A Randomized, Controlled Study of a Mandibular Advancement Splint for Obstructive Sleep Apnea

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Although there is increasing interest in the use of oral appliances to treat obstructive sleep apnea (OSA), the evidence base for this is weak. Furthermore, the precise mechanisms of action are uncertain. We aimed to systematically investigate the efficacy of a novel mandibular advancement splint (MAS) in patients with OSA. The sample consisted of 28 patients with proven OSA. A randomized, controlled three-period (ABB/BAA) crossover study design was used. After an acclimatization period, patients underwent three polysomnographs with either a control oral plate, which did not advance the mandible (A), or MAS (B), 1 wk apart, in either the ABB or BAA sequence. Complete response (CR) was defined as a resolution of symptoms and a reduction in Apnea/Hypopnea Index (AHI) to < 5/h, and partial response (PR) as a $\geq 50\%$ reduction in AHI, but remaining ≥ 5/h. Twenty-four patients (19 men, 5 women) completed the protocol. Subjective improvements with the MAS were reported by the majority of patients (96%). There were significant improvements in AHI (30 ± 2/h versus 14 ± 2/h, $p < 0.0001$), $MinSa_{O_2}$ ($87 \pm 1\%$ versus $91 \pm 1\%$, $p < 0.0001$), and arousal index (41 ± 2/h versus 27 ± 2/h, $p < 0.0001$) with MAS, compared with the control. The control plate had no significant effect on AHI and $MinSa_{O_2}$. CR ($n = 9$) or PR ($n = 6$) was achieved in 62.5% of patients. The MAS is an effective treatment in some patients with OSA, including those patients with moderate or severe OSA.

Obstructive sleep apnea (OSA) is a very common disorder, affecting approximately 4% of men and 2% of women in the middle-aged workforce (1). It is characterized by repetitive, complete or partial closure of the upper airway during sleep, resulting in sleep fragmentation and oxygen desaturation (2). Continuous positive airway pressure (CPAP) applied to the upper airway via a nose mask during sleep, first reported in 1981 (3), remains the accepted treatment of choice. Although it is an extremely effective treatment, its cumbersome nature makes tolerance and compliance less than optimal (4–6).

During the last decade, a number of studies have reported successful treatment of OSA by various oral appliances. Although they are thought to primarily act by advancing the mandible during sleep (7), other potential mechanisms such as stimulation of neuromuscular reflex pathways in the oral cavity and alteration of the bite relationship have not been explored to any great extent. They have potential advantages over nasal CPAP, in that they are far less obtrusive, more portable, make no noise, and are generally less costly. However, a number of methodologic deficiencies in previous studies of these appliances, including small sample sizes, weak study designs, and liberal definitions of treatment success, leave considerable doubt as to the role of these appliances in the routine management of OSA (7, 8). Furthermore, questions relating to appliance design and prediction of treatment outcome remain unresolved. Hence, the primary aim of this study was to assess the efficacy of a newly designed oral appliance for OSA in a controlled fashion. In addition, we aimed to examine the potential of anthropomorphic, polysomnographic, and radiographic parameters to predict treatment outcome.

METHODS

Study Population

Twenty-eight adult patients (22 men and six women) were recruited from a multidisciplinary Sleep Disorders Clinic in a university teaching hospital. Inclusion criteria were the presence of at least two symptoms of OSA (snoring, fragmented sleep, witnessed apneas, daytime sleepiness), *and* evidence of OSA on polysomnography, with an apnea/hypopnea Index (AHI) ≥ 10/h. Patients were excluded if there was evidence of periodontal disease, edentulism, an exaggerated gag reflex, or regular use of sedatives. The study was approved by the institutional ethics committee, and written informed consent was obtained from all patients.

Oral Appliance

Each mandibular advancement splint (MAS) was custom-made from dental impressions. A wax interocclusal record was taken with the mandible in the most protrusive position that the patient could comfortably maintain. The design features of the MAS (Figures 1 and 2) included the following: (*1*) Upper and lower removable clear acrylic plates with full occlusal coverage that fitted onto both dental arches. The average thickness of each upper and lower appliance was between 1.5 and 2.0 mm. (*2*) Two acrylic flanges, one on either side of the palatal aspect of the molars of the upper plate. These flanges fitted into slots cut into the acrylic on the lingual sides of the lower plate in the molar region. This unique coupling mechanism prevents posterior movement of the mandible, while permitting free opening of the mouth. (*3*) Two 10-mm screws to enable incremental anterior advancement of the lower plate.

In an attempt to control for some other potential effects of the MAS on upper airway function and, hence, apneic activity, such as stimulation of neuromuscular reflex pathways in the oral cavity and alteration of the bite relationship, we used the lower dental plate alone as a control. This had no protrusive effect on the mandible.

Study Design

A randomized crossover study design, with an extra period (ABB/BAA), was used (Figure 3). The ABB/BAA design has more statistical power than the conventional AB/BA design and allows the treatment effects to be estimated, even in the presence of carryover (9). After an acclimatization period, during which the mandible was incrementally advanced until resolution of symptoms or attainment of the maximal comfortable limit of advancement, each patient was randomized into either Group I (sequence ABB) or Group II (sequence BAA). After a 1-wk washout, patients underwent three nocturnal polysomnographs at 1-wk intervals, each being performed after 1 wk of treatment with control (A) or MAS (B), according to the randomly allocated sequence.

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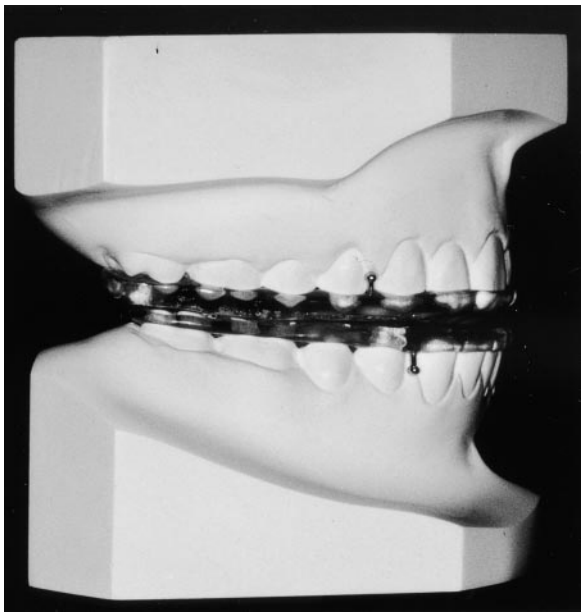

Figure 1. Photograph of upper and lower plates of the mandibular advancement splint mounted on a study model, with mandible in protrusion.

Outcome Measures

Questionnaires. A detailed questionnaire to assess subjective snoring frequency and intensity, quality of sleep, and daytime sleepiness (Epworth Sleepiness Scale: ESS) (10) was completed by patients at the beginning and the end of the acclimatization period. At the end of the study each patient was asked to rate their satisfaction with the MAS and whether they would choose to use the MAS as a long-term treatment.

Polysomnography. Standard nocturnal polysomnography was performed, with electroencephalogram (EEG), electrooculogram, and submental electromyogram (EMG) electrodes applied in the standard fashion for sleep stage determination (11). Respiratory variables included chest wall and abdominal movement, diaphragm EMG, nasal airflow and pressure, and oxygen saturation by pulse oximetry. Calculated respiratory variables were AHI (number of apneas and hypopneas per hour of sleep), and minimum oxyhemoglobin saturation ($MinSa_{O_2}$). *Apnea* was defined as cessation of airflow for at least 10 s with oxygen desaturation of more than 3% and/or associated with arousal. *Hypopnea* was defined as a reduction in amplitude of airflow or thoracoabdominal wall movement of greater than 50% of the baseline measurement for more than 10 s with an accompanying oxygen desaturation of at least 3% (no time limit), and/or associated with arousal. These events were considered obstructive if they occurred in association with continued diaphragm EMG activity and thoracoabdominal wall movement. EEG arousals were scored according to the ASDA 3-s rule (12), and arousal index was calculated as the number of arousals per hour of sleep. In addition, sound intensity was measured using a calibrated sound level meter positioned 1 m above the patient's head, and snoring frequency was calculated as the number of snores per hour. All variables were recorded continuously on a 20-channel computerized sleep monitoring system (Compumedics, Vic, Australia). Sleep recordings were scored in 30-s epochs by an experienced polysomnographer, who was blinded to the patients' treatment.

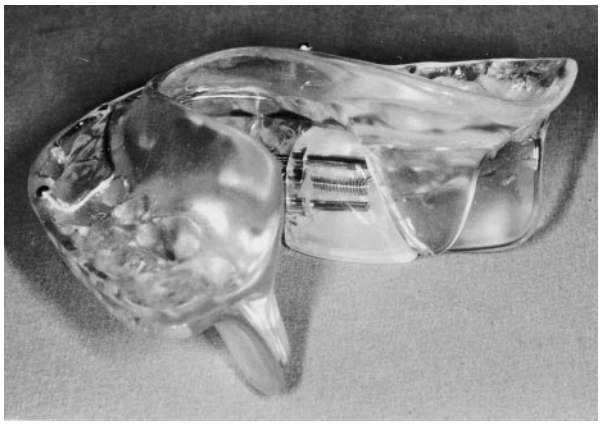

Figure 2. Oblique posterior view of the mandibular advancement splint, showing the coupling mechanism and titrating screw on one side.

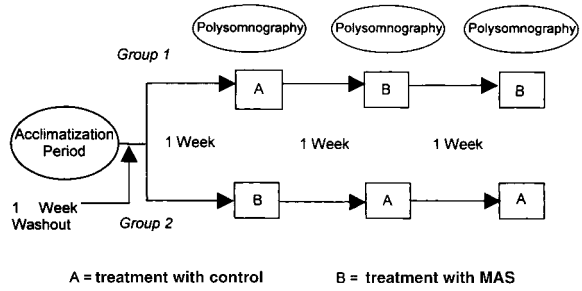

Figure 3. Schematic diagram summarizing the study design.

Treatment Outcome

Complete response was defined as a resolution of symptoms plus reduction in AHI to < 5/h. Partial response was defined as improved symptoms plus $\geq 50\%$ reduction in AHI, but AHI remaining ≥ 5/h. Treatment failure was defined as ongoing clinical symptoms and/or a $< 50\%$ reduction in AHI. Compliance failure was defined as an inability of the patient to continue to use the treatment.

Cephalometric Radiographs

A lateral cephalometric radiograph was taken for each subject before treatment, according to previously described methodology (13, 14). Radiographs were taken at end-expiration with the head in the natural position, achieved by asking the subjects to look into their own pupils reflected in a mirror located at eye level. All lateral head radiographs were hand-traced (by AM). The landmarks and measurements used for the cephalometric analysis are detailed in Figure 4. To quantify the level of random errors, 12 cephalograms were randomly chosen from the main series, and the tracings were replicated and measured under the same conditions a month later.

Statistical Analyses

Data were analyzed using a statistical package (SPSS Version 8.0; SPSS Inc, Chicago IL). Unpaired *t* tests were used to compare physical characteristics and baseline data between Groups I and II. Paired *t* tests were used to compare ESS before and with the use of the MAS at the end of the acclimatization period, and to determine whether there was a significant treatment effect of the control plate when compared with baseline polysomnographic variables. A General Linear Model (GLM) was used to analyze polysomnographic data from the crossover design. Type III sums of squares were used for tests, and adjusted treatment means were obtained (9). A multivariable regression model was constructed to examine the relationship between several variables and AHI (with MAS). All descriptive statistics are presented as mean $\pm$ SD. Estimated means are presented as mean $\pm$ SEM. Using data from a previous study (15), we estimated that a sample size of 30 was required to achieve a power of 0.80 and $2\alpha = 0.05$.

RESULTS

Study Population

From the sample of 28 patients recruited into the study, 24 completed the protocol. Two patients withdrew as they were unable to acclimatize to the MAS because of excessive saliva-

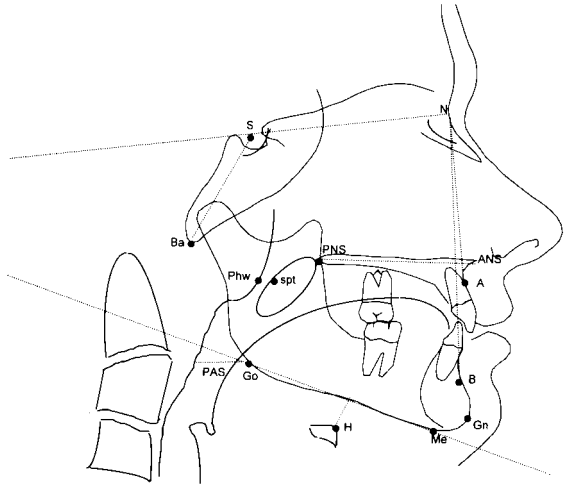

Figure 4. Definitions of cephalometric landmarks and measurements. *Anatomical landmarks*: ANS = Anterior Nasal Spine, the tip of the median sharp bony process of the palatine bone in the hard palate. A Point = deepest midline point on the maxillary alveolus between ANS and the maxillary alveolar crest. B Point = deepest midline point between the mandibular alveolar crest and the gnathion. Ba = Basion, the most inferior point on the anterior margin of the foramen magnum in the median plane. Go = Gonion, the most lateral external point at the junction of the horizontal and ascending rami of the mandible. Gn = Gnathion, the most anteroinferior point on the bony mandibular symphysis. H = Hyoidale, the most superior-anterior point on the body of the hyoid bone. Me = Menton, the lowest point on the bony outline of the mandibular symphysis. MP = Mandibular plane, line joining Me and Go. N = Nasion, the most anterior point of the frontonasal suture. PNS = Posterior nasal spine, the tip of the posterior spine of the palatine bone in the hard palate. spt = tangent point on a line parallel to the long axis of the soft palate at the maximum width. Phw = Posterior pharyngeal wall, the point on the posterior pharyngeal wall at the same horizontal level as spt. S = Sella, the center of the sella turcica. *Measurements*: BaSN (degrees) = Cranial base angulation in midsagittal plane, SN (mm) = anterior cranial base length. Go-Gn (mm) = mandibular length. SNA (degrees) = angle from S to N to A Point. SNB (degrees) = angle from S to N to B Point. ANB (degrees) = angle from A Point to N to B Point. SN-MP (degrees) = angulation of the mandibular plane with the SN line. H-MP (mm) = perpendicular distance from the MP to H. RPAS (mm) = width of nasopharynx from Phw to spt. PAS (mm) = distance between the posterior pharyngeal wall and the dorsal surface of the base of the tongue, measured on the line that intersects Go and B point.

tion and temporomandibular joint pain, and were classified as compliance failures. One patient developed unstable angina and was therefore excluded from the study. The other dropout did not wish to continue because of inability to comply with the time demands of the protocol. Patient characteristics at baseline for the entire group, and subgroups, are presented in Table E1 in the online data supplement to this article. Patients who completed the protocol (19M, 5F) had a mean (± SD) age of 48 ± 9 yr (range, 35 to 73 yr), body mass index of 29.4 ± 3.1 kg/m^2 (range, 24.8 to 36.3 kg/m^2), baseline AHI of 27 ± 17/h (range, 10 to 68/h), and $MinSa_{O_2}$ of 85 ± 8% (range, 61 to 96%). There was no significant difference in baseline characteristics between the two groups. The mean acclimatization period was 19.7 ± 8.8 weeks (range, 5 to 40 wk). The mean mandibular advancement with the MAS was 7.5 ± 1.8 mm (range, 5.0 to 11.5 mm), representing a mean of 78% (63 to 89%) of maximal protrusion at the end of the acclimatization period.

Subjective Outcomes

The MAS was well tolerated by 21 of the 24 patients who completed the protocol (87.5%). Side effects included excessive salivation (50%), gum irritation (20%), mouth dryness (46%), jaw discomfort (12.5%), and tooth grinding (12.5%). These were described as mild to moderate, lasting less than 3 wk, and they did not preclude continued use of the MAS. The majority of patients reported substantial improvements in snoring (70%), sleep quality (91%), and daytime sleepiness (ESS, 10.1 ± 1.1 versus 3.9 ± 0.6, $p < 0.01$). Twenty-one patients (87.5%) reported nightly use of the appliance. Twenty-three patients (96%) stated they would like to continue to use the MAS because of a perceived improvement in their symptoms.

TABLE 1. EFFECT OF MAS ON POLYSOMNOGRAPHIC VARIABLES*

Variable	Control	MAS	p Value
Sleep variables			
TST, min	372 ± 5	363 ± 5	NS
REM sleep, min	61 ± 4	75 ± 4	< 0.05
REM, %	16 ± 1	21 ± 1	< 0.005
NREM sleep, min	311 ± 4	287 ± 4	< 0.0001
NREM, %	84 ± 1	80 ± 1	< 0.005
TST spent supine, %	46 ± 4	55 ± 4	NS
Arousal Index/h	41 ± 2	27 ± 2	< 0.0001
Sleep efficiency, %	87 ± 1	85 ± 1	NS
Respiratory variables			
AHI/h	30 ± 2	14 ± 2	< 0.0001
$MinSa_{O_2}$, %	87 ± 1	91 ± 1	< 0.0001
Snoring frequency/h	402 ± 29	242 ± 28	< 0.005
Mean snoring intensity, dB	52 ± 1	49 ± 1	< 0.0001
Maximum snoring intensity, dB	70 ± 1	68 ± 1	NS

Definition of abbreviations: MAS = mandibular advancement splint; NREM% = time in NREM sleep as a % of TST; REM% = time in REM sleep as a % of TST; TST = total sleep time.

* All values represent mean ± SEM.

Objective Outcomes

Polysomnographic outcomes are summarized in Table 1. The control plate had no significant effect on AHI (30 ± 2 versus 27 ± 3, p = ns) or $MinSa_{O_2}$ (87 ± 1 versus 85 ± 2%, p = ns) compared to baseline. Total sleep time did not change with the MAS, but there was a significant redistribution to more REM sleep and less NREM sleep. Sleep efficiency was not significantly different. The MAS resulted in a significant reduction in AHI (by 53%), arousal index (by 34%), mean snoring frequency (by 47%), and mean intensity (by 3dB), compared with the control plate. There was a significant improvement in $MinSa_{O_2}$. No significant carryover, sequence, or period effects were identified for these polysomnographic variables.

Treatment Outcome

The MAS resulted in either partial or complete response in 15 patients (62.5%). Complete response was achieved in nine (37.5%) patients, and partial response in six (25%). Treatment failure occurred in nine (37.5%) patients. Baseline OSA severity category did not influence treatment outcome (Figure 5). For comparison with other published studies, treatment outcome was also examined at two other AHI cutoffs. At a cutoff of 10/h, complete response was achieved in 54%, partial response in 17%, and failure occurred in 29%. At a cutoff of 15/h, complete response was achieved in 75%, partial response in 4%, and failure occurred in 21%.

Model for Outcome Prediction

Multiple regression analysis identified four independent predictors of outcome: neck circumference (NC), baseline AHI, and two cephalometric measurements—retropalatal airway space (RPAS) and the angle between anterior cranial base

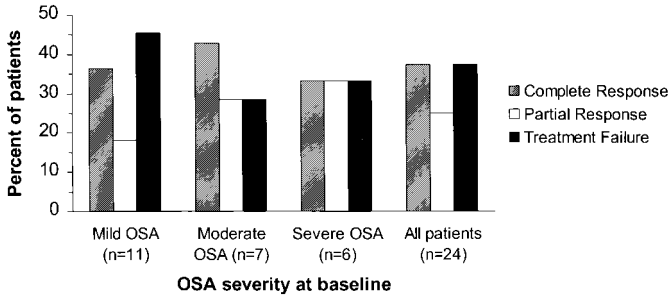

Figure 5. Graph showing treatment outcome in all patients and according to baseline OSA severity, defined as mild (AHI $<$ 20/h), moderate (AHI, 20 to 40/h), and severe (AHI $>$ 40/h).

and mandibular plane (SN-MP). The derived equation to predict AHI with the MAS was:

$$\text{AHI (MAS)} = 19.4 + 1.3\,\text{NC} - 2.7\,\text{RPAS} + 0.4\,\text{BaseAHI} - 1.0\,\text{SN-MP}\ (R^2 = 0.82,\ s = 8.06).$$

The reliability index of the repeated cephalometric measurements ranged from 0.98 to 0.99, indicating a high degree of reproducibility.

A power calculation indicated that the achieved power for the study was 0.96.

DISCUSSION

Although there has been increasing interest in the use of oral appliances to treat snoring and sleep apnea, numerous methodologic weaknesses in previous studies leave uncertainty about the role of this therapy in the routine management of OSA. In this randomized, controlled crossover study, we found the MAS was effective in completely controlling OSA in more than one third of patients. Hence, it is suggested that this MAS may be a viable alternative to nasal CPAP in a significant proportion of patients with OSA, including some with moderate or severe OSA.

As in other studies (7), the majority of our patients derived a significant subjective benefit from the MAS, with 83% reporting combined improvements in snoring, sleep quality, and daytime sleepiness. Similarly, the MAS was well tolerated by most patients (87.5%), although two were compliance failures, withdrawing from the study during the acclimatization period because they were unable to tolerate the appliance. The side effects that were reported in this short-term study were of mild to moderate intensity, and most symptoms resolved within 3 wk with continued use of the MAS. These included jaw discomfort, salivation, dryness of the mouth, and grinding of the teeth, as reported in other studies (7). However, the potential long-term side effects of the MAS warrant serious consideration, and close follow-up of patients who embark on long-term therapy is recommended (16). The short-term compliance rate with the MAS was high, at least by self-report. This compares favorably with the rates reported by other studies using oral appliances (7). It would be preferable to measure compliance objectively, but the technology to enable this is still under development (17). All but one patient stated they wanted to continue to use the MAS because they perceived it conferred a health benefit. This high acceptance rate contrasts with CPAP which, although more effective, is associated with poor acceptance and compliance because of its obtrusive nature (4).

The impressive subjective responses contrasted considerably with the objective responses, with 37.5% of patients being classified as treatment failures despite subjective improvement. This suggests that the MAS had a placebo effect on symptoms. Despite the symptomatic benefit in these patients, long-term therapy with the MAS would be inappropriate, highlighting the need for follow-up polysomnography. It remains uncertain whether treatment failure resulted from technical factors, i.e., the mandible was simply not advanced enough to achieve objective success, or whether failure was truly due to ineffectiveness of the treatment. Hence, we believe the observed success rate is conservative, and that more aggressive advancement may improve outcomes, albeit with the potential for more side effects. This study found a significant reduction in mean AHI of 53% with the MAS, compared with control. This result is similar to that reported in other studies (7, 18–23). However, our finding of a significant improvement in minimum oxygen saturation and arousal index has not been a consistent finding in other studies (15, 20, 21, 24). It is interesting to note that the mean arousal index did not return to the normal range. Although this raises the possibility of persistent upper airway resistance, the majority of patients reported resolution of daytime sleepiness. Furthermore, MAS treatment resulted in improved sleep architecture, with a redistribution to more REM sleep and less NREM sleep.

A particular strength of our study was the robust definition of complete response, a weakness of almost all previous studies (7, 18–23). This allows comparison of outcome with nasal CPAP treatment, where the goals of therapy are to return the AHI to the normal range ($<$ 5/h), improve sleep architecture, and symptoms. This outcome was achieved in 37.5% of our patients. Using more liberal definitions of success, for the purpose of comparing to previously published studies, complete response was achieved in 54 and 75% of patients at AHI cutoffs of $<$ 10/h and $<$ 15/h, respectively. These results are among the highest response rates reported. Moreover, in our study treatment outcome was similar across all categories of OSA severity, with complete response being achieved in some subjects with moderate and severe OSA. This finding is similar to that reported by Henke and colleagues (23), but contrasts with other studies, which have generally reported improvement at the mild end of the severity spectrum (7). Practice parameters on the use of oral appliances in the treatment of OSA, produced by the American Sleep Disorders Association (8), recommend oral appliances only in snorers or those with mild OSA, and in patients with moderate or severe OSA only if CPAP treatment is intolerable or refused. Although a number of studies comparing CPAP with oral appliances have shown that CPAP is more effective in lowering AHI (15, 24, 25), our data suggest that treatment with MAS merits consideration as first-line therapy, even in patients with moderate or severe OSA. However, we caution the need for close monitoring and polysomnographic evaluation of outcome in these patients. Notably, there has been no systematic comparison of different oral appliances to determine the potential influence of appliance design on treatment outcome. Hence at this stage it would seem prudent not to extrapolate the outcomes of this study to all other oral appliances.

Another strength of our study was that snoring was measured objectively, as well as subjectively. O'Sullivan and colleagues (21) found an 18% reduction in snoring frequency and a 15.8% reduction in snoring intensity, reflected by the proportion of snores $\geq$ 50 dB. The MAS used in our study resulted in a greater reduction (40%) in mean snoring frequency. Similarly, we observed a significant reduction in snoring intensity, with a mean 3 dB reduction. Notably, the maximum snoring intensity did not change, despite the major subjective improvements. These results indicate that the MAS is a very effective treatment for the symptomatic control of snoring.

The choice of control in this study was an oral plate that did not induce mandibular advancement. This choice was based on the possibility that part of the effect of the MAS could be related to factors other than mechanical advancement of the mandible such as the potential for stimulation of neuromuscular reflex pathways within the oral cavity and changes in the bite relationship. Although patients generally found the control plate easier to tolerate as it did not advance the mandible, none reported significant changes in symptoms. However, this was not systematically assessed in this study. Comparison of polysomnographic respiratory variables at baseline and with the control plate revealed no significant difference, confirming that the dominant mechanism of action of the MAS is mechanical advancement of the mandible, and that the other potential mechanisms we considered have little or no role.

Given that treatment success with oral appliances is not achievable in all patients, it would be advantageous to be able to predict which patients will derive benefit so as to avoid inappropriate delays in therapy and wastage of resources. From our data, we were able to derive an equation to predict AHI with the MAS. This highly predictive model indicates that AHI with the MAS is positively correlated with neck circumference and baseline AHI and, negatively correlated with the width of the retropalatal airway and angulation of the mandibular plane to the anterior cranial base. Notably, baseline AHI is only a minor, albeit significant, contributor to the model. Others have also attempted to predict the outcome of treatment with oral appliances (20, 26), but the utility of these models in the clinical setting is yet to be confirmed.

Our study has a number of potential limitations. Patients were selected from a specialized multidisciplinary sleep disorders clinic with a research interest in dental therapies for OSA. Hence, there may have been referral bias. In addition, patients elected to use the MAS as a treatment option rather than the conventionally advocated CPAP, leading to a further potential for sample bias. Nevertheless, we believe that our sample is reasonably representative of patients with OSA, and that our results can be extrapolated to a general OSA population. Although the sample size would appear to be modest, the power of the study was very high because of the robust study design. Symptoms were assessed before and after the acclimatization period, during which active treatment with the MAS was instituted and subsequently titrated. Hence, subjective outcomes were not assessed in a randomized, controlled fashion. There may have been an element of responding to the questionnaire in a socially desirable way (response bias). This may have contributed to the observed discrepancy between subjective and objective outcomes. Hence, this leaves some uncertainty as to the authenticity of the reported improvements in daytime sleepiness, even in those who were complete responders. Objective measures of daytime vigilance and performance are required in future studies to verify these subjective improvements.

In conclusion, we have demonstrated that the MAS used in this study is well tolerated, at least in the short term, and is associated with substantial subjective and objective improvements in a significant proportion of patients. Hence, we believe that this form of therapy is a viable alternative to nasal CPAP, even in some patients with more severe forms of OSA. However, follow-up polysomnography should be mandatory in these patients, as reliance on subjective response may be highly misleading. Our study also suggests that treatment outcome can be predicted by a combination of anthropomorphic, polysomnographic, and radiographic measurements, but this requires verification from a prospective study.

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