



Original article

Melatonin treatment in patients with atypical facial pain: A randomized, double-blind, placebo-controlled clinical trial

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A B S T R A C T

Background: The present study was carried out to evaluate the effect of melatonin and placebo in the patients with atypical facial pain (AFP).

Method: This double blind randomized controlled study was carried out on 30 patients who were suffering from AFP. During this period, patients were divided in 2 study and control groups. Then, they were treated with melatonin. Melatonin group used four 3-mg daily and placebo group received 4 placebo which were similar in size, shape, color with melatonin until the end of treatment, and then the severity of burning sensation was measured by physician. Sleep quality was measured using the visual analog scale using the Petersburg questionnaire.

Result: The results of the present study show that the use of melatonin and placebo in patients with AFP reduces sensation and improves their sleep quality, although it may not reduce it completely. In this study, severity of burning was 5.71 ± 1.42 after treatment in the study group and 5.93 ± 2.65 in the control group, which was not statistically significant ($p = .46$). The mean score of sleep before treatment was not significantly different between the study (9 ± 1.23) and the control (8 ± 1.56) groups. The mean score of sleep after treatment between the study group (8 ± 1.45) and the control group (7 ± 1.23) was not significantly different ($p = .43$).

Conclusion: According to the result of the study, melatonin was not superior placebo in treatment of AFP.

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Tratamiento con melatonina en pacientes con dolor facial atípico: ensayo clínico aleatorizado, doble ciego y controlado con placebo

R E S U M E N

Antecedentes: El presente estudio se realizó para evaluar el efecto de la Melatonina y Placebo en el paciente con Dolor Facial Atípico (PFA).

Método: Este estudio controlado, aleatorio, doble ciego se llevó a cabo en 30 pacientes que padecían AFP. Durante este período, los pacientes se dividieron en 2 grupos de estudio y control. Luego fueron tratados con melatonina. El grupo de melatonina utilizó cuatro dosis de 3 mg al día y el grupo de placebo recibió 4 placebos que eran similares en tamaño, forma y color a la melatonina hasta el final del tratamiento, y luego el médico midió la gravedad de la sensación de ardor. La calidad del sueño se midió mediante la escala VAS utilizando el cuestionario de Petersburgo.

Resultado: Los resultados del presente estudio muestran que el uso de melatonina y placebo en pacientes con AFP reduce la sensación y mejora la calidad del sueño, aunque puede no reducirlo por completo. En este estudio, la gravedad del ardor fue de $5,71 \pm 1,42$ después del tratamiento en el grupo de estudio y de $5,93 \pm 2,65$ en el grupo de control, lo que no fue estadísticamente significativo ($P = 0,46$). La puntuación media del sueño antes del tratamiento no fue significativamente diferente entre los grupos de estudio ($9 \pm 1,23$) y de control ($8 \pm 1,56$). La puntuación media del sueño después del tratamiento entre el grupo de estudio ($8 \pm 1,45$) y el grupo de control ($7 \pm 1,23$) no fue significativamente diferente ($P = 0,43$).

Conclusión: Según los resultados del estudio, la melatonina no fue superior al placebo en el tratamiento de la AFP.

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Introduction

Atypical facial pain (AFP) is a rare but severe condition that covers the facial area and may dramatically affect the quality of life.¹ The international association of facial and oral pain describes the features of pain in AFP. International Classification of Headache Disorder describes it as a relatively severe pain that is not unbearable, is not inherently aggressive, is not exacerbated by touching a specific area (trigger) or daily activity, and does not follow a specific anatomical area.²

AFP is a disorder commonly compared to trigeminal neuralgia. Unlike trigeminal neuralgia, the symptoms of AFP are persistent, not intermittent, the pain is usually unilateral, and there are no autonomic signs and symptoms. Patients usually have a burning sensation or severe pain, and there is no specific problem in clinical examinations and tests.³ AFP is a lesser-known condition that is difficult for clinicians to diagnose and treat.⁴ AFP can lead to disability and poor health, so clinicians should take patients' complaints of facial pain seriously and make a complete list of differential diagnoses based on the patient's history and complete clinical examination. Some studies have shown that up to 26% of people in the community have experienced AFP at some point in their lives.³ Chronic orofacial pain is a common and debilitating problem that affects at least 10% of the adult population and 50% of the elderly population.⁵ 1 per 100 000 cases, mainly adults, have AFP.

The etiology of AFP remains unknown; long ago, there was a common belief that AFP is caused by psychogenic pain. Psychological factors that can cause AFP include 'endogenous depression', 'atypical depression', 'hysteria', 'anxiety state', 'neurosis', and 'obsessional neurosis'.⁶

Recent reports of AFP suggest that two-thirds of people with AFP have a psychiatric disorder. The role of female hormones in the etiology of AFP has been suggested, as women are more likely to experience the condition.^{6,7}

AFP is persistent pain in the face that does not meet the specifications of cranial neuralgia and cannot be associated with another disorder. Four characteristics for the diagnosis of AFP are as follows:

1. The facial pain occurs most of the time or all day, and daily.
2. At first, the pain may be limited to a part of the face, but in fact, it is difficult to determine the area and depth of the pain.
3. It is *not* related to other physical symptoms or sensory disorders.
4. Radiological examinations do not help determine a clear or structural anatomical cause for pain.⁷

Therefore, this diagnosis is problematic because it can only be diagnosed by excluding organic diseases. Organic diseases that may cause similar chronic or facial pain are usually localized but may be located anywhere on the head, neck, or chest, making it difficult to diagnose.

Idiopathic facial pain (IFP) falls into the category of medically unexplained symptoms, which often has a psychological basis (psychogenic) and must be diagnosed. However, the patient with pain may experience psychological reactions.

The indicators that define IFP include:

- (1.) A persistent pain with burning or severe dullness in an area that is not well-defined (ambiguous area) with or without short healing periods.
- (2.) Lack of objective features.
- (3.) All tests have negative results.
- (4.) There is no clear explanation for the cause of the disease.
- (5.) Poor response to treatment.

There is usually various expert advice.

In fact, it would rather say what is not than say what is it.⁸

Melatonin is a pleiotropic molecule that acts on chronic pain by multiple mechanisms⁹ and gets involved in various chronic biological processes, the sleep-wake cycle. In addition, it regulates the antioxidant system and has an anti-inflammatory and neuroprotective effect,¹⁰ so melatonin is effective in improving sleep quality; and due to

regulating the antioxidant system, it affects patients with degenerative disorders such as Parkinson's, Alzheimer's MS, and post-menopausal women.^{11,12}

The effects of melatonin on mood improvement (MOOD), chronic anxiety, and pain such as fibromyalgia¹³ or TMJ disorders¹⁴ were observed. Melatonin activates gamma-aminobutyric acid (GABA) and increases the release of beta-endorphins (B-endorphins) in the central nervous system.¹⁵

Due to the insufficiency of strong evidence in treating patients with AFP, this clinical trial study was designed to compare the effect of melatonin and placebo in reducing pain and symptoms in patients with AFP. So, it can prevent economic, physical, emotional, and psychological damages, preclinical examinations—unnecessary and ineffective treatments and increase the efficiency of people in the community.

Material and methods

A total of 30 patients with AFP referring to the Oral Diseases Department, included in the study based on the inclusion and exclusion criteria. The study is approved by ethics committee of Zahedan University of Medical Sciences with code IR.ZAUMS.REC.1398.203 and the clinical trial cod is IRCT20141220020377N4. Written informed consent was obtained from participants.

They had symptoms like the pain of the face most of the time or all day and daily. At first, the burning may involve a part of the face, but it is difficult to determine the place and depth of pain; it is not related to other physical symptoms of sensory disorders. Radiological tests to assess the apparent anatomical or structural cause of burning are not helpful.⁷ The lack of known systemic disease and the use of chronic drugs, over-18 years' patients, non-smoking, absence of oral lesions, the elderly with glaucoma, those who take aspirin, heparin, or warfarin, those who take atenolol and metoprolol because it reduces the effect of melatonin, patients with epilepsy, those who drop-out of follow-up, and lose inclusion criteria while studying were excluded from the study.

The treatment protocol was explained to all patients, and written consent was obtained. Patients were examined by a dentist who was blind to the drug before treatment, and the rate of burning was assessed based on VAS (visual analog scale). In this regard, 0 shows non-burning, and 10 shows the most severe pain condition that the patient has experienced. The patients were asked to scale the severity of their pain between 0 and 10, and then they were divided into patient and control groups based on block randomization. At the next stage, the patients were treated with melatonin by an oral pathologist. So, 3 mg capsule (made in Iran, Alhawi company) was prescribed 4 times a day; this treatment lasts up to 5 months. In the control group, the placebo capsule was matched with melatonin in terms of color, shape, and size and taken 4 times a day were treated. After 5 months of treatment: T0, the first visit of the patient and start of treatment; T1, second visit 8 weeks after the start of treatment; T2, 4 weeks wash-out (no medication); T3, fourth visit, the second 8 weeks of treatment.¹⁶ First, the intensity of pain was measured by a physician who knew about the treatment to obtain a placebo melatonin capsule. To get the placebo capsule, melatonin inside the capsule was replaced with soluble medical starch powder and placed in glass jars named melatonin capsules. After treatment, they were re-examined, and the pain intensity was assessed.

Patients completed the Petersburg questionnaire, a measure of sleep quality and sleep patterns, during treatment (T0: first visit and the start of treatment; T1: second visit 8 weeks after treatment; T2: 4 weeks wash-out (not taking medication); T3: fourth visit of the second 8 week of treatment). This questionnaire identifies appropriate sleep and inappropriate sleep by evaluating 7 characteristics of individuals during the past month, which are:

- C1: Sleep quality from the point of view of patients.
- C2: Time-lapse to fall asleep.
- C3: Duration of sleep time.
- C4: Sleep efficiency.

Table 1

Overall score of sleep quality before and after treatment with melatonin and placebo in patients with atypical facial pain.

Feature	Overall score of sleep quality before the treatment	Overall score of sleep quality after the treatment	p-value
	Mean \pm SD	Mean \pm SD	
Control (Placebo)	7.10 \pm 1.20	5.93 \pm 2.65	.46
Case (Melatonin)	8.53 \pm 1.02	5.71 \pm 1.42	

C5: Sleep time problems.

C6: Use of sleeping pills.

C7: Daily dysfunction.

Results

Thirty people with AFP an included in the study (M = 12, F = 18). Then patients were divided into control and case groups based on block randomization.

The mean age was 13.11 \pm 27.55 years and 27.12 \pm 53.58 years in the control and case groups, respectively. Further, the results of the Mann–Whitney test showed that the ages of both groups were not significantly different ($p = .68$).

Examination of sex ratio using Fisher test showed no statistically significant difference between the 2 groups in terms of sex distribution. The mean time of involvement was 45.7 \pm 93.19 months and 75.8 \pm 27.17 months in the control and patient groups, respectively. Again, there was no statistically significant difference (p -value = .98).

Changes in the severity of pain in both groups before and after treatment have been shown. Based on statistical data, a significant difference was observed in both groups after treatment in terms of severity of burning mouth (p -value = .058).

The overall sleep quality score before and after treatment was calculated based on the Pittsburgh questionnaire provided to patients. Table 1 shows this information. No significant difference was observed between the 2 groups during the sleep quality score (p -value = .46).

The Pittsburgh Questionnaire consists of 7 scales, shown separately in Table 2.

Discussion

The present study aimed to evaluate the effect of melatonin and placebo therapy on AFP. For this purpose, an interventional study was used, and the results showed that melatonin and placebo therapy for patients with AFP mitigates burning and improves sleep disorders; there was no statistically significant difference between the 2 groups. Studies have reported the role of mental disorders in the progression of AFP. Most of them measured the level of mental disorders such as anxiety and depression in patients with AFP. Only 1 study examined the therapeutic effects of melatonin and placebo on burning mouth syndrome.¹⁷

Burning mouth syndrome and AFP interfere with a person's physiological mechanism. Contrary to other studies, the present study is

an interventional clinical study that compared the mean sleep before and after the treatment in the 2 groups besides comparing the severity of oral pain using the VAS scale before and after treatment in melatonin and placebo groups. Most importantly, the present study has been conducted for the first time in Iran and contains significant and sometimes different results due to the role of stress, the effect of sleep on mental disorders, differences in stressors, and changing sleep patterns in different societies. The present study includes significant and different results from similar studies. We aimed to treat patients with sleep disorders or psychological disorders along with treating oral pain. Since AFP is a disease with no specific treatment and less likely to experience complete recovery without recurrence by discontinuation of the drug, and on the other hand, the response to psychiatric treatment usually begins 3 weeks after the treatment, drug treatment continued for 5 months to stabilize the condition of patients. The Pittsburgh questionnaire was filled out before and after treatment according to the guide to assess patients' sleep quality and patterns. This questionnaire distinguishes appropriate from inappropriate sleep by assessing 7 characteristics of individuals during the past month.

In the present study, 30 patients with AFP were included in the melatonin and placebo treatment groups. The mean age was 55.27 \pm 11.13 and 58.53 \pm 12.27 years in the control and case groups. The mean participation period was 19.93 \pm 7.45 and 17.27 \pm 8.75 months in the control and patient groups, respectively, with no statistically significant (p -value = .58). AFP is a chronic disease that patients experience for months and even years. They refer to dentists and physicians with various complaints caused by physical changes in the teeth, mucous membranes, and gums. In many cases, patients complain of mental and intellectual stress and indicate mental disorders in patients.⁹

VAS criteria assessed pain intensity to determine changes and compare the pain intensity of patients in both groups. Statistical data showed a significant difference ($p = .036$).

In the Varoni study, melatonin significantly improved anxiety scores. In the present study, the Anxiety and Depression Inventory was not evaluated. This study was the first randomized, 3-way, randomized, placebo-controlled clinical trial. The reason for performing the present study was to evaluate the effect of melatonin on BMS and its functional mechanisms and regulating systemic mood, immune system, and circadian rhythms. Melatonin may help treat oral diseases, including BMS caused by neuroprotective, antioxidant, and anti-inflammatory activities. The present study showed that melatonin and placebo had a comparable effect in reducing pain caused by BMS. It found no association between melatonin and sleep quality improvement, consistent with a recent meta-analysis of melatonin for sleep disorders in patients with neurological disease because sleep disorders are associated with BMS.¹⁷

Despite the ineffectiveness of melatonin, as previously reported, melatonin exhibited completely safe drug profiles. The limitation of both treatments was the patient's self-reported sleep disorder. Minor side effects (such as dizziness, headache, and nausea) were similar in the melatonin and placebo groups.¹⁸

Reiter et al. believe that as a prescription (pill or sublingual), melatonin can reduce pre-operative anxiety in adults compared to placebo. Melatonin may be as effective as standard treatment with midazolam in reducing preoperative anxiety in adults.¹⁹

Table 2

Mean score of sleep quality scales before and after melatonin and placebo treatment in patients with atypical facial pain.

Sleep quality (C1)	Control group		Case group		p-value	
	Before the treatment	After the treatment	Before the treatment	After the treatment	Before the treatment	After the treatment
The time lapse of falling sleep (C2)	2	1	2	1	1.00	0.128
The time duration of sleep (C3)	2	2	2	2	.65	1.00
Effectiveness of sleep (C4)	2	1	2	1	.28	0.71
Disorders during sleeping (C5)	1	0	1	0	1	1.00
Taking sleeping pills (C6)	2	2	2	2	.36	0.86
Dysfunction (C7)	1	1	1	1	.69	0.77
	1	1	1	1	.55	0.67

The study of Nosratzahi et al.¹⁸ aimed to compare the frequency of complaints, type, and severity of stressful events in patients with AFP in case and control groups. The results of this study showed that 80.9% of patients complained of different kinds of non-toothache pains. There was no significant difference in pain intensity between the control and case groups ($p = .251$). The duration of complaints was statistically significant between patients with AFP and the control group ($p = .004$). Comparison of stressful events showed that, in the case group, 12.7% of spouse or family members deaths were caused by stress. The intensity of stressful events in both groups was statistically significant ($p = .032$).²⁰

Back et al.¹³ performed a study on oral-facial pain and its relationship with quality of life relating to oral health and mental disorders in middle-aged women in case and control groups. This study showed that women with oral-facial pain (7.7%, $n = 82$) had significantly higher mean scores on OHIP-5, HADS-A, and HADS-D and lower mean scores on SOC-13. Further, oral pain was significantly associated with lower OHRQoL ($or = 1.2$) and depressive symptoms ($or = 2$).¹³

In a cross-sectional study, Delavarian et al. (2020) performed a study on 132 patients with complaints of mental origin (the case group) and 132 patients with complaints of organic origin (the control group).

AFP was the most common clinical diagnosis of sensory impairment; 31.6% had psychiatric disorders in the case group, and 53.8% were prone to psychiatric disorders. This study showed that most patients who complained of mental origin had psychiatric problems.²⁰

Lan et al. examined 12 AFP patients ($F = 6$ females, $M = 6$ males, mean age = 48 ± 12 yrs) with the incidence of deep unilateral facial pain present at most hours of the day using three-dimensional TREZ MRI (trigeminal root entry). There was no significant difference between arteries and TREZ on the asymptomatic side and those on the symptomatic side. Thus, MVD microvascular decompression cannot be expected to improve their pain.¹⁵ In the study of Mursch et al., 61% of patients did not respond to trigeminal evoke potential, and 39% recovered. In AFP, positron emission tomography showed an increase in brain activity, suggesting a change in the mechanism in response to environmental stimuli leading to the release of neuropeptides and free radical products. Some researchers consider AFP a kind of trigeminal neuralgia.²¹

In the study of Melo NB et al.,¹⁶ which aimed to assess the effect of oral health on the quality of life of patients with head and neck cancer using the OHIP-14 (Oral Health Impact Profile-14) questionnaire on 130 patients, clinical aspects, cancer stages, and treatment strategies were evaluated, and the mean score of OHIP-14 in patients was 19.52 ± 11.79 . Physical pain (3.7 ± 2.44), physical disability (3.26 ± 2.45), and functional limitation (3.24 ± 2.45) were the main factors affecting patients' quality of life. Black patients, widows, and patients diagnosed with squamous cell carcinoma and TMJ joint pain showed a more inferior quality of life and thus, a more significant impact of oral health on the quality of life of patients with head and neck cancer. Accordingly, clinical features and demographic variables can affect patients' quality of life with head and neck cancer.¹⁶

Stressful events are created by a roughly common mechanism and a physiopathological approach. The pain nozzles, which start from the cerebral cortex, the hypothalamus, and the limbic system and end to thalamus, the reticular system, and the spinal cord nucleus, release chemical agents that can exacerbate or inhibit the neural waves injected into the spinal cord or thalamus. The serotonin (5-hydroxytryptamine, 5HT) and norepinephrine nozzles are the important chemical mediators of the sensory system. These neurotransmitters are changed due to psychological disorders and transmit to the thalamus and the spinal cord due to the inferior sensory system effects on the balance of sensory information. In this regard, the feeling of pain or burning, which does not have a clear physical stimulus or is not related to the presence of the stimulant, is emerged. On one hand, anxiety disrupts GABA receptors in the CNS and changes their activity, and on the other hand, the production of endorphins by the CNS reduces neural balance

(modulation) of the senses entering the spinal cord or thalamus, and ultimately causes severe pain. However, researchers consider vascular and CNS factors as the etiology of these complaints.²²

Oral healthcare providers should pay special attention to OHRQoLs considering the high prevalence of oral diseases in the community, the incidence of AFP, and the possibility of affecting the psychological, social, and economic conditions of patients from oral problems. Because, as mentioned, the use of standard clinical indicators for the diagnosis of oral diseases will no longer meet the real needs of patients in the community in the future.

One of the limitations of this study was the self-assessment of patients and a large number of female patients, which caused some problems in similar studies. Finally, studies should be done in a multi-center manner in different parts of the country with a higher sample volume to determine the effect of different types of disorders on quality of life, post-treatment study to examine the effect of different treatment methods.

Although evidence suggests an association between sleep disorders and AFP, melatonin was not superior to placebo in reducing the pain caused by AFP in the present study. Larger samples and higher oral doses, more extended follow-up periods and control of psychological factors, measurement of body mass index affecting pharmacokinetics are recommended.

In treating patients with AFP and other sensory disorders of mental and intellectual origin, they should be informed of the benign nature of the disease when these disorders are diagnosed. Talking to patients helps treat the nature of the disease because patients have undergone different treatments and many unnecessary tests. The patient should be assured that his illness is entirely benign and not a sign of malignancy. In patients with mild to severe complaints, talking is a good way, but in more severe cases, psychotherapy and sometimes, prescribing medication is needed.

Ethical consideration

The study is approved by ethics committee of Zahedan University of Medical Sciences with code IR.ZAUMS.REC.1398.203 and the clinical trial cod is IRCT20141220020377N4, Grant no 9248. Written informed consent was obtained from participants.

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