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Preoperative duloxetine to prevent postoperative shoulder pain after gynecologic laparoscopy: a randomized controlled trial

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Abstract

Background: Gynecological laparoscopies despite being minimally invasive, have challenging multifactorial postoperative pain profile. We aimed to evaluate the effect of duloxetine in improving postoperative pain after gynecologic laparoscopies.
Methods: A prospective randomized controlled trial that recruited 60 patients who underwent laparoscopic surgery was randomly assigned to two groups who received similar capsules 12 hours before surgery, either duloxetine 60 mg intervention (case group) or placebo (control group). Patients were followed up 12 hours after surgery utilizing VAS for assessment of pain at shoulder, upper abdominal and trocar site, and Ramsay sedation score at 2, 6 and 12 hours after surgery. The first analgesic request and total analgesic requirement were recorded. Patient satisfaction were assessed 12 hours after surgery.
Results: Postoperative shoulder pain, upper abdominal pain, and pain at the trocar site were significantly lower in the intervention group over 12 hours postoperatively compared to placebo ($p < 0.001$). Ramsay sedation scores were significantly higher in the intervention group than in placebo for the first 2 hours postoperatively ($p = 0.001$). The first analgesic request was significantly earlier in placebo than in intervention group ($p < 0.001$). The total analgesic requirement within 12 hours postoperatively was significantly lower in the intervention than in placebo group. Dry mouth and postural hypotension were significantly more in the intervention group.
Conclusions: Duloxetine 60 mg given 12 hours before gynecological laparoscopic surgery proved to be safe and effective in improving postoperative analgesia, sedation and Patient satisfaction.

Introduction

Postoperative pain control still remains a challenge for both surgeons and anesthesiologists even with recent progress in minimally invasive surgery.[1]

Laparoscopic surgery in patients with benign gynecological diseases has many advantages over open surgery, such as the earlier recovery, reduction of hospital stays, lower morbidity, and better cosmetic results. Although laparoscopic surgery leads to the improvement of patient satisfaction, a significant number of patients suffer from musculoskeletal pain. Postoperative shoulder pain is believed to be a result of pneumoperitoneum achieved by insufflation of CO_2 which induces the stretching of the serosa, irritation of the diaphragm, and phrenic nerve leading to shoulder pain.[2]

Pneumoperitoneum creates the obligatory space in which the operation should be performed laparoscopically.[3] Post laparoscopic shoulder pain (PLSP) incidence is 35% to 61% on the first day of surgery.[4] The severity ranges from mild to severe and some patients have PLSP for more than 72 hours after surgery.[5]

Duloxetine is a selective antidepressant that inhibits the reuptake of serotonin and noradrenaline (SSNRI) in the central nervous system. The analgesic properties of duloxetine in the treatment of diabetic neuropathy, chronic muscle or joint pain (for example low back pain and osteoarthritis pain), and central pain syndromes such as fibromyalgia are believed to be due to sodium ion channel blockade.[6] It also has a Level A approval for certain neuropathic pain as specified by the European Federation of Neurological Societies.[7] The current study advocated the use of duloxetine for PLSP as a special form of pain as well. Duloxetine has been approved for pain associated with diabetic peripheral neuropathy (DPN).[8]

Previous studies concentrated on the utilization of gabapentin and pregabalin (both are antineuropathic pain medications) to inhibit PLSP after laparoscopic ovarian cystectomy and laparoscopic cholecystectomy demonstrated positive results. Whereas duloxetine is an antineuropathic pain medication, we assume that its use will ameliorate PLSP after gynecological laparoscopy.[9,10]

To the best of our knowledge, it is the first study to assess the use of duloxetine in gynecological laparoscopy; therefore, the authors designed this randomized controlled trial to evaluate the effect of duloxetine in improving postoperative pain after gynecological laparoscopy.

Methods

This study was a prospective, double-blind randomized placebo - controlled clinical trial and conducted at Woman's Health Hospital from October 2017 to December 2018. After it was approved by the Local Research Ethics Committee of the Faculty of Medicine, Assiut University (Ref 17100236), registered at clinicaltrials.gov (NCT03249168) and followed the CONSORT 2010 statement for randomized clinical trials.

Study population

After obtaining written informed consent, the current study included 66 adult patients with American Society of Anesthesiologists (ASA) physical status I - II who had

undergone elective laparoscopic surgery, either diagnostic (cases of infertility) or surgical (ovarian cystectomy, ovarian drilling and adhesiolysis). Patients with medical conditions (hypertension, diabetes mellitus, renal or liver impairment), body mass index (BMI) ≥ 40 kg.m^{-2} who routinely used any analgesics within 48 hours of the procedure, patients with severe psychiatric disorders, epilepsy or seizure history, previous history of any previous laparotomy, laparoscopy, or other pelvic cancer manipulation or pathology, breast or mediastinal surgery or pathology, those who complained of shoulder pain just before surgery, preemptive infiltration of trocar sites with local anesthetics or intraperitoneal irrigation with local anesthetics were excluded. Also, suspended laparoscopy to laparotomy, complicated surgery like bleeding and persistent pain after planned analgesics, or 48 hours were excluded.

Randomization and blinding

The patients were randomized by using a computer-generated randomization list and assigned to two groups. The group assignment was kept in well-sealed opaque envelopes and the anesthesia group, patients, surgeons, and other staff were blinded until data processing time. As determined by the anesthesia team, patients received uniform capsules as an oral premedication 12 hours before surgery, either duloxetine 60 mg the intervention (case group) or placebo (control group). Patients in both groups ingested the capsules with about 50 mL of water. Both capsules had similar colors and appearance and were randomly packaged and numbered by the native pharmacy. The placebo group had glucose powder in the capsules.

General anesthesia

All patients were fasting for at least eight hours prior to the surgery. All patients received balanced general anesthesia and tracheal intubation by one attending anesthesiologist who was blinded to the groups. Anesthesia Induction was performed by propofol 2.0 - 2.5 mg.kg^{-1} and fentanyl 50 µg and was maintained by isoflurane inhalational anesthesia. Atracurium besylate 0.5 mg.kg^{-1} and thereafter intermittent 0.15 mg.kg^{-1} bolus doses were used to relax the muscles. All patients received ketorolac 60 mg intraoperative. Mechanical ventilation was performed for all patients with a 100% O_2. The Tidal Volume (TV) and/or respiration frequency were managed to maintain end-tidal CO_2 at the level of 30 - 35 mmHg. CO_2 gas was used for abdominal insufflation and to maintain the standard intra-abdominal pressure (12-15 mmHg). All

patients were monitored continuously by standard national monitoring including continuous electrocardiography, pulse oximetry, intermittent noninvasive blood pressure monitoring, and capnography.

At the end of the surgery, reversal of neuromuscular block was performed by neostigmine 50 $\mu g.kg^{-1}$ and atropine 20 $\mu g.kg^{-1}$. After tracheal extubation, patients were transferred to the recovery room. All patients received ibuprofen tablet 400 mg on the evening of operation day and on the next morning as well as acetaminophen (1000 mg) IV (intravenous) on their request for analgesics. In the case of sustained nausea or vomiting, ondansetron 4 mg was administered, intravenously.

Research outcome measures

The presence and severity of PLSP at rest were recorded as the primary outcome, utilizing a Visual Analog Scale (VAS, 0 = no pain and 10 = worst pain ever experienced) by a blinded research nurse 2, 6, and 12 hours after surgery. Also the severity of upper abdominal pain, and pain at the trocar site at rest were assessed and each recorded on a separate sheet. Patients were followed up only for 12 hours after surgery. When VAS was 3 or more, acetaminophen (1000 mg) IV was given. For additional pain, nonsteroidal anti-inflammatory drugs (NSAIDs) such as ketorolac (15 mg) were used as a rescue drug.

Sedation was measured by Ramsay Sedation Scale at 2, 6 and 12 hours after surgery by a blinded research nurse as follow: (1) anxiety and agitation or restlessness; (2) cooperation, orientation, and calmness; (3) replies to commands only; (4) abrupt response to mild glabellar tapping or loud auditory stimulus during asleep; (5) sluggish response to mild glabellar tapping or loud auditory stimulus during asleep; (6) no reaction to light glabellar tapping or loud auditory stimulus during asleep.

The occurrence of any other side effects was recorded such as respiratory depression, nausea, vomiting, vision changes, dry mouth, loss of appetite, increased sweating, and postural hypotension (P.H.). Furthermore, auscultation of intestinal peristalsis, postoperative hospitalization, first time for the analgesic request, and total dose of postoperative analgesics were reported.

Patient satisfaction was rated by using a scale (1= completely dissatisfied and 5= completely satisfied) 12 hours after surgery.

Statistical analysis

A pilot study was carried out prior to the actual study. We included 9 patients in each group, the mean VAS in the duloxetine treated group was 1.9 and 3.4 in the placebo group with a standard deviation of 2.2 in group A, 1.4 in group B. According to this pilot study and with a significance level of 0.05 and a potency of 0.8, we included 25 cases in each group to determine a clinically relevant reduction in pain level.

Statistical tests were performed using SPSS 20 (SPSS Chicago, II, USA). Shapiro-Wilk test was used to determine the normality of distribution. Parametric variables as BMI, age, and duration of surgery were analyzed using the Student t-test. Mann-Whitney U test was used for non-parametric variables. Nominal data were analyzed by using the Fisher Exact Test or Chi- Square Test as appropriate. Post hoc ANOVA tests (Bonferroni) were used to compare the mean differences between the groups over time. A significant *p*-value was considered when it is equal to or less than 0.05.

Results

Sixty-six patients were enrolled, and 60 were included in the data analysis. One patient in the intervention group (cases) and two patients in the control group were excluded because of a conversion to open surgery. Two patients in the intervention group (cases) and one patient in the control group were lost to follow up (left the hospital before 12 hours) (Fig. 1).

There were no significant differences among the groups with respect to age, weight, parity, BMI, duration of surgery, and procedures of laparoscopic surgery (Table 1).

The postoperative shoulder pain scores were significantly lower in the intervention group than in the control group at 2 hours (0 (0-0) vs. 4 (2-4); $p < 0.001$), 6 hours (0 (0-2) vs. 5.5 (4-6); $p < 0.001$), and 12 hours (2 (0-2) vs. 4 (2-6); $p < 0.001$) after the operation. Similarly, postoperative laparoscopy-induced upper abdominal pain scores were significantly lower in the intervention group than in the control group at 2 hours (0 (0-0.5) vs. 4 (2-4); $p < 0.001$), 6 hours (1 (0-2.5) vs. 5.5 (4-6); $p < 0.001$), and 12 hours (2 (0-2) vs.4 (2-6); $p < 0.001$) after the operation. Also, trocar site pain scores were significantly lower at 2, 6 and 12 hours post-operative in the intervention group compared to the control group. Post hoc ANOVA tests (Bonferroni) were used to compare the mean time differences in postoperative shoulder pain scores, which showed a significant difference in the intervention group between 2 and 12 hours with a *p*-value

of 0.020 while in the control group showed a significant difference between 2 and 6 hours with a *p*-value of 0.029. Postoperative laparoscopy-induced upper abdominal pain scores showed a significant difference in the intervention group between 2 and 6 hours with a *p*-value of 0.035, with no significant difference in the control group. The pain scores at the trocar site showed no significant difference in either group (Table 2).

The first analgesic requested by the patients was significantly earlier in the control group than in the case group (221.5 ± 56.5 vs 252.3 ± 50.7; $p = 0.03$). Also, the total analgesic required within the 12 hours postoperative was significantly higher in the control group than in the case group ($p = 0.031$ for 1g. paracetamol and $p < 0.001$ for 2g. paracetamol) (Table 3). No patients received any additional rescue analgesics.

The Ramsay scores showed a significant difference between the two studied groups at 2hours (2 (2- 3) vs 2 (1.75- 2); $p < 0.001$), as more sedation occurred in the intervention group, with no statistically significant difference between the two studied groups at 6 and 12hours postoperatively ($p > 0.05$) (Table 3).

There was a significant difference in the occurrence of dry mouth and postural hypotension between the two studied groups at 2 and 6hours postoperatively. Six cases (20%) in the intervention group complained from dry mouth and 2 cases (6.7%) complained from postural hypotension compared to only one case in the control group (3.3%) complained from dry mouth and no one complained from postural hypotension at 2hours postoperatively.

All the cases in the control group had no side effects at 6hours postoperatively compared to 3 cases (10%) in the intervention group who had dry mouth and 3 cases (10%) who had postural hypotension. While, at 12 hours postoperative, one case in the intervention group (3.3%) complained from dry mouth, 2 cases (6.7%) complained from loss of appetite and one case (3.3%) complained from loss of appetite together with postural hypotension. The results showed that only 2 cases (6.7%) complained of loss of appetite in the control group (Table 4).

There was no significant difference in the incidence of postoperative nausea and vomiting, time to return of intestinal peristalsis, and post-operative hospitalization between the two groups. Regarding patient satisfaction score, there was a significant difference between the two groups, where 23 cases in the intervention group (76.7%) were completely satisfied compared to 3 cases (10%) in the control group (Table 4).

Discussion

The pathophysiological mechanism of pain after laparoscopy differs from that after laparotomy. Severe pain conditions after laparotomy are of somatic or parietal sources, while that after laparoscopy operations are produced by visceral irritation.[11]

In this study, we used 60 mg duloxetine for preemptive analgesia in laparoscopic gynecologic surgeries, and the VAS score was improved postoperatively compared with the control group, suggesting that duloxetine has good analgesic and sedative effects.

The results of the current study reported that the postoperative shoulder pain, upper abdominal pain, and trocar site pain were significantly lower in the intervention (case) group compared to the placebo (control) group over 12 hours postoperatively. Ramsey sedation scores showed significantly higher scores in the intervention (case) group at the first 2hours postoperatively compared to the placebo (control) group. Also, the first analgesic request was significantly earlier in the control group than the intervention group, and the total analgesia required within 12 hours postoperatively was significantly lower in the intervention group than the control group.

Various causes of shoulder pain have been reported after laparoscopic surgery, but the main theory is built on CO2 in the abdominal cavity. It is believed that pneumoperitoneum causes overstretching of the diaphragmatic muscle fibers and irritation, with a subsequent sensation of pain mediated by the phrenic nerve.[12] For the provision of this theory, Sallam and colleagues advocated that a combination of intraperitoneal normal saline infusion and low-pressure CO2 pneumoperitoneum (8 mmHg) appears to reduce the strength and the frequency of shoulder pain and upper abdominal pain rather than the standard pressure pneumoperitoneum (12- 15mmHg) in gynecologic laparoscopic surgery.[13]

According to a meta-analysis was done by Pergialiotis and colleagues, stated that pulmonary recruitment maneuver appears to be a simply performed and preventive measure of post-laparoscopic shoulder pain.[14]

Ingelmo and partners indicated that nebulization of ropivacaine intraperitoneally before or after surgery reduced postoperative pain and related shoulder pain after laparoscopic cholecystectomy. Moreover, this reduced the need for morphine and allowed earlier patients movement.[15]

Barazanch and partners recommended in a systematic review the basic analgesic techniques after laparoscopic cholecystectomy. They stated that paracetamol and

NSAID should be started before or during operation + dexamethasone or cyclooxygenase-2-specific inhibitor + infiltration of local anesthetics at the surgical site. Opioid should only be reserved for the rescue of analgesia. Regarding surgery, they commended a low-pressure pneumoperitoneum, a saline rinse after surgery, and aspiration of pneumoperitoneum.[16]

Duloxetine is suggested as first-line therapy for the treatment of neuropathy induced by chemotherapy by the American Society of Clinical Oncology,[17] also as first-line therapy for fibromyalgia in the presence of mood disorders by the German Interdisciplinary Association for Pain Therapy, as a Grade B approval for treating diabetic neuropathy by the American Association for Neurology.[18] The possible mechanism of action of duloxetine in our study could be explained by the central pain inhibitory action secondary to the potentiation of serotonergic and noradrenergic activities in the CNS. Duloxetine would act as an adjuvant to other conventional analgesics.

In accordance with this study, a meta-analysis conducted by Zorrilla and partners approved the effectiveness of the perioperative use of duloxetine for the treatment of acute postoperative pain.[19]

Wang and colleagues reported the effectiveness and safety of duloxetine in Chinese patients with chronic osteoarthritic pain found that duloxetine-treated patients reported significant pain decline, compared with placebo.[20]

Hossain and colleagues reported a systematic review about the efficacy of duloxetine in the managing of painful diabetic neuropathy (PDN) and stated the use of duloxetine for treating the pain associated with PDN especially in patients who have cardiovascular complications.[21]

A systematic review with a meta-analysis conducted by Oliveira and partners did not support the clinical use of duloxetine for the treatment of acute postoperative pain despite the statistically significant effects of duloxetine in reducing postoperative pain and opioid consumption during the first 48 hours postoperatively.[22]

Limitations of the current study are 1) small sample size, 2) short postoperative follow-up time (12 hours only), 3) the study sample was female only. Further studies should be done by larger sample size, longer postoperative follow-up, the use of both sexes, and serum concentration measurement of duloxetine.

In conclusion, compared with placebo, the use of 60 mg duloxetine 12 hours preoperatively allowed better postoperative pain, caused less referred shoulder pain,

reduced total analgesic requirements, allowed earlier mobility, did not cause significant side effects, and resulted in better patient satisfaction. We here confirming that 60 mg duloxetine is safe and effective analgesic adjuvant in gynecological laparoscopies.

Conflicts of interest

The authors declare no conflicts of interest.

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Table 1 - Patients' characteristics and operative data of the study groups.

	Cases (n = 30)	**Control (n = 30)**	***p* value**
Age	26.8 ± 3.81	26.67 ± 4.22	0.898
BMI	32.4 ± 2.04	33.27 ± 1.98	0.101
Parity			
0 (No., %)	11 (36.7%)	8 (26.7%)	0.707
1 (No., %)	12 (40%)	14 (46.7%)	
2 (No., %)	7 (23.3%)	8 (26.7%)	
Operation duration(min)	20.67 ± 5.04	21.33 ± 6.01	0.643
Procedure			
Diagnostic	14 (46.7%)	14 (46.7%)	0.789
O. Cyst	6 (20%)	6 (20%)	
O. Drill	9 (30%)	10 (33.3%)	
Adhesiolysis	1 (3.3%)	0 (0%)	

O. Cyst, ovarian Cyst; O. Drill, ovarian Drill.

Data presented by mean ± standard deviation and number (%).

Independent sample t-test and Chi-square test,

[a] Statistically significant difference ($p < 0.05$).

[b] Statistically significant difference ($p < 0.01$)

Table 2 - VAS scores for shoulder (SH), upper abdominal (UA) and trocar site (TS) pain 12 hours postoperative.

VAS	**Cases (n = 30)**	**Control (n = 30)**	***p* value**
	Median (IQR)	**Median (IQR)**	
VAS SH			

2h	0 (0- 0)	4 (2- 4)	< 0.001[d]
6h	0 (0- 2)	5.5 (4- 6)	< 0.001[d]
12h	2 (0- 2)	4 (2- 6)	< 0.001[d]
^*p*. value	**0.020[a]**	**0.029[b]**	
VAS UA			
2h	0 (0- 0.5)	4 (2- 4)	< 0.001[d]
6h	1 (0- 2.5)	5.5 (4- 6)	< 0.001[d]
12h	2 (0- 2)	4 (2- 6)	< 0.001[d]
^*p*. value	**0.035[b]**	**0.133**	
VAS TS			
2h	2 (0- 2)	4 (2- 5)	0.011[e]
6h	2 (0- 2)	4 (2- 6)	0.001[d]
12h	0 (0- 2)	4 (2- 4.25)	< 0.001[d]
^*p*. value	**1.000**		

Data presented by median (IQR).

SH, shoulder; UA, upper abdominal; TS, trocar site pain.

^ Post hoc ANOVA tests (Bonferroni) were used to compare the mean differences over time

[a] Significant difference between 2h and12h.

[b] Significant difference between 2h and 6h.

[c] Significant difference between 6h and 12h, using Bonferroni test.

[d] statistically significant difference ($p < 0.01$).

[e] Statistically significant difference ($p < 0.05$).

Table 3 - First analgesic request, total analgesia required, and Ramsay Sedation score within 12 hours postoperative.

	Cases (n = 30)	**Control (n = 30)**	***p* value**
1st analgesic request(min)	252.3 ± 50.7	221.5 ± 56.5	0.03[a]
Total analgesic required within 12 h. postoperative			
1 g paracetamol	0 (0%)	6 (20%)	0.031[a]
2 g paracetamol	4 (13.3%)	20 (66.7%)	< 0.001[b]
Ramsay Sedation score	**Median ((IQR)**	**Median ((IQR)**	
2h	2 (2- 3)	2 (1.75- 2)	0.001[b]
6h	2 (2- 2)	2 (2- 2)	0.393
12h	2 (2- 2)	2 (2- 2)	1.000

Data presented by mean ± standard deviation, number (%) and median (IQR).

Independent sample t-test, Chi-square test, and Mann-Whitney test.

[a] Statistically significant difference ($p < 0.05$),

[b] Statistically significant difference ($p < 0.01$)

Table 4 - Postoperative side effects.

Side effects	Cases (n = 30)	Control (n = 30)	*p* value
	No. (%)	No. (%)	
2h			
No	22 (73.3%)	29 (96.7%)	0.038[a]
Dry mouth	6 (20%)	1 (3.3%)	
P.H.	2 (6.7%)	0 (0%)	
6h			
No	24 (80%)	30 (100%)	0.036[a]
Dry mouth	3 (10%0	0 (0%)	
P.H.	3 (10%)	0 (0%)	
12h			
No	26 (86.7%)	28 (93.3%)	0.557
Dry mouth	1 (3.3%)	0 (0%)	
Loss of app	2 (6.7%)	2 (6.7%)	
P.H. and Loss of app	1 (3.3%)	0 (0%)	
PONV	15 (50%)	17 (56.7%)	0.605
Intestinal peristalsis (h)	9.67 ± 1.32	9.43 ± 1.25	0.485
Discharge from hospital (days)	1.27 ± 0.45	1.33 ± 0.48	0.581
Patient Satisfaction Score			0.000[b]
Completely dissatisfied	0	1 (3.3%)	
Dissatisfied	1 (3.3%)	7 (23.3%)	
Neutral	2 (6.7%)	14 (46.7%)	
Satisfied	4 (13.3%)	5 (16.7%)	
Completely satisfied	23 (76.7%)	3 (10%)	

PONV, Postoperative nausea and vomiting; P.H., Postoperative Hypotension.

Data presented by number (%), mean ± standard deviation

Independent sample t-test and Chi-square test.

[a] Statistically significant difference ($p < 0.05$),

[b] Statistically significant difference ($p < 0.01$)

Figure 1 - Flow diagram of the participants in this study.