Original Article

Analgesic and Sedative Effects of Melatonin in Temporomandibular Disorders: A Double-Blind, Randomized, Parallel-Group, Placebo-Controlled Study

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Abstract

Context. The association between myofascial temporomandibular disorder (TMD) and nonrestorative sleep supports the investigation of therapies that can modulate the sleep/wake cycle. In this context, melatonin becomes an attractive treatment option for myofascial TMD pain.

Objectives. To investigate the effects of melatonin on pain (primary aim) and sleep (secondary aim) as compared with placebo in a double-blind, randomized, parallel-group trial.

Methods. Thirty-two females, aged 20−40 years, with myofascial TMD pain were randomized into placebo or melatonin (5 mg) treatment groups for a period of four weeks.

Results. There was a significant interaction (time vs. group) for the main outcomes of pain scores as indexed by the visual analogue scale and pressure pain threshold (analysis of variance; $P < 0.05$ for these analyses). Post hoc analysis showed that the treatment reduced pain scores by −44% (95% CI −57%, −26%) compared with placebo, and it also increased the pressure pain threshold by 39% (95% CI 14%, 54%). The use of analgesic doses significantly decreased with time ($P < 0.01$). The daily analgesic doses decreased by −66% (95% CI −94%, −41%) when comparing the two groups. Additionally, melatonin improved sleep quality, but its effect on pain was independent of the effect on sleep quality.

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Conclusion. This study provides additional evidence supporting the analgesic effects of melatonin on pain scores and analgesic consumption in patients with mild-to-moderate chronic myofascial TMD pain. Furthermore, melatonin improves sleep quality but its effect on pain appears to be independent of changes in sleep quality. J Pain Symptom Manage 2013;46:422–432.

Key Words
Melatonin, myofascial pain, temporomandibular pain, clinical trial, pain threshold

Introduction

Approximately 10–15% of the adult population has temporomandibular disorder (TMD).[1] Myofascial TMD pain occurs with pain in the masticatory muscles and tenderness to palpation in approximately 90% of patients.[2,3] More than 50% of patients report sleep disturbance (i.e., difficulty in falling or staying asleep), which is associated with increased clinical pain severity and psychological distress.[4]

Given the association of sleep disturbance with pain in TMD, interventions aimed at sleep regulation have been tested to treat TMD pain. Hypnotics in general are often used to treat sleep disturbances in patients with pain, but they do not provide restorative sleep or reduce the pain.[5] Tricyclic antidepressants are effective at alleviating pain and improving sleep quality,[6] but complaints related to common anticholinergic side effects such as dry mouth, sedation, constipation, and orthostasis[7] are common. Cyclobenzaprine has effects similar to those of tricyclic antidepressants on the improvement of sleep quality and pain, with an additional muscle relaxant effect.[8] However, a meta-analysis found significantly increased rates of drowsiness and dry mouth related to drug dosage in patients taking cyclobenzaprine.[9] In this context, investigation of further sleep-based treatments seems desirable. Therefore, we chose to further investigate the effects of melatonin on TMD pain and sleep quality.

Melatonin interacts with two receptors (MT1 and MT2) at different sites in the brain, and its action on the suprachiasmatic nucleus has been implicated in the initiation and maintenance of sleep.[10] Based on these effects, there were preliminary studies testing the effects of melatonin in some pain syndromes, especially fibromyalgia, which also is highly correlated with dysfunctional sleep patterns. The use of melatonin as a single treatment (3–6 mg) at bedtime[11,12] improved the pain score and sleep parameters in patients with fibromyalgia.[13] In another clinical trial, melatonin at night produced a normal sleep/wake cycle.[14] In addition, experimental studies have demonstrated melatonin's antinociceptive effects on inflammatory and neuropathic pain[15,16] and its ability to elevate pain thresholds.[17]

Given that nonrestorative sleep is commonly cited as a predisposing factor in trigger point formation,[18] the use of melatonin may reduce the influence of this important factor, blocking the cycle of impaired sleep at night, fatigue during the day, and altered pain perceptions.[11,13,19] A previous study showed that patients with fibromyalgia have low melatonin secretion, which could explain the lack of restorative sleep and dysfunctional pain modulation.[20] However, results seem mixed. Korszun et al.[21] showed elevated melatonin secretion, whereas others found no changes in melatonin concentrations.[22] Although this discrepancy can be explained by factors such as sample characteristics, differences related to technique, and time of dosage, use of melatonin to regulate sleep still seems an attractive option because of its involvement in the regulation of circadian rhythms and its sedative, analgesic, anti-inflammatory, and antioxidative effects.[23]

Despite melatonin's initial positive results in pain treatment, its clinical impact on pain has not been sufficiently explored to support its widespread use. To our knowledge, its effect on chronic pain has only been assessed in two randomized clinical trials in fibromyalgia,[13] one trial in functional dyspepsia[24] and one trial to treat irritable bowel syndrome.[25] Accordingly, there is a lack of studies that fully

examine melatonin's effect on pain with other pathophysiological mechanisms and those that explore whether melatonin's effect on pain is dependent on the improvement in a patient's sleep quality.

We aimed to fill this gap in knowledge by testing the hypothesis that melatonin would be more effective than placebo for the treatment of myofascial TMD pain. We also tested whether melatonin would be more effective than placebo in improving sleep quality and whether its effect on sleep would be correlated with pain improvement.

Methods

Design Overview, Setting, and Participants

This study was a randomized, double-blind, two-group parallel clinical trial. It was approved by the Research Ethics Committee at the Hospital de Clínicas de Porto Alegre and was in agreement with Resolution 196/96 of the National Health Council (Broad Research Area in accordance with the Declaration of Helsinki). All patients gave their written informed consent to participate in the study. As this study was an initial Phase II trial, we decided to increase the sample homogeneity and the power of the study by recruiting women aged 19–40 years with myofascial TMD pain in a primary care unit according to the Research Diagnostic Criteria for Temporomandibular Disorders (RDC/TMD) guidelines (Group I—Muscle Disorders).[2] The subjects who met the criteria for TMD diagnosis[2] were examined by the same independent examiner (L. P. V.), who specializes in orofacial pain and has more than 10 years' experience in the pain clinic. The assessment included examination of masticatory muscles and the temporomandibular joint to determine whether the cause of the symptomatology was muscular, joint, or a combination of both. Also, a complete dental evaluation was done to exclude infection of the ear, sinuses, and teeth. In specific cases, dental X-rays and CT scanning were performed to help define the bony detail of the joint, and magnetic resonance imaging was used to analyze soft tissues. The examiner used this information to decide whether a patient could be included in the study. This strategy was used to minimize bias in the diagnosis process. The participant flowchart is shown in Fig. 1.

The exclusion criteria included active dental caries lesions, pulpal lesions, emergency treatment for TMD, osteoarthritis of the temporomandibular joint, rheumatoid arthritis, fibromyalgia, neurologic deficits, history of psychiatric disorder, and/or language difficulties. Those individuals who had a history of

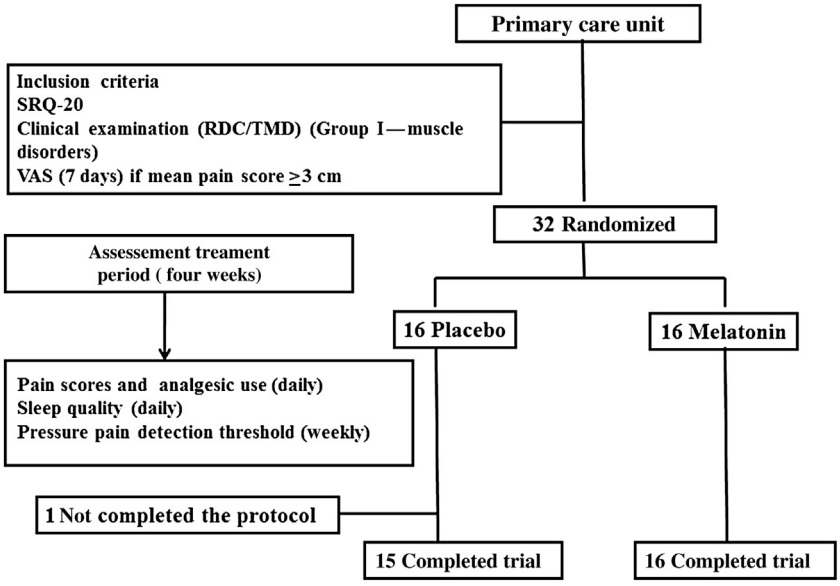

Fig. 1. Flow diagram of study, including the number of patients at each study time point. SRQ = Self-Report Questionnaire; RDC/TMD = Research Diagnostic Criteria for Temporomandibular Disorders; VAS = Visual Analogue Scale.

steroid or anticonvulsant use were excluded. Finally, individuals with one or more of the following group diagnoses according to RDC/TMD guidelines[2] also were excluded: disc displacement (Group II), and arthralgia, osteoarthritis, and osteoarthrosis (Group III).

Clinical Assessment and Diagnosis

Patient history data were collected and the clinical examination was conducted according to RDC/TMD[2,26,27] guidelines, using the Portuguese/Brazil version of this tool. An investigator who had received RDC/TMD calibration training by a "gold standard" examiner made the clinical assessments. The diagnostic criteria for myofascial TMD pain according to the RDC/TMD are the following: pain or aches in the jaw, temples, face, preauricular area, or inside the ear at rest or during function; in addition, pain in response to palpation of three or more of the following muscle sites (the right and left sides are considered as separate sites for each muscle): the posterior temporalis, middle temporalis, anterior temporalis, origin of the masseter, insertion of the masseter, posterior mandibular region, submandibular region, lateral pterygoid area, or tendon of the temporalis; at least one of the painful sites is on the same side as the complaint of pain. Additionally, myofascial pain could be present in conjunction with limited mouth opening, pain-free unassisted mandibular opening of less than 40 mm, or maximum assisted opening (passive stretch) that was 5 mm or more wider than pain-free unassisted opening.

Sample Size Justification

The number of subjects in each study group was determined based on previous clinical trials assessing myofascial pain in jaw muscles.[28] An a priori estimate indicated that a total sample size of 26 individuals divided in two balanced treatment groups ($n = 13$) was required to detect a reduction in pain intensity with melatonin at the minimum of 1.5 cm (average SD = 0.6 cm), with a power of 0.8 and an α-level of 0.05.[29] To account for the multiple outcomes and potential dropouts, we increased the sample size to 16 per group.

Interventions

Over a four-week period (28 days), oral medications were administered at bedtime to the two groups: 5 mg melatonin tablets (Sigma-Aldrich, São Paulo, Brazil, provided batch-by-batch certificates of analysis for authenticating the purity of each batch) or placebo. The tablets were manufactured in such a way that the placebo and active treatment were identical. The dose of 5 mg was chosen based on the positive results of 3 mg used for fibromyalgia[11] and in our previous studies using the 5 mg dose.[23,30]

To measure adherence to medication use, we used the following strategies: 1) a researcher counted the number of tablets consumed each week during the study period, 2) the patients were asked to make a diary entry if they failed to use the medication, and 3) blood samples were collected twice from all of the patients before treatment and two hours after the patient took the medication (5 mg melatonin or placebo). The blood samples were centrifuged in plastic tubes for 10 minutes at $3500 \times g$ at 4°C, and the serum was stored at −80°C for hormone assays. At the end of the study, we checked the amount of serum melatonin in the melatonin-treated samples to assess bioavailability. The mean ± SD of the serum melatonin levels two hours after oral medication consumption in the placebo or melatonin group in the third week of the treatment period were 13.93 ± 3.43 and 3784.03 ± 2251.34 pg/mL, respectively.

The serum melatonin concentration was determined by enzyme-linked immunosorbent assay using commercial kits from MP Biomedicals, Inc., Irvine, CA, which follow the basic principles of competitive immunoassays.[31] The detection limit of this assay was 300 pg/mL.

Randomization

We randomly assigned the patients to one of two groups (melatonin or placebo) using computer-generated numbers. A fixed block size of six was used to ensure that equal numbers of participants were randomized into the two treatment groups. Before the recruitment phase, sealed envelopes containing the allocated treatment were prepared and numbered sequentially. The envelopes were opened sequentially by the pharmacy technician who provided the medications after the subject signed the consent form. During the entire study period, only two investigators who were not involved in patient evaluation were

responsible for randomization. Other individuals involved in patient care were unaware of the treatment group to which each patient belonged.

Instruments and Assessments

All of the psychological tests used in this study were validated for the Brazilian population.[32,34] Two independent medical examiners who were blinded to the group assignments were trained to apply the pain scales and conduct psychological tests. The baseline depressive symptoms of the patients were assessed using the Beck Depression Inventory;[32] sleep quality was assessed using the Pittsburgh Sleep Quality Index.[33] Additionally, anxiety was measured with the refined version of the State-Trait Anxiety Inventory[34] and demographic and medical comorbidity data were collected using a standardized questionnaire. Patients were asked to report side effects using open questions and structured forms, in which changes in mood, sleepiness, dizziness, headache, and allergic reaction were assessed. Any side effects experienced during the study were registered.

Outcomes

The primary outcome was pain, as assessed by the pain score diaries, the amount of analgesics used throughout the treatment period, and the pressure pain threshold (PPT). The secondary outcome was the sleep quality of the patients. Outcomes are described below.

Assessment of Pain and Sleep

1. Pain intensity was measured by a 10 cm VAS.[35] The VAS scores ranged from no pain (zero) to worst possible pain (10 cm). The worst pain in the past 24 hours was recorded daily in the patients' diaries. Subjects were instructed to record pain at the end of each day. To improve patient compliance, an evaluator checked pain records weekly.
2. The analgesic used during the treatment period was acetaminophen 750 mg up to four times per day. In case it was not effective as a rescue analgesic, patients could use ibuprofen 200 mg at maximum of four times per day. If pain persisted, codeine 60 mg was permitted. If codeine was ineffective, patients could use Dorflex® (Sanofi Aventis, São Paulo, Brazil; 35 mg orfenadrine citrate combined with 300 mg dypirone and 50 mg caffeine). These medications could be used at a maximum of four times a day. The analgesics used during the treatment period were monitored from diary entries recording analgesic intake, which were assessed in each treatment session. The total analgesic doses taken after beginning treatment to the end of treatment were considered for the analysis.
3. The anatomic points in the masseter and temporal muscles were localized by digital pressure and then registered in the patient's record. The PPT values were quantified using a Fisher's pressure algometer (Pain Diagnostics and Thermography, Great Neck, NY).[36] The average values of PPT expressed in kilogram-force per square centimeter (kgf/cm^2) of the three successive readings taken at intervals of three to five minutes were used as the outcome. PPT was measured at baseline and once a week during the treatment period.
4. Sleep quality during the study period was assessed daily by the 10 cm VAS quality scale (VASQS). The VASQS scores ranged from worst possible (zero) to best possible (10 cm). Patients answered three questions for the sleep diary using the VASQS in the morning: 1) In general, how did you feel when you woke up?, 2) How does the sleep quality of last night compare to your habitual sleep?, and 3) How well did you sleep last night?

Statistical Analysis

T-tests for independent samples were used to analyze the continuous variables (i.e., the scores on the VAS related to pain and sleep, as well the PPT values), and the categorical variables (i.e., work activity) were examined by Chi-squared or Fisher's exact tests. We averaged the values collected in the pain and sleep diary (daily measurements) and generated a value for each of the four weeks of treatment. After first checking the assumptions of normality for the outcome measures by skewness and kurtosis tests, we conducted a group analysis by running a mixed analysis of variance model in which the independent variables were time, experimental group (melatonin and placebo),

the interaction between time and experimental group, and subject identification. If appropriate, we then performed Bonferroni's test for post hoc multiple comparisons to identify differences between groups at each time point and used a paired *t*-test to assess the effects of the variables on each experimental group. Stepwise multiple linear regression analysis was conducted with the pain scores assessed according to the VAS as the dependent variable and the experimental group (melatonin and placebo) and sleep quality last night as independent variables.

We also calculated the adjusted mean differences, which were defined as the relative changes of the melatonin group compared with the placebo group. This measurement was used to describe the treatment efficacy of the melatonin, which was calculated as the adjusted mean difference divided by the adjusted mean placebo group, expressed as a percentage. The 95% CI and the associated *P*-value also were calculated.[37] We considered all of the randomized patients as part of the analysis using the intention-to-treat method, with the last observation carried forward. The data were analyzed using SPSS version 18.0 (SPSS, Inc., Chicago, IL).

Results

Patient Characteristics

Thirty-two patients were randomized into one of two groups; one patient was subsequently withdrawn (Fig. 1). The reason for trial discontinuation for this patient (in the placebo group) was her dissatisfaction with the treatment effect. The baseline characteristics were similar across the groups of patients assigned to melatonin and placebo groups (all *P*-values > 0.05) (Table 1). We did not observe serixous or moderate side effects with treatment.

Analysis of the Main Outcome: Efficacy for Pain and PPT

The melatonin group had significantly lower pain VAS scores ($P < 0.001$) than the placebo-treated group (Table 2) at the end of treatment. The interaction between time and treatment group was significant ($P = 0.03$) for the VAS scores. The difference between the two treatment groups was significant ($P < 0.001$; Fig. 2). The melatonin-treated group, when compared with the placebo group, demonstrated a mean pain reduction of 44% (Table 2).

Similar to pain VAS scores, the interaction between time and group for PPT was significant ($P < 0.002$). The PPT was significantly higher in patients treated with melatonin ($P < 0.002$). The melatonin-treated group, when compared with the placebo group, had a mean PPT improvement of 39% (Table 2).

The results for the use of analgesics also showed a trend similar to that of the findings for pain outcomes. The use of analgesic doses significantly decreased with time ($P < 0.01$), and there was a trend for the interaction between treatment and time ($P = 0.1$). There

Table 1
Characteristics of the Study Sample ($n = 32$) (ITT)[a]

Variable	Placebo ($n = 16$)	Melatonin ($n = 16$)	*P*-value
Age (yrs)[b]	29.47 ± 5.01	32.27 ± 4.65	0.13
Formal education (yrs)[b]	13.67 ± 3.95	13.47 ± 3.09	0.94
Work activity (yes/no)[c]	11/4	15/1	0.09
Depressive symptoms according to the Beck Inventory[b]	5.80 ± 7.08	6.02 ± 6.48	0.98
Trait anxiety[b]	.26 ± 6.33	26.33 ± 7.90	0.89
State anxiety[b]	26.00 ± 4.45	25.73 ± 5.41	0.88
Pittsburgh Sleep Quality[b]	5.20 ± 3.21	6.87 ± 3.37	0.37
Mean of VAS pain scores at baseline[b]	4.71 ± 2.08	4.68 ± 2.31	0.43
Number of analgesic doses at baseline[b]	0.53 ± 0.21	0.48 ± 0.14	0.42
Pressure pain detection threshold (lb/cm^2)[b]	1.92 ± 0.81	1.89 ± 0.72	0.60
How well did you sleep last night?[b]	4.78 ± 2.15	4.89 ± 2.21	0.29
Sleep quality of the previous night compared with habitual sleep[b]	4.70 ± 1.85	4.87 ± 1.92	0.51
In general, how did you feel when you woke up?[b]	5.41 ± 1.69	5.26 ± 2.03	0.46

ITT = intention to treat.
Values are given as the mean ± SD or frequency.
[a]Intention-to-treat analysis, including all randomized patients; in patients with missing data, was regarded as the last observation carried forward.
[b]*t*-Test to compare means.
[c]Chi-squared or Fisher's exact test to compare frequencies.

Table 2
Treatment Effect on the Outcomes During the Four-Week Treatment Period ($n = 32$) (ITT)[a]

Treatment	Adjusted Mean (SD)	Adjusted Mean Difference (95% CI)[b]	Relative Change % (95% CI)[c]	*P*-value
Primary outcome—pain reported on the Visual Analogue Scale[b]				
Placebo ($n = 16$)	3.80 (2.05)			
Melatonin ($n = 16$)	2.13 (1.82)	−1.67 (−2.20, −0.99)	−44 (−57, −26)	<0.001
Analgesic doses (daily mean)[b]				
Placebo ($n = 16$)	0.32 (0.58)			
Melatonin ($n = 16$)	0.10 (0.36)	−0.21 (−0.30, −0.13)	−66 (−94, −41)	<0.01
Pressure pain detection threshold in lb/cm^2				
Placebo ($n = 16$)	2.28 (2.32)			
Melatonin ($n = 16$)	3.05 (0.77)	0.89 (0.32, 1.24)	39 (14, 54)	<0.002
Secondary outcomes—sleep outcome variables[b]				
How did you feel when you woke up?				
Placebo ($n = 16$)	5.20 (1.89)			
Melatonin ($n = 16$)	7.40 (1.23)	2.18 (1.59, 2.79)	42 (41, 53)	<0.001
Sleep quality of the previous night compared with habitual sleep				
Placebo ($n = 16$)	4.34 (1.62)			
Melatonin ($n = 16$)	7.60 (1.20)	−2.26 (−1.41, −3.12)	52 (32, 72)	<0.001
How well did you sleep last night?				
Placebo ($n = 16$)	5.36 (2.22)			
Melatonin ($n = 16$)	7.69 (1.72)	−2.33 (−1.49, −2.58)	43 (28, 48)	<0.001

ITT = intention to treat; ANOVA = analysis of variance.
Kilogram-force per square centimeter (kgf/cm^2).
[a]ITT analysis, including all randomized patients; in patient with missing data, was regarded as the last observation carried forward.
[b]Mixed ANOVA model. Mean difference groups.
[c]Relative change = adjusted mean difference/adjusted placebo mean × 100%.

was a significant reduction in the analgesic doses for patients receiving melatonin treatment compared with those who were treated with placebo ($P < 0.01$) (Table 2).

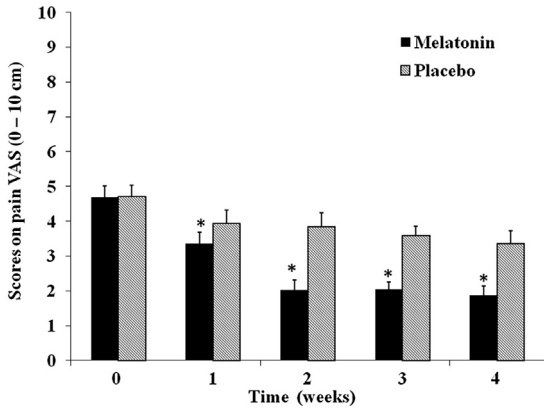

Fig. 2. Mean pain levels (as assessed by VAS) at baseline week (W0), W1, W2, W3, and W4 in the two experimental groups. The error bars indicate standard error of the mean. Asterisks positioned above the bars indicate significant difference ($P < 0.05$) at the time points. Asterisk (*) indicates differences between the placebo and melatonin treatment groups. All comparisons were performed by a mixed analysis of variance model, followed by the Bonferroni test for post hoc multiple comparisons. VAS = Visual Analogue Scale.

Secondary Outcomes: Sleep Quality

There was a significant interaction between time and treatment group ($P < 0.001$) for the VASQS scores (feelings when they woke up). The melatonin-treated individuals showed significantly better sleep quality ($P < 0.001$) than those who were in the placebo group (Table 2). When compared with placebo, the melatonin treatment produced a mean improvement of 42% in how patients felt when they awoke (Table 2).

There was a significant interaction between time and treatment group ($P < 0.001$) for the VASQS scores (sleep quality of previous night; Fig. 3). Melatonin treatment produced significantly better sleep quality ($P < 0.001$) than placebo (Table 2). When compared with placebo, the melatonin-treated group showed a mean improvement of 43%.

Although when compared with placebo, the melatonin group demonstrated a mean improvement of 52% in the VASQS scores for sleep quality of the previous night compared with habitual sleep (Table 2), the changes in scores over time and the interaction were not significant ($P > 0.3$ for these two analyses).

One important issue is whether the improvement in sleep is secondary to pain improvement or whether it is a primary effect of the

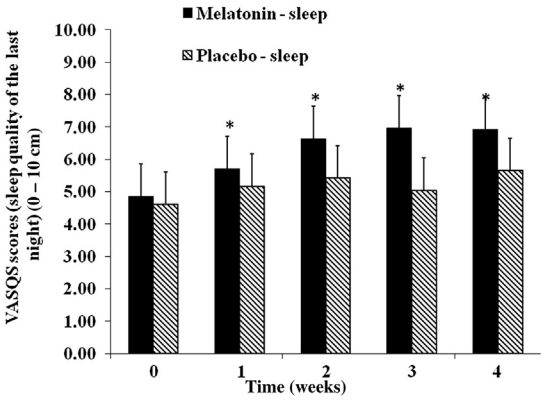

Fig. 3. The mean sleep quality from the previous night (as assessed by VASQS) at baseline week (W0), W1, W2, W3, and W4 in the two experimental groups. The error bars indicate standard error of the mean. Asterisks positioned above the bars indicate significant difference ($P < 0.05$) at the various time points. Asterisk (*) indicates the differences between the placebo and melatonin treatment groups. All comparisons were performed using a mixed analysis of variance model, followed by the Bonferroni test for post hoc multiple comparisons. VASQS = Visual Analogue Sleep Quality Scale.

intervention. To address this important issue, we conducted an additional regression model in which we controlled the improvement in pain for changes in sleep. This model revealed that the effect of group and sleep continued to be significant ($P < 0.001$), suggesting that its variability is dependent on the effects of the treatment group on the main outcome (pain). Additionally, the effect of sleep was not statistically significant when we analyzed the interaction between the intervention and sleep quality changes (Table 3).

Discussion

This study demonstrated that melatonin produces a reduction in overall pain compared with placebo in the treatment of myofascial TMD pain that, besides being statistically significant, can be considered clinically relevant. In addition, it shows that the effect of melatonin on pain is independent of the improvement in sleep quality. This finding suggests that melatonin has a direct effect on pain pathways or on the levels of signaling chemicals that regulate pain. This conclusion is clinically relevant because it suggests that melatonin's clinical use does not need to be restricted to patients with pain and sleep disturbances.

Melatonin's effect on pain is consistent with previous clinical and experimental data.[11,12,17] Although melatonin has been shown to have a positive effect on the sleep/wake cycle in some studies of fibromyalgia, it was not clear whether the compound's effect on pain was secondary to the improvement in sleep quality.[14] The present study corroborates the evidence of previous randomized clinical trials, in which melatonin performed much better than placebo in treating pain from fibromyalgia,[11,13] and it also suggests that melatonin's effect on pain is independent of improvements in sleep quality (Table 3). This finding has a biological plausibility because the antinociceptive effect of melatonin is known to involve the activation of supraspinal sites and the inhibition of "spinal windup.[38]" In addition, experimental evidence suggests that the analgesic effects of melatonin are mediated by opioids[39] and by gamma-aminobutyric acid systems.[40] Moreover, melatonin produces marked

Table 3
Multivariate Linear Regression of the Pain Reported Compared With VAS, Treatment Group, Sleep, and Quality ($n = 32$) (ITT)[a]

Linear Regression Model—Adjusted $R^2 = 0.142$				
Parameter	β	T	*P*	95% CI
Dependent variable: pain reported on the VAS				
Melatonin	−1.34	−7.47	<0.001	−1.78, −0.99
VASQS-sleep quality in the last night	−0.12	−2.19	<0.001	−0.20, 0.04
Interaction	4.48	17.05	<0.001	3.95, 4.97
VAS pain vs. group vs. VASQS-sleep quality in the last night				
VASQS-sleep quality in the last night vs. placebo	−0.24	−4.45	<0.001	−0.35, −0.13
VASQS-sleep quality in the last night vs. melatonin	0.05	0.80	0.42	−0.08, 0.18

VAS = Visual Analogue Scale; ITT = intention to treat; VASQS = Visual Analogue Sleep Quality Scale.
[a]ITT analysis, including all randomized patients; in patient with missing data, was regarded as the last observation carried forward.

anti-inflammatory effects on peripheral sites by inhibiting the release of proinflammatory cytokines.[41]

At least part of our finding may be explained by the involvement of melatonin in regulating circadian rhythms. Accordingly, the use of melatonin may be considered a valuable means for targeting the pathophysiologic mechanism behind TMD. Although melatonin is approved as a sleep aid, it also has a variety of other beneficial effects that may account for its potential role in the treatment of myofascial TMD pain. Obviously, pain relief is a major goal, but the additional treatment of restless sleep and sleep disturbances may lead to a further decrease in the pain threshold.[42] Our findings and the relationship between sleep and pain permit us to propose that melatonin might constitute an additional therapeutic option to treat chronic pain. Obviously, we cannot exclude that melatonin may influence pain via another mechanism, such as sleep improvement; the pain and sleep regulatory mechanisms may influence one another, although this is not a cause-effect relationship. This hypothesis has a neurobiological basis in that there is a reciprocal relationship between the structures associated with the generation and maintenance of sleep and pain modulatory systems.[43]

Although the effects of melatonin treatment on neurotransmitter levels in the central nervous system and/or melatonin rhythm are not completely known, the successful use of melatonin with respect to pain and sleep may be related to the modulation of the sleep/wake cycle,[44] normalization of neurotransmitters, and influence on the hypothalamus-pituitary-adrenal axis.[18] Melatonin's anti-stress properties may influence the hypothalamus-pituitary-adrenal axis, which may account for some of its effects. Additionally, melatonin's benefit could be explained by its effect in reducing the elevation of circulating cytokines,[45] which interrupt the melatonin surge by the pineal gland.[46] This may explain the high prevalence of sleep disorders in patients with chronic pain. Finally, as altered muscle physiology may be a part of the pathophysiology of myofascial pain, the functions of melatonin, in terms of its ability to enhance mitochondrial bioenergetics,[47] may be pertinent to its beneficial effects in TMD patients.

It is important to assess the strengths and limitations of this clinical trial. We conducted this trial according to CONSORT guidelines, and given that we used the Delphi List (a criteria list for quality assessment of randomized controlled trials), our trial can be considered to be of strong quality because all eight items in this list can be positively scored in our randomized controlled trial.[48] Although the homogeneity of this study population is methodologically advantageous, the issue of external validity arises. Thus, additional research with a larger number of patients is needed to more widely assess the potential benefits of melatonin in several different clinical settings, and future studies are required before definitive conclusions regarding melatonin and pain treatment can be made. In addition, before confirmatory Phase III trials are conducted, it is important that other Phase II studies explore the role of different doses of melatonin in TMD pain. In a recent study from our group in healthy subjects (data not published), we tested the melatonin dose-response effect on pain threshold. We found a dose-response effect, supporting the testing of different doses in clinical populations.

This study provides additional evidence supporting the analgesic effects of melatonin on pain scores and analgesic consumption in patients with mild-to-moderate chronic myofascial TMD pain. Furthermore, melatonin improves sleep quality but its effect on pain appears to be independent of changes in sleep quality. Overall, these findings provide preliminary data supporting further testing of melatonin as an additional approach to treat myofascial TMD pain. Further research is necessary to define long-term effects of melatonin use in chronic pain as well as the predictors of response to the analgesic effects of melatonin.

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