Original Article

Evaluating the Effect of Melatonin on Pain Control and Quality of Life in Patients with Chronic Low Back Pain: A Randomized Clinical Trial

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Abstract

Background: Almost everyone experiences low back pain at some point in his or her lives. Low back pain is becoming more prevalent in low-income and middle-income countries much more rapidly than in high-income countries. The objective of this study was to evaluate the effect of melatonin on pain control and quality of life in patients with chronic low back pain.

Materials and Methods: Sixty patients with low back pain aged 45 and 75 years, with a history of back pain more for than 12 weeks and visual analogue scale (VAS) score more than three, who were referred to pain clinics of Akhtar Hospitals (Tehran, Iran) during June to August 2018. Patients were randomly assigned to one of the melatonin or control groups. Control group received diclofenac sodium 25mg tablet two or three times daily and the experimental or melatonin group, in addition to receiving diclofenac sodium 25mg tablet twice a day, received melatonin tablet (3mg) 30 to 40 minutes before bedtime for four weeks. Before the beginning of the study, at the end of the fourth week, both groups underwent VAS test and the levels of IL-1β and TNF-α were measured in these groups and they were asked to complete the quality of life questionnaire. Analysis of the data done by using covariance and Shapiro-Wilk tests through SPSS 22.

Results: Melatonin consumption reduced the pain and level of IL-1β and TNF-α in the experimental group compared to the control group ($p<0.05$). However, use of melatonin did not have a significant effect on quality of life ($p>0.05$).

Conclusion: In general, it can be stated that use of melatonin, in addition to reducing the pain, reduces the anti-inflammatory factors in patients with chronic low back pain. Based on the results of this study, melatonin can be recommended as a supplement for treatment of chronic low back pain.

Keywords: Affective symptoms, Antipain, Low back pain, Quality of life, Adult

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Introduction

Pain is the most common physical problem, which individuals face with it during their life. As a very powerful factor, it affects the quality of life of people in different dimensions. Pain is the most common

clinical complaint of patients and treatment has been considered as one of the oldest treatments for humans[1]. Patients with chronic and severe pain gradually isolate themselves from all social activities and assume that the boundaries of their world are very limited and small. They are more concerned with their pain and pay less attention to world around them. The world of these people is limited to the home, office, pharmacy, frequent admission to medical clinics, high costs lead to general fatigue and disability, leading family problems[2].

Studies have shown that low back pain leads to reduced quality of life in this patients[3]. several therapies have been proposed for the treatment or improvement of this disease. Several therapeutic methods used for this disease include drug therapy, modification in lifestyle, weight loss, muscle strengthening, the use of various methods of rehabilitation and physiotherapy. However, definitive treatment has not been found for this disease[4,5,6]. Melatonin is an indoleamine neurohormone produced and secreted by the Pineal gland. Melatonin plays an important role in regulating neurological and physiological functions of the body such as circadian rhythms and reproduction in different seasons. Melatonin is secreted at night and is associated with sleep, lowering the body temperature and other night-time events. Melatonin secretion periods are known as biological night[7]. Melatonin is a sedative, antioxidant, anti-anxiety, anti-depressant and analgesic, its role in regulating circadian rhythms is completely associated with its drug properties[8]. Melatonin applies its effect by bonding with two types of melatonin receptors, called MT1 and MT2[9]. Recent results suggest that antioxidant properties of melatonin are much higher than other classical antioxidant[9,10]. Studies have revealed that melatonin concentration is significantly lower in patients with chronic pain[11]. Melatonin secretion is also abnormal in patients with fibromyalgia and melatonin concentration and is much lower in these individuals[11]. As melatonin concentration in blood regulates the circadian rhythms, the analgesic effect of it occurs at night and evening. In patients who removed the gland, circadian rhythms are disrupted[12]. Daily variations in the pain of those who have pain for any reason can be justified by this effect of melatonin[13]. Melatonin also has an antinociception effect and can block the sensors that stimulate the pain[12,13]. Melatonin also affected on the pain threshold and opioid system. For this reason, when naloxone is injected, the analgesic effect of melatonin is completely neutralized[14]. Studies have also shown that taking melatonin and injection of melatonin into intrathecal space can reduce tactile allodynia in different models of neuropathic pain[15]. Melatonin also affects the thermal hyperalgesia process. This effect is justified by the anti-inflammatory effect of melatonin. The anti-inflammatory effect of melatonin has been described and investigated in several studies[16]. Melatonin prevents the synthesis of pro-inflammatory cytokines such as TNF-α[17]. However, new studies indicate that pro-inflammatory cytokines such as TNF-α, IL-1 and IL-6 are important mediators in the process of allodynia and hyperalgesia, which are the most important symptoms of neuropathic pain[18].

In a study, it was found that taking melatonin led to secretion and release of β-endorphin in the periaqueductal (gray matter around the duct) in mouse. ß-endorphin can bind to the opioid receptors μ or κ and apply its effect[13]. Melatonin also applies its systemic effect through on the GABAA receptors in the spine cords[19]. some studies suggest that melatonin imitates the function of benzodiazepines by binding to GABAA receptors[20]. Several studies have been conducted on the analgesic effects of melatonin. These studies showed that taking melatonin was effective on fibromyalgia, headache, irritable bowel syndrome, chronic chest pain, and rheumatoid arthritis[21]. Low back pain can result in severe physical and mental disabilities and the therapeutic goals of the disease are weight loss, improved function, reduced pain, increased range of motion, reduced morning stiffness and facilitating the daily activities of life[4,5,6]. In addition, taking melatonin has advantages such as ease of use, low side effects, and cost-effectiveness, therefore this study was conducted to evaluate the effect of melatonin on pain control and quality of life in patients with chronic low back pain.

Methods

This study was a single-blind clinical trial. The sample size was determined to be 23 people with 95% confidence level, statistical power of 80%, and

standard deviation observed. To obtain sample size, Cohen's formula[22] was used. Participants were patients who referred to pain clinics of Akhtar Hospitals (Tehran, Iran) during June to August 2018. Out of 100 patients with low back pain for more than 12 weeks and age of 45 to 75 years who admitted to Akhtar Hospital and a VAS score of more than 3, 60 patients were selected randomly. A total of 30 subjects were considered in each group (control and case groups). The sampling method was simple non-random. They were randomly divided into two groups of 30 patients with control and melatonin. In this study, patients were not aware which belonged to either of the control or case groups (single-blind). Inclusion criteria of study included having at least reading and writing skills, having idiopathic low back pain in the age range of 45-75 years, walking ability, having a pain score of more than 3 based on VAS criterion, and having pain for more than 12 weeks. Exclusion criteria of study included neural-muscular diseases, history of accident, and spinal cord injury, radicular pains caused by lumbar spine disorders, having any rheumatologic disease, history of physiotherapy and intra-spinal injections in the past 6 months, mental and psychological diseases, neoplastic tissues in the spinal cord, infection, bleeding tissue, sensory and motor neurological disorders, history of surgery in the spinal cord and morbid obesity.

In the study implementation stage, goals of the study were described to the patients. It was also announced that they could be excluded from the study whenever they want and their lack of cooperation with the therapist and the hospital did not affect their treatment and all patient information would be kept confidential. All patients completed and signed the informed consent to participate in the study. In addition to presenting an educational brochure on the use of melatonin, time of follow-up tests, next visit and researchers provided face-to-face training for both groups on the importance of timely use of the drug and the way of taking them correctly. Then, drug was provided for them in uniform packages with a specific code to be used during first four weeks. Subjects were then assigned to control and melatonin groups. Control group received diclofenac sodium 25mg tablet two or three times daily and the experimental or melatonin group, in addition to receiving diclofenac sodium 25mg tablet twice a day, received melatonin tablet (3mg) 30 to 40 minutes before bedtime for four weeks (Figure1). Collaborator without previous knowledge assessed patients in terms of reducing pain and increasing the function before treatment and in the fourth week, using visual analogue scale (VAS) and patients completed the quality of life questionnaire (SF36). The level of IL-1β and TNF-α in the blood serum of individuals was also measured.

In data analysis section, mean, standard deviations, frequency, tables and charts were used to classify and summarize the collected data. To examine the normal distribution of the data, Kolmogorov-Smirnov test was used. Analysis of the data done by using covariance and Shapiro-Wilk tests through SPSS 22.

Ethical Criteria in this study was approved with the approval of the ethics committee of Shahid Beheshti University of Medical Sciences with ethics code of IR.SBMU.RETECH.REC.1397.581.

Results

In this clinical trial study, 60 patients were assigned into control and experimental groups. Clinical characteristics of patient groups showed in table 1. The mean age of the melatonin group was 51.4 ± 8.4 years and the mean age of control group was 50.9 ± 8.1 years, no statistically significant difference was found between two groups in this regard ($p>0.05$). Twenty-eight patients were man and the rest of them were woman, but no significant difference was found between the two groups in terms of gender due to matching them in terms of gender ($p>0.05$). The descriptive statistics of the research variables

Table 1: Number of subjects, age and gender in melatonin and control groups.

Parameter	Melatonin	Control
Number of subjects	30	30
age	51.4 ± 8.4	50.9 ± 8.1
Men/woman	13/17	15/15

Table 2: Descriptive indices of pre-test and post-test scores in Melatonin and Control groups.

variable	stage	group	MEAN± SD	s-w Z	p
VAS	Pre-test	Melatonin	53.5±0.11	2.1	0.88
		Control	56.5±0.12	87.0	1.12
	Post-test	Melatonin	7.2±0.14	86.0	1.08
		Control	44.5±0.11	98.0	0.98
IL-1β	Pre-test	Melatonin	2.09±0.034	82.0	1.1
		Control	2.08±0.018	93.0	0.97
	Post-test	Melatonin	1.52±0.073	87.0	1.13
		Control	2.06±0.016	9.0	0.98
TNF-α	Pre-test	Melatonin	15.52±0.017	96.0	0.94
		Control	15.49±0.017	1.13	0.83
	Post-test	Melatonin	13.08±0.021	1.24	0.75
		Control	15.47±0.016	0.83	1.12
Quality of life	Pre-test	Melatonin	71.68±0.18	0.87	1.09
		Control	71.73±0.19	0.99	0.99
	Post -test	Melatonin	72.36±0.19	0.83	1.2
		Control	72.19±0.19	0.94	0.98

Abbreviatoin: VAS, Visual Analogue Scale; IL-1β, Interleukin 1 beta; TNF-α, Tumor necrosis factor alpha

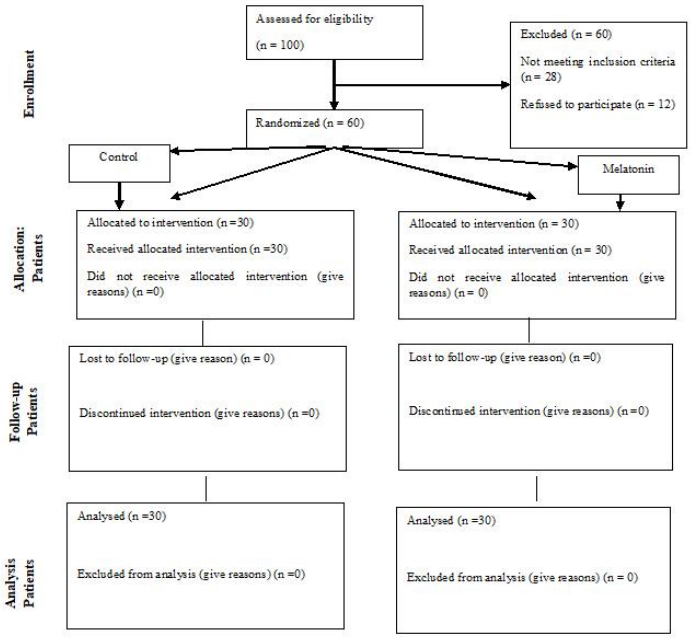

Figure 1. Modified CONSORT flow diagram.

presented in Table 2. The results of Shapiro-Wilk test showed that data were normally distributed ($p>0.05$). To analyze the data, covariance analysis was used. Table 3 shows the results of covariance analysis to compare the quality of life, VAS score, as well as IL-1β and TNF-α with control of initial levels. Based on this table information, after control of the pre-test effect ($\eta 2=0.001$, $p=0.856$, $F(1, 57)=0.33$), the effect of the group on the VAS scale was statistically significant ($\eta 2=0.776$, $p<0.001$, $F(1, 57)=93.747$), meaning that there is a significant difference between the VAS of the melatonin group and that of control group in the post-test. It can be also stated the pain level of the experimental group decreased significantly as a result of taking melatonin.

After control of the pre-test effect ($\eta 2=0.02$, $p=0.288$, $F(1, 57)=1.149$), the effect of the group on IL-1β was statistically significant ($\eta 2=0.469$, $p<0.001$, F (1,

Table 3: Analysis of covariance model to compare the vas, IL-1β, TNF-α and quality of life in the post-test with the control of the initial levels in Melatonin and Control groups.

Dependent variable	Source of variation	SS	df	MS	F	p	η^2
VAS	Pre-test	016.0	1	016.0	033.0	856.0	001.0
	group	747.93	1	747.93	295.197	0.001	776.0
	error	084.27	57	475.0			
	Total corrected	850.120	59				
IL-1β	Pre-test	098.0	1	098.0	149.1	288.0	02.0
	group	309.4	1	309.4	360.50	0.001	469.0
	error	877.4	57	086.0			
	Total corrected	518.9	59				
TNF-α	Pre-test	063.0	1	063.0	037.6	017.0	096.0
	group	167.87	1	167.87	509.8403	0.001	993.0
	error	591.0	57	01.0			
	Total corrected	885.89	59				
Quality of life	Pre-test	280.13	1	280.13	14.203	0.001	199.0
	group	614.0	1	614.0	0.657	0.421	011.0
	error	294.53	57	935.0			
	Total corrected	49.313516	60				

Abbreviatoin: VAS, Visual Analogue Scale; IL-1β, Interleukin 1 beta; TNF-α, Tumor necrosis factor alpha

57)=1.57), meaning that there was a significant difference between the groups in terms of IL-1β in post-test. It could be stated that the IL-1β in experienced group decreased significantly because of using melatonin. After control of the pre-test effect (η2=0.096, p=0.017, F (1, 57)=6.037), the effect of the group on TNF-α was statistically significant (η2=0.993, p<0.001, F (1, 57)=87.167), meaning that there was a significant difference between the groups in terms of TNF-α in post-test. After control of the pre-test effect (η2 = 0.199, p<0.001, F (1, 57) =14.203), the effect of the group on quality of life was not statistically significant (p=0.421).

Discussion

The objective of this study was to evaluate the effect of melatonin on pain control and quality of life in patients with chronic low back pain. Results showed that taking melatonin reduced the pain and reduced the level of IL-1β and TNF-α in the experimental group compared to the control group, while use of melatonin did not have a significant effect on quality of life.

Results showed that intake of melatonin has been effective in controlling pain. Studies have indicated that melatonin has a higher therapeutic effect than amitriptyline[23]. in a clinical study conducted to

examine the use of melatonin in a cluster headache, patients in the melatonin group received 10 mg melatonin or placebo for 14 days before bedtime. The severity of the pain and the frequency of the attack decreased in melatonin group, compared to the control group. In addition, the tendency to reduce painkillers was shown in the study group, although these results were not statistically significant[24]. In another study, patients with cluster headache received melatonin 2 mg and no significant improvement in pain syndrome was seen compared with placebo[25] this result might be due to the using low dose of melatonin. Results of studies used melatonin in the treatment of migraine showed that out of six patients; four patients reported reduced severity of pain in the morning after using the first dose, while the improvement was seen in other two patients after using the third dose[26]. No adverse effect was reported on the use of melatonin. Another clinical study conducted on 34 patients examined the effectiveness of melatonin in preventing migraines. Patients received melatonin 3mg 30 minutes before bedtime. Results revealed that the use of melatonin in 32 patients decreased the severity and duration of the headache[27].

Our results revealed that use of melatonin in addition to reducing the pain reduced the anti-inflammatory factors in patients with chronic low back pain. Several studies have shown a strong anti-inflammatory effect of melatonin in *in vitro* and *in vivo* models. For example, Amstrup *et al*. investigated the effect of melatonin supplementation in post-menopausal women with osteopenia, as a population characterized by a heightened risk of development of osteoporosis.[28] A one-year double-blind randomized placebo-controlled clinical trial was conducted on 72 women (56-73 years old), supplemented with 1 mg/day, 3 mg/day, or placebo. Results collected from melatonin treated groups showed an increase in bone mineral density at femoral neck and spine levels, in a dose-dependent manner. Mahmood *et al*. showed the anti-inflammatory effects of melatonin in a dose-dependent manner in a rat model of chronic inflammation, induced by formalin. The study, which lasted seven days, was conducted on 54 Sprague-Dawley rats subdivided into nine groups; these were treated with a saline solution, piroxicam, dexamethasone and melatonin, respectively[29]. These treatments were administered intraperitoneally 30 minutes before the induction of inflammation. Obtained results showed that all treated groups registered a significant inhibition in inflammation markers, except for melatonin administered at 0.25 mg/kg. Melatonin at 5.0 mg/kg induced an inhibition percentage in paw thickness comparable to that registered in the piroxicam 5.0 mg/kg group. Many research articles have reported the anti-inflammatory effects of melatonin, and linked these with an improvement in neurological function. Farhadi et al. showed that in addition to increasing the 16 levels of pro-inflammatory cytokines, patients with MS presented a decrease in serum levels of melatonin[26]. Kang JC et al. showed that supplementation with exogenous melatonin during the inflammatory-demyelinating process could be useful for the improvement of the myelin status of nerve fibers[27]. El-Shenawy *et al*. showed that melatonin, administered both systemically (0.5–1.0 mg/kg) and topically (20–40µg per paw) in rats, exerts anti-nociceptive and anti-inflammatory effects[16]. Melatonin was administered 30 minutes before the induction of acute inflammation, through a sub-plantar injection of carrageenan. A more recent study reported the beneficial effects of melatonin in the treatment of rats affected by inflammatory pain induced by intradermal injection of complete Freund's adjuvant (CEA) in rat paw. Melatonin or vehicle were administered intraperitoneal at doses of 60 mg/kg and 50 mg/kg. The results showed a reduction in spinal cord brain-derived neurotrophic factor (BDNF) concentration in the melatonin-treated group following three days' treatment, compared to the vehicle-treated group. In fact, BDNF is involved in the transmission of physiological and pathological pain[30]. Unfortunately, despite the positive evidence in rats reported by Laste et al.[28] that same 20 year Andresen et al.[29] published the results of a clinical trial on the analgesic effects of a single dose of melatonin in a validated human inflammatory model. In this case, no significant differences were registered between the treated group (10 – 100 mg melatonin) and the control group[31]. Several mechanisms have been proposed for the anti-inflammatory effect of melatonin. These mechanisms

include both antioxidative and immunoregulatory effects of melatonin. Melatonin and its metabolites can neutralize different types of free radicals to suppress inflammation in the first steps. It seems that potency and mechanisms of antioxidative and scavenging of melatonin differ from other classic antioxidants. The comparison of scavenging capacity of the melatonin with classic antioxidants including glutathione (GSH), vitamin C and vitamin E has shown that melatonin is up to ten folds more potent than others[31, 32]. Antioxidative properties of melatonin embody direct and indirect effects of melatonin in the neutralization of free radicals. The ability of melatonin to directly neutralize free radicals has been indicated in different studies[30, 33].
Limitation of this study was that due to high costs, we could not measure other inflammatory factors. Therefore, it is suggested that in future studies, the effect of melatonin on other inflammatory factors should be considered.

Conclusion

Finally, melatonin has inherent anticoagulant properties mediated through melatonin receptors and various neurotransmitter systems, which may further explain its positive effects. Although there is no reason to consider melatonin as an analgesic drug at present time, new clinical studies are needed to gain a better understanding of the mechanisms of analgesic action and its identification. Given the results of this study, melatonin can be recommended as a supplement for treatment of chronic low back pain.

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