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Comparing Two Methods of Rectal Diclofenac Administration for Pain Management in Second Trimester Abortion: A Randomized Clinical Trial

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ABSTRACT

Background & Objective: Pain is the most common side effect of induced medical abortion. However, the optimal analgesia method remains as a clinical challenge. This study aimed to compare the efficacy of two methods of administration of diclofenac as a prophylactic or a therapeutic in pain management in induced second-trimester medical abortion.

Materials & Methods: This randomized clinical trial study was conducted upon pregnant women who were candidates for induced medical abortion and referred to a tertiary educational hospital between October 2019 and December 2020. Participants were divided into two groups based on the mode of diclofenac administration, which was either simultaneously with the first dose of misoprostol or after beginning of the pain. Pain severity, induction-to-abortion time interval, total misoprostol dosage, Hemoglobin concentration, length of hospitalization, and size of retained pregnancy products by ultrasound, and the cumulative dose of opioid usage were compared between the groups.

Results: The severity of pain which was measured by a visual analog scale (VAS), residual of conceived products, hospitalization days, and the total misoprostol dosage were significantly lower (P<0.05) in the prophylaxis compared to the treatment group.

Conclusion: Simultaneous administration of diclofenac with misoprostol as prophylactic method of pain management may be an optimal method in induced medical abortion in the second trimester.

Keywords: Analgesia, Diclofenac, Medical abortion, Misoprostol, Pain management

Introduction

Medical abortion is an acceptable and safe method for pregnancy termination **(1, 2)** and in the second trimester it could be performed with a minimally invasive method via vaginal delivery of the conception products **(3, 4)**. Misoprostol is one of the most commonly used agents for medical abortion due to its high efficacy, easy storage and handling, and low cost **(5, 6)**.

Pain is the most common side effect of induced medical abortion **(7, 8)**. Women usually experience moderate to severe pain during medical abortion, ranging from 6 to 8 in a 10-point scale as maximum pain scores **(9)**. During the induced medical abortion, pain intensity increases as the fetus pass through the cervical canal **(10)**; therefore, analgesia requirement increases due to higher gestational age and longer induction-to-abortion interval **(11)**.

To achieve high-quality pain management, health professionals must provide appropriate, safe, and effective pain relief options. Although local clinical practice guidelines have been widely developed in many countries, there are few studies about pain management recommendations for induced abortion.

In the past studies, narcotics **(12)**, pregabalin **(13)**, as well as various non-steroidal anti-inflammatory drugs (NSAIDs) regimens **(7, 14)**, as prophylactic (starting before abortion induction) or therapeutic (starting after the onset of pain) were administered for pain management. Hence, the optimal method and timing of analgesics for pain management are still unclear **(3, 7)**.

This study aimed to compare the efficacy of prophylactic diclofenac (administered simultaneously with sublingual misoprostol) with therapeutic diclofenac

(administered upon pain onset) in pain management during the induced second-trimester medical abortion.

Materials and Methods

Study overview

In this clinical trial study, the participants who were candidate for induced second-trimester medical abortion were recruited. This study was performed between October 2019 and December 2020 in a tertiary referral hospital affiliated to Tehran University of Medical Sciences, Tehran, Iran.

The inclusion criteria were gestational age between 14 to 20 weeks, stable hemodynamic status with no clinical signs and symptoms of pelvic infection (purulent vaginal discharge, body temperature >38°C degrees, and lower abdominal tenderness) at admission and at least two sonographies indicating fetal demise. The exclusion criteria were the history of using of sedative, analgesic drugs or addiction or hypersensitivity to NSAID.

A recorded visual analog scale (VAS) questionnaire for pain assessment was assessed for all patients. VAS is a psychometric scale for pain intensity measurement. It is a standard 10 cm tool, the score zero at the left end indicates no pain, and the score ten at the right end indicates the most severe pain. Achieving a score of 1-3 means mild pain, 4-6 moderate pain, and 7-10 showing severe pain **(15)**. The primary outcome of the study was mean VAS score during the procedure and last VAS score before the completion of termination. Patient satisfaction with changes in pain level was measured by a 1-5 scale, from very low to very much.

The demographic, clinical, and obstetrical data including personal information, age, gestational age, gravity, parity, previous history abortion and body mass index were provided by each participant. Indeed, pain severity, induction-to-abortion time interval, total misoprostol dosage during the induction period, hemoglobin concentration changes 6 hours after complete abortion (bleeding estimation by pad count), length of hospitalization, pain reduction satisfaction, size of retained pregnancy products by ultrasound, and cumulative dose of opioid usage were gathered either.

After enrolment, randomization was performed with an allocation sequence generated by block randomization by the trial statistician. Participants were divided into two equal groups. In all patients, medical induction was performed with serial doses of misoprostol (400 µg), applied sublingually every four hours for a maximum of five doses.

The prophylactic group (n=108) received 100 mg rectal diclofenac made in Iran (Tolidaru Company) simultaneously with the first dose of misoprostol as a prophylactic, and the therapeutic group (n=112) received the same dose of diclofenac upon pain onset or four hours after misoprostol. In both groups, diclofenac was administered every 12 hours as patient request. Pethidine was infused intravenously in a bolus dose of 25 mg maximum to four doses for pain reduction when there was no response to diclofenac (VAS score 7-10).

After completing the abortion, a transvaginal ultrasound was performed to confirm a successful medically induced abortion. All ultrasound scans were performed by the same radiologist. A complete blood count was obtained before and after medical abortion. All patients were admitted in labor with continuous monitoring for vital sign and bleeding. Any complication during the admission was recorded and managed as possible.

Ethical Consideration

The protocol of the study was approved and registered by the ethical committee of Tehran University of Medical Sciences with reference code IR.TUMS.-MEDICINE.REC.1398.201. Participants then submitted a written consent form to attend the trial. This trial was conducted in agreement with the principles of the Helsinki Declaration.

Statistical Analysis

The data were analyzed by SPSS 20.0 (SPSS Inc., Chicago, IL., USA). Independent-Sample-T, Chi-Square, Kolmogorov-Smirnov, and Fisher Exact tests were used. The statistical significance for all outcomes was set at P-value less than 0.05.

Results

The mean age, gestational age and the body mass index in both groups were not significantly different (Table 1). The used diclofenac doses were not significantly different (P=0.801) in groups either.

Although the induction-to-abortion time, cumulative dose of misoprostol, length of hospitalization, and pain severity were significantly lower in prophylactic group, there were no significant differences in terms of the size of the retained pregnancy products (P=0.350) and blood loss (P=0.130). The post-induction characteristics of the participants in each group are compared in Table 2.

IV opioid analgesics were indicated for pain relief in 27 patients in prophylaxis group, and the pain was successfully subsided by a single dose of 25 mg of pethidine, whereas it was indicated in 43 patients in therapeutic group. The pain was subsided by an IV bolus injection of 25 mg of pethidine in 34 patients and a cumulative dose of 50 mg IV pethidine in the other nine patients. Therefore, patients in prophylaxis group achieved pain relief with non-opioid analgesics, more frequently. They also had experienced pain relief with less IV pethidine infusion in comparison with therapeutic group (Table 3).

Table 1. Demographic characteristics of the participants in each group

Characteristics	Prophylactic diclofenac (Mean±SD)	Therapeutic diclofenac (Mean±SD)	P-value
Age (year)	30.8±7.4	29.7±5.4	0.664
Body mass index (kg/m2)	27.8±1.77	27.4±1.7	0.524
Gestational age (week)	16.7±1.5	16.9±1.5	0.540

SD: standard deviation

Table 2. Post-induction characteristics of the participants in each group

Characteristics	Prophylactic diclofenac (Mean±SD)	Therapeutic diclofenac (Mean±SD)	P-value
Induction-to–abortion time (hours)	12.15±3.3	13.4±3.9	*P*<0.001
Hospitalization (days)	2.64±0.7	3.27±0.9	*P*<0.001
Pain intensity (VAS)	1.90±0.8	2.30±1.0	*P*=0.015
Pain reduction satisfaction (VAS)	2.1±0.8	1.74±0.92	*P*<0.001
Cumulative misoprostol dose (µg)	1114.81±328.30	1235.71±387.30	*P*<0.001
Hemoglobin decrease (mg/dl)	-0.43±1.89	-0.13±0.87	*P*=0.130
Size of the retained products of conception by ultrasound (mm)	14.09±3.6	14.66±3.8	*P*=0.350

VAS: visual analog scale
µg: microgram
mg/dl: milligram/deciliter
mm: millimeter

Table 3. Comparison of cumulative pethidine dosage between 2 groups

Cumulative Pethidine dosage	Therapeutic diclofenac (n)	Prophylactic diclofenac (n)	P-value
25 mg	34	27	-
50 mg	9	0	-
Total	43	27	X^2 =6.485 *P*=0.011

n: number of the participants

Discussion

This study revealed that the severity of pain, which was measured by a visual analog scale, residual of conceived products, hospitalization days, and the total misoprostol dosage were significantly lower in groups receiving diclofenac before the pain begins.

Both physical and psychological pain during the abortion process are experienced and described by women **(16)**. It is imperative to support women who are undergoing an induced abortion, especially when the fetus is not viable **(17, 18)**. Therefore, there is a clear need for standardized and evidence-based regimens for the management of pain associated with a medical abortion **(19)**.

Currently, few studies have examined pain management during induced medical abortion **(7, 14, 19)**. Heterogeneity of existing data limits comparison. Therefore, further research is needed to determine the optimal analgesia regimens for second trimester induced medical abortion **(9)**. NSAIDs are used to relieve the symptoms in various conditions characterized by acute pain such as induced first and second-trimester medical abortion.

Although theoretically prostaglandin is inhibited by NSAIDs, studies have shown that co-treatment with NSAID and misoprostol does not attenuate the efficacy of misoprostol **(20-22)**. In our study, prophylactic use of diclofenac did not interfere with the action of misoprostol to induce abortion, while significantly shortened induction-to-abortion interval, lowered cumulative dosage of misoprostol, and shortened hospitalization length. In another study, diclofenac significantly lowered the induction-to-abortion time, the need for opioid analgesic use, cumulative misoprostol dosage, and hemoglobin decrease during the first trimester induced medical abortion **(22)**.

NSAIDs eventually reduced the need for opiate injections when used for pain relief during second medical abortion **(20)**. In our study, the pain was a common experience between two randomized allocated

groups, who either received prophylactic or therapeutic diclofenac for pain relief. Prophylactic diclofenac administration resulted in a more satisfactory pain reduction experience and decreased pain intensity more vigorously. Additionally, in group one who received prophylactic diclofenac (with the first dose of misoprostol), the cumulative dose of opioid usage was significantly lower compared to those who received therapeutic diclofenac (with pain onset).

There was no significant difference between the two groups in terms of the size of the retained products of conception by ultrasound. It may be partly due to performing an ultrasound exam the day after abortion per hospital protocol, which was pretty soon to evaluate complete abortion.

The volume of blood loss was higher in patients who receive NSAIDs for pain relief during a medically induced abortion in comparison with those who received other analgesics, but this finding was not supported by the changes in hemoglobin levels **(20)**. In our study, the volume of blood loss was higher in group one than group two based on changes in hemoglobin levels checked on admission and before the women were discharged, but the difference was not significant. It needs to be studied in a larger group of patients to realize whether the difference between blood losses in these two methods of administration could be considerable.

Conclusion

The present study suggests that prophylactic administration of diclofenac acts better than therapeutic dose on relieving the pain, shortening the induction-to-abortion interval, lowering the total misoprostol usage, and minimizing the opioid analgesic injections in medical abortion and increasing satisfaction rate in patients when diclofenac was used prophylactically.

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Conflict of Interest

The authors report no conflict of interest.

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