Original Article

Effect of Duloxetine on Pain Relief in Patients Undergoing Arthoplasty

Relief in Arthoplasty

Inamullah[1], Hussain Ahmad[2], Muhammad Asghar Essa[3], Muhammad Zubair Farooq[3], Shafaat Ullah[4] and Yousaf Gul[1]

ABSTRACT

Objective: This trial was executed for investigating potential of duloxetine on alleviating pain in patients underwent arthroplasty surgery.

Study Design: Randomized controlled trial study.

Place and Duration of Study: This study was conducted at the Government Hospital Karachi from January 2021 to January 2023.

Materials and Methods: A randomized controlled trial was conducted at Government Hospital Karachi, comprising total of 140 patients undergoing arthroplasty surgery. Patients were stratified into two groups; Group A received duloxetine 60mg daily, and Group B received a placebo. Visual Analog Scale (VAS) was implied for pain assessment at baseline, post-surgery and endpoint and the improvement of pain alleviation was statistically compared. The primary outcome measure was change in pain scores from baseline to 6 months post-surgery.

Results: Mean age was 56.19+14.27 years, and 65.7% were females. Baseline VAS score for duloxetine was 6.5, while the endpoint VAS score was 2.9, indicating a significant improvement in pain reduction ($p<0.05$). The baseline VAS score for the Placebo group was 6.4, while the endpoint VAS score is 6.1, indicating a minor improvement in pain reduction. Thus the duloxetine was significantly more effective ($p<0.05$) in curtailing pain than placebo, as demonstrated by the significantly greater improvement in VAS score and the significant p-value ($p<0.05$). Incidence of adverse impacts was lower in patients treated with duloxetine.

Conclusion: Duloxetine is effective in reducing pain in patients undergoing arthroplasty surgery. It significantly improves pain relief at baseline, 24, 48 hours and 6 months after surgery. Therefore, it can be considered a safe and effective option to manage pain post arthroplasty surgery.

Key Words: Duloxetine, Arthroplasty, Pain relief, Post-surgical pain; Visual Analog Scale, Serotonin inhibitor.

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INTRODUCTION

Arthroplasty surgery is a common orthopedic procedure that involves the replacement of a damaged joint with prosthesis. Surgery is performed to lighten pain, refurbish joint function, and improve the comfort of patients suffering from a range of orthopedic conditions like osteoarthritis, rheumatoid arthritis, and fractures.

[1.] Department of Orthopedic, DHQ Teaching Hospital, Dera Ismail Khan.
[2.] Department of Orthopedic, Psychiatry MMMTH/ Gomal Medical College, Dera Ismail Khan.
[3.] Department of Orthopedic, Mufti Mehmood Memorial Teaching Hospital/ Gomal Medical College, Dera Ismail Khan.
[4.] Department of Orthopedic, Civil Hospital Thall, Hangu, KhyberPakhtunkhwa.

Correspondence: Inamullah, Orthopedic Department, DHQ Teaching Hospital, Dera Ismail Khan
Contact No: 03323850152
Email: dr.inamullah1982@gmail.com

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Arthroplasty surgery has become increasingly popular over the past few decades, with millions of surgeries performed worldwide each year. [1]

Arthroplasty surgery is recommended for patients with joint damage that causes significant pain and limits their ability to perform daily activities. The most common indication for arthroplasty surgery is osteoarthritis, influencing millions of people around the world. Other indications for arthroplasty surgery include rheumatoid arthritis, avascular necrosis, and fractures.[2] Arthroplasty surgery, like any surgical procedure, can cause pain. Sum of pain experienced by patients can vary with type of surgery, individual's pain threshold, and the patient's overall health. Pain after arthroplasty surgery can be caused by several factors, including incisional pain, deep tissue pain, and pain from swelling and inflammation.[3] Immediately after surgery, patients may experience acute pain, which is typically managed with pain medication. In some cases, a patient may receive a regional anesthetic such as an epidural or nerve block, which can provide pain relief for several hours or days following surgery. As the patient recovers from surgery, pain may persist, albeit at a lower intensity. This is usually managed with a combination of pain medication, physical therapy, and rehabilitation. Pain management is crucial to facilitate

recovery and improve patient outcomes.[4-6] Overall, pain management is an important aspect of the recovery process after arthroplasty surgery. Proper pain management can improve patient comfort, reduce the length of hospital stay, and improve patient satisfaction.[7] Duloxetine is effective to manage variety of chronic pains, including fibromyalgia, neuropathic pain, and chronic ache of lower spine.[8-9] Duloxetine acts by inhibiting reuptake of serotonin and norepinephrine CNS and subsequently increase the levels of neurotransmitters and modulation of pain perception. Given its mechanism of action, duloxetine has the potential to be an effective option to manage pain, post-arthroplasty surgery.[8] Duloxetine works by inhibiting reuptake of neurotransmitters (serotonin and norepinephrine), increasing their levels and leads to changes in mood and pain perception. It also has a mild effect on dopamine reuptake, which may contribute to its therapeutic effects.[10-11] Duloxetine is FDA approved drug to treat major depressive disorders, anxiety, chronic musculoskeletal pain and fibromyalgia. It is also used off-label to cure other psychiatric and pain disorders, like neuropathic pain and low spine ache,[12] available in capsule form and is typically taken once daily. The recommended starting dose is 30mg/day, which can be increased to 120mg/day at maximum, depending on the condition being treated and the individual's response to the medication. The dose may need to be adjusted in patients with liver or kidney impairment. Adverse effects of duloxetine be nausea, dry mouth, constipation, dizziness, and fatigue. Less commonly, it can cause sexual dysfunction, insomnia, and weight gain. A variety of pharmacological and non-pharmacological interventions have been used for treating pain during postoperative period. However, the optimal approach to pain management after arthroplasty remains unclear, and there is a need for more effective and safer options, therefore, this research trial was executed investigating impact of duloxetine on pain relief in patients undergoing arthroplasty.

MATERIALS AND METHODS

A randomized controlled trial was performed at Government Hospital Karachi from January 2021 to January 2023. Sample size comprising 140 patients was calculated using WHO sample size calculator keeping the population proportion at 10% and 95% confidence interval. Patients undergoing arthroplasty surgery were included.Using block randomization method, patients were assigned to two groups of equal size (n=70). Group A was administered duloxetine 60 mg, while group B was given a placebo (commercially available analgesic). Both groups received the drug intervention five times: 90 minutes before surgery, then at 12, 24, and 48 hours post-surgery, and 6 months after surgery. Pain assess was done by VAS at baseline at 12, 24, and 48 hours and 6 months post-surgery and primary outcome measure was change in pain scores from baseline to 6 months post-intervention. VAS is a tool used to measure pain intensity or other subjective experiences. It typically consists of a straight line, with the endpoints representing extreme levels of the experience being measured (e.g. no pain and worst imaginable pain). The individual being assessed is asked to mark line at a point revealing their current pain level. The distance from the starting point to the marked point is then measured and used as a numerical representation of the individual's pain intensity or experience level.The VAS score is a subjective measurement of pain severity, where patient indicates intensity of their pain by marking a point on 10-centimeter line (or a similar scale). It lists five degrees of pain, along with their corresponding VAS scores. Degrees of pain range from "No pain" (VAS score =0) to "Worst imaginable pain" (VAS score= 10). According to the table, a VAS score = 1-3 for "Mild" pain, while a VAS score = 4-6 indicates "Moderate" pain. A VAS score= 7-9 for "Severe" pain. A VAS score of 10 for "Worst imaginable pain" a patient could experience. This table helps healthcare professionals to interpret the VAS scores provided by patients, and classify the severity of their pain accordingly (Table No. 1.)

Included in the study were patients aged between 30 to 70 years, who were scheduled to undergo regional anesthesia for arthroplasty, and had plans to be discharged home. Exclusion criteria comprised of the inability to comprehend the study protocol, consumption of opioids for more than 3 months, planned use of general anesthesia, allergy or intolerance to duloxetine, patients already taking duloxetine medicine, hepatic insufficiency, estimated creatinine clearance of less than 50 mL/min. and drug abuse. As the research involved human samples, therefore, was granted ethical approval by the ethical review board of the institute. In addition, the study patients provided informed written consent before participating in the research.The continuous variables' statistics were reported by either mean or median with SD, based on data distribution. Normality of groups of categorical variables was assessed using chi-square testing, while continuous group variables were analyzed using ANOVA testing, with a confidence level of 5% being maintained.

RESULTS

Patients' demographic values such as age, gender, body mass index, employment status, and history of smoking were recorded on the questionnaire and presented in terms of number and percentage of patients in each category and analyzed statistically. Mean age of subjects was 56.19 years with an SD of 14.27. 48 patients (34.3%) were male, and 92 patients (65.7%) were female ($p<0.05$). BMI of the patients was

28.12+2.91. Significantly low ($p<0.05$) proportion of the participants *i.e.* 31 patients (22.1%) were working, while 109 patients (77.9%) were not working. Forty-one patients (29.3%) have a history of smoking, while 99 patients (70.7%) do not have a history of smoking ($p<0.05$) (Table 1). Study compared efficacy of duloxetine group versus placebo (Group B) in reducing pre-operative pain when used in combination with NSAIDs and opioids. Group A and Group B received NSAIDs in combination with Duloxetine and Placebo, respectively. Group A received Duloxetine, while Group B received Placebo. The numbers of patients in each group who received NSAIDs were 42 and 38, respectively. While Group A nor Group B received opioids (Table No. 2.).

The clinical manifestations and adverse effects of the patients of both groups were analyzed and our findings revealed that the major complaints received from both treatment groups of duloxetine and placebo, after administration of medications were fatigue (n=32 and 45), followed by dry mouth (23; 27), insomnia (18; 23), sweating (15; 31), headache (12; 20), nausea (8; 13), anorexia (2; 12), dizziness (5; 11), constipation (4; 7), liver damage (4; 6), blurred vision (3; 7), serotonin syndrome (2; 2) and allergic reactions to medicines prescribed were 1;3, duloxetine and placebo-treated groups, respectively (Figure No.1.).

The results of study comparing efficacy of the duloxetine versus placebo in reducing pain at different time phases before and after surgery were presented in Table 3. The table shows the mean pain score for both groups, along with their statistical analysis. Average pain score for the duloxetine group was 4.0+1.11, while for the placebo group was 4.1+1.28. Mean pain score for duloxetine group was 5.19+2.05, while for Placebo was 6.3+2.41. Mean pain score for duloxetine was 3.9+0.98, while for the placebo was 4.3+1.78. Mean pain score for duloxetine group was 3.3+1.17 and for placebo was 4.0 +0.9. Mean pain score for duloxetine was 2.14+0.19, while for placebo group was 3.19 +2.05 (Table No. 3.).

The reduction in pain was measured by VAS score at baseline, endpoint VAS score, and improvement in VAS score, which were statistically analyzed for both duloxetine and placebo groups. Baseline VAS score for duloxetine was 6.5, while the endpoint VAS score was 2.9, indicating a significant improvement in pain reduction ($p<0.05$). The baseline VAS score for the Placebo group was 6.4, while the endpoint VAS score is 6.1, indicating a minor improvement in pain reduction. The improvement in VAS score is 0.3, which is not statistically significant. Thus duloxetine was significantly more effective in dropping pain than placebo, as demonstrated by the significantly greater improvement in VAS score ($p<0.05$) (Table No. 4.).

Figure No. 1:Frequency of complications associated with administration of duloxetine and placebo.

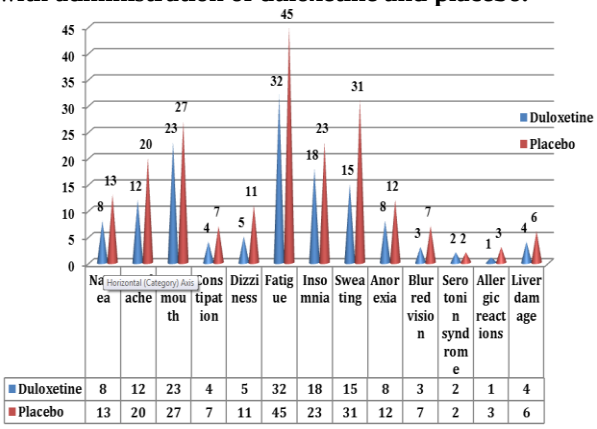

Table No. 1: Demographic data of participants

S #	Demographic value	Patients data n(%)	p-value
1	Age (Mean+SD) years	56.19+14.27	---
2	Gender n(%) Male Female	48 92	0.0031*
3	Body mass index (Mean+SD)	28.12+2.91	---
4	Employment status n(%) Working Not working	31 109	0.00001*
5	History of smoking n(%) Yes No	41 99	0.00083*

***indicated that the value is significant at p<0.05**

Table No. 2: Use of medications by the study population before surgical management for alleviating pain

S #	Pre-operative medication	Group A Duloxetine	Group B Placebo	Chi-square value	p-value
1	NSAIDs	42	38	0.0716	0.7889
2	Opioids	0	0	---	---

Table No. 3: Comparative analysis of duloxetine and placebo-treated groups in pain management

S. No	Time phase	Duloxetine	Placebo	Chi-square value	p-value
1	90 minutes before surgery	4.0+1.11	4.1+1.28	0.175	0.6557
2	12 hours after surgery	5.19+2.05	6.3+2.41	0.0178	0.8939
3	24 hours after surgery	3.9+0.98	4.3+1.78	0.013	0.9092
4	48 hours after surgery	3.3+1.17	4.0+0.9	0.0056	0.8901
5	6 months after surgery	2.14+0.19	3.19+2.05	0.01	0.9202

Table No. 4: Scoring for pain assessment using VAS

S. No	Degree of pain	VAS scores
1	No pain	0
2	Mild	1-3
3	Moderate	4-6
4	Severe	7-9
5	Worst imaginable pain	10

Table No. 5: Comparative study of VAS scores at baseline and endpoint treatment phase.

S. No	Name of Drug	Baseline VAS score	Endpoint VAS score	Improvement in VAS score	p-value
1	Duloxetine	6.5	2.9	3.6	**0.00093***
2	Placebo	6.4	6.1	0.3	

***indicated that the value is significant at p<0.05**

DISCUSSION

The most essential aspect of arthroplasty surgery is pain relief. Pain has a significant impact on life quality. In this regard, our findings suggested that reduction in pain, measured by VAS score at baseline, endpoint VAS score, and improvement in VAS score, were statistically significant in patients ($p<0.05$) treated with duloxetine than placebo groups. Baseline VAS score for duloxetine was 6.5, while the endpoint VAS score was 2.9, indicating a significant improvement in pain reduction ($p<0.05$). The baseline VAS score for the Placebo group was 6.4, while the endpoint VAS score is 6.1, indicating a minor improvement in pain reduction. The improvement in VAS score is 0.3, which is not statistically significant. Thus duloxetine was appreciably more effectual in reducing pain than placebo, as demonstrated by the significantly greater improvement in VAS score ($p<0.05$).

Pain following total knee arthroplasty can originate from both nociceptive and neuropathic origins, according to reports. Medications capable of treating both types of pain are therefore appropriate for knee arthroplasty pain management. Duloxetine has the ability to desensitize the central nervous system in patients with central sensitization, making it a viable option for the management of postoperative neuropathic pain.[13]

Previous studies investigating the effects of orally administering 60 mg of duloxetine to patients undergoing laparoscopic myomectomy supported the validity of our findings. These studies revealed a decrease in postoperative discomfort.[14] Examining the effect of oral duloxetine 60 mg (administered two hours prior to and 24 hours after surgery) on patients undergoing abdominal hysterectomy, it was discovered that pre-administration of duloxetine can reduce postoperative pain.[15] These results correspond with our own. In a second study, patients who took 60 mg of duloxetine two weeks before and three months after spinal surgery experienced a significant reduction in postoperative and chronic pain.[16]

Throughout the entire postoperative period (from 2 hours to 3 months), VAS levels were considerably lower in the duloxetine group than in the placebo group ($p<0.05$). Similar to the placebo group, the duloxetine group consistently demonstrated reduced VAS scores from 6 hours to 3 months after surgery ($p<0.05$). During the postoperative period from day 1 to day 7, patients in the duloxetine group consumed substantially fewer opioids per day than those in the placebo group ($p<0.05$). The duloxetine group demonstrated significantly better active range of motion (aROM) findings than the placebo group from 6 hours postoperatively to day 5 ($p<0.05$). On day six, however, the range of motion (ROM) of the two groups became comparable ($p>0.05$). The passive range of motion (pROM) was substantially greater in the duloxetine group from 6 hours postoperatively to day 4 ($p<0.05$). Following this, the pROM of the two groups was comparable ($p>0.05$). There were no significant differences between the two groups in the incidences of vertigo, bleeding, perspiration, fatigue, and parched mouth. However, a greater percentage of placebo patients encountered nausea, vomiting, and constipation ($p<0.05$). The findings suggest that duloxetine can effectively alleviate acute postoperative pain, reduce opioid consumption, and hasten postoperative recovery in patients undergoing total knee arthroplasty, without increasing the risk of adverse drug reactions. Therefore, duloxetine could be an advantageous addition to a multimodal approach to pain management for these patients.[17-18]

CONCLUSION

The DCS and LPF outcomes in treating distal femur fractures in adults were investigated. Both treatment methods resulted in comparable fracture healing, ROM and functional outcomes, indicating positive clinical and radiographic outcomes. The levels of patient satisfaction were comparable between two categories. Our study demonstrated, however, that locking plate fixation outperformed DCS in terms of patient performance and satisfaction, while also presenting fewer complications. LCP was discovered to be a less complicated and more user-friendly technique, which may explain why the majority of orthopedic surgeons prefer this method. The study emphasized the necessity of vigilant monitoring for implant-related complications and making individualized decisions based on patient-specific factors. These results provide orthopedic

surgeons with evidence-based recommendations for selecting the most appropriate fixation method for distal femoral fractures in adults. To validate and rectify any limitations of the current study, it is suggested that future prospective studies with larger sample sizes be conducted.

Author's Contribution:

Concept & Design of Study:	Inamullah
Drafting:	Hussain Ahmad, Muhammad Asghar Essa
Data Analysis:	Muhammad Zubair Farooq, Shafaat Ullah, Yousaf Gul
Revisiting Critically:	Inamullah, Hussain Ahmad
Final Approval of version:	Inamullah

Conflict of Interest: The study has no conflict of interest to declare by any author.

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