# EFFECTS OF PREOPERATIVE DULOXETINE ON SHORT-TERM OUTCOMES AFTER LAPAROSCOPIC SURGERIES: A SYSTEMATIC REVIEW AND META-ANALYSIS

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**ABSTRACT**

**Objective:** To conduct a systematic review and meta-analysis to investigate the effects of preoperative duloxetine on short-term outcomes after laparoscopic surgeries. Methods: MEDLINE, Embase, and the Cochrane Library were systematically searched for randomized controlled trials comparing preoperative duloxetine vs. placebo in adults undergoing laparoscopic surgery. Risk ratios (RRs) and mean differences (MDs) with 95% confidence intervals (CIs) were used for dichotomous and continuous outcomes, respectively, using a random-effects model. Statistical significance was considered at $p<0.05$. Results: Four trials (227 patients) were included. Compared to placebo, duloxetine provided significantly lower pain scores at 2 (MD -1.04; 95% CI -1.75, -0.33), 4 (MD -1.28; 95% CI -1.77, -0.79), 8 (MD -1.22; 95% CI -1.72, -0.72), 12 (MD -1.64; 95% CI -2.88, -0.41), and 24 hours (MD -1.05; 95% CI -1.72, -0.39) after surgery. Duloxetine led to a significantly longer time between the end of surgery and the first request for analgesia by the patient (MD 128.38 minutes; 95% CI 41.31, 215.46), compared to placebo. Furthermore, the group that received duloxetine had a significantly lower risk of nausea/vomiting (RR 0.48; 95% CI 0.25, 0.90), while there were no significant differences between the groups regarding the risk of dizziness, headache, and somnolence. Conclusion: Compared to placebo, the administration of duloxetine before laparoscopic surgeries significantly reduces postoperative pain intensity, delays the need for analgesia, and reduces the risk of nausea/vomiting.

**Keywords:** Postoperative; duloxetine; laparoscopic surgery; adult.

## INTRODUCTION

The implementation of the laparoscopic technique has significantly reduced postoperative complication rates; however, pain after surgical interventions remains a relevant clinical challenge and, in many cases, is inadequately managed[1], highlighting the need for new analgesic strategies, especially due to the toxicity of the most potent drugs[2]. Duloxetine, a serotonin-norepinephrine reuptake inhibitor, has demonstrated efficacy in managing painful conditions[3,4], acting by increasing serotonergic and noradrenergic neurotransmission in the descending inhibitory pathways of the central nervous system[5] and by inhibiting sodium channels[6]. Furthermore, duloxetine is generally well tolerated, with mild and transient adverse events, such as nausea, vomiting, dizziness, and headache[3].

Recent evidence has shown promising findings regarding the preoperative administration of duloxetine for pain control after non-laparoscopic surgeries[7,8]. Therefore, the objective was to conduct a systematic review and meta-analysis of randomized controlled trials (RCTs) to investigate the effects of preoperative duloxetine on short-term outcomes after laparoscopic surgeries.

## METHODS

### Study design and protocol

A systematic review and meta-analysis were conducted following the *Cochrane Handbook for Systematic Reviews of Interventions* and the *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* (PRISMA)^9,10^. The study protocol was prospectively registered (PROSPERO ID: CRD42024502840).

### Search procedure, eligibility criteria, and outcomes

Two reviewers independently conducted the systematic search in the MEDLINE, Embase, and Cochrane Library databases on July 19, 2024. Records were imported into the Rayyan software, and after removing duplicates, titles and abstracts were screened according to the eligibility criteria. Subsequently, the eligibility of each article was assessed based on a full-text review. Disagreements were resolved by a third author (MRC).

The inclusion criteria consisted of (i) RCTs, (ii) comparing preoperative duloxetine vs. placebo, (iii) in patients aged ≥18 years undergoing laparoscopic surgery, and (iv) reporting at least one outcome of interest. We included only original, peer-reviewed RCTs, published in English with full text available. There were no restrictions on publication date. Studies were excluded that: (i) administered duloxetine at doses ≥60 mg before surgery; (ii) administered duloxetine both before and after surgery; (iii) were retracted; or (iv) were *post-hoc* analyses, clinical trial registries, conference abstracts, comments, or brief reports.

The primary outcomes were pain scores on the visual analog scale (VAS) at 2, 4, 8, 12, and 24 hours after surgery. The secondary outcomes were (i) the time to the first need for analgesic and (ii) the risk of adverse events (nausea/vomiting, dizziness, headache, and somnolence).

## Data analysis

The *DerSimonian-Laird* random-effects model was used to calculate pooled estimates along with their 95% confidence intervals (CIs). Risk ratios (RRs) for dichotomous outcomes were estimated using the *Mantel-Haenszel* method, while mean differences (MDs) for continuous outcomes were calculated using the *Inverse-Variance* method. Heterogeneity was analyzed using the Cochrane Q test and $I^2$ statistic, employing the *DerSimonian-Laird* and *Restricted Maximum-Likelihood* estimators for dichotomous and continuous outcomes, respectively. R software 4.2.1 was used for the analyses. Statistical significance was considered at $p<0.05$. The risk of bias assessment was performed according to the *Cochrane Risk of Bias 2* (RoB 2) tool[11].

# RESULTS

## Study selection

The initial search yielded 340 records. After removing duplicates (n=132), 208 studies were screened by title and abstract. Subsequently, seven studies were reviewed in full text, and four RCTs were included[12-15].

## Baseline characteristics and risk of bias assessment

The four trials totaled 227 patients, of whom 111 (48.9%) were randomized to receive duloxetine 60 mg two hours before surgery. The patients had a mean age of 33.8 (±9.4) years, and 206 (90.7%) were female. Two of the four studies employed the laparoscopic technique in gynecological surgeries (107 [47.1%] patients), while the other two performed cholecystectomies (120 [52.9%] patients). The overall quality of the four studies was rated as having some concerns (n=2)[12,15] and low risk of bias (n=2)[13,14].

## Outcome analysis

Compared to placebo, duloxetine provided a statistically lower pain intensity on the VAS scale at all assessed time points; namely, 2 (MD -1.04; 95% CI -1.75, -0.33; $p<0.01$; $I^2=0\%$), 4 (MD -1.28; 95% CI -1.77, -0.79; $p<0.01$; $I^2=0\%$), 8 (MD -1.22; 95% CI -1.72, -0.72; $p<0.01$; $I^2=0\%$), 12 (MD -1.64; 95% CI -2.88, -0.41; $p<0.01$; $I^2=89\%$),

and 24 hours (MD -1.05; 95% CI -1.72, -0.39; $p<0.01$; $I^2=32\%$) after the surgical procedure.

Compared to placebo, the use of duloxetine led to a statistically longer time between the end of surgery and the first request for analgesia by the patient (MD 128.38 minutes; 95% CI 41.31, 215.46 minutes; $p<0.01$; $I^2=74\%$).

The group that received duloxetine had a statistically lower risk of nausea/vomiting compared to the placebo group (RR 0.48; 95% CI 0.25, 0.90; $p=0.02$; $I^2=53\%$); while there were no significant differences between the groups regarding the risk of dizziness (RR 0.51; 95% CI 0.24, 1.12; $p=0.09$; $I^2=0\%$), headache (RR 0.52; 95% CI 0.09, 2.86; $p=0.45$; $I^2=0\%$), and somnolence (RR 1.06; 95% CI 0.16, 6.95; $p=0.95$; $I^2=0\%$).

## CONCLUSION

It was demonstrated that preoperative duloxetine offers improvements in the quality of postoperative recovery after laparoscopic surgeries, including pain reduction, delayed need for analgesia, and reduced risk of nausea/vomiting. Despite being promising, new large-scale RCTs are needed to confirm these findings.

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