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Original Contribution

The effects of a short-term perioperative duloxetine treatment on post-colectomy pain: A randomized, controlled clinical trial

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ABSTRACT

Study objective: To test the hypothesis that duloxetine reduces postoperative morphine consumption and pain intensity in patients undergoing major colonic surgeries.
Design: Single-center, prospective, double-blinded, randomized, controlled trial.
Setting: Tertiary university hospital, from December 2019 to September 2021.
Patients: Sixty 18–85 years old, ASA I – III patients undergoing elective open major colonic surgeries were randomly allocated into duloxetine (duloxetine) or placebo (placebo) groups ($n = 30$ per group).
Interventions: Duloxetine 60 mg or placebo was administered orally 2 h before and 24 h after surgery.
Measurements: PCA morphine consumption, surgical pain at rest, and movement measured on 10-cm visual analog scales (VAS), Ramsay sedation scores, and the incidence of adverse effects potentially associated with duloxetine were assessed at patients' admission to the post-anesthesia care unit (PACU), 6, 24, and 48 h post-operatively (PO).
Main results: After adjusting for age, BMI, ASA physical status, education level, and incision type, no differences were found between groups in PCA morphine consumption 24 PO h (duloxetine = 5.44 ± 2.06 mg; placebo = 10.33 ± 2.06 mg, $p = 0.62$) or 48 h PO (duloxetine = 9.18 ± 2.06 mg, placebo = 12.93 ± 2.06, $p = 1$). Pain at rest also did not differ between groups at 24 h PO (duloxetine = 1.76 ± 0.67 cm; placebo = 1 ± 0.67 cm, $p = 1$) or at 48 h PO (duloxetine = 0.84 ± 0.67 cm; placebo = 0.49 ± 0.67 cm, $p = 1$). Similarly, groups did not differ regarding pain on movement at 24 h PO (duloxetine = 2.09 ± 0.68 cm; placebo = 1.80 ± 0.68, $p = 1$) or at 48 h PO (duloxetine = 1.16 ± 0.68 cm; placebo = 0.88 ± 0.68 cm, p = 1). Sedation scores and adverse effects also did not differ between groups.
Conclusion: Under this study's conditions, short-term duloxetine did not reduce total opioid consumption or pain intensity during the initial 48 h following major colon surgery.

1. Introduction

Substantial progress in understanding the mechanisms of acute pain has led to new treatment concepts, e.g., the multimodal approach to postoperative pain [1]. The release of chemicals (e.g., prostaglandins, bradykinin, ATP, H^+) in the injured tissues initiate the pathophysiological events of nociception, including spinal sensitization that may amplify and perpetuate postoperative pain [2,3]. Several mechanisms modulate pain (e.g., enkephalinergic, serotonergic, noradrenergic descending inhibitory pathways, central dopaminergic and GABAergic pain modulation), inhibiting the ascendent projection of pain signals and decreasing pain perception. Clinical analgesia is based on avoiding the transmission of pain along the pain pathways and enhancing pain modulation. Pain modulation explains most clinical analgesia approaches [4].

Duloxetine is a selective serotonin and norepinephrine reuptake inhibitor effective in reducing pain in chronic diseases. It acts on the neurotransmission of descending inhibitory pain pathways in the central nervous system, reducing the transmission of pain signals from receptors located in the periphery and treating depression, anxiety, diabetic

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neuropathy, and fibromyalgia [5]. Animal studies have shown that duloxetine affects hyperalgesia and allodynia by inhibiting nerve impulses arising from nociceptive stimuli [6,7] and reducing surgical incisional [8] and neuropathic pain intensity [9].

The short-term perioperative administration of duloxetine, consisting of 60-mg doses administered orally 2 h before and 24 h after surgery, has been associated with lower postoperative opioid consumption following abdominal hysterectomy [10], laparoscopic gynecological surgery [11,12], oncologic breast surgery [13], knee arthroplasty [14,15], hip [16,17] and lumbar spine surgery [18–20]. Nonetheless, two recently published meta-analyses provided controversial interpretations of the pooled effect sizes of duloxetine in preventing postoperative pain [21,22]. Moreover, the effects of short-term perioperative duloxetine on decreasing the postoperative pain associated with major colonic surgery have not been studied.

We hypothesized that administering duloxetine 60 mg two hours before and 24 h after surgery, compared to placebo, might reduce opioid consumption and pain intensity during the first 48 postoperative hours in patients undergoing open major colonic surgery under general anesthesia.

2. . Materials and methods

2.1. Trial design

This prospective, randomized, double-blind, placebo-controlled clinical trial, including patients undergoing open colectomy under general anesthesia, was conducted between December 5, 2019, and September 30, 2021. The institutional Human Research Ethics Committee approved the study under registration number 04031718.4.0000.0121). The study was registered in the Brazilian Registry of Clinical Trials under the identification code RBR-5jzmqq (https://ensaiosclinicos.gov.br/rg/RBR-5jzmqq). Participants signed written informed consents. The study is reported according to the 2010 Consolidated Standards of Reporting Trials (CONSORT) [23].

2.2. Inclusion criteria

Patients aged between 18 and 85 years of both sexes, ASA physical status I through III, scheduled for elective open colectomy (including any part of the colon) under general anesthesia in a university hospital tertiary surgery center were eligible for the study.

2.3. Exclusion criteria

Patients were excluded in case of age under 18 or over 85 years, ASA physical status class above III, urgent or emergency surgery, renal, hepatic insufficiency or coagulopathies, pregnant or postpartum women, psychiatric illness, cognitive or neurological disorders, use of analgesics or medications with an effect on the central nervous system in the three days before surgery, history of drug or alcohol abuse, chronic pain or daily intake of opioids, uncooperative or legally incapable, refusal or contraindication to performing any proposed procedure, known allergy to duloxetine or other drugs used in the study.

2.4. Allocation of patients to study groups, allocation concealment, and study drug blinding

An independent researcher not participating in anesthesia, surgery, or data collection performed randomization using an electronically generated random sequence allocation (www.randomization.com). Sixty cases were randomized in blocks of six cases in each study group (duloxetine or placebo).

For drug concealment, identical capsules filled with duloxetine 60 mg (Velija®, Libbs, Brazil) or maize starch 500 mg (placebo) were prepared by a compounding pharmacy. Sequentially numbered opaque sealed envelopes containing two identical capsules were provided to the ward nurse by a hospital pharmacist aware of the randomization list after patient admission. Group allocation was disclosed after completing data collection.

2.5. Interventions

2.5.1. Study drug administration

Ward nurses blindly administered one capsule of the study drug per os 2 h before surgery and one capsule 24 h after surgery.

2.5.2. Anesthesia

An anesthesiologist unaware of the study goals or the patient allocation group provided anesthesia according to the following standardized protocol. Upon arrival in the operating room, patients were monitored with a non-invasive blood pressure monitor, continuous EKG tracing, pulse oximeter, and accelerograph train-of-four (TOF). A peripheral venous catheter was placed in a hand or forearm vein; a 0.9% saline solution was started at 5 ml.kg-1.h-1, dexamethasone 0.1 mg.kg-1 and cefoxitin were administered intravenously (i.v.). The anesthesia induction sequence consisted of i.v. propofol 2 $mg.kg^{-1}$, fentanyl 1.5–2 $\mu g.kg^{-1}$, and atracurium 0.6–0.8 $mg.kg^{-1}$. Intermittent atracurium 0.15 $mg.kg^{-1}$ boluses were administered to maintain the TOF ratio at or below 0.25 but no less than two TOF responses. Anesthesia was maintained with sevoflurane at a 1.0–1.5 minimum alveolar concentration in an air and oxygen mixture. Intraoperative analgesia was provided with 0.5 $\mu g.kg^{-1}$ fentanyl boluses if there was a 20% increase in heart rate or mean arterial blood pressure, voluntary movements, or other autonomic responses [24]. Preventive analgesia was provided to all patients with morphine 0.1 $mg.kg^{-1}$, ketoprofen 100 mg IV, and dipyrone 2.5 g with n-butyl scopolamine bromide 20 mg IV 40 min administered before interrupting the sevoflurane administration. Neuromuscular block was reversed with neostigmine 20–50 μg.kg-1 preceded by atropine sulfate (10 to 20 μg.kg-1), aiming for a TOF ratio > 0.9. Ondansetron 8 mg was administered during skin closure for postoperative nausea or vomiting (PONV) prophylaxis. All patients were admitted to the post-anesthesia care unit after surgery, where PCA was initiated.

2.5.3. Background analgesia

2.5.3.1. Postoperative analgesia regimen. Ketoprofen (100 mg i.v. q12h) and dipyrone (1 g i.v. q6h) were administered for 48 h postoperatively to all patients.

2.5.3.2. Patient controlled analgesia (PCA). Upon patient arrival to the PACU, a 50-ml syringe (BBraun, Melsungen, Germany) filled with a 1 $mg.ml^{-1}$ morphine solution was attached to the PCA pump and connected to the peripheral intravenous catheter. The pump was programmed to deliver 1 ml (1 mg) of the solution on demand, with five-minute lockout intervals, limited to 8 mg of morphine per hour.

Respiratory rate and SpO_2 were measured at 15-min intervals in the PACU, every 2 h for 24 postoperative hours and 4 h after that. Respiratory depression was assumed in case of a respiratory rate less than six breaths per minute or SpO_2 below 92%. On the measurement occasions (PACU, 6, 24 and 48 PO h), patients were questioned by one investigator blinded to the patient's study group about the presence of nausea, vomiting, dry mouth, pruritus, headache, dizziness, and visual disturbances. In case of a positive answer, patients were requested to grade on a 3-point verbal scale as mild, moderate, or severe. Sedation level was assessed on the measurement occasions using the Ramsay sedation scale. Sedation levels ≥ 5 were considered deep sedation. PCA morphine bolus were increased by 1 mg in case of insufficient analgesia (VAS score > 5 cm), or decreased the bolus by the same amount if respiratory depression, excessive sedation, severe nausea or vomiting, or severe pruritus were observed. Further adjustments to the morphine PCA dose were

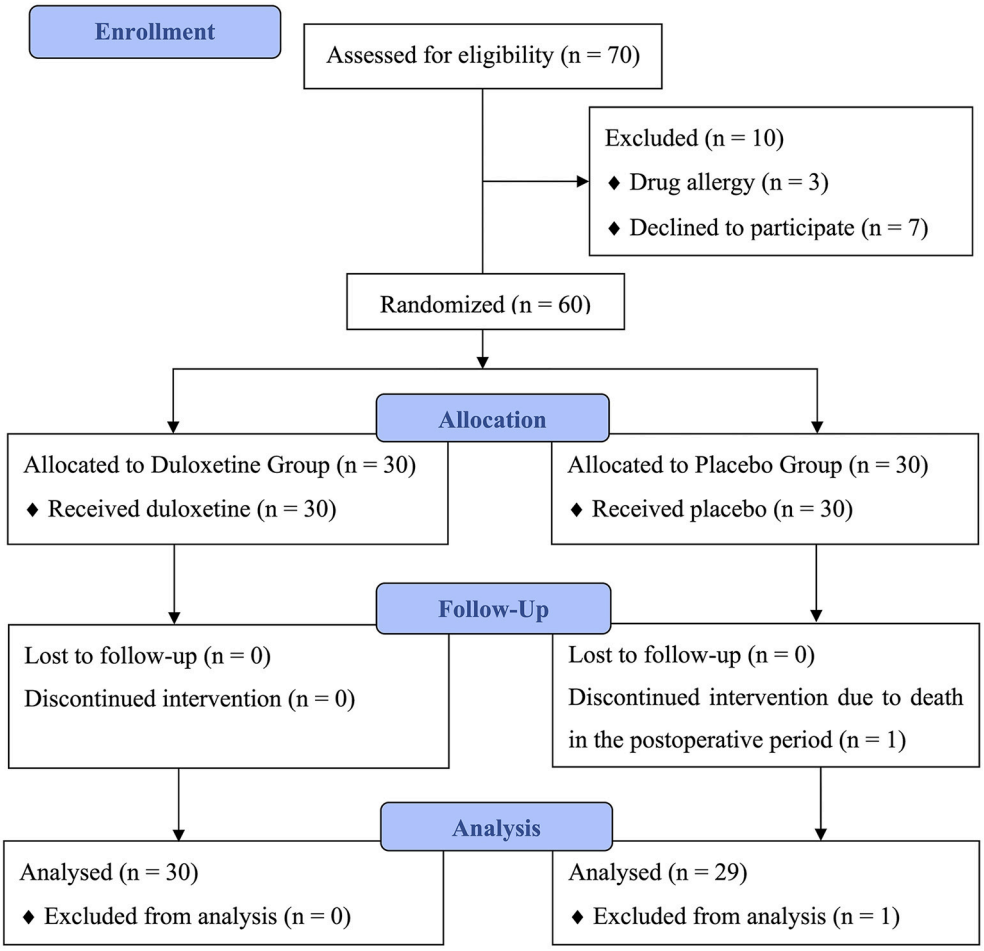

Fig. 1. CONSORT study flow diagram.

made by **the** anesthesiologist or anesthesia resident **on duty** under the ward nurse's request. Patient-controlled anesthesia was maintained for 48 h after surgery.

2.5.4. Outcomes

The primary outcome of this study was the cumulative morphine consumption during the first 24 and 48 postoperative hours. The secondary outcomes were visual analog pain scores at the 24th and 48th postoperative hours. Also, adverse effects attributable to duloxetine were investigated.

2.5.5. Data collection

2.5.5.1. Demographic, surgical, and anesthesia data. For every patient, age, weight, height, race, marital status, body mass index (BMI), gender, education level, comorbidities, symptoms associated with the underlying colonic disease, use of medications, smoking, and ASA physical status class, duration of surgery, intraoperative opioid consumption, incision type, and the time from incision to dressing were recorded in a dedicated spreadsheet.

2.5.5.2. Postoperative morphine consumption. Cumulative doses of morphine at 2, 6, 24, and 48 postoperative hours were extracted from the PCA pump using the manufacturer's proprietary software.

2.5.5.3. Postoperative pain assessment. Upon patient arrival in the PACU, at 6, 24, and 48 h postoperatively, an investigator blinded to the patient's study group assessed pain at rest (static) and during movement (dynamic) using a 10 cm, 11-point visual analog scale (VAS) where zero represented no pain, and ten indicated the worst imaginable pain.

Assessment of pain on movement was performed with the patient lying supine with hips and knees flexed, feet flat on the bed, and upper limbs parallel to the trunk. The patient was asked to elevate the hip from this position, keeping only the shoulders and feet on the bed (stable shoulder-bridge maneuver). The maneuver has been shown to activate the hip extensor muscles, the hamstrings, and the *transverse and oblique abdominis* muscles [25]. Patients were verbally stimulated to maintain the position for five seconds. The pain was assessed on a visual analog pain scale immediately after the patient returned to the resting position.

2.5.5.4. Statistical analysis

2.5.5.4.1. Descriptive statistics and normality tests. Descriptive statistics were calculated for patients' characteristics (demographic, surgical, and anesthesia-related variables) and the outcome variables for each study group. The Shapiro-Francia test was used to assess the respective distributions. Continuous variables were summarized as the mean ± standard deviation (SD) or the median (interquartile range – IQR) and nominal variables as frequency (percentage – %). Absolute standardized differences (ASD) were computed to assess between-group balance on patient's characteristics, assuming a 0.20 cut-off for imbalance.

2.5.5.4.2. Comparison of raw outcome data between groups. The Mann-Whitney *U* test was used to compare morphine consumption and VAS pain scores between the study groups at 24 and 48 PO hours. Kruskal-Wallis tests were used to compare primary outcomes according to the incision types (per editor request).

Table 1
Demographic data of the study sample.

	Duloxetine ($n = 30$)	Placebo ($n = 29$)	ASD
Age (years)	62.73 ± 11.56	56.93 ± 14.55	0.50
Gender (male/female)	15 (25.4) / 15 (25.4)	16 (27.1) / 13 (22.0)	0.06
Weight (kg)	68.86 ± 13.08	68.89 ± 11.23	0.04
Height (m)	1.64 ± 0.07	1.66 ± 0.10	0.25
BMI ($kg.m^{-2}$)	25.73 ± 5.34	25.00 ± 4.25	0.18
ASA physical status (class)			0.65
I	3 (5.1)	10 (16.9)	
II	20 (33.9)	16 (27.1)	
III	7 (11.9)	3 (5.1)	
Education (level)			0.29
Primary	15 (50)	18 (62)	
Secondary	10 (33.3)	6 (20.7)	
University	5 (16.7)	5 (17.2)	

2.5.5.4.3. Generalized linear model analyses of covariance (ANCOVA). Because the distribution of some patient characteristics variables was unbalanced across the study groups, secondary analyses were performed using a generalized linear model (GLM) repeated measures ANCOVA [26], where the potentially influential unbalanced variables controlled each outcome variable. As the first step in these analyses, the Tukey ladder of powers approach was used to find the best transform to convert or approximate distributions of the outcome variables to the Gaussian distribution and allow the use of GLM ANCOVA [27]. The Shapiro-Francia test was used to assess the normality of transformed-data distributions and for the ANCOVA's assumption of a normally distributed dependent variable. Next, Spearman rank tests were used to test correlations between unbalanced demographic and surgical-related variables and the outcome variables to test for the ANCOVA's covariate-outcomes relationship assumption. ANCOVA models were created using each outcome transformed variable as the dependent variable (postoperative opioid consumption, static and VAS pain scores), groups as the fixed factor, measurement occasions as the repeated-measures factor, and patient's age, body mass index, intraoperative fentanyl dose, ASA physical status, education level, and incision type as covariates. For these analyses, the categorical variables were split into dummy binary variables. The Greenhouse-Geisser correction was used to account for violations of the sphericity assumption [31]. Adjusted means, standard deviations, and 95% confidence intervals were back-transformed for reporting results.

2.5.5.4.4. Sample size calculation. When this study was conceived, seven studies [10,13,15,18,19,28,29] had compared postoperative opioid consumption and pain at rest between patients receiving short-term perioperative duloxetine or placebo. An average 36% (SD = 13%) reduction in the cumulative opioid consumption, measured as i.v. morphine equivalents, and a 14% (SD = 15%) between-group difference in VAS pain scores favoring duloxetine were reported at the 24th postoperative hour in these studies. Based on the opioid consumption outcome, a total of 10 patients was estimated for alpha = 0.05 and 1-beta = 0.1, while under the same probabilities of statistical type I and II errors, the sample was estimated as 52 patients, allocated into two groups in a 1:1 ratio to detect the 14% (SD = 15%) reduction in visual analog scores between groups 24 h after the operation (the secondary outcome) with a 90% power. The larger sample was chosen to avoid type II errors in the between-group comparisons of VAS pain scores. Considering possible losses, 30 patients were randomized to each study group.

2.5.5.5. Software. Statistical analyses were performed on G-Power, [30] SPSS version 23.0 (SPSS Inc., Chicago, IL, USA) or STATA/MP version 14 (StataCorp, College Station, TX, USA). Statistical significance was accepted at *p*-values smaller than 0.05.

Table 2
Surgical and anesthetic data.

	Duloxetine (n = 30)	Placebo (n = 29)	ASD
Primary surgical disease (type)			0.09
Malignant	26 (86.7)	26 (89.7)	
Benign	4 (13.3)	3 (10.3)	
Incision (type)			0.73
Midline supraumbilical	2 (3.4)	1 (1.7)	
Midline infraumbilical	13 (22.0)	18 (30.5)	
Midline supra and infraumbilical	15 (25.4)	7 (11.9)	
Midline infraumbilical and perineal	0 (0.0)	3 (5.1)	
Total surgical time – from incision to dressing (min)	161.3 ± 34.9	156.6 ± 38.98	0.12
Total operative time – from admission to leaving the operating room (min)	198.1 ± 32.22	196 ± 37.9	0.05
Intraoperative fentanyl consumption (μg)			−0.35
Overall	321.3 ± 163.2	373.6 ± 161.6	
Per incision type			
Midline infraumbilical	287.5 ± 88.4	125	
Midline supraumbilical	329.3 ± 162.73	342.8 ± 35.2	
Midline supra and infraumbilical	317.31 ± 113.9	392.17 ± 181.2	
Midline infraumbilical and perineal	–	406.67 ± 144.7	

Data are presented as mean ± SD or frequency (%).
ASD = absolute standardized difference; BMI: body mass index; ASA: American Society of Anesthesiologists.

3. Results

3.1. Participants and losses

Seventy patients were assessed for study eligibility. Ten patients were not eligible because of reported allergy to morphine ($n = 1$), allergy to dipyrone (methimazole) ($n = 2$), or refusal to participate in the study ($n = 7$). Sixty patients agreed to participate and were included in the study. One patient (placebo group) was lost to follow-up due to death in the immediate postoperative period (Fig. 1).

3.2. Demographic, surgery, anesthesia data

The demographic data of the study sample are shown in Table 1. Surgical and anesthetic data are summarized in Table 2. Raw morphine consumption and VAS pain scores data showed right-skewed distributions (Shapiro-Francia $p < 0.001$). The ladder of powers approach indicated that square root transformation produced the lowest chi-square values for primary and secondary outcome variables. Adherence to the normal distribution of the square root transformed variables was further confirmed with Shapiro-Francia tests. Absolute mean differences exceeded the 0.20 cut-off for age, height, BMI, ASA physical status, education levels, and incision type. In addition, group imbalance was found in incision types and intraoperative fentanyl consumption distribution.

3.3. Correlations between covariates and outcome variables

Morphine consumption correlated with ASA physical status (rho = −0.22; $p < 0.001$), school level (rho = 0.16; $p = 0.01$), incision type (rho = 0.24; $p < 0.001$; intraoperative fentanyl cumulative dose (rho = −0.14; $p = 0.02$), and patient age (rho = −0.50; $p < 0.001$). VAS pain at rest scores correlated significantly with education level (rho = 0.14; $p = 0.02$), and patient age (rho = 0.15; $p = 0.02$). Dynamic pain scores correlated significantly only with education level (rho = 0.15; $p = 0.02$). As ANCOVA assumes a relationship between covariates and dependent variables, only the variables with a significant correlation with the

Table 3
Between group comparisons of the primary and secondary outcomes of the study.

Outcomes	Duloxetine (n = 30)	Placebo (n = 29)	p-value
Postoperative PCA cumulative morphine consumption (mg)			
At 24 h	5.44 ± 2.06 [a]	10.33 ± 2.06[a]	0.62[c]
	4 (2–9) [0–31] [b]	7 (2–22) [0–70] [b]	
			0.08 [d]
At 48 h	9.18 ± 2.06 [a]	12.93 ± 2.06 [a]	1[c]
	6 (2–20) [0–48] [b]	8 (3–29) [0–94] [b]	0.34 [d]
Postoperative pain at rest (VAS - cm)			
At 24 h	1.76 ± 0.67[a]	1 ± 0.67 [a]	1[c]
	1.73 (1–2.66) [0–6.67] [b]	1.33 (0–3) [0–6] [b]	0.25 [d]
At 48 h	0.84 ± 0.67[a]	0.49 ± 0.67 [a]	1[c]
	0.8 (0–2) [0–5.13] [b]	0.2 (0–1.33) [0–5.33] [b]	0.32 [d]
Postoperative pain on movement (VAS – cm)			
At 24 h	2.09 ± 0.68[a]	1.80 ± 0.68 [a]	1[c]
	2.56 (1.33–3.33) [0–7.33] [b]	2.46 (1.2–3.8) [0–7.33] [b]	0.71[d]
At 48 h	1.16 ± 0.68[a]	0.88 ± 0.68 [a]	1[c]
	1.33 (0.66–2.66) [0–8.47] [b]	0.86 (0–2.13) [0–7] [b]	0.33 [d]

[a] adjusted mean ± standard deviation.
[b] median (25th – 75th percentiles) [minimum – maximum] of raw data.
[c] *p*-values for the adjusted means parametric comparisons (GLM ANCOVA).
[d] p-values for the raw data non-parametric comparisons (Mann-Whitney *U* tests).

outcomes were eligible for entering as covariates in the respective models.

3.4. Primary and secondary outcomes

The main results of this study are summarized in Table 3. Accordingly, morphine consumption and static and dynamic VAS pain scores did not differ between groups at 24 or 48 h postoperatively.

A significant increase in cumulative morphine consumption through the measurement occasions was found ($F_{(3\ d.f.)} = 25.38$, $p < 0.001$). However, no differences were observed between groups on the measurement occasions ($F_{(3\ d.f)} = 0.13$, $p = 0.80$) (Fig. 2).

3.4.1.1. *Pain at rest.*
Significant decrease in pain intensity was observed during the study period ($F_{(3\ d.f.)} = 4.82$, $p = 0.002$). No difference in the pain at rest scores was observed between groups on the measurement occasions ($F_{(3\ d.f.)} = 2.67$, $p = 0.06$) (Fig. 3).

3.4.1.2. *Pain on movement.*
Significant decrease in pain intensity was observed during the study period ($F_{(3\ d.f.)} = 4.72$, $p = 0.003$). However, no differences were observed between groups on the measurement occasions ($F_{(3\ d.f.)} = 1.36$, $p = 0.26$) (Fig. 4).

3.4.2. *Postoperative opioid consumption and VAS pain scores according to the incision type*

No differences in the postoperative morphine consumption and pain intensity at rest or on movement according to the incision type were observed within or between groups. (Supplemental Data File 1).

3.5. *Adverse effects*

The distributions of sedation scores did not differ between groups during the study period (Fig. 5). No differences were found between groups regarding the incidence of nausea, vomiting, dry mouth, pruritus, headache, dizziness, or visual disturbances at 24 or 48 h postoperatively. None of the reported adverse effects was graded severe enough to require changes in the PCA morphine regimen (Table 4).

4. Discussion

This randomized, placebo-controlled study tested the hypothesis that a short-course perioperative treatment with duloxetine 60 mg administered two hours before and 24 h postoperatively would decrease postoperative PCA morphine consumption and pain at rest or on movement. However, we failed to discard the null hypothesis. Accordingly, no reduction in postoperative opioid consumption or pain intensity could be attributed to duloxetine treatment.

Our findings disagree with other authors' results, who found that duloxetine decreases postoperative pain and analgesic consumption [10–12,32]. However, these contrasting results can be attributed to methodological differences between studies, including the type of

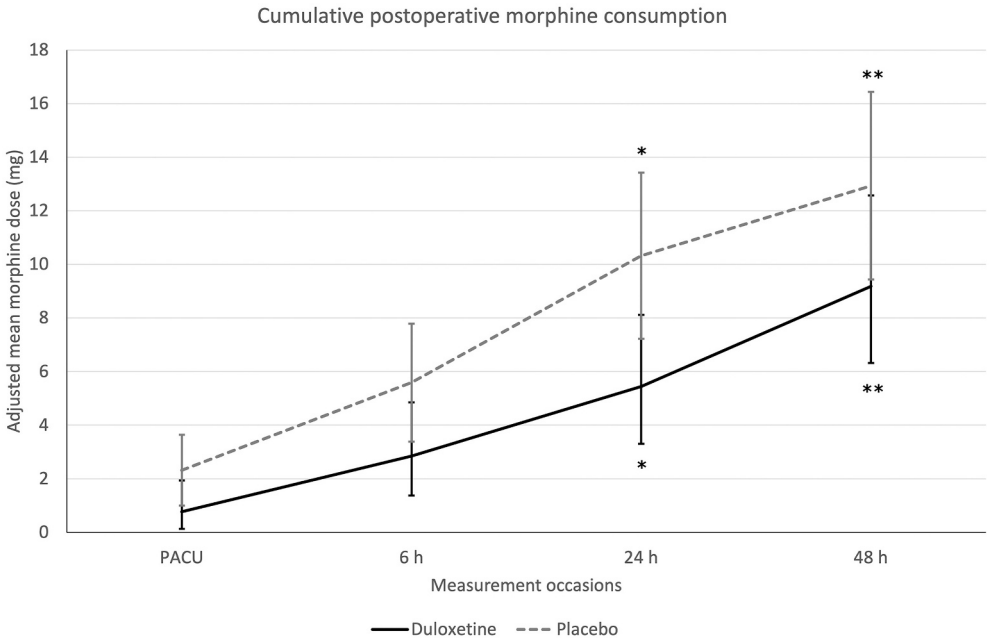

Fig. 2. Cumulative morphine consumption (mg) in both groups in the measurement occasions expressed as square root-transformed, age-adjusted adjusted means, and the respective 95% confidence intervals (error bars). Within-group comparisons: *: $p = 0.002$ compared to PACU in duloxetine and $p < 0.001$ in placebo; **: $p < 0.001$ compared PACU, $p = 0.007$ and $p = 0.02$ compared to 6 h in the duloxetine and placebo groups, respectively. No significant differences between groups were found. PACU = postoperative care unit.

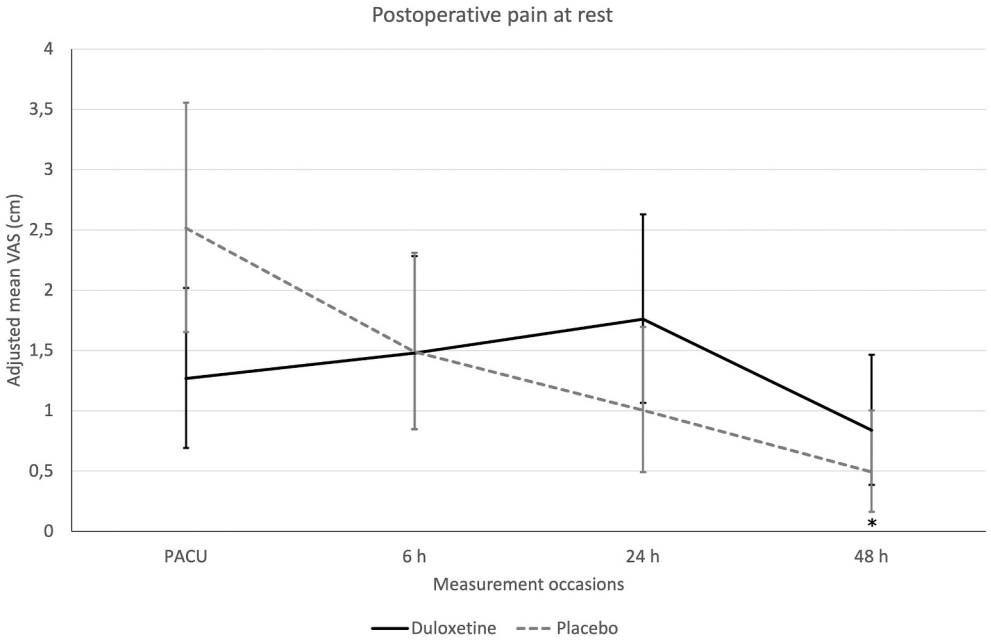

Fig. 3. VAS scores for pain at rest (cm) in both groups in the measurement occasions expressed adjusted means and the respective 95% confidence intervals (error bars). Within-group comparisons: *: $p = 0.001$ compared to PACU in the placebo group; No between-group differences were observed. PACU = postoperative care unit.

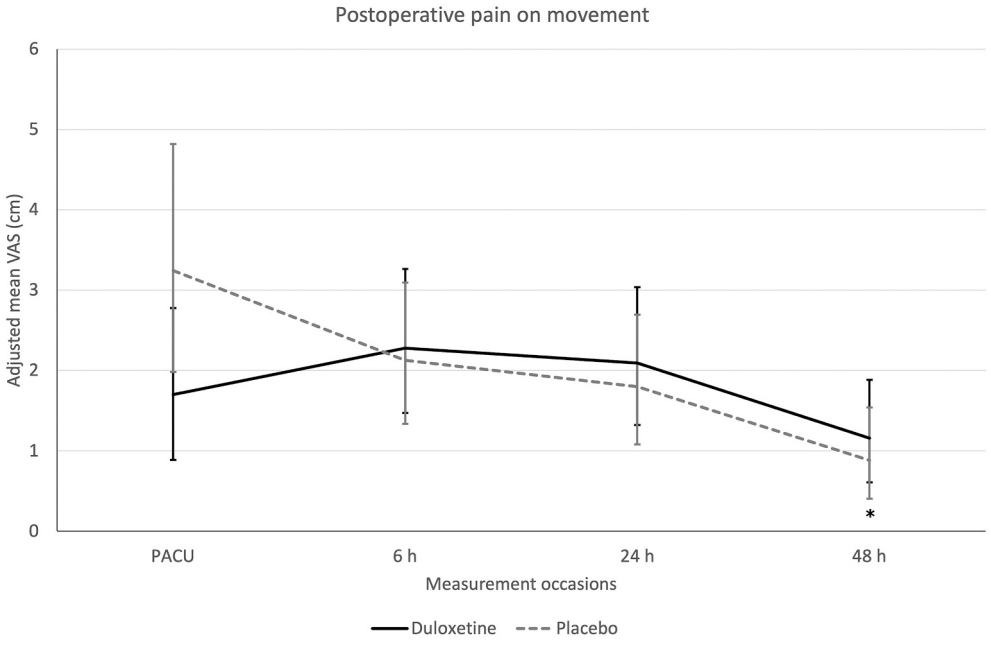

Fig. 4. VAS scores for pain on movement (cm) in both groups in the measurement occasions expressed adjusted means and the respective 95% confidence intervals (error bars). Within-group comparisons: *: p = 0.02 compared to PACU in the placebo group. No between-group differences were observed. PACU = postoperative care unit.

anesthesia, type and extent of surgery, patient characteristics, and background analgesia, which make direct comparisons with this study difficult.

Furthermore, as suggest the low-to-moderate VAS scores found in the placebo group of this study, an adequate background analgesia may have blurred any existing analgesic effects of duloxetine. However, contrasting effects have been found in studies addressing the effectiveness of duloxetine on postoperative pain with similarly low-to-moderate pain in the placebo control groups [21,22]. Therefore, the role of baseline postoperative pain level on the analgesic effectiveness of duloxetine deserves further investigation.

Similar to other studies addressing the analgesic effect of short-term perioperative duloxetine [10,12,13,16,17,33–36], no association between duloxetine and postoperative nausea, vomiting, dry mouth, headache, dizziness, excessive sedation or pruritus was found in this trial, confirming the low potential for adverse effects of the short-term administration of duloxetine [21,22].

This study assessed the effects of a short-term, perioperative dose consisting of two 60 mg doses of duloxetine. A few studies have addressed longer-term regimens with controversial results. Nars [13]

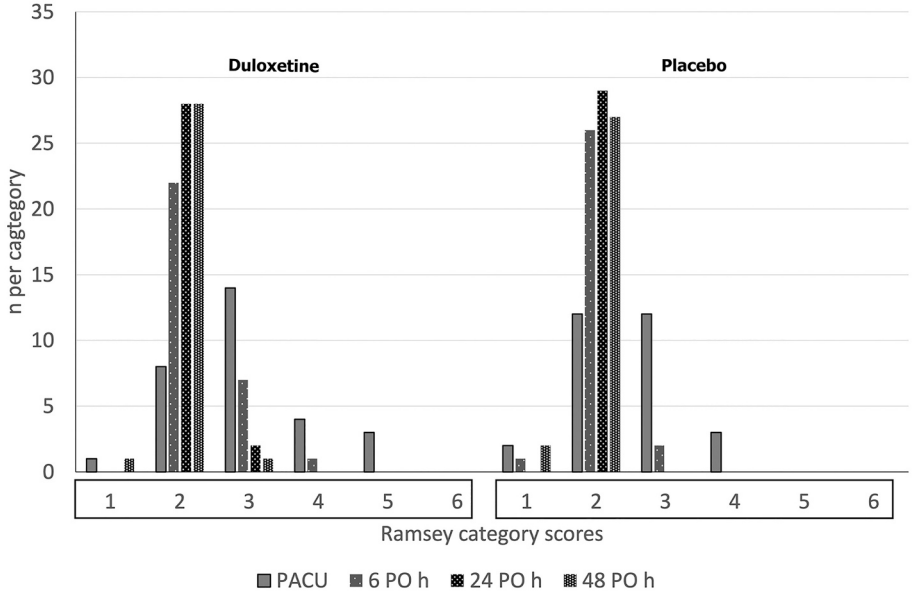

Fig. 5. Distribution of Ramsay scores at the measurement occasions in the study groups, according to the following criteria: 1 - Patient is anxious and agitated or restless, or both; 2 - Patient is cooperative, oriented, and tranquil; 3 - Patient responds to commands only; 4 - Patient exhibits a fast response to a light glabellar tap or loud auditory stimulus; 5 - Patient exhibits a sluggish response to a light glabellar tap or loud auditory stimulus; 6 - Patient exhibits no response. Bars represent the number of patients presenting the scores (on the x-axis) on each measurement occasion. No significant association between groups and sedation score distributions was found ($\chi^2_{(4\ d.f)} = 4.14$, $p = 0.35$).

Table 4
Cumulative incidence of postoperative adverse events.

	Duloxetine (n = 30)	Placebo (n = 29)	p-value
At 24 h			
Nausea	6 (20)	6 (27)	0.60
Vomiting	2 (6.7)	0 (0)	0.25
Dry mouth	30 (100)	29 (100)	N/A
Pruritus	0 (0)	4 (13.8)	0.05
Headache	3 (10)	1 (3.4)	0.32
Dizziness	8 (26.7)	8 (27.6)	1.00
Visual disturbances	0 (0)	0 (0)	N/A
At 48 h			
Nausea	1 (3.3)	0 (0.0)	1.00
Vomiting	0 (0)	1 (3.4)	0.49
Dry mouth	23 (76.7)	20 (69)	0.35
Pruritus	0 (0)	2 (6.9)	0.24
Headache	1 (3.3)	1 (3.4)	0.74
Dizziness	3 (10)	4 (13.8)	0.71
Visual disturbances	2 (6.7)	0 (0)	0.49

Data are presented as frequency (%). N/A = not applicable.

administered duloxetine 60 mg starting two days before surgery and 30 mg for 14 days postoperatively to patients undergoing mastectomy. They found that duloxetine significantly reduced postoperative analgesic requirements, VAS, and the incidence of chronic pain at 3 and 6 months postoperatively. In contrast, Yadeau and colleagues [15] administered daily 60 mg doses of duloxetine as part of comprehensive multimodal analgesia for 15 days, starting from the day of surgery to patients undergoing knee arthroplasty, and found that duloxetine did not reduce subacute pain with ambulation on the 14th postoperative day (the primary outcome). Further studies are needed to clarify the discrepant results.

Some methodological issues in this study may limit the generalizability of our findings. First, results were based on postoperative opioid consumption and visual analog pain scores. Both measures are unperfect surrogates for postoperative pain intensity because both are affected by factors dependent on individual patients (e.g., culture, altruism, expectation, beliefs, education level, age) [37]. Second, although allowing for a more precise measure of the dose of opioids administered, the same factors may affect the number of analgesic requests and, consequently, the total opioid consumption [38]. Third, although patients were educated preoperatively about the PCA pump and the visual analog pain scale, the pharmacologic effects of drugs administered in the postoperative period may have induced some information and response biases.

Our results confirmed the null hypotheses of the study, as no significant effect of duloxetine 60 mg administered 2 h before and 24 h after surgery to patients submitted to major colonic surgery under general anesthesia has been detected on the postoperative i.v. PCA morphine consumption or pain intensity scores during the initial 48 postoperative hours. In conclusion, under this study's conditions, short-term duloxetine did not reduce total opioid consumption or pain intensity during the initial 48 h following major colon surgery.

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Availability of data and material

The data supporting this study's findings are available from the corresponding author upon request.

Code availability

Not applicable.

Ethics approval

The Human Research Ethics Committee at the Federal University of Santa Catarina approved the study protocol (registration number 04031718.4.0000.0121). All procedures in this study followed international, national, and institutional ethical standards for studies involving human participants, according to the 1964 Helsinki Declaration and its later amendments.

Consent to participate

Informed consent was obtained from all individual participants included in the study.

Consent for publication

Not applicable.

CRediT authorship contribution statement

Thomas Rolf Erdmann: Conceptualization, Project administration, Formal analysis, Writing – original draft, Visualization. **Marlus Tavares Gerber:** Conceptualization, Investigation. **Patrick Barcelos Gaspareto:** Conceptualization. **Getúlio Rodrigues de Oliveira Filho:** Conceptualization, Supervision, Formal analysis, Writing – review & editing.

Declaration of Competing Interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jclinane.2022.110948.

References

[1] Wick EC, Grant MC, Wu CL. Postoperative multimodal analgesia pain management with nonopioid analgesics and techniques: a review. JAMA Surg 2017;152(7):691–7. https://doi.org/10.1001/jamasurg.2017.0898.
[2] Tiippana EM, Hamunen K, Kontinen VK, Kalso E. Do surgical patients benefit from perioperative gabapentin/pregabalin? A systematic review of efficacy and safety. Anesth Analg 2007;104(6):1545–56. https://doi.org/10.1213/01.ane.0000261517.27532.80.
[3] Mishriky BM, Waldron NH, Habib AS. Impact of pregabalin on acute and persistent post-operative pain: a systematic review and meta-analysis. Br J Anaesth 2015;114(1):10–31. https://doi.org/10.1093/bja/aeu293.
[4] Kirkpatrick DR, McEntire DM, Hambsch ZJ, Kerfeld MJ, Smith TA, Reisbig MD, et al. Therapeutic basis of clinical pain modulation. Clin Transl Sci 2015;8(6):848–56. https://doi.org/10.1111/cts.12282.
[5] Wang L, Tobe J, Au E, Tran C, Jomy J, Oparin Y, et al. Selective serotonin reuptake inhibitors and serotonin–norepinephrine reuptake inhibitors as adjuncts for postoperative pain management: systematic review and meta-analysis of randomised controlled trials. Br J Anaesth 2022;128(1):118–34. https://doi.org/10.1016/j.bja.2021.08.032.
[6] Wang CF, Russell G, Strichartz GR, Wang GK. The local and systemic actions of duloxetine in allodynia and hyperalgesia using a rat skin incision pain model. Anesth Analg 2015;121(2):532–44. https://doi.org/10.1213/ANE.0000000000000794.
[7] Le Cudennec C, Castagné V. Face-to-face comparison of the predictive validity of two models of neuropathic pain in the rat: analgesic activity of pregabalin, tramadol and duloxetine. Eur J Pharmacol 2014;735:17–25. https://doi.org/10.1016/j.ejphar.2014.04.003.
[8] Wang C-F, Russell G, Wang S-Y, Strichartz GR, Wang GK. R-duloxetine and N-methyl duloxetine as novel analgesics against experimental postincisional pain. Anesth Anal 2016;122(3):719–29. https://doi.org/10.1213/ANE.0000000000001086.
[9] Handa J, Sekiguchi M, Krupkova O, Konno S. The effect of serotonin–noradrenaline reuptake inhibitor duloxetine on the intervertebral disk-related radiculopathy in rats. Eur Spine J 2016;25(3):877–87. https://doi.org/10.1007/s00586-015-4239-9.
[10] Castro-Alves LJ, Oliveira de Medeiros ACP, Neves SP, Carneiro de Albuquerque CL, Modolo NS, De Azevedo VL, et al. Perioperative duloxetine to improve postoperative recovery after abdominal hysterectomy. Anesth Anal 2016;122(1):98–104. https://doi.org/10.1213/ANE.0000000000000971.
[11] Kassim D, Esmat I, Elgendy M. Impact of duloxetine and dexamethasone for improving postoperative pain after laparoscopic gynecological surgeries: a randomized clinical trial. Saudi J Anaesth 2018;12(1):95. https://doi.org/10.4103/sja.SJA_519_17.
[12] Abo Elfadl GM, Osman AM, Ghalyoom MF, Gad Al-Rab NA-A, Bahloul M. Preoperative duloxetine to prevent postoperative shoulder pain after gynecologic laparoscopy: a randomized controlled trial. Brazil J Anesthesiol (English Edition) 2021. https://doi.org/10.1016/j.bjane.2021.07.035. S0104001421003249.
[13] Nasr D. Efficacy of perioperative duloxetine on acute and chronic postmastectomy pain. Ain-Shams J Anaesthesiol 2014;7(2):129–33. https://doi.org/10.4103/1687-7934.133345.
[14] Ho KY, Tay W, Yeo MC, Liu H, Yeo SJ, Chia SL, et al. Duloxetine reduces morphine requirements after knee replacement surgery. Br J Anaesth 2010;105(3):371–6. https://doi.org/10.1093/bja/aeq158.
[15] YaDeau JT, Brummett CM, Mayman DJ, Lin Y, Goytizolo EA, Padgett DE, et al. Duloxetine and subacute pain after knee arthroplasty when added to a multimodal analgesic regimen. Anesthesiology 2016;125(3):561–72. https://doi.org/10.1097/ALN.0000000000001228.
[16] El-Hawary Salama I, Sadek Sameh M. Efficacy of duloxetine on the duration of spinal anesthesia and acute post-operative pain after hip surgery prospective randomized controlled study. Med J Cairo Univ 2019;87:3535–40. https://doi.org/10.21608/mjcu.2019.65651.
[17] Li H, Zeng W-N, Ding Z-C, Yuan M-C, Cai Y-R, Zhou Z-K. Duloxetine reduces pain after Total hip arthroplasty: a prospective, randomized controlled study. BMC Musculoskelet Disord 2021;22(1):492. https://doi.org/10.1186/s12891-021-04377-4.
[18] Bedin A, Caldart Bedin RA, Vieira JE, Ashmawi HA. Duloxetine as an analgesic reduces opioid consumption after spine surgery. Clin J Pain 2017;33(10):865–9. https://doi.org/10.1097/AJP.0000000000000471.
[19] Attia JZ, Mansour HS. Perioperative duloxetine and Etoricoxibto improve postoperative pain after lumbar laminectomy: a randomized, double-blind, controlled study. BMC Anesthesiol 2017;17(1):162. https://doi.org/10.1186/s12871-017-0450-z.
[20] Govil N, Parag K, Arora P, Khandelwal H, Singh A, Ruchi.. Perioperative duloxetine as part of a multimodal analgesia regime reduces postoperative pain in lumbar canal stenosis surgery: a randomized, triple blind, and placebo-controlled trial. Korean J Pain 2020;33(1):40–7. https://doi.org/10.3344/kjp.2020.33.1.40.
[21] Zorrilla-Vaca A, Stone A, Caballero-Lozada AF, Paredes S, Grant MC. Perioperative duloxetine for acute postoperative analgesia: a meta-analysis of randomized trials. Reg Anesth Pain Med 2019. https://doi.org/10.1136/rapm-2019-100687.
[22] de Oliveira Filho GR, Kammer RS, de dos Santos HC. Duloxetine for the treatment acute postoperative pain in adult patients: A systematic review with meta-analysis. J Clin Anesth 2020;63:109785. https://doi.org/10.1016/j.jclinane.2020.109785.
[23] Moher D, Hopewell S, Schulz KF, Montori V, Gotzsche PC, Devereaux PJ, et al. CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. BMJ 2010;340:c869. https://doi.org/10.1136/bmj.c869.
[24] Borracci T, Cappellini I, Campiglia L, Picciafuochi F, Berti J, Consales G, et al. Preoperative medication with oral morphine sulphate and postoperative pain. Minerva Anestesiol 2013;79(5):525–33.
[25] Cho M. The effects of bridge exercise with the abdominal drawing-in maneuver on an unstable surface on the abdominal muscle thickness of healthy adults. J Phys Ther Sci 2015;27(1):255–7. https://doi.org/10.1589/jpts.27.255.
[26] Roberts C, Torgerson DJ. Understanding controlled trials: baseline imbalance in randomised controlled trials. BMJ 1999;319(7203):185. https://doi.org/10.1136/bmj.319.7203.185.
[27] Buchner DM, Findley TW. Research in physical medicine and rehabilitation: VIII. Preliminary data analysis. Am J Phys Med Rehabil 1990;69(3):154–69. https://doi.org/10.1097/00002060-199006000-00011.
[28] Ho K-Y, Tay W, Yeo M-C, Liu H, Yeo S-J, Chia S-L, et al. Duloxetine reduces morphine requirements after knee replacement surgery. Br J Anaesth 2010;105(3):371–6. https://doi.org/10.1093/bja/aeq158.
[29] Altıparmak B, Güzel Ç, Gümüş Demirbilek S. Comparison of preoperative administration of pregabalin and duloxetine on cognitive functions and pain management after spinal surgery. Clin J Pain 2018;34(12):1114–20. https://doi.org/10.1097/AJP.0000000000000640.
[30] Faul F, Erdfelder E, Lang A-G, Buchner A. G*power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. Behav Res Methods 2007;39(2):175–91. https://doi.org/10.3758/bf03193146.
[31] Delaney HD, Maxwell SE. On using analysis of covariance in repeated measures designs. Multivariate Behav Res 1981;16(1):105–23. https://doi.org/10.1207/s15327906mbr1601_6.
[32] Sattari H, Noroozi M, Hashemian M, Doroodian M, Mansoori Nasab F. Evaluating the effect of preoperative duloxetine administration on postoperative pain in patients under abdominal hysterectomy. JBUMS 2020;22(1):203–9. https://doi.org/10.22088/jbums.22.1.203.
[33] Sattari H, Noroozi M, Hashemian M, Doroodian M, Mansoori Nasab F. Evaluating the effect of preoperative duloxetine administration on postoperative pain in patients under abdominal hysterectomy. JBUMS 2020;22(1):203–9. https://doi.org/10.22088/jbums.22.1.203.
[34] Koh IJ, Kim MS, Sohn S, Song KY, Choi NY, In Y. Duloxetine reduces pain and improves quality of recovery following Total knee arthroplasty in centrally sensitized patients: a prospective, randomized controlled study. J Bone Joint Surg - Am Volume 2019;101(1):64–73. https://doi.org/10.2106/JBJS.18.00347.
[35] Altıparmak B, Güzel Ç, Gümüş Demirbilek S. Comparison of preoperative administration of pregabalin and duloxetine on cognitive functions and pain management after spinal surgery. Clin J Pain 2018;34(12):1114–20. https://doi.org/10.1097/AJP.0000000000000640.
[36] Mostafa MF, Ali Ibraheim O, Ibrahim AK, Ibrahim RAE, Herdan R. Impact of duloxetine on succinylcholine-induced postoperative myalgia after direct

microlaryngoscopic surgeries: randomized controlled double-blind study. Pain Pract 2022;22(1):57–65. https://doi.org/10.1111/papr.13050.
[37] Gorczyca R, Filip R, Walczak E. Psychological aspects of pain. Ann Agric Environ Med 2013:23–7. Spec no. 1.
[38] Dolin SJ, Cashman JN, Bland JM. Effectiveness of acute postoperative pain management: I. evidence from published data. Br J Anaesth 2002;89(3):409–23.