Mandibular advancement device therapy in obstructive sleep apnea

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Chapter 3

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

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chapter 3

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

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-oral 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 polysomnografic registration (PSG2) of 10 OSA patients

	PSG1[a]	PSG2[a]	Test[b]	p
Respiratory parameters				
Apnea-hypopnea index (events/hour)	13.7±8.8	5.1±3.9	T= 2.91	0.017*
Desaturation index (events/hour)	22.7±8.3	10.2±8.9	T= 6.02	0.0002*
Snoring index (events/hour)	335.3±242.6	504.7±447.7	T= -0.58	0.581

[a]   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 polysomnografic registration (PSG2) of 10 OSA patients

	PSG1[a]	PSG2[a]	Test[b, c]	p
Sleep parameters				
Total sleep time (min)	377.6|388.8|461.5	405.0|447.0|526.9	W= -50.0|5.0	0.020
Stage 1 (%)	9.2±4.5	7.0±1.9	T= 1.39	0.197
Stage 2 (%)	61.1±7.1	57.8±5.8	T= 2.04	0.072
Stage 3 (%)	7.2±4.5	10.4±4.8	T= -2.52	0.033
Stage 4 (%)	0.0|0.0|3.4	0.0|2.6|4.3	W= -15.0|6.0	0.437
Stage REM (%)	20.8±4.0	22.2±5.5	T= -0.86	0.411
Stage nonREM (%)	79.2±4.2	77.9±5.5	T= 0.80	0.445
Total movement time (min)	3.3±1.9	3.6±1.7	T= -0.36	0.729
Sleep efficiency (%)	83.1±6.9	87.9±4.0	T= -2.41	0.040
Arousal index (events/hour)	29.4|43.6|52.8	14.7|19.6|39.0	W= -1.0|54.0	0.004*

[a]   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)
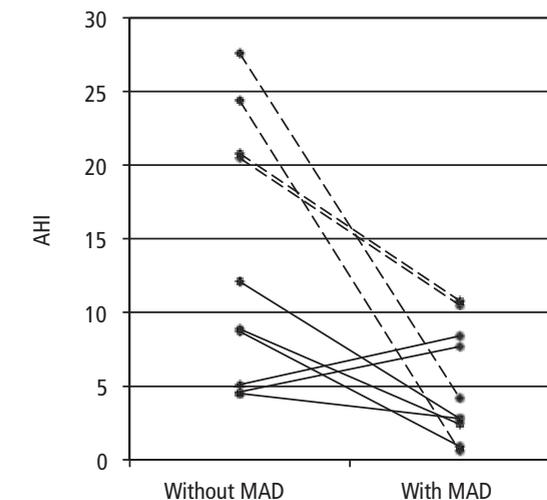
Fig. 2. Individual scores of the apnea-hypopnea index (AHI) before and after insertion of the MAD in a group of 10 OSA patients. The straight and dotted lines represent the mild and moderate OSA patients, respectively.

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.

chapter 3

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