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Contraception 82 (2010) 266–275

Contraception

Original research article

Comparison of two dose regimens of misoprostol for second-trimester pregnancy termination ☆

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Received 20 October 2009; revised 2 March 2010; accepted 3 March 2010

Abstract

Objective: The study was conducted to compare the efficacy of two different dose regimens of misoprostol administered vaginally in combination with mifepristone for second trimester termination of viable and non-viable pregnancies.

Design: Double-blind randomized controlled trial conducted at the University hospital in the Netherlands. One hundred seventy-six women between 14 and 24 weeks gestation with an intrauterine fetal death (n=31), congenital or genetic abnormalities of the fetus (n=116) or requesting a termination of pregnancy for psychosocial reasons (n=29) were studied.

Randomization was into one of two groups. Both groups ingested mifepristone 200 mg. Depending on the randomization group, this was followed by either 200 or 400 mcg misoprostol given vaginally beginning 36–48 h later at 4-h intervals (with a maximum of 10 administrations in 48 h) until the fetus was delivered. Randomization, administration of the medication and assessment of the outcome was performed independently from the investigators.

Main outcome measures were expulsion rate and the number of incomplete abortions warranting surgical evacuation of retained products of conception. Secondary outcome measures consisted of the time between the first administration of misoprostol to the delivery of the fetus, side-effects, blood loss, live births and changes in hemoglobin level.

Results: In the 200-mcg misoprostol group, 66% (57/86) had a complete expulsion of fetus and placenta compared to 73% (66/90) in the 400-mcg group (p=NS). The time between the first administration of misoprostol and delivery of the fetus was significantly longer in the misoprostol 200-mcg group: mean 11.6 h (range: 9.7–13.5 h) versus 9.3 h (range: 8.1–10.5 h) in the 400-mcg group (p=.042). No significant differences between the groups were found for frequency of side-effects like nausea, retching, vomiting, fever, headaches and diarrhea. Blood loss was similar in both groups with a mean of 337 mL in the 200 mcg misoprostol and 296 mL in the 400-mcg misoprostol group (p=NS). Of the women with a viable pregnancy at the beginning of the trial, 18.6% (13/70) in the 200 mcg misoprostol group delivered a live fetus compared to 22.8% (17/75) in the 400 mcg misoprostol group (p=NS).

Conclusions: Both regimens used in this trial proved to be equally effective for termination of both viable and non-viable pregnancies during the second trimester. The time between the first administration of misoprostol and delivery of the fetus was significantly longer in the 200-mcg group than in the 400-mcg group. This outcome may be used as the rationale for choosing a 400 mcg misoprostol regimen for termination of pregnancy during the second trimester.

Keywords: Termination of pregnancy; Second trimester; Misoprostol; Mifepristone; Medical abortion; Randomized controlled trial

1. Introduction

Since its introduction in the early 1990s, combination regimens of mifepristone and misoprostol have proven their efficacy for the termination of pregnancy, particularly during the first trimester [1]. However, the regimens and dosages used, of misoprostol in particular, were not based on proper dose-effect studies. As a result of the essentially non-

☆ Funding: The Mimis trial was funded by the Department of Obstetrics and Gynecology of the Academic Medical Center (AMC) Amsterdam. No external funding was received.

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doi:10.1016/j.contraception.2010.03.006

evidence-based introduction of this mode of termination of pregnancy, a wide variety of regimens has mushroomed.

In general, the intention of medical treatment is to achieve a maximum effect with the lowest possible dosage accompanied by a minimum of side-effects and risks to the patient involved. Regimen with mifepristone 200 mg, followed 36–48 h later by 800 mcg misoprostol as a "high" starting dose and misoprostol 400 mcg 3–4 h as repeat dose have shown good results concerning second-trimester complete abortion rates and time between the first misoprostol dose (induction) and delivery [2,3]. Still no randomized controlled trials (RCTs) are available comparing regimen with an 800, 600 and 400 mcg misoprostol starting dose (administered by identical routes) followed by identical treatment regimens of misoprostol. As all unanswered questions on mifepristone and misoprostol regimens cannot be addressed in one study, we chose to try to determine the better of two dosages of misoprostol in combination with mifepristone in terms of efficacy and side-effects.

As to decide on which regimens to compare, we took the following in consideration. Vaginal administration of misoprostol appears to be more effective than oral or sublingual administration [4–7]. The time to maximum serum levels after oral intake is 20–30 min falling steeply after 120 min. After vaginal application (posterior fornix), peak serum levels are reached after 60–90 min, declining slowly after 240 min. Peak concentration after oral ingestion is twice as high than after vaginal administration but plateaus are at a lower level [8–10]. It must be noted, however, that misoprostol plasma measurements are prone to large errors due to the very low concentrations in plasma and laborious assays. Side-effects of misoprostol are dose- and route-dependent [11]. The addition of mifepristone to misoprostol-only regimens reduces the induction to delivery time, reduces the incidence of retained products and reduces the total amount of misoprostol needed [8,12–14]. A dosing interval between mifepristone and misoprostol of more than 24 h seems to be more effective than simultaneous use [13].

We tested in a double-blind randomized trial, firstly, whether a reduction of dose of misoprostol of 400 to 200 mcg administered vaginally and repeated every 4 h, beginning 36–48 h after the administration of 200 mg mifepristone, increases the risk of retained products of conception. Secondly, we compared the time between the first administration of misoprostol and the delivery of the fetus, side-effects, need for other medication and blood loss. Although it has been some years since this trial was conceived, the essence of the problem, which is the optimal dose regimen to use, is still relevant today.

2. Material and methods

2.1. Participants

All women with gestational age between 14 and 24 weeks, confirmed by ultrasound, requesting termination of pregnancy, were asked to participate in the study. Women were excluded from the study if any of the following criteria were present: absence of informed consent, allergic reaction to mifepristone or misoprostol in the past, chronic adrenal gland insufficiency, kidney or liver problems, continuous use of corticosteroid medication, severe pulmonary disease, cardiovascular disease or glaucoma. Recruitment and follow-up took place between October 2000 and September 2004 at the Department of Obstetrics and Gynaecology of the Academic Medical Center of Amsterdam (AMC). Women not participating in the study were to be treated with Dilapam® hygroscopic cervical dilators and intravenous sulprostone, according to local standard practice at the time.

2.2. Interventions

The study was designed as a prospective double-blinded RCT, comparing to 200 to 400 mcg misoprostol given vaginally at 4-h intervals, starting 36–48 h after the oral administration of mifepristone 200 mg at a gestational age between 14 and 24 weeks. After counseling by the attending gynecologist and informed consent was obtained, women received a date and time for the ingestion of mifepristone and a date for admission to the ward to start misoprostol treatment. Before mifepristone was taken, blood was tested for blood group and irregular antibodies and the levels of hemoglobin and platelets. Thirty-six to 48 h after the observed oral ingestion of 200 mg mifepristone, the patient was admitted to the ward to start the administration of misoprostol.

The misoprostol trial medication was administered into the posterior fornix of the vagina by one of the senior nursing staff or the junior doctor responsible for the daily running of the ward. The content of the opaque trial medication applicator used for this was not visible and the amount of misoprostol given could not be determined accidentally. Misoprostol administration was repeated every 4 h until delivery of the fetus with a maximum of five administrations in 24 h. The same was repeated the following day if delivery did not occur. If retained products were suspected, the decision to evacuate the uterus was made at least 1 h after expulsion of the fetus or sooner if severe blood loss was present. Blood loss was measured by weighing sanitary pads and the use of a measuring jug.

On admission, the patient received an envelope with a questionnaire on side-effects and adverse events. This numbered questionnaire was confidential and only to be handed over to the ward secretary in a closed and sealed envelope at discharge. At discharge, blood sampling was repeated. Three to six months after discharge, a questionnaire concerning the duration of bleeding, time of return of the menstrual cycle and medical or surgical treatment received, was sent to all participants.

The women participating in the trial, the caretakers and the investigators were all blinded for the dose of misoprostol present in the applicators. The investigators were not