BJPS

Brazilian Journal of
Pharmaceutical Sciences

http://dx.doi.org/10.1590/s2175-97902023e21748

Article

Evaluation of the effect of melatonin in patients with Burning mouth syndrome: a double-blind, placebo-controlled randomized clinical trial

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The present study was carried out to evaluate the effect of Melatonin and Placebo in the patient with the Burning mouth (BMs). This double-blind, placebo-controlled randomized clinical trial study was carried out on 30 patients who were suffering from BMS. During this period patients were divided into 2 study and control groups. The study group used four 3 mg Melatonin daily and the control group received a placebo. Then the severity of the burning sensation was measured by the physician Sleep quality was measured using the VAS scale using the Petersburg questionnaire. Data in the application Enter SPSS 20 and then using T test or equivalent Nonparametric was analyzed, mean sleep score and mean severity of oral irritation before and after treatment in two the group was evaluated using T-test Independent. Level significance was considered 0.05. The results of the present study show that the use of melatonin and a placebo in patients with BMS reduces sensation and improves their sleep quality, although it may not reduce it completely. In this study severity of burning was 4.93±2.56 after treatment in the study group and 6.93±2.12 in the control group, which was statistically significant (P =0.036). No significant difference was observed between the two groups in the sleep quality score (P-value = 0.43). Using Melatonin can be a reliable way to treat pain for which there is no standard treatment to date. Although evidence suggests an association between sleep disorders and BMS, melatonin was not superior to a placebo in reducing BMS-induced burning in the present study. Identification of stressors and the ways to struggle with them, further studies with larger samples and higher oral doses, extended follow-up periods and control of psychological factors, and measurement of body mass index that may affect pharmacokinetics are recommended.

Keyword: Melatonin. BMS. Sleep.

INTRODUCTION

Burning mouth syndrome is defined as a burning sensation and neuropathic pain with no dental or organic medicine. The symptoms vary in patients, usually an intense pain during the day that gradually regresses or progresses (Lopez-Jornet, Camacho-Alonso, Lucero-Berdugo, 2008; Lopez-Jornet *et al.*, 2015). This pain intensity significantly reduces the quality of life of patients with irritable bowel syndrome (Sun *et al.*, 2013). The prevalence of mouth-burning syndrome ranges between 0.7% and 7% in the general population and 12% and 18% in women (Eliav, 2014).

The etiology of Burning Mouth Syndrome is unknown. However, recent findings have suggested changes in the central and peripheral nervous systems (Eliav, 2014; Imura *et al.*, 2016), antioxidant imbalances (Amenabar et al., 2008; Simcic et al., 2006), and defective inflammatory responses (Lopez-Jornet *et al.*, 2015) in the pathogenesis of this disease is involved. In addition, one cohort study and three case-control studies have shown an

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association between sleep disorders and Burning Mouth syndrome (Adamo *et al*., 2013; Almoznino *et al*., 2017; Chainani-Wu, Madden, Silverman, 2011; Lee *et al*., 2014).

Patients with Burning Mouth Syndrome showed poorer sleep quality, and an increased number of sleep-related disorders than the control group (Kisely *et al*., 2016). Patients with sleep disorders are more likely to experience Burning Syndrome. These findings suggest that sleep disorder can be a risk factor for Burning Mouth Syndrome and has set a therapeutic goal for this disease; however, the treatment of patients with Burning Mouth Syndrome is still not conclusive due to insufficient and robust evidence (McMillan *et al*., 2016).

Anxiety, antidepressant, and sedative drugs improve the symptoms of Burning Mouth Syndrome, but the results are still insufficient (Danilov, Kurganova, 2016). *Melatonin* is a pleiotropic molecule that affects chronic pain by multiple mechanisms (Boeve, 2003). In addition, the sleep-wake cycle involves various chronic biological processes, balances up the antioxidant system, and has anti-inflammatory and neuroprotective effects (Adamczyk-Sowa *et al*., 2014). So, melatonin is effective in improving sleep quality. Further, it affects patients with degenerative disorders such as Parkinson's, Alzheimer's MS, and postmenopausal women (de Zanette et al., 2014; Jehan *et al*., 2015) because of balancing the antioxidant system.

Study results showed the effects of melatonin on mood improvement (MOOD), chronic anxiety, and pain such as fibromyalgia (Vidor *et al*., 2013) or TMJ disorders (Zurowski *et al*., 2012). In addition, melatonin activates gamma-aminobutyric acid (GABA) and increases the release of beta-endorphins (B- Endorphin) in the central nervous system (Varoni *et al*., 2018).

Due to insufficient and robust evidence in the treatment of patients with Burning mouth syndrome, this clinical trial study aimed to compare the effect of melatonin in reducing pain and symptoms in patients with Burning mouth syndrome with a placebo.

MATERIAL AND METHODS

A total of 30 patients with burning mouth syndrome, referring to the Oral Diseases Department, were included in the study based on the inclusion and exclusion criteria. They had symptoms like the burning 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 the burning; 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 (Simcic *et al*., 2006). 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 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 Analogue Scale). In this regard, zero shows non-burning, and 10 shows the most severe burning condition that the patient has experienced. The patients were asked to scale the severity of their mouth burning between 0-10, 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, a 3 mg capsule (made in Iran, Alhawi company) was prescribed four 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 four times a day were treated; After five months of treatment:

(T0: the first visit of the patient and start of treatment, T1: second visit eight weeks after the start of treatment, T2: 4 weeks Wash Out (no medication), T3: fourth visit, the second 8 weeks of treatment (Arbabi-Kalati et al., 2015). 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 by a dental student, 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 eight 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 from inappropriate sleep by evaluating seven 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
C5: Sleep time problems
C6: Use of sleeping pills
C7: Daily dysfunction

RESULTS

Thirty people with burning mouth syndrome were included in the study (M=8, F=22). Then patients were divided into control and case groups based on block randomization.

The mean age was 50.27 ± 12.13 years and 51.53 ±14.27 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=0. 68).

Examination of the sex ratio using the Fisher test showed no statistically significant difference between the two groups in terms of sex distribution. The mean time of involvement was 17.93± 7.87 months and 22.27 ±19.75 months in the control and patient groups, respectively. Again, there was no statistically significant difference (P-value = 0.98).

Changes in the severity of the burning mouth 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 the burning mouth (P-value = 0.036)

The overall sleep quality score before and after treatment was calculated based on the Pittsburgh questionnaire provided to patients. Table I and Figure 1 show this information. No significant difference was observed between the two groups in the sleep quality score (P-value = 0.43). The Pittsburgh Questionnaire consists of seven scales, shown separately in Table II.

TABLE I - Overall score of sleep quality before and after treatment with melatonin and placebo in patients with Burning mouth syndrome

	Overall score of sleep quality before the treatment	**Overall score of sleep quality after the treatment**	**P value**
	Mean ± SD	**Mean ± SD**	
Control (Placebo)	10±1.44	8±1.84	0.43
Case (Melatonin)	10±1.66	8±1.59	

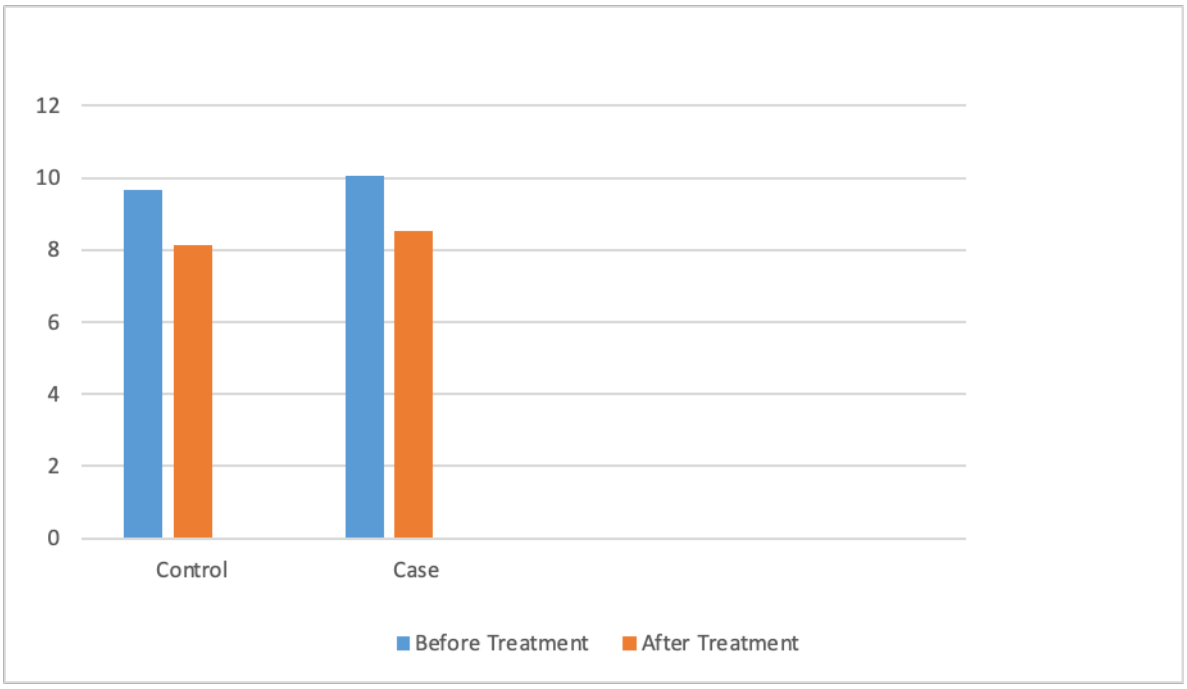

FIGURE 1 - Overall score of sleep quality before and after treatment with melatonin and placebo in patients with mouth-burning syndrome.

TABLE II - Mean score of sleep quality scales before and after melatonin and placebo treatment in patients with burning mouth syndrome

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 asleep (C2)	2	1	2	1	1.00	0.128
The time duration of sleep (C3)	2	2	2	2	0.65	1.00
Effectiveness of sleep (C4)	2	1	2	1	0.28	0.71
Disorders during sleeping (C5)	1	0	1	0	1	1.00
Taking sleeping pills (C6)	2	2	2	2	0.36	0.86
Dysfunction (C7)	1	1	1	1	0.69	0.77
	1	1	1	1	0.55	0.67

DISCUSSION

This study aimed to evaluate the effect of melatonin and placebo drug therapy in improving Burning mouth syndrome. The results showed that melatonin and placebo drug therapy for patients with Burning mouth syndrome reduce the severity of burning and improve sleep disorders. However, no statistically significant difference was observed between the two groups. However, there have already been studies on the relationship between sleep disorders and Burning mouth syndrome.

Moreover, studies have been reported on the role of mental disorders in the development of Burning mouth syndrome. Most of them measured anxiety disorders in patients with this Syndrome using criteria of mental disorders such as anxiety and depression. However, only one study examined the therapeutic effects of melatonin and placebo on Burning mouth syndrome (Arbabi-Kalati, Bakhshani, 2015).

Contrary to studies, the present study is an interventional clinical study that compared the mean sleep before and after treatment in the two groups and compared the severity of Burning mouth syndrome using the VAS scale before and after treatment in the melatonin and placebo group. Most importantly, the present study was conducted in Iran for the first time. The present study contains significant and sometimes different results from those of studies in other countries due to stressors and sleep in mental disorders and differences in stressors, and changing sleep patterns in different societies. Since we aimed to treat patients with sleep disorders or implement psychiatry to treat burning mouth syndrome, BMS is a disease without specific treatment that is hardly treated completely by stopping drug use. On the other hand, the response to psychiatric treatment is usually three weeks after the start of treatment, so pharmaceutical treatment, based on the available study protocol, continued for five months to stabilize the patients' condition.

According to the implementation method, the Pittsburgh questionnaire was filled out before and after treatment in the group to assess patients' quality of sleep and sleep pattern. This questionnaire identifies appropriate sleep from inappropriate sleep by evaluating seven features of individuals during the past month.

In the present study, 30 patients with BMS were included in the study group in the melatonin and placebo treatment groups. The mean age of patients in the control group (placebo) and case group (melatonin) was 50.27 ± 12.13 and 51.53 ±14.27 years, respectively. It was estimated that the frequency distribution of patients in women was 73.3%, which was consistent with similar studies on women (Arbabi-Kalati *et al*., 2015; Farhad Molashahi *et al*., 2012; Varoni *et al*., 2018) and the middle-aged (Arbabi-Kalati *et al*., 2015; Farhad Molashahi *et al*., 2012; Nosratzehi, Payandeh, DehYadegari, 2020).

The duration of involvement of patients in the control group (placebo) was 17.19 ± 7.8 months and in the case group (melatonin) was 22.19 ± 27.75 months. Mouth burning syndrome is a chronic disease that involves patients for months and even years. So, they refer to dentists and physicians with various complaints. However, most of these complaints result from physical changes in the teeth, mucous membranes, gums. In many cases, patients' complaints have mental and intellectual stress and indicate mental disorders (Cui *et al*., 2016). VAS criteria for all patients measured pain intensity at the beginning of the study. Pain intensity in the control group (placebo) was 8.20 ±1.3 before the treatment and 4.93 ± 2.56 after the treatment. On the other hand, in the case group, it was 8.1 ±53.24 (melatonin) before treatment and 6.93 ±2.12 after the treatment.

Determining the changes and comparing the severity of mouth burning in the two groups showed a significant difference based on statistical data (P = 0.036)

Various studies show a change in the severity of burning mouth syndrome in patients before and after similar treatments of our study *(*Arbabi-Kalati *et al*., 2015; Arbabi-Kalati *et al*., 2015; Reiter *et al*., 2015). In Nosrat Zehi et al.'s study, two groups of BMS and the control group were studied, each group consisting of 30 members. The results of the t-test for two independent samples showed that the mean severity of complaints, the mean severity of stressful events, the frequency of complaints, the frequency of various stressful events were significantly different between patients with BMS and the control group (P<0.01). This study was consistent with that of other studies (Nosratzehi, Payandeh, DehYadegari, 2020; Arbabi-Kalati *et al*., 2015). The sleep quality scores

were not significantly different between the two groups (P-value = 0.43)

Arbabi et al.'s study showed that people with burning mouth syndrome have more sleep disorders than the control group (Arbabi-Kalati *et al.*, 2015). Thus, patients' treatment is more psychological than pharmaceutical, and patients with chronic pain and burning have sleep disorders, but the relationship between pain and sleep disorder is complex and unclear.

Short term (2 months) A cross-over clinical trial involving intervention with a high melatonin dosage (12 mg/day) did not provide pain relief (SMD 0.24, 95% CI −0.39 to 0.87; RR 1.18, 95% CI 0.31–4.43) and sleep score improvement compared to placebo. Ten participants reported no changes in symptoms, and one participant reported worsening of symptoms. The value of VAS score and serum plasma melatonin concentration was negatively associated, but it was not statistically significant ($p > 0.05$). Two patients in the melatonin group demonstrated a positive correlation between decreased VAS scores and increased sleep hours. The Hamilton rating scale for anxiety (HAM) assessment scores was always higher in the melatonin group than placebo, with a statistically significant decrease in the melatonin group's anxiety score ($p < 0.05$). An approximate two-fold of patients reported sleep impairment using melatonin (n = 10, 62.5%) compared to placebo (n = 6, 37.5%). Mild daytime sleepiness was seen in melatonin and placebo groups, with high ESS scores but not significant between them ($p > 0.05$). The main adverse effect of melatonin that leads to the discontinuation of treatment on four patients were heavy tremor, sexual disturbances, blurred vision, and severe heavy headedness. Four patients were dropped from the study due to lack of efficacy, pain improvement, and follow-up loss (Varoni *et al*., 2018).

BMS has frequently been associated with psychological disorders such as depression, anxiety, hypochondriasis and cancerphobia (Scala *et al*., 2003). It remains unclear whether anxiety and depression precede BMS or if they are a consequence of chronic pain. Treatment-resistant patients may have a contributing psychological factor. Cognitive behavioural therapy (CBT) is a common psychotherapeutic intervention for patients with chronic pain, and its effectiveness is influenced by the level of empathy received by the patient. Interestingly, females have commonly better outcomes than males. CBT improves the patient's quality of life by allowing them to perform their daily activities without limitation and diverts their concentration on the pain, changing the thought and coping adaptive behaviours (Lim *et al*., 2018; Hofmann *et al*., 2012). A combination of psychopharmacological treatment may help the patient avoid the possibility of drug abuse and adverse effects. However, a larger sample size should be obtained to establish the benefit of CBT and to rule out the attention placebo effect, as the patient was reviewed more frequently.

Despite the ineffectiveness of melatonin shown in previous reports, melatonin exhibited completely safe pharmaceutical properties; the limitation of both treatments was the patient's self-reported sleep disorder. In addition, minor side effects, such as dizziness, headache, and nausea, were similar in the melatonin and placebo groups.

Reiter *et al.* (2015) believe that melatonin as a prescription (pill or sublingual) can reduce preoperative anxiety in adults compared to placebo. In addition, melatonin may be as effective as standard midazolam treatment for reducing preoperative anxiety in adults.

The limitations of this study included the small sample size, the high rate of trial dropouts, the failure to measure body mass index, which may affect pharmacokinetics, and the patient's self-reported sleep disorders. Further, because of the similarity with Varoni *et al.* (2018) study, it was not possible to discuss more.

Some believe that a psychological disorder in patients with BMS results from their sensory disturbance. Others believe that a psychological disorder has an etiological role in causing a burning mouth. There are many discussions about whether psychological problems cause pain and burning or other results. Some believe that chronic pain and burning are mental disorders. The prevalence of psychological disorders is generally higher in patients with chronic pain and burning than those without pain. Still, most patients with chronic pain and burning are not depressed. There are other hypotheses as follows: (Martin *et al.,* 2008).

1. 1. Psychological disorders increase pain sensitivity.
2. 2. Pain is a hidden form of psychological disorder.

3. 3. Psychological disorders are caused by the continuation of chronic pain.

It can be inferred that the present study, statistically and experimentally, showed that there is no definitive cure for burning mouth syndrome. Further, psychiatric treatments for improving sleep disorders caused by environmental stress and placebo treatments have the same effect on treatment. Even placebo medication can psychologically help improve the burning mouth of patients, and this issue can be interpreted with the following physiopathology:Stressful events are created with a roughly common mechanism and physio-pathologic approach to which we refer briefly. The pain nozzles which start from the cerebral cortex, the hypothalamus, and the limbic system and end to thalamus, the reticulation system, and the spinal cords nucleus release chemical agents that can exacerbate or inhibit the neural waves injected into the spinal cord or thalamus. The serotonin (5-hydroxytryptamine5HT) and epinephrine light (NE) nozzles are the important chemical mediators of the sensory system. These neurotransmitters undergo changes due to the psychological disorders andtransmit to the thalamus and the spinal cord as a result of the effect of the inferior sensory system on balancing the sensory information. In this regard, the pain or burning which does not have a clear physical stimulus or is not related to the presence of the stimulant will emerge.On the other hand, anxiety disrupts gamma-aminobutyric acid (GABA) receptors in the CNS and changes their activity, and, on the other hand, the secretion of endorphins in the CNS reduces the phenomenon of neural balance (modulation) of the senses entering the spinal cord or thalamus, and ultimately causes severe pain. However, other scientists consider vascular and central nervous system factors as the source of these complains (Boeve, 2003).

CONCLUSION

Using Melatonin can be a reliable way to treat pain for which there is no standard treatment to date. Although evidence suggests an association between sleep disorders and BMS, melatonin was not superior to placebo in reducing BMS-induced burning in the present study. Identification of stressors and the ways to struggle with them, further studies with larger samples and higher oral doses, extended follow-up periods and control of psychological factors, measurement of body mass index that may affect pharmacokinetics are recommended.

ABBREVIATIONS

BMS: Burning mouth syndrome
GABA: Gamma-aminobutyric acid
VAS: visual analogue scale

DECLARATIONS

Availability of data and materials

The detailed data supporting the study are available upon reasonable request.

Ethics approval and consent to participate

The study is approved by ethics committee of Zahedan University of Medical Sciences with code IR.ZAUMS.REC.1398.157 and the clinical trial cod is IRCT20141220020377N3. Written informed consent was obtained from participants.

Consent to publish

Not applicable.

Competing interests

All the authors declare no conflict of interest.

Authors' Contribution

TN: study design and concept, and drafting; AP: literature revew and performing the study; KA: analaysis and drafting. All authors read and approved the study.

REFERENCES

Adamczyk-Sowa M, Pierzchala K, Sowa P, Mucha S, Sadowska-Bartosz I, Adamczyk J, et al. Melatonin acts as

antioxidant and improves sleep in MS patients. Neurochem Res. 2014;39(8):1585-93.

Adamo D, Schiavone V, Aria M, Leuci S, Ruoppo E, Dell'Aversana G, et al. Sleep disturbance in patients with burning mouth syndrome: a case-control study. J Orofac Pain. 2013;27(4):304-13.

Almoznino G, Benoliel R, Sharav Y, Haviv Y. Sleep disorders and chronic craniofacial pain: Characteristics and management possibilities. Sleep Med Rev. 2017;33:39-50.

Amenabar JM, Pawlowski J, Hilgert JB, Hugo FN, Bandeira D, Lhuller F, et al. Anxiety and salivary cortisol levels in patients with burning mouth syndrome: case-control study. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2008;105(4):460-5.

Arbabi-Kalati F, Bakhshani N-M, Tahmtan B, Movahedinejad F. Association of impaired sleep quality in patients with burning mouth syndrome: A case-control study. Health Scope. 2015;4(2):e23795.

Arbabi-Kalati F, Tahmtan B. Evaluation of the effect of oral zinc sulfate on burning mouth syndrome: A Double blind randomized clinical trial. Dent Clin Exp J. 2015;1(1):e4601.

Boeve B. Melatonin for treatment of REM sleep behavior disorder in neurologic disorders: results in 14 patients. Sleep Medicine. 2003;4(4):281-4.

Chainani-Wu N, Madden E, Silverman S, Jr. A case-control study of burning mouth syndrome and sleep dysfunction. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2011;112(2):203-8.

Cui Y, Xu H, Chen FM, Liu JL, Jiang L, Zhou Y, et al. Efficacy evaluation of clonazepam for symptom remission in burning mouth syndrome: a meta-analysis. Oral Dis. 2016;22(6):503-11.

Danilov A, Kurganova J. Melatonin in chronic pain syndromes. Pain Ther. 2016;5(1):1-17.

de Zanette SA, Vercelino R, Laste G, Rozisky JR, Schwertner A, Machado CB, et al. Melatonin analgesia is associated with improvement of the descending endogenous pain-modulating system in fibromyalgia: a phase II, randomized, double-dummy, controlled trial. BMC Pharmacol Toxicol. 2014;15:40.

Eliav E. Altered structure and function in hippocampus and medial frontal cortex in patients with burning mouth syndrome. Pain. 2014;155(8):1424-5.

Farhad Molashahi L, Bakhshani N, Honarmand M, Shahri F, Teimuri S. Correlation between burning mouth syndrome and psychological symptoms in patients attending to zahedan dental school. SSU_Journals. 2012;20(2):187-93.

Hofmann SG, Asnaani A, Vonk IJJ, Sawyer AT, Fang A. The efficacy of cognitive behavioral therapy: A review of meta-analyses. Cognit Ther Res. 2012;36:427–440.

Imura H, Shimada M, Yamazaki Y, Sugimoto K. Characteristic changes of saliva and taste in burning mouth syndrome patients. J Oral Pathol Med. 2016;45(3):231-6.

Jehan S, Masters-Isarilov A, Salifu I, Zizi F, Jean-Louis G, Pandi-Perumal SR, et al. Sleep Disorders in Postmenopausal Women. J Sleep Disord Ther. 2015;4(5):212.

Kisely S, Forbes M, Sawyer E, Black E, Lalloo R. A systematic review of randomized trials for the treatment of burning mouth syndrome. J Psychosom Res. 2016;86:39-46.

Lee CF, Lin KY, Lin MC, Lin CL, Chang SN, Kao CH. Sleep disorders increase the risk of burning mouth syndrome: a retrospective population-based cohort study. Sleep Med. 2014;15(11):1405-10.

Lim JA, Choi SH, Lee WJ, Jang JH, Moon JY, Kim YC, et al. Cognitive-behavioral therapy for patients with chronic pain: Implications of gender differences in empathy. Medicine (Baltimore) 2018;97:e10867.

Lopez-Jornet P, Camacho-Alonso F, Lucero-Berdugo M. Quality of life in patients with burning mouth syndrome. J Oral Pathol Med. 2008;37(7):389-94.

Lopez-Jornet P, Lucero-Berdugo M, Castillo-Felipe C, Zamora Lavella C, Ferrandez-Pujante A, Pons-Fuster A. Assessment of self-reported sleep disturbance and psychological status in patients with burning mouth syndrome. J Eur Acad Dermatol Venereol. 2015;29(7):1285-90.

Lopez-Jornet P, Molino Pagan D, Andujar Mateos P, Rodriguez Agudo C, Pons-Fuster A. Circadian rhythms variation of pain in burning mouth syndrome. Geriatr Gerontol Int. 2015;15(4):490-5.

Martin S, Greenberg M, Glick M, Ship J. Burket's oral medicine. Diagnosis and treatment 11th ed Hamilton: BC Decker. 2008:191-206.

McMillan R, Forssell H, Buchanan JA, Glenny AM, Weldon JC, Zakrzewska JM. Interventions for treating burning mouth syndrome. Cochrane Database Syst Rev. 2016;11(11):CD002779.

Nosratzehi T, Payandeh A, DehYadegari F. The complaints, type, and severity of stressful events in patients with burning mouth syndrome referring to zahedan school of dentistry, Iran. Clin Cosmet Investig Dent. 2020;12:123-30.

Reiter RJ, Rosales-Corral SA, Liu XY, Acuna-Castroviejo D, Escames G, Tan DX. Melatonin in the oral cavity: physiological and pathological implications. J Periodontal Res. 2015;50(1):9-17.

Scala A, Checchi L, Montevecchi M, Marini I, Giamberardino MA. Update on burning mouth syndrome: Overview and patient management. Crit Rev Oral Biol Med 2003;14:275–291.

Simcic D, Pezelj-Ribaric S, Grzic R, Horvat J, Brumini G, Muhvic-Urek M. Detection of salivary interleukin 2 and interleukin 6 in patients with burning mouth syndrome. Mediators Inflamm. 2006;2006(1):54632.

Sun A, Wu KM, Wang YP, Lin HP, Chen HM, Chiang CP. Burning mouth syndrome: a review and update. J Oral Pathol Med. 2013;42(9):649-55.

Varoni EM, Lo Faro AF, Lodi G, Carrassi A, Iriti M, Sardella A. Melatonin treatment in patients with burning mouth syndrome: a triple-blind, placebo-controlled, crossover randomized clinical trial. J Oral Facial Pain Headache. 2018;32(2):178-88.

Vidor LP, Torres IL, Custodio de Souza IC, Fregni F, Caumo W. Analgesic and sedative effects of melatonin in temporomandibular disorders: a double-blind, randomized, parallel-group, placebo-controlled study. J Pain Symptom Manage. 2013;46(3):422-32.

Zurowski D, Nowak L, Machowska A, Wordliczek J, Thor PJ. Exogenous melatonin abolishes mechanical allodynia but not thermal hyperalgesia in neuropathic pain. The role of the opioid system and benzodiazepine-gabaergic mechanism. J Physiol Pharmacol. 2012;63(6):641-7.

Received for publication on 06th November 2021
Accepted for publication on 22nd March 2022