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Treatment Outcomes of Mandibular Advancement Devices in Mild, Moderate, and Severe Obstructive Sleep Apnea: A Preliminary Study

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Purpose: Mandibular advancement devices (MAD) are known to be insufficiently effective in all patients with obstructive sleep apnea (OSA). This study aimed to compare the treatment outcomes of MAD therapy according to OSA severity and to investigate the risk factors for the lack of response to MAD therapy.

Methods: A total of 29 patients diagnosed with OSA received an adjustable two-piece MAD treatment. Sleep parameters measured with the home sleep apnea test device, including apnea-hypopnea index (AHI) and oxygen saturation (SpO_2), and daytime sleepiness using the Epworth Sleepiness Scale (ESS) were retrospectively assessed both before and after the MAD treatment.

Results: The patients were classified into three groups according to AHI severity: mild (n=16, AHI<15), moderate (n=6, 15≤AHI<30), and severe OSA (n=7, AHI≥30). MAD therapy significantly improved the sleep parameters ($p<0.001$ for AHI and $p=0.004$ for minimum SpO_2) and daytime sleepiness ($p<0.001$ for ESS). Furthermore, successful outcomes (reduction in AHI>50% and AHI<10 events/h) were achieved in 83.3% and 71.4% of moderate and severe OSA cases, respectively. Of 13 patients with moderate and severe OSA, 10 were classified as responders and 3 as non-responders. The non-responders had significantly lower baseline value of SpO_2 ($p=0.049$ for average SpO_2 and $p=0.007$ for minimum SpO_2) and higher baseline AHI ($p=0.049$) than the responders.

Conclusions: The results of the present study suggest that MAD is effective in the majority of patients with OSA of varying severities. The success of MAD therapy does not seem to depend solely on AHI severity. In addition to AHI, minimum SpO_2 may be a prognostic measure of the efficacy of MAD treatment in clinical dental practice.

Keywords: Appliance; Efficacy; Hypoxia; Mandibular advancement; Obstructive; Sleep apnea syndromes

INTRODUCTION

Obstructive sleep apnea (OSA) is one of the most common respiratory disorders. It is characterized by apnea and hypopnea caused by repeated collapse of the upper airway during sleep. OSA can result in numerous medical sequelae, including cardiovascular and neurocognitive consequences [1].

Continuous positive airway pressure (CPAP) is the primary treatment for most patients with OSA owing to its higher efficacy, regardless of the OSA severity, compared with other treatment options, which range from conservative approaches to invasive interventions. Surgery is reserved for selected patients with anatomical limitations [2]. Although the use of mandibular advancement devices (MAD), an oral appliance (OA) that protrudes the mandible while keeping

the airway open and improving pharyngeal collapsibility, is currently viewed as a second-line treatment option in the "one-size-fits-all" paradigm [2,3], awareness of their clinical benefits is increasing as a result of high patient acceptance, low adherence to CPAP, and the challenges associated with surgical therapy [4,5]. Based on a 2018 systemic review comparing the various treatment outcomes of CPAP and MAD, the superior efficacy of CPAP does not necessarily lead to better health outcomes in clinical settings [4].

The American Academy of Sleep Medicine currently recommends diagnosing and managing patients with OSA based on a single metric, the apnea–hypopnea index (AHI). In the present paradigm, the use of MAD is limited to patients with mild and moderate OSA and patients with severe OSA who refused to receive CPAP [2]. Previous studies and case reports suggested that MAD is effective in some patients with severe OSA and is the preferred treatment for patients with OSA of varying severities [6-9]. However, some patients may not respond favorably to this treatment [10]. A previous study demonstrated that the outcomes of MAD therapy are less predictable than those of CPAP [11]. The lower predictability of MAD therapy than CPAP may be attributed to the complex pathophysiology of OSA, including high loop gain, arousal threshold, and airway dilator muscle activity in addition to pharyngeal collapsibility. This is because while MAD improves pharyngeal collapsibility, it leaves other factors unchanged [12]. As a result, studies aimed at efficiently identifying patients who are likely to benefit from MAD therapy to improve its efficacy and personalized medicine have been increasing.

This study investigated the treatment outcomes of MAD therapy in patients with OSA of varying severities. In particular, we sought to identify the predictors of response to MAD therapy based on clinical and sleep parameters. It was hypothesized that the outcomes of MAD therapy vary depending on the OSA severity.

MATERIALS AND METHODS

1. Subjects

Consecutive patients who complained of snoring and who were referred for OA therapy due to low adherence to CPAP during sleep were screened at the Department of Orofacial Pain and Oral Medicine, Dankook University Dental Hospital, from 2012 to 2020. Patients who completed OA titration after being diagnosed with OSA by a home sleep apnea test (HSAT) and patients diagnosed with mild OSA by laboratory polysomnography (lab-PSG) were included despite having AHI<5 in the HSAT.

The inclusion criteria for the subjects were an AHI of 5 or greater in the HSAT or lab-PSG, completion of the HSAT before and after MAD treatment, sufficient teeth to support MAD therapy in each arm, and no ongoing neurological disorders, jaw limitation, or pain due to temporomandibular disorders (TMD). The exclusion criterion was the lack of full titration due to noncompliance, TMD, or dental treatment during MAD therapy. Demographic data (age, sex, height, weight, and neck circumference) were collected as part of the initial clinical assessment during the first visit. Body mass index (BMI) was calculated from the patients' weight and height. The study was approved by the Institutional Review Board of Dankook University Dental Hospital (IRB No. DKUDH IRB 2020-04-004) and conducted in accordance with the principles of the Declaration of Helsinki. Furthermore, informed consent was obtained from the patients.

2. Oral Appliance and Treatment Procedure

Two types of custom-made, two-piece, adjustable MAD were used in this study. One was an anteriorly adjustable MAD device (Dr.Prevent Co.) [13], and the other was SomnoDent (SomnoMed Limited, Australia). The bite registration at a comfortable protrusion, approximately 50%-60% of the maximum protrusion with a minimum of 3-mm interarch space, was fabricated as an initial amount of protrusion. The device was advanced 0.5 to 1 mm with each titration until subjective symptoms (self-reported or witnessed snoring, fatigue, daytime sleepiness, headache) resolved. For optimal titration, HSAT was conducted when self-reported symptoms improved. Titration was continued until maximum comfortable protrusion was achieved. The patients were followed up monthly for 6 months and, after confirmation of good compliance with the MAD, at 6 months and 1 year. The protrusion ratio was calculated as the ratio of the amount of protrusion to the maximum amount of protrusion.

3. Epworth Sleepiness Scale (ESS) for Subjective Assessment

The ESS, a self-administered questionnaire with eight questions, was administered at the time of both the pre- and post-treatment visits [14]. The higher the ESS score, the more severe the patient's subjective sleepiness in daily life.

4. Home Sleep Apnea Test for Objective Assessment

Four sleep variables were selected and assessed at baseline and after the final titration of MAD therapy using an unattended HSAT device, ApneaLink (ResMed Ltd.): AHI, respiratory disturbance index (RDI), average oxygen saturation (average SpO_2), and minimum oxygen saturation (minimum SpO_2). OSA severity was evaluated using the AHI, and treatment outcomes were determined based on the success criteria that AHI should show a 50% improvement and be lower than 10.

5. Statistical Analysis

The sleep parameter-related data used for statistical analysis was based on HSAT data. Descriptive data were expressed as mean and standard deviation (SD) or median and interquartile range (IQR). The subjects were classified into three groups to compare the MAD therapy outcomes based on the OSA severity: mild (5≤AHI<15), moderate (15≤AHI<30), and severe (AHI≥30). The Wilcoxon signed-rank test was conducted to compare the sleep parameters and ESS scores of the three groups before and after MAD therapy.

The Kruskal–Wallis test was used to compare quantitative data derived from anthropometric data, sleep parameters, and ESS scores among the groups. Based on the success criteria of MAD therapy (reduction in AHI of more than 50% with an AHI of <10 events/h), patients with moderate and severe OSA were further classified into non-responders and responders. The Mann–Whitney U test was used to compare the treatment outcomes of the responders and non-responders. If there were significant factors resulting in different treatment outcomes for MAD therapy, Cohen's d effect sizes were calculated to compare the responders and non-responders in terms of these factors. Statistical calculations were performed using IBM SPSS Statistics for Windows, Version 23.0 (IBM Co.). Probability levels of $p<0.05$ were considered significant.

RESULTS

Among the 47 patients who received MAD therapy, 11 refused to participate in the study, and 3 did not undergo HSAT following OA therapy. During follow-up, two patients did not visit the hospital and two patients discontinued MAD therapy while undergoing dental prosthesis replacement. Therefore, only 29 patients were included in the study, of whom 10 were treated with an anteriorly adjustable MAD device and 19 with SomnoDent. Subjective preferences between the two appliances have not been reported.

As presented in Table 1, the mean (SD) age of the patients was 41.1 (15.4) years, and majority of them were men (82.7%). For all patients, the mean (SD) BMI and neck circumference were 25.5 (2.9) and 39.4 (1.7), respectively. Of the 29 patients, 7 were diagnosed with severe OSA (AHI≥30) and 6 with moderate OSA (15≤AHI<30). Sixteen patients were diagnosed with mild OSA (AHI<15) based on HSAT or lab-PSG data. The median protrusion ratio of all patients

Table 1. Demographic and physical characteristics of the enrolled subjects (n=29)

Demographics	Mean±standard deviation	Median (interquartile range)	KS test
Sex (n)			
Male	24		
Female	5		
Age (y)	41.1±15.4	40.0 (25.0-54.0)	0.059
BMI (kg/m^2)	25.5±2.9	25.4 (22.8-27.7)	0.200
Neck circumference (cm)	39.4±1.7	39.2 (38.0-41.0)	0.166

KS, Kolmogorov-Smirnov; BMI, body mass index.
Values are presented as number only, mean±standard deviation, or median (interquartile range).
Normality was tested using the Kolmogorov-Smirnov test.

was 77.8% (IQR, 75.0-83.3). Protrusion ratio (%) was not statistically different among three groups (p=0.252, Mann–Whitney U test).

Table 2 and Fig. 1 present the treatment outcomes, including four objective sleep parameters and a subjective measure of daytime sleepiness, both before and after MAD therapy for all patients and subgroups based on the OSA severity. Except for the average SpO_2, all sleep-related variables exhibited statistically significant improvements (p<0.001 for AHI, RDI, and ESS and p=0.004 for minimum SpO_2). In patients with severe OSA, subgroup analyses revealed that all sleep-related parameters exhibited statistically significant improvements after MAD therapy (p=0.018 for AHI from 49.0 to 9.0, p=0.018 for RDI from 53.0 to

Table 2. Comparisons of MAD outcomes on respiratory parameters and daytime sleepiness

Subjects	Parameters	Before MAD	After MAD	p-value
All subjects (n=29)	AHI (events/h)	10.0 (3.5-31.5)	2.6 (1.0-6.65)	<0.001
	RDI (events/h)	12.0 (7.0-31.5)	5.1 (3.6-10.4)	<0.001
	Average SpO_2 (%)	95.0 (92.5-96.0)	94.8±2.1	0.817
	Minimum SpO_2 (%)	84.2±6.7	88.5±3.6	0.004
	ESS	9.0±3.3	5.8±2.6	<0.001
Mild OSA (n=16)	AHI (events/h)	4.5 (0.4-5.9)	1.4 (0.3-2.9)	0.142
AHI<15	RDI (events/h)	8.0 (4.0-10.6)	3.6 (3.2-6.9)	0.046
	Average SpO_2 (%)	95.0 (94.0-96.0)	95.5 (95.0-96.7)	0.054
	Minimum SpO_2 (%)	89.0 (85.5-91.0)	89.0 (87.0-92.0)	1.000
	ESS	7.5 (6.0-9.7)	5.0 (3.0-7.7)	0.006
Moderate OSA (n=6)	AHI (events/h)	23.2 (15.0-27.0)	5 (1.4-7.7)	0.027
15≤AHI<30	RDI (events/h)	25.7 (19.0-29.2)	7.5 (5.5-10.0)	0.027
	Average SpO_2 (%)	96.3 (93.7-97.0)	96.5 (94.7-97.0)	0.102
	Minimum SpO_2 (%)	81.5 (79.0-84.2)	91.0 (89.0-93.3)	0.027
	ESS	12.0 (10.5-13.0)	5.5 (5.0-9.2)	0.039
Severe OSA (n=7)	AHI (events/h)	49.0 (35.1-55.0)	9.0 (3.0-15.0)	0.018
AHI≥30	RDI (events/h)	53.0 (48.0-58.0)	13.0 (5.0-18.3)	0.018
	Average SpO_2 (%)	91.0 (90.0-95.0)	95.0 (92.0-97.0)	0.024
	Minimum SpO_2 (%)	79.0 (72.0-83.0)	87.0 (84.0-89.0)	0.018
	ESS	11.0 (10.0-14.0)	7.0 (3.0-8.0)	0.017

MAD, mandibular advancement devices; OSA, obstructive sleep apnea; AHI, apnea-hypopnea index; RDI, respiratory disturbance index; SpO_2, oxygen saturation; ESS, Epworth Sleepiness Scale.
Values are presented as median (interquartile range) or mean±standard deviation.
The p-value was determined by the Wilcoxon signed-rank test.

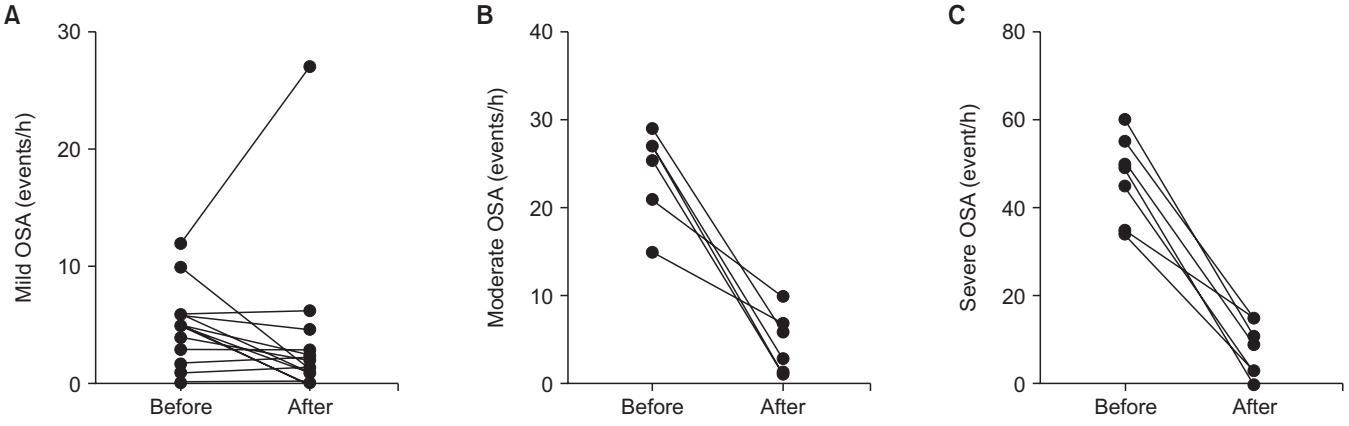

Fig. 1. Comparison of MAD therapy outcomes by AHI severity. (A) AHI<15 (n=16), AHI reduction ≥50.0% (n=5, 62.5%), and AHI<10 (n=7, 87.5%). (B) 15≤AHI<30 (n=6), AHI reduction ≥50.0% (n=6, 100.0%), and AHI<10 (n=5, 83.3%). (C) AHI≥30 (n=7), AHI reduction ≥50.0% (n=7, 100.0%), and AHI<10 (n=5, 71.4%). MAD, mandibular advancement devices; AHI, apnea-hypopnea index; OSA, obstructive sleep apnea.

13.0, p=0.024 for average SpO_2 from 91.0 to 95.0, p=0.018 for minimum SpO_2 from 79.0 to 87.0, p=0.017 for ESS from 11.0 to 7.0).

In patients with moderate OSA who received MAD therapy, significant differences were observed in sleep parameters (p=0.027 for AHI from 23.2 to 5.0, p=0.027 for RDI from 25.7 to 7.5, p=0.027 for minimum SpO_2 from 81.5 to 91.0, p=0.039 for ESS from 12.0 to 5.5), except for average SpO_2 (p=0.102). Compared with moderate and severe OSA cases, mild OSA cases did not exhibit significant differences in AHI and minimum SpO_2, but there were significant improvements in RDI (p=0.046) and ESS (p=0.006).

Table 3 presents a comparison of the clinical characteristics and outcomes of MAD therapy based on the OSA severity. The sex ratio and mean neck circumference did not differ among the three groups (p=0.276 and p=0.134, respectively). However, patients with mild OSA had a comparatively lower mean age than those with moderate and severe OSA (p=0.004). Patients with severe OSA had the highest mean BMI among the three groups, but the difference was not statistically significant (p=0.073). Before MAD therapy, the AHI (p<0.001), RDI (p<0.001), and ESS (p=0.006) increased in the order of mild, moderate, and severe OSA. The average (p=0.038) and minimum SpO_2 (p=0.001) levels decreased in the order of mild, moderate, and severe OSA. The severe OSA group had the highest decrease in the AHI and RDI and increase in the average and minimum SpO_2 levels among the groups; it also had a median (IQR) residual AHI after MAD therapy of 9 (3.0-15.0), which was higher than those of mild and moderate OSA groups (p=0.045). The severe OSA group had a median (IQR) residual minimum SpO_2 of 87.0 (84.0-89.0), which was not significantly lower than those of the mild and moderate OSA groups (p=0.092). No significant difference was observed in the median ESS

Table 3. Comparison of clinical characteristics and outcomes of MAD therapy by OSA severity (n=29)

Parameters	Mild OSA	Moderate OSA	Severe OSA	p-value
Demographics				
Sex (male, female)	13, 3	4, 2	7, 0	0.276
Age (y)	29.5 (20-46)	58.0 (49.7-63.2)	53.0 (39.0-58.0)	0.004
BMI (m/kg^2)	25.0 (22.6-27.6)	23.2 (21.5-24.9)	26.7 (26.3-28.7)	0.073
NC (cm)	39.0 (37.2-40.7)	39.2 (38.5-41.2)	40.0 (40.0-42.0)	0.134
Before MAD				
AHI (events/h)	4.5 (0.4-5.9)	23.2 (15.0-27.0)	49.0 (35.1-55.0)	<0.001
RDI (events/h)	8.0 (4.0-10.6)	25.7 (19.0-29.2)	53.0 (48.0-58.0)	<0.001
Average SpO_2 (%)	95.5 (95.0-96.7)	96.3 (93.7-97.0)	91.0 (90.5-95.5)	0.038
Minimum SpO_2 (%)	89.0 (85.5-91.0)	81.5 (79.0-84.2)	79.0 (72.0-83.0)	0.001
ESS	7.5 (6.0-9.7)	12.0 (10.5-13.0)	11.0 (10.0-14.0)	0.006
After MAD				
AHI (events/h)	1.4 (0.3-2.9)	5 (1.4-7.7)	9.0 (3.0-15.0)	0.045
RDI (events/h)	3.6 (3.2-6.9)	7.5 (5.5-10.0)	13.0 (5.0-18.3)	0.056
Average SpO_2 (%)	95.0 (94.0-96.0)	96.5 (94.7-97.0)	95.0 (92.0-97.0)	0.296
Minimum SpO_2 (%)	89.0 (87.0-92.0)	91.0 (89.0-93.3)	87.0 (84.0-89.0)	0.092
ESS	5.0 (3.0-7.7)	5.5 (5.0-9.2)	7.0 (3.0-8.0)	0.618
dAHI (events/h)	0.2 (−0.2-3.6)	17.4 (8.0-24.4)	41.0 (30.8-49.0)	<0.001
dRDI (events/h)	1 (0.2-4.3)	16.3 (10.0-23.6)	42.9 (39.0-47.0)	<0.001
daverage SpO_2 (%)	−0.5 (−1.7-0.0)	0.1 (0.0-1.0)	1.0 (1.0-3.0)	0.002
dminimum SpO_2 (%)	0 (−2.0-2.7)	8.0 (6.0-14.0)	10.0 (4.0-17.0)	0.001
dESS	2.0 (0.0-3.0)	5.5 (2.2-7.0)	4.0 (3.0-8.0)	0.020

MAD, mandibular advancement devices; OSA, obstructive sleep apnea; BMI, body mass index; NC, neck circumference; AHI, apnea-hypopnea index; RDI, respiratory disturbance index; SpO_2, oxygen saturation; ESS, Epworth Sleepiness Scale; dAHI, the difference in AHI before and after MAD therapy; dRDI, the difference in RDI before and after MAD therapy; daverage SpO_2, the difference in average SpO_2 before and after MAD therapy; dminimum SpO_2, the difference in minimum SpO_2 before and after MAD therapy; dESS, the difference in AHI before and after MAD therapy.

Values are presented as number only or median (interquartile range).

Mild OSA (n=16), AHI<15; moderate OSA (n=6), 15≤AHI<30; severe OSA (n=7), AHI≥30.

The p-value was determined by the Kruskal-Wallis test.

Table 4. Comparison of clinical and respiratory parameters between nonresponders and responders among patients with moderate and severe OSA (n=13)

Parameters	Non-responder (n=3)	Responder (n=10)	p-value
Sex			0.400
Male	3	8	
Female	0	2	
Age (y)	50.6±10.6	51.8±12.0	0.811
BMI (kg/m^2)	27.4±1.4	25.7±2.9	0.217
Neck (cm)	41.0±1.0	39.6±1.7	0.217
AHI (events/h)	50.0±13.1	32.2±12.0	0.049
RDI (events/h)	52.8±14.4	36.4±12.9	0.077
Average SpO_2 (%)	90.6±0.5	94.2±2.4	0.049
Minimum SpO_2 (%)	71.3±1.1	81.4±2.7	0.007
ESS	11.6±2.0	11.0±2.8	0.811

OSA, obstructive sleep apnea; BMI, body mass index; AHI, apnea–hypopnea index; RDI, respiratory disturbance index; SpO_2, oxygen saturation; ESS, Epworth Sleepiness Scale.
Values are presented as number only or mean±standard deviation.
Success criterion is a reduction in AHI greater than 50% and AHI<10.
The p-value was determined by the Mann-Whitney U test (chi-squared test for sex).

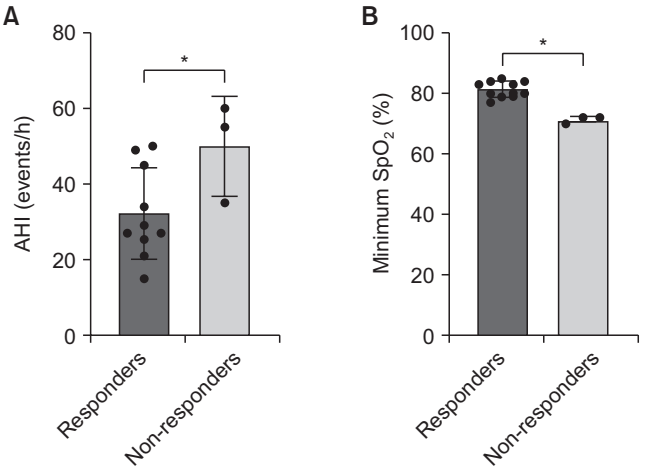

Fig. 2. Comparison of baseline AHI and minimum SpO_2 between responders and non-responders. Responders (n=10), non-responders (n=3). AHI, apnea-hypopnea index; SpO_2, oxygen saturation. *Indicates p<0.05 (p=0.049 for AHI and p=0.007 for minimum SpO_2).

scores of the three groups (p=0.618) after MAD therapy.

Of 13 patients with moderate and severe OSA, 10 and 3 were classified as responders and non-responders, respectively, as presented in Table 4 and Fig. 2. No statistical difference was observed in the protrusion ratio (%) between the responders and non-responders (p=0.342, Mann–Whitney U test). Furthermore, there were no significant differences between the two groups as regards sex ratio (p=0.400), age (p=0.811), BMI (p=0.217), neck circumference (p=0.217), and ESS (p=0.811). However, the mean baseline values of the average (p=0.049) and minimum (p=0.007) SpO_2 were found to be significantly lower in non-responders than in responders. The mean (SD) AHI of the non-responders was 50.0 (13.1), which was significantly higher (p=0.049) than that of the responders, which was 32.2 (12.0). The mean RDI followed a similar trend to the AHI, although the difference was not statistically significant (p=0.077). Cohen's d for AHI, average SpO_2, and minimum SpO_2 were 4.0613 (95% confidence interval [CI]=2.0361, 6.0866), 1.6504 (95% CI=0.2126, 3.0881), and 1.4605 (95% CI=0.0534, 2.8675), respectively, for the responders and non-responders.

DISCUSSION

The clinical practice guideline, issued jointly by the American Academy of Sleep Medicine and American Academy of Dental Sleep Medicine, recommends considering OA therapy for adult patients with primary snoring without OSA and those with OSA who are intolerant to CPAP or prefer alternative therapy [15]. Although CPAP is more effective than MAD in reducing AHI, there is increasing evidence that patients have better tolerance to MAD than to CPAP, with a self-reported compliance rate of around 80% [16]. Therefore, current evidence suggests that both OA and CPAP are equally important in the treatment of patients with mild to moderate OSA and even severe OSA. However, OA is suggested to be a potential first-line option despite the higher efficacy of CPAP in reducing AHI [16,17]. According to the clinical practice guideline published in 2015 [15], OA reduces AHI, RDI, and daytime sleepiness and modestly improves minimum SpO_2 in adult patients with OSA with the moderate level of evidence. Consistent with the findings of previous studies [15,18], significant improvements were observed in patients with mild OSA after MAD therapy, including reductions in RDI (p=0.046) and ESS (p=0.006), as presented in Table 2 and Fig. 1. Interestingly, 1 of 16 patients with mild OSA exhibited an increase in AHI (AHI=27 events/h) after titration of

MAD than at baseline (AHI=12 events/h). This patient was 50 years old, had obesity (BMI=28.7 kg/m^2), and had no medical history. His weight did not change during the follow-up period. This outlier case suggests that a diagnosis of mild OSA based on AHI does not necessarily ensure the efficacy of MAD therapy.

In patients with moderate OSA, significant reductions were observed in AHI (p=0.027), RDI (p=0.027), and ESS (p=0.006), alongside significant increases in minimum SpO_2 (p=0.039). Notably, patients with severe OSA reported significant improvements in all sleep-related parameters, including significant decreases in AHI (p=0.018) and RDI (p=0.018), significant increases in average SpO_2 (p=0.024) and minimum SpO_2 (p=0.018), and a significant decrease in ESS (p=0.017).

Comparison of the clinical characteristics and treatment outcomes of OA therapy based on the OSA severity revealed a positive correlation between OSA severity and patient age (p=0.004) (Table 3). This finding is consistent with that of a previous study that examined polygraphic data in 1090 patients with OSA and indicated that the older the patient, the higher the risk for pharyngeal collapsibility [19]. The median BMI of the patients in the severe OSA group was higher than those in the mild and moderate OSA groups, but the difference was not statistically significant (p=0.073). No differences were observed in the sex ratio or neck circumference between the groups. As expected, the differences in sleep-related parameters between pre- and post-MAD therapy followed the order of severe, moderate, and mild OSA groups. The present study showed successful outcomes in 83.3% and 71.4% of moderate and severe OSA cases, respectively, based on the previously stated success criteria (significant reduction in AHI of more than 50% and AHI less than 10 events/h).

Ramar's study reported that the efficacy of OA is limited to 60%-70% of patients due to the interindividual variability of the treatment outcomes [15]. Identification of patients who are likely to benefit from OA treatment is currently a challenge for clinicians in this context. To examine the relevant features that distinguish responders from non-responders to MAD therapy, a subgroup analysis was conducted between them based on the AHI criteria. Non-responders had a higher AHI (p=0.049) and lower average and minimum SpO_2 (p=0.049 and p=0.007, respectively) than responders (Table 4 and Fig. 2). The results suggest that higher AHI and lower nocturnal SpO_2 are associated with less effective therapy for MAD. Considering the high efficacy of MAD (71.4%) in the group with severe OSA categorized by AHI≥30, a high AHI score does not ensure the efficacy of MAD therapy. Cohen's d effect size indicated that the minimum SpO_2 had a greater predictive power than the AHI and average SpO_2 in determining responders and non-responders. Thus, these results suggest that the minimum SpO_2, which is considered a secondary measure, has a stronger predictive power than AHI, which is regarded as a primary measure, and average SpO_2, which is another oximetric measure, given the limited sample size of this study.

Although the AHI is still the most commonly used diagnostic metric for OSA, its predictability in clinical practice may not be adequate owing to its oversimplified single index, requiring a critical evaluation of its role as a primary biomarker for the diagnosis and management of OSA [20-25]. Previous studies have reported that OSA severity, graded by the AHI score, was not correlated with physiological consequences (e.g., cardiovascular events and related morbidity or mortality), CPAP titration pressure, and daytime sleepiness [20-22].

In this study, Spearman's rho calculated via correlation analysis was found to be high (p=−0.666, p<0.001) between the AHI and minimum SpO_2.

In fact, the AHI and minimum SpO_2 are closely related but are not the same parameter. The AHI is a quantifiable measure of the frequency of apnea–hypopnea events, whereas the minimum SpO_2 is a qualitative biomarker that indicates physiological consequences associated with AHI events. The AHI system has several inherent shortcomings. Hypoxic and nonhypoxic events, which are associated with different health outcomes, are not distinguished by the AHI [26]. It does not account for the duration of apnea and hypopnea as well as body position during these two events [23,27-29]. Furthermore, it gives equal weight to apnea and hypopnea, whereas apnea might have greater physiological consequences than hypopnea through severe hypoxemia and increased autonomic responses [23].

Prior research suggested possible prognostic markers as predictors of MAD efficacy [10,30]. Direct visual verification

of pharyngeal widening via videoendoscopy has been suggested as a potential predictor of good efficacy of MAD [30]. A 2022 systemic review examined phenotypic differences between responders and non-responders to MAD therapy and suggested that anatomic characteristics, sleep study findings, and high CPAP pressure are associated with low MAD efficacy [10]. Consistent with the findings of our study, a 2022 systemic review found that a high minimum SpO_2 during sleep can serve as a biomarker for the prediction of responders to MAD therapy [10].

Based on the results of the present study, consistent with those of previous ones, it seems adequate to consider the minimum SpO_2 level as a biomarker of nocturnal hypoxemia in addition to the AHI as a quantifiable respiratory cessation parameter for predicting MAD efficacy for the treatment of OSA. This can facilitate the screening and selection of patients for OA therapy. Although a statistically significant difference was observed in the mean (SD) between non-responders (71.3%, SD=1.1) and responders (81.4%, SD=2.7) in the present study, a clear-cut minimum SpO_2 level that can predict the efficacy of OA treatment is uncertain. Interestingly, a recent study suggested the usefulness of minimum SpO_2 as another success criterion of AHI in the treatment of OSA with MAD [31]. This study reported that there were three different phenotypes in terms of treatment outcomes for MAD, including a group with improvement in AHI only, other groups with improvement in minimum SpO_2 only, greater than 4% SpO_2, and a group with congruent improvement. The cutoff value of pretreatment minimum SpO_2 was 86.25% with a positive predictive value of 89.47%.

The success criteria to divide responders and non-responders to MAD discussed in this study were based on the AHI. The mean (SD) improvement of the minimum SpO_2 in the three non-responders in this study was 15.3% (4.72). Based on the AHI, all the non-responders showed improvement of the minimum SpO_2 greater than 4%. These results suggest that MAD treatment is beneficial for responders based on the minimum SpO_2, even if they are non-responders based on AHI. Given the detrimental effects of oxygen desaturation during sleep on long-term health outcomes [32], defining the success criterion for MAD treatment should not focus on a single metric of AHI. This is an important issue, and further investigation using a large sample size would provide diagnostic and prognostic information for OSA treatment with MAD therapy.

Future studies should explore various parameters associated with hypoxic burden beyond the minimum SpO_2. Several sleep parameters, such as arousal intensity, oxygen desaturation rate, heart rate variability, and apnea–hypopnea event duration, have been proposed as physiological surrogates beyond AHI [33-37]. Polysomnographic endotypes, such as ventilatory instability and high loop gain of non-responders to MAD therapy, were observed in a previous clinical trial [38]. Identifying and understanding the relevant factors would facilitate the development of individualized MAD treatment approaches for OSA. Knowledge of the underlying mechanism of MAD therapy needs to be continuously updated.

As a preliminary study, the main limitation of the current study with limited sample size should be mentioned. The lack of statistical power due to the small sample size of the non-responders would lead to overestimation of significance and false-positive results. Thus, the results of this study should be interpreted with caution, although previous studies have reported results similar to ours [10]. To strengthen our findings, further validation studies using a larger sample size of nonresponders are warranted. The possible effect on treatment outcomes related to the heterogeneity of two different types of MAD should also be addressed. The present study did not compare the treatment outcomes between the two appliances. However, considering the lack of a robust effect of OA design on efficacy of MAD therapy [39], the possible effects of different MAD designs would be minimal. Despite the drawbacks of this study, which was based on a small dataset, the findings encourage further research that considers various sleep-related metrics other than AHI in predicting the efficacy of MAD.

In conclusion, the results of the present study suggest that the MAD is effective in majority of patients with OSA of varying severities. The success of MAD therapy does not seem to depend solely on AHI severity. In addition to AHI, minimum SpO_2 level may serve as a prognostic marker for the efficacy of MAD treatment in clinical dental practice.

CONFLICTS OF INTEREST

Hye Kyoung Kim, Editor-in-Chief of the *Journal of Oral Medicine and Pain*, was not involved in the editorial evaluation or decision to publish this article. Mee Eun Kim serves on the editorial board of the *Journal of Oral Medicine and pain* and had no role in the editorial evaluation or decision to publish this article. Except for this, no other potential conflicts of interest relevant to this article have been reported.

DATA AVAILABILITY STATEMENT

The datasets used in the current study are available from the corresponding author upon reasonable request.

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None.

AUTHOR CONTRIBUTIONS

Conceptualization: HKK, MEK. Investigation: HKK. Methodology: HKK. Supervision: HKK, MEK. Data analysis and interpretation: HKK, MEK. Writing of original draft: HKK. Writing, review-editing: HKK, MEK.

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