Clinical Investigations

Respiration

Respiration 2011;81:411–419
DOI: 10.1159/000319595

Received: May 14, 2010
Accepted after revision: July 17, 2010
Published online: October 20, 2010

Oral Appliance Therapy versus Nasal Continuous Positive Airway Pressure in Obstructive Sleep Apnea: A Randomized, Placebo-Controlled Trial

Ghizlane Aarab[a] Frank Lobbezoo[a] Hans L. Hamburger[b] Machiel Naeije[a]

[a]Department of Oral Kinesiology, Academic Center for Dentistry Amsterdam, Research Institute MOVE, University of Amsterdam and VU University Amsterdam, and [b]Department of Clinical Neurophysiology and Center for Sleep-Wake Disorders, Slotervaart Medical Center, Amsterdam, The Netherlands

Key Words

Continuous positive airway pressure · Mandibular advancement device · Obstructive sleep apnea · Randomized controlled trial · Sleep-wake disorders

Abstract

Background: Previous randomized controlled trials have addressed the efficacy of mandibular advancement devices (MADs) in the treatment of obstructive sleep apnea (OSA). Their common control condition, nasal continuous positive airway pressure (nCPAP), was frequently found to be superior to MAD therapy. However, in most of these studies, only nCPAP was titrated objectively but not MAD. To enable an unbiased comparison between both treatment modalities, the MAD should be titrated objectively as well. ***Objective:*** The aim of the present study was to compare the treatment effects of a titrated MAD with those of nCPAP and an intraoral placebo device. ***Methods:*** Sixty-four mild/moderate patients with obstructive sleep apnea (OSA; 52.0 ± 9.6 years) were randomly assigned to three parallel groups: MAD, nCPAP and placebo device. From all patients, two polysomnographic recordings were obtained at the hospital: one before treatment and one after approximately 6 months of treatment. ***Results:*** The change in the apnea-hypopnea index (ΔAHI) between baseline and therapy evaluation differed significantly between the three therapy groups (ANCOVA; p = 0.000). No differences in the ΔAHI were found between the MAD and nCPAP therapy (p = 0.092), whereas the changes in AHI in these groups were significantly larger than those in the placebo group (p = 0.000 and 0.002, respectively). ***Conclusion:*** There is no clinically relevant difference between MAD and nCPAP in the treatment of mild/moderate OSA when both treatment modalities are titrated objectively.

Introduction

Obstructive sleep apnea (OSA) is defined as recurrent obstruction of the upper airway, often resulting in oxygen desaturation and arousal from sleep [1]. OSA is a common disorder in the general middle-aged population, affecting approximately 2% of women and 4% of men [2]. As reviewed extensively, OSA patients can suffer from a range of consequences of their condition, including not only complaints of snoring and excessive daytime sleepiness but also symptoms of neurocognitive impairment and mood disturbance [2, 3]. Further, they may develop cardiovascular problems, like myocardial infarction and stroke. Since these symptoms and problems have a great impact on an OSA patient's quality of life and life expectancy, adequate treatment is indicated.

KARGER

Fax +41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com

0025–7931/11/0815–0411$38.00/0

Accessible online at:
www.karger.com/res

Ghizlane Aarab, DDS
Department of Oral Kinesiology
Academic Center for Dentistry Amsterdam, Louwesweg 1
NL–1066 EA Amsterdam (The Netherlands)
Tel. +31 20 518 8412, Fax +31 20 518 8414, E-Mail g.aarab@acta.nl

Treatment options for OSA include, amongst others, behavioral modification (e.g. weight loss and alteration in sleep posture) and continuous positive airway pressure (CPAP), while particularly over the past decade mandibular advancement devices (MADs) are increasingly used [3–5]. During sleep, these devices advance the mandible and/or the tongue, thereby increasing the size of the upper airway. Various randomized controlled trials have addressed the efficacy of MADs in the treatment of OSA [6–12]. Their common control condition, CPAP, was found to be superior to MAD therapy. However, in most of these studies, CPAP was titrated objectively (i.e. by using polysomnography, PSG) but not the MAD. To enable an unbiased comparison between both treatment modalities, the MAD should be titrated objectively as well.

Therefore, the aim of the present study was to compare the effects of an MAD with those of nasal CPAP (nCPAP) following PSG-controlled titration of both treatment modalities. The hypothesis for this study was that MAD is as effective as nCPAP in the treatment of mild/moderate OSA. To control for possible placebo effects in subjective outcome variables like excessive daytime sleepiness and health perception, an intra-oral placebo device served as passive control condition for both active treatment modalities. The study was performed according to the CONSORT (consolidated standards of reporting trials) statement [13], employing a parallel-group, randomized, placebo-controlled trial design.

Patients and Methods

Setting and Participants

Eligible OSA patients, living in the greater Amsterdam area, were referred to the Slotervaart Medical Center by their family physician. All patients underwent a thorough medical examination, including a full PSG recording, at the Departments of Neurology, Pulmonary Medicine, and ENT, as well as a thorough dental examination at the Department of Oral Kinesiology of the Academic Center for Dentistry Amsterdam (ACTA). OSA patients were invited for participation in this study when they fulfilled the following inclusion criteria: age >18 years, an apnea-hypopnea index (AHI) between 5 and 45 events per hour, and a report of excessive daytime sleepiness (Epworth Sleepiness Score ≥10) or at least two of the symptoms suggested by the American Academy of Sleep Medicine Task Force, e.g. unrefreshing sleep and daytime fatigue [1, 14]. The medical and dental exclusion criteria are shown in table 1. Exclusion of temporomandibular disorders was based on a functional examination of the masticatory system [15, 16].

The scientific and ethical aspects of this study protocol were approved by the Medical Ethics Committee of the Slotervaart Medical Center (Nos. U/1731/0326 and U/2679/0326).

Table 1. Number of patients excluded based on the medical and dental exclusion criteria used in this study

Exclusion criteria	Patients excluded, n
Medical	
Respiratory/sleep disorder other than OSA	23
BMI >40	3
Medication usage that could influence respiration or sleep	2
Periodic limb movement disorder	21
Previous treatment with CPAP or MAD	–
Reversible morphological upper airway abnormalities (e.g. enlarged tonsils)	17
Other medical conditions (e.g. psychiatric disorders)	7
Dental	
Temporomandibular disorders	–
Untreated periodontal problems	1
Dental pain	–
Lack of retention possibilities for an oral appliance	28

Randomization and Allocation

After written informed consent was obtained, the patients were randomly allocated to one of three therapy groups (MAD, nCPAP or placebo). To ensure that the groups were of approximately the same size, block randomization was used. Block sizes were 6, 12 and 18; sizes were randomly varied. The allocation sequence was automatically generated and subsequently concealed by an independent co-worker, who kept a paper copy in a lockable drawer. Sealed opaque envelopes were used to conceal the allocation from the principal investigator.

Interventions and Blinding

Three forms of therapy interventions were used in this parallel-group study. First, an individually fabricated MAD with an adjustable protrusive mandibular position at a constant vertical dimension was used [17, 18]. Second, nCPAP of the REMstar Pro system was used (Respironics, Herrsching, Germany). Third, a thin (<1 mm), hard acrylic-resin palatal splint with only a partial palatal coverage was used as a placebo [19].

Patients were blinded to the nature of the assigned therapy (placebo or active). After evaluating the therapy, all patients were asked if they were of the opinion that they had received an active or placebo treatment. As indicated below, blinding of the analyst was ascertained by assigning codes to data sets and by analyzing these sets in random blocks.

Procedure

From all patients, two full PSG recordings were obtained in the sleep laboratory of the Slotervaart Medical Center, using Siesta hardware and Pro-Fusion software (Compumedics, Abbotsford, Vic., Australia): one before therapy assignment (baseline PSG) and one after 6 ± 2 months (mean ± SD) of treatment (therapy evaluation PSG). The primary and secondary outcome measures were obtained at baseline and therapy evaluation.

The MAD and nCPAP were titrated before the start of the treatment. The titration of the nCPAP was performed during a third sleep laboratory examination. The pressure was increased in incremental steps of 1 cm H_2O/h, until respiratory disturbances and respiration-related arousals were reduced to $\leq$5/h and snoring was minimized. The average value of the pressure was 7.3 cm H_2O (SD, 1.9; range, 4–11).

For the titration of the MAD, four ambulatory PSG recordings were obtained at regular intervals [18], using Monet hardware and Rembrandt Software (Medcare Automation, Amsterdam, The Netherlands). The most effective protrusion position of the MAD (i.e. the mandibular position that yielded the lowest AHI value) was chosen from among four randomly offered positions (viz. 0, 25, 50 and 75% of the maximum protrusion). The MAD was set at 25% of the maximum protrusion in 1 patient, at 50% in 7 patients and at 75% in 12 patients.

For the placebo group, the study procedure was made equally intense as that for the MAD group by making four ambulatory PSG recordings at regular intervals, too.

For all patients, the therapy evaluation PSG recordings were followed by a visit at ACTA, during which the patients were interviewed about (1) their compliance (% of nights per week usage), (2) the change in snoring sound (disappeared, decreased, remained unchanged or increased) as reported by a partner and (3) side effects (nature and number) of the patients' therapy.

Outcome Measures

The change in AHI (ΔAHI) between baseline and therapy evaluation was the primary outcome variable. Secondary outcome variables were the changes in other respiratory and sleep variables, in excessive daytime sleepiness and in health perception (short-form General Health Survey, SF-36) [20] between baseline and therapy evaluation. Other secondary outcome variables were self-reported compliance, snoring and side effects.

Data Analysis

An effect size of 0.8 standard deviations between two treatments is generally considered to be large [21] and should therefore not be overlooked. A sample size of 20 patients per intervention group was calculated to detect this effect size with a power of 80% and a significance level of 5% (two sided). Accordingly, it was decided to include 20 patients in each intervention group.

The patient characteristics at baseline of the three therapy groups were analyzed using one-way analyses of variance, followed by least-significant difference pair-wise comparisons. Patient characteristics that were significantly different between the three groups were used as covariate in the per-protocol analyses and in the intention-to-treat analyses.

The per-protocol analyses included only those patients who completed the trial. Except for compliance, snoring reports and side effects, which were analyzed differently, ANCOVAs were used to detect differences in therapy effect between the three groups for both the primary and the secondary outcome variables. For each variable, its baseline value was used as covariate. In the three sets of secondary outcome variables (viz. respiratory variables other than AHI, sleep and SF-36), the Bonferroni-Holm correction was used to correct for multiple comparisons [22]. For the primary and secondary outcome variables that thus showed a significant therapy effect between the groups, simple contrast analyses were performed. Further, the effect size (including the 95% confidence interval, CI) of the primary outcome variable between MAD and nCPAP was calculated, after correcting the ΔAHIs for the influence of baseline. According to the guidelines by Cohen [21], an effect size of 0.2 is small, of 0.5 is medium and of 0.8 is large.

ANOVA was used to detect differences in compliance between the three therapy groups. To evaluate the association between self-reported snoring and the three groups, a χ^2 test was conducted. Finally, the nature and number of side effects were described and counted.

In an intention-to-treat analysis, the effect of missing ΔAHI values was tested in a series of sensitivity analyses following the suggestion by Petri et al. [23]. In the worst-case scenario, a failure pattern was chosen for the missing ΔAHI values of the MAD group, and a success pattern for the nCPAP and placebo groups. In the best-case scenario, a success pattern was chosen for the missing ΔAHI values of the MAD group and a failure pattern for the nCPAP and placebo group. The failure pattern was defined as the missing ΔAHI value being equal to the smallest value in the group of interest; the success pattern as the missing ΔAHI value being equal to the largest value in the group of interest. In case that the AHI value at therapy evaluation would then become negative, the ΔAHI was chosen such that the AHI at therapy evaluation was equal to zero. One-way analysis of covariance (ANCOVA), using the baseline value of AHI as covariate, and simple contrast analyses were used to detect differences in therapy effect in the worst-case and in the best-case scenario.

Statistical tests were performed with the SPSS 15.0 software package (SPSS, Chicago, Ill., USA).

Results

Figure 1 shows a flow chart for the 219 patients who were eligible for the study. Seventy-three patients were excluded for medical reasons, and 29 patients for dental reasons (table 1). Thirty-one patients refused to participate and 22 patients did not participate for various other reasons, e.g. loss of contact. Finally, 64 patients were enrolled in the study and 57 patients completed the study.

The patient characteristics at baseline are presented in table 2. Body mass index (BMI) was the only baseline characteristic that differed between the three therapy groups ($F = 5.170$; $p = 0.008$). Analyses of least-significant differences revealed that the MAD group had a significantly lower BMI than the placebo and nCPAP groups ($p = 0.002$ and 0.006, respectively). Therefore, BMI was entered as covariate in the below-described analyses of covariance. Within the three treatment groups, the BMI showed no change from baseline to therapy evaluation (paired t tests; $p = 0.408–0.752$).

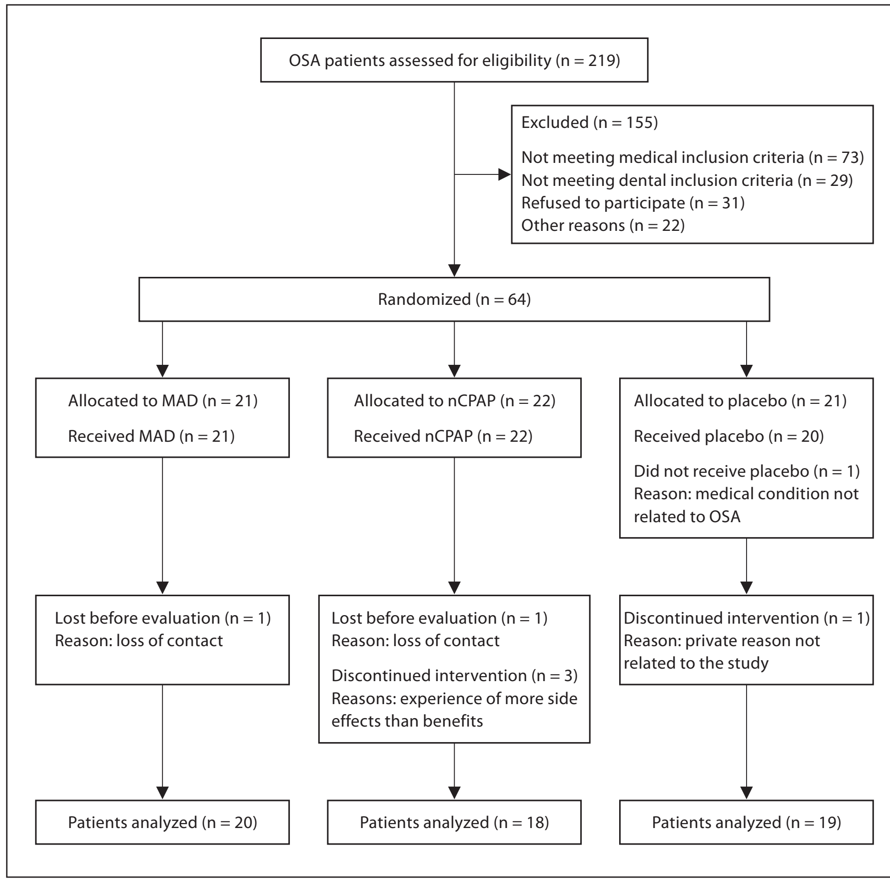

Fig. 1. Flow chart of the patients through each stage of the trial.

Table 2. Patient characteristics at baseline (mean ± SD) of the three study groups and dropouts

Characteristics	MAD (n = 20)	nCPAP (n = 18)	Placebo (n = 19)	Dropouts (n = 7)
Age, years	50.3 ± 9.1	55.4 ± 9.8	51.3 ± 10.1	49.3 ± 7.3
Males/females	16/4	12/6	14/5	5/2
AHI	22.1 ± 10.8	20.9 ± 9.8	20.1 ± 8.7	14.8 ± 3.8
BMI	27.1 ± 3.2	30.7 ± 3.7	31.1 ± 4.7	27.8 ± 4.1
Neck circumference, cm	41.7 ± 3.0	43.6 ± 4.0	42.6 ± 3.2	41.4 ± 4.8
Epworth sleepiness score	11.8 ± 5.8	10.2 ± 4.7	10.6 ± 4.1	13.7 ± 1.9
36-item short-form Health Survey				
Physical functioning	82.9 ± 22.7	61.1 ± 24.8	77.4 ± 24.2	73.8 ± 18.4
Social functioning	75.0 ± 23.6	64.8 ± 25.5	75.7 ± 29.0	77.5 ± 22.3
Role physical	53.9 ± 48.1	64.7 ± 45.1	69.7 ± 39.6	45.0 ± 51.2
Role emotional	77.2 ± 41.7	76.5 ± 40.4	78.9 ± 37.2	73.3 ± 43.5
Mental health	66.7 ± 14.1	64.5 ± 22.7	69.9 ± 21.9	69.6 ± 19.3
Vitality	49.7 ± 18.0	46.3 ± 19.5	48.7 ± 26.1	56.0 ± 12.9
Bodily pain	79.6 ± 27.9	65.9 ± 28.8	82.1 ± 26.2	71.0 ± 35.4
General health perception	54.7 ± 22.3	49.6 ± 16.5	60.3 ± 21.3	52.0 ± 8.4
Health transition	41.3 ± 24.7	38.3 ± 29.7	45.8 ± 21.4	50.0 ± 17.7

[a] MAD patients had a significantly lower BMI than placebo and nCPAP patients (p = 0.002 and 0.006, respectively).

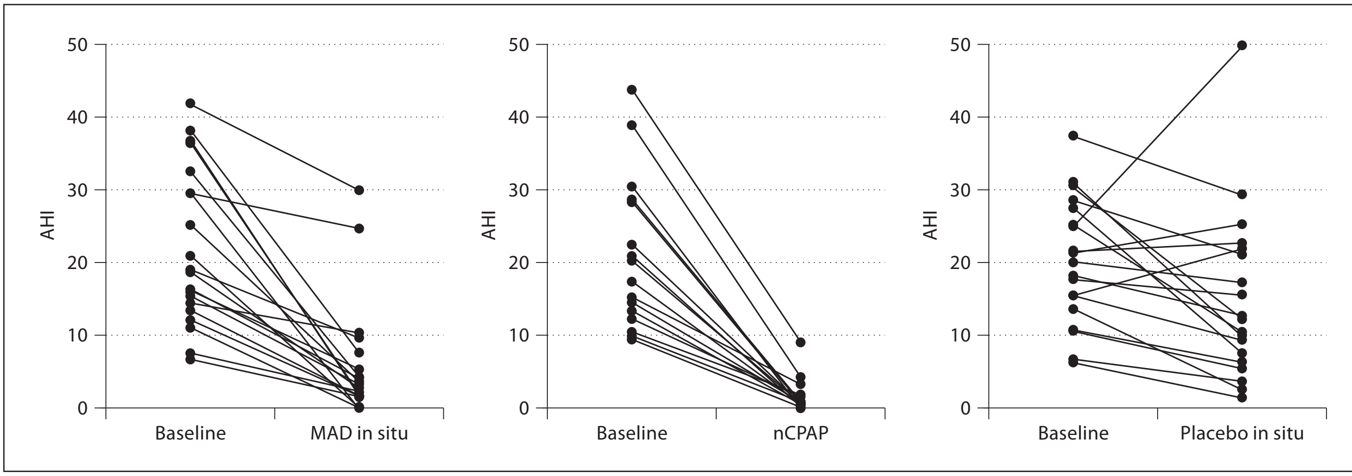

Fig. 2. Individual AHI values of 57 patients completing the trial: baseline and therapy evaluation PSG recordings with the MAD (n = 20), nCPAP (n = 18) and placebo appliance (n = 19) in situ.

Table 3. The mean (±SD) baseline and delta (i.e. difference between baseline and therapy evaluation) values of the respiratory and sleep outcome variables of the three groups (MAD, nCPAP and placebo)

	MAD (n = 20)		nCPAP (n = 18)		Placebo (n =19)		p
	baseline	Δ value	baseline	Δ value	baseline	Δ value	
Respiration, events/h							
AHI	22.1 ± 10.8	16.3 ± 10.3	20.9 ± 9.8	19.5 ± 8.7	20.1 ± 8.7	5.2 ± 10.5	0.000[a]
AHI_REM_supine	24.6 ± 31.5	12.5 ± 34.8	31.2 ± 30.5	26.7 ± 30.4	32.2 ± 28.1	5.6 ± 31.1	0.002[b]
AHI_NREM_supine	33.0 ± 23.9	25.1 ± 21.4	39.2 ± 25.9	34.0 ± 24.4	22.1 ± 16.4	–2.6 ± 23.1	0.000[b]
AHI_REM_non-supine	15.1 ± 14.9	7.5 ± 13.0	16.4 ± 16.5	14.1 ± 21.3	15.1 ± 15.7	4.4 ± 21.5	0.064
AHI_NREM_non-supine	11.3 ± 11.9	8.6 ± 10.8	10.2 ± 9.8	8.9 ± 9.4	12.6 ± 12.1	5.9 ± 9.0	0.081
Sleep							
Total sleep time, min	425.0 ± 128.6	–11.8 ± 143.2	473.8 ± 83.2	58.8 ± 101.2	444.2 ± 82.9	–7.8 ± 113.4	0.229
Stage 1 and 2, %	68.8 ± 10.8	8.2 ± 14.7	67.0 ± 8.5	0.8 ± 9.1	66.2 ± 11.9	0.8 ± 11.8	0.293
Stage 3 and 4, %	14.5 ± 10.9	–3.1 ± 9.6	12.9 ± 8.4	–1.4 ± 8.7	14.1 ± 7.9	–0.1 ± 9.4	0.788
Stage REM, %	18.3 ± 6.4	–1.9 ± 6.4	20.0 ± 6.4	0.6 ± 8.2	19.7 ± 6.7	–0.7 ± 6.1	0.752
Sleep in supine position, %	47.4 ± 26.3	7.7 ± 32.9	38.5 ± 22.2	–10.1 ± 30.3	39.5 ± 25.3	5.8 ± 38.7	0.161
Respiratory arousal index, events/h	17.0 ± 9.6	13.0 ± 9.0	16.4 ± 8.9	13.9 ± 11.8	13.8 ± 6.6	3.5 ± 8.2	0.008[b]

ANCOVA was applied to compare differences among the three groups, controlled for the effect of the baseline value and BMI.
[a] Statistically significant at the 0.05 probability level.
[b] Statistically significant after Bonferroni-Holm correction.

The mean baseline values (±SD) of the respiratory and sleep variables as well as the changes in these variables from baseline to therapy evaluation are shown in table 3.

Primary Outcome Variable

In the per-protocol analysis, the three groups showed significant differences in the changes in AHI from baseline to therapy evaluation (F = 14.886, p = 0.000; table 3, fig. 2). No differences in the ΔAHI were found between the MAD and nCPAP therapy (p = 0.092), whereas the changes in AHI in the two therapy groups were significantly larger than those in the placebo group (p = 0.000 and 0.002, respectively). The effect size between MAD and nCPAP was 0.48 (range from –0.17 to 1.12). More-over, the placebo group showed a small but significant reduction in AHI between baseline and therapy evaluation (paired t test; p = 0.044).

Also, in the intention-to-treat analysis, the three groups differed significantly in their change in AHI (worst case: F = 14.890, p = 0.000; best case: F = 16.972, p = 0.000). In the worst-case scenario, contrast analysis showed a small but significant difference in ΔAHI between the MAD group and the nCPAP group (p = 0.043); the reduction in the nCPAP group being larger than that in the MAD group. The best-case scenario showed similar results as the per-protocol analyses.

Secondary Outcome Variables

Respiration. In the non-supine position, no significant differences were found in the changes in secondary respiratory variables between the three groups. However, in the supine position, the nCPAP group showed larger reductions in AHI in the rapid eye movement (REM) and non-REM (NREM) sleep than the placebo group (p = 0.000), while the MAD group showed only a larger reduction in AHI during the NREM sleep (p = 0.001).

Sleep. Of the sleep variables analyzed, only the changes in the respiratory arousal index were different between the three therapy groups (table 3). The MAD and nCPAP groups showed significantly larger reductions than the placebo group (p = 0.032 and 0.003, respectively).

Questionnaires. The changes in excessive daytime sleepiness between baseline and therapy evaluation were not different between the three groups (F = 0.070; p = 0.933). The pooled data of the three groups showed a significant decrease with treatment (paired t test, p = 0.002). Within the pooled data of the MAD and nCPAP groups, and also within the placebo group, the improvements in excessive daytime sleepiness were also significant (p = 0.037 and 0.012, respectively). The changes in the domains of the SF-36 were not significantly different between the three groups, while the pooled data of the three groups showed a significant improvement in vitality and health (paired t tests, p = 0.000 and 0.003, respectively). Within the placebo group itself, vitality also showed an improvement (p = 0.013). Whether health also had improved within the placebo group could not be analyzed due to too many missing values for this specific item.

Compliance. The MAD group had used their appliance 90.6% (SD, 13.3) of the nights; the nCPAP group 82.9% (SD, 27.2) of the nights, and the placebo group 93.9% (SD, 15.7) of the nights. No significant group differences in compliance were found (F = 1.518; p = 0.228). In the MAD and nCPAP group, none of the patients were of the opinion that they had received a placebo treatment. On the other hand, 5 of the 19 patients of the placebo group were convinced that they had received placebo treatment.

Snoring. None of the patients reported an increase in snoring. Changes in snoring differed significantly between the three therapy groups (χ^2 = 32.069; p = 0.000). Snoring had decreased more frequently in the MAD group and had disappeared more frequently in the nCPAP group. The placebo group more frequently reported no change in snoring.

Side Effects. The MAD group reported the following side effects: sensitive teeth upon awakening (n = 9), tenderness in the masseter muscle region upon awakening (n = 13), discomfort in wearing (n = 10), hypersalivation (n = 9), dry mouth (n = 4), feeling of a changed occlusion upon awakening (n = 9) and difficulty in swallowing with the MAD in situ (n = 3). The following side effects were reported by the nCPAP group: dry mouth (n = 3), problems with expiration against the positive pressure (n = 5), pain due to pressure of the mask (n = 6), nasal congestion (n = 2), air leaks due to the mask (n = 2), conjunctivitis (n = 2) and difficulty in changing sleep position (n = 3). In the placebo group, no side effects were reported.

Discussion

The aim of this randomized, placebo-controlled trial was to compare the effects of an MAD with those of nCPAP following PSG-controlled titration of both treatment modalities.

Previous randomized controlled trials have also addressed the efficacy of MADs in the treatment of OSA [6–12, 24]. In these studies, the MAD was either set in a fixed protrusion position [8, 11, 12] or it was titrated by the patients themselves or by their dentist. This titration was then based on the patient's subjective evaluation of improvement [6, 10, 24]. However, it can be questioned whether this titration method will yield the most effective mandibular position (i.e. the position that leads to the lowest values of the AHI). To enable an unbiased comparison between MAD and nCPAP, the MAD has to be titrated as objectively as possible. Therefore, in this study, four ambulatory PSG recordings were made for each MAD patient, with the MAD set at four different positions. This method had as disadvantage that four full-night recordings had to be made. A recent study suggests that this disadvantage may be overcome by using a 1-night MAD titration procedure [9].

In the per-protocol analysis, no significant difference between MAD and nCPAP was found in the improvement of AHI. In the worst-case scenario, with the failure and success patterns set at their extreme values in favor of nCPAP, the difference between the two treatment modalities was significant ($p = 0.043$). No difference in treatment results between MAD and nCPAP has been found in a previous trial by Tan et al. [24]. On the other hand, better treatment results for CPAP are also reported [6–12]. Differences in results may be due to differences in the study design, in the way the MAD was titrated, in the baseline characteristics of the study participants (e.g. the severity of the OSA condition), in the primary outcome variable chosen or in the specifics of the appliances and devices used.

Figure 2 shows that 2 patients in the MAD group did not at all respond to the treatment given. As not all patients are able to achieve a successful outcome when treated with an MAD, the development of methods to assist in the selection of who will respond to treatment would be of significant importance. Previous studies have identified a range of anthropomorphic, physiologic and PSG variables associated with a better treatment outcome [25–28]. However, more research is needed to improve the prediction of the treatment outcome of an MAD [5].

Another way of looking at treatment results is by focusing on the treatment outcome values themselves and not by evaluating the changes in AHI. A cutoff point of 5 is often used for the AHI, not only to recognize the presence of OSA, but also to define an OSA treatment to be successful or not [29, 30]. Unfortunately, OSA has a strong time-variant nature, and this complicates the use of a single cutoff point. An AHI value of 9.8, obtained from a single night recording, is at the threshold of the 95% probability band around the cutoff point of 5 [31]. Therefore, Aarab et al. [31] recommended using this value in the recognition of OSA. Taking this recommendation into account, 85% of the MAD group and 100% of the nCPAP group were treated successfully. Considering the clinical relevance of a difference between a new treatment (in this case MAD) and a standard one (nCPAP), the concept of the number needed to treat (NNT) is often used. Comparing MAD and nCPAP, NNT is 7. This means that when 7 patients are treated in both groups, nCPAP would treat 7 out of these 7 patients successfully and MAD only 6. In the worst-case scenario of the intention-to-treat analysis, NNT is 6; in the best-case scenario it is 26. An NNT of 5 or more is usually interpreted as being an indication that there is no clinically relevant difference between the two treatments being compared [32]. This indicates that the non-significant difference between the MAD and nCPAP is not clinically relevant.

The placebo appliance also resulted in a small but significant reduction in the AHI. This observed reduction in the AHI may be due to a change in lifestyle as a result of the information given to the patients at baseline, or it may be related to a placebo response. The AHI responses to the placebo treatment indicate that these factors may also play a role in the improvements seen in the MAD and nCPAP groups.

The results of the secondary respiratory variables indicate that the MAD and nCPAP are especially effective in the supine position. A part of this finding corresponds with the previous findings of Marklund et al. [33], who found that successful reduction of the overall AHI with an MAD is related to the higher number of apnea/hypopneas in supine position. In the supine position, the nCPAP is effective in both sleep stages (REM and NREM), while the MAD shows no reduction compared to placebo in the REM sleep. During REM sleep, there is a reduction in activity of the pharyngeal musculature [34] and the positive airway pressure of nCPAP may be better capable of preventing a collapse of the upper airway during this reduced activity than the MAD.

Within the placebo group, an improvement in excessive daytime sleepiness could be observed. Therefore, it cannot be excluded that the improvement in Epworth sleepiness scale, observed in the pooled data of the MAD and nCPAP group, and also reported in other studies [7, 10, 24, 35], is unrelated to the mechanisms of the treatments (advancement of the mandible or the application of positive airway pressure) but is merely the result of a placebo effect, inevitably associated with these treatments, or due to a change in lifestyle. The same may be true for the changes found in the domains of the short-form General Health Survey, SF-36 [20].

The relatively high compliance rates of approximately 90% (i.e. the percentage of nights per week usage) for the three therapies are probably related to the frequent visits the patients paid to ACTA (once every 4 weeks) for interviews about, amongst others, the frequency of wearing. This regular contact with the examiner has probably motivated the patients to use their device on an almost nightly basis. The compliance rates in daily practice are probably lower and may also be different between MAD and nCPAP.

Snoring is one of the most frequently reported complaints of OSA patients, and in most cases the primary reason to seek help. However, it is seldom reported in OSA studies [6, 8, 10, 11]. This is probably due to difficulties in measuring this condition [36, 37]. In this study, snoring was evaluated at therapy evaluation by interviewing the patient. This approach has limitations in its dependency upon a bed partners' report about the snoring habit of the patient. The present study suggests that both the MAD and the nCPAP treatment had a favorable influence upon the snoring of the patient.

Most of the side effects reported by the MAD patients were mild and did not differ from those reported previously [5, 36]. In the nCPAP group, 3 patients dropped out of the study, because they experienced more side effects than benefits of the treatment. This suggests that nCPAP patients may show more problems in accepting their treatment modality than MAD patients.

Within the limits of this study, it can be concluded that the results do not point to a clinically relevant difference between MAD and nCPAP in the treatment of mild/moderate OSA. Placebo effects probably play a role in the subjective treatment results.

Acknowledgments

The authors thank the staff of the Center for Sleep-Wake Disorders of the Slotervaart Medical Center in Amsterdam, The Netherlands, for their assistance with this work; Drs. Corine Visscher and Irene Aartman for their assistance with the statistical analyses of this study, and the Dental Laboratory Excent, Amsterdam, The Netherlands, for the assistance in the development of the MAD used in this study. The Netherlands Institute for Dental Sciences supported this work.

Financial Disclosure and Conflicts of Interest

No actual or potential conflicts of interest exist for any of the authors, nor is there any personal or financial support and author involvement with organizations with financial interest in the subject matter of the paper to be disclosed for any of the authors.

References

1 American Academy of Sleep Medicine Task Force: Sleep-related breathing disorders in adults: recommendations for syndrome definition and measurement techniques in clinical research. Sleep 1999;22:667–689.

2 Young T, Palta M, Dempsey J, Skatrud J, Weber S, Badr S: The occurrence of sleep-disordered breathing among middle-aged adults. N Engl J Med 1993;328:1230–1235.

3 Cistulli PA, Gotsopoulos H, Marklund M, Lowe AA: Treatment of snoring and obstructive sleep apnea with mandibular repositioning appliances. Sleep Med Rev 2004;8:443–457.

4 Lim J, Lasserson TJ, Fleetham J, Wright J: Oral appliances for obstructive sleep apnoea. Cochrane Database of Systematic Reviews 2006;1: CD004435.

5 Chan AS, Cistulli PA: Oral appliance treatment of obstructive sleep apnea: an update. Curr Opin Pulm Med, E-pub ahead of print.

6 Barnes M, McEvoy RD, Banks S, et al: Efficacy of positive airway pressure and oral appliance in mild to moderate obstructive sleep apnea. Am J Respir Crit Care Med 2004;170: 656–664.

7 Clark GT, Blumenfeld I, Yoffe N, Peled E, Lavie P: A crossover study comparing the efficacy of continuous positive airway pressure with anterior mandibular positioning devices on patients with obstructive sleep apnea. Chest 1996;109:1477–1483.

8 Engleman HM, McDonald JP, Graham D, Lello GE, Kingshott RN, Coleman EL, Mackay TW, Douglas NJ: Randomized crossover trial of two treatments for sleep apnea/hypopnea syndrome: continuous positive airway pressure and mandibular repositioning splint. Am J Respir Crit Care Med 2002;166: 855–859.

9 Gagnadoux F, Fleury B, Vielle B, Pételle B, Meslier N, N'Guyen XL, Trzepizur W, Racineux JL: Titrated mandibular advancement versus positive airway pressure for sleep apnoea. Eur Respir J 2009;34:914–920.

10 Hoekema A, Stegenga B, Wijkstra PJ, van der Hoeven JH, Meinesz AF, de Bont LG: Obstructive sleep apnea therapy. J Dent Res 2008;87:882–887.

11 Lam B, Sam K, Mok WY, et al: Randomised study of three non-surgical treatments in mild to moderate obstructive sleep apnoea. Thorax 2007;62:354–359.

12 Randerath WJ, Heise M, Hinz R, Ruehle KH: An individually adjustable oral appliance vs continuous positive airway pressure in mild-to-moderate obstructive sleep apnea syndrome. Chest 2002;122:569–575.

13 Altman DG, Schulz KF, Moher D, et al: CONSORT GROUP (Consolidated Standards of Reporting Trials). The revised CONSORT statement for reporting randomized trials: explanation and elaboration. Ann Intern Med 2001;134:663–694.

14 Johns MW: A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep 1991;14:540–545.

15 Dworkin SF, LeResche L: Research diagnostic criteria for temporomandibular disorders: review, criteria, examinations and specifications, critique. J Craniomandib Disord 1992;6:301–355.

16 Lobbezoo F, van Selms MK, John MT, Huggins K, Ohrbach R, Visscher CM, van der Zaag J, van der Meulen MJ, Naeije M, Dworkin SF: Use of the Research Diagnostic Criteria for Temporomandibular Disorders for multinational research: translation efforts and reliability assessments in The Netherlands. J Orofac Pain 2005;19:301–308.

17 Aarab G, Lobbezoo F, Wicks DJ, Hamburger HL, Naeije M: Short-term effects of a mandibular advancement device on obstructive sleep apnoea: an open-label pilot trial. J Oral Rehabil 2005;32:564–570.

18 Aarab G, Lobbezoo F, Hamburger HL, Naeije M: Effects of an oral appliance with different mandibular protrusion positions at a constant vertical dimension on obstructive sleep apnoea. Clin Oral Invest 2010;14:339–345.

19 van der Zaag J, Lobbezoo F, Wicks DJ, Visscher CM, Hamburger HL, Naeije M: Controlled assessment of the efficacy of occlusal stabilization splints on sleep bruxism. J Orofac Pain 2005;19:151–158.

20 Ware JE Jr, Sherbourne CD: The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. Med Care 1992;30:473–483.

21 Cohen J: A power primer. Psychol Bull 1992; 112:155–159.
22 Holm S: A simple sequentially rejective multiple test procedure. Scand J Stast 1979;6:65–70.
23 Petri N, Svanholt P, Solow B, Wildschiødtz G, Winkel P: Mandibular advancement appliance for obstructive sleep apnoea: results of a randomised placebo controlled trial using parallel group design. J Sleep Res 2008; 17:221–229.
24 Tan YK, L'Estrange PR, Luo YM, Smith C, Grant HR, Simonds AK, Spiro SG, Battagel JM: Mandibular advancement splints and continuous positive airway pressure in patients with obstructive sleep apnoea: a randomized cross-over trial. Eur J Orthod 2002; 24:239–249.
25 Marklund M, Stenlund H, Franklin KA: Mandibular advancement devices in 630 men and women with obstructive sleep apnea and snoring: tolerability and predictors of treatment success. Chest 2004;125:1270–1278.
26 Ng AT, Qian J, Cistulli PA: Oropharyngeal collapse predicts treatment response with oral appliance therapy in obstructive sleep apnea. Sleep 2006;29:666–671.
27 De Backer JW, Vanderveken OM, Vos WG, Devolder A, Verhulst SL, Verbraecken JA, Parizel PM, Braem MJ, Van de Heyning PH, De Backer WA: Functional imaging using computational fluid dynamics to predict treatment success of mandibular advancement devices in sleep-disordered breathing. J Biomech 2007;40:3708–3714.
28 Battagel JM, Johal A, Kotecha BT: Sleep nasendoscopy as a predictor of treatment success in snorers using mandibular advancement splints. J Laryngol Otol 2005;119: 106–112.
29 Mehta A, Qian J, Petocz P, Darendeliler MA, Cistulli PA: A randomized, controlled study of a mandibular advancement splint for obstructive sleep apnea. Am J Respir Crit Care Med 2001;163:1457–1461.
30 Gotsopoulos H, Chen C, Qian J, Cistulli PA: Oral appliance therapy improves symptoms in obstructive sleep apnea: a randomized, controlled trial. Am J Respir Crit Care Med 2002;166:743–748.
31 Aarab G, Lobbezoo F, Hamburger HL, Naeije M: Variability in the apnea-hypopnea index and its consequences for diagnosis and therapy evaluation. Respiration 2009;77:32–37.
32 Kalso E, Edwards J, McQuay HJ, Moore RA: Five easy pieces on evidence-based medicine (3). Eur J Pain 2001;5:227–230.
33 Marklund M, Persson M, Franklin KA: Treatment success with a mandibular advancement device is related to supine-dependent sleep apnea. Chest 1998;114:1630–1635.
34 Wiegand L, Zwillich CW, Wiegand D, White DP: Changes in upper airway muscle activation and ventilation during phasic REM sleep in normal men. J Appl Physiol 1991;71: 488–497.
35 Ferguson KA, Ono T, Lowe AA, al-Majed S, Love LL, Fleetham JA: A short-term controlled trial of an adjustable oral appliance for the treatment of mild to moderate obstructive sleep apnoea. Thorax 1997;52:362–368.
36 Ferguson KA, Cartwright R, Rogers R, Schmidt-Nowara W: Oral appliances for snoring and obstructive sleep apnea: a review. Sleep 2006;29:244–262.
37 Hoffstein V: Review of oral appliances for treatment of sleep-disordered breathing. Sleep Breath 2007;11:1–22.