Pre-emptive effect of ibuprofen versus placebo on pain relief and success rates of medical abortion: a double-blind, randomized, controlled study

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Objective: To determine the efficacy of pre-emptive administration of the nonsteroidal anti-inflammatory drug (NSAID) ibuprofen vs. a placebo on pain relief during medical abortion and to evaluate whether NSAIDs interfere with the action of misoprostol.
Design: Prospective, double-blind, randomized, controlled study.
Setting: University-affiliated tertiary hospital.
Patient(s): Sixty-one women who underwent first-trimester termination of pregnancy.
Intervention(s): Patients received 600 mg mifepristone orally, followed by 400 μg oral misoprostol 2 days later. They were randomized to receive pre-emptively two tablets of 400 mg ibuprofen orally or a placebo, when taking the misoprostol. The patients completed a questionnaire about side effects and pain score and returned for an ultrasound follow-up examination 10–14 days after the medical abortion.
Main Outcome Measure(s): Significant pain, assessed by the need for additional analgesia, and failure rates, defined by a need for surgical intervention.
Result(s): Pre-emptive ibuprofen treatment was found to be more effective than a placebo in pain prevention, as determined by a significantly lower need for additional analgesia: 11 of 29 (38%) vs. 25 of 32 (78%), respectively. Treatment failure rate was not statistically different between the ibuprofen and placebo groups: 4 of 28 (14.2%) vs. 3 of 31 (9.7%), respectively. History of menstrual pain was predictive for the need of additional analgesia.
Conclusion(s): Pre-emptive use of ibuprofen had a statistically significant beneficial effect on the need for pain relief during a mifepristone and misoprostol regimen for medical abortion. Ibuprofen did not adversely affect the outcome of medical abortion.
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Key Words: Pain, medical abortion, ibuprofen, mifepristone, misoprostol, analgesics, pre-emptive, placebo

Mifepristone, a P antagonist, is currently the drug most widely used to induce medical abortion (1). Most protocols combine the use of 200–600 mg of oral mifepristone with misoprostol, a prostaglandin (PG) E_1 analogue, usually in an oral or buccal dose of 400 μg (1, 2). High efficacy rates are usually reported, with success rates of up to 97.5% (3). Pain is the most common side effect during medical abortion, mainly after PG administration, and is recognized as an important factor in women's decisions regarding whether to resort to surgical or medical abortion (4).

Penney (5), in a review concerning medical abortion, reported that approximately 75% of women need to use narcotic analgesics to obtain pain relief during early medical abortion with PG administration. Increasing gestation, young age, white race, and nulliparity were associated with increased need for analgesia (5, 6).

We have previously reported the results of a double-blind, randomized trial, in which ibuprofen and paracetamol were compared for pain relief during medical abortion using a mifepristone and misoprostol protocol (7). We found that ibuprofen was superior to paracetamol in pain reduction and also reduced the need for additional analgesia. In that study, analgesia was administered at the onset of pain. However, because pain and fear of it are described by many women as their greatest concerns regarding the medical abortion procedure (8), we chose to

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investigate a new protocol for pain relief whereby ibuprofen is administered pre-emptively at the same time as the misoprostol.

The use of pre-emptive analgesia may offer a means to reduce the pain experienced after a medical procedure. For instance, pre-emptive local anesthesia was shown in a randomized blinded trial to successfully lower pain levels 24 hours after laparoscopic surgery (9). Little has been reported to date regarding the use of pre-emptive analgesia for pain management during medical abortion (10). Weib (11) used an uncommon protocol of methotrexate combined with vaginal misoprostol. He found no difference in pain scores after pre-emptive administration of acetaminophen and codeine, ibuprofen, or placebo. No differences in maximal pain levels were also reported after the use of pre-emptive acetaminophen, alverine, or placebo, before a no longer used protocol combining mifepristone with a sulprostone injection (12). To date no studies have been reported regarding the use of pre-emptive analgesia during the most commonly implemented mifepristone and misoprostol protocol.

The aim of this study was to investigate the pre-emptive administration of analgesia to allow a less painful experience during medical abortion. Because pain score data are often difficult to compare, owing to little or no information about the distribution of error (13), we decided to use as our primary outcome variable the need for additional analgesia, because this could serve as a good proxy for significant pain experienced after taking misoprostol.

MATERIALS AND METHODS

In a randomized, placebo-controlled, double-blind trial we studied 61 women who chose to undergo a medical abortion. The study protocol was approved by our medical center's review board for human investigation.

The medical abortion regimen used was 600 mg mifepristone given orally (Mifegyne; Exelgyn) followed by an oral dose of 400 μg misoprostol after 36–48 hours (Cytotec; Searle), given under medical supervision for 6 hours in the hospital. The women were sent home between the treatments.

Study Group

The study group comprised women aged 18–45 who had chosen to undergo a medical abortion, with an ultrasound-documented intrauterine pregnancy of up to 7 weeks' gestation, after approval from the Ministry of Health's committee for termination of pregnancy. Women with chronic disease, renal insufficiency, or known allergy to misoprostol or non-steroidal anti-inflammatory drugs were excluded.

Study Process

The 61 women were randomized at the time of misoprostol administration into two treatment groups by providing a sealed envelope, using a computer-generated random list, with serial numbers from 1 to 61. One group received two tablets of ibuprofen 400 mg (Adex; Dexon), and the second group received two placebo tablets. The tablets of ibuprofen and the placebo were of the exact same size, shape, and color.

Information about the effect of the analgesics on pain and on the course of the medical abortion was prospectively gathered from three questionnaires, filled out by all women participating in the study. The first was a demographic questionnaire, and the second documented side effects after mifepristone. In the third questionnaire the women were asked to document the level of pain 1 and 2 hours after misoprostol ingestion, as well as the need for another analgesic and any side effects that they experienced during the 6 hours of hospital observation (e.g., fever, headache, vaginal bleeding, nausea, vomiting, diarrhea, dizziness, or shivering).

Pain was assessed using an 11-point numeric pain scale, from 0 (no pain) to 10 (the most severe pain). Time and need for another analgesic was also recorded by the nurses. The second-line analgesic was dipyrone (Drop Optalgin, 1 g; Teva), given at any time at patient request. Dipyrone or metamizole sodium is banned in more than 30 countries (including United States, Japan, Australia, and several of the European Union member nations) because of the associated risk of agranulocytosis.

The women returned for a follow-up by ultrasound examination after 10–14 days. Endometrial thickness >15 mm was considered a failure of the medical abortion, and these patients were referred for a surgical evacuation. Under any suspicion for retained products of gestation, women were invited for another follow-up after menstrual period and evaluated for the need for intervention (14).

Statistical Analysis

The groups were compared in frequency tables, using the appropriate statistical tests. Dichotomous variables were analyzed using the Pearson χ^2 test with linear step-up correction for multiple analyses. When asymptotics could not be assumed, Fisher's exact test was used. Student's t test was used for normally distributed metric variables, and numeric ones were analyzed with the Wilcoxon rank test. To adjust for interaction between independent variables and pain levels or demand for additional analgesia, a logistic regression model was used. Statistical significance was defined as a P value $<.05$.

RESULTS

Sixty-one women participated in the study. Twenty nine were randomized to receive ibuprofen at the time of misoprostol administration, and 32 received placebo pills. Four women did not fill out the questionnaires properly and therefore information about side effects and pain levels was not complete. Another woman did not report on menstrual pain. Information about the need for analgesia (recorded by the nurse at real time), demographics, and success of the treatment was taken from their medical files. Two women, one in each group, did not show up for follow-up, and data about the success of the abortion were not established. They were considered in our analysis as failure of the medical abortion.

There was no significant difference between the two groups regarding marital status, age, parity, religion,