Impact of an Oral Appliance on Obstructive Sleep Apnea Severity, Quality of Life, and Biomarkers

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Objective/Hypothesis: To investigate outcomes including efficacy, quality of life, and levels of inflammatory markers of a mandibular advancement device (MAD) for moderate-to-severe obstructive sleep apnea (OSA).

Study Design: Case-control study.

Methods: Patients with apnea-hypopnea index (AHI) ≥15/hr who only accepted MAD therapy (study group) or who refused any treatment (control group) were recruited. At baseline and at 6 months, polysomnography, Epworth Sleepiness Scale (ESS), Functional Outcomes of Sleep Questionnaire (FOSQ), C-reactive protein (CRP), interleukin 1β, interleukin 6, and tumor necrosis factor α (TNF-α) were assessed in both groups.

Results: At baseline, the study group (n = 30) showed a higher percentage of rapid eye movement sleep and higher CRP levels (P < .05) than the control group (n = 10). At 6 months, the MAD significantly improved AHI and lowest oxygen saturation (P < .01), non–rapid eye movement (N)1 and N3 sleep stages (P < .05), ESS score (P < .05), FOSQ total score (P < .01), interleukin 1β (P < .05), and TNF-α (P < .01) compared with the untreated group. In the overall, moderate, and severe OSA groups, 63.3%, 75%, and 50%, respectively, achieved at least good response.

Conclusions: Use of a MAD significantly improved polysomnographic parameters, quality of life, and some inflammatory markers (CRP, IL-β, and TNF-α) in a significant proportion of patients with moderate OSA and in some patients with severe OSA. Hence, a MAD may be a viable alternative therapy in patients with moderate-to-severe OSA who refuse continuous positive airway pressure.

Key Words: Oral appliance, inflammatory markers, quality of life, sleep parameters.

Level of Evidence: 3b.

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INTRODUCTION

Hypoxemia/hypercapnia and fragmented sleep, as well as the exaggerated fluctuations in heart rhythm, blood pressure, and intrathoracic pressure, characteristic of untreated obstructive sleep apnea (OSA), can lead to sequelae such as cardiovascular morbidity and mortality, metabolic morbidity, neurocognitive impairment, and poorer quality of life, an increased risk for motor vehicle accidents, and systemic inflammation, with higher serum levels of proinflammatory cytokines such as tumor necrosis factor α (TNF-α), interleukin 1β (IL-1β), interleukin 6 (IL-6), and C-reactive protein (CRP).

For patients who are intolerant of continuous positive airway pressure (CPAP), currently considered as the first-line treatment for OSA, particularly in moderate-to-severe cases, other therapies include surgery, oral appliances (OAs), and sleep position training. The American Academy of Sleep Medicine (AASM) recommends OAs as the first-line therapy for mild-to-moderate OSA and as salvage therapy for severe OSA.

The most common type of OA currently used for OSA treatment is the mandibular advancement device (MAD), and a custom-made device is preferred. Studies on the efficacy of OAs for moderate-to-severe OSA are scarce, and in many instances did not analyze their effects on sleep structure and quality of life. There have also been few reports on inflammatory markers in OSA patients treated with OAs. To our knowledge, only two have been published. Against this background, the aim of this study was to analyze the neurophysiological and respiratory parameters of sleep, quality of life, and levels of some inflammatory markers in patients with moderate-to-severe OSA treated with a MAD versus untreated patients.

MATERIALS AND METHODS

Study Design and Sample Size Calculation

In patients with apnea-hypopnea index (AHI) ≥15/hr, a case-control study on the efficacy of a MAD versus no treatment was designed. This study was conducted between January 2015 and December 2016 and was approved by the hospital’s...
research consent before participating in the study.

For the study group, sample estimation was based on the efficacy of a MAD in moderate-to-severe OSA. Treatment is considered effective if, with a MAD in place, a 50% reduction of the initial AHI and a final AHI <10 are achieved. We expected that the treatment would be effective in at least 50% of patients, but we believed that 25% efficacy would be interesting given the moderate or severe nature of the OSA.27,28

To study the rate of treatment efficacy, a bilateral binomial test and the associated confidence interval were used. Using a significance of \( z = 0.05 \), if the efficacy is 50%, with a sample size of \( n = 30 \), a power of 82% is obtained to reject the null hypothesis that the efficacy percentage is only 25%.

Regarding the control group, we believed that we could recruit 10 patients during this time interval, although it could be difficult because patients with moderate or severe sleep apnea/hypopnea syndrome may refuse some specific treatments but not all.

**Setting and Patients**

Patients aged 18 years or older with moderate-to-severe OSA (AHI \( \geq 15/hr \)) who refused even to try CPAP treatment were referred from the Department of Pulmonary Medicine to the Otorhinolaryngology Department at the Clinical University Hospital of Valencia for surgery or MAD treatment. To examine the treatment benefits, the patients were divided into two groups, those with and without treatment. Some patients opted for the MAD treatment (study group), whereas others rejected any type of treatment (control group). It is not uncommon to see patients, even those with severe obstructive sleep apnea syndrome and symptoms, who reject any treatment for various reasons, including low disease severity perception, the opinion that being connected to a medical device is unacceptable, self-esteem in terms of their relationship with a partner, patient impression that sleepiness is due to overwork, early awakening or shift work, invasive nature of the treatment (surgery), and the economic cost of OAs. In a recent publication,29 nearly half (46%) of all patients with diagnosed OSA were not being actively treated for this condition. The groups were matched by age, sex, body mass index (BMI), and AHI.

The exclusion criteria for both groups were: severe somatic or psychiatric disease, severe respiratory or cardiovascular disease, pregnancy, acute or chronic inflammatory disease, and BMI \( \geq 32kg/m^2 \). Additional exclusion criteria for the study group were less than eight healthy teeth in the arch, periodontal disease, and temporomandibular dysfunction.

**Oral Appliance**

The MAD used in this study was a custom-made, acrylic, adjustable, two-piece device (Aditas, Asturias, Spain) (Fig. 1). Maxillary and mandibular impressions and an occlusal protrusive wax index using a George Gauge instrument (Great Lakes Orthodontics, Ltd., Tonawanda, NY) were taken.30 After taking the impressions, two separable acrylic resin splints were manufactured and connected by means of a platen, frontally positioned, which allows limited movements with a 5-mm vertical opening in front and protrusion and lateral displacements of the mandible, but no retraction. The laboratory also provides a series of platens that can be unscrewed by the clinician and exchanged with another platen, providing more or less advancement. Initially, the mandibular position of the MAD was preset at 50% of maximal protrusion. Afterward, its position was advanced by 0.5 to 1 mm every 1 to 2 weeks until patients were either satisfied with their symptoms or could not tolerate increased discomfort.

**Outcome Measures**

**Protocol.** In both groups, we assessed at baseline and at 6 months the polysomnographic outcomes, daytime sleepiness, quality of life, and inflammatory markers CRP, IL-1β, IL-6, and TNF-α.

**Sleep assessment.** Standardized polysomnography (PSG) was performed using a Life Lines Portable Device, Track-it model (Lifelines Neurodiagnostic Systems, Inc., Troy, IL), with reading software Polysmith 5.0 (Nihon Kohden Corp., Tokyo, Japan), and scored according to AASM criteria.31 We assessed the AHI per hour and lowest oxygen saturation (LSAT), as well as the percentage of sleep stages (non-rapid eye movement [N1, N2, N3], and rapid eye movement [REM]). OSA was defined as mild (AHI \( 5-14/hr \)), moderate (AHI \( 15-29/hr \)), or severe (AHI \( \geq 30/hr \)).

**Daytime sleepiness and quality of life assessment.** Daytime sleepiness was assessed with the Epworth Sleepiness Scale (ESS), a reliable, validated, self-administered questionnaire.32 ESS >10 indicates daytime sleepiness.32 Sleep-related quality of life was evaluated with the Functional Outcome of Sleep Questionnaire (FOSQ), a 30-item instrument that measures the effect of excessive daytime sleepiness on activities of daily living.33 Unlike with most questionnaires, a low score indicates more pathology than a high score.

**Inflammatory marker assessment.** By means of peripheral venous blood analysis, the levels of CRP, IL-1β, IL-6, and TNF-α were determined in the biochemistry laboratory using the high-sensitivity kit HSTCMAG-28SK-03 from Merck Chemicals and Life Science, S.A. (Madrid, Spain).

Fasting venous blood samples were collected between 8 AM and 10 AM in two different periods: before treatment and 6 months later. The blood samples were immediately sent to the Laboratory of Biochemistry of the Clinical University Hospital of Valencia, where they were frozen and preserved for 2 years.

**Treatment Outcomes and MAD Compliance**

For the purpose of comparison with previously published studies in patients with moderate-to-severe OSA,26,28,34–43 a complete response was defined as post-treatment AHI <5/hr, good response as post-treatment AHI <10/hr but \( >5/hr \), and treatment failure as ongoing AHI \( \geq 10/hr \). However, we were stricter and added ESS \( \leq 10 \) to the concepts of complete and good response and ESS \( >10 \) to the concept of treatment failure. Criteria for compliance or regular use of a MAD were defined as using the appliance for \( \geq 5 \) hours every night on \( \geq 5 \) nights a week, similar to CPAP therapy.21,44
### TABLE I.
Baseline Demographic, Clinical, and Polysomnographic Characteristics of the Study Group and Control Group.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Study Group (n = 30)</th>
<th>Control Group (n = 10)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>54.8 ± 10.1</td>
<td>55.7 ± 7.1</td>
<td>.7</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>19/11</td>
<td>5/5</td>
<td>.4</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27.8 ± 1.7</td>
<td>27.8 ± 1.7</td>
<td>.6</td>
</tr>
<tr>
<td>Neck circumference (cm)</td>
<td>41.7 ± 1.2</td>
<td>41.4 ± 1.2</td>
<td>.9</td>
</tr>
<tr>
<td>ESS (0–24)</td>
<td>10.1 ± 3.6</td>
<td>10.2 ± 1.5</td>
<td>.9</td>
</tr>
<tr>
<td>FOSQ total score</td>
<td>16.7 ± 0.2</td>
<td>16.5 ± 0.2</td>
<td>.3</td>
</tr>
<tr>
<td>General productivity</td>
<td>3.5 ± 0.5</td>
<td>3.3 ± 0.5</td>
<td>.7</td>
</tr>
<tr>
<td>Social outcome</td>
<td>3.7 ± 0.5</td>
<td>3.4 ± 0.5</td>
<td>.7</td>
</tr>
<tr>
<td>Activity level</td>
<td>3.2 ± 0.4</td>
<td>3.5 ± 0.5</td>
<td>.6</td>
</tr>
<tr>
<td>Vigilance</td>
<td>3.2 ± 0.5</td>
<td>3.1 ± 0.3</td>
<td>.8</td>
</tr>
<tr>
<td>Intimate relationships</td>
<td>3.1 ± 0.6</td>
<td>3.2 ± 0.6</td>
<td>.9</td>
</tr>
<tr>
<td>AHI/hr</td>
<td>28.7 (22–29.5)</td>
<td>24 (23–31.6)</td>
<td>.4</td>
</tr>
<tr>
<td>LSAT (%)</td>
<td>79 (78–80)</td>
<td>78 (78–78.8)</td>
<td>.2</td>
</tr>
<tr>
<td>Stage N1 (%)</td>
<td>18 (18–19)</td>
<td>19 (16.5–19.8)</td>
<td>.3</td>
</tr>
<tr>
<td>Stage N2 (%)</td>
<td>56.5 (55.3–58)</td>
<td>56.5 (54.3–57.8)</td>
<td>.6</td>
</tr>
<tr>
<td>Stage N3 (%)</td>
<td>14 (8–11.8)</td>
<td>9 (8–10)</td>
<td>.8</td>
</tr>
<tr>
<td>REM (%)</td>
<td>16 (12.3–16.8)</td>
<td>13 (13–13.8)</td>
<td>.03</td>
</tr>
</tbody>
</table>

Continuous variables are described as mean ± SD or as median (interquartile range) according to whether they have a normal or a non-normal distribution, respectively.

AHI = apnea-hypopnea index; BMI = body mass index; ESS = Epworth Sleepiness Scale; F = female; FOSQ = Functional Outcome of Sleep Questionnaire; LSAT = lowest oxygen desaturation; M = male; N = non-rapid eye movement; REM = rapid eye movement; SD = standard deviation.

### Statistical Analysis

Statistical analysis was performed using SPSS 11.5 for Windows (IBM, Armonk, NY). Continuous variables were described as mean ± standard deviation for variables with a normal distribution and median with interquartile ranges for variables with a non-normal distribution. Normality of the distribution was assessed using the Shapiro-Wilk test. Continuous variables were compared using parametric or nonparametric tests according to whether or not they had a normal distribution, respectively. Thus, we used parametric tests (unpaired and paired t test) to analyze demographic, ESS, and FOSQ data, and nonparametric tests (Mann-Whitney U test and Wilcoxon signed rank test) to analyze both the PSG results and the concentration of inflammatory markers. When performing the statistical analysis, we took into account the variables of comorbidity and the changes that can occur in BMI throughout the study. We considered P < .05 statistically significant.

### RESULTS

Five of 35 patients (study group) initially enrolled were excluded from the final analysis because of noncompliance (n = 3) and side effects of the MAD (n = 2). In the control group, all 10 subjects completed the study. In total, the protocol was completed by 30 patients in the study group and 10 subjects in the control group. At baseline, the control group showed a lower percentage of REM sleep (P < .05) (Table I) and higher levels of CRP (P < .05) (Table II).

At the last follow-up, the BMI of both groups had not changed significantly from baseline (27.6 ± 1.5 vs. 27.8 ± 1.7, P = .6, for study group; and 28.7 ± 1.8 vs. 29 ± 7.3, P = .9, for control group). The second PSG with the MAD in situ was performed at 24 weeks (24–29 weeks). Baseline PSG showed that 16 patients in the study group had moderate OSA (53.3%) and 14 had severe OSA (46.6%), and that six patients in the control group had moderate OSA (60%) and four had severe OSA (40%).

The MAD showed an overall effectiveness of 63.3%. Complete response was achieved in seven patients (23.3%) and good response in 12 (40%). Treatment failure occurred in 11 patients (36.6%). In moderate OSA, the MAD was effective in 12 patients (75%); six patients (37.5%) achieved complete response and six (37.5%) good response. Treatment failure occurred in four patients (25%). In severe OSA, the MAD was effective in seven patients (50%); one patient (7.1%) showed complete response and six (42.9%) good response. Treatment failure occurred in seven patients (50%).

### Polysomnographic Outcomes

At 6 months, the MAD significantly improved AHI and LSAT (P < .01), as well as N1 and N3 sleep stages (P < .05) in the study group, whereas in the control group there were no significant differences. In moderate

### TABLE II.
Baseline Concentrations of Inflammatory Markers in the Control Group and Study Group.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Study Group (n = 30)</th>
<th>Control Group (n = 10)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP (mg/L)</td>
<td>1.5 (0.9–2.3)</td>
<td>2.1 (1.3–2.5)</td>
<td>.03</td>
</tr>
<tr>
<td>IL-1β (pg/mL)</td>
<td>0.9 (0.4–1.5)</td>
<td>0.9 (0.5–3)</td>
<td>.5</td>
</tr>
<tr>
<td>IL-6 (pg/mL)</td>
<td>7.1 (2.9–13.1)</td>
<td>10.7 (6.3–16.1)</td>
<td>.4</td>
</tr>
<tr>
<td>TNF-α (pg/mL)</td>
<td>11.3 (3.7–12.6)</td>
<td>13.2 (12.2–15.1)</td>
<td>.2</td>
</tr>
</tbody>
</table>

Data are presented as median (interquartile range).

CRP = C-reactive protein; IL-1β = interleukin 1β; IL-6 = interleukin 6; TNF-α = tumor necrosis factor α.
Inflammatory Markers Outcomes

Daytime Sleepiness and Quality-of-Life Outcomes

Inflammatory Markers Outcomes

DISCUSSION

Effect of the MAD on Polysomnographic Variables

Currently, there are still insufficient data to suggest that the MAD is an effective treatment for patients with moderate-to-severe OSA. Several studies reported that the MAD significantly improves AHI and LSAT, as well as sleep structure, particularly slow-wave sleep, in patients with moderate OSA and in some with severe OSA.

Comparison of MAD outcomes for OSA involves some difficulties for several reasons. First, at present, there is no universal agreement on a definition of successful treatment with a MAD for OSA. Treatment successes are variously expressed as an AHI < 5 or < 10, or by a 50% AHI reduction from baseline. However, we believe that success criteria should be more ambitious, including improving both AHI and symptoms. Thus, within the concept of response, we have added a final AHI < 10/hr and ESS ≤ 10.

Second, various patient factors have been associated with treatment outcome, including less severe disease as well as supine-predominant OSA, younger age, female gender, lower BMI, and neck circumference, and craniofacial features assessed by lateral cephalometry, including shorter soft palate length, lower hyoid bone position, greater angle between the cranial base and mandibular plane, and a retrognathic mandible. Because in most studies on moderate-to-severe OSA treatment, patients were overweight or obese on average, with mean BMI ranging from 28 kg/m² to 33 kg/m², and less obesity (lower BMI and neck circumference) has been suggested as an indicator of treatment success in several studies. We used a BMI less than 32 as an exclusion criterion in both groups.

Third, a systematic review comparing adjustable with fixed devices or custom-made devices with prefabricated ones showed that in both cases the former were more effective. Finally, there is a notable disparity with respect to some variables such as the time of follow-up, type of

<table>
<thead>
<tr>
<th>Variables</th>
<th>Control Group (n = 10)</th>
<th>Study Group (n = 30)</th>
<th>Moderate OSA (n = 16)</th>
<th>Severe OSA (n = 14)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline 6 Months</td>
<td>Baseline 6 Months</td>
<td>Baseline 6 Months</td>
<td>Baseline 6 Months</td>
</tr>
<tr>
<td>AHI (h)</td>
<td>24 (23–31.6)</td>
<td>28.7 (22–29.5)</td>
<td>24.7 (23.4–26)</td>
<td>31.4 (31.1–32.1)</td>
</tr>
<tr>
<td>LSAT (%)</td>
<td>78 (78.8–77.8)</td>
<td>79 (78–80)</td>
<td>80 (79–80.3)</td>
<td>78 (77–78.8)</td>
</tr>
<tr>
<td>Stage N1 (%)</td>
<td>19 (16.5–19.8)</td>
<td>18 (18–19)</td>
<td>18 (17–18)*</td>
<td>18 (17–18)*</td>
</tr>
<tr>
<td>Stage N2 (%)</td>
<td>56.5 (54.3–57.8)</td>
<td>56.5 (55.3–58)</td>
<td>55.5 (55–58.3)</td>
<td>56 (55.5–56)</td>
</tr>
<tr>
<td>Stage N3 (%)</td>
<td>9 (8–10)</td>
<td>9 (8–11.8)</td>
<td>9 (7–12)</td>
<td>9 (6–9)</td>
</tr>
<tr>
<td>REM (%)</td>
<td>13 (13–13.8)</td>
<td>14 (12.3–16.8)</td>
<td>14 (12.8–17)</td>
<td>16 (12.3–15.5)</td>
</tr>
</tbody>
</table>

Data are presented as median (interquartile range).

*No significant difference.

P < .01.

P < .001.

P < .05.

OSA, the MAD significantly improved the AHI (P < .001), LSAT (P < .01), and percentages of N1 and N3 stages (P < .05). In severe OSA, there were significant improvements in AHI and LSAT (P < .05), but not in sleep structure (Table III).

Daytime Sleepiness and Quality-of-Life Outcomes

At 6 months, the MAD significantly improved ESS (P < .05), general productivity, activity level, and vigilance (P < .01), and total FOSQ score (P < .05), whereas in the untreated group there were no significant changes. The MAD significantly improved ESS score in both moderate and severe OSA (P < .001 and P < .05, respectively). In moderate OSA, there were significant improvements for general productivity (P < .001), activity level (P < .001), vigilance (P < .001), intimate relationships (P < .05), and total FOSQ score (P < .05) at 6 months, whereas in severe OSA only vigilance showed significant improvement (P < .05) (Table IV).

Inflammatory Markers Outcomes

At 6 months, the MAD significantly improved IL-1β (P < .05) and TNF-α (P < .01) levels, whereas in the untreated group there were no significant changes. In moderate OSA, the MAD significantly improved CRP and IL-1β (P < .05) as well as TNF-α (P < .01). However, in severe OSA, the MAD only significantly improved TNF-α (P < .05) (Table V).

DISCUSSION

Effect of the MAD on Polysomnographic Variables

Currently, there are still insufficient data to suggest that the MAD is an effective treatment for patients with moderate-to-severe OSA. Several studies reported that the MAD significantly improves AHI and LSAT, as well as sleep structure, particularly slow-wave sleep, in patients with moderate OSA and in some with severe OSA.

Comparison of MAD outcomes for OSA involves some difficulties for several reasons. First, at present, there is no universal agreement on a definition of successful treatment with a MAD for OSA. Treatment successes are variously expressed as an AHI < 5 or < 10, or by a 50% AHI reduction from baseline. However, we believe that success criteria should be more ambitious, including improving both AHI and symptoms. Thus, within the concept of response, we have added a final AHI < 10/hr and ESS ≤ 10.

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Third, a systematic review comparing adjustable with fixed devices or custom-made devices with prefabricated ones showed that in both cases the former were more effective.

Finally, there is a notable disparity with respect to some variables such as the time of follow-up, type of
TABLE IV.
Data on Daytime Sleepiness and Quality of Life of the Control Group and Study Group at 6 Months Versus Baseline

<table>
<thead>
<tr>
<th>Variables</th>
<th>Control Group (n = 10)</th>
<th>Study Group (n = 30)</th>
<th>Moderate OSA (n = 16)</th>
<th>Severe OSA (n = 14)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline 6 Months</td>
<td>Baseline 6 Months</td>
<td>Baseline 6 Months</td>
<td>Baseline 6 Months</td>
</tr>
<tr>
<td>ESS</td>
<td>10.2 ± 1.5</td>
<td>10.6 ± 2.2*</td>
<td>10.1 ± 3.6</td>
<td>8.5 ± 3.6†</td>
</tr>
<tr>
<td>General productivity</td>
<td>3.3 ± 0.5</td>
<td>3.3 ± 0.7*</td>
<td>3.5 ± 0.5</td>
<td>3.8 ± 0.6§</td>
</tr>
<tr>
<td>Social outcome</td>
<td>3.4 ± 0.7</td>
<td>3.5 ± 0.8*</td>
<td>3.7 ± 0.5</td>
<td>3.6 ± 0.5*</td>
</tr>
<tr>
<td>Activity level</td>
<td>3.5 ± 0.5</td>
<td>3.2 ± 0.9*</td>
<td>3.2 ± 0.4</td>
<td>3.8 ± 0.5§</td>
</tr>
<tr>
<td>Vigilance</td>
<td>3.1 ± 0.3</td>
<td>2.9 ± 0.3*</td>
<td>3.2 ± 0.5</td>
<td>3.6 ± 0.8§</td>
</tr>
<tr>
<td>Intimate relationships</td>
<td>3.2 ± 0.6</td>
<td>3.4 ± 0.5*</td>
<td>3.1 ± 0.6</td>
<td>3.3 ± 0.5*</td>
</tr>
<tr>
<td>FOSQ total score</td>
<td>16.5 ± 0.2</td>
<td>16.3 ± 0.1*</td>
<td>16.7 ± 0.2</td>
<td>18.1 ± 0.1†</td>
</tr>
</tbody>
</table>

Data are presented as mean ± SD.
*No significant difference.
†P < .05.
‡P < .005.
§P < .01.

ESS = Epworth Sleepiness Scale; FOSQ = Functional Outcome of Sleep Questionnaire; OSA = obstructive sleep apnea; SD = standard deviation.

PSG, respiratory variables measured, and the time interval between the diagnostic and with-appliance PSG. We have considered all of these factors when comparing our results with other studies in moderate to severe OSA patients.

Our results are similar to those of other studies,28,34,36–39,42,52 although there are authors who have reported worse results than ours,35,37,39,40 perhaps because the sample size, BMI, and AHI were higher in these studies, and because of a certain degree of retrognathia in some patients. Better results than ours have been shown in other studies,26,41,43,53 although there are authors who have reported worse results than ours,35,37,39,40 perhaps because the sample size, BMI, and AHI were higher in these studies, and because of a certain degree of retrogna-thia in some patients. Better results than ours have been shown in other studies,26,41,43,53 in our opinion due to a shorter follow-up, irregular use of a MAD, a larger sample, and inclusion of mild OSA in these studies.

Effect of a MAD on Daytime Sleepiness and Quality of Life

In our study, both patients with moderate OSA and those with severe OSA showed significant improvements in ESS scores. Several studies have shown no difference between a MAD and CPAP treatments in reducing ESS scores in moderate-to-severe OSA patients,41,54 although Engleman et al.55 showed that ESS scores were better with CPAP compared with a MAD even in mild OSA patients.

In most studies, a MAD significantly improved ESS scores in patients with moderate-to-severe OSA,34,36–39,42,43,53,54 although it should be noted that some of these studies included mild OSA. Our results on the impact of a MAD on the quality of life of patients with moderate-to-severe OSA are similar to those of other studies. In a randomized controlled trial, Phillips et al.41 found that both CPAP and a MAD similarly improved sleepiness, driving simulator performance, and disease-specific quality of life, although a MAD was superior to CPAP for improving four general quality-of-life domains (FOSQ). Banhiran et al.43 showed that global FOSQ scores and most of the subscale scores increased after MAD treatment. However, half of the patients had mild OSA.

A MAD had a significant beneficial effect on the vitality domain of 36-item Short Form Health Survey in a randomized placebo-controlled trial by Petri et al.38 In
addition, Blanco et al. showed that total FOSQ score significantly improved after 3 months of MAD treatment.

**Effect of a MAD on Levels of Inflammatory Markers**

Although the exact mechanism is unknown, both sleep deprivation and hypoxemia are believed to be important causative factors that could lead to chronic systemic inflammation and increased levels of cytokines in OSA patients. which could accelerate the development of atherosclerosis. A recent meta-analysis showed significant improvements in CRP and TNF-α levels and a general trend of decreasing IL-6 levels with CPAP therapy. Some studies, however, showed that CPAP therapy does not alter the levels of inflammatory markers. According to a few studies, OSA surgery significantly reduces CRP levels, as well as TNF-α and IL-6.

However, to our knowledge, there are only two studies on inflammatory markers in OSA patients treated with a MAD. One showed a significant reduction in IL-1β, among other inflammatory markers. The other showed a significant reduction in CRP after a minimum of 30 days of treatment with a custom-made MAD. However, unlike our study, both studies included patients with mild OSA.

Our study has some limitations. First, the size of the current study was small; however, the subjects were representative of patients with moderate-to-severe OSA. Second, the follow-up period was short, and it is possible that regular use of a MAD diminishes over time, although it is well known that its compliance is greater than that of CPAP. The main reasons for noncompliance with a MAD were discomfort and perception of little or no benefit. OAs and CPAP treatment are comparatively effective at improving health outcomes, even in more severe OSA, presumably due to greater overall use of OAs compared with CPAP. Objective data show that less than half of CPAP users met criteria of regular use defined as ≥4 hours per night for at least 70% of the days monitored. However, although several studies have shown relatively good short-term adherence to OAs exceeding that of CPAP, these data essentially remain limited to patient self-reports.

In a prospective clinical trial, Vanderveken et al. showed that the overall objective mean rate of OA use was 6.6 ± 1.3 hours per day with a regular OA users’ rate of 82% at the 3-month follow-up. Third, a statistically significant association does not always mean a cause–effect relationship, particularly when the samples are small. Further studies are thus needed to assess the efficacy of a MAD in moderate-to-severe OSA with larger samples and a longer follow-up.

**CONCLUSION**

In this controlled trial, we found that a MAD significantly improved neurophysiological and respiratory sleep parameters, quality of life, and some inflammatory markers such as CRP, IL-1β, and TNF-α in more than 50% of patients with moderate-to-severe OSA. Hence, it is suggested that a MAD may be a viable alternative to CPAP in a significant proportion of patients with OSA, including some with moderate or severe OSA.

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