***Effect of peri-operative Duloxetine on postoperative analgesia after knee Arthroplasty; a Systematic review and meta- analysis.***

 Running title: Duloxetine for Postoperative Analgesia after TKA

**Abstract**

Background: The number of total knee arthroplasties performed each year has seen a significant rise. About 20% of patients who undergo TKA may still experience chronic pain, impacting all aspects of their health-related quality of life and resulting in functional limitations despite a successful treatment outcome. Duloxetine, a selective serotonin and norepinephrine reuptake inhibitor (SNRI), is also FDA-approved for treating various chronic painful syndromes.

Methods: A comprehensive search of the English literature was conducted using the Medline, Scholar Google, and Science Direct databases from inception to March 2021, with key terms including ("Duloxetine" or "Cymbalta") and ("total knee replacement" or "total knee arthroplasty" or "TKR" or "TKA" or "knee replacement surgery") and ("acute pain management" or "acute postoperative pain" or "postoperative analges\*" or "pain control"). Each study included in the research was evaluated objectively for its methodological quality by employing methods aligned with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines. (PROSPERO ID: CRD42022307595).

Results: Research involving 684 patients across five studies found that, at 24 hours post-surgery, the group receiving duloxetine experienced a reduction in VAS compared to the control group (placebo) with a mean difference of −0.68 (95% confidence interval, −1.26 to −0.1; p < .05). Two studies involving 147 patients assessed the VAS at 48 hours post-surgery, with a mean difference of -0.41 and a 95% confidence interval of [-1.38 - 0.55], and the results did not reach statistical significance (P > 0.05). The VAS was compared 48 hours after surgery in two investigations with 147 patients (MD = -0.41; 95% CI, [-1.38-0.55]; P >.05. Fig. 6).
Conclusions: Duloxetine was found to be helpful in reducing Visual Analogue Scale (VAS) scores and opiate intake without increasing the risk of problems. When used as part of a multimodal pain treatment plan prior to surgery, duloxetine can be a useful pain control tool.

**KEYWORDS:** Peri-operative Duloxetine, Postoperative Analgesia, knee Arthroplasty

**Introduction**

Knee osteoarthritis is a complicated condition affecting the peripheral joints. Options for surgery include joint-sparing techniques like arthroscopy and osteotomy, or joint replacement procedures. The annual number of total knee arthroplasties (TKAs) is rising significantly. While many patients have positive outcomes, around 20% of patients continue to suffer from chronic pain following total knee arthroplasty. Chronic pain following total knee arthroplasty (TKA) can impact multiple aspects of health-related quality of life and is linked to functional impairments including flexion instability, arthrofibrosis, pain-related distress, depression, decreased overall health, and social isolation. Developments in rapid recovery protocols have been achieved using a collaborative, multidisciplinary approach, with the goal of enhancing both patient satisfaction and outcomes. (1)

A drug known as a selective serotonin norepinephrine reuptake inhibitor (SNRI) is duloxetine, an antidepressant. For the treatment of post-traumatic stress disorder, the U.S. Food and Drug Administration has authorised a drug. In addition to major depression, there is also generalised anxiety disorder. Additionally, the FDA has authorised duloxetine for the treatment of a number of chronic painful illnesses, such as fibromyalgia, chronic musculoskeletal pain, and neuropathic pain, which can develop in diabetics (2) Research has demonstrated the effectiveness of duloxetine in providing improved pain relief when given to patients in the short term before and after surgery, as part of a comprehensive pain management plan, for those undergoing orthopedic (3, 4), gynecological (5, 6), and breast surgery (7).

In individuals with increased central sensitivity following total knee replacement, duloxetine reduces pain and improves post-operative rehabilitation results. Central sensitisation, in which the central nervous system becomes hyperactive and causes an increased sensitivity to both painful and non-painful stimuli, can be brought on by a persistent and detrimental peripheral input, such as the pain from chronic osteoarthritis in the knee. After a TKA, those who are centrally sensitised may be more likely to have unexplained discomfort (8).

This study used a systematic literature review to assess the impact of duloxetine treatment on the decrease in postoperative pain following total knee replacement operations.

**Methods**

The study was conducted in Assiut University Hospital, Department of Anaesthesia and Intensive care after the approval from the ethical committee (17101446).

Inclusion criteria were randomized controlled trials, cohort and observational studies including patients who received perioperative duloxetine for acute pain management after TKA, adult age group older than 18 years, English language articles, studies with minimum follow up of 48 hours postoperative, studies with pain scores as their primary outcomes. Procedures other than TKA, data published from case report studies, abstracts or conference proceedings non-English language studies were excluded.

**Identifications of studies:**

A search of the English literature between January 2018 and March 2021 in the Medline, Scholar Google, and Science Direct databases was conducted using the search terms: ("Duloxetine" or "Cymbalta") and ("total knee replacement" or "total knee arthroplasty" or "TKR" or "TKA" or "knee replacement surgery") and ("acute pain management" or "acute postoperative pain" or "postoperative analges\*" or "pain control"). The selection of studies for inclusion in this review was guided by the PICOS criteria, specifically population, intervention, control, outcomes, and study design: population - patients who underwent total knee replacement; intervention - perioperative duloxetine administration; control - patients receiving placebo or standard care; outcomes assessed - postoperative pain; and study design - randomised controlled trials, observational studies, and cohort studies. Manual cross-referencing of citations in identified papers was conducted, and further articles meeting the specified criteria were incorporated into the literature review.

Study selection:

During the initial stage, two researchers reviewed the titles and abstracts of the identified studies for relevance to the research topic, verifying them against pre-established eligibility criteria. Unrelated studies were excluded, while those related to the topic but not meeting the inclusion criteria were referred to the team for further assessment. Articles from Stage 2 were evaluated for compliance with the eligibility criteria, with justification provided for inclusion or exclusion in the review. The studies selected were subsequently submitted for data analysis. The PRISMA flow chart was generated to enhance the transparency of the review process.

Data extraction:

Information was retrieved from the full text of articles selected for review, which contained details on study methodology, the first author's name, publication year, type of surgery, sample size, the intervention group including dosage and administration schedule, the control group, and postoperative pain management protocol from each study.

Quality assessment:

Each included study will undergo a rigorous evaluation of its methodological quality, ideally conducted in accordance with the guidelines outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA).

Statistical Approach

Descriptive statistics, along with significance tests (T-test and chi-square), will. The calculation will be significant, with the resulting P-value being less than 0.05.

**Results**

According to our search strategy, (("Pain, Postoperative"[Mesh]) AND "Duloxetine

Hydrochloride"[Mesh]) AND "Arthroplasty, Replacement, Knee"[Mesh]. Ten studies in all were retrieved; two were eliminated due to the fact that their sole published research protocols were included, and three more were eliminated based on the abstract and title since the postoperative patient follow-up duration was six months. Ultimately, we chose five RCTs for our meta-analysis.

Assessment for risk of bias

Computer-generated randomisation or a web-based computerised block randomisation service were employed in two of the five RCTs. Six researchers used the double-blind technique, whereas three randomised controlled trials explained how allocation concealment was done using sealed envelopes or other techniques.

Findings from a meta-analysis

Analysis of Visual Analogue Scale (VAS) data in a resting state. A total of five studies [8,9,10,11,12] encompassed 684 patients.

The duloxetine group had lower VAS scores at 24 hours post-surgery compared to the control group receiving a placebo, with a mean difference of −0.68 and a 95% confidence interval of [−1.26–−0.1], indicating a statistically significant result (p < .05). Two studies, referenced as [26,29], involving 147 patients examined the VAS at 48 hours post-surgery and found a mean difference of −0.41, with a P-value higher than 0.05 and a 95% confidence range between -1.38 and 0.55. Results from four trials [6, 12, 27, 29] with 325 patients showed that the duloxetine and control groups had significantly different VAS ratings 72 hours after surgery, with a mean difference of −0.54 (95% CI, [−0.92, −0.16]; P <.05). Results from three studies [12,27,29] involving a total of 219 patients showed a comparison of VAS on the fifth postoperative day, yielding a mean difference of −1.05 and a 95% confidence interval of −1.75 to −0.35, with a p-value less than 0.05. Analysis of combined data reveals that patients in the duloxetine group experienced a significant improvement in VAS scores when at rest, with a mean difference of -0.59; the 95% confidence interval ranged from -0.82 to -0.37, and the probability value was less than 0.05.

**Discussion**

Total knee replacement (TKR) is one of the most effective treatments for severe knee osteoarthritis; however, effective postoperative pain management remains challenging. Chronic postoperative pain can impair rehabilitation and patient outcomes. Recently, preoperative analgesia has gained attention as a strategy to mitigate postoperative pain, with duloxetine—a serotonin-norepinephrine reuptake inhibitor (SNRI)—showing promise due to its impact on central pain modulation.

Duloxetine exerts its analgesic effect through the modulation of serotonin and norepinephrine, which play a role in the central descending pain pathway. By enhancing these neurotransmitters, duloxetine potentially reduces hyperalgesia and decreases pain perception post-surgery, thus making it an attractive option for TKR pain management.

This meta-analysis evaluated the short term analgesic effects of duloxetine i.e. 14 days immediate postoperative. Our meta-analysis found that duloxetine has the potential to decrease equivalent morphine use as well as VAS scores during movement in patients undergoing total knee arthroplasty (TKA). In this meta-analysis, five randomised controlled trials were examined, in which 684 patients recorded their VAS scores at 24 hours post-surgery and were compared to a control group receiving a placebo. A VAS score was employed to assess the analgesic effect. The duloxetine group exhibited a significant decrease in postoperative pain both at rest and during movement.

Studies have shown that taking duloxetine before surgery can significantly decrease the severity of pain and lower opioid use after a total knee replacement. For 148 patients who had total knee arthroplasty (TKA) and received a modern analgesic regimen that combined nerve blockade and oral multimodal pain management without patient-controlled analgesia (PCA), researchers led by YaDeau J. in 2022 examined the effects of giving 60 mg of duloxetine daily, starting on the day of surgery, to provide analgesia lasting up to 14 days. Patients who took duloxetine required fewer opioids to achieve comparable levels of pain relief compared to those given a placebo. Patients who used duloxetine expressed more satisfaction with their pain management, and they discovered that pain had less of an effect on their mood, ability to walk, job, social interactions, sleep, and general quality of life. There were no notable adverse effects noted (9)

In 2021, Kim et al. conducted a study involving 290 patients who were given either opioids or duloxetine to manage their pain from the first postoperative day for a period of 6 weeks. Their key discovery was that duloxetine treatment for six weeks had comparable effectiveness to opioid treatment in terms of pain relief and functional improvement following Total Knee Arthroplasty (TKA). The Visual Analogue Scale (VAS) pain score and the WOMAC Pain and Function score at each time point, both before to and following surgery, did not differ statistically significantly (all p>0.05). Furthermore, duloxetine resulted in minimal side effects compared to opioids. This suggests that it could serve as a suitable alternative to opioids in a multimodal pain management strategy for patients being discharged following total knee arthroplasty. (10)

Patients who underwent either total hip or knee replacement in 2021 and received pre-operative oral treatment with duloxetine at a dose of 60 mg/day for 7 weeks in addition to their standard analgesic regimen were compared to those receiving usual care in a multicenter randomized clinical trial conducted at three secondary care hospitals in the Netherlands. Unfortunately, the results failed to validate the hypothesis that preoperative targeted treatment for desensitization would decrease chronic pain that persists after surgery. We can only assess the combined impact of the drug's pharmacological activity and its side effects, such as placebo and nocebo, when comparing duloxetine therapy to conventional care. A nocebo effect might be caused by the duloxetine treatment group's high incidence of adverse events and absence of blinding, especially during and soon after the intervention period (11).

The Central Sensitisation Inventory (CSI) was used to screen for central sensitisation prior to surgery in 80 patients with primary osteoarthritis having unilateral total knee arthroplasty. These 80 individuals were enrolled in research by Koh et al. that determined they were centrally sensitised. Forty were randomised to receive 30 mg of duloxetine the day before surgery and for six weeks afterward - while the other 40 were assigned to a control group that did not receive duloxetine. The Central Sensitisation Inventory (CSI) was used to screen for central sensitisation prior to surgery in 80 patients with primary osteoarthritis having unilateral total knee arthroplasty. These 80 individuals were enrolled in a research by Koh et al. that determined they were centrally sensitised. Forty were randomised to receive 30 mg of duloxetine the day before surgery and for six weeks afterward.(8)

YaDeau J et al. carried out a triple-blind, randomised, placebo-controlled study in 2016. 160 TKA patients participated in the trial, and they were given either duloxetine or a placebo for 15 days starting on the day of the procedure. Additionally, patients were given a wide range of pain management techniques, including as epidural pain management, an adductor canal nerve block, and the prescription drugs oxycodone/acetaminophen and meloxicam when needed. Following ambulation on postoperative day 14, the patient's pain level, graded on a 0–10 scale, was the primary outcome measure documented.

 Research showed that giving duloxetine to patients for 2 weeks after total knee arthroplasty did not reduce pain while walking. Duloxetine was found not to induce significant side effects. In addition, secondary outcomes were comparable across groups, with duloxetine also found to decrease opioid use and alleviate nausea, both of which were statistically significant and of substantial clinical impact.(12)

Effective pain management with duloxetine can contribute to a smoother rehabilitation process. Patients experiencing less pain are more likely to engage fully in physical therapy, that is crucial for functional recovery. Though generally well-tolerated, duloxetine does carry a risk of side effects such as dry mouth, fatigue, and nausea. Furthermore, it may not be suitable for patients with certain comorbidities, such as hepatic impairment. Therefore, careful patient selection is crucial when considering duloxetine for preoperative pain management in TKR.

Conclusion

Duloxetine, which can assist reduce opioid consumption, can be beneficial for certain patients having knee replacements as long as they can be properly watched for any drug adverse effects. To determine the best course of treatment, determine the frequency of rare adverse effects, and examine if postoperative duloxetine is appropriate for additional surgical procedures, more study is needed.

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