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Chapter 6

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 H_2O/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 H_2O. 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 (ΔAHI) 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 in- 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 (± 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.

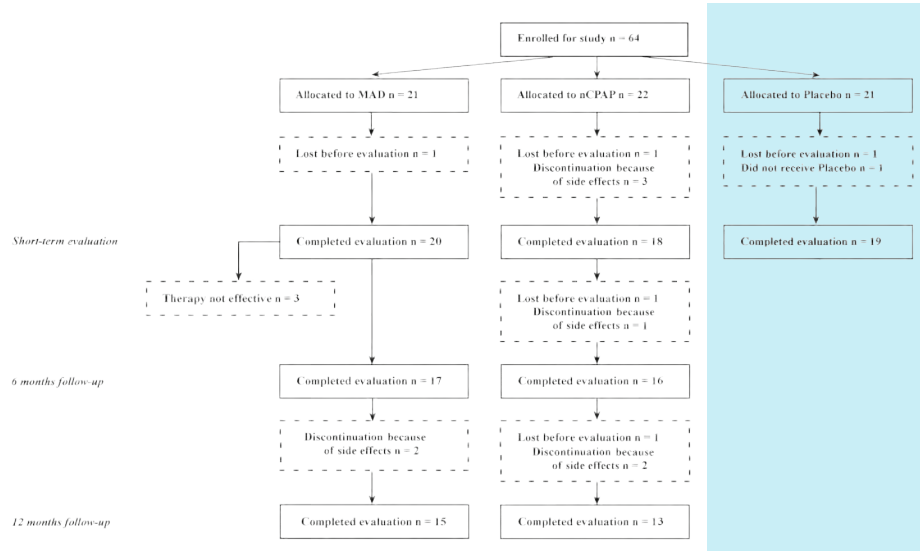

Fig. 1. Flow chart of the patients through each stage of the trial. MAD = mandibular advancement device; nCPAP = nasal continuous positive airway pressure. The placebo group (blue area) was excluded from the long-term part of the study for ethical reasons.

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/m^2)*	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.

Table 2. The mean (± SD) baseline and Δ 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.

	MAD				nCPAP			
	Baseline value	Δ value at short-term therapy evaluation	Δ value at 6 months after short-term therapy evaluation	Δ value at 12 months after short-term therapy evaluation	Baseline value	Δ value at short-term therapy evaluation	Δ value at 6 months after short-term therapy evaluation	Δ value at 12 months after short-term therapy evaluation
	(n = 21)	(n = 20)	(n = 17)	(n = 15)	(n = 22)	(n =18)	(n = 16)	(n = 13)
Respiration								
AHI (events/hour)	21.4 ± 11.0	16.3 ± 10.3	15.6 ±10.1	15.0 ± 10.5	20.1 ± 9.0	19.5 ± 8.7	19.6 ± 10.7	20.2 ± 8.6
Subjective								
Excessive daytime sleepiness	12 ± 5.7	1.6 ± 4.2	4.8 ± 5.1	4.7 ± 4.5	11.0 ± 4.3	1.2 ± 4.9	3.6 ± 5.0	5.2 ± 4.6
Sleep								
Stage NREM (%)	81.5 ± 6.4	2.1 ± 6.4	0.6 ± 7.8	4.1 ± 4.3	80.4 ± 6.3	0.7 ± 7.1	0.6 ± 8.6	0.3 ± 8.5
Stage REM (%)	18.6 ± 6.4	-1.9 ± 6.4	-0.5 ± 7.7	-4.0 ± 4.1	19.6 ± 6.3	-0.7 ± 7.1	-0.5 ± 8.5	-0.3 ± 8.5
Respiratory arousals (events/hour)	17.5 ± 10.4	14.6 ± 10.2	13.7 ± 9.8	13.1 ± 10.5	17.9 ± 13.0	15.7 ± 8.3	15.4 ± 9.6	16.9 ± 8.4

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 (see Fig. 1).

At the end of the present study, patients were advised to continue with their treatment, and were monitored with polysomnography on yearly basis.

Primary outcome variable

Analyses of the imputed data sets showed that the MAD group had a significantly smaller ΔAHI value than the nCPAP group (P = 0.000; Table 3). The mean difference between both groups in ΔAHI was 4.1 events/hour (Table 3). The change in AHI was stable over time as indicated by the non-significant time effect (P = 0.650; Table 3). For the ΔAHI, there was no significant interaction of the groups with time.

In Figure 2, the AHIs over time for each patient who completed the trial are shown. nCPAP treatment was offered to the patient who had AHI of 20 events/ hour at the 6 months evaluation, because the

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.

	Treatment effect* (MAD versus nCPAP)		**Time effect***	
	Mean difference between groups (95% conf. interval)	*P*†	Mean difference over time within groups (95% conf. interval)	*P*†
Primary outcome variables				
Δ AHI (events/hour)	**-4.1 (-5.7, -2.5)**	**0.000‡**	**0.2 (-0.7, 1.1)**	**0.650**
Secondary outcome variables				
Δ Excessive daytime sleepiness (EDS)	-0.9 (-2.8, 1.0)	0.367	1.9 (1.3, 2.5)	0.000‡
Δ Respiratory arousals (events/hour)	-3.2 (-4.5, -1.8)	0.000‡	0.1 (-0.6, 0.7)	0.816
Δ Stage NREM (%)	0.2 (-1.8, 2.2)	0.854	0.2 (-0.7, 1.1)	0.692
Δ Stage REM (%)	-0.1 (-2.2, 1.9)	0.897	-0.2 (-1.1, 0.7)	0.703

Δ value = difference between baseline and therapy evaluation value.
* 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.

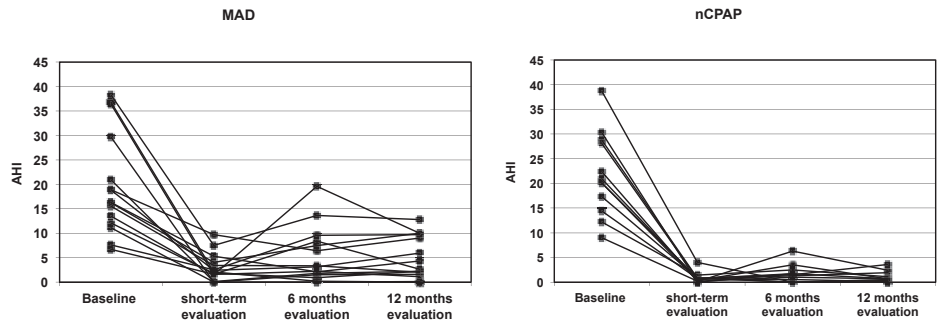

Fig. 2. Individual values of the apnea-hypopnea index (AHI) of the 28 patients who completed the entire study protocol (MAD, n = 15; nCPAP, n = 13) obtained from the baseline polysomnographic (PSG) recordings and from the subsequent therapy evaluation PSG recordings.

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 (ΔEDS). The ΔEDS 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). In the

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 ΔAHI 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 ΔAHI of 4.1 events/ hour was found between the two therapies. However, this small difference may not to 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 suprising, 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 detoriation 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.

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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.

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