Mandibular advancement device therapy in obstructive sleep apnea
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Ghizlane Aarab was born on July 8, 1979, in Berkane, Morocco. In 1997, she obtained her high school diploma at the Stevin College, The Hague, The Netherlands. In the same year, Ghizlane started her dentistry study at the Academic Centre for Dentistry in Amsterdam (ACTA), The Netherlands. Starting in September 2001, she worked as a "student-assistant" at the department of Oral Kinesiology at ACTA. After graduating as a dentist in November 2002, she began a part-time PhD study at the same department. Further, from 2002, Ghizlane is working part-time as a dentist specialized in sleep medicine, orofacial pain, and restorative dentistry at a dental clinic in The Hague. Since February 2009, Ghizlane is an assistant professor at ACTA. She teaches at the undergraduate, graduate, and postgraduate levels. Moreover, she is currently the head of the clinic of Oral Kinesiology and is working on further research projects.
Mandibular Advancement Device Therapy in Obstructive Sleep Apnea

Ghizlane Aarab
Mandibular Advancement Device Therapy in Obstructive Sleep Apnea

ACADEMISCH PROEFSCHRIFT
ter verkrijging van de graad van doctor
aan de Universiteit van Amsterdam
op gezag van de Rector Magnificus
prof. dr. D.C. van den Boom
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Chapter 1

General Introduction
Obstructive sleep apnea (OSA) is a condition characterized by repetitive complete or partial obstruction of the upper airway during sleep [1]. These obstructions manifest themselves as a complete cessation or reduction of airflow, despite ongoing inspiratory efforts, and are often terminated by arousals from sleep. The lack of adequate ventilation during an obstructive event usually results in oxygen desaturation.

OSA patients often complain about daytime symptoms, such as excessive daytime sleepiness, unrefreshing sleep, poor concentration, and fatigue [2-4]. Loud snoring is another typical feature of OSA and is commonly reported by the patient’s sleep partner or family [5]. Based on available population-based studies, the prevalence of obstructive sleep apnea is approximately 3-7% for adult men and 2-5% for adult women in the general population [6-11].

There is evidence that links OSA to long-term cardiovascular morbidity, including hypertension, myocardial infarction, and stroke [12-17]; and to an increased risk of motor vehicle accidents [18, 19]. These cardiovascular co-morbidities and motor vehicle accidents result in an increased risk of mortality in OSA patients [20, 21]. Hence, untreated OSA is associated with serious medical consequences, which underlines the importance of timely recognition, accurate diagnosis, and effective treatment of this disorder.

Pathogenesis and risk factors

The pathogenesis of upper airway closure in patients with OSA is still not fully understood [22, 23]. OSA is thought to result from a combination of anatomical upper airway predisposition and changes in neural activation mechanisms [22]. OSA patients tend to have an anatomically compromised upper airway, resulting from skeletal abnormalities (e.g., retrognathia), soft tissue abnormalities (e.g., macroglossia), or a combination of these factors. During wakefulness, the activity of pharyngeal dilator muscles compensates for these anatomic characteristics. This compensatory effect is substantially diminished when the action of upper airway reflexes and pharyngeal dilator muscles decreases during sleep [24].

Obesity is the main risk factor of OSA [25, 26]. Fat deposition around the upper airway may narrow the upper airway lumen and increase the collapsibility of the pharynx [27]. Craniofacial anomalies like retrognathia or micrognathia, which may be a result of a genetic syndrome, are accompanied by posterior positioning of the tongue and can thus result in narrowing of the upper airway lumen [28-32]. Further, thickening of the pharyngeal wall, tongue, and tonsils also causes upper airway narrowing [33]. Older age can be considered a risk for developing OSA [34]. Mechanisms proposed for the age-related increase in OSA prevalence include increased deposition of fat in the parapharyngeal area and lengthening of the soft palate, which both result in a narrowed upper airway, and a deterioration of upper airway neuromuscular reflexes [35, 36].

OSA prevalence is higher in diabetes and in metabolic syndrome patients (i.e., insulin-resistance syndrome; an emerging disorder associated with accelerated atherosclerosis) [37-39]. The mechanisms underlying the predisposition to diabetes in OSA patients are not clear [34]. An association between OSA and the metabolic syndrome is suggested, although a unequivocal causality between the two has not been demonstrated yet [40].

OSA is more common in males, in patients with polycystic ovary syndrome, as well as in postmenopausal patients [41]. Although the exact mechanisms are unknown, gender differences in hormones and in fat deposition around the upper airway are thought to play a role [42]. Progesterone increases the activity of the upper airway dilator muscles and therefore plays a protective role against collapse of the upper airway in premenopausal women [41]. Obese men are more susceptible to the development of OSA than obese women, most likely because of more fat deposition in the neck, causing narrowing of the pharyngeal lumen [24].

Smoking and alcohol are both considered risk factors for OSA [34]. Airway inflammation due to cigarette smoke could alter the mechanical and neural properties of the upper airway and increase its collapsibility during sleep [34, 43]. Alcohol relaxes upper airway dilator muscles, which in turn increases upper airway resistance, and may thus induce OSA [44].
Diagnosis

The diagnosis of OSA requires the combined assessment of relevant clinical features and the objective demonstration of abnormal breathing during sleep [1, 5]. Signs and symptoms suggestive of OSA include, amongst others, snoring, witnessed apnea and/or gasping by family or bed partner, obesity, excessive daytime sleepiness, a positive family history, non-restorative sleep, and hypertension [45]. An objective measure of sleep-disordered breathing at night is generally required to confirm the diagnosis of OSA. The “gold standard” for the objective demonstration of abnormal breathing during sleep in OSA patients is full polysomnography, which provides detailed information on sleep state, respiration, and gas exchange abnormalities, in addition to a host of other variables including body position, heart rate and rhythm, and snoring sounds [46] (Fig. 1).

In 1999, the American Academy of Sleep Medicine Task Force reported standard definitions, criteria, and severity ratings for abnormal breathing events during sleep [1]. Apnea is defined as a cessation of airflow for at least of 10 seconds. Hypopnea is a decrease in nasal-oral airflow of more than 50% for at least 10 seconds, or a substantial decrease of less than 50% in nasal-oral airflow if associated with an arousal and/or an oxygen desaturation of greater than 3%. The apnea-hypopnea index (AHI) is the number of apneas and hypopneas per hour of sleep [1]. An AHI of at least 5 events/hour and the presence of excessive daytime sleepiness (measured objectively or subjectively) that is not explained by other factors, are commonly used for an OSA diagnosis (based on the American Academy of Sleep Medicine Task Force report, 1999). When excessive daytime sleepiness is absent, at least two symptoms, e.g., recurrent complaints of unrefreshing sleep and daytime fatigue, should be present. Based on the AHI, the American Academy of Sleep Medicine Task Force classified the severity of OSA in mild (AHI 5-15), moderate (AHI 15-30), and severe (AHI >30) [1].

Fig. 1a. An obstructive sleep apnea patient prepared for a full polysomnographic recording. The different electrodes measure variables like sleep state, respiration, body position, heart rate and rhythm, and snoring sounds.

Fig. 1b. The output of a full polysomnographic recording. Two obstructive apneas are highlighted with blue squares in the airflow channel. The graph represents an increment of 60 seconds.
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General introduction

Treatment strategies

Most common treatment options for OSA include behavioral strategies, such as weight reduction, alcohol avoidance, smoking cessation, and alteration of sleeping position [47-50]; a range of surgical procedures of the upper airway [51]; continuous positive airway pressure (CPAP); and oral appliances [52, 53]. In this thesis, an oral appliance is compared with CPAP in the treatment of OSA. Therefore, only oral appliance therapy and CPAP therapy are further introduced below.

CPAP is generally considered the "gold standard" treatment for OSA [52]. CPAP is administered through a nasal or facial mask, held in place by straps around the patient’s head. The mask is connected by a tube to a small air compressor (Fig. 2). The CPAP machine sends air under pressure through the tube into the mask. This essentially “splints” the upper airway open and keeps it from collapsing during sleep [54]. In several short-term randomized controlled trials (RCTs), CPAP has been proven to normalize sleep architecture, reduce daytime sleepiness, enhance daily function, elevate mood, reduce automobile accidents, and decrease blood pressure and other cardiovascular consequences [52, 55]. Although CPAP is a highly efficacious treatment, there is nevertheless a need for other treatment options, because the effectiveness of CPAP is often limited by poor patient acceptance and tolerance, and suboptimal compliance [56, 57].

Nowadays, oral appliances are widely prescribed for the treatment of mild and moderate OSA [53]. Most of the prescribed oral appliances are mandibular advancement devices (MADs) (Fig. 3). The rationale behind the efficacy of MADs is that advancement of the mandible and tongue improves upper airway patency during sleep by enlarging the upper airway and by decreasing upper airway collapsibility, thereby preventing collapse during sleep [58-61]. There are many types of MADs, and they all have the potential advantages over CPAP that they are unobtrusive, make no noise, do not need a power source, and are potentially less costly [62]. Further, they are often considered by patients to be a more acceptable treatment modality compared to CPAP [63].

Fig. 2. An obstructive sleep apnea patient using nasal continuous positive airway pressure during sleep.

Fig. 3. Lateral view of a mandibular advancement device (MAD).

In 2002, when we started with our randomized placebo-controlled trial (RCT), especially case series were published on the therapeutic efficacy of mandibular advancement devices (MADs) in OSA patients [60, 64]. Consequently, there was not enough sound scientific evidence for the efficacy of MADs. Therefore, we decided to investigate three important aspects of MAD therapy in an RCT: (1) the time-variant nature of the AHI and its consequences for diagnosis and therapy evaluation in OSA patients; (2) the influence of mandibular
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General introduction

1. To determine the apnea-hypopnea index variability over time, and to discuss its consequences for diagnosis and therapy evaluation in OSA patients (chapter 2).
2. To assess the influence of four mandibular protrusion positions on OSA signs and symptoms (chapter 3 and 4).
3. To compare the short-term and long-term effects of an MAD with those of nasal continuous positive airway pressure in the treatment of OSA (chapter 5 and 6).

Synopsis

The topic of this thesis is the effects of mandibular advancement device (MAD) therapy on obstructive sleep apnea (OSA). The objectives were:

MAD should be titrated objectively as well. Therefore, the aim of the study in chapter 5 of this thesis was to compare the effects of an MAD with those of nasal CPAP (nCPAP), following polysomnographically controlled titration of both treatment modalities. To control for a possible placebo effect in subjective outcome variables like excessive daytime sleepiness and health perception, an intra-oral placebo device served as passive control condition for both active conditions. Although the short-term therapeutic efficacy of MADs has been compared with CPAP in several RCTs (e.g., 74-79), long-term parallel-group trials are needed to capture information regarding the persistence of efficacy and loss to follow-up [52]. Therefore, the aim of the study in chapter 6 of this thesis was to compare these treatment aspects between MAD and nCPAP in a one-year follow-up.
References


Mandibular Advancement Device Therapy in Obstructive Sleep Apnea

General introduction

Chapter 2

Variability in the Apnea-Hypopnea Index and its Consequences for Diagnosis and Therapy Evaluation

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Mandibular Advancement Device Therapy in Obstructive Sleep Apnea

variability in the apnea-hypopnea index

Abstract

**Background:** The apnea-hypopnea index (AHI) is frequently used to recognize obstructive sleep apnea (OSA) and to evaluate therapy. **Objectives:** The aim of this study was to determine the AHI variability during a 10-week period, and to discuss its consequences for diagnosis and therapy evaluation. **Methods:** Fifteen OSA patients (50.8 ± 11.2 years) underwent four polysomnographic (PSG) recordings, with a mean interval between recordings of 3.3 weeks. **Results:** No differences were found in the average AHI values of the four PSG recordings (p = 0.985). Nevertheless, pooling all data of the 15 participants yielded a smallest detectable difference for AHI of 12.8. Linear regression between the individual means and standard deviations (SDs) of AHI showed that participants with a higher AHI tended to have a higher SD (p < 0.044). **Conclusions:** These results suggest a considerable intra-individual variability in AHI recordings. Hence, a single night recording can only recognize OSA when the AHI lies outside a cut-off band surrounding the AHI cut-off point. AHI variability should also be taken into account when evaluating OSA therapy. In this context, it should be noted that it is mainly the approach that we would like to convey to the reader and not the cut-off values per se.

**Key words:** apnea-hypopnea index ∙ diagnosis of apnea ∙ evaluation of obstructive sleep apnea therapy ∙ obstructive sleep apnea ∙ polysomnographic recordings

Introduction

Obstructive sleep apnea (OSA) is characterized by recurrent obstruction of the upper airway, often resulting in oxygen desaturation and arousal from sleep [1]. In 1999, the American Academy of Sleep Medicine Task Force reported standard definitions, criteria and severity ratings for abnormal breathing events during sleep [1]. The purpose of that report was to facilitate comparability of studies for research purposes by defining the apnea-hypopnea index (AHI). The AHI is used as the main outcome variable to recognize OSA and to evaluate therapeutic success [2]. When using the AHI for diagnostic and therapy evaluation purposes, the AHI variability has to be borne in mind.

Several reports described considerable variability in AHI values over time. In studies investigating the AHI variability during consecutive nights, the average AHI did not significantly differ between nights on a group level, but on an individual level, a considerable variability was sometimes observed [2–11]. The numerical consequences for diagnosis and therapy evaluation, however, were not elaborated in these studies. So far, the AHI variability over longer periods of time has been studied less frequently [7, 8, 10]. This long-term variability, however, is clinically even more important than the short-term variability, because the time interval between diagnostic and therapeutic evaluation of polysomnographic (PSG) recordings is at least several weeks. Therefore, the aim of this study was to determine the AHI variability during a long-term follow-up study of 10 weeks, and to discuss its consequences for diagnostic and therapeutic evaluation purposes.

Methods

**Overview**

This paper is part of a series of studies that includes a controlled randomized clinical trial (RCT), in which the therapeutic efficacy of a mandibular advancement device (MAD) [12] was compared with both nasal continuous positive airway pressure (nCPAP) and a control
condition. Both MAD and nCPAP required multiple visits to our clinic and laboratory between the baseline and follow-up assessments of OSA, amongst others for titration of the devices. By introducing a placebo appliance in the control group, the three experimental conditions were made as comparable as possible, especially in terms of the personal attention that was being paid to the patients. Four extra placebo assessments were thus performed, which could be used in the present study to determine the variability in our patients, provided that the placebo appliance would turn out to be inert (i.e., no significant difference in AHI between the baseline and follow-up assessments).

All patients were selected from the multidisciplinary Center for Sleep-Wake Disorders at the Slotervaart Medical Center, which collaborates with the Academic Centre for Dentistry (ACTA). The multidisciplinary team consisted of a neurologist, ENT specialists, pulmonologists, a dentist, a psychologist, and technicians trained in sleep medicine. All patients underwent a thorough medical examination and a baseline polysomnographic (PSG) recording at the Slotervaart Medical Center. The PSG recording took place in a dark hospital room, using Siesta hardware and Pro-Fusion software (Compumedics, Abbotsford, Australia).

The criteria for inclusion of patients in the RCT were: age > 18 years and an AHI between 5 and 45 events/ hour. Criteria for exclusion were: evidence of respiratory/sleep disorders other than OSA, a Body Mass Index (BMI) > 40, medication usage that could influence respiration or sleep, periodic limb movement disorder, previous treatment with continuous positive airway pressure or a mandibular advancement device, and reversible morphological upper airway abnormalities (e.g., enlarged tonsils). Additional dental exclusion criteria were: temporomandibular disorders (based on a functional examination of the masticatory system [13, 14]), untreated periodontal problems, dental pain, and a lack of retention possibilities for a mandibular advancement device or placebo appliance.

After written informed consent was obtained, the patients were randomly allocated to one of three therapies (MAD, nCPAP, or placebo). Patients were not told which one of the three therapies was the placebo therapy. The placebo group was used in the present study. The scientific and ethical aspects of the RCT protocol were reviewed and approved by the Medical Ethics Committee of the Slotervaart Medical Center.

Patients

Initially, seventeen OSA patients were included in the placebo group, thirteen of them being men. For private reasons that were unrelated to this study, one female OSA patient dropped out of the study after the second ambulatory PSG recording (see study protocol). One male OSA patient failed one of the ambulatory PSG recordings, and was therefore excluded from the analyses of the present data. Thus, fifteen patients had a complete set of data and were included in this study. Their mean age was 50.8 years (SD, 11.2; range, 30 to 70); their mean BMI, 30.1 (SD, 4.5; range, 23 to 39). Their mean Epworth Sleepiness Score (ESS) [15] was 11.2 (SD, 4.2; range, 5 to 20). Their mean baseline AHI was 19.5 (SD, 9.6; range, 6 to 37).

Study protocol

After allocation of the patients to the placebo group, a thin palatal splint was made, using alginate impressions of both jaws, at the Clinic of the Department of Oral Function of ACTA. The splint was a thin (< 1 mm) hard acrylic resin splint, worn on the upper jaw with only a partial palatal coverage (Fig. 1). In our clinic, this splint has been used before as a placebo appliance in a study on sleep bruxism [16]. The patients were instructed to wear the splint every night during the follow-up period of ten weeks.

All patients underwent four PSG recordings (PSG1-PSG4) at home, with the splint in situ, and with an interval of 3.3 (SD, 1.7; range, 1-9) weeks between recordings. Monet hardware and Rembrandt Software (Medcare Automation B.V., Amsterdam, The Netherlands) were used for these recordings. The montage was performed at the Slotervaart Medical Center by a trained coworker. The channels of the recording consisted of two electro-encephalographic leads (C3-A2; O2-A1), two electro-oculographic leads, mental surface electromyography, nasal-oral airflow using a thermistor, oximetry, abdominal and
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Variability in the apnea–hypopnea index

Fig. 1. The placebo splint in situ; a thin (< 1mm) hard acrylic splint, worn on the upper jaw with only a partial palatal coverage.

Thoracic respiratory effort, body position, electrocardiography, leg electromyography (m. tibialis anterior), and a piezo-electric lead for the detection of snoring vibrations. Each PSG home recording was analyzed twice manually, under a blind condition, by the same examiner, who was experienced in scoring PSG recordings, using internationally accepted criteria [1, 17]. Sleep stages were scored in 30-s epochs and standard sleep and respiratory outcome variables were obtained (see left column of Table 1).

Prior to each PSG recording, the patient received sleep hygiene advises, e.g., avoiding copious meals and alcoholic beverages 3 hours preceding bedtime, and creating a good sleeping environment [18]. Each PSG recording was followed by a visit to ACTA. During this visit, the BMI (kg/m²) and ESS were determined. The patients were also asked about their compliance (i.e., frequency of wearing the placebo splint) and about possible side effects of the appliance.

After the four recordings at home, all patients had a follow-up PSG recording in the hospital, under the same conditions as the baseline PSG recording (see overview), with the placebo appliance in situ.

Statistics

The BMI, ESS, AHI, and standard sleep variables were analyzed for the within-subject effects (i.e., the four home recordings: Night effect), using a General Linear Model (GLM) with repeated measures, which was preceded by Mauchly’s Test of Sphericity as to assess normality of the variables measured.

The standard error of measurement (SEM; the average SD among observations from the same subject) of the AHI, a measure of the within-subjects variability, was calculated according to Fleiss and Kingman [19]. The smallest detectable difference (SDD) in the AHI (the SDD between two AHI outcomes of an individual, which is significant at a 95% probability level [19-21]) was calculated according to the following formula: SDD= 1.96*√2*SEM.

The intra class correlation coefficient (ICC) was used to determine the intra-examiner reliability of the AHI scoring of the home recordings. Further, paired samples t-tests were used to test the null hypothesis that there were no within-subject differences in the AHI between the baseline and follow-up PSGs that were both obtained in the hospital. Finally, the linear regression was calculated between the individual’s mean values and standard deviations from the four AHI recordings. All statistical tests were performed with SPSS 12.0 software package (SPSS Inc., Chicago, IL). Probability levels of p < 0.05 were considered statistically significant.

Results

For the duration of the study, none of the patients showed any adverse effects due to wearing the placebo appliance. All patients wore their appliance during at least 90% of the nights of the 10-week study period. Table 1 shows the average (± SD) values of the BMI, ESS, AHI, and standard sleep variables for each of the four home PSG recordings. The BMI and ESS did not differ significantly between the four nights, nor did the standard sleep variables (F = 0.167 – 1.078; p = 0.918 – 0.369).
The examiner’s intra-observer reliability in the AHI scoring was excellent, with an ICC of 0.96; that of the sleep scoring could be qualified as at least fair-to-good, with ICC values ranging from 0.63 to 0.94. The AHI values of the baseline hospital recordings without the placebo appliance did not differ significantly from the AHI values of the hospital recordings with the placebo appliance in situ (T = 1.881; p = 0.079).

Figure 2 shows the course of the AHI of the fifteen patients for the four home recordings (PSG1-4). No differences were found between the average AHI values of the four nights (F = 0.051; p = 0.985). Based upon the data of the four nights, the standard error of measurement SEM of the AHI was 4.6 events/hour and the smallest detectable difference was 12.8 events/hour. For each participant, the mean value and standard deviation of the four AHI outcomes were also calculated. A significant linear regression was found between the mean value and the standard deviation (R² = 0.276; p < 0.044), with a tendency of higher standard deviations for participants with higher mean values (Fig. 3).

**Table 1.** Descriptive statistics (mean ± SD) of the patient characteristics, the apnea-hypopnea index (AHI), and sleep variables of the fifteen OSA patients as derived from four polysomnographic recordings (PSG1-4)

<table>
<thead>
<tr>
<th></th>
<th>PSG 1</th>
<th>PSG 2</th>
<th>PSG 3</th>
<th>PSG 4</th>
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<tr>
<td><strong>Patient characteristics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>30.1 ± 4.5</td>
<td>30.2 ± 4.6</td>
<td>30.2 ± 4.6</td>
<td>30.1 ± 4.8</td>
</tr>
<tr>
<td>ESS</td>
<td>9.9 ± 4.2</td>
<td>9.4 ± 5.2</td>
<td>9.1 ± 5.5</td>
<td>9.4 ± 5.2</td>
</tr>
<tr>
<td><strong>Respiratory</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AHI (events/hour)</td>
<td>10.7 ± 8.2</td>
<td>10.1 ± 8.3</td>
<td>9.9 ± 6.2</td>
<td>9.2 ± 6.7</td>
</tr>
<tr>
<td><strong>Sleep</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total sleep time (min)</td>
<td>432.7 ± 61.9</td>
<td>449.2 ± 85.4</td>
<td>415.4 ± 73.2</td>
<td>421.9 ± 64.6</td>
</tr>
<tr>
<td>Stage 1 and 2 (%)</td>
<td>65.5 ± 10.2</td>
<td>64.3 ± 13.3</td>
<td>66.9 ± 12.4</td>
<td>66.3 ± 15.2</td>
</tr>
<tr>
<td>Stage 3 and 4 (%)</td>
<td>12.8 ± 8.9</td>
<td>14.4 ± 11.9</td>
<td>12.8 ± 12.6</td>
<td>11.9 ± 12.6</td>
</tr>
<tr>
<td>Stage REM (%)</td>
<td>21.3 ± 6.7</td>
<td>21.0 ± 6.1</td>
<td>20.1 ± 9.2</td>
<td>21.4 ± 6.5</td>
</tr>
<tr>
<td>Total sleep supine (%)</td>
<td>39.4 ± 21.3</td>
<td>34.9 ± 30.7</td>
<td>36.8 ± 25.9</td>
<td>43.5 ± 28.1</td>
</tr>
</tbody>
</table>

Fig. 2. Individual values of the apnea-hypopnea index (AHI) in the 15 OSA patients, as derived during the four polysomnographic recordings (PSG1-4).

Fig. 3. Linear regression between the mean values and the standard deviations of the AHI of the 15 OSA patients. The broken vertical line represents the cut-off criterion of 5 for the AHI.
Discussion

In this study, a considerable intra-individual variability was found between the four AHI recordings obtained during a follow-up period of ten weeks. It is of importance to take this variability into account when using this index in clinical practice and research.

A so-called first-night effect may contribute to the AHI variability over time. To avoid this first-night effect, a first PSG recording, used solely for habituation to sleeping under experimental conditions, often precedes the recording that is used for diagnosis and research purposes [22]. In this study, a first-night effect could not be detected in the four home PSG recordings. The standard sleep variables and the AHI recorded during the first night were not significantly different from those recorded during the following nights. This may be due to the fact that the first home PSG recording was preceded by a baseline PSG recording at the hospital (as part of the inclusion procedure), thus giving the patients the opportunity of habituation to the equipment.

In the present study, the AHI variability was studied in a group of patients with a placebo appliance in situ. One could wonder whether this placebo appliance could have influenced the respiratory variables. However, the AHI did not differ significantly between the baseline PSG (without the placebo appliance) and the follow-up PSG recording (with placebo appliance in situ) that were both obtained at the hospital. This indicates that the placebo appliance used in this study may be considered inert. Hence, this study provides proper insight into the natural variability in the AHI in OSA patients.

In this study, no differences in the average AHI values from one night to the other were found. Similar results were found in other studies [3-5, 7-10]. However, in a prospective study, Bittencourt et al. [2] already pointed out that a small AHI variability between consecutive nights at a group level does not necessarily mean also a small variability at an intra-individual level: thirteen out of their twenty patients presented a difference between nights in the AHI value equal to or higher than 10 events/hour. A similar result could be found in six of the fifteen patients in the present study which had a much longer period between the four recording nights. The excellent intra-examiner reliability found in this study indicates that the variability of the examiner only played a minor role in the AHI variability. A more plausible explanation for AHI variability would be a relation to the intrinsic variability of the OSA phenomenon under study, which in turn can be influenced by variables like behavioural factors and differences in body position and sleep architecture between recordings. Thus, despite the small variability in the AHI observed at a group level, this long-term study revealed that there may be a considerable variability in AHI present at an intra-individual level.

According to the American Academy of Sleep Medicine Task Force [1], OSA is defined as the combination of symptoms (e.g., excessive daytime sleepiness) with 5 or more obstructive breathing events per hour of sleep. The number of obstructed breathing events is usually quantified by the number of apneas and hypopneas per hour of sleep (AHI). The cut-off point of 5 for the AHI is widely used to recognize OSA, but it should be noted that the clinical value of any particular cut-off point has not been adequately determined yet and is mainly based on consensus [1, 23]. Moreover, in a systematic review of Franklin et al. [24] the establishment of specific AHI cut-off criteria for both genders and for different age groups is recommended. To that end, large study samples should be included in future studies to this topic. However, the time-variant nature of the disorder complicates the use of any cut-off point of the AHI. If the recorded values of the AHI lie close to this point, the value may for one night be above and for another night below this point. This suggests that conclusions about the presence or absence of OSA can only be drawn when the single-night AHI recordings lie far enough away from the cut-off point; that is outside the limits of a cut-off band surrounding that point. Supposing that the chances of a single-night PSG recording of a non-OSA patient to indicate the presence of OSA should be smaller than 5% (false positive) and that the chances of a PSG recording of an OSA patient to deny the presence of OSA should also be smaller than 5% (false negative), then, under the assumption that the single-night recordings are normally distributed, the cut-off band is the 90% probability interval around the cut-off point, with its upper and lower limits at a distance of 1.645 times the standard deviation from
that point. In the present study, the linear regression found between the standard deviations and mean values of the AHI variable (Fig. 3) suggests that the best estimate for the standard deviation of single-night AHI recordings for patients with an AHI value close to the cut-off point of 5 is 2.9. Based upon this estimate and within the limitations of the present study, the cut-off band for the AHI variable will range from 0.2 to 9.8 (5 ± 1.645*2.9). For single-night AHI recordings lying above or below this cut-off band, the PSG recordings indicate that OSA is present or absent. For single-night AHI recordings within the cut-off band, the PSG recordings do not allow conclusions to be drawn about the presence or absence of OSA. When decisions are not based upon single-night AHI recordings but upon the average of n recordings, the cut-off band will become narrower, since the standard deviation of the average of n recordings is that of a single recording divided by √n.

An observed difference between pre- and post-therapeutic outcome variables does not necessarily reflect a possible therapeutic effect, but may also be related to the natural course of the disorder, the biological fluctuation of the variables measured, and possible inconsistencies in measurement. The smallest detectable difference (SDD) is an appropriate measure for assessing these possible sources of variability within individual patients [19-21]. In this study, a SDD of the AHI of 12.8 events/hour was found when the follow-up data of all 15 participants were used in its calculation. This suggests that a change in AHI should be > 12.8 events/hour before it can be considered statistically significant at a 95% probability level. However, Fig. 3 indicates that participants with a lower mean AHI value have a tendency to have a smaller SDD than those with a higher mean value. In the calculation of the SDD, this tendency was ignored because taking it into account would have required a much larger group of patients than the 15 participating in the present study. In this context, it should be mentioned that the variability in AHI is not expected to decrease with a larger sample size; only its estimate will be more accurate. Further, it should be noted that the calculated SDD may be dependent on factors, which are specific for the study setting (e.g., sample characteristics). Therefore, we recommend establishing SDDs for individual clinics and sleep laboratories when using the AHI for research purposes. Moreover, it should be kept in mind that a statistically significant change in the AHI value is not necessarily also a clinically relevant change; the latter remains to be determined by the responsible clinician and must also be based upon medical grounds.

In conclusion, our results suggest a considerable intra-individual variability between AHI recordings. Hence, single-night recordings can only confirm or deny the presence of OSA when the recordings lie outside a cut-off band surrounding the AHI cut-off point. The large AHI variability should also be taken into account when evaluating therapy success. In this context, it should be noted that it is mainly the approach that we would like to convey to the reader; not the cut-off values per se.
References


Chapter 3

Short-term effects of a mandibular advancement device on obstructive sleep apnea: an open-label pilot trial

G. Aarab, F. Lobbezoo, D.J. Wicks, H.L. Hamburger, M. Naeije

Abstract

**Background:** Obstructive sleep apnea (OSA) is a common sleep disorder, which is, among others, associated with snoring. OSA has a considerable impact on a patient’s general health and daily life. Nasal continuous positive airway pressure (nCPAP) is frequently used as a ‘gold standard’ treatment for OSA. As an alternative, especially for mild/moderate cases, mandibular advancement devices (MADs) are prescribed increasingly. Their efficacy and effectiveness seem to be acceptable. Although some randomized clinical trials (RCTs) have been published recently, most studies so far are case studies. Therefore, our department is planning a controlled RCT, in which MADs are compared with both nCPAP and a control condition in a parallel design. As a first step, an adjustable MAD was developed with a small, more or less constant vertical dimension at different mandibular positions. **Objectives:** To test the device and the experimental procedures, a pilot trial was performed. **Methods:** 10 OSA patients (6 mild, 4 moderate; 1 women, 9 men; mean age = 47.9 ± 9.7 years) underwent a polysomnographic (PSG) recording before, as well as, 2 to 14 weeks after insertion of the MAD (adjusted at 50% of the maximal protrusion). **Results:** The apnea-hypopnea index (AHI) was significantly reduced with the MAD in situ ($P = 0.017$). When analysed as separate groups, the moderate cases showed a significantly larger decrease in AHI than the mild cases ($P = 0.012$). **Conclusions:** This MAD might be an effective tool in the treatment of, especially, moderate OSA.

**Key words:** obstructive sleep apnea · mandibular advancement device · polysomnography · apnea-hypopnea index · short-term effects

Introduction

Obstructive sleep apnea (OSA) is characterized by repetitive obstructions of the upper airway, often resulting in oxygen desaturation and arousal from sleep [1]. Complaints of snoring and excessive daytime sleepiness are often the primary reason for a patient’s referral to a sleep laboratory, where polysomnography is used to establish a diagnosis of OSA [2, 3]. OSA is a common sleep disorder, especially in obese, middle-aged men, with an estimated prevalence of 2% in women to 4% in men [2].

OSA can have a considerable and even life-threatening impact on a patient’s general health. For example, patients with OSA more frequently suffer from cardiovascular diseases than healthy controls [4, 5]. Further, the OSA symptoms ‘snoring’ and ‘excessive daytime sleepiness’ may have a large impact on the daily life of OSA patients. Heavy snoring can lead to significant impairment of social life and family relations [6], while excessive daytime sleepiness can result in problems functioning at work, and even in car accidents [7].

The treatment of OSA usually includes counselling. For example, OSA patients are instructed to loose weight and to avoid alcohol, sedatives, and sleeping in the supine position [8]. In addition to these behavioural strategies, OSA can be treated, amongst others, with nasal continuous positive airway pressure (nCPAP; the current ‘gold standard’ therapy) [9, 10], or with oral appliances like the so-called mandibular advancement devices (MADs) [3, 11].

To date, five controlled clinical trials with a crossover design have been performed to test the efficacy of MADs as compared with nCPAP [12]. Four of these trials were randomized [10, 13-15]; one was non-randomized [16]. In all five studies, nCPAP turned out to be more effective in the treatment of OSA patients than MAD. Unfortunately, patients do not always tolerate nCPAP due to the occurring side effects and pressure intolerance, which frequently leads to less usage of the nCPAP therapy [17]. In such cases, MADs are often suggested as an alternative treatment.

The main advantages of MADs are the relative simplicity of the treatment, their reversibility, and their cost-effectiveness [11].
Although side effects are frequently reported during MAD treatment, these are usually mild and acceptable [11]. In addition, their efficacy and effectiveness seem to be acceptable [3, 11]. In 1995, the American Sleep Disorders Association (ASDA) published practice parameters [18], which state that oral appliances may even be considered a primary treatment option for patients with mild OSA and a secondary treatment option for patients with moderate and severe OSA who cannot tolerate treatment with nCPAP.

As yet, the mechanisms of action of an MAD are not fully understood, leading, amongst others, to difficulty in predicting the outcome of the treatment in individual cases. For example, the exact nature of the relation between position of the mandible and the efficacy of the oral device is still obscure. Therefore, our department is planning a controlled randomized clinical trial (RCT) shortly, in which MADs in different mandibular positions are investigated. The most effective MAD will then be compared with both nCPAP and a control condition in a parallel design. As a first step, an adjustable MAD was developed with a small, more or less constant vertical dimension at different mandibular positions. For this pilot trial, the MAD was anchored at 50% of the maximal protrusion [19, 20]. The aim of the present open-label pilot study was to study the initial efficacy of this MAD in a group of OSA patients. Further, it was aimed to evaluate the patients’ compliance to the MAD therapy, as well as, to determine the feasibility of the procedures of this pilot trial for use in the future RCT.

Materials and methods

Participants

Between July 2001 and June 2002, 17 potential participants (1 woman and 16 men) from the multidisciplinary Center for Sleep-Wake Disorders at the Slotervaart Medical Center in Amsterdam, the Netherlands were invited to participate in this study. All patients underwent a thorough medical examination and a polysomnographic recording (PSG) at the Slotervaart Medical Center. Subsequently, a functional examination of the masticatory system and a dental examination were performed at the Academic Centre for Dentistry Amsterdam (ACTA).

Exclusion criteria were (1) evidence of respiratory/sleep disorders other than OSA (based on the PSG recording; e.g., central sleep apnea syndrome); (2) systemic disorders (based on the medical history and examination; e.g., rheumatoid arthritis); (3) temporomandibular joint disorders (based on the function examination of the masticatory system); and (4) untreated periodontal problems, dental pain, and a lack of retention possibilities for an MAD (based on the dental history and examination). Inclusion criterion was the presence of mild/moderate OSA. Largely following the recommendations of the American Academy of Sleep Medicine Task Force, OSA is defined as mild, when an apnea-hypopnea index (AHI; see sleep and respiratory outcome variables) of 5 to 15 events per hour is present, and as moderate, when an AHI of 16 to 30 events per hour is present [1].

Five out of the 17 potential participants were excluded, because they did not meet the criteria for mild/moderate OSA. The AHI was higher than 30 events per hour in two patients and lower than 5 events per hour in three patients. Two of the remaining 12 potential participants did not complete the protocol of the study for personal reasons that were not related to the treatment procedure and were thus excluded. As a consequence, a total of ten OSA patients (1 woman and 9 men) was included. Their mean age was 47.9 years (SD, 9.7; range, 35 to 62); their mean body mass index (BMI), 27.9 (SD, 5.1; range, 22 to 38). Two of the ten patients used antihypertensiva; the remaining patients were free of any medical disorders other than OSA. Out of the ten patients, six had mild OSA; four, moderate OSA.

The board of the Netherlands Institute for Dental Sciences (IOT) gave scientific and ethical approval for this study, and informed consent was obtained from all patients.

MAD

For all patients, an MAD was fabricated in the Oral Kinesiology Clinic of the Department of Oral Function of the Academic Centre for Dentistry Amsterdam (ACTA), the Netherlands. To that end, alginate impressions of both jaws and an interocclusal record, with the mandible at 50% of the maximal protrusive position, were obtained. The maximum amount of protrusion was measured with
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a ruler between the labial surfaces of the upper and lower central incisors as the horizontal distance from maximum intercuspidation to the maximum protrusion position. The MAD was developed in collaboration with a dental laboratory (Amsterdams Tandtechnisch Laboratorium (ATL), Amsterdam, the Netherlands).

The MAD (Figure 1) consists of two hard acrylic resin splints (Vertex Orthoplast, Vertex-Dental B.V., Zeist, the Netherlands), worn on the upper and lower jaws. The two splints are connected by an adjustable screw mechanism in the front (Hyrax®-Schrauben, Dentaurum, Ispringen, Germany). The screw makes it possible to change the protrusion position in the anterior and posterior directions. Within a patient, the MAD has a small, more or less constant vertical dimension at different mandibular positions (variance approx. 1 mm). Orthodontic elastics in the side parts support the front connection. This design does not permit jaw movements during sleep. For this pilot trial, the MAD was anchored at 50% of the maximal protrusion.

Fig. 1. Lateral view of the mandibular advancement device (MAD) used in this study.

Study protocol

As part of the intake procedure (see ‘Participants’), all patients underwent overnight polysomnography (PSG) in the sleep laboratory of the Slotervaart Medical Center. This recording was used as the baseline for this study. After inclusion in the study, an MAD was fabricated and fitted at ACTA. One week later, any necessary adjustments to the MAD were made to prevent, among others, pain or discomfort related to wearing the device. After a period of another 4.8 (SD, 3.8; range, 2 to 14) weeks, i.e., as soon as the patients were adapted to wearing the MAD, a second PSG recording was made with the MAD in situ. Subsequently, the patients underwent another inspection of the MAD, as well as an examination of their dentition and masticatory system at ACTA. During the visits at ACTA the patients were asked if possible adverse effects (e.g., sensitive teeth, tenderness of jaw muscles, and excessive salivation) occurred during treatment.

Both PSG recordings took place in a dark hospital room. Siesta hardware (32 channels, 16 bit recorder) and Pro-Fusion software (Compumedics, Abbotsford, Australia) were used for the recordings. The channels were two electro-encephalographic leads (C3-A2; O2-A1), two electro-oculographic leads, mental surface electromyography, nasal-oral airflow using a thermistor, oximetry, abdominal and thoracic respiratory effort, body position, electrocardiography, leg electromyography (m. tibialis anterior), and a piezo-electric lead for the detection of snoring vibrations.

Sleep and respiratory outcome variables

A technician, especially trained in sleep medicine, scored the PSG records. Sleep stages were scored manually in 30-s epochs according to Rechtschaffen and Kales [21], and standard sleep and respiratory outcome variables were obtained (see Table 1 and 2; left column).

Following the American Academy of Sleep Medicine Task Force [1], apnea was defined as a cessation of airflow for at least of 10 seconds. Hypopnea was defined as a decrease in nasal-oral air flow of more than 50% for at least 10 seconds, or less than a 50% decrease
in nasal-orl air flow if associated with an arousal and/or an oxygen desaturation of greater than 3%. The apnea-hypopnea index (AHI), defined as the number of apneas and hypopneas per hour of sleep, was considered the main outcome variable in this study. A clinically satisfactory treatment outcome was adapted from Mehta et al. [22] and Gotsopoulous et al. [23] and was defined as a decrease in AHI of at least 50% during treatment.

The desaturation index was defined as the number of oxygen desaturations of greater than or equal to 4% per hour of sleep. The assessment of snoring was based upon the technician’s interpretation of the piezo-electric traces. The snoring index was defined as the number of snores per hour of sleep.

Compliance and feasibility

The patients’ compliance to the treatment regimen was assessed after the completion of the study by asking them, over the telephone, about the frequency of wearing the splint. The procedures of this pilot trial were considered feasible for use in the future RCT when none of the participants would drop out of the study due to technical or logistic problems.

Statistics

For all biometric variables (body mass index), sleep variables (e.g., total sleep time, sleep efficiency), and respiratory variables (e.g., apnea-hypopnea index, desaturation index), Shapiro-Wilk normality tests were used to test the null hypothesis of the input data values being a random sample from a normal distribution.

To test the null hypothesis that there are no within-subject differences between the baseline PSG and the PSG with the MAD in situ, Wilcoxon signed rank tests were used for the not-normally distributed variables. For the normally distributed variables, paired samples T-tests were used. In addition, Bonferroni–Holm [24] correction for multiple comparisons was used for all sleep variables.

Results

None of the participants showed any adverse effects in the dentition or masticatory system due to wearing the MAD. Their mean BMI during the first and second polysomnographic recording was 27.9 (SD, 5.1; range 22 to 38) and 28.2 (SD, 5.2; range 22 to 36), respectively. In all cases, the BMI did not change significantly during the study period. The mean maximal protrusion capacity in mm of the 10 patients was 8.7 (SD, 1.3; range 6 to 10). Their mean vertical overbite in mm was 2.4 (SD, 1.9; range 0 to 7).

The within-subject results of the respiratory parameters can be gathered from Table 1. The apnea-hypopnea index (AHI) showed a significant reduction with the MAD in situ. The AHI’s, without and with the MAD, in the 10 patients are shown in Figure 2. The moderate cases showed a significantly larger decrease in AHI with the MAD in situ than the mild cases (MANOVA: F(1, 8) = 10.6; P = 0.012). The desaturation index (DI) also decreased significantly. The snoring index did not change significantly between both PSGs. The within-subject results of the sleep parameters can be gathered from Table 2. The arousal index (ARI) was the only sleep parameter that decreased significantly with the MAD in situ.

A clinically satisfactory treatment outcome was reached in five out of 10 patients, showing a decrease in AHI of at least 50% (average, 84%). Treatment did not meet the criteria for satisfactory result in the other five patients. However, two of these five patients showed an almost satisfactory result (decrease in AHI of 48-49%).

As none of the participants dropped out of the study for reasons related to this research, the procedures, used in this pilot study, were considered feasible for use in the future RCT.
Table 1. Respiratory parameters from the first (PSG1) and second nocturnal polysomnographic registration (PSG2) of 10 OSA patients

<table>
<thead>
<tr>
<th>Respiratory parameters</th>
<th>PSG1*</th>
<th>PSG2*</th>
<th>Testb</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apnea-hypopnea index (events/hour)</td>
<td>13.7±8.8</td>
<td>5.1±3.9</td>
<td>T= 2.91</td>
<td>0.017*</td>
</tr>
<tr>
<td>Desaturation index (events/hour)</td>
<td>22.7±8.3</td>
<td>10.2±8.9</td>
<td>T= 6.02</td>
<td>0.0002*</td>
</tr>
<tr>
<td>Snoring index (events/hour)</td>
<td>335.3±242.6</td>
<td>504.7±447.7</td>
<td>T= -0.38</td>
<td>0.581</td>
</tr>
</tbody>
</table>

* The mean ± SD is given for the normally distributed variables

b T= paired-sample t-test

* Statistically significant at the 0.05 probability level

Table 2. Sleep parameters from the first (PSG1) and second nocturnal polysomnographic registration (PSG2) of 10 OSA patients

<table>
<thead>
<tr>
<th>Sleep parameters</th>
<th>PSG1*</th>
<th>PSG2*</th>
<th>Testb,c</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total sleep time (min)</td>
<td>377.6</td>
<td>388.8</td>
<td>461.5</td>
<td>405.0</td>
</tr>
<tr>
<td>Stage 1 (%)</td>
<td>9.2±4.5</td>
<td>7.0±1.9</td>
<td>T= 1.39</td>
<td>0.197</td>
</tr>
<tr>
<td>Stage 2 (%)</td>
<td>61.1±7.1</td>
<td>57.8±5.8</td>
<td>T= 2.04</td>
<td>0.072</td>
</tr>
<tr>
<td>Stage 3 (%)</td>
<td>7.2±4.5</td>
<td>10.4±4.8</td>
<td>T= -2.52</td>
<td>0.033</td>
</tr>
<tr>
<td>Stage 4 (%)</td>
<td>0.0</td>
<td>0.0</td>
<td>3.4</td>
<td>0.0</td>
</tr>
<tr>
<td>Stage REM (%)</td>
<td>20.8±4.0</td>
<td>22.2±5.5</td>
<td>T= -0.86</td>
<td>0.411</td>
</tr>
<tr>
<td>Stage nonREM (%)</td>
<td>79.2±4.2</td>
<td>77.9±5.5</td>
<td>T= 0.80</td>
<td>0.445</td>
</tr>
<tr>
<td>Total movement time (min)</td>
<td>3.3±1.9</td>
<td>3.6±1.7</td>
<td>T= -0.36</td>
<td>0.729</td>
</tr>
<tr>
<td>Sleep efficiency (%)</td>
<td>83.1±6.9</td>
<td>87.9±4.0</td>
<td>T= -2.41</td>
<td>0.040</td>
</tr>
<tr>
<td>Arousal index (events/hour)</td>
<td>29.4</td>
<td>43.6</td>
<td>52.8</td>
<td>14.7</td>
</tr>
</tbody>
</table>

* The mean ± SD is given for the normally distributed variables; The 25%|50% (= median)|75% percentiles are given for the not normally distributed variables

b T= paired-sample t-test; W= Wilcoxon signed rank test

c Sum of the negative ranks|sum of the positive ranks

* Statistically significant after Bonferroni-Holm correction (i.e., p = 0.004 times the number of comparisons = 0.04, which is smaller than 0.05 and therefore significant)

Discussion

The MAD in this pilot trial reduced the AHI significantly in, especially, the moderate cases. Despite the small sample size and the open-label character of this study, we therefore carefully conclude that this MAD might be effective in the treatment of especially moderate OSA. The MAD was not found to be effective in the treatment of snoring, as the snoring index did not change significantly. Short-term compliance to the therapy was excellent: all patients wore their MAD on a nightly basis for the entire study period. This pilot study also shows that its procedures are feasible. The MAD and the procedures of this pilot trial can therefore be used in the future RCT that will be performed in our laboratory.

The improvement in several respiratory (DI and AHI) and sleep variables (ARI) with the MAD in situ, as shown in this pilot trial, is in accordance with several previous studies [e.g., 25-29]. Further, the clinically satisfactory treatment result in the present study corresponds with a review by Pancer et al. [26], who concluded that on average, a reduction of more than 50% in AHI was achieved using MADs. Pancer
et al. [26] also described a large variability between studies in the reduction of AHI with an MAD in situ, probably caused by differences in the initial severity of OSA, type of appliances used and whether the appliance was at the optimum setting at the time of sleep study, methods of end point assessment, and so forth.

The moderate cases showed a significantly larger decrease in AHI with the MAD in situ than the mild cases. However, the much higher initial values of AHI in the moderate cases leads to a higher possibility of large decreases in AHI in these moderate cases than in the mild cases. The tendency of high values to return towards an individual’s more typical average state is known as “regression to the mean”. Due to that phenomenon, uncontrolled evaluations of treatment in persons selected with high initial values may lead to faulty conclusions concerning the effects of treatment by patients, providers, and/or researchers [30]. The future RCT, in which a control group is included, will give us more clarity about this outcome.

Snoring can be socially disruptive and is often one of the main complaints of an OSA patient. Subjective reduction of snoring is essential for a good compliance of an OSA patient to the therapy of choice. Unfortunately, in the present study, the snoring index did not change significantly with the MAD in situ. Snoring was assessed using the data of eight out of ten patients; the data of two patients were missing due to technical problems during the recording of the snoring signals. In this pilot trial, we used a piezo-electric lead for measuring snoring. Although there are some previous studies that used methods for objective evaluations of snoring [22, 23], to date and to our knowledge, there are no studies in which the current method has been used for measuring snoring. Evaluations of snoring in most previous studies have been based on patient’s and/or bed partner’s subjective reports [e.g., 25, 26, 28]. In these studies, a decrease in snoring was reached in a high proportion of patients treated with an MAD. The fact that we did not use subjective reports for the assessment of snoring makes it difficult to compare these studies with ours. Future studies to this aspect of OSA should therefore use both a subjective assessment of snoring (i.e., patient’s and/or partner’s reports) and an objective assessment of this phenomenon by means of an instrumental technique.

There are many different MADs available on the market nowadays [31]. All of them advance and slightly rotate the mandible to varying extents. The MADs used in previous studies differ in the position of the mandible [3, 11], which makes it difficult to compare the results of these studies. Clearly, there is still no consensus in the literature which protrusion position of the mandible is the most optimal one for the treatment of an OSA patient. In this pilot trial, we investigated the efficacy of the MAD adjusted at 50% of the maximal protrusion position, which is in accordance with Sjöholm et al. [19] and Tegelberg et al. [20]. Because we have examined only one position, this pilot trial gives no answer to the question whether 50% of the maximal protrusion position is the most optimal position of the mandible in these patients. In the future RCT that will be performed in our laboratory, the effects of different horizontal mandibular positions with a constant vertical dimension will be investigated.

The duration between the baseline PSG and that with the MAD in situ was, on average, 5 weeks. The long-term efficacy was not assessed in this pilot trial. Marklund et al. [32] found at a long-term (6-year) follow-up visit, that the AHI was reduced from 22 events per hour without the device to 5 events per hour with the device. This result is similar to their findings at the short-term follow-up visit after almost one year. Walker-Engström et al. [33], on the other hand, reported in a follow-up of a group of mild to moderate OSA patients that, the AHI and DI increased significantly between 1 year and 4 years. Similarly, Rose et al. [34] found, that the initial improvement in respiratory parameters in a group of mild-to-moderate OSA patients, treated with an MAD, decreased during the study period. They suggested that the soft-tissue advancement, which initially results in tightening of the structures surrounding the oropharynx, decreases as the soft tissue structures adapt to the mandibular advancement and lose their tightness, thereby leading to a relapse into a more serious condition over those 2 years. It is clear from the above reports that long-term evaluations are important and should be included in future studies to the efficacy of MADs in the treatment of OSA.

In short, we conclude from this pilot study that the MAD under study might be effective in the treatment of OSA. The procedures, used in this pilot study, were considered feasible for use in the future RCT.
References


Effects of an oral appliance with different mandibular protrusion positions at a constant vertical dimension on obstructive sleep apnea

Ghizlane Aarab, Frank Lobbezoo, Hans L. Hamburger, Machiel Naeije

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Abstract

Objectives: The aim of the study was to assess the influence of four mandibular protrusion positions, at a constant vertical dimension, on obstructive sleep apnea (OSA). Methods: Seventeen OSA patients (49.2 ± 8.5 years) received an adjustable mandibular advancement device (MAD). The patients underwent four polysomnographic recordings with their MAD in situ at, in random order, 0%, 25%, 50%, and 75% of the maximum protrusion. Results: The mean apnea-hypopnea index (AHI) values of the patients differed significantly between the protrusion positions ($P < 0.000$). The 25% protrusion position resulted in a significant reduction of the AHI with respect to the 0% position, while in the 50% and 75% position even lower AHI values were found. The number of side effects was larger starting at the 50% protrusion position. Conclusions: We recommend coming to a weighted compromise between efficacy and side-effects by starting an MAD treatment in the 50% protrusion position.

Key words: obstructive sleep apnea · oral appliance · mandibular advancement device · protrusion · vertical dimension

Introduction

Obstructive sleep apnea (OSA) is characterized by recurrent obstructions of the upper airway, often resulting in oxygen desaturation and arousal from sleep [1]. Continuous positive airway pressure (CPAP) is generally considered the ‘gold standard’ treatment for OSA [2]. However, CPAP is not always tolerated by patients, and it is used less frequently than medically required [3]. As an alternative, oral appliances can be prescribed to prevent upper airway collapse during sleep, especially for mild and moderate cases [4, 5].

In a recent, evidence-based review regarding the use of oral appliances in the treatment of OSA, Ferguson et al. [6] indicated that more information is needed about the key design elements of oral appliances that are related to improvements of OSA signs (polysomnographic variables) and symptoms (e.g., reports of snoring and excessive daytime sleepiness). According to Ferguson et al. [6], a larger mandibular protrusion will produce a larger decrease in OSA events. However, shortcomings in the available literature and conflicting data do not yet allow definitive conclusions to be drawn [7]. Since the role of vertical opening remains a controversy (i.e., negative or positive influence on the OSA condition; [8]), it is of importance to keep this variable constant when investigating the effects of a gradual increase in mandibular advancement on OSA. Therefore, the aim of the present study was to assess the influence of four mandibular protrusion positions, at a constant vertical dimension, on OSA signs and symptoms. The hypothesis thereby was that larger protrusions would yield larger improvements in OSA characteristics.

Materials and Methods

Participants

OSA patients were recruited from the Center for Sleep-Wake Disorders at the Slotervaart Medical Center, Amsterdam, The Netherlands. The center’s multidisciplinary team consists of a neurologist, ENT specialists, pulmonologists, a dentist, a psychologist,
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and technicians trained in sleep medicine. All patients underwent a thorough medical examination, including a polysomnographic (PSG) recording (baseline recording; see ‘Polysomnographic recordings’), as well as an extensive dental examination, including an assessment of the overbite and overjet. The inclusion criteria for participation were: age > 18 years, an Apnea-Hypopnea Index (AHI) between 5 and 45 events/hour, and two or more OSA symptoms (e.g., reports of snoring and excessive daytime sleepiness; [1]). Criteria for exclusion were: evidence of respiratory/sleep disorders other than OSA, a Body Mass Index (BMI) > 40, medication usage that could influence respiration or sleep, periodic limb movement disorder, previous treatment with CPAP or a mandibular advancement device (MAD), and reversible morphological upper airway abnormalities (e.g., enlarged tonsils) as assessed by the ENT specialist. Additional dental exclusion criteria were: a diagnosis of temporomandibular disorders (based on a functional examination of the masticatory system; [9, 10]), untreated periodontal problems, dental pain, and a lack of retention possibilities for the MAD.

The scientific and ethical aspects of the protocol were reviewed and approved by the Medical Ethics Committee of the Slotervaart Medical Center (# U/1731/0326).

Mandibular advancement device

An MAD, set at a constant vertical dimension but with an adjustable protrusion position, was made in the clinic of the Department of Oral Function of ACTA (Fig. 1). This MAD, which has been described in detail previously [11], was slightly modified to make it possible to keep the vertical dimension constant at the different protrusion positions of the MAD. The resulting vertical opening was 6 mm, measured between the first incisors with the MAD in the mouth.

Polysomnographic recordings

The study consisted of six PSG recordings per patient: a baseline recording at the hospital, four ambulatory recordings at home, and a follow-up recording at the hospital. The patients received the MAD on average 5 weeks before the first ambulatory recording at home. The patients were instructed to wear the MAD every night upon delivery.

The baseline and follow-up PSG recordings were obtained at the sleep laboratory of the Center for Sleep-Wake Disorders at the Slotervaart Medical Center, where the recordings took place in a dark hospital room, using Siesta hardware and Pro-Fusion software (Compumedics, Abbotsford, Australia). The baseline recording was also part of the inclusion procedure (see ‘Participants’). On average, the follow-up recording was obtained 39 weeks after the baseline recording, with the MAD in situ in its most effective protrusion position (i.e., the one that resulted in the lowest ambulatory-established AHI value; see below). At follow-up, a complete response to the MAD treatment was defined as a reduction in AHI to less than five events
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per hour. A partial response was defined as a reduction of at least 50% in AHI as compared to baseline, while the AHI remained at five or more [12].

In between the two sleep laboratory recordings, the patients underwent four ambulatory PSG recordings at home, using Monet hardware and Rembrandt software (Medcare Automation B.V., Amsterdam, the Netherlands). These recordings were made with the MAD in situ at 0%, 25%, 50%, and 75% of the maximum protrusion in a random order, with average interval duration of 3 weeks between subsequent recordings.

For both the sleep laboratory recordings and the ambulatory recordings, the mounting was performed at the hospital by a trained coworker. The channels of the recordings consisted of two electroencephalographic leads (C3-A2; O2-A1), two electro-oculographic leads, mental surface electromyography, nasal-oral airflow using a thermistor, oximetry, abdominal and thoracic respiratory effort, body position, electrocardiography, leg electromyography (m. tibialis anterior), and a piezo-electric lead for the detection of snoring vibrations.

Prior to each of the six PSG recordings, all participants received sleep hygiene advice, e.g., avoiding copious meals and beverages three hours before bedtime, and creating a good sleeping environment [13]. Each PSG recording was followed by a visit at ACTA, during which the BMI (kg/m²) was determined and the Epworth Sleepiness Scale (ESS; [14]) was completed. The participants were also interviewed (1) about their compliance (% of nights per week of wearing), (2) about possible side effects (nature and number; determined in an open question) of the MAD during the study period, and (3) about the change (increased, unchanged, or decreased) in snoring intensity, based on information they obtained from their bed partner. Finally, the visits at ACTA were used to adjust the protrusion position of the MAD according to the random order of the study protocol.

Data analysis

The PSG recordings were scored manually in 30-s epochs, and standard sleep and respiratory outcome variables were obtained [1, 15]. All data analyses were performed under blind conditions.

The baseline and follow-up PSG recordings were analyzed by a single technician trained in sleep medicine. This technician’s intra-observer reliability of AHI scoring was excellent, with an ICC of 0.99; that of sleep scoring was also excellent, with ICC values ranging from 0.94 to 0.99.

The ambulatory PSG recordings were also analyzed by a single, experienced examiner. This examiner’s intra-observer reliability of AHI scoring was excellent, with an ICC of 0.96; that of sleep scoring could be qualified as at least fair-to-good, with ICC values ranging from 0.63 to 0.94.

Statistics

Paired-samples t tests were used to test the null hypothesis of no differences in sleep laboratory-established respiratory and sleep data, BMI, and ESS between the baseline and follow-up PSG recordings. The Bonferroni-Holm technique was used to correct for multiple comparisons [16].

The ambulatory-established respiratory and sleep data, BMI, and ESS were organized in order of increasing amount of mandibular protrusion. For the effect of protrusion, one-way repeated measures analyses of variance (ANOVA) were used. These analyses were preceded by Mauchly’s Test of Sphericity. Subsequently, the Bonferroni-Holm technique was used to correct for multiple comparisons. Finally, least-significant difference (LSD) pairwise comparisons were used for variables that were significant in the ANOVA.

The self-reported variables “compliance” and “number of side effects” per mandibular protrusion position were analyzed using one-way repeated measures ANOVA, preceded by Mauchly’s Test of Sphericity and followed by LSD pairwise comparisons. To evaluate the association between the self-reported snoring intensity and the four mandibular protrusion positions, a chi-square test was conducted.

All statistical tests were performed with the SPSS 12.0 software package (SPSS Inc., Chicago, IL). Probability levels of \( P < 0.05 \) were considered statistically significant.
Results

Initially, 20 OSA patients (13 men; mean ± SD [range] age = 49.5 ± 8.1 [37 - 66] years) were included in the present study. Two patients (a man and a woman) refused one of the ambulatory PSG recordings, viz., the one with the MAD set at 0% of the maximum protrusion, because they felt distressed (“feeling of choking”) in that position. Three other patients also reported difficulty with breathing in that position, but they nevertheless completed the entire study. For private reasons that were unrelated to the study, one male patient dropped out of the study after the second ambulatory PSG recording. The three patients who did not complete the entire study were excluded from the data analyses. Thus, a total of 17 patients (12 men; mean ± SD [range] age = 49.2 ± 8.5 [37 - 66] years) completed the study protocol. The mean maximal mandibular protrusion capacity of these 17 patients was 9.6 (SD, 2.1; range 6 - 14) mm. These patients had a mean overjet of 3.2 (SD, 2.0; range, 0 - 9) mm and a mean overbite of 3.0 (SD, 2.2; range, -2 - 7) mm.

Table 1 summarizes the mean (± SD) values of the respiratory and sleep parameters, BMI, and ESS of the baseline (no MAD in situ) and follow-up (most effective MAD in situ) PSG recordings at the hospital. The MAD in its most effective protrusion position (viz., the 25% protrusion position in 1 patient, the 50% position in 6 patients, and the 75% position in 10 patients) resulted in a significant reduction in AHI with respect to baseline (P = 0.000). At an individual level, 12 of the 17 patients showed a complete response to the most effective MAD, while one other patient responded partially.

Table 2 presents the mean (± SD) values of the respiratory and sleep parameters, BMI, and ESS of the four ambulatory PSG recordings. The MAD set at the 0% protrusion position was worn less frequently than the MAD set at the 25% and 50% positions (P = 0.031 and 0.018, respectively). The reasons for non-compliance were: forgotten to insert the MAD before going to sleep, illness (e.g., a cold), and transient side effects (see below).

During the study, all patients reported (mild) transient side effects due to wearing of the MAD. Apart from hypersalivation and a feeling of a dry mouth (xerostomia), the side effects that might possibly be related to jaw position were: tenderness in the masseter muscle region upon awakening (n = 12), sensitive teeth upon awakening (n = 9), uncomfortable wearing (n = 9), feeling of changes in occlusion upon awakening (n = 7), and difficulty swallowing with the MAD in situ (n = 4). The number of reported side effects differed significantly between the various mandibular positions (F = 4.467, P = 0.023); they were reported more frequently with the MAD in situ set at the 50% and 75% protrusion positions than at the 0% and 25% positions (P = 0.011 – 0.038).

Finally, a decrease in self-reported snoring intensity was found more frequently with the MAD in situ set at the 50% and the 75% protrusion positions ($\chi^2 = 6.0$ and 14.0; $P = 0.050$ and 0.001, respectively).
Table 1. Respiratory and sleep variables (mean ± SD) from the baseline and follow-up PSG of 17 OSA patients

<table>
<thead>
<tr>
<th>Respiratory AHI (events/hour)</th>
<th>PSG 0</th>
<th>PSG 1</th>
<th>T</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Desaturation Index ≥ 3% (events/hour)</td>
<td>21.6 ± 11.1</td>
<td>6.4 ± 8.4</td>
<td>6.276</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Lowest saturation O2</td>
<td>82.7 ± 8.4</td>
<td>81.7 ± 5.0</td>
<td>-1.765</td>
<td>0.105</td>
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</table>

<table>
<thead>
<tr>
<th>Sleep Total sleep time (min)</th>
<th>PSG 0</th>
<th>PSG 1</th>
<th>T</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>163 ± 116</td>
<td>163 ± 116</td>
<td>0.406</td>
<td>0.001*</td>
<td></td>
</tr>
<tr>
<td>−1.195</td>
<td>0.105</td>
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</table>

<table>
<thead>
<tr>
<th>Sleep Stage 1 and 2 (%)</th>
<th>PSG 0</th>
<th>PSG 1</th>
<th>T</th>
<th>P</th>
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</thead>
<tbody>
<tr>
<td>63.7 ± 10.6</td>
<td>63.7 ± 10.6</td>
<td>0.464</td>
<td>0.709</td>
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</tbody>
</table>

<table>
<thead>
<tr>
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<th>PSG 0</th>
<th>PSG 1</th>
<th>T</th>
<th>P</th>
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</thead>
<tbody>
<tr>
<td>19.0 ± 10.6</td>
<td>19.0 ± 10.6</td>
<td>0.464</td>
<td>0.709</td>
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</table>

<table>
<thead>
<tr>
<th>Sleep Stage REM (%)</th>
<th>PSG 0</th>
<th>PSG 1</th>
<th>T</th>
<th>P</th>
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</thead>
<tbody>
<tr>
<td>13.7 ± 9.9</td>
<td>13.7 ± 9.9</td>
<td>0.464</td>
<td>0.709</td>
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</table>

<table>
<thead>
<tr>
<th>Sleep Sleep in supine position</th>
<th>PSG 0</th>
<th>PSG 1</th>
<th>T</th>
<th>P</th>
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<tbody>
<tr>
<td>84.7 ± 5.0</td>
<td>84.7 ± 5.0</td>
<td>0.464</td>
<td>0.709</td>
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</table>

<table>
<thead>
<tr>
<th>Patient characteristics BMI</th>
<th>PSG 0</th>
<th>PSG 1</th>
<th>T</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>27.2 ± 5.9</td>
<td>27.2 ± 5.9</td>
<td>0.464</td>
<td>0.709</td>
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<th>PSG 1</th>
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<tbody>
<tr>
<td>12.3 ± 6.5</td>
<td>12.3 ± 6.5</td>
<td>0.464</td>
<td>0.709</td>
<td></td>
</tr>
</tbody>
</table>

* Statistically significant at the 0.05 probability level after Bonferroni-Holm correction

Table 2. Respiratory and sleep variables (mean ± SD) from the four ambulatory nocturnal polysomnographic recordings in 17 OSA patients

<table>
<thead>
<tr>
<th>PSG 0</th>
<th>PSG 25%</th>
<th>PSG 50%</th>
<th>PSG 75%</th>
<th>F</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>AHI (events/hour)</td>
<td>23.0 ± 14.4</td>
<td>10.7 ± 7.4</td>
<td>7.5 ± 6.0</td>
<td>5.8 ± 6.0</td>
<td>20.403</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>PSG 25%</th>
<th>PSG 50%</th>
<th>PSG 75%</th>
<th>F</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage 1 and 2 (%)</td>
<td>64.8 ± 11.8</td>
<td>65.5 ± 10.6</td>
<td>62.1 ± 14.1</td>
<td>60.0 ± 14.0</td>
</tr>
<tr>
<td>Stage 3 and 4 (%)</td>
<td>11.8 ± 7.3</td>
<td>12.2 ± 10.9</td>
<td>13.5 ± 12.3</td>
<td>14.7 ± 12.5</td>
</tr>
<tr>
<td>Stage REM (%)</td>
<td>23.3 ± 8.8</td>
<td>22.4 ± 7.4</td>
<td>22.7 ± 7.5</td>
<td>25.0 ± 6.5</td>
</tr>
<tr>
<td>Sleep in supine position</td>
<td>51.6 ± 25.8</td>
<td>49.6 ± 24.5</td>
<td>45.3 ± 19.6</td>
<td>41.4 ± 24.1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PSG 50%</th>
<th>PSG 75%</th>
<th>F</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI</td>
<td>27.7 ± 3.4</td>
<td>27.6 ± 3.3</td>
<td>27.6 ± 3.3</td>
</tr>
<tr>
<td>ESS</td>
<td>12.3 ± 6.5</td>
<td>11.6 ± 6.2</td>
<td>11.8 ± 7.0</td>
</tr>
</tbody>
</table>

* Statistically significant at the 0.05 probability level after Bonferroni-Holm correction
Mandibular Advancement Device Therapy in Obstructive Sleep Apnea

Figure 2. Individual values of the apnea-hypopnea index (AHI) from the ambulatory polysomnographic recordings with the MAD set at 0%, 25%, 50%, and 75% of the maximum protrusion of the mandible (PSG_0%-PSG_75%) in 17 OSA patients

Discussion

In this study, the influence of four mandibular protrusion positions, at a constant vertical dimension, on OSA signs and symptoms was assessed. Our hypothesis was that larger protrusions would yield larger improvements in OSA characteristics.

Vertical dimension

Two of the 20 initially recruited patients refused to sleep with the MAD set at 0% of the maximum protrusion, because they felt too distressed in that position (i.e., they perceived difficulty in breathing). Three more patients perceived breathing difficulties with the MAD in the 0% position as well, but they were nonetheless willing and able to sleep with the appliance in situ. A possible explanation for these perceived difficulties in breathing is that in OSA patients, airway patency is reduced during sleep, particularly in the supine position when the jaw is more open and the posterior displacement of the tongue and hyoid bone tends to be more pronounced [17, 18, 19]. Via this mechanism, it could be possible that, following an increase in vertical dimension without protrusion (viz., with an MAD set at the 0% protrusion position), the mandible rotates posteriorly, thereby reducing airway patency even more than while sleeping without an intraoral appliance in situ [20, 21]. However, since only 5 out of the 20 initially recruited patients experienced breathing difficulties, the validity of this possible mechanism needs to be assessed in future studies.

Mandibular protrusion position

The present results show that the MAD set at 50% and 75% of the maximum protrusion yielded significantly lower values of the AHI than the MAD in the 25% protrusion position. Further, all three protrusion positions resulted in lower AHI values than the 0% position. These findings suggest a dose dependency, i.e., larger protrusions yielded larger improvements in OSA, which is in line with our hypothesis. Tegelberg et al. [22], who reported that the 50% and 75% protrusion positions were equally effective in groups of mild-moderate OSA patients, did not study smaller protrusion positions, so that a dose dependency could not be derived from their study. Other studies, however, do show indications of a dose dependency, thereby corroborating the present findings. For example, Kato et al. [23] found that each 2 mm of mandibular advancement gave a 20% improvement in the number of nocturnal desaturations. Likewise, Walker-Engström et al. [24] observed that the efficacy of MAD treatment in a severe OSA group was significantly higher with a more pronounced advancement compared with less advancement. Thus, a dose dependency seems to be a consistent finding in the literature. The present study, however, is the first to demonstrate this for a wide range of protrusion positions (including the 0% position) at a fixed vertical dimension and by using a random order for the mandibular positions as an important aspect of the study design.

Although self-reported compliance has been suggested to overestimate the actual use of oral appliances, covert compliance...
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monitoring has shown excellent agreement between objective and subjective compliance [25]. Reviewing self-report data, Ferguson et al. [6] found a median use of 77% of nights in the studies with a one-year follow-up. In the present study, compliance rates of up to 97% were found. The reason for this relatively high compliance, especially for the 25% and 50% protrusion positions, may be the fact that during the study period the patients frequently visited ACTA to be interviewed about, amongst others, the frequency of wearing. This regular contact with the examiner could have motivated the patients to use their MAD on an almost nightly basis. A possible explanation for the finding that MADs set at the 25% and 50% protrusions positions were worn more frequently than those set at the 0% position is, that patients were probably less willing to use the 0% protrusion position, amongst others due to the perceived difficulties with breathing in that position (see above).

Side-effects in relation to MAD usage are frequently reported [7]. These effects are usually described as mild and acceptable; resolution normally occurs within several days or weeks when the appliance is used regularly and its fit adjusted occasionally [6, 7]. In the present study, the patients reported several mild, transient side-effects caused by the MAD during the study period, which in some cases led to a less frequent use of the appliance. Due to its design, an MAD transmits forces upon the mandible via the dental arches. In addition, the mandibular part of the temporomandibular joint is forced out of its natural resting position during overnight use of the MAD. The nature of the side effects observed in this study, like sensitive teeth, masseter muscle tenderness, and a feeling of changes in occlusion upon awakening, might (at least in part) be due to these mechanisms [26]. Consequently, more side effects could be expected at larger protrusion positions. Indeed, side-effects where reported more frequently with the 50% and 75% protrusion position than with the smaller mandibular protrusions.

**Most effective protrusion position**

In the present study, the most effective MAD resulted in a decrease in AHI to normal levels (i.e., less than five events per hour) in 12 of the 17 patients. This success rate of approx. 70% is higher than the average success rates of 52% and 54% reported by Ferguson et al. [6] and Hoffstein [27], respectively. A possible reason for the differences in success rates between the present study and previous ones may be sought in methodological disparities, e.g., differences in baseline patient characteristics like OSA severity and BMI, and in the amount of mandibular protrusion of the MAD, but also in a difference in the definition of treatment success. In the present study, only objective variables were considered when determining treatment success. However, since patients primarily report to physicians with subjective complaints of OSA, a uniform definition of treatment success that includes not only objective criteria (e.g., AHI and oxygenation) but also subjective symptoms (e.g., self-reports of snoring and sleepiness) needs to be established [6].

Unlike other studies [27], the ESS did not improve with the most effective MAD *in situ* in the present group of OSA patients. A similar finding of persisting daytime sleepiness was reported in the studies by Engleman et al. [28] and Neill et al. [29]. In the present study, the number of respiratory arousals did reduce significantly with MAD treatment. Since arousals are known to change the sleep architecture, and an increase in arousals may yield daytime sleepiness as one of its possible consequences [30], it was assumed that the daytime sleepiness would improve with the reduced number of respiratory arousals. Possibly, there is a delay in the effect of improved sleep architecture on daytime sleepiness. This remains to be studied in future research. Another possible explanation is the relatively low ESS score at baseline of on average 12.2 (out of a maximum possible score of 24). This value is close to the sleepiness threshold of 10, so that there is little left to be gained [31].

In the present study sample, a relatively small protrusion of the mandible (viz., 25% of the maximum protrusion) already resulted in a significant reduction of the AHI with respect to the 0% position, while at the 50% and 75% protrusion positions even lower AHI values were found; suggesting the existence of a dose dependency. The number of side effects is larger starting at the 50% protrusion position. Within the limitation of the present study, we therefore recommend coming to a weighted compromise between efficacy and side-effects by
starting an MAD treatment in the 50% protrusion position. Only when this position does not result in an AHI reduction and/or a satisfactory relief of symptoms, may more advancement of the mandible to 75% of the maximum protrusion be considered.

Acknowledgements

The authors would like to thank the staff of the Center for Sleep-Wake Disorders of Slotervaart Medical Center in Amsterdam, The Netherlands, for their assistance with this work. The Netherlands Institute for Dental Sciences (IOT) supported this work.

Conflict of interest

All authors declare that they have no conflict of interest in this study.

References

Mandibular Advancement Device Therapy in Obstructive Sleep Apnea

Effects of an oral appliance with different mandibular protrusion


Chapter 5

Oral appliance therapy versus nasal continuous positive airway pressure in obstructive sleep apnea: a randomized, placebo-controlled trial

Ghizlane Aarab, Frank Lobbezoo, Hans L. Hamburger, Machiel Naeije

Respiration 2011; 81: 411-419
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 intra-oral placebo device. **Methods:** Sixty-four mild/ moderate OSA patients (52.0 ± 9.6 years) were randomly assigned to three parallel groups: MAD, nCPAP, and placebo device. From all patients, two polysomnographic (PSG) recordings were obtained at the hospital: one before treatment and one after approximately six 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 to moderate OSA when both treatment modalities are titrated objectively. **Key words:** mandibular advancement device ∙ continuous positive airway pressure ∙ placebo ∙ randomized controlled trial ∙ obstructive sleep apnea ∙ therapy ∙ treatment

Introduction

Obstructive sleep apnea (OSA) is defined as a 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 approx. 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.

Treatment options for OSA include, amongst others, behavioural modification (e.g., weight loss and alteration of 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.
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 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’s protocol were approved by the Medical Ethics Committee of the Slotervaart Medical Center (# U/1731/0326, U/2679/0326).

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

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<thead>
<tr>
<th>Exclusion criteria</th>
<th>Number of patients excluded</th>
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<tbody>
<tr>
<td>Medical</td>
<td></td>
</tr>
<tr>
<td>Respiratory /sleep disorder other than OSA</td>
<td>23</td>
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<tr>
<td>Body Mass Index &gt; 40</td>
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<tr>
<td>Previous treatment with CPAP or MAD</td>
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<tr>
<td>Reversible morphological upper airway abnormalities (e.g., enlarged tonsils)</td>
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<tr>
<td>Other medical conditions (e.g., psychiatric disorder)</td>
<td>7</td>
</tr>
<tr>
<td>Dental</td>
<td></td>
</tr>
<tr>
<td>Temporomandibular disorders</td>
<td>-</td>
</tr>
<tr>
<td>Untreated periodontal problems</td>
<td>1</td>
</tr>
<tr>
<td>Dental pain</td>
<td>-</td>
</tr>
<tr>
<td>Lack of retention possibilities for an oral appliance</td>
<td>28</td>
</tr>
</tbody>
</table>

Randomisation 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 randomisation 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, 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 H₂O/h, until respiratory disturbances and respiration-related arousals were reduced to ≤5/h, and snoring was minimized. The average value of the pressure was 7.3 (SD, 1.9; range, 4-11) cm H₂O.

For the titration of the MAD, four ambulatory PSG recordings were obtained at regular intervals [18], using Monet hardware and Rembrandt Software (Medcare Automation B.V., 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 one 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 as well.

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 the apnea-hypopnea index (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 deviation (SD) 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 (LSD) 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 (see below).

The per-protocol analyses included only those patients who completed the trial. Except for compliance, snoring reports, and side effects, which were analyzed differently (see below), 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 chi-square 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 Inc., Chicago, IL).

**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; 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 enrolled into the study and 57 patients completed the study.

The patient characteristics at baseline are presented in Table 2. BMI was the only baseline characteristic that differed between the three therapy groups (F = 5.170; P = 0.008). LSD analyses 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).

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.
Fig. 1. Flow-chart of the patients through each stage of the trial. MAD = mandibular advancement device; nCPAP = nasal continuous positive airway pressure.

Table 2 Patient characteristics at baseline of the mandibular advancement device (MAD) group, nasal continuous positive airway pressure (nCPAP) group, placebo group, and drop-outs.

<table>
<thead>
<tr>
<th></th>
<th>MAD (n = 20)</th>
<th>nCPAP (n = 18)</th>
<th>Placebo (n = 19)</th>
<th>Drop-outs (n = 7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>50.3 ± 9.1</td>
<td>55.4 ± 9.8</td>
<td>51.3 ± 10.1</td>
<td>49.3 ± 7.3</td>
</tr>
<tr>
<td>Number of man/woman</td>
<td>16/4</td>
<td>12/6</td>
<td>14/5</td>
<td>5/2</td>
</tr>
<tr>
<td>Apnea-hypopnea index</td>
<td>22.1 ± 10.8</td>
<td>20.9 ± 9.8</td>
<td>20.1 ± 8.7</td>
<td>14.8 ± 3.8</td>
</tr>
<tr>
<td>Body Mass Index (kg/m²)*</td>
<td>27.1 ± 3.2</td>
<td>30.7 ± 3.7</td>
<td>31.1 ± 4.7</td>
<td>27.8 ± 4.1</td>
</tr>
<tr>
<td>Neck circumference (cm)</td>
<td>41.7 ± 3.0</td>
<td>43.6 ± 4.0</td>
<td>42.6 ± 3.2</td>
<td>41.4 ± 4.8</td>
</tr>
<tr>
<td>Epworth sleepiness score</td>
<td>11.8 ± 5.8</td>
<td>10.2 ± 4.7</td>
<td>10.6 ± 4.1</td>
<td>13.7 ± 1.9</td>
</tr>
</tbody>
</table>

36-item short-form health survey

<table>
<thead>
<tr>
<th></th>
<th>MAD (n = 20)</th>
<th>nCPAP (n = 18)</th>
<th>Placebo (n = 19)</th>
<th>Drop-outs (n = 7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical functioning</td>
<td>82.9 ± 22.7</td>
<td>61.1 ± 24.8</td>
<td>77.4 ± 24.2</td>
<td>73.8 ± 18.4</td>
</tr>
<tr>
<td>Social functioning</td>
<td>75.0 ± 23.6</td>
<td>64.8 ± 25.5</td>
<td>75.7 ± 29.0</td>
<td>77.5 ± 22.3</td>
</tr>
<tr>
<td>Role physical</td>
<td>53.9 ± 48.1</td>
<td>64.7 ± 45.1</td>
<td>69.7 ± 39.6</td>
<td>45.0 ± 51.2</td>
</tr>
<tr>
<td>Role emotional</td>
<td>77.2 ± 41.7</td>
<td>76.5 ± 40.4</td>
<td>78.9 ± 37.2</td>
<td>73.3 ± 43.5</td>
</tr>
<tr>
<td>Mental health</td>
<td>66.7 ± 14.1</td>
<td>64.5 ± 22.7</td>
<td>69.9 ± 21.9</td>
<td>69.6 ± 19.3</td>
</tr>
<tr>
<td>Vitality</td>
<td>49.7 ± 18.0</td>
<td>46.3 ± 19.5</td>
<td>48.7 ± 26.1</td>
<td>56.0 ± 12.9</td>
</tr>
<tr>
<td>Bodily pain</td>
<td>79.6 ± 27.9</td>
<td>65.9 ± 28.8</td>
<td>82.1 ± 26.2</td>
<td>71.0 ± 35.4</td>
</tr>
<tr>
<td>General health perception</td>
<td>54.7 ± 22.3</td>
<td>49.6 ± 16.5</td>
<td>60.3 ± 21.3</td>
<td>52.0 ± 8.4</td>
</tr>
<tr>
<td>Health transition</td>
<td>41.3 ± 24.7</td>
<td>38.3 ± 29.7</td>
<td>45.8 ± 21.4</td>
<td>50.0 ± 17.7</td>
</tr>
</tbody>
</table>

*MAD patients had a significantly lower BMI than placebo and nCPAP patients (P = 0.002 and 0.006, respectively).
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).

<table>
<thead>
<tr>
<th>Respiration</th>
<th>MAD (n = 20)</th>
<th>nCPAP (n = 18)</th>
<th>Placebo (n = 19)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>Δ value</td>
<td>Baseline</td>
<td>Δ value</td>
<td>Baseline</td>
</tr>
<tr>
<td>AHI (events/hour)</td>
<td>22.1 ± 10.8</td>
<td>16.3 ± 10.3</td>
<td>20.9 ± 9.8</td>
<td>19.5 ± 8.7</td>
</tr>
<tr>
<td>AHI REM_supine (events/hour)</td>
<td>24.6 ± 31.5</td>
<td>12.5 ± 34.8</td>
<td>31.2 ± 30.5</td>
<td>26.7 ± 30.4</td>
</tr>
<tr>
<td>AHI NREM_supine (events/hour)</td>
<td>33.0 ± 23.9</td>
<td>25.1 ± 21.4</td>
<td>39.2 ± 25.9</td>
<td>34.0 ± 24.4</td>
</tr>
<tr>
<td>AHI REM_non-supine (events/hour)</td>
<td>15.1 ± 14.9</td>
<td>7.5 ± 13.0</td>
<td>16.4 ± 16.5</td>
<td>14.1 ± 21.3</td>
</tr>
<tr>
<td>AHI NREM_non-supine (events/hour)</td>
<td>11.3 ± 11.9</td>
<td>8.6 ± 10.8</td>
<td>10.2 ± 9.8</td>
<td>8.9 ± 9.4</td>
</tr>
</tbody>
</table>

Sleep

<table>
<thead>
<tr>
<th>Total sleep time (min)</th>
<th>MAD (n = 20)</th>
<th>nCPAP (n = 18)</th>
<th>Placebo (n = 19)</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>425.0 ± 128.6</td>
<td>-11.8 ± 143.2</td>
<td>473.8 ± 83.2</td>
<td>58.8 ± 101.2</td>
</tr>
<tr>
<td>Stage 1 and 2 (%)</td>
<td>68.8 ± 10.8</td>
<td>8.2 ± 14.7</td>
<td>67.0 ± 8.5</td>
<td>0.8 ± 9.1</td>
</tr>
<tr>
<td>Stage 3 and 4 (%)</td>
<td>14.5 ± 10.9</td>
<td>-3.1 ± 9.6</td>
<td>12.9 ± 8.4</td>
<td>-1.4 ± 8.7</td>
</tr>
<tr>
<td>Stage REM (%)</td>
<td>18.3 ± 6.4</td>
<td>-1.9 ± 6.4</td>
<td>20.0 ± 6.4</td>
<td>0.6 ± 8.2</td>
</tr>
<tr>
<td>Sleep in supine position (%)</td>
<td>47.4 ± 26.3</td>
<td>7.7 ± 32.9</td>
<td>38.5 ± 22.2</td>
<td>-10.1 ± 30.3</td>
</tr>
<tr>
<td>Respiratory arousal index (events/hour)</td>
<td>17.0 ± 9.6</td>
<td>13.0 ± 9.0</td>
<td>16.4 ± 8.9</td>
<td>13.9 ± 11.8</td>
</tr>
</tbody>
</table>

Definition of abbreviations: AHI = apnea-hypopnea index, REM = rapid-eye-movement, NREM = non-rapid-eye-movement. Δ value = difference between baseline and therapy evaluation values.

* P-value as result of the ANCOVA comparing the three groups, controlled for the effect of the baseline value and BMI.
† Statistically significant at the 0.05 probability level.
‡ Statistically significant after Bonferroni-Holm correction.

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; see Table 3 and Figure 2). No difference in AHI was found in the nCPAP group (P = 0.092), whereas the changes in AHI in the MAD and placebo groups were significantly larger than those in the nCPAP group (P = 0.000 and 0.000, respectively). The effect size between MAD and nCPAP was 0.48 (range from -0.17 to 1.12). Moreover, 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 = 14.886, P = 0.000; see Table 3 and Figure 2). In the worst-case scenario, the contrast between the MAD group and the nCPAP group was significantly larger than those in the placebo group (P = 0.000 and 0.000, respectively). The effect size between MAD and nCPAP was 0.48 (range from -0.17 to 1.12). Moreover, the placebo group showed a small but significant reduction in AHI between baseline and therapy evaluation (paired T-test: P = 0.044).
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 REM and 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 analysed, only the changes in 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 group, 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 the health also had improved within the placebo group could not be analysed 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 a placebo treatment.

Snoring – None of the patients reported an increase in snoring. Changes in snoring differed significantly between the three therapy groups ($X^2 = 32.069, P = 0.000$). 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 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 nasal CPAP (nCPAP) following PSG controlled titration of both treatment modalities.

Previous RCTs have also addressed the efficacy of MADs in the treatment of OSA [6-12, 24]. In these studies, the MAD was set in a fixed protrusion position [8, 11, 12], or the MAD 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). As 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 one-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 favour 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 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 two patients in the MAD group did not respond at all 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 polysomnographic 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 not by evaluating the changes in AHI, but by focusing at the treatment outcome values themselves. A cut-off point of 5 for the AHI is often used, 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 cut-off point. An AHI value of 9.8, obtained from a single night recording, is at the threshold of the 95% probability band around the cut-off 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. In 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, the NNT is 7. This means that when 7 patients are treated in both groups, the 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, the NNT is 6; in the best-case scenario it is 26. A 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 life style as the 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 ESS, 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 life style. 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 approx. 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 four 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 favourable 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, three 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.

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Declarations 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


Long-term follow-up of a randomized controlled trial of oral appliance therapy in obstructive sleep apnea

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Abstract

**Background:** Long-term trials are needed to capture information regarding the persistence of efficacy and loss to follow-up of both mandibular advancement device (MAD) therapy and continuous positive airway pressure (CPAP) therapy. **Objectives:** The aim of the study was to compare these treatment aspects between MAD and nasal CPAP (nCPAP) in a one-year follow-up. **Methods:** 43 mild/moderate OSA patients (52.2 ± 9.6 years) with a mean apnea-hypopnea index (AHI) of 20.8 ± 9.9 events/hour were randomly assigned to two parallel groups: MAD (n = 21) and nCPAP (n = 22). Four polysomnographic (PSG) recordings were obtained: one before treatment, one for the short-term evaluation, and two recordings 6 and 12 months after the short-term evaluation. Excessive daytime sleepiness (EDS) was also evaluated at the PSG recordings. **Results:** The initially achieved improvements in the AHI remained stable over time within both groups (P = 0.650). In the nCPAP group the AHI improved 4.1 events/hour more than in the MAD group (P = 0.000). The EDS values showed a gradual improvement over time (P = 0.000), and these improvements were similar for both groups (P = 0.367). In the nCPAP group more patients withdrew from treatment due to side-effects than in the MAD group. **Conclusions:** The absence of significant long-term differences in EDS improvements between the MAD and the nCPAP groups with mild/moderate OSA may indicate that the larger improvements in AHI values in the nCPAP group are not clinically relevant. Moreover, nCPAP patients may show more problems in accepting their treatment modality than MAD patients.

**Key words:** obstructive sleep apnea · long term · mandibular advancement device · continuous positive airway pressure · randomized controlled trial · treatment · compliance

Introduction

Obstructive sleep apnea (OSA) is characterized by recurrent obstruction of the upper airway, often resulting in oxygen desaturation and arousal from sleep [1]. Excessive daytime sleepiness, snoring, and reduction in cognitive functions are among the common symptoms of this condition [2].

Although continuous positive airway pressure (CPAP) has been proposed as the most effective treatment for OSA [3], nowadays mandibular advancement devices (MADs) play an important role in the treatment of mild/moderate OSA patients [2, 4]. These devices increase the pharyngeal space by protruding the mandible and advancing the tongue.

The short-term therapeutic efficacy of mandibular advancement devices (MADs) has been compared with that of CPAP and was proven to be satisfactory in several randomized controlled trials [e.g., 5-12]. However, long-term parallel-group trials are needed to capture information regarding the persistence of efficacy and the loss to follow-up [3]. Therefore, the aim of the present study was to compare these treatment aspects between MAD and nasal CPAP (nCPAP) in a one-year follow-up study.

Materials and methods

**Participants**

This study is the one year follow-up of a short-term randomized controlled trial (RCT), in which three therapy groups (viz, MAD, nCPAP, and placebo) were compared [12]. OSA patients were invited for participation in the initial short-term study when they fulfilled the following inclusion criteria: age > 18 years, an apnea-hypopnea index (AHI) between 5 and 45 events per hour, and an Epworth Sleepiness Score ≥ 10 [13] 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]. The placebo group was excluded from the long-term study for ethical reasons. Moreover, OSA patients
with an AHI > 10 events/hour and less than 50% reduction in AHI at the short-term evaluation were also excluded from the long-term study. The baseline characteristics of the patients at the time of therapy allocation are presented in Table 1. This long-term study was also approved by the Slotervaart Hospital’s Ethics Committee (# U/1731/0326, U/2679/0326).

Randomisation and interventions

At the start of the short-term RCT, using block randomisation, consenting patients were allocated to the interventions. The allocation sequence was automatically generated and concealed by an independent co-worker. The two interventions studied in this parallel-group follow-up study were: an MAD [14, 15] and nCPAP (REMstar Pro; Respironics, Herrsching, Germany).

Both MAD and nCPAP were titrated before the start of the treatment [12]. The titration of nCPAP was performed during a polysomnographic (PSG) recording. The pressure was increased in incremental steps of 1 cm H2O/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 (SD, 1.9; range, 4-11) cm H2O. For the titration of the MAD, four ambulatory PSG recordings were obtained at regular intervals [15]. 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 one patient, at 50% in 7 patients, and at 75% in 12 patients.

Analyst blinding was ascertained by assigning codes to data sets and by analyzing these sets in random blocks. For more details, see Aarab et al. [12].

Procedure

From all patients, four PSG recordings were obtained in the sleep laboratory of the Slotervaart Medical Center: one before treatment, one for the short-term evaluation (approximately 6 months after therapy assignment), and two recordings for the long-term evaluation (approximately 6 and 12 months after the short-term evaluation). The montage was performed at the Slotervaart Medical Center by a trained coworker. Each PSG recording was analyzed manually, under blind conditions, by the same examiner, who was experienced in scoring PSG recordings, using internationally accepted criteria [1, 16]. Sleep stages were scored in 30-s epochs and standard sleep and respiratory outcome variables were obtained. The mounting and procedure of the PSG recordings were described in detail in Aarab et al. [17]. The primary and secondary outcome measures were obtained at the time of the PSG recordings.

The therapy evaluation PSG recordings were followed by a visit at ACTA, during which the participants were interviewed about their compliance (% of nights per week of usage) and possible side effects (nature and number).

Outcome measures

The change in the apnea-hypopnea index between baseline and therapy evaluation (\( \Delta \)AHI) was the primary outcome variable. Secondary outcome variables were the changes in sleep variables and in excessive daytime sleepiness (EDS) between baseline and therapy evaluation. Other secondary outcome variables were self-reported compliance and side-effects.

Statistical analysis

Differences in patient characteristics at baseline between the two therapy groups were analyzed using independent t-tests and Chi-square tests. Outcome variables that showed significant between-groups differences at baseline were used as covariate in the subsequent analyses (see below).
The associations between one or more predictors and missing values in AHI at the therapy evaluations were studied using logistic regression analyses. Several variables were found to be related to the missing values. These predictors of missing values were included in an imputation model to estimate the missing values by applying multiple imputation (MI) [18]. MI was based on the Multivariate Imputation by Chained Equations (MICE) procedure [19]. MICE allows one to specify the multivariate structure in the data as a series of conditional regression models, based on the information of other variables included in the imputation model. Ten separate imputation samples were generated, for both treatment groups separately.

Following the MI procedure, generalized estimating equation (GEE; [20]) analyses were performed to study differences between both groups (MAD and nCPAP) for the primary and secondary outcome variables. For each variable, its baseline value was used as a covariate to protect against potential regression to the mean effects. Interactions of treatment groups with time were used to study if differences in treatment effects increased or decreased over time. GEE analyses were done in each imputed dataset, and the results were summarized using Rubin’s rules [21].

All statistical tests were performed with the SPSS 17.0 (SPSS Inc., Chicago, IL) and R (R Foundation for Statistical Computing, Vienna, Austria) software packages.

Results

A total of 64 patients were enrolled in the initial short-term study, and were randomized at the start of the RCT as shown in Figure 1. The placebo group was excluded from the long-term part of the study. In Table 1, it is illustrated that the MAD group had a significantly lower BMI than the nCPAP group ($T = 3.921; P = 0.001$). This difference was constant over time ($F = 1.456, P = 0.242$).

The mean ($\pm$ SD) baseline values of the respiratory, subjective, and sleep variables as well as the changes in these variables from baseline to therapy evaluation are shown in Table 2.

| Table 1. Patient characteristics (mean ± SD) at baseline of the mandibular advancement device (MAD) group and of the nasal continuous positive airway pressure (nCPAP) group. |
|-----------------|-----------------|-----------------|
| **MAD** (n = 21) | **nCPAP** (n = 22) |
| Age (years) | 50.4 ± 8.9 | 54.9 ± 10.1 |
| Number of man/ woman | 17/ 4 | 15/ 7 |
| Apnea-hypopnea index (events/hour) | 21.4 ± 11.0 | 20.1 ± 9.0 |
| Body Mass Index (kg/m²)* | 27.1 ± 3.1 | 30.5 ± 3.4 |
| Neck circumference (cm) | 41.7 ± 2.9 | 43.2 ± 3.8 |
| Excessive daytime sleepiness | 12.0 ± 5.7 | 11.0 ± 4.4 |

* Statistically significant at the 0.05 probability level.
Mandibular Advancement Device Therapy in Obstructive Sleep Apnea

Long-term follow-up of a randomized controlled trial

Table 2. The mean (± SD) baseline and ∆ values (i.e., difference between baseline and therapy evaluation) of the respiratory, subjective, and sleep outcome variables of the MAD group and the nCPAP group.

<table>
<thead>
<tr>
<th></th>
<th>MAD</th>
<th>nCPAP</th>
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<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>∆ value at</td>
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<tr>
<td></td>
<td>value</td>
<td>short-term</td>
</tr>
<tr>
<td></td>
<td>(n = 21)</td>
<td>therapy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>evaluation</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(n = 17)</td>
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<tr>
<td></td>
<td></td>
<td>(n = 18)</td>
</tr>
<tr>
<td>Respiration</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AHI (events/hour)</td>
<td>21.4 ± 11.0</td>
<td>16.3 ± 10.3</td>
</tr>
<tr>
<td></td>
<td>20.1 ± 9.0</td>
<td>19.5 ± 8.7</td>
</tr>
<tr>
<td>Subjective</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Excessive daytime sleepiness</td>
<td>12 ± 5.7</td>
<td>16.3 ± 10.3</td>
</tr>
<tr>
<td>Sleep</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage NREM (%)</td>
<td>81.5 ± 6.4</td>
<td>21.6 ± 6.4</td>
</tr>
<tr>
<td></td>
<td>0.6 ± 7.8</td>
<td>-0.5 ± 7.7</td>
</tr>
<tr>
<td>Stage REM (%)</td>
<td>18.6 ± 6.4</td>
<td>-1.9 ± 6.4</td>
</tr>
<tr>
<td>Respiratory arousals (events/hour)</td>
<td>17.5 ± 10.4</td>
<td>14.6 ± 10.2</td>
</tr>
<tr>
<td></td>
<td>13.7 ± 9.8</td>
<td>15.7 ± 9.8</td>
</tr>
</tbody>
</table>

Definition of abbreviations: AHI = apnea-hypopnea index, REM = rapid-eye-movement, NREM = non-rapid-eye-movement.

Loss to follow-up

At the short-term evaluation, three patients in the MAD group were instructed to stop with therapy, because the therapy was not effective (AHI > 10 events/hour and less than 50% reduction in AHI). These three patients were offered a treatment with nCPAP instead. After the short-term evaluation, a total of thirty-five patients in the MAD and nCPAP groups started with a one year follow-up. In the MAD group, two patients dropped out, because they experienced more side-effects than benefits from the treatment. These two MAD patients reported the following side-effects: discomfort in wearing (n = 2), tenderness in the masseter muscle region upon awakening (n = 1), and feeling of a changed occlusion upon awakening (n = 1).

In the nCPAP group, two patients dropped out because of private reasons that were unrelated to the study, and three patients dropped out, because they experienced more side-effects than benefits from the treatment. The following side-effects were reported by these three nCPAP patients: problems with expiration against the positive pressure (n = 3), pain due to pressure of the mask (n = 1), and difficulty in changing sleep position (n = 2). Finally, a total of twenty-eight patients completed the entire study protocol (Fig. 1).
therapy was considered ineffective. This patient, however, wanted to continue the MAD treatment for 6 months, because he experienced subjective benefits of the treatment (viz, improvement in excessive daytime sleepiness and a decrease in snoring sound).

Table 3. Outcomes of the GEE analyses for the primary and secondary outcome variables.

<table>
<thead>
<tr>
<th>Primary outcome variables</th>
<th>Treatment effect*</th>
<th>Time effect*</th>
</tr>
</thead>
<tbody>
<tr>
<td>△ AHI (events/hour)</td>
<td>-4.1 (-5.7, -2.5)</td>
<td>0.000†</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Secondary outcome variables</th>
<th>Treatment effect*</th>
<th>Time effect*</th>
</tr>
</thead>
<tbody>
<tr>
<td>△ Excessive daytime sleepiness (EDS)</td>
<td>-0.9 (-2.8, 1.0)</td>
<td>0.367</td>
</tr>
<tr>
<td>△ Respiratory arousals (events/hour)</td>
<td>-3.2 (-4.5, -1.8)</td>
<td>0.000†</td>
</tr>
<tr>
<td>△ Stage NREM (%)</td>
<td>0.2 (-1.8, 2.2)</td>
<td>0.854</td>
</tr>
<tr>
<td>△ Stage REM (%)</td>
<td>-0.1 (-2.2, 1.9)</td>
<td>0.897</td>
</tr>
</tbody>
</table>

Table 3: *For all variables, there was no significant interaction of the groups with time. Therefore, only the between-groups effect and the time effect within groups are reported. †P-value as result of the GEE-analyses, controlled for the effects of the baseline value and of BMI. ‡Statistically significant at the 0.001 probability level.

Fig. 2. Individual values of the apnea-hypopnea index (AHI) of the 28 patients who completed the entire study protocol (MAD, n = 15; nCPAP, n = 13) obtained from the baseline polysomnographic (PSG) recordings and from the subsequent therapy evaluation PSG recordings.

Secondary outcome variables

The MAD group had a significantly smaller change in respiratory arousal index than the nCPAP group (P = 0.000; Table 3). The mean difference between both groups in change of respiratory arousal index was 3.2 events/hour (Table 3). There was no significant difference between both groups in the change of excessive daytime sleepiness (△EDS). The △EDS increased over time as indicated by the time effect (P = 0.000; Table 3).

The MAD patients who completed the trial used their appliance 85.8% (SD, 18.8) of the nights; the nCPAP patients, 84.8% (SD, 20.6) of the nights. There was no significant difference between both groups in compliance.

The nature and number of side-effects at the first evaluation are described in detail in Aarab et al. [12]. The side-effects in the MAD group had in most cases a dental nature (e.g., sensitive teeth upon awakening, tenderness in masseter muscle region, and feeling of changes in occlusion upon awakening). The side-effects in the nCPAP group were in most cases related to the mask and the cumbersome nature of the CPAP device (e.g., pain due to pressure of the mask, and problems with expiration against the positive pressure). The number of side-effects decreased over time within both groups (P = 0.000).
MAD group, the number of side-effects reduced from 1.5 at the short-term evaluation to 0.7 at the 12 months evaluation. In the nCPAP group, the number of side-effects reduced from 2.2 at the short-term evaluation to 1.0 at the 12 months evaluation. For all secondary outcome variables, there was no significant interaction of the groups with time.

**Discussion**

The short-term improvement in AHI was maintained in both the MAD group and the nCPAP group in this one-year follow-up. The excessive daytime sleepiness further improved over time for both treatment modalities.

Randomized clinical trials are a powerful tool for investigating treatment effects, but in human trials there are often problems of noncompliance, where the patient does not adhere to the treatment assigned. A common approach to the analysis of data with missing values is to exclude the patients with missing values. Typically, this leads to a reduction of statistical power and to estimates that can potentially be biased when the probability of a missing value is related to the characteristics of the patients [22]. To overcome this problem, imputation methods for missing data have been developed [23]. There is increasing evidence of the superiority of multiple imputation methods to replace missing values, suggesting that these methods should be preferred over other imputation methods [18, 22]. Therefore, in this study, the multiple imputation method was used to replace the missing values.

In the short-term evaluation, no difference in the \( \Delta \)AHI was found between the MAD and nCPAP therapy. Only in the worst-case scenario, with the failure and success patterns set at their extreme values in favour of nCPAP, the difference between the two treatment modalities was significant [12]. In the present long-term evaluation, with more measurement points, a significant difference in \( \Delta \)AHI of 4.1 events/hour was found between the two therapies. However, this small difference may not be clinically relevant, because there was no significant difference between the two groups in the improvement of excessive daytime sleepiness.

Similar to the present study, a 4-year follow-up study of CPAP therapy reported that AHI values were stable over time [24]. Surprisingly, there are no other studies to determine whether the efficacy of CPAP is still adequate more than 3 months after the start of treatment [25]. In line with our findings, MADS were still effective in the long term in other studies [26, 27]. Others also found that MADS were effective, but they both observed a tendency for the efficacy to reduce over time [28, 29]; a tendency which was not found in the present study. Since OSA is usually a lifelong condition [30], it is of importance that therapy is effective in the long term. Although all above-mentioned studies followed patients in the long term, studies including both MAD therapy and nCPAP therapy are lacking [3]. Differences between these treatment modalities can only be found by including both modalities in a single study. This is the first study in which this treatment aspect is compared between MAD and nCPAP in a single study.

Interestingly, the improvement in excessive daytime sleepiness, which was already seen in the short-term evaluation [12], further improved in this one-year follow-up. This was surprising, because the AHI value and the respiratory arousal index value did not reduce anymore. It indicates that excessive daytime sleepiness in OSA patients may need time to show further improvement in mild/moderate OSA patients, which was also found in another study [24]. As hypothesized by Meurice et al [24], a slow progressive reversibility of abnormal cerebral functions under long-term treatment may be possible. On the other hand, also a deterioration or no change in the initially achieved improvement in excessive daytime sleepiness has been reported in the long term [26, 27]. Future studies are needed to confirm and explain a possible delayed effect on excessive daytime sleepiness.

The side-effects reported by both groups were comparable with those in previous studies [31-34]. Side-effects can lead to discontinuation of treatment [34, 35], which was also found in the present study. From the start of the short-term RCT until the end of long-term RCT, six patients in the nCPAP group and two patients in the MAD group withdrew from treatment due to the occurrence of side-effects, suggesting that nCPAP patients show more problems in accepting their treatment modality than MAD patients. Further,
it should be noted that in the MAD group, three patients withdrew from treatment after the short-term evaluation, because the therapy was not effective.

In conclusion, the absence of significant long-term differences in EDS improvements between the MAD and the nCPAP groups with mild/moderate OSA may indicate that the larger improvements in AHI values in the nCPAP group are not clinically relevant. In the nCPAP group, more patients withdrew from treatment due to the occurrence of side-effects, suggesting that nCPAP patients show more problems in accepting their treatment modality than MAD patients.

Acknowledgements

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Declarations 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


Chapter 7

General Discussion
In 2002, when we started with our randomized placebo-controlled trial (RCT), especially case series were published on the therapeutic efficacy of mandibular advancement devices (MADs) in patients with obstructive sleep apnea (OSA) [1, 2]. Consequently, there was not enough sound scientific evidence for the efficacy of MADs. Therefore, we decided to investigate three important aspects of MAD therapy in an RCT: (1) the time-variant nature of the apnea-hypopnea index and its consequences for diagnosis and therapy evaluation in OSA patients; (2) the influence of mandibular protrusion on OSA signs and symptoms; and (3) the short-term and long-term effects of both MAD and continuous positive airway pressure (CPAP) in the treatment of OSA.

In this chapter, the methodological aspects of this thesis and the main research outcomes are discussed in a broader context, and suggestions for future studies are made.

Methodological considerations

One of the main clinical features of OSA patients is excessive daytime sleepiness. It is therefore one of the diagnostic criteria for an OSA diagnosis [3]. Because of its reliability and validity, as well as for its ease of administration, the Epworth Sleepiness Scale was used in our RCT to evaluate excessive daytime sleepiness [4]. When excessive daytime sleepiness is absent, at least two of the symptoms suggested by the American Academy of Sleep Medicine Task Force, e.g., complaints of unrefreshing sleep and daytime fatigue, should be present for an OSA diagnosis [3]. It was surprising to notice that measurement methods for these symptoms nor their severity criteria are reported in the literature. As long as this information is not present, we cannot be certain if we are studying groups that have the same diagnostic characteristics as OSA groups that are already described in the literature by others. Future research should therefore focus on the development of evidence-based methods for measuring symptoms of OSA and their severity criteria.

As a consequence of their disturbed sleep condition, OSA patients often complain about daytime symptoms as described above. These symptoms, however, are not specific for OSA and
can be caused by other disorders. Therefore, the diagnosis of OSA requires the combined assessment of relevant clinical features and the objective demonstration of at least five obstructive respiratory events per hour of sleep [3]. The “gold standard” for the objective demonstration of abnormal breathing during sleep in OSA patients is full polysomnography (PSG), which provides detailed information on sleep state and respiratory abnormalities [5]. Therefore, this technique was used in this thesis for diagnostic and therapy evaluation purposes. These full polysomnographic studies, however, are resource-intensive, because they generally require the facilities of a sleep laboratory and a trained technician. Although less comprehensive diagnostic systems have been developed, these systems have not yet been proven to be acceptable replacements for full polysomnography [6]. Nevertheless, the high prevalence figures for OSA make it necessary to consider simplified approaches for the diagnosis of OSA. Future research should therefore focus on the further development of such simplified techniques.

OSA is characterized by repetitive complete or partial collapses of the upper airway during sleep. For the quantification of these upper airway collapses in our RCT, we used the apnea-hypopnea index (AHI). Patients with the so-called “upper airway resistance syndrome” (UARS) show increased inspiratory efforts during sleep without breathing stops, but with frequent arousals. Since such events of respiratory effort-related arousals (RERAs) represent a form of upper airway obstruction, the International Classification of Sleep Disorders recommends that UARS should be considered as a part of OSA, and not as a separate entity [3, 7]. As a consequence, the respiratory disturbance index (RDI) was introduced to be used for the diagnosis of OSA. However, to enable comparison with previously performed RCTs, the AHI was chosen for the diagnosis of OSA in our RCT instead of the RDI.

The appropriate number of apneas and hypopneas for diagnosing clinically relevant OSA is uncertain. While a number of five or more apneas and hypopneas per hour is historically considered abnormal, the rationale for this cut-off value is unclear [8, 9]. It was therefore surprising to see that in the past decades, the AHI was preceded by the apnea index (AI; the number of apneas per hour of sleep), and that it was later replaced by the RDI for the diagnosis of OSA, but that the cut-off value of five events/hour for these indices has never been changed over time. You may question if a patient with, for example, twenty apneas per hour of sleep has the same negative consequences of his/her OSA condition (symptoms and co-morbidities) as a patient with twenty RERAs per hour of sleep. This can only be clarified by investigating the negative consequences of OSA in relation to the value of the used index (viz., AI, AHI, or RDI). In this way, a clinically meaningful diagnostic cut-off criterion for these indices can be established.

When an AHI cut-off point of five events per hour is used in the diagnosis of OSA, it is difficult to diagnose those patients with an AHI value near this cut-off point, because of the natural fluctuation of the AHI over time. If the recorded values of the AHI lie close to the cut-off point, the value may as well lie for one night above this point and for another night below this point. This suggests that conclusions about the presence or absence of OSA can only be drawn when the AHI recording lies far enough away from the cut-off point; that is, outside the limits of a cut-off band surrounding that point. In the study in chapter 2, we therefore suggested to use cut-off bands instead of cut-off points in the diagnosis of OSA. This means that in a research setting, it may be better to exclude those patients that have an AHI inside the cut-off band, because one cannot be certain about their diagnosis. This approach on the usefulness of cut-off bands in the diagnosis of OSA was recognized in the scientific field, as evidenced by an Editorial in “Respiration” [10]. Importantly, also studies on other disorders, for example on sleep bruxism [11], that use variables that are not stable over time, have the same problem in diagnosing these disorders. The use of cut-off bands is therefore recommended for these disorders as well.

Upper airway collapse during sleep is prevented by the MAD by both opening and protruding the mandible. In chapter 4, we used an MAD with a constant vertical dimension in different mandibular protrusions to investigate the pure influence of mandibular protrusion (i.e., a movement in the horizontal plane) on OSA signs and symptoms. The study described in chapter 4 demonstrated a dose-response relationship for a relatively wide range of protrusion positions.
Ferguson et al. indicated in a review of the literature that a larger mandibular protrusion will produce a larger decrease in OSA events [12], which was corroborated in our study. However, in that review, reference is made to studies that did not investigate a wide range of mandibular protrusion positions during sleep [13-16]. Consequently, there was not enough scientific evidence for a recommendation in which protrusion position an MAD treatment should be started. On the basis of the study in chapter 4, we can now recommended to start an MAD treatment in the 50% protrusion position.

**RCT**

In the RCT described in chapter 5, there were three patients in the MAD group that did not respond to the MAD therapy. The changes in airway configuration produced by MADs show inter-individual differences, which is likely a major factor in the inconsistent clinical response [17, 18]. A recent study showed that these airway configuration changes could not be predicted from the anatomical characteristics of the upper airway in OSA patients at baseline [18]. The mechanism of action of an MAD is generally considered to relate to the anterior movement of the mandible and the consequent increase in the cross-section area at the level of the velo-, oro- and/or hypopharynx [18-21], and to an improvement in the collapsibility of the upper airway [22]. However, the precise mechanism of action of an MAD appears to be rather complex and is not yet completely understood. This is not surprising, because the pathogenesis of upper airway closure in patients with OSA is not fully understood either [23, 24]. Therefore, one of the main objectives of future research should be the clarification of the relative contributions of the different morphological and pathophysiological factors to the development of recurrent sleep-related collapse of the upper airway in OSA patients [25]. Such research could lead to improvement in our selection of OSA patients for an MAD treatment. Moreover, this kind of research could also result in the development of new treatments of OSA that would target the specific pathways that lead to upper airway collapse.

Based on our RCT described in chapter 5, it was concluded that there is no clinically relevant difference between MAD and nasal CPAP (nCPAP) in the treatment of mild-to-moderate OSA, which corresponds with the findings of a recent study [26]. Although in most previous cross-over studies MADs were considered less effective in reducing the AHI value than CPAP in mild-to-moderate OSA patients [e.g., 27-30], similar improvements in subjective and objective measures of daytime sleepiness were found. Therefore, the question remains whether the differences found between MAD and CPAP in the reduction of AHI in these studies are really clinically relevant. Further, it should be noted that these studies also indicated that, in general, patients find MADs a more acceptable treatment compared to CPAP. This means that although a small difference in efficacy between MAD and CPAP may be present, the better acceptance by patients of MADs can result in better treatment adherence and can thus provide comparable or even better treatment results than CPAP. Moreover, the follow-up study in chapter 6 showed that the difference between both therapies in treatment effect remained to be clinically irrelevant over a one-year period. Therefore, based on the outcomes of this RCT, we can recommend the use of MADs as a primary treatment in patients with mild-to-moderate OSA.

**Conclusions**

The following conclusions can be drawn from this thesis:

- It should be taken into account that in the diagnosis and therapy evaluation of OSA, there is considerable intra-individual variability between AHI recordings (chapter 2).
- It is recommended to start an MAD treatment in the 50% protrusion position in the treatment of mild-to-moderate OSA (chapter 3 and chapter 4).
- There is no clinically relevant difference between MAD and nCPAP in the treatment of mild-to-moderate OSA, neither at the short-term (chapter 5) nor at the long-term (chapter 6).
Clinical recommendations

Based on the outcomes of this thesis, MADs may be considered a primary treatment for mild-to-moderate OSA patients. Importantly, the dentist should only treat OSA patients on referral of a physician. Following this referral, the primary tasks of the dentist are a comprehensive dental assessment of the patient, and the selection and fitting of the MAD. After a period of acclimatization to the device, a medical review and an objective overnight assessment are required to determine the effects of the treatment. Regular visits of the patient to their physician and dentist are required to monitor the treatment response, adverse effects, and compliance.

References

Obstructive sleep apnea (OSA) is characterized by recurrent collapse of the upper airway during sleep despite ongoing inspiratory efforts. As a consequence of their disturbed sleep condition, OSA patients often complain about daytime symptoms, such as excessive sleepiness and unrefreshing sleep. Continuous positive airway pressure (CPAP) is generally considered the “gold standard” treatment for OSA. Although CPAP is a highly efficacious treatment, there is a need for other treatment options, because the effectiveness of CPAP is often limited by poor patient acceptance and tolerance, as well as by a suboptimal compliance. Nowadays, mandibular advancement devices (MADs) are widely prescribed for the treatment of mild-to-moderate OSA. These oral appliances are often considered by patients to be a more acceptable treatment modality compared to CPAP. In 2002, when we started with our placebo-controlled randomized clinical trial (RCT), especially case series were published on the therapeutic efficacy of mandibular advancement devices (MADs) in OSA patients. Consequently, there was not enough scientific evidence for the efficacy of MADs. Therefore, we decided to investigate three important aspects of MAD therapy in an RCT: (1) the time-variant nature of the apnea-hypopnea index (AHI) and its consequences for diagnosis and therapy evaluation in OSA patients; (2) the influence of mandibular protrusion on OSA signs and symptoms; and (3) the short-term and long-term effects of both MAD and CPAP in the treatment of OSA.

When using the AHI in the diagnosis and therapy evaluation of OSA, it is of importance that the AHI is stable over time. Therefore, in chapter 2 of this thesis, the AHI variability was determined during a 10-week period, and a mathematical technique was described to assess its possible consequences for diagnostic and therapy evaluation purposes. From this study, it can be concluded that recordings can only confirm or deny the presence of OSA when obtained AHI values lie outside a cut-off band surrounding the AHI cut-off point.

As a first step for the RCT described in this thesis, an adjustable MAD was developed with a constant vertical dimension at different mandibular positions. In chapter 3 of this thesis, the initial efficacy of this MAD in the treatment of OSA was assessed in a pilot study. Further, it was aimed to evaluate the patients’ compliance to the MAD therapy and to determine the feasibility of the procedures of this pilot trial for
use in a future RCT. In chapter 4 of this thesis, the influence of four mandibular protrusion positions, at a constant vertical dimension, on OSA signs and symptoms was assessed. On the basis of this study, it was recommended to start an MAD treatment in the 50% protrusion position as a result of a weighted compromise between efficacy and side-effects.

After the start of our RCT, several other RCTs have addressed the efficacy of MADs in the treatment of OSA. Their common control condition, CPAP, was usually found to be superior to MAD therapy. However, in these studies, only CPAP was titrated objectively. To enable an unbiased comparison between both treatment modalities, the MAD should be titrated objectively as well. Therefore, the aim of the study in chapter 5 of this thesis was to compare the effects of an MAD with those of nasal CPAP (nCPAP), following polysomnographically controlled titration of both treatment modalities. Further, in the study in chapter 6, both modalities were followed over a one-year period. Based on both studies, it was concluded that there is no clinically relevant difference between MAD and nCPAP in the treatment of mild-to-moderate OSA.

Conclusions

The following conclusions can be drawn from this thesis:

• It should be taken into account that in the diagnosis and therapy evaluation of OSA, there is considerable intra-individual variability between AHl recordings (chapter 2).
• It is recommended to start an MAD treatment in the 50% protrusion position in the treatment of mild-to-moderate OSA (chapter 3 and chapter 4).
• There is no clinically relevant difference between MAD and nCPAP in the treatment of mild-to-moderate OSA, neither at the short-term (chapter 5) nor at the long-term (chapter 6).
Het obstructieve slaapapneu syndroom (OSAS) wordt gekenmerkt door het herhaald optreden van volledige of partiële obstructies van de hogere luchtweg. Snurken, overmatige slaperigheid en vermoeidheid overdag zijn veel voorkomende klachten. Deze klachten kunnen een grote invloed hebben op iemands leven, mogelijk zelfs met invaliderende gevolgen. Continue positieve luchtdruk behandeling ("continuous positive airway pressure"; CPAP) wordt internationaal beschouwd als de gouden standaard in de behandeling van OSAS. Hoewel CPAP als een zeer effectieve en veilige behandeling voor OSAS wordt beschouwd, is er toch behoefte aan andere behandelingsopties, omdat CPAP vaak niet wordt geaccepteerd door patiënten. Een afname in therapietrovew is hiervan het gevolg. Tegenwoordig worden voornamelijk mandibulaire repositié-apparaten (MRA’s) voorgeschreven voor de behandeling van milde en matige OSAS, omdat deze behandeling vaker wordt geaccepteerd door OSAS-patiënten dan een CPAP-behandeling. Ten tijde van de start van onze gerandomiseerde gecontroleerde studie (RCT) in 2002 was het MRA voornamelijk onderzocht in de vorm van casuïstiek. Dit resulteerde in onvoldoende wetenschappelijk bewijs voor de therapeutisch effectiviteit van het MRA. Wij besloten daarom drie belangrijke aspecten van de MRA-behandeling te onderzoeken in een RCT: (1) de variabiliteit van de apneu-hypopneu index (AHI) en de gevolgen hiervan voor diagnostiek en therapie-evaluatie (hoofdstuk 2); (2) de invloed van mandibulaire protrusie op tekenen en symptomen van OSAS (hoofdstuk 3 en 4); en (3) de korte en lange termijneffecten van zowel MRA als CPAP in de behandeling van OSAS (hoofdstuk 5 en 6).

De AHI wordt in de meeste studies gebruikt als primaire uitkomstmaat in de diagnostiek en de therapie-evaluatie van OSAS-patiënten. Het is daarom van belang dat deze variabele stabiel is over de tijd. In hoofdstuk 2 van dit proefschrift is de variabiliteit van de AHI gedurende tien weken bepaald, en een wiskundige techniek beschreven om de mogelijke gevolgen hiervan voor diagnostiek en therapie-evaluatie bij OSAS-patiënten te bepalen. Op basis van deze studie kan er geconcludeerd worden dat er een aanzienlijke intra-individuele variabiliteit bestaat tussen AHI-registraties. Dit betekent dat een enkele registratie de aanwezigheid van OSAS alleen kan
bevestigen of ontkennen als de uitkomst van die registratie buiten een cut-off-band valt die rondom een cut-off-punt ligt.

Ten behoeve van de RCT werd een MRA ontwikkeld met een schroefmechanisme dat het mogelijk maakte om de protrusiestand van de mandibula te veranderen bij een constante verticale dimensie. In hoofdstuk 3 van dit proefschrift is de initiële effectiviteit van dit MRA bepaald in een pilotstudie. Er is tevens gekeken in hoeverre de procedures van deze pilotstudie ook gebruikt konden worden in de toekomstige RCT. In hoofdstuk 4 van dit proefschrift is de invloed van vier verschillende mandibulaire protrusiestanden, bij een constante verticale dimensie, op tekenen en symptomen van OSAS onderzocht. Op basis van deze studie werd aanbevolen om het MRA bij de start van de behandeling in te stellen in de 50%-protrusiestand voor het optimale effect en minimale bijwerkingen.

Na de start van onze RCT hebben een aantal andere RCT’s aangetoond dat de effectiviteit van MRAs kleiner is dan die van CPAP. In deze voorgaande studies was echter alleen CPAP objectief getitred. Om een gelijkwaardige vergelijking te kunnen maken tussen beiden therapieën, is het van belang om ook het MRA objectief te titreren. Het doel van hoofdstuk 5 van dit proefschrift was daarom een vergelijking tussen MRA en nasale CPAP (nCPAP) in effectiviteit, na objectieve titratie van beiden therapieën met behulp van polysomnografie. Bovendien werden deze behandelresultaten van beide groepen over een periode van één jaar geëvalueerd in hoofdstuk 6. Op basis van beide studies werd er geconcludeerd dat er geen klinisch relevant verschil is tussen MAD en nCPAP in de behandeling van milde en matige OSAS.

Conclusies

• Er moet rekening worden houden met een aanzienlijke intra-individuele variabiliteit tussen AHI-registraties in de diagnostiek en de therapie-evaluatie van OSAS (hoofdstuk 2).
• Het is aan te bevelen om een MRA-behandeling in de 50%-protrusiestand te starten bij de behandeling van milde en matige OSAS (hoofdstuk 3 en 4).
• Er is zowel op de korte termijn als op de lange termijn geen klinisch relevant verschil tussen MRA en nCPAP in de behandeling van milde en matige OSAS (hoofdstuk 5 en 6).
Publications in this thesis


Other publications


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