ISSN: 2581 – 3633
PubMed - National Library of Medicine - ID: 101745081

International Journal of Medical Science and Advanced Clinical Research (IJMACR)

Available Online at:www.ijmacr.com

Volume – 7, Issue – 4, July - 2024, Page No. : 22 – 29

The Effect of Perioperative Duloxetine on Global Post-Operative Quality of Recovery After Laparoscopic Cholecystectomy

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How to citation this article: Dr. Sana Parvez, Dr. Bushra Rehman, "The Effect of Perioperative Duloxetine on Global Post-Operative Quality of Recovery After Laparoscopic Cholecystectomy", IJMACR- July- 2024, Volume – 7, Issue - 4, P. No. 22 – 29.

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Type of Publication: Original Research Article

Conflicts of Interest: Nil

Abstract

Introduction:Duloxetine has been commonly prescribed for the treatment of major depression and anxiety and improve post-surgical quality of recovery. Duloxetine also has been used in the treatment of chronic pain conditions, such as osteoarthritis and musculoskeletal pain. The aim of the study is to examine the effect of perioperative duloxetine on global post-operative quality of recovery after laparoscopic cholecystectomy.

Material and Methods: This prospective, double-blind randomized placebo controlled and conducted at Acharya Shri Chander College of Medical Sciences and Hospital, Jammu for a period of one-year on patients undergoing LC after approval from IEC. Patients were randomly divided into two groups of 50 each on the day of surgery to receive 60 mg duloxetine as a single oral dose 2h before the surgery or placebo. The outcome was the difference in visual analogue scale (VAS) scores and Quality of Recovery (QoR) scores between the two studied groups.

Results: It was observed that the patients administered one dose of perioperative duloxetine, 60 mg 02 h preoperative, a second dose 24 h postoperative, had a significant lower postoperative morphine consumption, intraoperative fentanyl consumption, a significant decreased postoperative pain and better quality of recovery for 48 h postoperatively.

Conclusion: The study concluded that the preoperative duloxetine administration considerably lowers postoperative pain when compared to placebo in patients undergoing LC.

Keywords: Post-operative, Duloxetine, Cholecystectomy

Introduction

Pain after abdominal or thoracic surgeries leads to hypoventilation from splinting. Chronic post-surgical pain develops after surgical intervention and lasts at least

02 months while other causes for pain have been explored and excluded. The incidence of the CPSP shows a wide variability between 20 and 50% [1]

The goal of post-operative pain management is to provide adequate analgesia with the minimum of medication and to minimize as much as possible the side effects of the administered drugs. There is a consensus regarding the fact that an optimal/ dynamic post-operative pain management is necessary for an early post-operative recovery [2].

Although opioids are considered as the analgesics of choice but their use carries the risk of side effects and hyperglesia. Therefore, multimodal analgesia provides better analgesia synergistically as compared with conventional analgesia. Multi-modal analgesia is advocated for perioperative pain management, to reduce opioid use and its associated adverse effects. In multimodal analgesia lower doses of each drug can be provided with few overall side effects obtained from individual compounds [3].

Duloxetine hydrochloride is the chloride salt of duloxetine, a fluoxetine derivative belonging to the class of selective serotonin (5HT) and norepinephrine (NE) reuptake inhibitors (SSNRIs) and exhibiting antidepressant activity.

Duloxetine has been commonly prescribed for the treatment of major depression and anxiety [4] and improve post-surgical quality of recovery. Duloxetine also has been used in the treatment of chronic pain conditions, such as osteoarthritis and musculoskeletal pain [5].

Till date the beneficial effects of duloxetine have been demonstrated in patients undergoing laparoscopic hysterectomy and other surgeries including radical mastectomy, open hysterectomy, spine surgeries, total knee and hip replacement.

The main objective of the current investigation was to examine the effect of perioperative duloxetine on global post-operative quality of recovery after laparoscopic cholecystectomy.

Material and Methods

This study was a prospective, double-blind randomized placebo controlled and conducted at Acharya Shri Chander College of Medical Sciences and Hospital, Jammu for a period of one-year w.e.f 2019 to 2020 after approval from IEC.

The current study included 100 adult patients with American Society of Anesthesiologists (ASA) physical status I - II who had Journal Pre-proof undergone elective laparoscopic surgery.

Exclusion Criteria

- Patients with medical conditions (hypertension, diabetes mellitus, renal or liver impairment)
- Body mass index (BMI) ≥ 40 kg.m-2
- Patients 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
- Also, suspended laparoscopy to laparotomy, complicated surgery like bleeding and persistent pain after planned analgesics, or 48 hours were excluded.

Patients will be randomized by the use of a computer generated table of random numbers to receive duloxetine 60 mg orally 2 hours before the surgical procedure and

at 24 hours after the surgical procedure or a placebo pill following the same time schedule. The placebo pill was assembled by the resident on duty, not participating in study ensuring that the placebo and the duloxetine pills appeared to be identical.

After obtaining written informed consent from the patients; complete pre-anaesthetic checkup was done on the day of surgery. A detailed history of present and past illness, history of drug allergy and any medication in pre-operative period was recorded.

General physical examination, systemic examination and airway management was conducted. Basic investigations were ordered. Baseline demographic profile including age, sex, weight and height were noted.

Preoperative Medication

Patients were given Tab alprazolam 0.25 mg the night before surgery. Patients belonging to group D received 60 mg duloxetine 2hrs prior to surgery whereas patients in group C received placebo 2hrs prior to surgery.

Technique of Anesthesia

In the preoperative room, an intravenous line with an 18-gauge cannula was established for infusion of fluids and administration of drugs. After receiving the patient in Operation Theatre, with the intravenous line, Ringer lactate started. Basic monitors like Noninvasive Blood Pressure, 5- lead electrocardiography (ECG), Plethysmography (SPO2) was applied.

Induction

All patients received injection Fentanyl 2mcg/kg body weight intravenous before induction:

Patients were pre-oxygenated with 100% oxygen for 3 minutes and induced with injection Propofol 2.5 mg 3/ body weight and injection Atracurium 0.5 mg /kg followed by ventilation for 3 minutes followed by intubation with polyvinyl chloride endotracheal tube of appropriate size. End- Tidal carbon dioxide monitors were applied.

Maintenance

Anesthesia was maintained with a mixture of 60% nitrous oxide and 40% oxygen and Isoflurane in the range of 1-2.5%. Muscle paralysis was maintained with injection Atracurium0.1 mg/kg body weight.

Controlled mechanical ventilation with the initial volume of 8ml/kg body weight, respiratory rate 14 breaths per minute, I: E ratio of 1:2 was adjusted to maintain ETCO2 of 35-45 mmhg. Injection diclofenac 1.5 mg per kg was administered in by slow intravenous infusion. Injection ondansetron 0.1 mg intravenous was administered towards the end of procedure.

Reversal:

Isoflurane was stopped at the start of skin closure. The residual neuromuscular blockade was reversed using injection neostigmine 0.05 mg per kg body weight and injection glycopyrrolate 0.01 mg per kg body weight and patient was extubated following adequate reversal and transferred to the recovery room.

Postoperative Management:

Pain assessment was done at 0 hr., 1hr, 2hr, 4hrs, 12 hrs., 24 hrs. The patient was monitored in the recovery ward regarding the analgesic requirement and adverse effects. The time to first, second and third rescue analgesia was recorded and the total analgesia received by patient in 24hrs postoperative period was noted. Pain and adverse effects were treated accordingly. Patients in group D were administered 60 mg of Duloxetine 24 hrs. Postoperatively and patients belonging to group c were administered placebo.

A detailed questionnaire was conducted regarding the quality of recovery at 24hrs and 48hrs after surgery. Postoperative pain was treated with Infusion

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paracetamol 1 gram and for further analgesic requirement (if any) injection Tramadol 1 milligram per kg shall be administered intravenously. Postoperative vomiting was done with Injection ondansetron 0.1 mg per kg body weight intravenous. Postoperative adverse effects such as headache, nausea, vomiting, hypotension, bradycardia, respiratory depression, itching, and sedation reported were recorded accordingly.

IBM-SPSS 24.0 (IBM-SPSS Inc., Chicago, IL, USA) was used for data verification, coding by the researcher and analysis.

Observations and Results

In our study 100 patients were assessed who undergone laparoscopic cholecystectomy and equally distributed in two groups (n=50 patients per group).

Table 1: Demographic data and patient's characteristics

Variables	Duloxetine Group (N=50)	Placebo Group (N=50)
Age/ Years	35.66±8.4	36.86±9.3
Sex		
Male	23 (46%)	24(48%)
Female	27(54%)	26(52%)
Weight/ kg	67.77±9.5	65±8.4
Height/cms	162±4.8	164±5.2
BMI	27±2.8	28.6±3.2
ASA		
I	20(40%)	23(46%)
II	25(50%)	21(42%)
III	5(10%)	6(12%)
Intravenous fluid (L)	2.7±0.50	2.7±0.56

Table 1 depicts the demographic and baseline characteristics of study participants. It was observed that the two groups were similar regarding demographic and baseline characteristics of study participants.

Table 2: Post-operative VAS score in 48 h

Variables	Duloxetine Group (N=50)	Placebo Group (N=50)
VAS 0-2 H	3±0.59	4.47±0.93
VAS 2-4 H	2.47±0.57	4.30±0.91
VAS 4-8 H	2.23±0.77	3.97±0.76
VAS 8-12 H	1.63±0.71	3.67±0.84
VAS 12-24 H	1.17±0.87	3.70±0.75
VAS 24-36 H	0.77±0.77	3.53±0.81
VAS 36-48 H	0.50±0.67	3.40±0.76

Table 2 depicted the post-operative VAS score in 48h. It was observed in our study that the duloxetine group had significantly lower pain scores than the placebo group represented by VAS score in the first 48 postoperative hours than the placebo group at all-time intervals: 0–2, 2–4, 4–8, 8–12, 12–24, 24–36 and,36–48. (P value <0.01).

Figure 1: Line diagram showing VAS Scores at different intervals of time in two groups

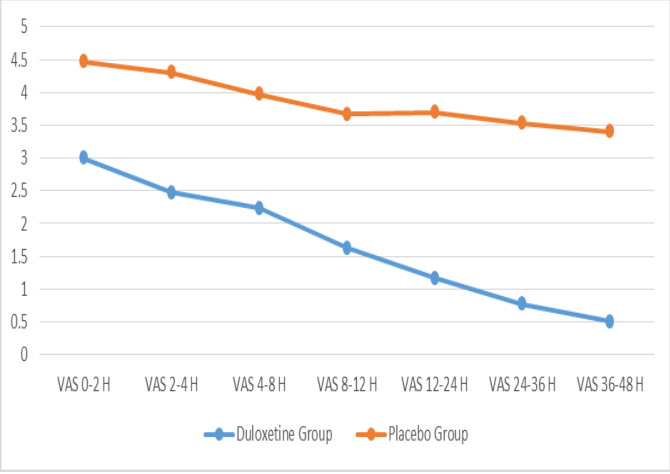

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Table 3: Intraoperative/ total post- operative fentanyl and morphine consumption

Variables	**Duloxetine Group (N=50)**	**Placebo Group (N=50)**
Intraoperative fentanyl consumption	28.33 ± 22.20	64.16 ± 25.45
Total postoperative morphine consumption	4.6 ± 2.9	10.3 ± 1.7

Table 3 depicts the intraoperative/ total post- operative fentanyl and morphine consumption in our study. It was observed in our study that the total intraoperative fentanyl consumption was decreased in the duloxetine group compared to the placebo group, mean and standard deviation (mean ± SD) (28.33 ± 22.20) vs. (64.16 ± 25.45), P value <0.01. Further, the cumulative 48 h morphine consumption was significantly reduced in the Duloxetine group compared to the placebo group, (mean ± SD) (4.6 ± 2.9 mg vs. 10.3 ± 1.7 mg), P < 0.01.

Table 4: Quality of recovery (QOR) questionnaire

Variables	Duloxetine Group (N=50)	Placebo Group (N=50)
Psychological support	32.2 ± 1.7	29.2 ± 1.9
Emotional state	41.9 ± 1.8	35.4 ± 3.4
Physical comfort	52.3 ± 1.7	47 ± 3.3
Physical Independence	22.1 ± 1.6	18.9 ± 1.3
Pain	32 ± 1.6	25.3 ± 2.3
Total	180.8 ± 4.5	156 ± 5.9

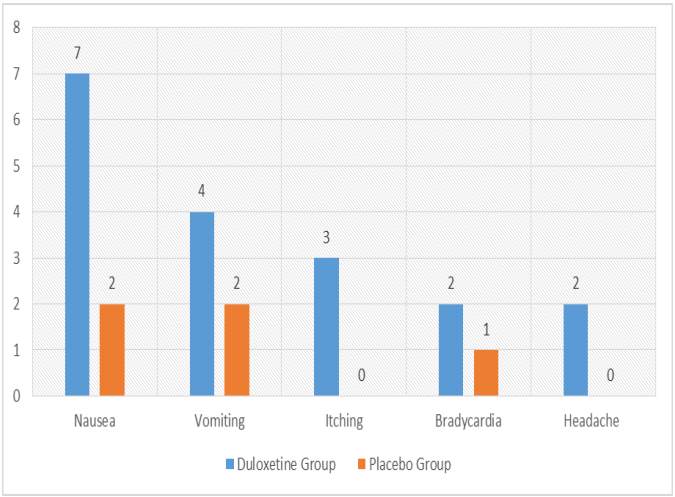
Table 4 depicts the scores of Quality of recovery questionnaire among study participants in two groups. It was observed in our study that the duloxetine group had better postoperative quality of recovery than the placebo group. The mean and standard deviation (mean ± SD) of total QoR-40 score for the duloxetine group was (180.8 ± 4.5) compared to (156 ± 5.9) in the placebo group ($P < 0.01$) at 48 h postoperatively, moreover the individual subcomponents in the QoR-40 showed that the duloxetine group had better results than the placebo group in the psychological support, emotional status, physical comfort, physical independence and, pain.

Table 5: Post-operative side effects

Variables	Duloxetine Group (N=50)	Placebo Group (N=50)
Nausea	7 (14%)	2(4%)
Vomiting	4(8%)	2(4%)
Itching	3(6%)	0
Bradycardia	2(4%)	1(2%)
Headache	2(4%)	0

Table 5 depicts the post-operative side effects among the study participants in two groups. It was observed that umber and percentage of nausea, vomiting, bradycardia and headache were more in the duloxetine group than the placebo group. In our study participants in Duloxetine group reported nausea in 7 (14%), vomiting in 4 (8%), itching in 3(6%), bradycardia in 2 (4%) & Headache in 2 (4%) participants.

Figure2: Bar diagram showing Post-operative side effects among study groups



Discussion

The present study had shown that patients subjected to laparoscopic cholecystectomy surgery who administered one dose of perioperative duloxetine, 60 mg 02 h preoperative, a second dose 24 h postoperative, had a significant lower postoperative morphine consumption, intraoperative fentanyl consumption, a significant decreased postoperative pain and better quality of recovery for 48 h postoperatively. The adverse effects including nausea, vomiting, bradycardia, and headache were higher in the duloxetine group compared with the placebo group; however, they did not reach the statistical significant level.

It was It was observed in our study that the two groups were similar regarding demographic and baseline characteristics of study participants. It was observed in our study that the duloxetine group had significantly lower pain scores than the placebo group represented by VAS score in the first 48 postoperative hours than the placebo group at all-time intervals. In a similar study conducted by **Nasr A et al. 2014** wherein Duloxetine 60 mg was administered 2 days before surgery till 2 weeks postoperatively in patients undergoing mastectomy and found that it not only reduced pain postoperatively but also improved chronic pain at 3 months and 6 months postoperatively.

Also, in accordance with our study, a meta-analysis conducted by **Zorrilla-Vaca A et al., 2019** found the effectiveness of the perioperative use of Duloxetine for the treatment of acute postoperative pain. **Altiparmak B et al., 2018** compared pregabalin and duloxetine in their role as adjuvants in a multimodal analgesia regime and postoperative effects on cognitive function after spinal surgery. They found that the analgesic efficacy of duloxetine and pregabalin were similar and significantly greater than a placebo.

It was observed in our study that the duloxetine group had significantly lower pain scores than the placebo group represented by VAS score in the first 48 postoperative hours than the placebo group at all-time intervals. Further, the total intraoperative fentanyl consumption and cumulative 48 h morphine consumption was significantly decreased in the duloxetine group compared to the placebo group. The similar findings were reported by **Kassim et al., 2018** wherein impact of duloxetine and dexamethasone was studied for improving pot\st-operative pain after laparoscopic gynecological surgeries**. Castro-Alves LJ et al., 2016** in a prospective randomized, double blinded, placebo controlled study also finds that duloxetine improves post-operative opioid consumption, even in the presence of a robust multimodal analgesic strategy. In contrast to our study, **Erdmann et al., 2022** studied the effects of a short-term perioperative duloxetine treatment on 60 patients undergo open colectomy surgery and they concluded that duloxetine did not reduce total opioid consumption or pain intensity during the initial 48 h following major colon surgery. They found reduction in opioid consumption and VAS score but not reach the statistical significance level as they administered only two doses for operation (open colectomy) with known sever postoperative pain.

It was observed in our study that the duloxetine group had better postoperative quality of recovery than the placebo group. The mean and standard deviation (mean ± SD) of total QoR-40 score for the duloxetine group was (180.8 ± 4.5) compared to (156 ± 5.9) in the placebo group ($P < 0.01$) at 48 h postoperatively, moreover the individual subcomponents in the QoR-40

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showed that the duloxetine group had better results than the placebo group in the psychological support, emotional status, physical comfort, physical independence and, pain. The results are consistent with the similar studies conducted by **Melnyk et al., 2011**wherein it was found that duloxetine reduces surgical stress and accelerate recovery in patient's elective surgery. **Zahang et al., 2020** also found the results consistent to our results in a similar study.

It was observed that umber and percentage of nausea, vomiting, bradycardia and headache were more in the duloxetine group than the placebo group. In a study conducted by **Govil N et al., 2020** the similar results were observed related to side effects of duloxetine group.

Conclusion

The current study has demonstrated that preoperative duloxetine administration considerably lowers postoperative pain when compared to placebo. These results imply that non-opioid analgesics, including duloxetine, can be important during the acute perioperative phase in patients having LC.

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