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Effect of Preoperative Duloxetine on Opioid Consumption in Women Undergoing Abdominal Hysterectomy: A Randomized, Double-Blinded, Placebo-Controlled Trial

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Abstract

Background: Pain is one of the most challenging issues following surgery, and it is crucial to provide adequate and appropriate pain control measures.
Objectives: This study assessed the efficacy of preoperative duloxetine in controlling postoperative pain in women following an abdominal hysterectomy in Yas Hospital affiliated to Tehran University of Medical Sciences between December 2019 and April 2020.
Methods: The study involved 80 women who were candidates for elective abdominal hysterectomy. The participants were randomly assigned to one of two groups. Group 1 received a 60 mg duloxetine capsule two hours before surgery. Group 2 received placebo following the same schedule. The amount of administrated opioids and the time from surgery to the administration of opioids were recorded, along with the frequency of nausea and vomiting experienced.
Results: Two patients from each group withdrew before the study ended. In total, 38 women in each group were assessed. There were no significant differences in age, duration of surgery, and the amount of administrated opioids between the two groups. However, the number of patients who had nausea and vomiting differed significantly between the two groups (65% vs. 34%; P = 0.006).
Conclusions: Our findings showed that duloxetine was not effective in controlling pain after abdominal hysterectomy. In addition, patients who received duloxetine had a significantly higher rate of nausea/vomiting.

Keywords: Duloxetine, Pain, Hysterectomy, Opioid Consumption

1. Background

One of the most significant challenges for the patient and clinician following surgery is the effective and timely management of pain. Preoperative factors play a significant role in making sure that the right postoperative care is given to facilitate timely discharge and recovery (1).

Women experience more recovery-related problems, more opioid-related side effects, and a greater level of pain than men. Therefore, if we get it wrong for women requiring abdominal surgery, this will be devastating for them (2, 3). Long recovery times and high levels of pain are experienced following abdominal hysterectomy. This is the second most common gynecological surgery after a cesarean section (4-6).

Duloxetine is a serotonin-norepinephrine reuptake inhibitor (SNRI) that is used for treating major depression, anxiety, and chronic pain (7, 8). As it can help regulate emotions and has perioperative analgesic effects, some studies regard it as a beneficial medication to be taken following a hysterectomy (9, 10). Some studies suggested that further research is needed to determine the effectiveness of duloxetine and its optimal dose for the management of acute postoperative pain (11, 12).

There are a few studies, but not in Iran, evaluating the role of preoperative duloxetine in controlling pain before a hysterectomy.

2. Objectives

This study aimed to assess the effects of preoperative duloxetine on controlling postoperative pain in women

undergoing abdominal hysterectomy.

3. Methods

A randomized clinical trial was conducted in Yas Hospital affiliated to Tehran University of Medical Sciences between November 2019 and April 2020. The study involved 80 women who were candidates for elective abdominal hysterectomy. Two patients in each group withdrew before the study ended, two of whom for surgical plan alteration during the surgery and two others for the unexpected surgery duration.

The inclusion criteria were women aged 30 - 60 years and ASA class I or II. The exclusion criteria were women with an allergy to the medication, estimated duration of surgery for more than three hours, pelvic pathology, surgical incisions (except for Pfannenstiel incision), renal and/or liver disease, and chronic consumption of opioids and/or antidepressants.

The study was approved by a Local Ethics Committee (code: IR.TUMS.MEDICINE.REC.1397.286) and has been registered in the Iranian Registry of Clinical Trials (code: IRCT number 20120624010102N2).

All the participants were fully explained about the study, and they were free to ask questions before completing informed consent forms. Guidelines were followed throughout the study. A specialist nurse researcher did the randomization using a computerized single random generation. Group 1 received a 60 mg duloxetine capsule two hours before the surgery. Group 2 took a placebo following the same schedule. It was a double-blinded trial, with patients and physicians being unaware of which patients were receiving which treatments.

After arrival in the operating room and IV line insertion, standard American Society of anesthesiologists monitors were applied. All subjects were pre-medicated with 2 μg/kg fentanyl and 2 mg midazolam. Anesthesia was induced with 0.5 mg/kg atracurium and 2 - 2.5 mg/kg propofol. For the maintenance of anesthesia, the isoflurane gas with 1 - 1.5 MAC was used.

For postoperative pain control, ketorolac 15 mg was injected intravenously every eight hours. When oral medication could be tolerated, ibuprofen 400 mg was administered every six hours. In cases where the VAS score was higher than 3, the nurses administered 2 mg of intravenous morphine sulfate. The time taken from the end of the surgery to the first opioid administration was measured, along with any subsequent administrations. Data regarding the age of participants, the actual duration of the surgery, and the frequency of nausea and vomiting were also recorded.

SPSS version 22 software (SPSS Inc., Chicago, IL, USA) was used to do data analysis. The data are presented as mean $\pm$ SD for continuous variables and frequency for categorical variables. The independent sample *t*-test and Fisher exact test were used for the comparison of quantitative and qualitative variables. A P value of less than 0.05 was considered significant.

4. Results

Eighty women who met the inclusion criteria were randomly assigned to one of the two study groups. Two patients in each group withdrew before the study ended. In total, 38 women in each group were assessed. There was no significant difference between the groups in age, the duration of surgery, the time interval from the end of surgery to the first opioid consumption, and the number of opioid administrations. There was a difference between the two groups in the number of patients experiencing nausea and vomiting (Table 1).

5. Discussion

The main finding of this study is that there were no significant differences in opioid consumption and the amount of administered opioids after the surgery between the two groups. There was a difference in the frequency of nausea and vomiting, which was significantly higher in women who received duloxetine before surgery.

In a previous study conducted by Castro-Alves et al. (9), 31 women received duloxetine before abdominal hysterectomy, and 32 women received a placebo. The results showed that the pain score after 24 h was significantly lower in the duloxetine group, while there was no significant difference regarding nausea and vomiting between the two groups (9). The result is not in line with our findings. This may be due to the different methods of anesthesia, spinal versus general anesthesia.

Takmaz et al. (10) randomly assigned 80 women who were candidates for laparoscopic hysterectomy into two groups. Group 1 received duloxetine, and group 2 received a placebo. The study found no significant difference in the pain, the need for narcotic analgesia, and the length of hospital stay. There was also no difference in physical discomfort, including nausea and vomiting. This was the same in the two groups (10). Although the method of surgery was different from what we studied, the findings were in agreement with ours.

Table 1. Findings of Variables in Two Groups[a, b]

	Group One (N = 38)	Group Two (N = 38)	P Value	Test
Age, y	50.34 ± 7.8	51.24 ± 7.7	0.6	Independent sample *t*-test
Duration of surgery, h	3.2 ± 0.6	3.1 ± 0.4	0.3	Independent sample *t*-test
The time interval from the end of surgery to the first opioid consumption, h	5.35 ± 1.89	6 ± 2.38	0.2	Independent sample *t*-test
Nausea/vomiting	25 (65.8)	13 (34.2)	0.006	Fisher exact tests
Number of opioid administrations				Fisher exact tests
0	5 (13.2)	6 (15.8)	0.9	
1	26 (68.4)	26 (68.4)		
2	7 (18.4)	6 (15.8)		

[a] Values are expressed as mean ± SD or No. (%).
[b] Group One: Duloxetine Group, and Group Two: Placebo Group.

In a randomized controlled trial, Bedin et al. (13) found that preoperative duloxetine was useful for reducing opioid consumption after spinal surgery. In the study, duloxetine was repeated 24 h after the surgery, and the time of follow-up was 48 hours. Their result was not consistent with our findings. Unlike our outcome, Koh et al. (14) reported better pain management in the duloxetine group (receiving 30 mg duloxetine a day before the surgery) than in the control group after total knee arthroplasty. There was no difference between the two groups in adverse effects. Our study differs from this study in the time of taking duloxetine, the dosage of duloxetine, the duration of follow-up, and the method of anesthesia.

Duloxetine is used for the management of postoperative pain. It inhibits serotonin and norepinephrine reuptake in the CNS, which results in pain pathway alteration (10). It also modulates emotional status during the perioperative period and may reduce the need for opioid consumption (15). Duloxetine could balance pain perception and help control it (16). However, Kammer et al. , in a meta-analysis demonstrated that there is not enough evidence on the clinical use of duloxetine for acute postoperative pain (11).

As we found, duloxetine did not significantly reduce postoperative pain. On the other hand, it increased the number of nausea and vomiting cases. Previous studies also showed an increase in nausea and vomiting with duloxetine dose-dependently (17).

5.1. Conclusions

The study showed that duloxetine was not effective in controlling pain after abdominal hysterectomy. Patients who received duloxetine had a significantly higher rate of nausea and vomiting.

Footnotes

Authors' Contribution: Study concept and design: FZ, PP, and EB. Analysis and interpretation of data: FZ and SS. Drafting of the manuscript: EB and SS. Critical revision of the manuscript for important intellectual content: SS, KA, and EB. Statistical analysis: FZ, EB, and SS.

Clinical Trial Registration Code: The clinical trial registration code was number 20120624010102N2.

Conflict of Interests: The authors declare no conflict of interest.

Ethical Approval: The ethical approval code was IR.TUMS.MEDICINE.REC.1397.286.

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Informed Consent: Patients signed informed consent forms before entering the study.

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