International Journal of Medical Anesthesiology

E-ISSN: 2664-3774
P-ISSN: 2664-3766
www.anesthesiologypaper.com
IJMA 2023; 6(4): 16-24
Received: 05-08-2023
Accepted: 11-09-2023

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Duloxetine for post-operative analgesia after modified radical mastectomy: A prospective randomized study

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DOI: https://doi.org/10.33545/26643766.2023.v6.i4a.429

Abstract
Background: Insufficient management of postoperative pain has been shown to be correlated with prolonged hospitalization, escalated healthcare expenses, disrupted sleep patterns, heightened risk of depression, compromised functional abilities, and a worse quality of life. The objective of this research is to assess the efficacy of duloxetine in managing postoperative pain following radical mastectomy.
Methods: This prospective randomised controlled work was performed on (40) individuals scheduled for modified radical mastectomy in Tanta University Hospital. The criteria for inclusion for this study consisted of adult female patients between the ages of 18 and 60 who were scheduled to have a modified radical mastectomy (MRM), ASA I, II and III. A total of 20 participants were recruited for this research, with an equal number of participants being randomly assigned to each of the two groups. The process of randomization was conducted using a computer-generated method. The patients were allocated by closed envelop into 2 groups: Group (1) (control group): Participants received 500 mg of IV acetaminophen (every 6 hours post operatively). Group (2): Participants received duloxetine 30 mg every 12 h for 3 days prior to operation, 30 mg 2 h prior to surgery and 30 mg 12 h following surgery and 500 mg of IV acetaminophen (every 6 hours following surgery).
Results: There was significant decrease at 2,4,6,18,30,36 and 48 h in group 2 contrasted to group 1 (P value <0.001) and statistically insignificant difference in postoperative HR at baseline, PACU, 12, 24 and 42 h among both groups. A substantial decrease in postoperative MAP was existed at 2,4,6,18,30,36 and 48 h in group 2 contrasted to group 1 and statistically insignificant difference at baseline, PACU, 12, 24 and 42 h among both groups (P value <0.001). A statistically substantial decrease in intraoperative fentanyl consumption was existed in group 2 compared to groups 1 (P value <0.001). There was substantial decrease in VAS at 2,4,6,18,30,36 and 48 hours in group 2 contrasted to group 1 (P value<0.05). The satisfied patients in group 2 were significantly higher in group 2 compared to group 1.
Conclusions: The current work showed that the use of perioperative duloxetine was safe and effective in controlling pain after modified radical mastectomy.

Keywords: Duloxetine, analgesia, modified radical mastectomy

Introduction
Insufficient management of postoperative pain has been shown to be correlated with extended duration of hospitalization, escalated healthcare expenses, disrupted sleep patterns, depressive symptoms, compromised physical functioning, and a negative impact on overall quality of life [1]. The operation known as modified radical mastectomy (MRM) is often performed and has been shown to be correlated with significant levels of postoperative discomfort.
Pre-emptive analgesia refers to the administration of analgesic medication prior to surgical operation with the aim of preventing the development of central sensitization resulting from the exposure to painful stimuli. Pharmaceutical substances which include pre-gabalin, gabapentin, dexamethasone, serotonin–norepinephrine reuptake inhibitors, and cyclooxygenase-2 inhibitors were employed in the context of preemptive analgesia [2, 3].
There are conflicting findings about the efficacy of duloxetine in the treatment of acute postoperative pain.
In this research, we will examine the findings of a recent meta-analysis conducted in 2020. The analysis found that the existing evidence does not provide sufficient support for the therapeutic application of duloxetine in the treatment of acute postoperative pain [4], Therefore, we will delve into the details of this analysis.

Numerous studies have demonstrated that the administration of duloxetine during the perioperative period for a limited duration has a substantial impact on mitigating postoperative pain and minimizing the need for analgesics [5-7].

Duloxetine is a pharmacological agent with dual anti-depressant properties, functioning by inhibiting the reuptake of serotonin (5-HT) and norepinephrine (NE) at neuronal synapses. This mechanism of action leads to the modulation of downstream inhibitory pain pathways, ultimately resulting in increased levels of serotonin and norepinephrine within the central nervous system [8]. Duloxetine has been authorized for therapeutic use in the management of post-traumatic depression, severe depression, and generalized anxiety disorder. Furthermore, this medication has been authorized for the management of several chronic painful syndromes, such as neuropathic pain linked to diabetes, chronic pain in the muscles and joints, and fibromyalgia [9].

The explained mechanisms of action indicate that duloxetine has the potential to serve as a valuable supplement in managing immediate postoperative pain.

The objective of this research is to assess the efficacy of duloxetine in managing postoperative pain following radical mastectomy.

Patients and Methods

This prospective randomised controlled work was performed on (40) individuals scheduled for modified radical mastectomy in Tanta University Hospital. The researchers received an informed written agreement from either the participant or the participant's family. After approval from institutional ethical committee of the faculty of medicine, Tanta University with approval code 35146/12/21 and registered on clinical trials.gov with registration code NCT05442268, an informed consent was taken from each participant. The duration of the work was from April 2022 until April 2023.

The criteria for inclusion for this study consisted of adult female patients between the ages of 18 and 60 who were scheduled to have a MRM. Additionally, individuals who had ASA classifications I, II, and III were included.

The exclusion criteria were individuals who were recognized to have allergy to duloxetine, as well as abnormal hepatic or kidney function tests. Narrow-angle glaucoma, an individual who engages in persistent drug abuse for a period exceeding three months. The use of gabapentin or pregabalin over an extended period of time, exceeding three months, taking monoamine oxidase inhibitors or tricyclic antidepressants, Pregnant women, as well as any individual diagnosed with mental problems or seizure disorders.

Randomization

A total of 20 individuals were recruited for participation in this research, with an equal number of patients assigned to each group. The allocation of participants into the two groups was done randomly. The process of randomisation was conducted using a computer-generated approach. The patients were allocated by closed envelop into 2 groups:

Group (1) (control group)

Participants received 500 mg of IV acetaminophen (every 6 hours post operatively).

Group (2)

Participants received 30 mg of duloxetine every 12 h for 3 days prior to operation,30 mg 2 h prior to surgery and 30 mg 12 h postoperatively and 500 mg of IV acetaminophen (every 6 hours following surgery).

Anaesthetic technique

The preoperative evaluation had many components, which includes taking of history, clinical assessment, and regular laboratory tests, which included the analysis of full blood picture, coagulation profile, as well as renal and hepatic testing. In the context of preoperative care, the pre-anesthetic evaluation is conducted, all participants were familiarized with Visual Analouge Score Scale (VAS). On arrival to the operating room, all standard monitors were applied to each patient that include, 5 leads ECG, noninvasive blood pressure (NIBP) and pulse oximetry.

Two intravenous lines of optimum size were inserted in the dorsum of the hand and forearm of the opposite side, then IV fluids in the form of ringer solution were started. Each participant were administered the same conventional general anesthetic treatment. The induction process included the administration of intravenous fentanyl at a dosage of 1 µg/kg, intravenous propofol at a dosage range of 1-2 mg/kg, and the facilitation of endotracheal intubation by the intravenous administration of atracurium at a dosage of 0.5 mg/kg. Maintaining a state of anesthesia was achieved by administering inhalation of isoflurane at a concentration of 1-2% in a 50% oxygen mixture. Additionally, a drug that relaxes muscles, atracurium, was administered intravenously at a dosage of 0.1 mg/kg intermittently to guarantee adequate muscular relaxation throughout the surgery. The participants received an infusion of Ringer solution in order to address the fluid deficit, and they were subjected to mechanical ventilation at an adequate level to maintain the end-tidal carbon dioxide (EtCO2) within the range of 35-45 mmHg. A rescue analgesia of fentanyl IV at a dosage of 0.5 µg/kg was administered.

Following the completion of skin closure and the successful reversal of relaxation of the muscles using neostigmine (0.04-0.08 mg/kg) and atropine (0.01-0.02 mg/kg), the participant underwent extubation and was subsequently transferred to the PACU for a period of two hours. During this time, the individual's hemodynamics were closely monitored. Following the monitoring period, the individuals was transferred to the ward where the Visual Analog Scale (VAS) was utilized to evaluate their pain level. If the VAS score was found to be equal to or greater than 4, the individuals received intravenous morphine at a dosage of 0.05 mg/kg. Subsequently, a dosage of 500 mg of acetaminophen was administered intravenously every 6 hours to manage pain following surgery in both experimental groups.

Measurements

- **Demographic data:** (Age, weight, ASA classification) at admission. **Intraoperative Hemodynamics:** Blood pressure and HR (were assessed pre and post-induction, after intubation then every 15 minutes intraoperative.
- **Total Intraoperative fentanyl consumption:** Total intraoperative fentanyl consumption was measured.
- **Postoperative Hemodynamics:** HR and MAP were measured at 0 h at PACU then at 2, 4, 6 h at ward then every 6 hrs for 48 hours postoperatively.

- **Time to 1st rescue analgesia:** Time to 1st rescue analgesia was assessed.
- **Total postoperative morphine consumption:** Was measured.
- **Post-operative pain:** Was evaluated by VAS scale from 0 (no pain) to 10 (the worst imaginable pain) at 2, 4, 6 h then every 6h for 48 hours following surgery.
- **Patient Satisfaction:** Was assisted by self-administered satisfaction scale (very satisfied, somewhat satisfied, somewhat dissatisfied, very dissatisfied).
- **Adverse effects:** Bradycardia, hypotension, vomiting, mouth dryness, diarrhea, nausea, sleeplessness, somnolence, tiredness, hyperhidrosis, and pruritis were recognized and subsequently managed.
- **Our primary outcome:** It was measured total morphine consumed in the initial 48 hours following surgery.
- **Secondary outcome:** The duration until first rescue analgesia. The pain levels were assessed utilizing the VAS, with a score of 0 indicating the absence of pain and a score of 10 representing the most severe pain possible. Additionally, the duration till ambulation was recorded.

Sample size calculation

The determination of the sample size was conducted using data on morphine consumption from individuals who had undergone MRM. In order to identify a 50% variance in morphine consumption among the groups at 48 hours postoperative, a total of 17 individuals in each group were determined to be necessary. This calculation was performed with a power of 0.8 and an α level of 0.05. However, the sample size was subsequently raised to 20 in order to account for potential dropouts.

Statistical analysis

The statistical analysis was conducted using SPSS v26, a software developed by IBM Inc. in Chicago, IL, USA. The quantitative parameters were reported as the mean and standard deviation (SD) and were contrasted among both groups using an unpaired Student's t-test. The qualitative parameters were reported in terms of frequencies and percentages (%), and their analysis was conducted using the Chi-square test or Fisher's exact test, as deemed suitable. A two tailed P value < 0.05 was considered statistically significant

Results

In this investigation, a prospective randomised double-blind design was employed to test the eligibility of 73 individuals. Out of these individuals, 21 didn't match the predetermined criteria, while an additional 12 individuals declined to take part in the trial. The remainder of 40 individuals were assigned to 2 groups at random, with 20 individuals in each group. The patients who were assigned to certain groups were thereafter monitored and subjected to statistical analysis. (Fig. 1)

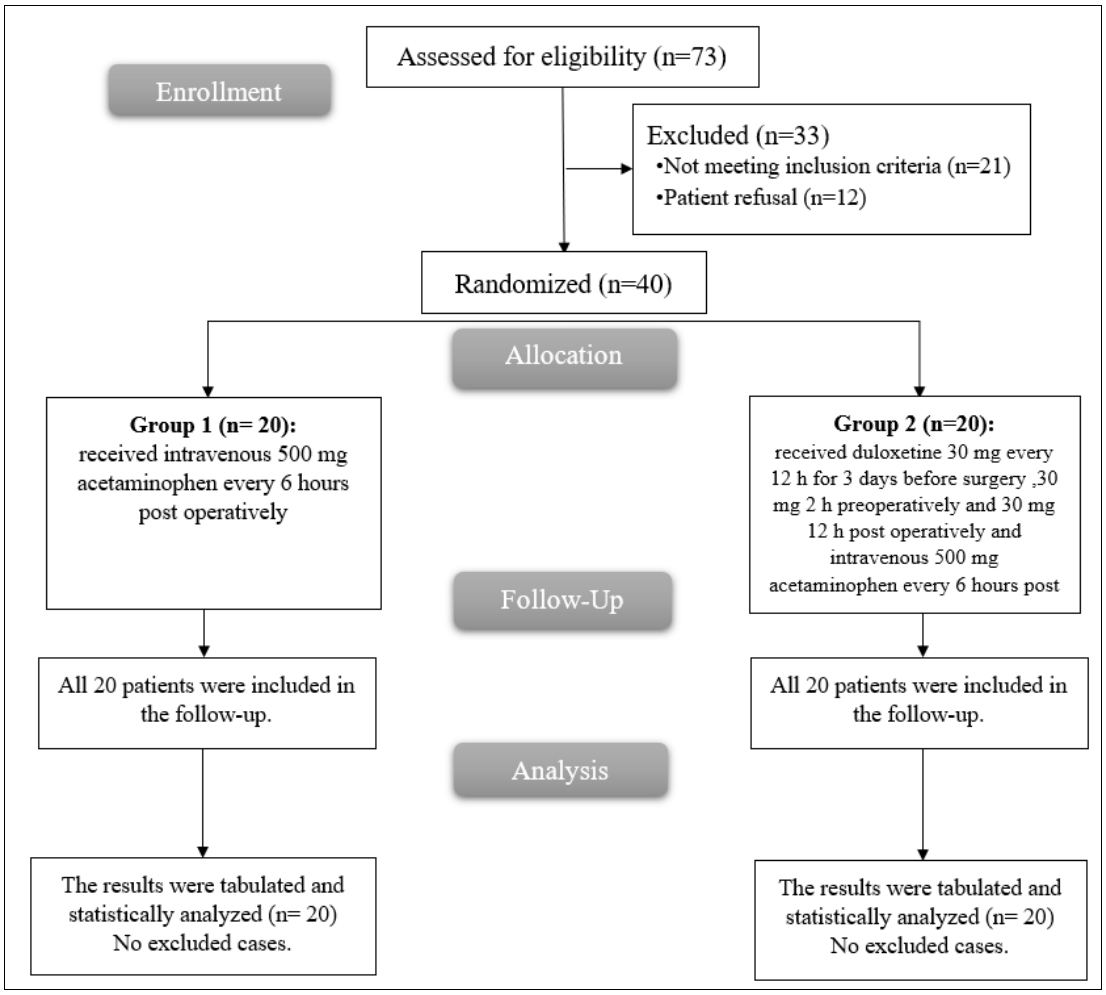

Fig 1: CONSORT flowchart of the enrolled patients

No statistically substantial variation was existed among both groups according to age, ASA, Weight, height, BMI and duration of surgery. [Table 1]

Table 1: Patient's baseline characteristics data between the three groups.

		Group 1	Group 2	P value
Age (years)	Mean ± SD	46.2 ± 9.04	48.65 ± 7.29	0.351
	Range	31-60	33-59	
ASA physical status	II	12 (40.0%)	13 (43.33%)	0.744
	III	8 (26.67%)	7 (23.33%)	
Weight (kg)	Mean ± SD	84.75 ± 11.29	87.2 ± 13.03	0.529
	Range	65-104	62-103	
Height (m)	Mean ± SD	1.66 ± 0.06	1.66 ± 0.06	0.939
	Range	1.56-1.76	1.56-1.75	
BMI (kg/m^2)	Mean ± SD	30.78 ± 4.61	31.73 ± 4.99	0.537
	Range	24.8-37.7	20.9-39.2	
Duration of surgery (min)	Mean ± SD	149.1 ± 14.28	150 ± 13.12	0.837
	Range	126-178	120-176	

ASA: American society of anesthesiologists BMI: body mass index, *: significant as P value <0.05.

A statistically substantial reduction was existed among intraoperative HR after intubation, 15, 30, 45, 60, 75, 90, 105 and 120 min in group 2 contrasted to group 1 (P value < 0.05). And statistically insignificant variation at baseline, following induction and at the end of operation between the two groups. There was significant decrease at 2,4,6,18,30,36 and 48 h in group 2 contrasted to group 1 (P value <0.001) and statistically insignificant difference in postoperative HR at baseline, PACU, 12, 24 and 42 h among both groups. [Table 2].

Table 2: Intraoperative heart rate and Postoperative heart rate (beats/min) changes between the studied groups.

	Group 1 (n = 20)		Group 2 (n = 20)		P value
	Mean	± SD	Mean	± SD	
Baseline	79.4	13.39	83.5	9.20	0.266
After induction	78	15.04	82.5	9.28	0.262
After intubation	91.7	17.35	75.4	8.04	<0.001*
15 min	85.5	18.10	73.2	8.10	0.009*
30 min	89.25	17.59	75.5	8.17	0.003*
45 min	85.15	18.13	74.4	8.91	0.022*
60 min	89	18.03	72.85	8.82	0.001*
75 min	88.65	18.62	71.3	8.77	0.001*
90 min	89.35	17.92	73.75	8.90	0.001*
105 min	89.25	18.18	75.2	8.79	0.004*
120 min	88.3	17.62	75.35	8.97	0.006*
End of surgery	87.4	13.35	81.55	8.38	0.105
Postoperative heart rate (beats/min)	**Group 1 (n = 20)**		**Group 2 (n = 20)**		**P value**
	Mean	**± SD**	**Mean**	**± SD**	
Baseline	79.40	13.39	80.80	9.91	0.709
PACU	88.65	15.63	79.55	16.34	0.080
2h	97.40	16.22	76.55	9.69	<0.001*
4h	96.05	14.11	78.20	11.79	<0.001*
6h	94.20	18.51	77.65	11.82	0.002*
12h	92.00	13.38	92.75	18.13	0.882
18h	96.65	13.96	80.95	11.10	<0.001*
24h	98.55	16.56	89.60	15.97	0.090
30h	99.25	14.36	88.95	17.30	0.047*
36h	99.45	15.91	86.25	18.68	0.021*
42h	83.55	17.07	85.65	14.87	0.681
48h	98.15	18.41	78.95	16.85	0.001*

PACU: post-anesthesia care unit *: significant as P value <0.05.

There was statistically substantial reduce in intraoperative MAP following intubation, at 15, 30, 45, 60, 75, 90, 105 and 120 min in group 2 contrasted to group 1 (P value <0.001) and statistically insignificant variation at baseline, following induction and at the end of surgery (P value <0.05**).** a substantial reduce was existed in postoperative MAP at 2,4,6,18,30,36 and 48 h in group 2 contrasted to group 1 and statistically insignificant difference at baseline, PACU, 12, 24 and 42 h among both groups (P value <0.001) [Table 3].

Table 3: Intraoperative mean arterial pressure (mmHg) changes and postoperative mean arterial pressure between the studied groups

	Group 1 (n = 20)		Group 2 (n = 20)		P value
	Mean	± SD	Mean	± SD	

Baseline	77.65	10.23	79.75	11.40	0.543
After induction	83.95	10.80	73.05	11.96	0.004*
After intubation	87.7	17.09	71.60	12.07	0.001*
15min	80.95	14.93	70.40	11.86	0.018*
30mins	83.75	18.28	71.15	10.89	0.012*
45min	84.6	11.87	72.25	10.79	0.001*
60min	82	12.44	72.15	11.85	0.014*
75min	81.6	16.29	71.90	10.66	0.032*
90min	86.3	17.38	71.90	10.47	0.003*
105min	80.95	15.07	71.95	11.31	0.039*
120min	83.05	9.31	72.15	12.15	0.003*
End of surgery	81.9	10.47	80.90	8.80	0.745
	Group 1 (n = 20)		**Group 2 (n = 20)**		**P value**
	Mean	**± SD**	**Mean**	**± SD**	
Baseline	77.65	10.23	79.75	11.40	0.543
PACU	87.95	12.17	79.25	16.12	0.062
2h	96.85	15.41	85.40	8.89	0.007*
4h	92.65	13.34	84.20	10.29	0.031*
6h	91.85	16.99	82.15	8.41	0.028*
12h	91.50	15.56	94.40	11.92	0.512
18h	100.05	15.25	85.10	10.18	0.001*
24h	94.95	17.76	93.50	13.99	0.776
30h	94.20	13.68	86.70	7.91	0.040*
36h	94.75	16.08	85.70	9.79	0.038*
42h	81.55	12.35	84.20	14.64	0.540
48h	91.55	18.67	81.65	10.62	0.046*

PACU: post-anesthesia care unit. *: significant as P value <0.05, Intraoperative fentanyl consumption

A statistically substantial reduce was existed in intraoperative fentanyl consumption in group 2 compared to groups 1 (P value <0.001) [Table 3].

Table 4: Total intraoperative fentanyl consumption between the studied groups

	Group 1 (n = 20)	**Group 2 (n = 20)**
Mean ± SD	169.5 ± 22.35	87 ± 13.8
Range	130 – 210	60-100
P value		<0.001*

A substantial reduce was existed in VAS at 2,4,6,18,30,36 and 48 hours in group 2 contrasted to group 1 (P value<0.05). There was statistically insignificant difference in VAS at PACU, 12, 24 and 42 hours. [Fig. 2]

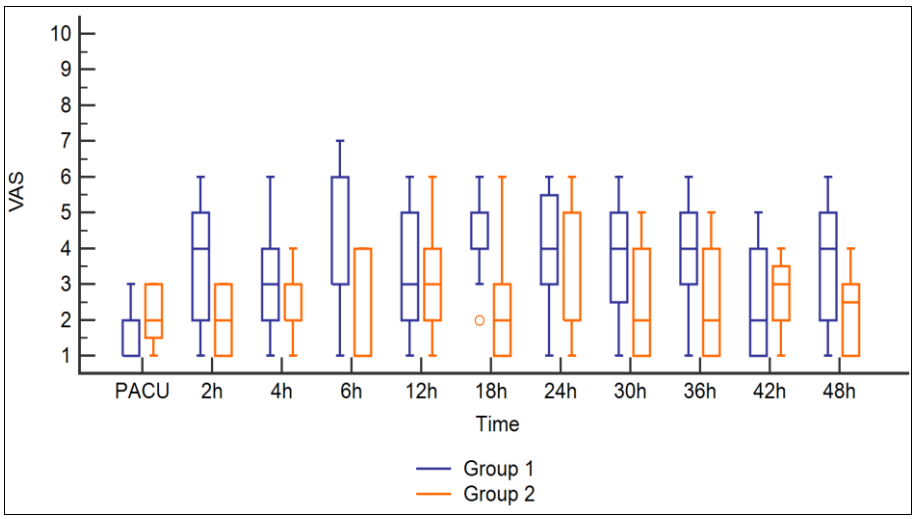

Fig 2: VAS between the studied groups

Time to first rescue analgesic requirement was ranged from (2-4) and (4-12) hours in group 1 and 2 respectively. A statistically substantial delay was existed in group 2 contrasted to group 1 (P value <0.001). There was statistically substantial decrease in total postoperative morphine consumption in group 2 contrasted to group 1 (P value<0.001). [Table 5]

Table 5: Time to first rescue analgesia, Total postoperative morphine consumption between the studied groups

	Group 1 (n = 20)	Group 2 (n = 20)
Mean ± SD	2.7 ± 0.98	7.9 ± 3.14
Range	2-4	4-12
P value		< 0.001*
Mean ± SD	22.9 ± 5.7	11.1 ± 3.01
Range	15-35	6-15
P value		<0.001*

The satisfaction was substantially varied among the studied groups. The satisfied participants in group 2 were significantly higher in group 2 contrasted to group 1. [Table 6].

Table 6: Patient satisfaction between the studied groups.

	Group 1 (n = 20)	Group 2 (n = 20)	P value
Very satisfied	0(0%)	4 (20%)	0.106
Satisfied	2(10%)	16(80%)	< 0.001*
Dissatisfied	6(30%)	0(0%)	0.020*
Very dissatisfied	12 (60%)	0(0%)	< 0.001*

*: significant as P value <0.05

Regarding the side effects, PONV occurred in 8 (40%) participants in group 1 and in 3 (15%) participants in group 2. Dizziness occurred in 2 (10%) participants in group 1 and in 7 (35%) participants in group 2. Hypotension occurred in 2 (10%) participants in group 1 and in 1 (5%) participant in group 2. Bradycardia occurred in 1 (5%) participant in group 1 and in 3 (15%) patients in group 2. Headache was observed in 3 (15%) participants in group 1 and in 4 (20%) participants in group 2. Pruritis, somnolence, dry mouth, diarrhea, constipation, insomnia and fatigue did not observe in any participant in both groups. Side effects were insignificantly varied among the studied groups [Table7].

Table 7: Side effects between the three groups.

	Group 1 (n = 20)	Group 2 (n = 20)	P value
PONV	8 (40%)	3 (15%)	0.155
Dizziness	2 (10%)	7 (35%)	0.127
Hypotension	2 (10%)	1 (5%)	1
Bradycardia	1 (5%)	3 (15%)	0.605
Headache	3 (15%)	4 (20%)	1
Pruritis	0 (0%)	0 (0%)	---
Somnolence	0 (0%)	0 (0%)	---
Dry mouth	0 (0%)	0 (0%)	---
Diarrhea	0 (0%)	0 (0%)	---
Constipation	0 (0%)	0 (0%)	---
Insomnia	0 (0%)	0 (0%)	---
Fatigue	0 (0%)	0 (0%)	---

PONV: Post-operative nausea and vomiting.

Discussion

Duloxetine is utilized for the management of many forms of chronic pain. Nevertheless, there is little knowledge about the impact of this factor on pain experienced after surgery [10].

Therefore, the primary objective of this research was to assess the efficacy of perioperative administration of duloxetine in the management of acute pain following MRM. The primary measure of interest was the cumulative amount of morphine administered during the first 48-hour period after the surgical procedure. The secondary outcomes assessed in this study were the postoperative VAS scores, the time until the first administration of rescue analgesia, and the time until ambulation.

The present research included a sample of 40 individuals who were scheduled to undergo MRM at Tanta University Hospitals. The study design used a prospective randomised controlled approach. The participants were assigned at random to 2 groups, with each group consisting of 20 participants. The control group (Group 1) was administered IV acetaminophen at a dosage of 500 mg every 6 hours following the surgical procedure. On the other hand, the duloxetine group (Group 2) was given duloxetine at a dosage of 30 mg every 12 hours for a period of 3 days prior to the surgery. Additionally, this group was given 30 mg of duloxetine 2 hours prior to the surgery, followed by another 30 mg 12 hours after the operation, along with IV acetaminophen at a dosage of 500 mg every 6 hours postoperatively.

The primary findings of this investigation were as follows:

In relation to hemodynamics, the duloxetine group exhibited a notable reduction in MAP and HR when contrasted to the control group. This observation might perhaps be attributed to the intraoperative anxiety-relieving properties of duloxetine, as well as its postoperative analgesic effects.

The findings of our study are consistent with those of Kassim *et al*. [11], who conducted a study on the effects of duloxetine and dexamethasone in reducing postoperative pain following laparoscopic gynaecological procedures. They observed a notable reduction in hemodynamic measures in the duloxetine and dexamethasone groups compared to the control group at various time points

postoperatively (30 minutes, 1 hour, 2 hours, and 6 hours). In their study, a total of 75 female patients were randomly assigned to one of three equally sized groups. In this study, participants were divided into three groups. Group 1 was given an oral dose of Duloxetine at 60 mg, along with an intravenous infusion of 100 ml of 0.9% sodium chloride over a period of 15 minutes. Group 2 received the same oral dose of Duloxetine at 60 mg, but in addition, Dexamethasone at a dosage of 0.1 mg/kg was combined with 100 ml of 0.9% sodium chloride and administered intravenously. Lastly, group 3 was given a placebo that was identical in appearance to the Duloxetine capsule, as well as an intravenous infusion of Dexamethasone over a period of 2 hours prior to the surgical procedure. The vital signs of the patients, together with the VAS and sedation score, were evaluated at certain time intervals after the surgical procedure, namely at 30 minutes, 1 hour, 2 hours, 6 hours, and 12 hours. The study monitored the total amount of pethidine required, plasma cortisol levels, the incidence of postoperative nausea and vomiting (PONV), and patients' satisfaction.

In addition, in a study conducted by Nath *et al*. (2022) [12], the researchers examined the impact of preoperative oral administration of duloxetine on pain following surgery and total analgesic usage during the post Laparoscopic Cholecystectomies period. The findings revealed that placebo resulted in substantially greater hemodynamic levels contrasted with duloxetine across various time intervals in the perioperative period. The study involved a sample of 60 individuals, regardless of gender, who were scheduled for laparoscopic cholecystectomies and classified as American Society of Anaesthesiologists (ASA) I and II. The participants were stratified into two cohorts (n=30), whereby one group received duloxetine 60 mg capsules and the other group received placebo capsules, administered two hours prior to the surgical procedure.

According to intraoperative fentanyl consumption, we found that there was statistically substantial decrease in consumption of fentanyl in duloxetine group contrasted to control group, this may be due to the synergetic impact of duloxetine with anesthetic drugs.

As regard to the analgesic effect of duloxetine it was found that there was a substantial reduce in postoperative morphine consumption, delay in time to first rescue analgesia and decrease in VAS in duloxetine group compared to control group with more patient satisfaction and less side effects.

In relation to the cumulative morphine use during the first 48 hours after surgery, our findings indicate a significant decrease in total postoperative morphine intake among participants in the duloxetine group compared to those in the control group.

In accordance with the research conducted by Mantay *et al*. [13], the objective of this study was to assess the effectiveness of duloxetine in preventing post-mastectomy pain syndrome (PMPS) and its associated adverse effects among individuals who have had mastectomy. The study included a cohort of 50 individuals who were scheduled to undergo MRM. These participants were randomly assigned to receive either 60 mg of duloxetine or a placebo prior to their surgery. This treatment was then maintained every morning for 7 days following the surgery. The results of the study indicated that the total amount of morphine consumed was lower in the group receiving duloxetine compared to the control group. Additionally, the time until the first instance of rescue analgesia was substantially longer in the duloxetine group contrasted to the control group.

The findings of our study were corroborated by Hetta *et al*. [14], who conducted a study with the objective of determining the most effective analgesic dosage of preoperative Duloxetine. They administered varying fixed doses of Duloxetine (30 mg, 60 mg, and 90 mg) to four separate groups of individuals undergoing mastectomy with axillary lymph node dissection. Additionally, they assessed the impact of preoperative Duloxetine on the postoperative recovery quality in these individuals. The study included a total of 88 female patients who were randomly assigned to one of four groups. Each group consisted of 22 recipients. Prior to their surgery, the participants in each group were given different treatments: a placebo (D0 group), Duloxetine 30 mg (D30 group), Duloxetine 60 mg (D60 group), or Duloxetine 90 mg (D90 group). The study found that the median (interquartile range) amount of morphine consumed in the initial 24 hours after surgery was substantially reduced in the D60 and D90 groups contrasted to the control and D30 groups.

In addition, Baradwan *et al*. [15] conducted a systematic review and meta-analysis to assess the effectiveness and safety of preoperative duloxetine in managing postoperative pain following gynaecologic laparoscopic procedures. The meta-analysis included a total of 244 individuals, with 123 of them in the duloxetine group and 121 individuals in the placebo group. The findings indicated that duloxetine demonstrated a substantial reduction in postoperative analgesic consumption in contrast to placebo among individuals undergoing gynaecologic laparoscopic procedures.

Regarding the VAS, it was found that there was significant decrease in VAS in most time measurements except at 12 and 24 h and insignificant increase at 42 h postoperatively, this may be explained by the duration of action of duloxetine.

In agreement with the current study Mantay *et al*., (2016) [13] revealed that VAS score was significantly lower in Duloxetine group than control group at 48 hr. however, no significant difference was detected between placebo and Duloxetine group at PACU, 24 hr, 30 days and 90 days.

Also, Kassim *et al*., [13] found that there was a significant less VAS in duloxetine group and dexamethasone compared to control at 30 min, 1, 2, and 6 h postoperatively laparoscopic gynecological surgeries.

In contrary to the findings of our study on acute pain, Hoi *et al*. observed a minor elevation in pain levels during the first postoperative hours among participants in the duloxetine group contrasted to those in the placebo group. This disparity might perhaps be attributed to the timing of duloxetine given. In the trial conducted by Hoi *et al*., the first dosage of medication was administered a mere two hours prior to the surgical procedure.

Also, Nasr, (2014) (137) revealed that a statistically substantial reduction was existed in VAS scores at all time points between Duloxetine group and control group ($P < 0.001$), the contrast with our results may be due to the difference in sample size and the study settings including the follow-up time points.

In the current work we revealed that time to first rescue analgesics requirement was substantially delayed in duloxetine group contrasted to control group.

In agreement with the present work Nasr, [16] revealed that in the duloxetine group contrasted to the placebo group duration to first rescue analgesics was longer.

Also, Attia & Mansour, (2017) (6) reported that the use of preoperative duloxetine sugnficantly delayed the first rescue analgesic in lumbar Laminectomy surgery.

Regarding patient satisfaction between the studied groups, we found that the satisfaction was substantially varied among the studied groups. The satisfied participants in duloxetine group were significantly higher compared to control group.

Our results were supported by Attia & Mansour, [6] who revealed that the usage of duloxetine was associated with significantly higher satisfaction compared to control group in lumbar Laminectomy surgery.

Also Kassim *et al*., [13] who revealed that patient satisfaction was substantially greater in duloxetine group contrasted to control group after laparoscopic gynecological surgeries.

Regarding the side effects, insignificant comparable side effects occurred in the two groups

In agreement with our results Nasr, [16] reported that no substantial variation was existed in the incidence of nausea and dizziness, vomiting, somnolence, headache, and pruritus among both groups.

Also, Attia & Mansour, [6] reported that there were no significant differences in the incidence complications between the two groups in lumbar Laminectomy surgery.

As well, Baradwan *et al*., [15] revealed that both groups didn't vary in side effects and the length of hospital stay after laparoscopic gynecological surgeries.

However, Mantay *et al*., [13] revealed that the incidence of nausea and insomnia where comparable between groups, but dizziness and dry mouth were significantly more in duloxetine group compared to controls.

In contrast to our results, Hoi *et al*., [17] and Bedin *et al*., [18] aimed to reduce opioid consumption after spine surgery, The trial subjects were divided into two groups: Group C, which served as the control group and got a placebo, and Group D, which took 60 mg of duloxetine one hour prior to to operation and again the next morning. No adverse consequences of the medicine were detected, since participants were given just two oral doses of duloxetine.

The present investigation was limited by a very modest sample size and the fact that it was conducted at a single site. Additional comparison studies with a bigger sample size and an extended follow-up period are necessary to validate our findings and determine the optimal dosage of the intervention. Also, we measured postoperative pain intensity in general not in relation to rest or movement.

Conclusions

The current study showed that the use of perioperative duloxetine was safe and effective in controlling pain after modified radical mastectomy. The use of duloxetine was associated with significant reduction in opioid consumption, delayed time to first rescue analgesic requirement, more patient satisfaction and also associated with significant reduction in hemodynamics intra and postoperatively.

Financial support and sponsorship

Nil

Conflict of Interest

Nil

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How to Cite This Article
Elfeky DAM, Alzeftawy AE, Ghafar MSA, Moez MAA. Duloxetine for post-operative analgesia after modified radical mastectomy: A Prospective randomized study. International Journal of Medical Anesthesiology. 2023; 6(4): 16-24.