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CLINICAL ARTICLE

Dosing interval of 24 hours versus 48 hours between mifepristone and misoprostol administration for mid-trimester termination of pregnancy

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ABSTRACT

Objective: To compare the efficacy of a shorter interval (24 hours) between misoprostol and mifepristone administration with that of the conventional dosing interval (48 hours) for second-trimester termination of pregnancy (TOP). *Methods:* This was a prospective randomized, controlled, open-label study of 98 healthy women opting for mid-trimester TOP. The women were randomized to receive 200 mg mifepristone orally, followed 24 hours (Group 1) or 48 hours (Group 2) later by misoprostol (800 μg, then 400 μg every 3 hours). The primary outcome measure was the percentage of successful abortions within 24 hours. Secondary outcome measures were the induction-to-abortion interval (measured from misoprostol administration) and the frequencies of complications and adverse effects. *Results:* The rate of successful abortions was similar with the 24-hour and 48-hour dosing intervals (95.8% and 93.6%, respectively; $P = 0.38$). The mean induction-to-abortion interval was also comparable between the 2 groups (8.6 ± 4.1 hours versus 8.7 ± 3.9 hours; $P = 0.37$). Nulliparous women and women with a pregnancy duration of 16 weeks or more had a longer induction-to-abortion interval in both groups. *Conclusion:* The 24-hour dosing interval between misoprostol and mifepristone administration seems to be as effective as the 48-hour dosing interval for second trimester TOP.

Clinical Trial Registry India: CTRI/2011/05/001770.

1. Introduction

Terminations of pregnancy (TOP) in the second trimester represent 10–15% of all induced abortions worldwide and account for two-thirds of all major abortion-related complications [1]. During the last decade, induced abortion in the second trimester became safer with the advent of a combination of mifepristone and misoprostol.

Mifepristone increases the sensitivity of the myometrium to prostaglandins by 5 times, with the peak effect on uterine contractility and cervical ripening occurring 36–48 hours following its administration [2]. The use of mifepristone prior to misoprostol for induction of abortion shortens the induction-to-abortion interval and reduces the requirement of misoprostol [3,4]. Administration of misoprostol 36–48 hours after mifepristone has been recommended by the WHO [1] and the Royal College of Obstetricians and Gynecologists [5] for mid-trimester TOP.

Given that sensitization of the myometrium starts within 24 hours of mifepristone administration [2,6], researchers have conducted trials with simultaneous dosing and with shorter dosing intervals between the 2 drugs for mid-trimester TOP. A randomized study [7] compared a simultaneous dosing regimen with the conventional regimen (36–38 hours) and found the former to be less effective than the latter. In addition, 2 retrospective studies [8,9] and 2 randomized studies [10,11] have compared a shorter interval (1 day) between mifepristone and misoprostol administration for second-trimester TOP with the standard interval (2 days). The results were in favor of the short interval. However, none of these studies used the recommended dosage of misoprostol (initial dose 800 μg, followed by 400 μg every 3 hours). Therefore, research needs to be continued in search of the optimum dosing interval between the 2 drugs for maximum efficacy and the least inconvenience to patient and provider. The present study was a randomized, prospective, open-label trial to compare the efficacy of a short (24 hours) interval between mifepristone and misoprostol administration with the conventional (48 hours) interval using the standard recommended dosage of misoprostol for second-trimester TOP.

2. Materials and methods

The present study was conducted in the Department of Gynecology and Obstetrics, Nilratan Sircar Medical College and Hospital, Kolkata, West Bengal, India, from April 15, 2011, to January 14, 2013, following approval by the institutional ethics committee.

Women requesting a mid-trimester TOP (between 13 and 20 weeks of pregnancy) were screened for eligibility by interview, clinical examinations, and laboratory investigations including determination of the hemoglobin concentration and liver and renal function tests. Duration of pregnancy and viability of the fetus were confirmed by ultrasound

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scan. Healthy women who fulfilled the legal criteria for a TOP and had a singleton viable pregnancy of 13–20 weeks' duration were included. Exclusion criteria were hypersensitivity to mifepristone or misoprostol/prostaglandins and contraindications for the use of the 2 drugs, previous transmural uterine incision (cesarean delivery, myomectomy), hemoglobin level below 8 g/dL, and serious medical disease such as severe hypertension, uncontrolled diabetes, or renal and liver disease. Women who had clinical features indicative of an inevitable abortion were also excluded. All participants provided written informed consent.

The participants were stratified into 2 subgroups according to the duration of pregnancy (less than 16 weeks and 16 weeks or more). This ensured an even distribution of participants because pregnancy duration is 1 of 2 important variables (the other being parity) affecting the induction-to-abortion interval [12].

Using computer-generated randomization numbers and sealed envelopes, the patients from each subgroup were assigned to treatment with a shortened dosing interval (24 hours, Group 1) or with the conventional dosing interval (48 hours, Group 2). The participants were admitted to the study hospital for better adherence to the dosing schedule. Women in Group 1 received 200 mg of mifepristone (Mifeprin; Sun Pharmaceutical Industries, Mumbai, India) orally followed 24 hours later by 800 μg of misoprostol in the form of 4 vaginal tablets containing 200 μg of misoprostol (Zitotec; Sun Pharmaceutical Industries, Mumbai, India), followed by 400 μg misoprostol every 3 hours vaginally for a maximum of 4 doses. Women in Group 2 received 200 mg of mifepristone orally followed 48 hours later by misoprostol, with dosing and route of administration being similar to that in Group 1. With the onset of vaginal bleeding, misoprostol was administered by the oral route. Randomization, drug administration, and record-keeping were done by resident doctors who were not involved with the study.

Pulse, blood pressure, temperature, uterine contractions, and findings on pelvic examination were recorded every 4 hours. The products of conception were examined for completeness. Immediate surgical evacuation under anesthesia was indicated if excessive bleeding occurred (as judged by the attending resident), or if complete expulsion of the placenta did not occur within 24 hours of administration of the first dose of misoprostol. Within 24 hours of abortion, an ultrasound scan was performed. Visualization of placental or fetal parts within the cavity was a criterion for late evacuation. If the fetus, the placenta, or both were not expelled during the stipulated period, the woman underwent another medical, surgical, or combined method for TOP.

With the exception of women who opted for sterilization and those who had complications, all participants were discharged after 24 hours and advised to return for a follow-up visit after 6 weeks or earlier if necessary.

Adverse effects were recorded from the time of mifepristone administration until 24 hours after the abortion. Complications were recorded for 6 weeks.

The primary outcome measure was the rate of successful abortion, defined as complete expulsion without additional intervention within 24 hours of the first dose of misoprostol. Secondary outcome measures were the interval between induction and abortion (defined as the time elapsed between the first misoprostol dose and complete expulsion of the fetus and placenta) and the rates of adverse effects and complications. In addition, subgroup analyses according to the history of previous vaginal birth and the pregnancy duration were performed.

A previous study [13] of mifepristone followed by misoprostol after 36–48 hours showed a rate of successful abortion of 98%. Based on an assumption of no difference between standard and experimental treatment, the present study had to include 86 patients to be 90% certain that a 2-sided 90% confidence interval excluded a difference between the standard and experimental treatment groups of more than 10%. The calculation was based on the following formula: $n = 2 \times f(\alpha, \beta/2) \times \pi \times (100 - \pi)/d^2$, where π is the true rate of successful abortion in each treatment group and $f(\alpha, \beta) = [\Phi^{-1}(\alpha) + \Phi^{-1}(\beta)]^2$, with Φ^{-1} being the cumulative distribution function of a standardized normal deviate and α, β, and d being the significance level, power, and equivalence limit, respectively. To account for a default rate of 5%, 98 women were randomized.

The analysis was by intention-to-treat. Excel version 7 (Microsoft, Redmond, WA, USA) and MedCalc version 11 (MedCalc Software, Ostend, Belgium) were used for the statistical analyses. The *t*, χ^2, and Fisher exact tests were used as appropriate to compare variables. $P < 0.05$ was considered statistically significant.

3. Results

In total, 132 women who opted for a medical termination of pregnancy during the second trimester (13–20 weeks of pregnancy) were screened for eligibility (Fig. 1). Twenty-six women were ineligible and 8 women declined participation. The remaining 98 women were stratified into 2 subgroups according to their pregnancy duration; 70 had a pregnancy duration of 16 weeks or more and 18 had a pregnancy duration of less than 16 weeks. The women in each subgroup were randomly allocated to Group 1 (24-hour dosing interval) or Group 2 (48-hour dosing interval). Subsequently, 2 women in Group 1 and 1 woman in Group 2 declined participation. Therefore, 47 and 48 women in Groups 1 and 2, respectively, completed the study and their data were analyzed.

There were no significant differences between the 2 groups in terms of demographic and obstetric characteristics such as age, parity, incidence of previous vaginal birth, and previous abortion (Table 1). The 2 groups were also comparable in terms of pregnancy duration and pre-intervention hemoglobin concentration.

The fetal indications for TOP were a major fetal anomaly or a disease not compatible with survival or well-being, as diagnosed by standard prenatal tests. The 2 major non-fetal and legally acceptable indications for a termination in accordance with the Medical Termination of Pregnancy Rules in India were social and economic constraints and pregnancy resulting from contraceptive failure.

The primary outcome measure—incidence of successful abortion within 24 hours without any additional intervention—was more common in the group with the conventional dosing interval group (95.8%) than in the group with a 24-hour interval (93.6%) (Table 2). However, this difference did not reach statistical significance ($P = 0.38$).

Three (6.4%) women in the 24-hour group required surgical evacuation, compared with no women in the 48-hour group ($P = 0.1$). In the group with the 24-hour dosing interval, 2 (4.3%) women required immediate surgical evacuation because of excessive bleeding, and 1 (2.1%) woman required late evacuation following detection of retained products on the ultrasound scan. In the group with the 48-hour dosing interval, 2 (4.2%) women needed another intervention because the products of conception were not expelled within 24 hours. Incidentally, 3 of the 5 women requiring immediate surgical evacuation or another TOP intervention were nulliparous and all 5 had a pregnancy duration of 16 weeks or more.

The induction-to-abortion interval was similar between the 2 groups ($P = 0.37$) (Table 2). Moreover, there were no significant differences between the groups in the rates of complete abortion within 12 hours or less ($P = 0.7$), the average number of required misoprostol doses ($P = 0.7$), and the need for fewer than 3 doses of misoprostol ($P = 0.6$) (Table 2).

A subgroup analysis showed that medical abortions were significantly faster among parous women than among nulliparous women (Table 3); this was evident in both groups (Group 1, $P = 0.01$; Group 2, $P < 0.001$). Women with a pregnancy duration of 16 weeks or more had a longer induction-to-abortion interval than those with a shorter pregnancy duration (Table 3), but the difference was only significant in the group with the conventional dosing interval (Group 1, $P = 0.68$; Group 2, $P = 0.003$).

Major complications such as uterine perforation, cervical injury, or sepsis were not encountered in the present study. One woman in Group 1 needed a blood transfusion because her initial hemoglobin