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Melatonin Versus Duloxetine for Managing Symptoms of Osteoarthritis: A Randomized Controlled Trial Study

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ABSTRACT

Background: Osteoarthritis (OA) is a degenerative joint disorder causing pain and disability. The present treatments are inadequate to improve the underlying pathogenesis of OA. Melatonin, because of its chondroprotective, anti-inflammatory, and antioxidant properties, may have a role in the management of OA. Duloxetine is presumed to modulate pain through serotonergic and noradrenergic pathways. In the present study, as a first study, melatonin has been compared with duloxetine for its efficacy in reducing OA-related knee pain.

Methods: This randomized controlled trial (RCT) study involved 60 knee OA patients treated at Imam Hossein Hospital in Tehran, Iran. Participants were randomly assigned to receive either melatonin, 3-10 mg per day, or duloxetine, 60-120 mg per day. The primary outcome measure was the 3-month change in the Western Ontario and McMaster universities OA index (WOMAC) score.

Results: Compared to the duloxetine group, a reduction in the total WOMAC score was noted in the melatonin group (P=0.001 and P=0.09, respectively). Changes in WOMAC pain score were significant in both groups (P=0.0001). Additionally, the need for naproxen for breakthrough pain was significantly lower in the melatonin group (318.33±16 mg vs 810±35 mg with a P<0.001).

Conclusion: Melatonin is more potent than duloxetine in pain reduction and functional improvement in patients with knee OA. Considering the ability of melatonin to reduce the usage of nonsteroidal anti-inflammatory drugs, melatonin may be a safer agent for managing pain in OA.

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Introduction

Osteoarthritis (OA), the most common arthritis worldwide, is a degenerative joint disease characterized by progressive cartilage degradation, subchondral remodeling, and synovial inflammation. It is also a significant cause of pain and disability worldwide. Its prevalence steadily increases due to demographic shifts and lifestyle factors [1]. Furthermore, OA is a non-reversible disease that progresses slowly. Current non-surgical treatments can only delay the progression of the disease, so early treatment of OA is a focus of recent research. While conventional pharmacologic therapies aim to prevent further cartilage loss and joint dysfunction, no ideal strategy targets OA's pathogenesis [2].

Melatonin, a naturally occurring hormone, exhibits various regulatory properties by binding to specific receptors and downstream molecules. It exerts numerous receptor-independent activities through intracellular targets, acting as a chondrocyte protector, anti-inflammatory modulator, and free radical scavenger. Melatonin also modulates cartilage repair and degradation. Considering its effects on cartilage homeostasis, researchers have proposed melatonin's potential role in OA prevention and treatment through reduced chondrocyte apoptosis, anti-inflammatory activity, and free radical elimination [3, 4].

Recently, duloxetine was approved as a new drug for knee OA treatment. Acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs) are referred to as typical analgesics that should not be used for long periods of OA, requiring broader knowledge of alternative therapeutic strategies. Duloxetine, a serotonin-norepinephrine reuptake inhibitor, has been shown to reduce pain in OA patients, but the mechanisms behind this effect are still obscure. Serotonin and norepinephrine are believed to be essential players in the descending pain inhibitory control system. The study hypothesized that the analgesic action of duloxetine could involve these pathways, thus indirectly reducing sensitivity and pain to stimuli [5].

This research could provide important information regarding the comparative effectiveness of melatonin versus duloxetine in managing OA pain and serve as a guide for clinical practice and future research directions, as no other studies directly compare melatonin and duloxetine.

Methods

This study will employ a randomized controlled trial (RCT) design to compare the efficacy of melatonin and duloxetine in alleviating knee pain in patients with OA. The RCT design will ensure randomization of participants to either the melatonin or duloxetine group, minimizing selection bias and enhancing the study's internal validity. The study was conducted at the Rheumatology Clinic of Imam Hossein Hospital, a tertiary care center in Tehran City, Iran. This setting provides access to a large pool of eligible participants and the necessary data collection and follow-up resources.

Participants would be adult patients (≥40 years) diagnosed with knee OA based on the American College of Rheumatology (ACR) criteria [6]. Participants must have experienced knee pain or discomfort for at least three months and have a high Western Ontario and MacMaster Universities (WOMAC) score indicating significant pain or functional limitations. WOMAC score measures three separate dimensions: Pain (5 questions), stiffness (2 questions), and function (17 questions) [7]. To ensure a homogeneous study population, participants would be excluded if they had a history of inflammatory arthritis, diabetes, uncontrolled hypertension, significant cardiovascular disease, or major psychiatric disorders.

Patients attending the Rheumatology Clinic for OA management were screened for eligibility by an expert rheumatologist (PD). Eligible participants were provided detailed study information and invited to participate. After obtaining informed consent, participants underwent a comprehensive assessment, including a physical examination, laboratory tests, and a structured psychiatric interview in for of structured clinical interview for DSM-5 (SCID-5) to screen for major psychiatric disorders by an expert psychiatrist (RV) [8, 9].

Participants were randomly assigned to either the melatonin or duloxetine group using a permuted block randomization method. Stratification was performed based on sample size into blocks of sizes 2, 6, 4, 8, 10, or above using the "ralloc" package in STATA software. Patients were assigned to groups based on the predetermined sample size and a randomized list of individuals (along with their unique research codes) within each group. This method will ensure a balanced distribution of potential confounders across the groups and minimize the risk of selection bias. Participants will be blinded to their treatment allocation, and the investigators involved in data collection and outcome assessment will also be blinded to maintain randomization integrity.

Table 1. Comparing clinicodemographic information of patients and duration of onset of pain and diagnosis of OA in two groups

Variables		Mean±SD/No.		P
		Melatonin Group	Duloxetine Group	
Age (y)		65.2±3.9	64.7±3.8	0.62
Duration of OA (m)		7.4±1	7.3±1	0.39
BMI (kg/m^2)		29.36±1.6	29.46±1.7	0.81
Duration of pain (m)		4.7±0.9	4.96±1.3	0.9
Gender	Female	17	19	0.5
	Male	11	10	

OA: Osteoarthritis; BMI: Body mass index.

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The inclusion criteria will be patients aged 40 or older, diagnosis of OA of the knee based on ACR criteria for at least 6 months, knee pain or discomfort for at least 3 months daily, or significant limitation of movement in the affected joint for 1 month based on WOMAC, no history of underlying diseases (including diabetes, inflammatory arthritis), no combined oral contraceptive (OCP) use or smoking. The exclusion criteria were body mass index (BMI) >30 kg/m^2, recent (one-year) knee surgery, any secondary OA, use of narcotic or antidepressant medications during the study, and significant psychiatric disorder such as anxiety disorder, major depressive disorder, bipolar mood disorder, schizophrenia, etc. which was examined by an expert psychiatrist (RV) [10].

Study interventions

Group 1 received duloxetine 60 mg once daily, titrated up to 120 mg as needed, and

Group 2 melatonin 3 mg once daily, titrated up to 10 mg as needed.

Study outcomes

Primary outcomes included a change in the WOMAC index from baseline to 3 months.

To manage breakthrough pain or inadequate pain control with the assigned treatment, both groups had access to rescue medication in the form of naproxen 250 mg tablets. Participants would be instructed to record their naproxen consumption throughout the study.

Data collection would occur at baseline and three months after treatment initiation. Data would be collected using standardized questionnaires, structured interviews, and a review of medical records.

Statistical analysis

Data were analyzed using appropriate statistical methods, including descriptive statistics, independent t-test, and repeated measures analysis of variance (ANOVA). Intention-to-treat analysis would be the primary approach, with missing data handled using multiple imputation techniques.

Results

The study demonstrated the difference in efficacy between melatonin and duloxetine in managing knee pain arising from OA. In this RCT, 60 patients with knee OA were enrolled and randomized into two groups: Melatonin and duloxetine. Two patients in the duloxetine group and one in the melatonin group were lost to follow-up.

The patients' characteristics were similar in the two groups regarding age, gender distribution, BMI, and the presence of pain and OA for a similar duration. The detailed data are shown in Table 1.

The primary outcome was the change in WOMAC score. There was a significant reduction in the WOMAC score by comparing WOMAC score before, and after treatment with melatonin, although patients treated with duloxetine didn't experience a statistically significant decrease in WOMAC score (P=0.001 vs 0.09), more detailed data are shown in Table 2.

Another aim of this study was to compare the effectiveness of melatonin with duloxetine on the knee pain of OA patients based on the WOMAC pain score. There were statistically significant reductions in WOMAC scores in both the duloxetine and melatonin groups after

Table 2. Changes in WOMAC scores in melatonin and duloxetine groups

Group	Mean±SD		P
	Before the Intervention	After the Intervention	
Melatonin	8.83±1.8	5.36±1.1	0.001*
Duloxetine	8.7±1.5	7.93±1.3	0.09

WOMAC: Western Ontario and McMaster universities osteoarthritis index.
*Statistically significant difference (P<0.05).
Notes: The unpaired t-test was done.

treatment with these drugs (P=0.0001). Additional information on the results of the above is shown in Table 3.

Notably, the melatonin group used less dosage of NSAIDs compared to the duloxetine group (P<0.001) (318.33±16 mg in the melatonin group vs 810±35 mg in the duloxetine group).

Discussion

This RCT investigated the efficacy of melatonin compared with duloxetine for managing knee pain due to OA. To the best of our knowledge, we have compared these two medications for the first time to manage OA. The results indicated that melatonin was more effective than duloxetine in reducing the pain of OA. Results provide critical insight into the potential for using melatonin instead of the SNRI duloxetine in treating pain associated with OA.

The primary outcome measured was a change in WOMAC score for pain, stiffness, and functional impairment. A greater reduction in WOMAC score was found in the melatonin group than in the duloxetine group. Specifically, the melatonin-treated patients showed a statistically significant improvement (P=0.001), while the duloxetine-treated patients did not achieve a statistically significant improvement (P=0.09). The result implies that melatonin is probably better at reducing OA-related pain than duloxetine. Its efficacy can be attributed to the multifaceted properties of melatonin: It is a chondrocyte protector, anti-inflammatory modulator, and free radical scavenger, properties that might support or have positive roles in maintaining cartilage homeostasis and the progression of OA [11, 12]. While duloxetine is recognized to affect the descending pain inhibitory control system with serotonergic and noradrenergic pathways, the mechanisms by which it may reduce pain in patients with OA are at least less clear, which could account for lesser improvement seen in the present study [13]. This discrepancy could be due to dosage differences, treatment duration, or patient demographics. Variations in the design of clinical trials are another problem. Biases could occur from randomization techniques to blinding methods or inclusion and exclusion criteria. Such specific criteria in our research, which excluded patients with a BMI of more than 30 and those having continuous consumption of either narcotics or antidepressants during the study period, may therefore yield a study population that is too homogeneous and thereby overestimate the opposing effect of melatonin.

Our results align with previous studies, such as one by Favero et al., which demonstrated that melatonin reduced inflammation and inhibited the apoptosis of chondrocytes to alleviate symptoms of OA patients [14]. Also, Claustrat and Leston suggested that melatonin might reduce oxidative stress and have an antioxidant property that can be of considerable significance to the protection of cartilage, therefore supporting its use in OA management [12]. In contrast, our findings are discordant with the literature reporting the efficacy of duloxetine use in

Table 3. Comparing WOMAC scores before and after intervention between melatonin and duloxetine groups

Group	Mean±SD		P
	Duloxetine	Melatonin	
Before the intervention	8.7±1.5	8.83±1.8	0.76
After the intervention	7.93±1.3	5.36±1.1	0.0001*

WOMAC: Western Ontario and McMaster universities osteoarthritis index.
*Statistically significant difference (P<0.05).

pain management for OA management. For example, this is evident in the report by Skljarevski et al. in an RCT that duloxetine significantly reduces the severity of pain in patients with various chronic pain disorders that include OA [13].

A notable finding of this study was the lower consumption of NSAIDs in the melatonin group compared to the duloxetine group. Patients in the melatonin group required significantly less naproxen for breakthrough pain (318.33±16 mg vs 810±35 mg, P<0.001). This cut down in NSAIDs use is of clinical interest since it shows that melatonin could be used to treat OA pain using fewer additional drugs and, therefore, avoiding complications from the use of NSAID. This decrease in the use of NSAIDs is of clinical relevance in identifying the role of melatonin in reducing OA pain with lesser use of adjunctive medications and, thus, lowering the chances of side effects of NSAIDs. This finding is especially valuable given the contraindications documented with chronic NSAIDs use, including gastrointestinal ulceration, cardiovascular events, and renal dysfunction [15].

Conclusion

This RCT demonstrates that melatonin is more effective than duloxetine in reducing pain and improving function in patients with knee OA. The significant reduction in WOMAC scores and lower NSAIDs consumption in the melatonin group suggest that melatonin could be a promising alternative for managing OA pain. These findings warrant further investigation through larger and longer-term studies to establish melatonin's role in OA treatment fully.

Study limitations and future directions

This study has some limitations that should be considered. The sample was small, and the follow-up period was limited to three months. Larger and longer-term studies are needed to confirm these findings and further investigate melatonin's long-term safety and efficacy in OA management. Moreover, the study was conducted in a single center, which may limit the generalizability of the results. Future research should explore the mechanisms underlying melatonin's effects on OA in more detail and investigate its potential benefits in other forms of arthritis.

Ethical Considerations

Compliance with ethical guidelines

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and approved by the Ethics Committee of Shahid Beheshti University of Medical Sciences (Code: IR.SBMU.RETECH.REC.1402.761) and was registered by the Iranian Registry of Clinical the Trials (IRCT) (Code: IRCT20200516047468N2). Informed consent was obtained from all participants, and their confidentiality would be protected throughout the study.

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Authors' contributions

All authors equally contribute to preparing all parts of the research.

Conflict of interest

The authors declared no conflict of interest.

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