Comparing the Analgesic Effects of Duloxetine and Memantine after Total Knee Arthroplasty: A Double-Blind Randomized Placebo Controlled Clinical Trial

Abstract

Introduction: Osteoarthritis (OA) is a prevalent and debilitating musculoskeletal disease characterized by chronic pain. Given the suboptimal efficacy of current analgesic drugs, identifying novel therapeutic strategies remains a clinical priority. This double-blind randomized controlled trial aimed to compare the efficacy of duloxetine and memantine in managing postoperative pain following total knee arthroplasty (TKA). A randomized, double-blind placebo controlled.

Materials & Methods: A clinical trial was conducted on 187 patients undergoing TKA. Participants were assigned into three groups: placebo (n=63), Memantine (10 mg/day, n=62), and Duloxetine (20 mg/day, n=62). All groups followed a standardized perioperative protocol. Pain intensity was assessed preoperatively and at two weeks and three months postoperatively using the Visual Analog Scale (VAS; 0–10). Demographic variables and opioid consumption (morphine sulfate equivalents) were recorded during hospitalization.

Results & Discussion: The mean opioid consumption during hospitalization was 70.5 ± 2.01, 71.29 ± 2.6, and 76.07 ± 2.5 mg in placebo, memantine and duloxetine respectively. One-way ANOVA revealed no statistically significant intergroup differences in opioid consumption ($p > 0.05$). Similarly, no significant differences in mean pain intensity were observed across groups at any timepoint ($p > 0.05$). However, longitudinal analysis (Friedman test) demonstrated a statistically significant reduction in pain intensity over time within all groups ($p < 0.05$), consistent with typical postoperative recovery trajectories.

Conclusion: While both Duloxetine and Memantine were associated with temporal reductions in pain intensity, neither intervention demonstrated statistically significant superiority over placebo in mitigating postoperative pain or opioid demand. Further research into optimal dosing regimens, longer follow-up periods, and synergistic effects with these drugs may provide different findings in TKA pain management.

Keywords: Total knee arthroplasty, Pain, Memantine, Duloxetine.

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Introduction

Osteoarthritis (OA) is the most common joint disease, affecting approximately 15% of the population[1-3].However, in cases of joint destruction with clinical symptoms such as pain, deformity, and limitation of motion, total knee arthroplasty (TKA) is a final treatment for knee problems[4-6] Pain is the most important complication of all surgeries, especially TKA, and half of the patients experience persistent pain for up to one month after TKA, which can be distressing[7,8]. Common interventions include prescribing non-opioid and opioid analgesics to alleviate pain[9]. Duloxetine, an inhibitor of serotonin and norepinephrine reuptake (SNRI) antidepressant with analgesic effects[10], has approving by the U.S. Food and Drug Administration (FDA) for major depressive disorder, generalized anxiety disorder, peripheral neuropathic pain due to diabetic neuropathy, fibromyalgia, and chronic musculoskeletal pain syndromes[11], It is also recommended in some guidelines as a first choice for treatment of neuropathic pain[12]. Another analgesic, memantine, is a non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist with low-to-moderate affinity, acting directly on the phencyclidine site of the NMDA receptor channel[13].

Evidence suggests that administering memantine one hour before TKA significantly reduces postoperative pain and morphine requirements[14]. Effectiveness of memantine in pain relief is much greater compared to dextromethorphan in patients undergoing orthopedic surgery, leading to greater patient satisfaction[14]. However, the findings of various studies on the analgesic effects of duloxetine in postoperative pain control have been contradictory so far. For instance, one study found duloxetine improved chronic back pain with good patient tolerability[15], while another showed no benefit when added to multimodal analgesia for TKA patients[16].

Despite various pain management strategies and surgical and anesthetic techniques, pain remains a major postoperative challenge for TKA patients[17]. Given that joint replacement is an invasive and costly procedure performed to reduce pain, minimize analgesic use, and improve function, effective postoperative pain control is critical. Patients with OA often rely on analgesics like NSAIDs or opioids, which, particularly in the elderly, may cause significant and sometimes irreversible side effects. Thus, identifying drugs with fewer side effects and shorter durations of prescription can play a significant role in pain control, patient satisfaction, functional outcomes, and reduce the financial burden of analgesics and opioids. This study was designed to compare the analgesic effects of these drugs, namely duloxetine and memantine on post-TKA pain and reducing the need for opioids in patients referred to Imam Khomeini and Shafa Hospitals in Sari in 2024 (1403 Iranian calendar).

Materials & Methods

This study was in accordance with the Declaration of Helsinki. The reporting followed the CONSORT 2025 statement: extension to randomized trials and this randomized, double-blind placebo controlled clinical trial. The sample size was calculated according to the study by Kim et al.[18] and using the sample size formula for the difference between population means with only type I error control and considering a significance level of 5%, according to the following formula, a total of 180 patients (60 per group) was determined.

The study was designed on 187 patients scheduled for TKA at Imam Khomeini and Shafa Hospitals in Sari 2024. Inclusion criteria were: inclination to participate with informed consent, age over 18, no diagnosis of Major Depressive Disorder or other acute and severe psychiatric disorders, no intellectual disability, no psychotropic drug use in the past 8 weeks, absence of cognitive disorders (e.g., dementia or delirium), and no opioid use. Exclusion criteria included drug hypersensitivity or severe adverse reactions, changes in treatment protocol during the study, inability to take oral medications, pregnancy, lactation, or use of drugs interacting with duloxetine or memantine. Ultimately, 180 patients (60 per group) were enrolled and evaluated for outcomes for every protocol. They were randomly assigned to three groups—placebo, duloxetine, and memantine. Due to the lack of visual similarity, the drugs were packaged in 28 packages that were completely similar and identical in appearance by this person

- Group 1 received one 20 mg duloxetine capsule (manufactured by Actoverco, same batch).
- Group 2 received one 10 mg memantine tablet (manufactured by Loghman Pharmaceutical Co., same batch).
- Group 3 received a placebo tablet.

Patients, investigators, and staff involved in intervention, data collection, and follow-up were blinded to group assignments. An independent individual, uninvolved in other study phases, numbered and packaged the drugs.

On the morning of surgery, all patients received one 200 mg celecoxib cap and an intravenous ketorolac injection immediately post-surgery. Postoperatively, all received 1 g Apotel IV TDS and ketorolac IV BD. If pain persisted despite these measures before discharge, patients received 2 mg morphine sulfate IV, and the amount of this medication was recorded. Spinal anesthesia was used for all patients. Patients were mobilized with a walker the day after surgery and discharged on day two with 200 mg celecoxib and 325 mg acetaminophen every 8 hours for 6 weeks. Study drugs were administered for two weeks post-surgery, with other analgesics continued for three months.

Demographic data and VAS scores were recorded pre-surgery, at 14 days, and at 3 months post-surgery. Drug's adverse effects were monitored and documented at each visit.

Descriptive analysis of the collected data was performed. The data were summarized using central tendency (mean, standard deviation) for quantitative variables and frequency (percentage) for qualitative variables. To evaluate the normality of the

distribution of quantitative variables, the Kolmogorov-Smirnov test was used.

One-way ANOVA compared quantitative variables across groups, while chi-square or Fisher's exact tests assessed qualitative variable associations. Generalized Estimating Equations (GEE) and multiple linear regression models were used for confounders in comparing pain intensity and opioids use across groups. After obtaining written informed consent, eligible participants were requested to complete a socio-demographic questionnaire, which collected information on their age, gender, education level, job, body mass index (BMI), residency, income level and marital status and medical history, Smoking. anesthesia duration, surgery duration, disease type were collected from hospital documents.

All groups followed a standardized perioperative protocol. Pain intensity was assessed preoperatively and after two weeks and three months postoperatively using the Visual Analog Scale (VAS; 0–10)[19]. Its validity and reliability are confirmed internationally[20] and in Iran (r = 0.88)[21]. Comparing the analgesic effects of duloxetine and memantine on post-TKA pain and then comparison of the amount of opioid (morphine sulfate) consumed during the hospitalization period among the three groups was done.

Results

In the present study, 187 TKA patients participated. According to the Table 1, the mean age of patients in the placebo, memantine and duloxetine groups were 65.97 ± 7.22 years, 64.98 ± 9.85 years, and 66.24 ± 7.99 years, respectively. One-way ANOVA showed no significant differences in mean age or BMI among groups ($p > 0.05$).

The Chi-square test, showed that there was no statistically significant difference between the three groups in terms of the gender variable ($P > 0.05$). Therefore, the three groups were homogeneous in terms of age, body mass index, and gender variables. Also, there was a statistically significant difference in the frequency distribution of patients in the three groups according to the level of education ($P < 0.05$).

Table 1: Demographic data of Patients in Three Groups: Placebo, Memantine, and Duloxetine.

Variable	Placebo (n=63)	Memantine (n=62)	Duloxetine (n=62)
Age (Mean ± SD)	65.97 ± 7.22	64.98 ± 9.85	66.24 ± 7.99
BMI (Mean ± SD)	29.12 ± 3.97	29.58 ± 4.15	30.08 ± 3.58
Gender			
Female	53 (84.10%)	54 (87.10%)	53 (85.50%)
Male	10 (15.90%)	8 (12.90%)	9 (14.50%)
Education			
Illiterate	24 (38.10%)	21 (33.90%)	25 (40.30%)
Below Highschool Diploma	28 (44.40%)	17 (27.40%)	25 (40.30%)
Highschool Diploma and Above	11 (17.50%)	24 (38.70%)	12 (19.40%)
Marital Status			
Married	56 (88.90%)	50 (80.60%)	55 (88.70%)
Divorced or widowed	7 (11.10%)	12 (19.40%)	7 (11.30%)
Job			
Homemaker	47 (74.60%)	45 (72.60%)	42 (67.70%)
Employee/Retired	5 (7.90%)	13 (21.00%)	8 (12.90%)
Other	11 (17.50%)	4 (6.50%)	12 (19.40%)
Residence			
City	49 (77.80%)	44 (71.00%)	41 (66.10%)
Village	14 (22.20%)	18 (29.00%)	21 (33.90%)
Income Level			
Low/Medium	54 (85.70%)	45 (72.60%)	50 (80.60%)
High	9 (14.30%)	17 (27.40%)	12 (19.40%)
Smoking Status			
Smoker	59 (95.20%)	56 (93.30%)	55 (91.70%)
Non-Smoker	3 (4.80%)	4 (6.70%)	5 (8.30%)

*Statistically significant ($P < 0.05$)

According to the Table 2, 28.60% of patients in the placebo group, 6.50% in the memantine, and 19.40% of in the duloxetine group had heart disease and there was a statistically significant difference among the three groups (P < 0.05). However, the observed difference in frequency distribution of the variables underlying disease, diabetes, hypertension, and hyperlipidemia among the three groups studied was not statistically significant (P > 0.05). According to the Table 3, the comparison of the amount of opioid (morphine sulfate) consumed during the hospitalization period among the three groups studied was performed using the Kruskal-Wallis test. The results demonstrated that the mean amount of opioids consumed during the hospitalization period was 5.2 ± 70.01 mg in the control group, 6.2 ± 11.29 mg in the memantine group, and 5.2 ± 76.07 mg in the duloxetine group. There was no statistically significant difference in the mean amount of opioid (morphine) consumed during the hospitalization period among the three groups (P > 0.05). To compare the amount of opioids consumed among the three study groups while controlling for confounding effects, a univariate linear regression model was first fitted to the data, and then all variables that had a P < 0.25 in the univariate state were included in the multiple linear regression model. By adjusting the effect of other variables in the model, the variables of education level (below high school diploma compared to illiterate) and preoperative pain intensity had a statistically significant relationship with the amount of opioid (morphine) consumed during the hospitalization period (P < 0.05). There was no significant relationship between the three groups and other variables with the amount of opioid consumed during the hospitalization period (P > 0.05).

Specifically, by controlling the effect of another variables in the model, the mean opioid consumption in the memantine and duloxetine groups was 0.12 and 0.01 units higher, respectively, compared to the placebo group, but this difference in the amount of opioid consumed among the three groups was not statistically significant (P > 0.05). Also, the mean opioid consumption in patients with education below high school diploma was 0.93 units lower compared to illiterate individuals, and this difference was statistically significant (P < 0.05).

The mean consumption of opioid in individuals with a high school diploma and higher education was also 0.28 units lower than illiterate individuals, without statistically significant difference (P > 0.05). Furthermore, for each unit increase in pre-operative pain intensity, the mean opioid consumption during the hospitalization period increased by 0.54 units, which was also statistically significant (P < 0.05). Similarly, for each unit increase in patients' age, opioid (morphine) consumption increased by 0.01 units, without statistically significant differences (P > 0.05). The interpretation for other variables is similar. According to the Table 4, the comparison of severity of pain among the three groups studied was performed at the times before surgery, two weeks after surgery, and three months after surgery. At all three times studied, according to the results of the one-way.

Table 2: Data of Patients Among the Three Groups: Placebo, Memantine, and Duloxetine

Variable	Duloxetine (n=62)	Memantine (n=62)	Placebo (n=63)	P-value
Underlying Disease				0.89
No	20 (32.30%)	22 (35.50%)	20 (31.70%)	
Yes	42 (67.70%)	40 (64.50%)	43 (68.30%)	
Diabetes				0.46
No	48 (77.40%)	51 (82.30%)	46 (73.00%)	
Yes	14 (22.60%)	11 (17.70%)	17 (27.00%)	
Hypertension				0.65
No	30 (48.40%)	30 (48.40%)	26 (41.30%)	
Yes	32 (51.60%)	32 (51.60%)	37 (58.70%)	
Hyperlipidemia				0.50
No	37 (59.70%)	43 (69.40%)	42 (66.70%)	
Yes	25 (40.30%)	19 (30.60%)	21 (33.30%)	
Heart Disease				0.006*
No	50 (80.60%)	58 (93.50%)	45 (71.40%)	
Yes	12 (19.40%)	4 (6.50%)	18 (28.60%)	

*Statistically significant (P < 0.05)

Table 3: Comparison of the Amount of Opioid (Morphine) Consumed Among the Three Groups, Controlling for Confounding Effects Using a Multiple Linear Regression Model

Variable (Reference Level)	Coefficient (95% Confidence Interval)	P-value
Group (Placebo)	-	-
Memantine	-0.61 (-0.87, 0.12)	0.73
Duloxetine	-0.70 (-0.72, 0.01)	0.97
Age	-0.02 (-0.05, 0.01)	0.37
Pre-Surgery Pain Intensity	0.54 (0.21, 0.87)	0.001*
Gender (Female)	-	-
Male	-0.13 (-1.61, 0.79)	0.77
Education Level (Illiterate)	-	-
Below Diploma	-1.93 (-2.66, -0.20)	0.01*
Diploma and Above	-0.28 (-1.16, 0.58)	0.51
Marital Status (Married)	-	-
Widowed	-0.20 (-1.54, 0.67)	0.13
Family Income (Low/Medium)	-	-
High/Excellent	-0.36 (-1.43, 0.53)	0.24
Heart Disease (No)	-	-
Heart Disease (Yes)	-0.99 (-1.61, 0.18)	0.64

*Statistically significant (P < 0.05)

Table 4: Pain intensity in the Three Groups: Placebo, Memantine, and Duloxetine, Based on Measurement Times

Group	Before Surgery	2 Weeks after Surgery	3 Months after Surgery	P-value
Placebo	8.87 ± 0.90	3.96 ± 0.96	1.68 ± 0.60	<0.001*
Memantine	8.94 ± 0.92	3.53 ± 0.93	1.65 ± 0.79	<0.001*
Duloxetine	8.81 ± 0.92	3.52 ± 1.00	1.55 ± 0.59	<0.001*
P-value	0.65	0.56	0.88	

*Statistically significant (P < 0.05)

A multivariate Generalized Estimating Equations (GEE) model was employed for comparison of pain intensity among the three study groups (memantine, duloxetine, and placebo) while controlling for confounding variables. Results demonstrated that only the time variable exerted a statistically significant effect on pain intensity reduction (P<0.05). No significant differences were observed between the three groups or other variables in pain intensity (P>0.05). After adjusting for covariates, the mean pain intensity decreased by 0.06 units per postoperative day, which was statistically significant (P<0.05). At baseline (preoperative measurement), the mean pain severity in the memantine and duloxetine was 0.13 and 0.05 units higher, respectively, compared to the placebo group. However, these differences were not statistically significant (P>0.05). Furthermore, daily pain reduction rates in the memantine and duloxetine groups (0.0015 and 0.0012 units/day, respectively) did not differ significantly with the placebo group (P>0.05). A 0.15-unit higher pain intensity was observed in rural residents compared to urban residents, though this difference was not statistically significant (P>0.05).

Discussion

This randomized controlled study aimed to instigate the analgesic efficacy of duloxetine (20 mg) and memantine (10 mg) administered pre- and postoperatively in patients undergoing total knee arthroplasty (TKA). Key findings include:

Time-Dependent Pain Reduction: Pain intensity decreased significantly over time across all groups, consistent with typical postoperative recovery trajectories where inflammation and tissue trauma gradually subside and this is consistent with Cheng, H. Y et al system review (2025) which found that postoperative pain declines over weeks, regardless of pharmacological interventions [22]. In our study, neither duloxetine nor memantine demonstrated statistically significant superiority over placebo in reducing postoperative pain or opioid consumption.

The lack of significant differences between the duloxetine, memantine, and placebo groups suggests that the doses administered may not have been sufficient to modulate pain pathways, even though all groups followed a standardized perioperative protocol including celecoxib, an intravenous acetaminophen, and intravenous ketorolac.

Duloxetine is a SNRI which can modulate pain by enhancing descending inhibitory pathways in the CNS [23]. The analgesic mechanism works with adjustment of serotonin and norepinephrine, so it increases inhibition in pathways of pain in the brain and spinal cord and activate parts from the prefrontal lobe of the brain [24]. There are few studies suggested that duloxetine works as an antinociceptive effect by blocking Na^+ channels and inhibits nerve cell firing due to peripheral injury [25]. Recent researches about duloxetine's role in TKA pain management have given mixed findings. For instance, Piya Pinsornsak et al. (2024) reported that low-dose duloxetine could decrease the morphine consumption after surgery and recovery of KOOS symptoms after six and twelve weeks. Although, reduce pain at rest or in walking was not significant, and consequently, low-dose duloxetine could be used as an adjunct to contemporary multifaceted pain treatment after TKA [26]. This finding is consistent with our results. In our study, duloxetine was associated with temporal reductions in pain intensity; however, neither intervention demonstrated statistically significant superiority over placebo in mitigating postoperative pain or reducing opioid demand. Yuan et al. (2022) found that duloxetine could decrease acute pain after surgery immediately, reduce opioid use, and facilitate recovery, without increasing the risk of drug side effects in patients after TKA [27].

Memantine is a non-competitive NMDA receptor antagonist which is hypothesized to alleviate pain by reducing central sensitization and hyperalgesia.

Memantine has a low dependency for NMDA-receptor antagonist action and does not guide to psycho-mimetic symptoms or dissociation at doses of 20–60 mg/day. The consumption of memantine as an opioid-free adjunctive medication when administered before surgery has been reported in many studies with different results [28].

The results of a systematic review and meta-analysis by Nair et al. (2024) shows that using memantine before operation could decrease the pain just after surgery without uncommon adverse effects. However, document in literature is not enough to recommend the use of memantine as a routine before the elective surgeries [29]. M Saadat Fakhr et al. (2025) in a RCT Evaluated memantine's effectiveness in decreasing acute pain postoperatively compared to vitamin C in abdominal surgery patients. Memantine significantly lowered pain scores at 24 hours and reduced narcotic use. Both groups experienced declining pain, but memantine showed greater reductions over time [30]. Similarly in our study both duloxetine and memantine were associated with temporal reductions in pain intensity, neither intervention demonstrated statistically significant superiority over placebo in mitigating postoperative pain or opioid demand.

According to our study a multivariate GEE model was employed to compare pain intensity among the three study groups while controlling for confounding variables. Results demonstrated that only the time variable exerted a statistically significant effect on pain intensity reduction ($P<0.05$). No significant differences were observed between the groups or other variables in terms of pain intensity ($P>0.05$). After adjusting for covariates, the mean pain intensity decreased by 0.06 units per postoperative day, which was statistically significant ($P<0.05$).

Higher opioid consumption correlated with lower educational attainment ($P<0.05P<0.05$) and baseline pain intensity, aligning with psychosocial models of pain perception. Similarly to our study, individuals with lower educational attainment may experience diminished health literacy, which can lead to heightened perception of pain or less efficient pain coping mechanisms [31]. A study conducted by Hadden et al. in 2016 revealed that reduced health literacy correlates with higher opioid use and worse pain results in orthopedic patients, emphasizing the role of psychosocial factors. The intensity of preoperative pain was a significant predictor of opioid usage [32].

Limitations

First, our clinical results were based on a small sample size and should therefore be interpreted with caution. Second, pain assessment was based solely on VAS questionnaire. Combining multidimensional tools, such as the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), could provide a stronger assessment of pain and functional outcomes. Third, the three-month follow-up duration might not reflect ongoing postoperative pain. Forth, the study did not assess central sensitization which are known to modulate pain perception.

Finally, TKA is a surgical procedure with significant tissue trauma, some patients may experience psychological distress such as depression, anxiety or insomnia, so it is not yet clear whether the reduction in symptoms is related to the drug's effect on mood and anxiety or through its effect on pain pathways.

Conclusion

The findings suggest that low dose duloxetine (20 mg) and memantine (10 mg) do not confer clinically significant analgesic effects in TKA patients compared to placebo. Future studies should:

1. Evaluate higher Duloxetine doses (30–60 mg) and extended follow-up periods.
2. Investigate Memantine's efficacy at alternative dosages.
3. Conducting systematic reviews to harmonize conflicting evidence on adjunctive analgesia in orthopedic surgery

Ethical Considerations

This study was conducted following approval from the Ethics Committee of Mazandaran University of Medical Sciences (code: IR.MAZUMS.REC.1403.205) and registered in the Iranian Registry of Clinical Trials (code: IRCT20241013063346N1). Ethical standards were rigorously adhered to throughout the research process. Participants were fully informed about the confidentiality of their information and provided written informed consent before completing the questionnaires. was approved by the Ethics Committee

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