The Effect of Preoperative Administration of Duloxetine on Postoperative Pain After Laparoscopic Myomectomy

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Abstract- The purpose of this study was to evaluate the effect of preoperative administration of duloxetine on postoperative pain after laparoscopic myomectomy. In this double-blind clinical trial study, 57 patients aged 18-55 years with ASA I or II undergoing laparoscopic myomectomy involved. The case group received oral duloxetine 60 mg, and the control group received placebo 2 hours before the surgery. Pain scores, total analgesic consumption during 24 hours, recovery discharging time, nausea, vomiting, dizziness, and hemodynamic changes were recorded and compared between two groups. The pain severity was significantly lower in the case group at 2, 12, and 24 hours after the operation (P<0.05). There were no significant differences in dizziness, nausea, vomiting, systolic and diastolic blood pressure, and heart rate of patients between two groups before the surgery, 5 and 30 minutes after the induction, and after the recovery. Duloxetine administration prior to laparoscopic surgery myomectomy can reduce postoperative pain without inducing side effects in patients.

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Introduction

Postoperative pain is one of the main issues in postoperative care and plays an important role in accelerating the improvement of surgical patients' general condition (1). The laparoscopy technique is a revolutionary in women's surgery, presenting several advantages such as smaller surgical incisions, less bleeding, shorter hospitalization time, and lower hospital costs. However, postoperative pain is still a complication that results in an unpleasant experience and delayed discharge for women (2). One of the strategies to prevent chronic postoperative pain is to reduce the acute pain in the initial phase using effective medications with the least side effects. Duloxetine is a thiophene derivative and a selective neurotransmitter reuptake inhibitor for serotonin, norepinephrine, and to lesser degree dopamine. It belongs to a class of heterocyclic antidepressants known as serotonin-norepinephrine reuptake inhibitors (SNRIs), and it is used to treat the major depressive disorder, generalized anxiety disorder, neuropathic pain, chronic musculoskeletal pain, and fibromyalgia (3). However, its effect on postoperative pain has not been fully examined yet (4). Serotonin and norepinephrine are descending-inhibitory pain pathway mediators in the CNS (5). Disturbances in the central serotonin and norepinephrine cause pain and depression. Duloxetine induces an analgesic mechanism in the spinal cord by affecting the pain pathways (6). Wang *et al.*, investigated the effect of duloxetine in systemic (intraperitoneal) and local (subcutaneous) administration one hour before the surgery on the rat in vitro. They found that this medication is effective in reducing postoperative pain (7). In this study, we intended to evaluate the effect of preoperative administration of oral Duloxetine on postoperative pain in patients undergoing laparoscopic myomectomy.

Materials and Methods

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After approval by the local ethics committee and obtaining written informed consent, in this double-blind, randomized clinical trial study, 57 patients aged 18-55 years with ASA I or II was undergoing laparoscopic myomectomy involved. Patients with a history of liver disease, kidney disease, heart failure, drug abuse, and history of taking antidepressants were excluded. Patients were divided into two groups using a random number table. Patients in the first group (case) received 60 mg of oral duloxetine two hours before the surgery, and patients in the second group (placebo) received a placebo. After patients' admission to the operation room, the standard monitoring (BP-HR-Spo2-Capnography) was performed for all the patients, and the data were recorded. All the patients underwent general anesthesia. Laparoscopies were done by the same surgeon who was blinded about the medications. Nausea, vomiting, and dizziness were recorded after the surgery. If nausea or vomiting occurred, 4 mg of Ondansetron was prescribed. Patients with Aldert's score >9 were discharged from the recovery. After transferring to the ward, patients received 1 gr of Apotel every 6 hours. The number of prescribed analgesics was measured. The intensity of pain was measured and recorded 0.5, 1, 2, 6, 12, and 24 hours after the surgery based on the visual analog scale (VAS). (The visual analog scale (VAS) is a validated, subjective measure for acute and chronic pain. Scores are recorded by making a handwritten mark on a 10-cm line that represents a continuum between “no pain” and “worst pain) (8). Our patients described their pain severity using numbers 1 to 10 (“no pain” to “worst pain). The person who assessed the severity of pain and complications after the operation was blinded about the medications. The time of the first request for analgesic dose as well as recovery discharge time was recorded too. Each patient's hemodynamic (HR-SBP-DBP) was recorded before the surgery, 5 and 30 minutes after the surgery, and after entering the recovery room. The collected data were analyzed using SPSS version 20. $P<0.05$ considered significant.

Results

In this double-blind, randomized clinical trial study, 57 patients aged 18-55 years with ASA I or II involved. The patients’ mean age in the case group was 28.500±6.512 years, and in the placebo group was 31.37±7.16 years ($P=0.19$). Pain score, assessed using VAS, was significantly lower in the Duloxetine group ($P<0.05$) than the placebo group at 2, 6, 12, and 24 hours after the operation. However, there was no significant difference between the two groups, 0.5 and 1 hour after the surgery. In addition, the results of the two groups were similar in terms of the time interval between the end of surgery and the first patient’s request for analgesia. Regarding recovery discharge time and the dose of consumed analgesic, no significant difference was observed between two groups (Table 1). There were no significant differences in patients’ hemodynamic between two groups, before 5 and 30 minutes after the induction of anesthesia and in the recovery room (Tables 2, 3, 4). No significant differences were observed between two groups considering complications such as nausea, vomiting, and dizziness after the surgery.

Table 1. Mean VAS score, the dose of consumed analgesic, recovery discharging time and the time interval for the first request for analgesic between two groups

Variable	Duloxetine Mean ± standard deviation	Placebo Mean ± standard deviation	*P*
Pain 0.5 hour after the operation	2.92±1.33	3.06±1.53	0.074
Pain 1 hour after the operation	2.92±1.11	3.44±1.18	0.094
Pain 2 hours after the operation	4.035±1.40	4.96±1.78	0.033
Pain 6 hours after surgery	3.17±1.54	3.79±1.89	0.018
Pain 12 hours after the operation	2.46±1.57	3.51±1.93	0.029
Pain 24 hours after the operation	1.75±0.7	2.55±1.54	0.015
The dose of consumed analgesic (mg)	64.28±63.62	98.27±64.75	0.06
Recovery discharging time (min)	59.64±20.04	62.41±27.43	0.66
The time interval for the first request for analgesic	210.55±207.767	139.800±137.54	0.186

Table 2. Mean systolic blood pressure between two groups

Time	Group	number	Mean	Standard Deviation	*P*
Before induction of anesthesia	Case	28	111.39	21.41	0.133
	Placebo	29	118.24	11.04	
5 minutes after induction of anesthesia	Case	28	121.00	8.35	0.546
	Placebo	29	119.03	15.02	
30 minutes after induction of anesthesia	Case	28	124.67	9.22	0.932
	Placebo	29	124.44	10.88	
In recovery room	Case	28	120.60	11.57	0.265
	Placebo	29	113.65	30.63	

Table 3. Mean diastolic blood pressure between two groups.

Time	Group	number	Mean	Standard Deviation	*P*
Before induction of anesthesia	Case	28	70.71	8.44	0.451
	Placebo	29	72.34	7.77	
5 minutes after induction of anesthesia	Case	28	73.64	8.99	0.956
	Placebo	29	73.79	11.10	
30 minutes after induction of anesthesia	Case	28	74.35	8.57	0.273
	Placebo	29	76.86	8.48	
In recovery room	Case	28	74.28	9.59	0.800
	Placebo	29	74.93	9.53	

Table 4. Mean heart rate between two groups.

Time	Group	number	Mean	standard Deviation	*P*
Before induction of anesthesia	Case	28	85.39	7.29	0.258
	Placebo	29	88.03	9.90	
5 minutes after induction of anesthesia	Case	28	87.50	10.9	0.672
	Placebo	29	89.00	15.17	
30 minutes after induction of anesthesia	Case	28	87.92	9.99	0.903
	Placebo	29	87.55	13.07	
In recovery room	Case	28	86.28	9.26	0.998

Discussion

Acute postoperative pain is a serious problem that results in serious complications such as rehabilitation disorders, prolonged hospital stay, and other side effects associated with analgesia overdose. New analgesic techniques have been introduced to manage pre and postoperative pain, which are more efficient than the old ones. One of these techniques is the use of anti-anxiety medications, anticonvulsants, and Non-steroidal anti-inflammatory drugs (NSAIDS) before the surgery (9). Duloxetine is used to treat a wide range of chronic pain. However, little is known about its effect on postoperative pain (4). The present study concluded that preoperative administration of 60 mg oral Duloxetine in patients undergoing laparoscopic myomectomy could reduce postoperative pain. Castro *et al.*, examined the effect of oral Duloxetine 60 mg (2 hours before and 24 hours after the surgery) on patients undergoing abdominal hysterectomy, and it was found that the pre-administration of duloxetine can reduce postoperative pain (10) confirming the results of our study. Hyer L *et al.*, evaluated the effect of Duloxetine 60 mg two weeks before and three months after spinal column operation. They observed that Duloxetine reduces postoperative pain and the incidence of chronic pain (11). However, K-Yho's study on postoperative pain in total knee replacement surgery showed that Duloxetine (60 mg) does not affect the post-operative pain score (12). This contradictory result may be due to the fact that the pain following knee replacement surgery is more severe than that of laparoscopy. In our study, systolic and diastolic blood pressure and heart rate were not significantly

different between two groups before induction of anesthesia, 5 minutes after induction of anesthesia, and in the recovery room. MA derby *et al.*, (2007) examined the effect of Duloxetine on blood pressure and heart rate and concluded that a dose exceeding up to 200 mg twice a day can produce small and asymptomatic changes in these vital signs (13). In another study by Phil Lee *et al*., it was concluded that taking 60 mg of Duloxetine daily in major depressive disorder patients (MDD) does not change the vital signs and it can be used as an effective and safe treatment for emotional and physical symptoms, and it can significantly reduce pain in patients (14). CHAPPELL (2013) also found that taking 60 mg of Duloxetine for 11 days has no significant clinical effects on heart rate changes (15). Concerning the incidence of complications such as nausea, vomiting, and dizziness, no significant difference was observed between two groups of our study that is in line with the results of previous studies (10,12,15). In this study, the results showed that recovery discharging time was similar between two groups, which is consistent with the findings provided by CASTRO *et al*., It should be mentioned that taking Duloxetine enhanced recovery quality, but no difference was between the two groups (10). There was no significant difference between the two groups concerning the time of the first request for analgesic dose. However, the meantime for the first request for analgesic dose was higher in the case group. Abdel Fattah Saoud *et al*., explored the effect of daily oral administration of Duloxetine two weeks before and after the operation (anterior cervical microdiscectomy). It was found that the administration of Duloxetine postponed the time of the first request for analgesic dose (15). Hyer L showed that the initial dose usage of morphine in patients is reduced (11). The difference in the amount of analgesic consumption in two groups was marginally significant that can be turned into statistically significant if the number of samples was more and then confirms the results reported by Castro-Alves *et al*., and Ho *at al.*, (10,12).

The present study concluded that the administration of 60 mg oral Duloxetine 2 hours before the laparoscopic myomectomy could reduce postoperative pain without inducing side effects and changing in patients' hemodynamic variables.

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