Ibuprofen and paracetamol for pain relief during medical abortion: a double-blind randomized controlled study

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Objective: To determine the efficacy of a nonsteroidal anti-inflammatory drug vs. paracetamol in pain relief during medical abortion and to evaluate whether nonsteroidal anti-inflammatory drugs interfere with the action of misoprostol.
Design: A prospective double-blind controlled study.
Setting: University-affiliated tertiary hospital.
Patient(s): One hundred twenty women who underwent first-trimester termination of pregnancy.
Intervention(s): Patients received 600 mg mifepristone orally, followed by 400 μg of oral misoprostol 2 days later. They were randomized to receive ibuprofen or paracetamol when pain relief was necessary. Patients completed a questionnaire about side effects and pain score and returned for an ultrasound follow-up examination 10–14 days after medical abortion.
Main Outcome Measure(s): Success rates, as defined by no surgical intervention, and pain scores were assessed.
Result(s): Ibuprofen was found to be statistically significantly more effective for pain relief after medical abortion compared with paracetamol. There was no difference in the failure rate of medical abortion, and the frequency of surgical intervention was slightly higher in the group that received paracetamol (16.3% vs. 8.5%).
Conclusion(s): Ibuprofen was found to be more effective than paracetamol for pain reduction during medical abortion. A history of surgical or medical abortion was predictive for high pain scores. Despite its anti-prostaglandin effects, ibuprofen use did not interfere with the action of misoprostol. (Fertil Steril® 2009;91:1877–80. ©2009 by American Society for Reproductive Medicine.)

Key Words: Medical abortion, pain relief, nonsteroidal anti-inflammatory drugs

The use of medical abortion with the P antagonist mifepristone and the prostaglandin analogue misoprostol is rapidly expanding throughout the world (1). The most common side effect observed during this procedure is abdominal pain, which occurs with uterine contraction in response to misoprostol. Several studies that followed women who underwent medical abortion reported that many experienced severe pain, causing significant distress. For instance, three studies found on an 11-point numeric pain scale that the mean worst pain was 6.3, 6.4, and 6.1 during abortions induced with methotrexate and misoprostol (2, 3). Approximately 20% of the patients included in those studies reported pain scores of 9 or 10, indicating severe pain (2, 3). Moreover, the percentage of women who required the use of analgesics was in the range of 80%–100% in several studies (4, 5). Another study by Hamoda and Tempelton (6) found that among 4,343 women who underwent medical abortion, 3,139 (72%) asked for analgesia, among whom 3,054 (97%) used oral analgesia and 75 (2.4%) required narcotics. Predictors of severe pain were found to be low maternal age, low parity, anxiety, and dysmenorrhea (7).

Nonsteroidal anti-inflammatory drugs (NSAIDs) often were avoided in protocols studied for medical abortion because of concern over their potential inhibition of prostaglandin-induced uterine contractions. However, recent studies have not shown interference by ibuprofen on the action of methotrexate and misoprostol in medical abortions at up to 56 gestational days (8). Fiala and Gemzell-Danielsson (9) found that preventive use, and the use at the time of pain onset, of paracetamol or diclofenac sodium in second-trimester medical abortion that was induced by mifepristone and misoprostol did not attenuate the efficacy of the two drugs. In addition, there was no significant difference between the NSAIDs and the non-NSAIDs groups in the induction-to-abortion interval or in the total number of misoprostol doses needed.

Received November 1, 2007; revised and accepted January 22, 2008; published online March 21, 2008.
A.L. has nothing to disclose. R.M. has nothing to disclose. L.B.D. has nothing to disclose. M.S. has nothing to disclose. A.M.-Z. has nothing to disclose. D.S.S. has nothing to disclose.
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The American College of Obstetricians and Gynecologists' practice bulletin on the management of medical abortion (10) concluded that although NSAIDs inhibit the synthesis of new prostaglandins, they do not block the action of prostaglandin receptors, and therefore such agents should not inhibit the action of a prostaglandin used for medical abortion. A retrospective analysis of the use of ibuprofen in 416 women who received misoprostol after methotrexate for medical abortion of pregnancies at $\leq$56 days of gestation was presented at the 2005 American College of Obstetricians and Gynecologists' annual conference (8, 10). Those investigators concluded that the use of ibuprofen did not appear to interfere with the action of misoprostol to induce uterine contractions and pregnancy expulsion.

Pain is recognized as a common and significant problem during medical abortion. Yet very little is known about the optimal management of pain during medical abortion. This is especially true regarding the popular mifepristone–misoprostol protocol, because most of the studies have been conducted using the methotrexate–misoprostol protocol. We still do not know which analgesics are more effective and interfere least with the induction of medical abortion, nor do we know whether every woman should be offered analgesics, even before the onset of pain, or whether pain killers should routinely be given only to women with multiple predictors of severe pain.

The aim of our study was to evaluate the use of ibuprofen compared with paracetamol in early medical abortions induced by mifepristone and misoprostol.

MATERIALS AND METHODS

This was a prospective, double-blind, randomized controlled trial. The study protocol was approved by our medical center's review board for human investigation. The participants in this study were 120 women who chose to undergo a medical abortion. Inclusion criteria included agreeing to sign informed consent, age between 18 to 35 years, and gestational age of $\leq$7 weeks. Exclusion criteria were drug or alcohol abuse; abnormal blood tests; chronic disease; renal insufficiency; and known allergy to mifepristone, misoprostol, paracetamol, or NSAIDs. All women received approval from the Ministry of Health's committee for termination of pregnancy after an intrauterine pregnancy was demonstrated by an ultrasound exam.

The women received mifepristone (600 mg orally; Mifegyne; Exelgyn SA, Paris, France), went home, and returned 36–48 hours later to receive misoprostol (400 μg orally; Cytotec; Searle, for High Wycombe, Bucks, United Kingdom). Ten to 14 days later, they returned for follow-up by ultrasound examination. Endometrial thickness of >15 mm was considered to be a failure of medical abortion, and the patient was referred for surgical evacuation (11, 12).

We randomized the 120 women into two treatment groups by providing a sealed envelope by using a computer-generated random list that included serial numbers from 1 to 120. The envelope was given by the nurse at the time at which the patient received the misoprostol tablets. Each envelope contained four tablets of either paracetamol (500 mg; Acamol; Teva, Petah-Tikva, Israel) or ibuprofen (400 mg; Adex, Dexon, Israel). The ibuprofen and paracetamol tablets were identical in size, color, and shape. In addition, the women were asked to complete three questionnaires: one with demographic details; a second to allow documentation of the onset of pain; and a third that assessed pain by using a numeric pain score, both immediately after ingesting the misoprostol tablets and 1 hour after taking the analgesic tablets contained in their sealed envelopes. We used an 11-point numeric pain scale, from 0 (no pain) to 10 (most severe pain). In addition, the women were asked to fill out a scale about pain that was experienced after mifepristone, to evaluate a possible need for analgesia at this stage of medical abortion. The third questionnaire was about other side effects (nausea, vomiting, fever, diarrhea, dizziness, vaginal bleeding) that were experienced during medical abortion.

The women were instructed to report to the nurse once they felt pain after receiving misoprostol. The time of onset of pain was recorded. The women then marked their pain score and took the analgesic pills from their envelopes. Once the patients felt relief from the pain, they filled out the second pain scale. If there was no pain relief, the women received a second line of oral analgesia from the nurse, which was two tablets of dipyrone (500 mg; Optalgin, Teva).

After 10–14 days, the women returned for follow-up by ultrasound examination. If the pregnancy sac remained in the uterus, the woman underwent a dilation and curettage. When there was a sonographic suspicion of residual pregnancy tissue, the patient was invited for further evaluation after her next menstruation. If there still was suspicion of retained products of gestation, the woman underwent a diagnostic hysteroscopy, and any remaining tissue was removed by hysteroscopy. The data about success of medical abortion and the frequency of surgical intervention were recorded.

Statistical Analysis

Power analysis A power analysis showed that assuming a baseline pain relief rate of 65% in the paracetamol group and expecting an increase in pain relief to 85% in the ibuprofen group at a significance level (α) of 0.05 and a power (β) of 0.80, 57 patients needed to be included in each group.

Statistical tests Fisher's exact test was used to analyze nominal variables in the form of frequency tables. Normally distributed (Kolmogorov-Smirnov test with Lilliefors correction) metric variables were tested by using the *t*-test for independent samples, whereas nonnormally distributed metric variables were analyzed with the Mann-Whitney *U* test. All tests were two-tailed. In addition, a stepwise linear multiple regression was performed to analyze the interaction between the final pain score and the independent variables such as abortion in the past, pain score before the analgesia, and the use of ibuprofen.

TABLE 1

Mean pain scores before and after analgesia in women randomly receiving paracetamol or ibuprofen for pain relief during medical abortion.

Parameter	Paracetamol (n = 49)	Ibuprofen (n = 59)	*P* value
Time (h) of pain appearance after misoprostol	1.05 ± 1.08	0.87 ± 0.9	.35
Mean pain score before the analgesics	8.35 ± 1.59	8.2 ± 1.72	.65
Mean pain score after analgesics	5.67 ± 1.93	3.41 ± 2.0	<.0001
Mean difference in decrease in pain score	2.67 ± 1.39	4.8 ± 1.47	<.0001

Note: Data are mean ± SD.

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RESULTS

A total of 120 women were recruited to the study. Eight of them completed the questionnaires but did not use any analgesia. Four women did not properly fill out the questionnaires and were excluded from the study. At completion of the study, the group that received paracetamol included 49 women, and the group that received ibuprofen included 59 women. There were no significant differences between the two groups with respect to age, gestational age, abortion or pregnancy in the past, socioeconomic status, and religion. Side effects that were reported by the patients included headache (25%), dizziness (32%), nausea (64.7%), vomiting (22%), chills (27.4%), and fever (3.8%). There also were no significant differences between the two groups with respect to the side effects experienced during the process of medical abortion. The majority of women (118 of 120) complained about abdominal pain after receiving misoprostol. A pain score of ≥7 was reported by 96 of them (80%).

There was no significant difference in mean pain score after misoprostol and no significant difference in the time of onset of pain (Table 1). However, there was a significant difference between the two groups in mean pain scores after the analgesia ($P<.0001$). The group that received ibuprofen achieved greater reduction in pain, 4.8 points, compared with a reduction of only 2.7 points in the group that received paracetamol (Fig. 1). In addition, the number of women who asked for second-line analgesia (dipyrone) was significantly higher ($P=.005$) in the group that received paracetamol compared with in the group receiving ibuprofen, 13 (26.5%) vs. 4 (6.2%).

The final pain score was analyzed by using a stepwise linear regression model that included the patient's age, gestational age, socioeconomic status, pain score before analgesia, side effects other than abdominal pain, previous abortion, and the use of ibuprofen. We found that the pain score after analgesia was significantly and directly affected by the pain score before the analgesia and by a previous abortion and was affected inversely by ibuprofen (Table 2).

As for the outcome of medical abortion, the success rate was high in both groups, with a predominance in the group that received ibuprofen, 54 (91.5%) successful cases, vs. 41 (83.7%) successful cases in women who received paracetamol. There was a higher rate of surgical intervention in the group that received paracetamol than in the group that received ibuprofen, 8 (16.3%) vs. 5 (8.5%). However, this difference was not statistically significant ($P=.21$).

DISCUSSION

The majority of women participating in this study had severe abdominal pain after ingesting misoprostol. The mean pain score was about 8 on a scale of 0 to 10. These data show that abdominal pain during medical abortion was a serious issue for women undergoing this procedure.

Our data clearly show that the pain can be effectively managed by administering NSAIDs, such as ibuprofen. These drugs, which previously have been avoided in many protocols for medical abortion, were proven in this study to be significantly more effective for pain reduction compared with

FIGURE 1

Comparison of pain reduction after receiving paracetamol vs. ibuprofen, in women undergoing medical abortion.

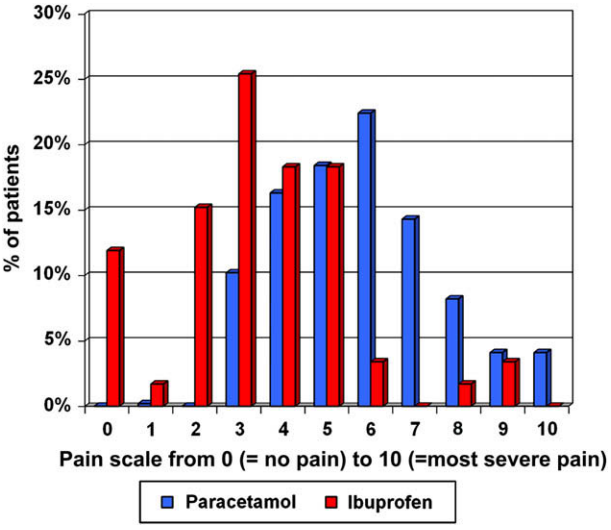

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TABLE 2

Results of a stepwise linear regression of variables that could influence the pain score after analgesia, including pain before treatment, previous abortion, and use of ibuprofen.

Variables that influence the pain score after analgesics	Parameter estimate	SE	Pr < |t|
Constant	−1.86	0.73	.0128
Pain score before analgesics	0.88	0.08	<.0001
Previous abortion	0.916	0.36	.0121
Ibuprofen	−2.06	0.27	<.0001

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paracetamol. To strengthen this conclusion, significantly more women in the group who received paracetamol asked for a second-line analgesic. Not only was ibuprofen better than paracetamol, but the degree of pain reduction itself was higher: 4.8 points (Fig. 1, Table 1). No woman in the study needed stronger analgesics, such as opiates. There was no decrease in the incidence of other side effects of misoprostol in the group that received ibuprofen, compared with the case of paracetamol.

We examined whether there were other factors besides ibuprofen that significantly influenced the pain score. In the study of Abdel-Aziz et al. (13), young, nulliparous women with gestational age of between 56 and 63 days were likely to experience more pain during medical abortion. In our study, using a stepwise linear regression, we found that women who had higher pain scores immediately after ingesting misoprostol had increased pain intensity, no matter which analgesic they received. Another factor that was associated with lower effectiveness of pain reduction in both groups was a previous abortion, regardless of whether it was a surgical or a medical abortion. The patient's age, gestational age, socioeconomic status, and side effects other than abdominal pain were not found to be related to the severity of the pain score.

The concern that existed in the past regarding the use of NSAIDs in the protocol of medical abortion, stemming from the possible inhibition of misoprostol by the NSAIDs, was not confirmed by our results. In the study of Li et al. (14), co-treatment with NSAID and misoprostol did not attenuate the efficacy of the cervical ripening effect of misoprostol. In our study, the use of NSAIDs did not adversely affect the action of misoprostol. Furthermore, the frequency of surgical intervention was found to be lower in the group that received ibuprofen. It should be noted, however, that this difference did not reach statistical significance, probably because of the size of our study groups.

We also examined the need for analgesia after administering mifepristone (data not shown). We found that few women reported abdominal pain after ingesting mifepristone. Those who did reported a low pain score (3–5), which occurred only several hours (10–24 h) after receiving mifepristone. Therefore, the pain may not be directly related to the drug, and we do not see a need to routinely administer analgesics after mifepristone.

In conclusion, we found that ibuprofen is highly effective in reducing pain during medical abortion. The efficacy was apparent not only in comparison to paracetamol but also in the reduction of the pain score after ibuprofen was administered. We also found that a previous abortion was a significant predictor for a high pain score. In addition, we observed that the use of the NSAID ibuprofen neither interferes with the action of misoprostol nor increases the rate of surgical intervention.

REFERENCES

1. Fiala C, Gemzel-Danielsson K. Review of medical abortion using mifepristone in combination with a prostaglandin analogue. Contraception 2006;74:66–86.
2. Weibe ER. Choosing between surgical abortions and medical abortion induced with methotrexate and misoprostol. Contraception 1997;55:67–71.
3. Wiebe ER. Comparing abortion induced with methotrexate and misoprostol to methotrexate alone. Contraception 1999;59:7–10.
4. Gemzell Danielsson K, Ostlund E. Termination of second trimester pregnancy with Mifepristone and gemeprost. The clinical experience of 197 consecutive cases. Acta Obstet Gynecol Scand 2000;79:702–6.
5. Aschok PW, Templeton A, Wagaarachchi PT, Flett GM. Mid trimester medical termination of pregnancy: a review of 1002 consecutive cases. Contraception 2004;69:51–8.
6. Hamoda H, Tempelton A. Analgesia requirements and predictors of analgesia use for women undergoing medical abortion up to 22 weeks of gestation. Br J Obstet Gynecol 2004;111:996–1000.
7. Wiebe E. Pain control in medical abortion. Int J Gynaecol Obstet 2001;74:275–80.
8. Creinin MD, Shulman T. Effect of non steroidal anti-inflammatory drugs on the action of misoprostol in a regimen for early abortion. Contraception 1997;56:165–8.
9. Fiala C, Gemzell-Danielsson K. The effect of non steroidal anti-inflammatory drugs on medical abortions with mifepristone and misoprostol at 13-22 weeks of gestation. Hum Reprod 2005;20:3072–7.
10. American College of Obstetricians and Gynecologists. ACOG practice bulletin. Clinical management guidelines of obstetrician-gynecologists. Number 67, October 2005. Medical management of abortion. Obstet Gynecol 2005;106:871–2.
11. Machtinger R, Seidman DS, Goldenberg M, Stockheim D, Schiff E, Shulman A. Transvaginal ultrasound and operative hysteroscopy in women undergoing medical termination of pregnancy as a part of routine follow-up. Fertil Steril 2005;84:1536–8.
12. Machtinger R, Seidman DS. Medical termination of pregnancy with mifepristone—initial experience at the Sheba Medical Center. Harefuah 2003;142:666–8.
13. Abdel-Aziz E, Hassan I, Al-Taher HM. Assessment of pain associated with medical abortion. Int J Gynecol Obstet 2004;84:264–5.
14. Li CF, Wong CY, Chan CP, Ho PC. A study of co-treatment of nonsteroidal anti-inflammatory drugs (NSAIDs) with misoprostol for cervical priming before suction termination of first trimester pregnancy. Contraception 2003;67:101–5.