The efficacy of ibuprofen lysine on first-trimester abortion-related pain and hemorrhage: A randomized triple-blinded clinical trial

ABSTRACT

Background: High efficacy of nonsteroidal anti-inflammatory drugs (NSAIDs) in relieving medical abortion-related pain has been pointed in some recent trials. The aim of this study was to determine the beneficial effect of oral NSAIDs (ibuprofen lysine) in reduction of pain and hemorrhage in first-trimester medical abortion.

Methods: This randomized triple-blinded clinical trial was performed on 98 pregnant women who were candidate for medical abortion within first-trimester period (gestational age less than 12 weeks). The patients were randomly assigned to receive ibuprofen lysine (684mg orally every 4 hours) or placebo. All patients were initially treated with misoprostol (800µg every 3 hours). The pain intensity and rate of hemorrhage were assessed every one hour up to 15 hours after receiving the first dose of misoprostol.

Results: Assessing the mean pain score within 15 hours of receiving misoprostol showed significantly lower pain intensity within the first 10 hours of assessment in the group receiving NSAID as compared to the control group. As indicated in Figure 2, the rate of bleeding was also significantly lower in NSAID group at fifth and ninth hours of receiving misoprostol when compared to control group. We showed no difference in abortion-related complication rate between NSAID group and placebo (8.3% versus 8.0%, p = 0.952).

Conclusion: The use of NSAIDs (ibuprofen lysine) is a good pharmacological analgesic option for relieving medical abortion-related pain and hemorrhage

INTRODUCTION

Induction of abortion is common in pregnant women for medical reasons of the mother or fetus; however this phenomenon may be accompanied with some major complications including pain, bleeding, infection, and even septic shock (1). Abortion in the first trimester is associated with moderate pain, however such pain may be more severe especially with increasing gestational age (2,3). Various painkillers are used to relieve post-abortion pain, the most important of which are opioids. Although opioids are very effective in controlling abortion-related pain, due to their side effects such as drowsiness, nausea and vomiting, ileus, constipation, respiratory suppression, central nervous system inhibition and even addiction, the clinicians aimed to identify other analgesic medications with acceptable efficacy along with higher safety (4). Optimal pain management for outpatient abortion surgery has not been established. Recently, oral and intravenous nonsteroidal anti-inflammatory drugs (NSAIDs) have been used successfully (5). NSAIDs can effectively inhibit the biosynthesis of prostaglandins through blocking some especial enzymes including cyclooxygenase enzymes (COX-1 or COX-2) (6). However some evidences proposed pain relieving effect of NSAIDs unrelated to its inhibitive effects on prostaglandins synthesis. In this regard, it has been shown that interference with G-protein-mediated signal transduction by NSAIDs may form the basis of an analgesic mechanism unrelated to inhibition of prostaglandin synthesis (7). Despite high efficacy of NSAIDs in relieving induced abortion-related pain reported from some observations, a few interventional studies have been conducted to demonstrate its analgesic effects as well as its safety in patients who are candidate for induced abortion. The aim of this study was to determine the beneficial effect of oral NSAIDs (ibuprofen lysine) in reduction of pain in first-trimester medical abortion.

MATERIALS AND METHODS

Study population

This randomized triple-blinded clinical trial was performed on pregnant women who were candidate for medical abortion within first-trimester period (gestational age less than 12 weeks) referred to Ayatollah Mousavi Hospital in Zanjan in 2018. All subjects aged 18 to 40 years satisfied with the inclusion of the study. All patients had one of the indications for medical abortion including blighted ovum or missed abortion based on the gynecologist recommendation. Those with the history of drug allergy to NSAIDs, history of gastrointestinal problems or coagulation problems and patients with underlying chronic diseases such as cardiovascular, pulmonary, renal, or rheumatic diseases were all excluded from the study. Hypertensive and diabetic patients were also not included into the present trial. Before the study, patients were asked to complete and sign the informed consent form if they wished to participate in this study. After enrolling patients, demographic information including age, history of underlying diseases such as diabetes, hypertension, heart disease, smoking, history of gestational diseases including gestational diabetes, gestational hypertension and previous history of miscarriage were asked and recorded into the checklist.

Study interventions

All patients were initially treated with misoprostol (800µg every 3 hours). The patients were then categorized into two groups using the Balanced Block Randomization as the intervention group receiving ibuprofen lysine (684mg orally every 4 hours) or the control group receiving placebo with same shape and size as ibuprofen lysine tablets. Random selection was performed by a physician who was unaware of the study process and did not intervene in any of the study stages. Patients were also completely unaware of the study process, however before the intervention, the method of drug administration and the probable side effects of the drugs such as gastrointestinal bleeding, peptic ulcer, and coagulation disorders were explained for the candidate patients. In the data analysis stage, the analysis was performed by the project consultant and the project manager who were not aware of the contents of the drug packages and thus the trial was triple-blinded. The present study entered the implementation stage after the approval of the Vice Chancellor for Research of Zanjan University of Medical Sciences and the approval of the Regional Ethics Committee.

Study assessments

The patients were monitored by a single gynecologist during the treatment period every one hour. Before intervention, the level of pain was assessed every one hour up to 15 hours after receiving the first dose of misoprostol using the Visual Analogue Scaling (VAS) method that scored the pain from 0 (without any pain) to 10 (the most severe pain expected). The patient's bleeding rate were assessed every one hour up to 15 hours after receiving the first dose of misoprostol and recorded based on Pictorial Blood Loss Assessment Chart (PBAC) method. In this method, the number of tampons or towels used and the degree to which they are stained with blood were recorded. In PBAC, the patient receives a score of 5, 1, 0 and 20 based on the amount of bleeding, and at the end, according to the number of sanitary pads used, the total score was determined and the severity of bleeding is estimated. Blood pressure was measured by a digital sphygmomanometer with a Novin S100 monitor while lying on the right arm. The heart rate and respiratory rate were also determined by Novin S100 monitoring system. Body mass index was measured by dividing weight by height squared. Patients monitoring was continued for up to 6 hours after delivery of pregnancy products and lasted up to 15 hours. In case of non-excretion of pregnancy products within 15 hours from the beginning of the initial intervention for abortion, the patient was excluded from the study. The primary endpoint was to assess the pain intensity before and after medication in the intervention and placebo group. The secondary endpoint was also to assess and compare time to start analgesia after drug treatment, the prevalence rate of interventions-related complications such as hemodynamic instability, postoperative nausea and vomiting or loss of consciousness, the rate for requiring emergency surgery, and bleeding rate.

Statistical analysis

For statistical analysis, results were presented as mean ± standard deviation (SD) for quantitative variables and were summarized by frequency (percentage) for categorical variables. Continuous variables were compared using t test or Mann-Whitney test whenever the data did not appear to have normal distribution or when the assumption of equal variances was violated across the study groups. Categorical variables were, on the other hand, compared using chi-square test. For the statistical analysis, the statistical software SPSS version 23.0 for windows (IBM, Armonk, New York) was used.

RESULTS

In total, 98 women candidate for medical abortion were stratified into two interventional (n = 48) and placebo (n = 50) groups. As shown in Table 1 and with regard to baseline characteristics no difference was revealed between the two groups in average age, mean body mass index (BMI), mean gestational age, type of abortion (Blighted Ovum, missed abortion, legal abortion), history of abortion or gravid.

Assessing the mean pain score within 15 hours of receiving misoprostol (Figure 1) showed significantly lower pain intensity within the first 10 hours of assessment in the group receiving NSAID as compared to the control group. As indicated in Figure 2, the rate of bleeding was also significantly lower in NSAID group at fifth and ninth hours of receiving misoprostol when compared to control group.

We showed no difference in abortion-related complication rate between NSAID group and placebo (8.3% versus 8.0%, p = 0.952).

Tables 2 to 4 summarize the impact of baseline factors (patient’s age, BMI and history of abortion) on pain severity in the two groups receiving NSAID and placebo. In this regard, we showed first that in the group receiving NSAID, obese women experienced more pain intensity especially in the last hours of evaluation that non-obese ones. Second, the pain intensity in both groups was independent to age or history of abortion.

DISCUSSION

Due to high efficacy of NSAIDS with respect to anti-inflammatory and analgesic effects of these medications, various types of these drugs have been employed in both pregnancy-related pain as well as pain related to medical abortion. In line with the previous trials, we aimed to assess analgesic effects of ibuprofen lysine as a common NSAID used in different clinical settings in relieving abortion-related pain. We could show higher efficacy of this drug on relieving post-abortion pain (within 10 hours of administrating misoprostol) when compared to placebo. Due to this fact that abortion is an inflammation-based process, the use of NSAIDs not only can inhibit inflammatory cascade and thus accelerate post-abortion recovery, but also can effectively reduce pain intensity as well as reduce the likelihood of menorrhagia (8). Such effectiveness has been also demonstrate in similar trials. In a systematic review by Jackson et al in 2020 (9), the prophylactic use of NSAIDs could decrease pain severity as well as additional opioid requirements in those women who were scheduled for medical or surgical termination of pregnancy compared with placebo. More interestingly, in their study, paracervical block was not significantly effective. In a clinical trial by Livshits et al (10) and compared to paracetamol as a common analgesic drug used among deciders for medic abortion, ibuprofen was more effective than paracetamol in relieving abortion-related pain. However some other types of NSAIDs even recent generations could not be helpful in abortion pain relief. As indicated by Tintara et al in 2018 (11) with respect to the efficacy of celecoxib for abortion pain relief, single-dose 400 mg celecoxib had an inadequate beneficial effect on pain relief but significant antipyretic effect during second trimester abortions. It seems that the dose, method of administration and even the background conditions of the patients admitted to the study can all be effective factors in the effectiveness of these drugs on the pain caused by medical abortion.

We also demonstrate high effectiveness of NSAIDs on preventing menorrhagia. The effect of these drugs on preventing menorrhagia in different stages of pregnancy (not only in abortion) has been well understood. In other words, NSAIDs have been very helpful managing menorrhagia by reducing menstrual blood loss. Reviewing the literature shows 30 to 40% reducing the risk for menorrhagia following the use of different types of NSAIDs (12-14). It seems that the mechanisms for reducing abortion-related bleeding can be similar to those revealed in menorrhagia.

As another important finding, we showed higher abortion-related pain intensity in obese than in non-obese patients. Regarding the link between obesity and abortion-related complications, contradictory findings have been published. Although in some studies, no association was found between BMI and abortion complications (15), in some others, obesity was identified as a main determinant for abortion related complication (16). Overall, medical abortion does not seem to be the preferred option for women with morbid obesity.

CONCLUSION

It can be finally concluded that the use of NSAIDs (ibuprofen lysine) is a good pharmacological analgesic option for relieving medical abortion-related pain and hemorrhage. Such medication is preferred to non-obese patients because of increasing the likelihood of painful abortion in obese women.

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**Conflict of interest**

The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

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Table 1: Baseline characteristics in the two study groups

|  |  |  |  |
| --- | --- | --- | --- |
| Characteristic  | Intervention group | Placebo group | P value |
| Mean age, year | 28.39±5.64 | 27.60±6.53 | 0.521 |
| Mean body mass index, kg/m2 | 26.14±4.12 | 25.13±3.74 | 0.204 |
| Mean gestational age, week |  |  |  |
| Based on LMP | 10.33±1.61 | 10.18±1.76 | 0.345 |
| Based on sonography  | 7.18±1.81 | 7.62±1.78 | 0.236 |
| Type of abortion  |  |  | 0.326 |
| Blighted Ovum | 31 (64.6) | 38 (76.0) |  |
| Missed abortion | 16 (33.3) | 12 (24.0) |  |
| Legal abortion | 1 (2.1) | 0 (0.0) |  |
| History of abortion  | 14 (29.2) | 6 (12.0) | 0.135 |
| History of vaginal delivery | 21(43.8) | 21 (42.0) | 0.861 |

Table 2: Pain severity according to patient’s age

|  |  |  |  |
| --- | --- | --- | --- |
| Group  | Time | Pain score | P value |
| <20 years | >30 years |
| NSAID group |  |  |  |  |
|  | First 4 hours | 2.09±1.68 | 2.68±1.89 | 0.280 |
|  | Second 4 hours | 3.43±1.70 | 4.15±2.22 | 0.221 |
|  | Third 4 hours | 1.73±2.01 | 1.85±1.98 | 0.834 |
|  | Last 3 hours | 0.71±2.02 | 0.94±1.99 | 0.704 |
| Placebo group |  |  |  |  |
|  | First 4 hours | 4.30±2.18 | 4.67±2.60 | 0.595 |
|  | Second 4 hours | 6.80±2.09 | 6.33±2.24 | 0.467 |
|  | Third 4 hours | 3.56±2.55 | 2.53±2.34 | 0.136 |
|  | Last 3 hours | 0.73±1.58 | 0.78±1.79 | 0.921 |

Table 3: Pain severity according to patient’s body mass index

|  |  |  |  |
| --- | --- | --- | --- |
| Group  | Time | Pain score | P value |
| <20 | 20 to 30 | >30 |
| NSAID group |  |  |  |  |  |
|  | First 4 hours | 2.25±1.06 | 2.42±1.86 | 1.75±1.63 | 0.704 |
|  | Second 4 hours | 3.75±2.47 | 3.59±1.71 | 4.58±3.12 | 0.518 |
|  | Third 4 hours | 1.75±1.06 | 1.38±1.74 | 3.92±2.67 | 0.013 |
|  | Last 3 hours | 1.33±1.88 | 0.37±1.20 | 3.22±4.12 | 0.003 |
| Placebo group |  |  |  |  |  |
|  | First 4 hours | 7.00±1.73 | 4.19±2.18 | 3.87±2.50 | 0.121 |
|  | Second 4 hours | 8.50±0.50 | 6.54±2.08 | 5.87±3.27 | 0.521 |
|  | Third 4 hours | 2.83±2.02 | 3.21±2.55 | 3.62±3.30 | 0.889 |
|  | Last 3 hours | 0.00±0.00 | 0.82±1.69 | 1.17±2.33 | 0.657 |

Table 4: Pain severity according to history of abortion

|  |  |  |  |
| --- | --- | --- | --- |
| Group  | Time | Pain score | P value |
| History (-) | History (+) |
| NSAID group |  |  |  |  |
|  | First 4 hours | 2.21±1.27 | 2.54±2.64 | 0.662 |
|  | Second 4 hours | 3.51±1.76 | 4.11±2.25 | 0.335 |
|  | Third 4 hours | 1.88±1.95 | 1.50±2.10 | 0.549 |
|  | Last 3 hours | 0.78±2.09 | 0.81±1.79 | 0.969 |
| Placebo group |  |  |  |  |
|  | First 4 hours | 4.42±2.31 | 4.50±2.64 | 0.938 |
|  | Second 4 hours | 6.68±2.08 | 6.25±2.70 | 0.647 |
|  | Third 4 hours | 3.17±2.47 | 3.33±3.03 | 0.883 |
|  | Last 3 hours | 0.73±1.71 | 0.89±1.17 | 0.824 |

Figure 1: The trend of the change in pain intensity score

Figure 2: The trend of the change in level of hemorrhage