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Treatment efficacy of a titratable oral appliance in obstructive sleep apnea patients: a prospective clinical trial

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Abstract. *Treatment efficacy of a titratable oral appliance in obstructive sleep apnea patients: a prospective clinical trial. Purpose*: This prospective clinical trial assessed the therapeutic outcomes of patients with obstructive sleep apnea (OSA) treated with a novel duobloc custom-made titratable mandibular advancement device (OAm).
Material and methods: The modular Somnomed G2® OAm (Somnomed Europe AG, Zurich, Switzerland) with 'click-to-fit' adjustability provides instant feedback on the mandibular advancement. 161 consecutive patients with established diagnoses of OSA. Dental impressions were made and a bite registration in 75% of the maximal protrusion being the starting protrusion. Treatment response was defined as ≥50% decrease in apnea-hypopnea index (AHI). Treatment success was defined as 1a) AHI with OAm <5 events/h sleep or 1b) AHI with OAm <10 events/h. Treatment success and response were combined to define additional criteria: 2a) reduction in AHI ≥50% and AHI <5 events/h; and 2b) reduction in AHI ≥50% and AHI <10 events/h.
Results: In 112 patients AHI decreased significantly from 25±18/h sleep at baseline to 12±13/h with the OAm ($p<0.001$). The visual analogue scoring for snoring (VAS) decreased significantly from 7±3 to 2±2 ($p<0.001$). Treatment response was achieved in 65 of 112 patients (58%); 31% and 57% of patients were treated successfully according to criteria 1a and 1b, respectively. Furthermore, 31% and 50% of patients were treated successfully according to criteria 2a and 2b, respectively.
Conclusions: This clinical trial indicates that treatment with a novel custom-made OAm can reduce the severity of sleep-disordered breathing by significantly decreasing the AHI and VAS scores.

Introduction

Obstructive sleep apnea (OSA) is a serious health problem.[1] OSA is the most common sleep-related breathing disorder, affecting at least 10% of 30-49-year-old men; 17% of 50-70-year-old men; 3% of 30-49-year-old women; and 9% of 50-70-year-old women.[2] OSA is characterized by repetitive episodes of upper airway obstruction during sleep. This obstruction, which can be partial (hypopnea) or complete (apnea), results in hypoxemia, arousal from sleep, and sleep fragmentation.[3] The daytime symptoms associated with OSA, such as excessive daytime sleepiness (EDS), cognitive impairment, and other effects on quality of life, require appropriate treatment.[4] Furthermore, OSA is an independent risk factor for cardiovascular complications and can be associated with high morbidity and mortality.[5]

The gold standard treatment for OSA is continuous positive airway pressure (CPAP),[6] which acts as a pneumatic splint in the upper airway via constant positive pressure throughout the respiratory cycle. Although CPAP is highly effective for avoiding upper airway collapse, compliance is rather low, resulting in limited clinical effectiveness.[7,8] Oral appliances (OAs) and weight loss are currently the primary noninvasive treatment options for patients with OSA and for those who do not comply with or who refuse CPAP treatment.[9-11] OAs are worn at night and are designed to prevent or reduce upper airway collapse by altering the tongue and jaw position[8,12] while grasping the teeth for retention. For the most

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commonly used OAs, the mechanism of action involves placing and holding the mandible in a more anterior position; such devices are termed OAms. The reduction in the severity of OSA using OAm therapy is on the same order of magnitude as reductions using CPAP.[8] The literature indicates that OAms as well as CPAP have a beneficial effect on OSA-related adverse health consequences like elevated blood pressure, endothelial dysfunction, and left ventricular dysfunction.[13]

Custom-made OAms are manufactured in a dental laboratory based on the individual impressions of a patient's tooth arches.[12,14] There are many OAm designs that have varying rates of treatment success, adherence, compliance, and side effects.[15] The literature suggests that custom-made OAms have higher patient adherence and are more effective than thermoplastic appliances.[9,16] Initially, OAms were available as "monobloc" devices that consisted of a single unit that had both upper and lower parts, but they have gradually evolved into the current "duobloc" generation of devices that have separate upper and lower parts that are dynamically interconnected. The interconnecting mechanism allows gradual forward positioning of the mandible, a process termed titration, until the optimal mandibular position is reached within the patient's anatomical limits.

The type of OAm used in the present study is a duobloc style device that has upper and lower jaw clips with click-on components on the sides that allow stepwise titration (Figure 1). The components are labeled, allowing instant feedback about the degree of mandibular advancement. In this prospective clinical study, we evaluated the efficacy of this novel custom-made OAm using the reduction in OSA severity as the main outcome.

Materials and methods

Study population

A total of 161 consecutive adult (age >18 years) OSA patients were included after they provided written informed consent. All patients included in this study suffered from either mild (5/h < AHI ≤ 15/h) or moderate to severe (AHI >15/h) OSA; the included patients with AHI >20/h sleep were intolerant, noncompliant, or refused CPAP. A diagnosis of OSA was made based on the results of each patient's most recent full-night attended type I polysomnography (PSG) session. All patients underwent a standard ear, nose, and throat (ENT) clinical examination that including a detailed clinical history, clinical examination of the ear, nose, and throat, and examination of the pharyngeal and laryngeal findings (webbing and size of the uvula, soft palate, and tonsils). Patients that were considered candidates for OAm treatment were referred to a dental sleep professional for a full dental examination, including an X-ray ortho-pantomogram. All patients underwent a drug-induced sleep endoscopy (DISE) and were excluded if no widening of airway was seen with chin lift or simulation bite.[17] Exclusion criteria were predominantly dental: compromised dental status or periodontal health or being fully edentulous.[14] The baseline characteristics of the patients are shown in Table 1. OAm therapy started between January 1, 2013 and June 1, 2014.

Figure 1
The Somnomed G2® OAm (photo courtesy of SomnoMed AG). The OAm consists of two main parts, an upper and a lower part, both of which are pink in this photo. The advancement clips that enable stepwise titration are blue. The advancement clip that fits on the upper part is labeled with a letter (A, B, or C; labeled A in the photo above); clip B is 3.5-mm wider than clip A, and clip C is 3.5-mm wider than clip B. The advancement clip that fits on the lower part is labeled with a number (1-7; labeled 5 in the photo above); clip 2 is 0.5-mm wider than clip 1, clip 3 is 0.5-mm wider than clip 2, and so on. Using these clips, it is possible to adjust the protrusion of the device in 0.5-mm stepwise increments up to 10 mm.

The oral appliance

This study evaluated the Somnomed G2® device (Somnomed Europe AG, Zurich, Switzerland), which is a custom-made, titratable, commercially

Table 1

Baseline characteristics of the study population (n = 161)

Parameter	Mean ± SD
Age, years	48.1 ± 9.7
Sex	81% male
Body mass index (BMI), kg/m^2	27.6 ± 3.7
Weight, kg	84.2 ± 17.1
Apnea hypopnea index (AHI), events/h sleep	24.0 ± 17.7
Epworth sleepiness scale (ESS), 0-24	10 ± 5
Visual analogue scale for snoring (VAS), 0-10	6 ± 3

Data are expressed as means ± standard deviation (SD) or as percentages.

available duobloc OAm. The titration mechanism is located at the lateral sides and uses click-on components that enable stepwise titration. These components are labeled, allowing instant feedback about the amount of mandibular advancement (Figure 1).

The maximal protrusion was measured three times in each patient and the measurements were averaged. Dental bite registration allowed the determination of the starting protrusion, which was the maximal comfortable protrusion or 75% of the maximal protrusion, depending on the range of mandibular advancement for each patient. The fitting as well as the protrusive start position of the OAm was checked by a qualified dental sleep professional. After three or four nights of habituation to the appliance, the patients were instructed to titrate the device every 3 days at a maximal rate of 0.5 mm per titration step until either symptoms such as snoring and/or excessive daytime sleepiness improved or resolved or until the anatomic protrusive limit was reached.

Objective outcome measurement: PSG

Overnight type I PSG included electroencephalography, right and left electrooculography, electromyography of the genioglossus and tibialis anterior muscles, electrocardiography, and oxygen saturation (determined using pulse oximetry with a finger probe). The respiratory variables were recorded, including nasal airflow using an external thermistor and nasal pressure using a nasal pressure cannula. Respiratory effort was measured using respiratory inductance plethysmography. Snoring was recorded qualitatively using a microphone and a piezo-electrical sensor that monitored body position. The sleep recordings were scored manually in a standardized way by a qualified sleep technician.[18,19] Obstructive apnea was defined as an interruption in nocturnal breathing ≥ 10 sec despite continued respiratory effort. Hypopneas were defined as abnormal respiratory events lasting ≥ 10 sec with ≥ 30% reduction in thoracoabdominal movement or airflow and ≥ 4% oxygen desaturation. The AHI was calculated as the average number of apneas and hypopneas per hour of sleep. All patients in this prospective clinical study underwent two overnight PSGs. The first PSG was used to diagnose sleep-related breathing issues and was considered the baseline recording. Once the OAm was optimally titrated in terms of maximal resolution of symptoms or when it reached the anatomical limits of mandibular protrusion, a follow-up PSG was performed with the OAm in situ during sleep. This allowed the therapeutic effect of the OAm to be assessed objectively by comparing the baseline PSG without OAm with the follow-up PSG with OAm. The time lag between fitting of the OAm and the follow-up PSG with OAm in situ was an average of 120 ± 41 days.

Subjective outcome measurements: the Epworth sleepiness scale (ESS) and the visual analogue scale (VAS) for snoring

The ESS

The ESS is a self-administered questionnaire that assesses the degree of daytime sleepiness. Patients were asked to rate the probability that they would fall asleep in a variety of daily life situations (n = 8) on a scale of 0 to 3. The sum of these 8 items could range from 0 to 24 and represents the actual ESS score. A score higher than 10/24 was defined as excessive daytime sleepiness (EDS).

The VAS for snoring

To evaluate the subjective snoring status of each patient, we asked each patient's bed partner to complete a standard 10-point VAS that ranged from 0 to 10, with 0 being no snoring and 10 being snoring that caused the bed partner to leave the room or sleep separately. A VAS snoring index of at least 7 was defined as heavy snoring. A "satisfactory" reduction was defined as a decrease of at least 3 points on the VAS for snoring during

treatment with the OAm compared to baseline. A decrease to a snoring index that was no longer considered bothersome, i.e. to 3 points or less, was defined as an important reduction.[14]

Primary outcome measures

"Responders" were defined as patients who, following OAm treatment, showed AHI reduction ≥50% compared to baseline. "Non-responders" were defined as patients with AHI reduction <50%. Treatment success was defined as an AHI decrease to <5 events/h (1a) or <10 events/h sleep (1b) using the OAm. These treatment success and response criteria were combined into two additional treatment criteria: 2a, which indicated both a decrease ≥50% in the AHI and AHI <5 events/h; and 2b, which indicated both a decrease ≥50% in the AHI and an AHI <10 events/h. Deterioration was defined as an increase in the AHI while using the OAm relative to the baseline AHI.

Secondary outcomes

For the subjective secondary outcomes, we analyzed patient questionnaires that were filled out at baseline and at the time of the follow-up PSG. The VAS for snoring was assessed in the 88 patients who had a bed partner that reported on the effect of the snoring.

Statistical analysis

Statistical analysis was performed using SPSS software (SPSS version 22.0, Statistical Package for Social Sciences, SPSS Inc., Chicago, IL, USA). The normality of the distribution was assessed using QQ plots, and the distribution was not normal for all data. The nonparametric Wilcoxon-signed rank test for paired observations was used to test the evolution of the different variables, and $p<0.05$ was considered significant.

Results

Study population

PSG re-evaluation with the OAm in situ was obtained in 112 out of 161 patients (74.5%), while 49 patients were lost to follow-up (either they declined to undergo re-evaluation or quit therapy). The remaining patients (n=112) included 93 men and 19 women who had a mean age of 47.9±9.7 years, a mean AHI of 24.5±18.1 events/h sleep at baseline, and a mean BMI of 27.6±3.7 kg/m^2. The mean ESS score was 9.7±5.5, and the mean score on the VAS for snoring was 7±3. The average patient weight and BMI did not change significantly during OAm therapy.

Effect of the OAm on outcome measures

Primary outcome

There was a statistically significant decrease in the AHI at the follow-up PSG with the OAm in situ as compared to baseline. The AHI decreased from 25±18 events/h of sleep at baseline to 12±13 events/h with the OAm in place ($p<0.001$) (Figure 2). Table 2 summarizes the treatment success and response results. Of the 112 patients, 65 (58.0%) were responders who showed an AHI reduction ≥50% with OAm treatment as compared to baseline. Thirty-five patients (31.3%) met the 1a criteria for treatment success i.e. AHI <5 events/h with the OAm in situ, while 64 patients (57.1%) met the 1b criteria i.e. AHI <10 events/h with the OAm in situ. Thirty-five patients (30.4%) also fulfilled the 2a success criteria of an AHI reduction ≥50% and AHI <5 events/h, while 56 patients (50.0%) fulfilled the 2b criteria of treatment success with AHI reduction ≥50% and AHI <10 events/h with the OAm in situ. Deterioration occurred in 24 patients (21.4%). Table 3 shows the response rates in different groups of patients. Response was defined as an AHI reduction ≥50% with the OAm relative to baseline, and there were significant differences between patients in the mild, moderate, and severe sleep apnea categories (Table 3).

Secondary outcomes

Table 4 summarizes the evolution of the scores on the VAS for snoring and the ESS and changes in EDS during OAm treatment in subgroups with differing OAS severity. Of 41 patients (37%) with EDS (ESS >10/24) before starting OAm treatment, 18 (44%) reported ESS ≤10 following OAm treatment. The scores on the VAS for snoring were obtained in 86 patients who had a bed partner, and the mean VAS score decreased significantly from 7±3 to 2±2 during OAm treatment. Of the 86 patients, 42 (49%) patients had a VAS score of 7 or higher before OAm treatment as reported by their

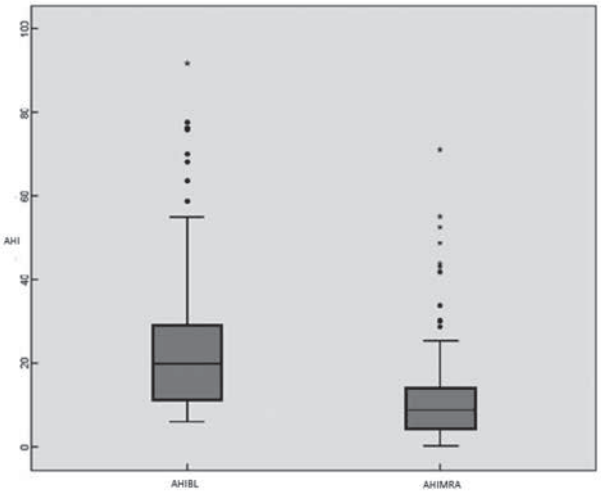

Figure 2
Evolution of the apnea-hypopnea index (AHI). The AHI at baseline (AHIBL) is shown in the left boxplot, and the AHI with OAm therapy (AHIMRA) is shown in the right boxplot.

bed partners; this is considered heavy snoring. During OAm treatment 72 (84%) patients had an important reduction in VAS, i.e., a VAS score of 3 points or less.

Discussion

This prospective clinical study is the first to evaluate this particular novel, custom-made, titratable OAm, which has a laterally located titration mechanism that enables progressive stepwise titration of the mandible (Figure 1). The findings demonstrate that this OAm was effective in most of the OSA patients in the study. Specifically, the OAm significantly reduced OSA severity as measured by the AHI (from 25 ± 18 to 12 ± 13 events/h sleep, $p < 0.001$), significantly decreased the VAS for snoring as reported by the bed partners (from 7 ± 3 to 2 ± 2, $p < 0.001$), and also decreased the degree of EDS as assessed by the ESS (from 37% to 16% of patients, $p < 0.001$). The success rates in this study population are comparable to those reported in similar studies of other OAms.[9,20-22] In the present study, 58% of patients were defined as treatment responders; this value ranges from 34% to 89% in similar studies.[11] Of the 161 patients included in this study, the success and response rates were calculated for the 112 (74.5%) patients who completed the follow-up PSG.

Table 2
Definitions of success and the results of the present study

Success definition	Percentage, %
Treatment response: AHI reduction ≥ 50%	58.0
Treatment success: AHI < 5 events/h	31.3
Treatment success: AHI < 10 events/h	57.1
AHI reduction ≥ 50% and AHI< 5 events/h	30.4
AHI reduction ≥ 50% and AHI< 10 events/h	50.0
Treatment failure: AHI increase	21.4

AHI: apnea-hypopnea index.

One interesting finding was that patients who suffered from more severe OSA showed greater reductions in AHI, VAS, and ESS (Tables 3 and 4). Clearly it is more difficult for this group to achieve an AHI < 5 events/h or 10 events/h. However, taking into account the response rates, the mean decrease in AHI was higher in the subgroup of patients with the more severe OSA, and relatively more patients achieved an AHI reduction ≥ 50%. Almost three-quarters of the patients with severe OSA showed an AHI reduction ≥ 50%, with a significant decrease of the mean AHI from 50 ± 18 to 18 ± 18 events/h sleep. These findings contrast with the general view that OAm therapy is most effective in patients with less severe OSA, but they support recent findings showing that predictions regarding treatment success or response to OAm therapy cannot be based solely on OSA severity and/or on BMI.[23]

EDS is defined as an ESS score ≤10. Following OAm treatment, there was a significant decrease in ESS in the study population, from 37% at baseline to 16% after OAm therapy. This value is slightly lower than the prevalence of 18% found in an unselected general population.[24] However, a number of patients show little or no improvement in daytime sleepiness despite a complete response to OAm therapy for sleep disordered breathing (SDB) severity, which is defined as residual excessive sleepiness (RES). Of the 35 patients who achieved an AHI of < 5 events/h, 9 (25.7%) continued to suffer from RES despite effective treatment based on AHI normalization. This value was similar to the values described by Verbruggen *et al.*,[25] demonstrating that RES is associated with higher baseline ESS and younger age. We found that treatment success and ESS decrease are dissociated in some patients i.e. they can change independently

Table 3

Success rates in the severity subgroups according to the indicated criteria

	Treatment response: AHI reduction ≥50%	Treatment success 1a: AHI <5 events/h	Treatment success 1b: AHI <10 events/h	Deterioration
Mild OSA (5/h<AHI≤15/h) n=44	47.7%	40.9%	65.9%	34.1%
Moderate OSA (15/h<AHI≤30/h) n=41	58.5%	29.3%	56.1%	17.1%
Severe OSA (AHI>30/h) n=27	74.1%	14.8%	44.4%	7.4%
Entire population n=112	58.0%	31.3%	57.1%	21.4%

AHI: apnea-hypopnea index; OSA: obstructive sleep apnea.

Table 4

Evolution of primary and secondary outcome measures according to obstructive sleep apnea (OSA) severity

OSA severity (variables)	Baseline	Post-OAm	*p*-value
Mild OSA (5/h<AHI≤15/h) (n=44)			
AHI	10.5±2.4	7.5±5.5	0.003
VAS	7±3	2±2	<0.001
ESS	10±6	8±6	<0.001
Patients suffering from EDS	17 (38.6%)	10 (22.7%)	Not applicable
Moderate OSA (15/h<AHI≤30/h) (n=41)			
AHI	21.7±4.1	12.4±11.0	<0.001
VAS	6±2	2±2	<0.001
ESS	8±5	6±5	0.016
Patients suffering from EDS	11 (26.8%)	5 (12.2%)	Not applicable
Severe OSA (AHI>30/h) (n=27)			
AHI	50.0±18.2	18.2±18.1	<0.001
VAS	7±3	3±3	<0.001
ESS	10±6	6±4	0.004
Patients suffering from EDS	13 (48.1%)	3 (11.1%)	Not applicable
All patients (n=112)			
AHI	24.5±18.2	12.0±12.5	<0.001
VAS	7±3	2±2	<0.001
ESS	10±5	7±5	<0.001
Patients suffering from EDS	41 (36.6%)	18 (16.1%)	Not applicable

AHI: apnea hypopnea index; EDS: excessive daytime sleepiness; ESS: Epworth sleepiness scale; VAS: visual analogue scale for snoring.

of each other. RES has a known negative impact on daily functioning and quality of life; accordingly, it would be interesting and worthwhile to evaluate the causes underlying ESS. Further research on this subject is needed.

There was deterioration in 21% of the patients, this is higher compared to the 14% reported by Ferguson.[26] Deterioration of AHI during OAm therapy is rarely described in studies evaluating the efficacy of OAm therapy. Identifying the factors that lead to an increase in AHI is of the utmost importance and could help optimize OAm therapy, especially in terms of comparing different types of OAm devices.

Conclusion

Based on these data, we conclude that this novel OAm, which has unique stepwise titration features, was efficacious for treating snoring in 76% of the patients included in the study, for treating EDS in 56% of the patients, and for treating OSA in 58% of the patients. Patients suffering from more severe OSA showed better results during therapy with this type of OAm, emphasizing that predicting treatment success based on the AHI at baseline is not reliable.

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