion conducted in Nepal.

In this study, the participant's perception of side effects was investigated by asking them to fill a questionnaire by themselves at home. Most of the studies have reported that the side effects of mifepristone and misoprostol regimen were subjective, and the frequency of side effects was shown to be varied among the various studies.[9,12,14,15] The incidence of side effects observed in the present study was found to be comparable with these aforementioned previous studies. Also, the present study revealed that the majority of the study participants experienced side effects after the use of misoprostol. This finding is consistent with the previous studies.[9,14,15]

Unlike the present study, two studies conducted by Tang et al.[9,15] had shown slightly more proportion of participants experienced nausea. But, both the studies of Tang et al. included the side effects observed only on the day of administration of misoprostol while the present study included the side effects observed from Day 3 to follow-up day, which might explain the cause of the discrepancy. The present study reported that all

women complained of abdominal pain after taking misoprostol and the similar finding was observed in two studies.[9,12] However, different observations were reported by another two studies[14,15] showed 98.7% and 89% of participants complained of abdominal pain respectively.

A study[14] compared two different doses (400 and 800 mcg sublingual or vaginal) of misoprostol and found that the side effects of misoprostol were dose-dependent i.e., the incidence of side effects with 800 mcg sublingual misoprostol were more common than with 400 mcg sublingual misoprostol. Conversely, when comparing the studies[9,12,14,15] of 800 mcg sublingual misoprostol with a study[10] of 600 mcg sublingual misoprostol revealed that most of the side effects were common with 600 mcg misoprostol. In the study of 600 mcg sublingual misoprostol, a repeat dose of 400 mcg misoprostol was used (after 3 hours of administration of misoprostol) for the women over 8 weeks' gestation in case of failure of abortion which might describe the cause of more frequency of side effects.

Vaginal bleeding is an expected and natural consequence of the abortion process, and it occurs in all the women whose pregnancies terminate medically. In this study, the majority (50.5%) of the women bled less than 1 week after taking misoprostol. The proportions of women who experienced bleeding 'more than menstrual' decreased (from Day 3 to Day 9) while the proportions of women who experienced 'menstrual type' (from Day 1 to Day 7) and 'less than menstrual type' bleeding (from Day 4 to Day 10) increased. The type of vaginal bleeding up to the 15th day of administration of mifepristone was analysed by Spitz et al.[3] in which the similar pattern of bleeding was observed. However, unlike in the study of Spitz et al., all the women bled on Day 3 (i.e. on the day of administration of misoprostol) in the present study. Since the study of Spitz et al. used the oral route and the present study used the sublingual route for misoprostol, the observed difference might be attributed to the difference in onset of action caused by a different route of administration. Comparing with the study done by Spitz et al., there was a sharp decrease in the percentage of total bleeding women on Day 9 in the present study. And only 13.6% of women still complained of bleeding on Day 14 which is less than that observed in the study of Spitz et al. This difference observed in the present study might be due to the intake of ergometrine prescribed by the physician in case of heavy bleeding; three women took the prescribed ergometrine on the 5th day, five women on the 6th day and nine women on their 8th day.

Pain is a common and predictable side effect observed in a medical abortion procedure. However, only a few studies were concerned about the severity of pain observed and its management during the medical abortion. The present study observed that all the women experienced abdominal pain after taking misoprostol, among them, the majority (66.0%) of women experienced pain as 'more than dysmenorrhoea', but did not require medicines for pain relief. A similar finding was reported in a study[14] wherein the degree of pain was analysed in a scale from 0 to 10 and showed most (40–42% in all regimens) of the women felt a moderate degree of pain (score of 5–8). No woman reported more than eight (intolerable pain) during the whole duration of the study.

Previous studies that used the same regimen claimed the efficacy ranging from 93.9 to 98.2%.[9,12,14,15] The present study revealed the overall outcome of the regimen was 98.1%, which lies within the range of previous studies. There were 2 (1.9%) incomplete abortion cases in which ultrasonography showed the remnants of products of conception (POC) and MVA was done for them. Many studies found that the outcome of a medical abortion depends on the gestational age and the efficacy of regimen decreases with increasing gestation.[9,12,14] A similar finding was observed in the present study as well; more success rate in ≤49 days group than >49days group and there was no significant association between the period of gestation and the success rate of abortion (p-value 0.352).

Mifepristone stimulates uterine contraction and sensitizes the myometrium to prostaglandins. The sensitization of the myometrium starts within 24 hours and becomes maximum after 36 to 48 hours of mifepristone administration.[23] As stated in WHO recommended regimen, misoprostol can be taken after 24-48 hours of ingestion of mifepristone.[2] In this study, a time interval of 48 hours was maintained in between the mifepristone and misoprostol administration and the efficacy of the regimen was found nearly equal to a study[9] conducted by Tang et al. (98.2%) that used the same regimen and followed the same 48 hours interval. A review study[24] compared the success rate of 24 hours interval studies with 24-48 hours interval studies and found that the efficacies of 24 hours interval studies were slightly lower than the studies of 24-48 hours interval (94.2% compared with 96.8%, p <0.001). Furthermore,

the lower efficacy associated with the shorter interval (24 hours) was found in both lower (≤49 days' gestation) and higher (50–63 days' gestation) gestation groups.

While considering the studies that used lower doses of misoprostol, 600 mcg sublingual misoprostol regimen showed the efficacy of 96 to 98.9%[10,25,26] and 400 mcg sublingual misoprostol regimen showed the efficacy of 90.5 to 98.7%[11,14,16,27–32]. These studies suggest that even the slightly low dose of misoprostol can provide nearly the same efficacy as with 800 mcg misoprostol and might lessen the incidence of side effects as well. Further studies are needed to find out the appropriate dose of misoprostol that can provide high efficacy with the lowest frequency of side effects and complications.

Limitations of the study

Since the study was conducted in a single clinic, the findings of the study may not be generalised. All the incidences of side effects were not observed by the investigator and were self-reported by the respondents. So, it might be the subjective assessment. Since the duration of the study was relatively short, the number of study population may be less for the assessment of the efficacy of the regimen.

Conclusion

Medical termination of pregnancy using 200 mg oral mifepristone followed by 800 mcg sublingual misoprostol (after 48 hours interval) regimen had few side effects like nausea, vomiting, diarrhoea, dizziness, fever, chills/shivering, headache, lower abdominal pain, anorexia, lower back pain. No serious side effects or complications were reported. Efficacy of this regimen in termination of pregnancy for gestation up to 63 days was high. There was no ongoing pregnancy. There was no association between the period of gestation and the success rate of this regimen (p-value 0.352). This study will help to estimate the possible side effects, complications and effectiveness of the given regimen, which are required for proper counselling to the women who opt for the medical termination of pregnancy.

Conflicts of interest: None declare

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