CLINICAL STUDY

Is Mifepristone Needed for Second Trimester Termination of Pregnancy?

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Abstract

Objectives: To assess the safety, efficacy and the induction-abortion interval of combination of mifepristone/misoprostol for termination of pregnancy in the second trimester between 13 to 20 weeks gestation.

Materials and Methods: We performed a retrospective analysis of prospectively collected data among 70 healthy pregnant women aged 16 to 40-years, requesting second trimester termination of pregnancy. The research was conducted from August 2004 to January 2006 at All India Institute of Medical Sciences, New Delhi, India. Each woman received a single oral dose of mifepristone 200 mg on D_1 followed by 800 μg vaginal misoprostol, 36 to 48 hours later. Four to 6 hours after the last dose of misoprostol, 4 doses of 400 μg sublingual or vaginal misoprostol were given 3 hourly for a maximum of four doses. Statistical analysis was done using SAS software version 8.2.

Results: Of the 70 women, 1 aborted before administration of misoprostol. The median induction-abortion interval (IAI) was 6.33 hrs. The average duration of hospital stay was 16 hrs; dose of misoprostol required was 800 μg in 45 (64.28%) and 1200 μg in 17 (24.28%) women. Complete abortion rate was 91.42% after 15 hrs of initial misoprostol instillation. Side effects were mild, and 5 (7.14%) women required analgesia. The IAI had no correlation with parity (p=0.33), increasing gestation (p=0.5), and increasing age (p=0.7). Of the patients 48.6% opted for tubal ligation postabortion.

Discussion: The mifepristone/misoprostol regimen is a highly effective and safe regimen for second trimester nonsurgical termination of pregnancy; with a short induction abortion interval and hospital stay.

Keywords: mifepristone, misoprostol, second trimester termination of pregnancy

Özet

Mifepriston İkinci Trimester Gebeliklerini Sonlandırmada Gerekli midir?

Amaç: Mifepriston ve mizoprostol kombinasyonunun ikinci trimesterde 13.-20. gebelik haftasındaki gebelikleri sonlandırmadaki güvenliğini, etkinliğini ve indüksiyon-abort intervalini değerlendirmek.

Materyal ve Metot: Yaşları 16-40 arasında olan ve ikinci trimesterde gebeliğinin sonlandırılmasını isteyen 70 sağlıklı kadından elde edilen prospektif verilerle analiz yapıldı. Araştırma Ağustos 2004 ve Ocak 2006 tarihleri arasında Hindistan, Yeni Delhi, All India Tıbbi Bilimler Enstitüsü'nde gerçekleştirilmiştir. Her kadına 1. gün 200 mg tek oral doz mifepristonu takiben, 36-48 saat sonra 800 μg vajinal mizoprostol verilmiştir. Son doz mizoprostolden 4 ila 6 saat sonra en fazla 4 doz olacak şekilde 400 μg sublingual veya vajinal mizoprostol üçer saat arayla verildi. İstatistiksel analiz için SAS 8.2 versiyon yazılımı kullanıldı.

Sonuçlar: Takip edilen 70 kadından biri mizoprostol uygulamasına geçmeden abort yaptı. Medyan indüksiyon-abort intervali (IAI) 6.33 saat idi. Hastanede ortalama yatış süresi 16 saat; 45 kadında (%64.28) kullanılan mizoprostol 800 μg ve 17 kadında (%24.28) 1200 μg idi. İlk mizoprostol uygulamasından 15 saat sonra, toplam abort oranı %91.42 idi. Yan etkiler hafifti ve sadece 5 kadının (%7.14) analjezik ihtiyacı oldu. IAI'nin parite (p=0.33), gravidite (p=0.5), hasta yaşı (p=0.7) ile bir korelasyonu yoktu. Kadınların %48.6'sı abort sonrası tubal ligasyon yapılmasını talep etti.

Tartışma: İkinci trimesterde gebeliklerin cerrahi olmayan yolla sonlandırılmasında, mifepriston/mizoprostol kombinasyonu kısa indüksiyon-abort intervali ve hastanede kısa yatış süresi ile yüksek dereceli etkili ve güvenli bir rejimdir.

Anahtar sözcükler: mifepriston, mizoprostol, gebelik sonlandırması, ikinci trimester

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Introduction

Research to identify an ideal (safe, effective) method for termination of second trimester pregnancy is still ongoing. A number of medical and surgical methods have been tried in the past. Medical methods include drugs like prostaglandins (gemeprost, sulprostone, misoprostol), antiprogesterones (mifepristone), alone or in combination. Surgical methods are dilatation and evacuation, extraamniotic ethacridine lactate, intraamniotic saline, urea etc; hysterotomy if any of the above fails, or in case of excessive bleeding. The two most commonly used drugs for medical abortion are mifepristone and misoprostol. Mifepristone is an orally active progesterone antagonist; available as a 200 mg tablet. After pre-treatment with mifepristone, there is shortening of the induction-abortion interval, when used in combination with misoprostol.

Rarely, allergy has been reported. In case of failure, women should be counseled to resort to another method of termination, as congenital malformations have been reported. The goal of research is to identify safe, affordable and acceptable methods for termination of second trimester pregnancy. In this study, we have assessed the efficacy and safety of vaginal/sublingual misoprostol regimen after mifepristone priming in patients requesting second trimester pregnancy termination. We now report our experience in 70 such women.

Aims and objectives

The aim of this study has been to assess the safety and efficacy of the combination of mifepristone and misoprostol for termination of pregnancy in the second trimester between 13 to 20 weeks gestation. The main study outcomes were: efficacy i.e. effectiveness to induce complete abortion, induction to abortion interval, safety profile i.e. occurrence of side effects and acceptability of the treatment by the women.

Study design

Retrospective analysis of prospectively collected data.

Setting

Tertiary care teaching hospital, All India Institute of Medical Sciences, New Delhi, India.

Material and Methods

Seventy healthy pregnant women aged 16 to 40-years, over the age of legal consent and requesting second trimester termination of pregnancy were recruited, from August 2004 to January 2006 at All India Institute of Medical Sciences, New Delhi. Duration of pregnancy, corresponding to 13 to 20 weeks of amenorrhoea was calculated from the first day of last menstrual period, and verified with ultrasound. Each woman (n=70) received a single oral dose of mifepristone 200 mg on D_1 followed by 800 µg vaginal misoprostol, 36 to 48 hours later. Four to 6 hours after the last dose of misoprostol, 400 µg sublingual or vaginal misoprostol were given 3 hourly for a maximum of four doses. Successful outcome was measured in terms of complete abortion at 15 hours of the first dose of misoprostol administration. Vaginal misoprostol was moistened with normal saline before insertion in the posterior fornix. Side effects were observed at 1 hour and 3 hours after misoprostol administration. The side effects including nausea, vomiting, diarrhea, headache, dizziness, rash, shivering, fever and pain were recorded. Pain was measured by the NRS (0 to 10) scale and paracetamol was given to women as a request for analgesia. Blood pressure, pulse, temperature and frequency of uterine contractions were monitored every 3 hours. Paracetamol for pain relief and fever, injection chlorpheniramine for shivering and chills was used when required. Final outcome was assessed at 24 h and classified as complete, incomplete, missed abortion or continuing live pregnancy. If surgical abortion was performed according to the woman's wish, but was not clinically indicated, outcome was classified as undetermined. Treatment failure was defined as failure of abortion to take place within 15 hours of initial misoprostol instillation. The primary outcome measure, the induction-abortion interval was calculated from the time of administration of first dose of misoprostol to the time when fetus and placenta aborted, and further classified as interfetus interval (IFI) and interplacental interval or induction abortion interval (IPI/IAI). After abortion, the products of conception were examined to look for the completeness of abortion. If the placenta was found to be incomplete, suction evacuation or check curettage was performed or if fetus was not expelled, then prostaglandin gel or oxytocin infusion was used. Women were given a menstrual calendar to record the duration and amount of bleeding. Next visit was scheduled at D_{15} of the study unless women were still bleeding and required an unscheduled visit. At follow up, women were asked about their bleeding pattern, pain or fever. Hemoglobin was measured and a pelvic examination done to assess the uterine size. Pelvic ultrasonography was performed in case of any clinical suspicion of retained products. They were clearly informed about the purpose of the trial, the investigations that would be done, number of clinic visits and the alternative methods of pregnancy termination that might be required in case of failure. Exclusion criteria were multiple pregnancy, hemoglobin less than 9 g/dl, history of chronic liver disease, haemolytic or haemorrhagic disorder, diastolic blood pressure more than 90 mmHg or systolic blood pressure less than 90 mmHg, allergy to misoprostol and history of tendency to allergy, previous caesarean section or surgery on the uterus or cervix, IUCD *in situ*, anticoagulant and corticosteroid therapy, lactation (should not breastfeed on the day of abortion and one day thereafter), history of thromboembolism, suspected breast or genital neoplasm or any systemic illness that contraindicates the use of prostaglandins (mitral stenosis, sickle cell anemia, glaucoma). A written informed consent was taken. All patients were hospitalized at the time of administration of misoprostol. Height and weight were measured for all patients. Preliminary investigations included hemoglobin, blood group, ultrasonography for confirmation of length of amenorrhoea and dating. Rhesus negative women were given anti-Dimmunoglobulin on the first day of administration of misoprostol. All baseline characteristics of the subjects

recruited were calculated as described. Statistical analysis was done using SAS software version 8.2.

Results

A total of 100 women were screened; 70 eligible women who were to have a legal second trimester termination of pregnancy with gestation between 13 to 20 weeks were recruited. Baseline characteristics of women assessed were age, height, weight, gestational age (Table 1). Mean age was 28.27±4.6 years and mean gestational age at termination of pregnancy was 15.87±2.11 weeks. The ethnic groups included were Indoaryans (69) and Mongolians (1). Of the women, 50% had an education up to 5 years and 95% were housewives. Women with history of abortions were 26 (37.1%) and those using contraception prior to pregnancy and abortion were 31 (44.3%). The side effects were mild in 33 patients (47%) and fever was the commonest seen in 12 (17.1%) (Table 2). Analgesia (paracetamol) was required by 5 women (7.14%) and the maximum pain score was 2 (NRS scale) in 27 women (38.6%). The sequential data of the abortion process are shown in Table 3. The IFI was 5.91±4.26 h and IPI 6.33±4.15 h. The mean length of hospital stay was 16 hrs. Four women required check curettage (5.79%) and one required surgical evacuation (1.44%) (Table 4). The average number (median dose) of misoprostol tablets necessary for expulsion was 800 µg (4 tablets) in 45 women (64.28%), 1200 µg (6 tablets) in 17 (24.28%) and 1600 µg (8 tablets) in 8 (11.42%). (Table 5). Complete abortion rate was 91.42% (64/70); incomplete abortion requiring evacuation was 7.14% (5/70) and one patient had failure (0.7%) (1/70) i.e. continuing live pregnancy (Table 6). Her gestational age was 16 weeks. She finally aborted with extraamniotic ethacridine lactate instillation. Changes in hemoglobin levels before and after abortion were 107.9 and 99.39 g/L, respectively, and average duration of bleeding post abortion was 4.24 days (Table 7).

None of the patients in either group received any blood transfusion or came for any unscheduled visit. No relation was found between parity and IAI (p=0.28), advanced gestational age and IAI (p=0.28). Most popular method of contraception postabortion was female sterilisation in 48.6% (34/70). Acceptability forms were filled postabortion in both groups admitting knowledge of their experience of abortion and ex-

Table 1. Baseline characteristics of patients

	n=70
Age (years)	28.27±4.6
Gestational age (wks)	15.87±2.11
Height (cm)	148.46±6.68
Weight (kg)	47.19±7.25

Results are expressed as mean ±SD.

Table 2. Incidence of side effects after misoprostol administration

Side Effects	n=70
Nausea	2 (2.85%)
Vomiting	3 (4.3%)
Diarrhea	7 (10%)
Dizziness, fatigue	1 (1.42%)
Headache	3 (4.3%)
Shivering	5 (7.1%)
Fever (temp >38°C)	12 (17.1%)
Adverse event	0 (0%)
Total	33 (47%)

Results are expressed as number (%).

Table 3. Characteristics of the abortion process (Median hours from first dose of misoprostol to delivery of placenta and fetus)

Side Effects	n=70
Induction fetus interval (IFI) (hrs)	5.91±4.265
Induction placental interval (IPI) (hrs)	6.33±4.153
Total hours in hospital	16

Results are expressed as mean ±SD.

Table 4. Any other abortion procedure required

Abortion procedure	n=70
Check curettage	4 (5.79%)
Suction evacuation	1 (1.44%)

Table 5. Amount of misoprostol used (number of tablets)

Dose (No. of tablets)	n=70
800 µg (4 tabs)	45 (64.28%)
1200 µg (6 tabs)	17 (24.28%)
1600 µg (8 tabs)	8 (11.42%)
2000 µg (10 tabs)	0 (0%)
4000 µg (20 tabs)	0 (0%)

Results are expressed as number (%).

Table 6. Final outcome in relation to parity and gestation

Final outcome	n=70
Success (complete)	91.42% (64/70)
Incomplete	7.14% (5/70)
Failure	0.7% (1/70)

Results are expressed as % (number).

Table 7. Changes in hemoglobin (Hb) levels prior to and after abortion and duration of bleeding postabortion

	n=70
Hb preabortion (g/L)	107.09±14.6
Hb at follow up (g/L)	99.39±7.02
Duration of bleeding (days)	4.24±1.91

Results are expressed as mean ±SD.

Table 8. Previous studies comparing IAI and complete abortion rates

Year	First author	Study protocol	No.	Induction abortion interval	Complete abortion rate
1996	Jannet D	Mife 600 mg+400 μg vag miso 6 hrly till expulsion	106	12.5±7.5 h	97.16%
1999	Ashok PW	Mife 200 mg, 36-48 hrs later, 800 μg vag miso-400 μg miso orallyx4 doses	500	6.5 h	97%
2000	Ngai WS	Mife 200 mg Grp I vag miso (200 μg 3 hrly) Grp II oral miso (400 μg 3 hrly)	142	Oral 10.4 h Vag. 10 h	81.4% 75.4%
2001	Le Roux PA	Mife 600 mg Grp I 800 μg vag miso+400 μg 3 hrlyx4 doses Grp II 1 mg vag gemeprost 3 hrlyx5 doses	68	Grp I 8.9 h Grp II 19.8 h (p<0.01)	94% 68% (p=0.02)
2002	Bartley J	Mife 200 mg, 36-48 hrs later Grp I 1 mg vag gemeprost 6 hrlyx18 hrs Grp II 800 μg vag miso-400 μg oral miso 3 hrlyx12 hrs	100	Grp I 6.6 h Grp II 6.1 h (p=0.22)	96% 94% at 24 hrs
2004	Ashok PW	Mife 200 mg, 36-48 hrs later, 800 μg vag miso-3 hrs-400 μg oral misox4 doses	1002	6.25 h	97.1%
2005	Tang OS	Mife 200 mg, 36-48 hrs later, 400 mg subl. or oral misox5 doses	120	Sublingual 5.5 h Oral 7.5 h	91.4% 85%
2005	Hamoda H	Mife 200 mg, 36-48 hrs later, 600 mg subl. or 800 mg vaginal miso-400 mg subl. or vaginal misox4 doses	76		91.6% 97.5%
Our Study	Gupta N	Mife 200 mg, 36-48 hrs later, 800 μg vag miso-400 μg vag/subl. misox4 doses	70	6.33±4.15 h	91.42%

pectations about this method. Normal menses were reported in all patients, 4 to 6 weeks after the abortion.

Discussion

Mifepristone is a 19-nor-steroid antiprogesterone drug which competes with progesterone at the progesterone receptor level. It is rapidly absorbed orally in 30 min and reaches peak plasma concentration in 90 min. It also improves the therapeutic effectiveness of misoprostol by sensitizing the myometrium to the action of these drugs at the dose of 1 mg/kg. The interval between the administration of mifepristone and misoprostol (36 to 48 hrs) was based on previously published reports. When mifepristone had been used for second and third trimester termination of pregnancies in combination with gemeprost (vaginal) or sulprostone (IM/IV).

Misoprostol is a synthetic analogue of naturally occurring prostaglandin E_1 discovered at Searle in 1973. It can be administered by various routes (oral, vaginal, sublingual, and rectal) but the best method has been vaginal application in view of its effect on peak plasma concentration and uterine contractility. Side effects include pain due to uterine contractions; usually felt between 2-3 hours (range 5 minutes to 12 hours) of misoprostol administration. Diarrhea is dose related; other reported side effects include nausea, vomiting, headache, chills, fever, dizziness and rash (1). Misoprostol is less expensive than gemeprost, available as 200 μg tablet and has a half life of 90 min.

Hadded et al. (1990) used oral mifepristone 600 mg with sulprostone 0.1 mg/hr IV after 36 hrs in 20 patients with an average expulsion interval of 12 hrs (2). Pons et al. (1992) reported use of 400 mg mifepristone orally with sulprostone 500 μg IM after 48 hrs in 25 patients with IAI of 13.1 hrs (3). El Refaey et al. (1993) in a randomized prospective study on a group of 60 patients undergoing therapeutic abortion between 13 and 20 weeks' gestation, did not find a significant difference between the expulsion interval of patients receiving misoprostol orally, [400 μg every 3 hrs (maximum 3 doses)] and the group of patients receiving gemeprost [1 mg vaginal suppositories every 3 hrs (maximum 5 doses)].

Both groups received 600 mg mifepristone orally, 36 to 48 hrs earlier (4). Jannet D et al. (1996) evaluated the role of combination of mifepristone 600 mg orally with misoprostol 400 µg 6 hrly for termination of second trimester pregnancy in 106 women. The IAI was 12.5 hrs (5). Ashok PW et al. (1999) assessed the effectiveness of a regimen comprising mifepristone 200 mg orally followed by a combination of vaginal 800 µg then, oral 400 µg misoprostol 3 hrly for 4 doses for midtrimester termination of pregnancy in 500 women. The complete abortion rate was 97%; median dose of misoprostol required was 1200 µg, median IAI was 6.5 hrs and 9.4% required surgical evacuation (6). The results are comparable to our study. Ngai SW et al. (2000) reported a randomized comparison of vaginal (200 µg 3 hrly) and oral (400 µg 3 hrly) misoprostol when combined with mifepristone in termination of second trimester pregnancy in 142 patients and found that oral misoprostol was as effective as vaginal misoprostol. There was no significant difference in complete abortion rate/median IAI and % of women who aborted in 24 hrs (7). Le Roux et al. (2001) compared mifepristone/misoprostol to gemeprost for second trimester termination of pregnancy for fetal anomaly or death in 68 patients. The gemeprost group received 1 mg gemeprost vaginally 3 hrly to a maximum of 5 doses. The mifepristone/misoprostol group received 600 mg mifepristone orally followed by 800 µg vaginal misoprostol; then, 400 µg orally 3 hrly to a maximum of 4 oral doses. The mifepristone/misoprostol group had a lower IAI (median 8.9 hrs versus 19.8 hrs; $p<0.01$), and abortion was more successful than with the gemeprost group (94% vs 68%; $p=0.02$) (8). Bartley J et al. (2002) reported a randomized comparison of misoprostol and gemeprost in combination with mifepristone for induction of abortion in the second trimester of pregnancy in 100 women. Each woman received 200 mg mifepristone and 36-48 hrs later, either 1 mg vaginal gemeprost 6 hrly for 18 hrs, or 800 µg vaginal misoprostol followed by 400 µg oral misoprostol 3 hrly for 12 hrs. Median prostaglandin–abortion interval was comparable in both groups; gemeprost (6.6 hrs) and misoprostol (6.1 hrs) ($p=0.22$). The cumulative abortion rates at 24 hrs were 96% versus 94% respectively and surgical evacuation rates (12% and 10%) were similar (9).

Ashok PW et al. (2004) reported the effectiveness and safety of a combination of mifepristone and misoprostol in 1002 women requesting second trimester termination of pregnancy. Of the women 97% aborted successfully. Surgical evacuation was required in 81 (8.1%) women (10). Tang OS et al. (2005) showed that the IAI was shorter ($p=0.009$) when sublingual misoprostol (5.5 hrs) was used as compared to oral (7.5 hrs) misoprostol when combined with mifepristone for medical abortion at 12-20 weeks gestation in 120 women (11). Hamoda H et al. (2005) published a randomized trial of mifepristone 200 mg orally followed 36 to 48 hrs later, by misoprostol (600 µg sublingual or vaginal 800 µg) in 76 women undergoing second trimester termination of pregnancy at 13 to 20 weeks gestation. The study showed no significant difference in the surgical evacuation rates between the sublingual (8.3%) and vaginal (2.5%) groups (12). Misoprostol in combination with mifepristone, as used in our study and other mentioned studies, is a cheap and effective alternative to gemeprost. Table 8 highlights the IAI and complete abortion rates of previous studies. We did not include patients with previous uterine surgery, since its usefulness still needs to be confirmed by further randomized controlled trials.

In our study, using a combination of mifepristone/misoprostol, 91.42% aborted within 15 hrs of prostaglandin administration, which is comparable to previous studies. The results of our study show that mifepristone/misoprostol association was found to have good efficacy i.e. short induction abortion interval without increase in risk of complications.

The mifepristone/misoprostol regimen has demonstrated remarkable safety and efficacy with respect to induction abortion interval, hospital stay, the amount of misoprostol and analgesia required to complete abortion. The adverse effects were mild and dose dependent and there was only one treatment failure.

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