Efficacy of Oral Appliance Therapy as a First-Line Treatment for Moderate or Severe Obstructive Sleep Apnea: A Korean Prospective Multicenter Observational Study

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Background and Purpose Responses to oral appliances (OAs) in obstructive sleep apnea (OSA) vary, and have not been fully evaluated in Korean patients. In this study we aimed to determine the efficacy of OAs for the first-line treatment of Korean patients with moderate or severe OSA.

Methods This multicenter prospective observational study included 45 patients with moderate or severe OSA that had been newly diagnosed between March 2017 and May 2018 and who underwent OA treatment for 1 month. Questionnaires were completed and polysomnography (PSG) was performed before and after OA treatment. The primary outcome measures were improvement in the absolute apnea-hypopnea index (AHI) and the percentage reduction in the AHI. The secondary outcomes were improvements in the questionnaire scores related to sleep-associated symptoms and PSG parameters.

Results The patients were aged 47.4 ± 12.1 years (mean ± SD), only two of them were female, and their AHI at baseline was 29.7 ± 10.9/h. After OA treatment the AHI had reduced by 63.9 ± 25.8%, with the reduction was similar between the patients with moderate OSA and those with severe OSA. Overall 31.1% of the patients achieved a normal AHI (<5/h), and 64.4% had an AHI of ≤10/h after the treatment. The body mass index (BMI) was the most reliable factor for predicting the percentage reduction in the AHI. The OAs also improved the sleep architecture and subjective sleep-related symptoms.

Conclusions The OAs were effective in patients with moderate or severe OSA. The OAs reduced the mean AHI to 63.9% of the baseline value, and this reduction was influenced by the BMI.

Key Words oral appliance, obstructive sleep apnea, treatment, apnea, hypopnea.

INTRODUCTION

Patients with moderate or severe obstructive sleep apnea (OSA) are prone to cardiovascular and metabolic comorbidities, and so they should receive treatment. Although continuous positive airway pressure (CPAP) is a treatment mainstay for moderate and severe OSA, oral appliance (OA) therapy can be a useful alternative option. An OA is a device that advances the mandible in order to reduce the collapsibility of the upper airway, which will improve OSA in most patients. OAs are generally recommended for patients with mild or moderate OSA and those who are intolerant of or refuse CPAP therapy. Some studies have found that OAs may even be useful for treating severe-OSA patients.

There is only weak evidence for the use of OA treatment as a first-line therapy in Korean patients with moderate or severe OSA. Asian patients with OSA generally have a lower
body mass index (BMI), smaller mandibles, and more-collapsible airways. Nonanatomical pathophysiological factors such as the arousal threshold, muscle responsiveness, and ventilatory control instability have also been suggested to be less important in Asians. Therefore, the influence of race on OA treatment outcomes needs to be clarified. A few retrospective Korean studies found that the rates of successful OA treatment in patients with moderate OSA and those with severe OSA were 71–82% and 70–75%, respectively. One prospective study performed in Thailand included a subset of these patients, and found success rates of 55% and 75% in individuals with moderate OSA and those with severe OSA, respectively.

Since the responses to OA treatment vary, careful patient selection is crucial for achieving treatment success in clinical practice. Previous studies have applied various cutoff criteria to indicate successful treatment, such as a follow-up apnea-hypopnea index (AHI) of <5/h or <10/h. Researchers have reported that being younger and having a lower BMI, smaller neck circumference, lower baseline AHI, and positional OSA are predictors of a good outcome, but these assertions have not been consistent across studies. These variable outcomes might be due to OSA being a heterogeneous disorder. Many factors contribute to OSA, including upper airway anatomical abnormalities, airway dilator muscle dysfunction, an increased loop gain, and a decreased arousal threshold. OAs improve the anatomy of the upper airway by decreasing its collapsibility, but they appear to have no effect on muscle function, loop gain, or the arousal threshold. The responses to OAs may be greatly affected by nonanatomical characteristics of OSA. We hypothesized that OAs can ameliorate the portion of the AHI that is affected by anatomical factors. Therefore, we evaluated factors that are associated with the percentage reduction in the AHI rather than the cutoff criteria of the AHI.

In this multicenter prospective observational study we evaluated the efficacy of OA treatment in Korean patients with moderate or severe OSA. We evaluated the objective and subjective efficacies at 1 month after treatment initiation, and determined the clinical predictors of the percentage reductions in the AHI.

**METHODS**

**Patients**

This multicenter prospective observational study was performed in three sleep centers in South Korea (Kyung Hee University Hospital at Gangdong, Keimyung University Dongsan Medical Center, and Soonchunhyang University Hospital Cheonan). Patients who underwent overnight polysomnography (PSG) and were newly diagnosed with moderate or severe OSA between March 2017 and May 2018 were considered for inclusion. Moderate OSA was defined as an AHI of 15–29.9/h, and severe OSA was defined as an AHI ≥30/h. The exclusion criteria were 1) OA contraindications (periodontal disease, insufficient teeth, or temporomandibular joint dysfunction), 2) predominantly central sleep apnea, and 3) significant pulmonary or cardiac disease. This study was approved by the Institutional Review Board of each center (IRB No. Kyung Hee University Hospital at Gangdong: 2017-02-046, Soonchunhyang University Dongsan Medical Center: 2017-02-046, Soonchunhyang University Hospital Cheonan: 2017-03-027), and written informed consent to participate was obtained from all of the enrolled patients.

**Procedures**

At baseline we obtained medical histories, performed physical examinations, collected self-reported questionnaires, and gathered overnight PSG data. PSG was performed using a digital polygraph system (Grass-Telefactor twin version 2.6, West Warwick, RI, USA) according to standard protocols. Airflow was measured using both an oronasal thermal sensor and a nasal pressure sensor. The data were manually scored according to version 2.2 of the Manual for the Scoring of Sleep and Associated Events published by American Academy of Sleep Medicine. The patients who met the inclusion criteria received a customized two-piece OA (SomnoDent, SomnoMed, Sydney, Australia). The treatment protocol for the OA was identical in all centers: the OA was incrementally titrated to the maximum comfortable limit over an acclimatization period lasting 4–6 weeks, and the results were confirmed by a qualified dentist. The degree of mandibular advancement was set by the dentist according to the maximum comfortable (or tolerable) limit for each patient. The patients were followed up 1 month after the completion of OA titration, and the questionnaires and PSG were repeated. Compliance during OA treatment was determined objectively after 1 month using a temperature-sensitive microsensor (Dentitrac, Braebon, Ontario, Canada) embedded in the upper right side of the OA device.

**Questionnaires**

Questionnaires were completed by the participants prior to each PSG session. Sleep-related symptoms were evaluated using the Korean version of the Pittsburgh Sleep Quality Index (PSQI), the Epworth Sleepiness Scale (ESS), and the Insomnia Severity Index (SI). The PSQI measures the quality and patterns of sleep over a 4-week period, the ESS is an eight-item self-reported questionnaire that evaluates the level of daytime sleepiness, and the ISI is a seven-item questionnaire that mea-
asures insomnia as perceived by the patient. Depression was evaluated using Beck Depression Inventory-II (BDI-II), which includes 21 multiple-choice questions, each of which is scored from 0 to 3 points.

**Outcomes**
The primary outcomes were the improvement in the AHI after the treatment, as quantified by the absolute change and the percentage reduction. The improvement was classified into the following three groups according to the 1-month follow-up: AHI: 1) <5/h, 2) <10/h, and 3) >50% reduction. The secondary outcomes were the improvement in sleep architecture and the improvements in questionnaire scores evaluating sleep, depression, and OA compliance.

**Statistical analysis**
All analyses were performed on the intention-to-treat principle, with dropouts and missing values excluded from the analysis. Continuous data were tested for conformity to a normal distribution using the Kolmogorov-Smirnov test, and are presented as mean±SD values. Continuous data were compared using the t-test or Mann-Whitney U-test as appropriate, and the chi-square test was used to analyze categorical data. We used the paired t-test or Wilcoxon signed-rank test to evaluate changes from baseline to 1 month after treatment titration. An initial linear regression was applied to identify factors associated with the percentage change in AHI, and the results are expressed as Pearson correlation coefficients. A multivariate regression model was then developed using stepwise selection, with age and the p-value criterion for inclusion in the model set at <0.10. The criterion for statistical significance was set at p<0.05. All statistical comparisons were performed with SPSS (version 22.0, Armonk, NY, USA).

**RESULTS**

**Clinical features and demographics**
Fifty patients (25 with moderate OSA and 25 with severe OSA) were considered for enrollment, of which three patients were excluded for the following reasons: 2 had dental problems and 1 withdrew consent. Two further patients (1 with moderate OSA and 1 with severe OSA) were lost during the 1-month follow-up, and so the remaining 45 patients (AHI=15.0±49.0/h; 21 with moderate OSA and 24 with severe OSA) were included in the analysis (Supplementary Fig. 1 in the online-only Data Supplement). They were aged 47.4±12.1 years, and only two of them were female. Their BMI was 26.8±3.3 kg/m², and 15.6% of the patients were obese (BMI ≥30 kg/m²), with one patient being morbidly obese (BMI ≥35 kg/m²). Their neck circumference was 39.1±2.5 cm, which was similar between the patients with moderate OSA and those with severe OSA. The mean OA compliance rate (the percentage of days on which the OA was worn for more than 4 h) was 63.4±28.4%, which was higher in the severe-OSA patients than in the moderate-OSA patients (72.8±24.6% vs. 52.7±29.2%, p=0.018); however, the average daily usage time was similar between the two groups (Table 1).

**Primary outcomes (changes in respiratory indices)**
The overall mean percentage reduction in the AHI was 63.9±25.8% (range=40.0–99.4%), which was similar between the patients with moderate OSA and those with severe OSA. The AHI decreased from 29.8±11.0/h to 11.6±10.7/h, the apnea index decreased from 10.5±10.4/h to 1.6±2.7/h, and the hypopnea index decreased from 18.6±9.9/h to 9.0±7.7/h 1 month after OA therapy compared with the same parameters at baseline (all p<0.001) (Fig. 1, Table 2).

The patients with moderate or severe OSA included 31.1% with a normal AHI and 64.4% with an AHI of <10/h at the 1-month follow-up. The proportion of patients who had an AHI of <10/h at the follow-up was higher among those with moderate OSA (81.0% vs. 50.0%, p=0.03). However, the proportion of patients with a normal AHI at the follow-up was similar between the two groups. Three-quarters of the patients exhibited a >50% reduction in the AHI (Table 2).

| Total (n=45) | Moderate OSA (n=21) | Severe OSA (n=24) | p |
|-------------|---------------------|-------------------|---|
| Age, years  | 47.4±12.1           | 44.6±13.4         | 49.8±10.4 | 0.159 |
| Sex, male   | 43 (95.6)           | 20 (95.2)         | 23 (95.8) | 0.923 |
| Height, cm  | 170.6±7.8           | 172.0±7.5         | 169.3±7.9 | 0.253 |
| Weight, kg  | 77.9±11.2           | 79.6±11.5         | 76.5±10.9 | 0.357 |
| BMI, kg/m²  | 26.8±3.3            | 26.8±2.9          | 26.7±3.8 | 0.871 |
| BMI ≥30 kg/m² | 7 (15.6)          | 3 (14.3)          | 4 (16.7) | 0.826 |
| Neck circumference, cm | 39.1±2.5         | 39.5±2.3          | 38.7±2.7 | 0.298 |
| SBP, mm Hg  | 129.9±16.0          | 129.0±16.8        | 130.8±15.5 | 0.72 |
| DBP, mm Hg  | 81.6±14.9           | 80.4±14.3         | 82.7±15.6 | 0.612 |
| HTN         | 11 (24.4)           | 5 (23.8)          | 6 (25.0) | 0.826 |
| DM          | 4 (8.9)             | 1 (4.8)           | 3 (12.5) | 0.363 |
| HL          | 5 (11.1)            | 1 (4.8)           | 4 (16.7) | 0.205 |
| CVD         | 4 (8.9)             | 2 (9.5)           | 2 (8.3) | 0.889 |
| OA compliance*, % | 63.4±28.4     | 52.7±29.2         | 72.8±24.6 | 0.018 |
| OA use, h/day | 6.3±1.2           | 6.1±1.3           | 6.5±1.0 | 0.253 |

Data are mean±SD or n (% values).
*Percentage of days that OA worn for >4 h.
BMI: body mass index; CVD: cardiovascular disease; DBP: diastolic blood pressure; DM: diabetes mellitus; HL: hyperlipidemia; HTN: hypertension; OA: oral appliance; OSA: obstructive sleep apnea; SBP: systolic blood pressure.
Table 2. Respiratory outcome after 1 month of OA therapy

|                       | Total (n=45) | Moderate OSA (n=21) | Severe OSA (n=24) | p   |
|-----------------------|--------------|---------------------|-------------------|-----|
| 1-month F/U AHI <5/h | 14 (31.1)    | 9 (42.9)            | 5 (20.8)          | 0.111 |
| 1-month F/U AHI <10/h| 29 (64.4)    | 17 (81.0)           | 12 (50.0)         | 0.030 |
| Reduction in AHI, /h | 19.0±11.1    | 11.1±6.0            | 25.9±10.0         | <0.001 |
| Reduction in AI, /h  | 8.9±10.3     | 3.1±4.6             | 13.9±11.4         | <0.001 |
| Reduction in HI, /h  | 9.6±8.5      | 8.0±6.8             | 11.0±9.7          | 0.245 |
| Reduction, %         | 63.9±25.8    | 59.8±29.5           | 67.4±22.0         | 0.340 |
| >50% reduction in AHI| 34 (75.6)    | 16 (76.2)           | 18 (75.0)         | 0.685 |

Data are mean±SD or n (%) values.
AHI: apnea-hypopnea index, AI: apnea index, F/U: follow-up, HI: hypopnea index, OSA: obstructive sleep apnea.

Secondary outcomes (questionnaire scores and PSG results)
Some of the PSQI, ESS, ISI, and BDI-II scores improved significantly after 1 month of OA treatment. The ESS and BDI-II scores improved only in the patients with moderate OSA. The treatment increased the proportions of time spent in sleep stages N1 and N3, and also the minimum oxygen saturation, and decreased the incidence of wake after sleep onset (WASO) and the arousal index. The changes in WASO and the minimum oxygen saturation were significant only in the severe-OSA patients. All of the respiratory indices decreased, but the proportion of hypopnea in the AHI increased after the treatment (Table 3 and Supplementary Table 1 in the online-only Data Supplement).

Clinical factors associated with the AHI percentage reduction
In the initial linear regression analysis, the percentage reduction in the AHI was negatively correlated with the BMI ($r=-0.368, p=0.013$) and positively correlated with the apnea index ($r=0.336, p=0.024$). The percentage reduction in the AHI tended to be negatively correlated with the proportion of time spent in REM sleep ($r=-0.265, p=0.079$) and the hypopnea index ($r=-0.259, p=0.085$), and tended to be positively correlated with the arousal index ($r=0.273, p=0.070$).

Stepwise multivariate linear regression analysis revealed an independent negative correlation between the BMI and the percentage reduction in the AHI ($\beta=-0.368, p=0.013$) (Table 4, Fig. 2).

DISCUSSION
This study found OA treatment to be an effective first-line therapy in Korean patients with moderate or severe OSA. The
The overall percentage reduction in the AHI was $63.9 \pm 25.8\%$, and was similar between patients with moderate OSA and those with severe OSA. The baseline BMI was the best predictive factor for the reduction. Approximately one-third (31.1%) of the patients had a normal AHI of <5/h at 1 month after the initiation of OA therapy, while around two-thirds (64.4%) had an AHI of <10/h. The treatment not only ameliorated respiratory symptoms during sleep but also improved the sleep quality and depression level.

This study evaluated the effect of OAs as a first-line treatment in Korean patients with moderate or severe OSA. The cohorts in previous retrospective and prospective studies only included some patients with moderate OSA (30–60%) or severe OSA (6–57%). One study evaluated the effect of OA treatment in 34 Chinese patients with severe OSA who refused CPAP therapy. Most of the patients enrolled in the present study were males, who are known to respond less to OSA treatment, and most of them were not obese (BMI <30 kg/m$^2$), which is known to be associated with a better response. However, the proportions of patients with AHIs of <5/h or <10/h at the follow-up were similar to those in previous studies. The objectively measured percentage of days with good adherence (i.e., the percentage of days on which the OA was worn for >4 h) was $63.4 \pm 28.4\%$, and the duration of OA use was $6.3 \pm 1.2$ h/day, which is similar to the results of previous studies.

The present patients with severe OSA benefited from the OA treatment. Half of the patients had an AHI of <10/h, and 20% had a normal AHI after the treatment. The OA improved not only the respiratory indices of the participants but also

### Table 4. Results of univariate and multivariate linear regression analyses

|                      | Univariate | Multivariate stepwise regression |
|----------------------|------------|---------------------------------|
|                      | $r$       | $p$          | $\beta$ | $p$ |
| Age, years           | -0.178    | 0.242        | -0.165  | 0.249 |
| BMI, kg/m$^2$        | -0.368    | 0.013        | -0.368  | 0.013 |
| Neck circumference, cm | -0.064   | 0.677        |         |     |
| OA compliance, %     | 0.128     | 0.403        |         |     |
| OA use, h/day        | 0.138     | 0.367        |         |     |
| Polysomnography      |           |              |         |     |
| TST, minutes         | -0.062    | 0.686        |         |     |
| N1 sleep, %          | 0.069     | 0.651        |         |     |
| N2 sleep, %          | -0.112    | 0.464        |         |     |
| N3 sleep, %          | 0.161     | 0.292        |         |     |
| REM sleep, %         | -0.265    | 0.079        | -0.135  | 0.393 |
| WASO                 | -0.018    | 0.907        |         |     |
| Sleep efficacy       | -0.018    | 0.906        |         |     |
| Arousal index        | 0.273     | 0.070        | 0.166   | 0.275 |
| Sleep latency        | 0.131     | 0.389        |         |     |
| REM sleep latency    | 0.050     | 0.745        |         |     |
| AHI                  | 0.017     | 0.909        |         |     |
| AI                   | 0.336     | 0.024        | 0.220   | 0.160 |
| HI                   | -0.259    | 0.085        | -0.108  | 0.511 |
| Hypopnea, %          | -0.249    | 0.099        | -0.106  | 0.510 |
| Min sat, %           | 0.125     | 0.414        |         |     |

AHI: apnea-hypopnea index, AI: apnea index, BMI: body mass index, HI: hypopnea index, Min sat: minimum oxygen saturation, OA: oral appliance, TST: total sleep time, WASO: wake after sleep onset.

![Fig. 2. Correlations of the percentage reduction in the AHI with the baseline AHI (A) and BMI (B). AHI: apnea-hypopnea index, BMI: body mass index.](image-url)
their sleep architecture and subjective sleep-related symptoms. OAs are known to improve subjective daytime sleepiness, but contradictory results have also been reported. The subjective sleep quality and insomnia improved in both the patients with moderate OSA and those with severe OSA, but daytime sleepiness and the depression level improved only in those with moderate OSA. Patients with severe OSA had more frequent arousal and a lower minimum oxygen saturation during sleep, which could have led to this discrepancy.

We hypothesized that OAs can improve the part of the AHI associated with anatomical factors. The overall reduction in the AHI after OA treatment in our study was 63.9±25.8%, which was similar between patients with different severities of OSA. The percentage reduction in the AHI after OA treatment was reported previously in small studies or in specific OSA types. One study found that the reduction after OA therapy in seven patients ranged from 98.1% to 100%. A reduction of 62.6±7.5% was found during non-REM sleep, with a median reduction of 13.4% during REM sleep. Reductions of 74.69±16.92% and 46.03±36.44% were found in patients with positional and nonpositional OSA, respectively. OAs can improve airway collapsibility, but they do not affect muscle function, loop gain, or the arousal threshold. The heterogeneity in the results obtained might therefore be attributable to the various pathophysiological characteristics underlying OSA, such as increased loop gain and a decreased arousal threshold.

The BMI and apnea index were associated with the percentage reduction in the AHI in this study. Most previous studies have used different criteria to assess treatment success, including various cutoff values, and naturally a lower baseline AHI will be predictive of a good response. The baseline apnea index—but not the AHI—was associated with the AHI percentage reduction in this study. Apnea and hypopnea episodes have different mechanisms, with the former representing the absence of flow due to a static obstruction and the latter representing flow limitations due to a dynamic obstruction. Anatomical changes produced by OAs might affect static obstructions more than dynamic obstructions, thus explaining the increased proportion of hypopnea episodes after OA treatment.

The strongest predictive factor for the AHI percentage reduction was the BMI. Most studies have found the BMI to be a predictor of a poor response to OA therapy. A previous review showed that the BMI has large negative predictive value along with CPAP pressure and cephalometry measures. However, some studies performed in Western countries have found that age, the baseline AHI, and cephalometric measures were more significant predictors than the BMI. The BMI might be more important for predicting OA treatment responses in Koreans. Higher BMIs are associated with fat deposition, which can narrow pharyngeal wall diameters and increase upper airway collapsibility. Higher BMIs can also increase the loop gain, which is an independent predictor of a poor response to OA therapy, and the arousal threshold, which is not changed when using an OA. Moreover, a high BMI can cause pharyngeal dilator muscle dysfunction and reduce the respiratory functional residual volume. Our results support the idea that a higher BMI can contribute to OSA in more ways than only via affecting the anatomy of the upper airway.

This was the first prospective study of Korean patients with moderate or severe OSA, but the treatment period was only one month, which might have been too short to provide a full evaluation of the compliance and treatment effects. Moreover, the sample was of modest size and predominantly consisted of males, which limits the generalizability of our findings. Moreover, we did not consider cephalometric measures, sleeping position, or REM predominance, which can be important predictors of OA treatment responses.

In conclusion, this study found that OA therapy was effective for patients with either moderate or severe OSA. OA therapy improved not only respiratory indices but also subjective and objective sleep indices. The OAs reduced the mean AHI to 63.9% of the baseline value, and the percentage reduction was lower in patients with higher BMIs. It can therefore be predicted that the follow-up AHI after OA therapy in patients with moderate or severe OSA will be one-third of their baseline AHI, with some variation according to the BMI. Future larger studies are required to confirm the efficacy of OA therapy, treatment predictors for patients with moderate or severe OSA, and the influence of race on outcomes.

**Supplementary Materials**
The online-only Data Supplement is available with this article at [https://doi.org/10.3988/jcnen.2020.16.2.215](https://doi.org/10.3988/jcnen.2020.16.2.215).

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Conflicts of Interest
The authors have no potential conflicts of interest to disclose.

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