Available online at www.sciencedirect.com
ScienceDirect
Taiwanese Journal of Obstetrics & Gynecology 50 (2011) 11–14
www.tjog-online.com

Original Article

Simultaneous use of mifepristone and misoprostol for early pregnancy termination

Yiu-Tai Li [a], James Ching-Hung Hsieh [a,b], Guang-Qiong Hou [a], Tien-Hui Chen [c], Yi-Chih Chu [a], Ta-Chin Lin [a], Long-Ching Kuan [a], Mau Lin [a], Hsun-Han Tang [a,d,*], Tsung-Cheng Kuo [a]

[a] *Department of Obstetrics and Gynecology, Kuo General Hospital, Tainan, Taiwan*
[b] *Department of Obstetrics and Gynecology, Clinic of Fu Jen Catholic University, Taipei, Taiwan*
[c] *Department of Gynecology and Obstetrics, Chang Bing Show Chwan Memorial Hospital, Changhua, Taiwan*
[d] *Southern-Taiwan Technology University, Tainan, Taiwan*

Accepted 23 September 2010

Abstract

Objective: Simultaneous mifepristone 200 mg and vaginal misoprostol 800 μg produces a complete abortion rate of approximately 90% at up to 63 days of gestation. The aim of this study was to determine the effectiveness of concurrent administration of mifepristone 200 mg and vaginal misoprostol 600 μg with respect to early medical abortion.
Materials and Methods: A total of 254 women with undesired pregnancies of less than 49 days of gestation were enrolled. All women received oral mifepristone 200 mg and vaginal misoprostol 600 μg concurrently. Follow-up assessment by transvaginal ultrasonography was performed 3 days and 2 weeks after treatment.
Results: Efficacy outcome was analyzed for 242 women (95.3%) after excluding 12 individuals lost to follow-up. The complete abortion rate was 92.6%. The mean induction to abortion interval was about 5.8 hours. The mean bleeding duration was about 12.6 days. The women indicated that the side effects were tolerable and 90% of them said that their experience was satisfactory.
Conclusion: Concurrent administration of oral mifepristone 200 mg and vaginal misoprostol 600 μg is an efficacious regimen for medical abortion of pregnancies up to 49 days of gestation.

Keywords: Concurrent medical abortion; Mifepristone; Misoprostol

Introduction

Surgical treatment has been used as the method of choice for early termination of pregnancy for many years, but significant complications do occur, including uterine perforation, hemorrhage, and retained products of conception. Recently, the medical management of pregnancy termination has become more popular than surgical management. Medical management with misoprostol is most frequent and is regularly offered for the termination of pregnancy. Different doses of misoprostol for the termination of early pregnancy have been reported.

The use of medical abortion to terminate early pregnancy has evolved greatly. Clinical studies have demonstrated that oral administration of mifepristone (RU 486) 600 mg, followed by the oral use of misoprostol 400 μg 36–48 hours later, results in a complete abortion rate of 87–96% at up to 49 days of gestation [1–4]. Large randomized trials have proved that regimens using a lower dose of mifepristone are equivalently effective [5,6]. Furthermore, alternative means of administration of misoprostol, including vaginal, buccal, and sublingual approaches, have also been used at 49 days of gestation or less.

Research has shown that the vaginal administration of misoprostol is characterized by a slow absorption but a long

* Corresponding author. Department of Obstetrics and Gynecology, Kuo General Hospital, 22 Ming-Sheng Road, Section 2, Tainan 700, Taiwan
E-mail address: drgynobs@yam.com (H.-H. Tang).

1028-4559/$ - see front matter
doi:10.1016/j.tjog.2010.09.002

duration at a high-serum concentration; this avoids first-pass metabolism by the liver. In these circumstances, the vaginal bioavailability of misoprostol is three times greater than the oral bioavailability [7]; thus, vaginal administration of misoprostol has a relatively higher success rate for abortion than oral administration.

A recent study has shown that effectiveness remains the same even if the interval between the administration of mifepristone and the subsequent administration of misoprostol is decreased from 36−48 hours to 6−8 hours [8]. Shortening the interval between the administration of mifepristone and misoprostol is scientifically plausible. Furthermore, research has revealed that the therapeutic effect is also good even when the two drugs are used concurrently.

In a previous report, we demonstrated a 97.8% abortion rate by the concurrent administration of mifepristone 200 mg and vaginal misoprostol 800 μg when used for early pregnancy termination [9]. However, we envisaged in this study the use of a lower dose of misoprostol in order to reduce any adverse effects. Evidence suggests that any adverse effects associated with early pregnancy terminations using mifepristone and misoprostol, such as nausea, gastrointestinal complaints, and pain from cramping, may be related to the dose of misoprostol and the route by which it is administered [10]. Vaginal administration of misoprostol 800 μg seems to have more adverse effects in previously published reports [11−13]; therefore, this had led to investigate the efficacy of mifepristone 200 mg and misoprostol 600 μg vaginally in order to determine the effectiveness and its adverse events of this procedure on early medical abortion. Given that low dose of misoprostol is thought to be insufficient or effective uterine contractions to produce high-abortion rate, we did not try misoprostol 400 μg or 200 μg in this study.

Materials and methods

From November 2005 to October 2009, a total of the 254 women seeking elective termination of pregnancy were progressively enrolled. All the consenting women who presented for abortion services met the following inclusion criteria: (1) the patient requested a medical abortion; (2) an intrauterine pregnancy up to 49 days gestational was confirmed using vaginal ultrasonography and the ultrasound was also used to exclude an ectopic pregnancy and to estimate gestational age; (3) the patient had signed an consent agreement, had been informed of the advantages/risks of medical abortion, and understood the necessity of receiving a surgical abortion if the medical abortion failed; and (4) the patient promised to attend the follow-up appointments.

No medical abortions were performed on pregnant women with any of the following exclusion criteria: (1) allergy to mifepristone or prostaglandins; (2) the presence of symptoms associated with threatened abortion; (3) a medical history of heart, respiratory system, kidneys, liver, or adrenal disease; (4) a medical history of thromboembolism, hypertension, coagulopathy, glaucoma, or diabetes mellitus; (5) a medical history of uterine pathology; (6) a hemoglobin level of less than 10 g/dL; (7) a pregnancy involving an intrauterine device *in utero*; or (8) the presence of an active pelvic infection.

To induce abortion, the women received 200 mg of oral mifepristone followed by the immediate intravaginal placement of 600 μg misoprostol. To relieve symptoms due to misoprostol, subjects were given a prescription for three tablets of 500 mg acetaminophen for the treatment of abdominal pain if they needed it. Participants returned 3 days after administration of the combination. After being questioned regarding side effects, a vaginal ultrasound was performed. The side effects involved were pelvic pain, shivering (generalized tremor $\geq$30 seconds), fever ($\geq$37.5 °C), nausea, vomiting, diarrhea, and dizziness. All participants were scheduled for a second follow-up visit at Day 14 after the procedure. At the follow-up visits, each woman's abortion and clinical status were assessed again. A result was considered to be a complete abortion when the transvaginal sonography demonstrated a regular smooth endometrial cavity. Women with retained products in the uterus were offered the option of waiting an additional week to see if these products would evacuate on their own. Suction curettage was also performed at any time if it was clinically necessary because of uterine hemorrhage, incomplete abortion, or at the subject's request.

Complete medical abortion without surgical intervention was classified as treatment success. All outcomes that resulted in a surgical intervention were classified as treatment failure. At each of the participant's final follow-up visit, she completed a visual analog scale (VAS) measuring the amount of pain experienced during the abortion process. On a 100-mm line, "0" represent no pain and "100" represented severe pain. In addition, at the same time, the patients filled out a questionnaire designed to determine whether they agreed that the medical abortion was performed to their satisfaction. The questionnaire consisted of multiple-choice questions with the following choices: strongly disagree; disagree; neutral; agree; strongly agree. This study was approved by the Institutional Review Board and written informed consent was obtained from all participants.

Results

Of the 254 enrolled patients, 12 were lost to follow-up and were not included in analysis; as a result, 242 participants completed this study. The mean age of the 242 women was about 25.2 years (range, 18−46 years), and the mean gestational age was about 45.2 days (range, 36−49 days). When parity was analyzed, 140 (57.9%) women were nulliparous, 38 (15.7%) were primiparous, and 64 (26.4%) were multiparous. The mean time from drug administration to bleeding was about 3.2 hours (range, 1.2−6.5 hours), and the mean time to expulsion of the products of the pregnancy was about 5.8 hours (range, 3.2−10 hours). The mean duration of self-assessed bleeding days was about 12.6 days (range, 9−32 days).

The efficacy outcome was analyzed for the 242 women. Overall, 224 (92.6%) of the participants underwent complete abortion after completion of the treatment regimen. In the end, 18 (7.4%) women opted for dilatation and curettage, including

Table 1
Number and percentage of side effects ($n = 242$)

Side effects	*n* (%)	Remarkable
Pelvic pain	174 (71.9)	Mean VAS 48 (10–88) mm
Nausea	77 (31.8)	Mean 3.6 (1–8) episodes
Fever	67 (27.7)	Mild, 3 patients ≥ 38 °C
Shivering	60 (24.8)	Mean 3 (1–20) min
Vomiting	36 (14.9)	Mean 2.2 (1–6) episodes
Headache	26 (10.8)	Mild
Diarrhea	24 (9.9)	Mild
Dizziness	19 (7.9)	Mild

VAS = visual analog scale.

nine (3.7%) due to an ongoing pregnancy, seven (2.9%) due to medical indications (incomplete abortion and hemorrhage), and two (0.8%) due to patient request. All the histopathological findings of the curettage specimens revealed the presence of retained products of conception without involvement of malignancy.

Adverse effects included abdominal pain in 174 (71.9%) women, nausea in 77 (31.8%), fever in 67 (27.7%), shivering in 60 (24.8%), vomiting in 36 (14.9%), headache in 26 (10.7%), diarrhea in 24 (9.9%), dizziness in 19 (7.9%), and the symptoms were mostly mild to moderate with the participants not requiring any medication except analgesia. The mean level of pain reported via the post-questionnaire was 48 mm (range, 10–80 mm). The mean number of episodes of vomiting was 2.2 (range, 1–6 episodes). Hemorrhage and pelvic infection were rare after treatment. No patient was found to have endometritis and only three (1.2%) patients had a temperature of 38.0 °C or greater but this was without any infectious sign. Two (0.8%) patients required some uterotonic medication (ergometrine) due to excessive vaginal bleeding and no one needed a blood transfusion. Table 1 provides details of the women's reports of the adverse effects experienced following vaginal misoprostol administration. Regarding how much patients agreed that the therapy they had received was performed to their satisfaction, the following answers were received: strongly agree by 181 women (75%), agree by 37 women (15%), neutral by 18 women (7%), disagree by 6 women (3%); which gives a satisfaction rate of 90% (218/242).

Discussion

To achieve a medical abortion, patients typically take misoprostol 36–48 hours after taking mifepristone. Clinical trials are currently underway to investigate variations in the dose, timing, and route of misoprostol when it is used in conjunction with mifepristone, the aim being to simplify follow-up procedures so that they are more convenient for the patient [4–6,14]. No previous studies have tested a 600 μg dose of vaginal misoprostol and 200 mg of oral mifepristone simultaneously in the first trimester. The result of our study indicated that when 600 μg misoprostol was administered vaginally concurrent with mifepristone, a 92.6% success rate for complete abortion at up to 49 days' gestation was demonstrated. The efficacy and adverse effects are consistent with those previously reported using other medical abortion protocols, and the approach achieved a high satisfaction rate of 90%. There was no need to hospitalize any individual because of the presence of hemorrhage or endometritis.

We used vaginal misoprostol in our study based on what we have learned from other medical abortion studies. When used in regimens for medical abortion after mifepristone treatment, vaginal misoprostol results in a higher rate of complete abortion than oral misoprostol, as well a more rapid rate of pregnancy expulsion [1]. The simultaneous use of mifepristone and misoprostol is able to shorten the amount of time necessary for a medical abortion, and has the potential to reduce patient anxiety. To the best of our knowledge, this protocol has not been attempted or reported before.

In 2005, Murthy and associates [11] reported that, in 40 women with pregnancies less than 7 gestational weeks who received oral mifepristone 200 mg and concurrent vaginal administration of misoprostol 800 μg, a complete abortion rate of 98% was achieved after 2 weeks, with only one woman requiring suction and curettage because of an incomplete abortion. Their conclusion was that the combined administration of mifepristone and misoprostol to pregnant women less than 7 gestational weeks is an efficacious way of achieving medical abortion.

Similarly, Schreiber and colleagues [12] tested 40 pregnant women in a 50–56 days' gestation (Group 1) and 40 pregnant women in a 57–63 days' gestation (Group 2) using oral mifepristone 200 mg and immediate vaginal administration of misoprostol 800 μg; these individuals underwent vaginal ultrasonography 24 hours and 2 weeks afterwards. They found that by the second week, the complete abortion success rates were 93% and 90% in Groups 1 and 2, respectively. They concluded that mifepristone and misoprostol are efficacious in women with pregnancies of 8–9 gestational weeks, whether administered concurrently or one after the other 36–48 hours later. However, these results are slightly unsatisfactory because, compared to the study of Murthy et al, Schreiber et al's study involved pregnant women at 50–56 days' gestation (8 weeks) and 57–63 days' gestation (9 weeks), compared to <49 days of gestation in Murthy et al's study.

In same way, Creinin and colleagues [13] minimized the dosing interval by simultaneously administering mifepristone

Table 2
Comparison of the side effects of clinical trials of mifepristone and vaginal misoprostol administered simultaneously for abortion

Authors	Dose of misoprostol (μg)	Cramping (%)	Nausea (%)	Fever/chills (%)	Dizziness (%)	Vomiting (%)	Headache (%)	Diarrhea (%)
Murthy et al [11]	800	100	60	55	53	25	18	–
Schreiber et al [12]	800	100	63	53	–	40	–	40
Creinin et al [13]	800	97	58	69	39	31	40	35
Present study	600	71.9	31.8	27.7	7.9	14.9	10.7	9.9

Table 3
Comparison of the clinical trials of mifepristone and vaginal misoprostol administered simultaneously for abortion

Authors	Patient number	Gestational day	Mifepristone dose (mg)	Misoprostol dose (μg)	Mean VAS score	Success rate (%)
Murthy et al [11]	40	≤49	200	800	5.7	98
Schreiber et al [12]	40	50−56	200	800	6.3	93
Schreiber et al [12]	40	57−63	200	800	6.1	90
Creinin et al [13]	554	≤63	200	800	6.4	95.1
Present study	254	≤49	200	600	4.8	95.3

VAS = visual analog scale.

200 mg orally and misoprostol 800 μg vaginally. In this study, 1,128 participants with an intrauterine pregnancy at 63 days of gestation ingested mifepristone 200 mg and then the subjects were randomized into groups. The first group was treated vaginally with misoprostol 800 μg immediately and the other group was treated orally with misoprostol 800 μg 24 hours later. They found this regimen to be as effective when compared to regimens using a 24-hour dosing interval; the complete abortion rates were 95.1% versus 96.9%, respectively. However, the benefit of mifepristone added to 800 μg of vaginal misoprostol when dosed in concert can be questioned because the high-abortion efficacy may potentially be solely due to the high-misoprostol dose.

In another study reported by Lohr et al [15], a pilot trial was performed with the primary objective of evaluating 24-hour expulsion rate after simultaneous administration of mifepristone 200 mg and buccal misoprostol 800 μg. This trial involved 120 women, with 40 women in each of the gestational age ranges of 49 days or less, 50−56 days, and 57−63 days of gestation. The expulsion rates were 73%, 69%, and 73% respectively. However, the women achieved relatively high-complete abortion rates at 2 weeks of 97.5%, 100%, and 94.9% respectively.

It should be noted that women who want to avoid surgery seem to value the option of a medical abortion and tend to be satisfied regardless of the regimen used. This was also true in our study in which 90% of subjects were satisfied with our method. In addition, the administration of misoprostol 600 μg vaginally in this study appears a trend of less frequently in all side effects without interfering with the efficacy of medical abortion for early pregnancy. The comparison of side effects of this study with previously published reports of administering oral mifepristone 200 mg and 800 μg misoprostol vaginally for medical abortion concurrently is listed in Table 2. And the comparison of baseline characteristics, methods and efficacy outcome of these reports are listed in Table 3.

The ultimate goal of our research is to improve the technique used for termination of early pregnancy. Guidelines for mifepristone medical abortion in the USA have widely recommended vaginal misoprostol based on the view that it is more effective and more acceptable [16]. Our hypothesis is that vaginal 600 μg will be sufficient and that a dose of 800 μg is not needed. In fact, if the lower dose has a similar efficacy, it would be unethical to continue using a dose that is unnecessarily high because this is likely to cause more side effects and increase the costs of the treatment [10]. Based on our results, simultaneous 200 mg mifepristone and 600 μg misoprostol vaginally, given its simplicity, and ease of administration, is recommended for further study as a treatment for medical abortion.

References

[1] El-Refaey H, Rajasekar D, Abdalla M, Calder L, Templeton A. Induction of abortion with mifepristone (RU486) and oral or vaginal misoprostol. N Eng J Med 1995;332:983−7.
[2] Peyron R, Aubeny E, Targosz V. Early termination of pregnancy with mifepristone (RU486) and the orally active prostaglandin misoprostol. N Engl J Med 1993;328:1509−13.
[3] Kahn JG, Beaker BJ, Maclsaa L. The efficacy of medical abortion: a meta-analysis. Contraception 2000;61:29−40.
[4] Lin HW, Chien TY, Jeng CJ, Chen SC, Chen HF, Hwang JL. Comparison of two doses of mifepristone in combination with misoprostol for early pregnancy termination. Taiwanese J Obstet Gynecol 2002;41:155−61.
[5] Mckinley C, Thong KJ, Baird DT. The effect of dose of mifepristone and gestation on the efficacy of medical abortion with mifepristone and misoprostol. Hum Reprod 1993;8:1502−5.
[6] Marions L. Mifepristone dose in the regimen with misoprostol for medical abortion. Contraception 2006;74:21−5.
[7] Zieman M, Fong SK, Benowitz NL, Banskter D, Darney PD. Absorption kinetics of misoprostol with oral or vaginal administration. Obstet Gynecol 1997;90:88−92.
[8] Fiala C, Gemzell-Danielsson K. Review of medical abortion using mifepristone in combination with prostaglandin analogue. Contraception 2006;74:66−86.
[9] Li YT, Chen FM, Chen TH, Li SC, Chen ML, Kuo TC. Concurrent use of mifepristone and misoprostol for early medical abortion. Taiwan J Obstet Gynecol 2006;45:325−8.
[10] Elul B, Ellertson C, Winikoff B. Side effects of mifepristone−misoprostol abortion versus surgical abortion: data from a trial in China, Cuba, and India. Contraception 1999;59:107−14.
[11] Murthy AS, Creinin MD, Harwood B, Schreiber C. A pilot study of mifepristone and misoprostol administered at the same time for abortion up to 49 days gestation. Contraception 2005;71:333−6.
[12] Schreiber CA, Creinin MD, Harwood B, Murthy AS. A pilot study of mifepristone and misoprostol administered at the same time for abortion in women with gestation from 50 to 63 days. Contraception 2005;71:447−50.
[13] Creinin MD, Schreiber CA, Bednarek P, Lintu H, Wagner MS, Meyn LA. Mifepristone and misoprostol administered simultaneously versus 24 hours apart for abortion. A randomized controlled trial. Obstet Gynecol 2007;109:885−94.
[14] von Hertzen H, Piaggio G, Wojdyla D. Two mifepristone doses and two intervals of misoprostol administration for termination of early pregnancy: a randomized factorial controlled equivalence trials. BJOG 2009; 116:381−9.
[15] Lohr PA, Reeves MF, Hayes JL. Oral mifepristone and buccal misoprostol administered simultaneously for abortion: a pilot study. Contraception 2007;76:215−20.
[16] American College of Obstetricians and Gynecologists Committee on Practice Bulletins—Gynecology. ACOG practice bulletin. Clinical management guidelines for obstetrician−gynecologists. Medical management of abortion. Obstet Gynecol 2001;97:1−13.