Is mifepristone 100mg an effective alternative to standard dose for medical abortion

Tıbbi abortus için 100 mg mifepriston standart doza etkili bir alternatif midir?

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Abstract

Objective: To study the efficacy of a low dose of mifepristone (100 mg) in combination with misoprostol, in women undergoing medical termination of pregnancy up to gestation of 49 days.

Material and Methods: A prospective study was performed in 50 women (mean age 26.54±3.68 years) with single intrauterine pregnancy of up to 49 days of gestation, presenting to our institution between November 2007 and October 2009. 100 mg mifepristone was given orally, followed 24 hours later by 400 micrograms misoprostol vaginally. Misoprostol 400 micrograms was repeated vaginally on the third day if indicated. The primary outcome of complete abortion rate and secondary outcomes of induction-abortion interval and adverse effects, especially bleeding, were assessed.

Results: Mean period of gestation was 38.74±3.90 days. None of the women expelled the products of conception before misoprostol insertion. A second dose of misoprostol was needed in four patients. Complete abortion was achieved in 94.00% of patients, incomplete abortion in 4% and missed abortion in 2%. Approximately all the women reported one or more adverse effects but none of them had any serious ones, the most common being pain in 42 (84%) women followed by nausea, vomiting, fever and diarrhoea in 12 (24%), 6 (12%), 4 (8%) and 3 (6%) women respectively. The overall acceptability rate of the dosing regimen in our study was 94%.

Conclusion: A regimen of low dose mifepristone (100 mg) followed 24 hours later by vaginal misoprostol can be safely and effectively used for early abortion. (J Turkish-German Gynecol Assoc 2010; 11: 204-7)

Key words: Mifepristone, misoprostol, medical abortion

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Özet

Amaç: Kırk dokuz güne kadar olan gebeliklerin sonlandırılmasında, düşük doz mifepriston (100 mg) ile misoprostol kombinasyonunun etkinliğini değerlendirmek.

Gereç ve Yöntemler: Kasım 2007 ve Ekim 2009 tarihleri arasında kurumumuza başvuran, en fazla 49 günlük intrauterin tek gebeliği olan 50 kadın ile (ortalama yaş 26,54±3,68 yıl) prospektif bir çalışma yapıldı. 100 mg mifepriston oral yolla verildi, 24 saat sonra bunu 400 μg vajinal misoprostol uygulaması izledi. Endike ise, 400 μg vajinal misoprostol uygulaması üçüncü gün tekrarlandı. Primer sonuç olarak tam düşük (komplet abortus) oranı, sekonder sonuçlar olarak indüksiyon-düşük aralığı ve advers etkiler -özellikle kanama- değerlendirildi.

Bulgular: Ortalama gebelik süresi 38,74±3,90 gündü. Kadınların hiçbirinde misoprostol yerleştirilmeden önce gebelik ürünü atılımı olmadı. Dört hastada ikinci doz misoprostole ihtiyaç duyuldu. Hastaların %94'ünde tam düşük, %4'ünde tam olmayan düşük (inkomplet abortus) ve %2'sinde atlanmış düşük (missed abortus) görüldü. Kadınların hemen hepsi bir veya daha fazla advers etki bildirdi fakat bunların hiçbiri ciddi değildi. En yaygın advers etki ağrı olup 42 kadında (%84) görüldü, bunu bulantı 12 (%24), kusma 6 (%12), ateş 4 (%8) ve diyare 3 (%6) izledi. Çalışmamızda doz rejiminin kabul edilebilirlik oranı %94'dü.

Sonuç: Düşük doz mifepristonu (100 mg) takiben 24 saat sonra uygulanan vajinal misoprostol rejimi erken düşük için güvenli ve etkili bir şekilde kullanılabilir.

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Anahtar kelimeler: Mifepriston, misoprostol, tıbbi abortus

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Introduction

An estimated 19 million unsafe abortions occur worldwide each year, resulting in the deaths of about 70,000 women (1). According to the World Health Organization (WHO), every 8 minutes a woman in a developing nation will die of complications arising from an unsafe abortion (2). Medical methods are a safe alternative, because their administration requires little training and has a simpler infrastructure compared to surgical procedures (3).

Mifepristone (RU 486) is an orally active, synthetic antiprogestogen that has been primarily used for the termination of pregnancy, usually in combination with a prostaglandin agent administered either simultaneously (4, 5) or at an interval of 4-6 (6), 6-8 (7), 24 (8), 48 (9),or even up to 72 hours (10). It binds to the glucocorticoid receptor (GR), and oral administration of the drug results in a compensatory, dose-dependent activation of the hypothalamic-pituitary-adrenal (HPA) axis (11). However, due to saturation of alpha 1-acid glycoprotein (AAG), the serum binding protein for RU 486, the serum levels remain similar within the dose range of 100- 800 mg of RU 486 (12) and similar efficacy is expected with 100 mg mifepristone in medical abortion regimens (13). On the other hand, the efficacy decreases with further lowering of the mifepristone dose to 50 mg (14).

The use of mifepristone for abortion in high doses is well established. The present study is an attempt to assess the efficacy of 100 mg of mifepristone, in combination with misopro-

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stol, in women undergoing medical termination of pregnancy up to a gestation time of 49 days.

Material and Methods

In this prospective observational study, we enrolled 59 women with up to 49 days of gestation and confirmed a single intrauterine pregnancy presenting at our institution for voluntary termination of pregnancy between November 2007 and October 2009.
Both surgical and medical methods of abortion together with their side effects and cost were explained to the patients. Only those patients who were willing to use the medical method, ready for the follow up schedule and agreed to have a surgical abortion if indicated were included in the study.
Women who conceived with an intrauterine contraceptive device (IUCD) in situ and had a history of more than two lower segment caesarean sections (because of uterine rupture risk) were excluded from the study. Other exclusion criteria were patients allergic to either mifepristone or misoprostol, chronic adrenal failure and patients on corticosteroids or anticoagulants. With this selection protocol, 50 women (mean age 26.54±3.68 years) were included in the study, as 6 women refused to participate and 3 women did not meet the inclusion criteria (two had asthma and were on corticosteroid and one had deep vein thrombosis and was on anticoagulants).
All women gave informed written consent and had a medical and gynaecological examination along with the assessment of haemoglobin level, and Rh-antigen status.
Transvaginal ultrasonography was performed to confirm the gestational age and if there was any discrepancy between the gestational age calculated from the last menstrual period (LMP) to that from ultrasonography, the ultrasonologically estimated age was used for further data analysis. The departmental ethical committee approved the study.
Women were instructed to take 100 mg mifepristone (one half tablet of mifepristone 200 mg, Cipla pharmaceuticals) orally on day 1, and to insert 400 micrograms misoprostol (two tablets of 200 micrograms misoprostol, Cipla pharmaceuticals) vaginally at home, 24 hours after taking mifepristone (Day 2). The women were asked to keep a record of the time of onset of bleeding, expulsion of products of conception and number of days of bleeding as well as adverse effects. No routine antibiotic prophylaxis was used.
The first follow up visit was scheduled for 24 hours after misoprostol insertion. At this visit, they were questioned regarding bleeding, expulsion of products of conception and the side effects. If there was no bleeding until 24 hours after administration of the first dose of misoprostol, they were asked to repeat 400 microgram misoprostol vaginally. The second follow-up visit was scheduled on day 14, or earlier if bleeding was excessive, and the women were questioned in detail about the side effects, especially excessive bleeding, abdominal cramps, headache, nausea, fever and dizziness. All women underwent transvaginal ultrasonography at this visit and if the gestational sac was still present, a surgical abortion was performed. If the woman's blood group was Rh-negative, she was also given Rh-immune globulin 50 μg intramuscularly.
The procedure was considered successful if complete expulsion of the products of conception occurred without the need for any surgical procedure. Failure of the procedure was classified as incomplete abortion, missed abortion, and continuing pregnancy and these women were managed with suction and evacuation.
Statistical analysis was done using SPSS software (version 16.0).

Results

The demographic profile of the study group is shown in Tables 1 and 2. The mean age of the women was 26.54±3.68 years. The mean parity was 1.38±0.94. The gestational age was set by the LMP and confirmed by ultrasonography in 43 women. In 7(14%), it was calculated by the ultrasound examination. The mean period of gestation was 38.74±3.90 days. Eighteen (36%) women had a previous history of abortions. Thirteen (26%) women had a history of previous LSCS, with 2 among them having a history of two caesareans.
Four women could be followed-up only by multiple telephone conversations until their three next menstrual cycles. The reported findings were consistent with complete expulsion and there were no signs of continuing pregnancy. These cases were thus included in the successful procedures.
None of the women expelled the products of conception before misoprostol insertion.
At the first follow up visit, four women had only minimal bleeding and they were asked to insert 400 micrograms misoprostol again at home. In the remaining 46 patients, onset of bleeding occurred at 4.90±1.26 hours. 45 women expelled the products

Table 1. Patient Characteristics

Parameter	Number of women	Percentage
Age group (years)		
≤20	2	4.00%
21-25	19	38.00%
26-30	20	40.00%
31-35	8	16.00%
36-40	1	2.00%
Parity		
0	11	22.00%
1	13	26.00%
2	23	46.00%
3	2	4.00%
4	1	2.00%
Previous Abortion	18	36.00%
Previous caesarean section	13	26.00%

Table 2. Distribution of women according to gestational age

Gestational age(days)	Number of women	Percentage (%)
29-35	4	8.00%
36-42	35	70.00%
42-49	11	22.00%

Table 3. Outcome of the regimen used for medical abortion

	Number of women	Percentage
Complete Abortion	47	94.00%
Incomplete Abortion	2	4.00%
Missed Abortion	1	2.00%
Continuing pregnancy	0	0

Table 4. Adverse effects of drugs used

	Number of women	Percentage
Intolerable abdominal pain	3	6.00%
Nausea	12	24.00%
Vomiting	6	12.00%
Fever	4	8.00%
Diarrhoea	3	6.00%
Dizziness	0	0

of conception within 24 hours after misoprostol insertion and suction aspiration had to be performed on day 6 for excessive bleeding in one patient. In this patient, there was a decline of haemoglobin level from 10.9 gm% to 10.0 gm%.

46 women came for a second follow up visit. Out of four women in whom a repeat dose of misoprostol was inserted, two were found to have had a complete abortion, one a missed and one an incomplete abortion. In the remaining 42 women, transvaginal sonography showed the uterine cavity to be empty. Four women were followed by telephone calls for their next three menstrual cycles. Their histories were suggestive of complete abortion. Success rate in our study was 94.00%. There were no continued pregnancies.

The induction-abortion interval in the whole study group was 8.17±1.08 hours. The mean number of days of bleeding was 9.04±2.38 days, with heavy bleeding on day 2, which then decreased steadily. Only one woman reported spotting up to the next menstrual cycle.

All the women tolerated the dose well,but almost all the women (98%) reported at least one adverse event during the study period. 42(84%) women complained of pain, of whom three reported pain of severe intensity.None of them required parenteral analgesics or reported to the hospital. Nausea, vomiting, fever and diarrhea were reported by 12(24%), 6(12%), 4(8%) and 3(6%) women respectively. Serious adverse events were not reported by any patient in our study. None of them had bleeding requiring blood transfusion and none had any signs of pelvic infection.

Despite the failures and adverse events, the majority (94%) of the women in our study reported that they were satisfied with the medical abortion and would like to utilize this method if needed in future (Table 3, 4).

Discussion

Termination of pregnancy has been practiced since antiquity and an estimated 42 million abortions are performed worldwide each year (2). For many years, termination of early pregnancy was done surgically with the risk of complications like incomplete abortion, uterine perforation, and haemorrhage etc. using vacuum aspiration. Currently, however, agents are available which can terminate pregnancy if administered orally, vaginally or parenterally, obviating the need for the surgical procedures, and thus reducing the complications associated with the procedure. Furthermore, the incidence of miscarriage and postpartum haemorrhage has been found to be significantly lower in the pregnancies following a medical abortion (15).

In September 2000, the U.S. Food and Drug Administration (FDA) approved mifepristone (also known as “RU-486”), the first drug specifically designed for use as a method of medical abortion. This drug, in conjunction with misoprostol (originally intended for use to prevent NSAID-induced gastric ulcers), has become established as one of the most effective means for terminating pregnancies (16).

FDA-approved regimen of mifepristone/misoprostol is mifepristone 600 mg orally followed 2 days later by 400 micrograms of misoprostol vaginally (16). Multicenter trials conducted by the WHO have shown the equivalent efficacy of 600 mg dose and 200 mg dose of mifepristone (17). Now trials are on which further lower the dose of mifepristone in order to decrease the cost and adverse effects.

The success rate in our study with a 100 mg dose was 94%, which is comparable to those seen in standard regimens with mifepristone 200mg i.e. 92-98% (8,9,17,18) and 600 mg i.e. 87-97% (19,20), demonstrating the potential efficacy of 100 mg mifepristone for medical abortion. Efficacy of low dose mifepristone was also reported by Jerbi et al (13).

von Hertzen et al, in a large multicentre trial, compared the efficacy of 100mg with 200mg mifepristone and the two intervals of misoprostol administration (800 μg vaginal) i.e. 24 vs 48 hours for medical abortion. They found them to be equally efficacious with the rate of complete abortion of 92.0% for women assigned 100 mg of mifepristone as compared to 93.2% for those assigned 200 mg, and 93.5% for 24-hour interval and 91.7% for the 48-hour interval (8). No studies to date have reported the efficacy of the regimen using 100 mg mifepristone along with 400 microgram vaginal misoprostol at an interval of 24 hours. A 24-hour interval is more convenient than 48-hours and, if found effective with the 100 mg dose, the regimen would be more acceptable and cheaper. This is especially important as the relatively high cost of mifepristone has limited its use as pre-treatment in some countries. Further, the lower dose i.e. 400 microgram of misoprostol has fewer side effects compared with higher doses (21).

The adverse effect profile was quite acceptable. None of the women in our study had reported any serious side effect or needed hospital admission. Schaff et al in their study reported the need for hospitalization in 2 women (0.1%) for treatment with intravenous antibiotics for pelvic infections (22). In another study by Creinin et al, 10 women (0.9%), were diagnosed with acute pelvic infection after the medical abortion but were treated as outpatients (23). None of the women in our study required blood transfusion, whereas Creinin et al. (23) and Ruangchainikhom et al. (24) had reported the need of blood transfusion in 0.4% and 3.2% women respectively. Even though this complication is uncommon, the risk of haemorrhage emphasizes the need for vigilance and ready access to medi-

cal care. There are also limitations to medical terminations, including a longer duration of bleeding, longer waiting period for completion and more office visits.

Congenital anomalies in continuing pregnancy are a concern. In our study, none of the patients had a continuing pregnancy. Creinin et al had found continuing pregnancy in 1% women after medical abortion with 100mg mifepristone and 400 μg oral misoprostol (25).

The acceptability rate of the present dosing regimen in our study has been 94%, which is comparable to other series where medical methods have been found to be acceptable by 91% (9) and 97% (26) women respectively. However, women who had previous surgical abortions were more satisfied with the medical abortion.

Although the small sample size is probably a limitation of our study, the efficacy of the regimen using 100 mg mifepristone along with 400 microgram vaginal misoprostol at an interval of 24 hours has not yet been reported by any other study. However, large randomized controlled trials are required from high volume centres in order to accept this regimen as the standard of care.

Conclusion

The present study demonstrated that the decrease in dose of mifepristone from the usual dose of 200mg to 100mg, when followed 24 hours later by 400 microgram misoprostol, can be safely carried in medical abortion regimens without loss of efficacy.

Conflict of interest

No conflict of interest is declared by authors.

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