

Investigation of positional and non-positional OSA: impact on outcomes in patients treated with mandibular advancement devices

Short title:

Oral Appliances in positional and non-positional OSA

JIN WOO CHUNG ^{1, 2}, REYES ENCISO ³, DANIEL J. LEVENDOWSKI ⁴, TODD D. MORGAN⁵, PHILIP R. WESTBROOK ⁴, and GLENN T. CLARK ¹

¹ Orofacial Pain/Oral Medicine Center, Division of Diagnostic Sciences, School of Dentistry, University of Southern California

² Department of Oral Medicine and Oral Diagnosis, School of Dentistry and Dental Research Institute, Seoul National University

³ Division of Craniofacial Sciences and Therapeutics, School of Dentistry, University of Southern California

⁴ Advanced Brain Monitoring, Inc., Carlsbad, CA

⁵ Scripps Memorial Hospital, Encinitas, CA

Corresponding author:

Dr Glenn T. Clark

Orofacial Pain/Oral Medicine Center, Division of Diagnostic Sciences

School of Dentistry, University of Southern California

925 West 34th Street, Room 127, Los Angeles, CA 90089-0641

Tel: 213-740-3410, Fax: 213-740-3573

E-mail: gtc@usc.edu

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Mr. Levendowski and Dr. Westbrook are employees of and shareholders in Advanced Brain Monitoring, Inc. The other authors have no conflicts of interest to disclose.

Abstract

Identifying patients as being either positional or non-positional OSA cases may have implications in selecting therapy. We investigated the treatment outcome of mandibular advancement devices (MADs) for positional and non-positional OSA using multi-night in-home recordings of sleep. Subjects were 44 positional (supine apnea-hypopnea index [AHI] at least 2x's > their lateral AHI) and 35 non-positional (supine AHI less than 2x's > their lateral AHI) OSA patients. Two-nights of recordings were collected using the Apnea Risk Evaluation System Unicorder both before and after insertion and adjustment of the MADs. Age, gender, body mass index (BMI), and percentage time in supine of the subjects were obtained. Compared data included percent changes of overall AHI, supine AHI, non-supine AHI, and percentage time with snoring >40dB and with SpO₂ <90%. Results showed that the percent decrease in overall AHI (p=0.004) and for supine AHI (P=0.002) after MADs therapy were significantly higher for the positional OSA than non-positional OSA group. A multiple linear regression analysis showed that the percent change of overall AHI was significantly associated with being in the positional group ($\beta=0.448$, p<0.001). Age, BMI, gender, and time in supine position during sleep did not show any significant associations with the percent change of overall AHI after MAD therapy. Percent change in supine AHI was significantly higher than percent change in non-supine AHI in the positional group, (p=0.006), conversely, there was no significant differences in the non-positional group. Our data suggest that MADs are more effective in positional OSA than non-positional OSA patients.

Key words: Sleep disordered breathing; Mandibular advancement device; Home monitoring; Snoring; Sleep position

Introduction

Mandibular advancement devices (MADs) have become a common treatment for obstructive sleep apnea (OSA) and are used as a treatment alternative to continuous positive airway pressure (CPAP) (Clark *et al.*, 1996, 2000). These devices are designed to protrude the mandible and increase the caliber of the airway during sleep. Many clinical studies have reported that MADs are less effective than CPAP in reducing the RDI but that these oral devices have been preferred by more patients and are more readily accepted than CPAP (Clark *et al.*, 1996). The primary use of MADs has been considered for the patient who has snoring or mild to moderate, but not severe OSA (Eveloff *et al.*, 1994; Ferguson *et al.*, 1997; Pancer *et al.*, 1999). Previous reports also suggest that the MAD effect is influenced by sleep position and may be more effective in supine dependent OSA (Marklund *et al.*, 1998, 2004; Yoshida, 2001), and increased BMI and neck circumference may contribute to less optimal MAD treatment efficacy (Levendowski *et al.*, 2007). Thus, it may be possible to obtain efficacious outcomes in positional OSA patients even though they have moderate to severe OSA.

Positional OSA patients have been defined as those who have a supine respiratory disturbance index (RDI) or apnea-hypopnea index (AHI) that is at least two times higher than their lateral RDI or AHI (Cartwright, 1984). Positional OSA patients have been reported to be younger, and less obese, therefore they have less severe respiratory disturbance than non-positional patients (Cartwright, 1984; Oksenberg *et al.*, 1997). We hypothesized that there may be factors other than age and BMI that influence the differences in disordered breathing between positional and non-positional OSA patients and if so, the treatment outcome of MADs should be different between these two groups of OSA patients. The aim of the study was to investigate the treatment outcome of MADs for positional and non-positional OSA using multi-night in-home recordings.

Materials and Methods

Subjects

Seventy-nine OSA patients (55 men and 24 women) were recruited from three dental practices. After obtaining an informed consent (approved by the BioMed IRB, San Diego, CA, USA) patients completed a two-night pretreatment in-home sleep study (described below). Upon insertion of the MRD, patients self-adjusted their appliance to an end point based on typical subjective measures (e.g., reduced snoring, daytime somnolence or nocturia, and/or increased dreaming, etc.). Upon conclusion of this self adjustment period

(after the patient had reached their optimal end point) a follow-up sleep study was performed.

Patient information including age, gender, height, weight, and their neck size were obtained and Epworth Sleepiness Scale (ESS) for daytime sleepiness was acquired at the time of both sleep studies.

Mandibular advancement devices (MADs)

All appliances used advanced the mandible and were custom made. The three used in this study were the the TAP II and III (Airway Management, Dallas, TX, USA) and Herbst appliance (Great Lakes Orthodontics, Ltd., Tonawanda, NY). For the positional patients, 12 were fitted with the TAP II, 18 with TAP III, and 14 with the Herbst appliance. For the non-positional patients, 12 were fitted with the TAP II, 12 with TAP III and 11 with the Herbst appliance.

A starting MAD position for the TAP II was established as the point whereby the patient could just hook the lower tray with the upper tray using active protrusion with both trays in place. The TAP III and the Herbst appliances were articulated by the respective laboratories to (presumably) 60% protrusion using George Gauge measures taken at the time the impressions were made. In the rare occasion that this level of advancement was not tolerated by the patient, the starting protrusion was reduced. Patients were instructed to begin adjusting the MAD in one-half turn increments as soon as it was tolerable, until a cessation in snoring or the symptoms had resolved.

Sleep study data

Two-night in-home recordings were performed for each pre- and post-treatment study with Apnea Risk Evaluation System (ARES) Unicorder (Advanced Brain Monitoring, Carlsbad, CA, USA). The ARES Unicorder measures oxygen saturation, pulse rate, airflow, respiratory effort, snoring levels, head movement, and head position from a wireless recorder self applied with a single strap to the forehead. Reflectance oximetry is used to obtain the SpO₂ and pulse rate signals. Respiratory effort is derived from the measurement of changes in forehead venous pressure acquired using a combination of photoplethysmography and changes in surface pressure of the reflectance oximetry sensor, and head movement. Airflow is obtained via a nasal cannula and a pressure transducer. A calibrated acoustic microphone is used to acquire quantified snoring levels (dB). Accelerometers are used to measure head movement and derive head position. The recorder

was designed to be easily affixed by the patient, and provide alerts during the study if poor quality airflow or SpO₂ is detected so the device could be adjusted.

The description and validation of this device has been reported in two studies. The first had 284 valid comparisons of the in-laboratory simultaneous PSG and ARES and 187 valid comparisons of the in-laboratory PSG with a separate two nights unattended self-applied ARES Unicorder (Westbrook *et al.*, 2005). The second study with 102 participants had 92 simultaneous in-laboratory comparisons and 86 in-home to in lab comparisons. Both studies showed that the ARES had high sensitivity and specificity (Ayappa *et al.*, 2008).

Automated scoring algorithms were applied off-line to detect sleep disordered breathing. The AHI was computed using a time-in-bed measure based on recording time with acceptable signal quality minus periods when the patient was upright or presumed to be awake based on actigraphy. Automated algorithms were used to detect apnea (based on a 10-s cessation of airflow) and hypopnea events (based on a 50% reduction and recovery in airflow, a minimum 3.5% reduction in SpO₂ and at least a 1.0% recovery) for calculation of the apnea-hypopnea index (AHI). After the automated scoring was applied, the full disclosure recordings were visually inspected by a sleep medicine physician to confirm the accuracy of the automated scoring, and to reclassify as central and/or exclude auto-detected events if necessary. The physiological data, including AHI values, percent time with SpO₂ below 90%, and percentage time snoring greater than 40 dB were then calculated.

Data Stratification

The patients were divided into two groups as having positional or non-positional OSA following the criteria suggested by Cartwright (1984). Specifically, these criteria state that positional OSA patients have a supine AHI at least two times higher than their lateral AHI, and non-positional patients have their supine AHI less than two times higher than their lateral AHI. Forty-four positional OSA patients and 35 non-positional OSA patients were evaluated. Demographic data of the subjects are shown in Table 1.

Statistical analysis

The comparison of all measures of apnea severity and the effect of MAD between positional and non-positional OSA groups was performed by t-test for normal variables and Mann Whitney test for non-parametric. Normality of the variables was evaluated with the formal Kolmogorov-Smirnov test. The effect of MAD on AHIs was calculated from the percent changes of AHIs after MAD therapy compared to the pre-treatment AHI. The

comparison of percent changes of overall AHI, supine AHI, and non-supine AHI was also performed by paired t-test in each group. A second measure of treatment efficacy assessed the percentage of positional and non-positional patients with pre-treatment AHIs ≥ 10 and 20 events/hr at baseline who had a post-treatment AHI ≤ 5 .

To evaluate the relative influence of each independent variable (age, BMI, gender, positional OSA, and percent time of supine position) on overall AHI values, multiple linear regression analyses were performed. The linear regression assumptions of linearity, homoscedasticity and normality of the residuals were successfully evaluated.

Results

Pre-treatment sleep study data

Pre-treatment sleep study data of the subjects are shown in Table 2. There were no statistically significant differences on percentage of time in supine position, overall AHI, percentage time with snoring above 40 dB, percentage time with below 90% SpO₂, and ESS between the two groups. Supine AHI was higher in positional OSA patients and non-supine AHI was higher in non-positional OSA patients.

Post-treatment sleep study data

Post-treatment sleep study data of the subjects are shown in Table 2. Only non-supine AHI values were significantly higher in non-positional OSA patients. Supine AHI values were not significantly different between the two groups after MAD treatment.

Comparison of the effects of MADs between positional and non-positional OSA patients

Mean and standard deviation of percent change of overall AHI after MADs therapy in total subjects was 61.99 ± 30.19 %. Table 3 shows the descriptive data of the effects of MADs in each positional and non-positional OSA group. Percent change of overall AHI ($p=0.004$) and percent change of supine AHI ($p=0.002$) after MADs therapy were significantly higher in positional OSA patients than non-positional OSA patients. However, percent change of non-supine AHI, change of percentage time of snoring >40 dB, and change of percentage time with SpO₂ $<90\%$ after MADs therapy did not show any statistically significant difference between two groups.

Percentages of the patients in whom the effect of MAD on overall AHI were above 50% were 88.6% in the positional OSA group and 57.1% in the non-positional OSA group.

Figure 1 shows pre-post treatment changes of three AHIs in each patient of two groups. For positional patients with pre-treatment clinical cut-offs of $AHI \geq 10$ and 20, 61% (23 of 38) and 45% (9 of 20) respectively, were successfully treated such that residual AHIs were less than 5 (Figure 1a). For non-positional patients the corresponding results were 30% (6 of 20) and 23% (3 of 23).

Impacts of risk factors on the effect of MADs on overall AHI

In Table 4 we present the results of the multiple linear regression analysis. After adjusting for the covariates in the model (age, BMI, gender, % of time in supine), the percent change of overall AHI was significantly associated only with membership in the positional OSA group ($\beta=0.448$, Coefficient=27.646, 95% CI=12.630, 42.662). Age, BMI, gender, and percent of time in supine did not show any significant associations with the percent change of overall AHI after MADs therapy.

Discussion

Most of the previous studies assessing outcomes with oral appliance therapy focused on changes in the overall severity of obstructive sleep apnea and have not examined defined subgroups of OSA patients (e.g positional versus non-positional OSA patients). To date, MAD therapy has only been recommended as first line therapy in mild and moderated OSA patients. In our clinical experience, it is not uncommon for some patients with more severe OSA to have efficacious outcomes, but to date we are unable to predict when this might occur. This is one of the first studies to investigate the contribution of positional vs. non-positional OSA in predicting successful MAD outcomes, independent of OSA severity level.

In this study we found that patients with positional OSA had substantially better treatment outcomes than patients with non-positional OSA, regardless of OSA severity. Because the mean age and BMI and percentage of females were significantly different between the two groups, we elected to perform the same statistical analyses with a subset of our 25 subjects in each group who were gender, age and BMI matched (data not shown in tables). The results for the matched group analysis confirmed our original results and even slightly improved it. Whether matched or unmatched, our data suggest that positional patients are better treated with MRD than non positional OSA patients. Moreover this effect cannot be explained by differences in OSA severity, as there were no significant differences in the overall AHI in the two groups (matched or unmatched). These findings begin to make sense

if we hypothesize the non-positional OSA group had a substantially more collapsible airway than our positional OSA group.

Interestingly, in our positional OSA patients, MAD efficacy increased as the percentage of time in supine increased, and the percent reduction in supine AHI was significantly greater than the percent change in non-supine AHI (data not shown). The lack of change in the lateral AHI may be due to a floor effect since the pretreatment lateral AHI in our positional group was low to begin with so less subject to change. A previous cephalometric study reported that positional OSA patients were found to have a larger posterior airway space, less elongated soft palate and somewhat more prominent retrognathia (Fleetham, 1992; Hudgel, 1992). Regardless of these putative anatomic changes, the ultimate determinant of the effectiveness of MADs therapy is the degree of upper airway collapsibility during sleep. Since MAD's are designed to protrude the mandible and thus the tongue and epiglottis during sleep, preventing airway occlusion, we were surprised to find the effects of gravity on the pharyngeal airway were not equally resolved by MAD therapy in our positional and non-positional OSA patients. Previously, Levendowski *et al.* (2007) found that BMI and neck circumference were predictors of patients who had less efficacious outcomes with MADs. Oksenberg *et al.* (1997) found that the positional OSA patients were younger and less obese than non-positional OSA patients. They speculated that age and BMI might explain the difference between the two groups and they also suggested that the two conditions (positional and non-positional OSA) are part of the same disorder with the only difference being a progression in severity. However, in our subjects, positional OSA group had a lower BMI than the non-positional OSA group, there was no significant difference in neck circumference between the two groups, and our positional OSA subjects were older than those with non-positional OSA. There was also no significant difference in overall AHI severity in positional and non-positional OSA groups in our study.

One limitation of this study is the patients were treated at a limited number of dental sleep medicine practices and may not generalize across all OSA patients or dental practices. A larger, multi-site study may be required to confirm these results.

In summary, we have shown that MADs are more effective in positional OSA patients than non-positional OSA patients. We speculate that the non-positional group may have more inherent pharyngeal airway collapsibility which distinctly worsens with weight gain but this is not so in the positional group. Possibly, other factors beyond BMI are contributory to OSA in these subjects. Additional studies, such as evaluation of dynamic pharyngeal airway collapsibility, will be required to identify factors contributing to the

differences in positional and non-positional OSA patients.

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Table 1 Demographic data of the subjects

Variables	Positional OSA (n=44)	Non-positional OSA (n=35)	P-value
Age (years)	55.20 ± 10.36	50.03 ± 9.08	0.023 ^a
Gender (% of male)	84.1	51.4	0.003 ^b
BMI	27.82 ± 3.47	30.92 ± 5.92	0.008 ^a
Neck circumference (inch)	16.39 ± 1.14	16.35 ± 1.53	0.890 ^a

^a P-values were obtained from independent T-test

^b P-values were obtained from Chi-square test

Table 2 Comparison of positional and non-positional OSA patients in pre- and post-treatment

Variables	Pre-treatment			Post-treatment		
	Positional	Non-positional	P-value	Positional	Non-positional	P-value
% of time supine	48.36 ± 27.01	45.71 ± 26.21	0.683 ^a	46.98 ± 25.16	49.73 ± 28.22	0.661 ^a
Overall AHI	20.55 ± 11.81	19.91 ± 16.60	0.128 ^b	5.55 ± 4.86	7.71 ± 6.53	0.086 ^b
Supine AHI	38.66 ± 18.66	27.25 ± 26.00	0.034 ^a	10.23 ± 11.23	11.45 ± 11.36	0.546 ^b
Non-supine AHI	5.60 ± 4.53	17.14 ± 15.97	<0.001 ^{b, c}	2.63 ± 3.63	5.80 ± 6.26	0.004 ^{b, c}
% time snoring >40dB	21.75 ± 16.89	25.85 ± 19.50	0.320 ^a	8.93 ± 12.00	14.95 ± 17.20	0.359 ^b
% time SpO ₂ <90%	2.96 ± 3.56	6.22 ± 8.45	0.333 ^b	2.27 ± 6.65	3.06 ± 4.96	0.175 ^b
ESS	11.00 ± 4.26	10.66 ± 4.78	0.737 ^a	5.52 ± 4.75	5.35 ± 4.33	0.872 ^a

^a P-values were obtained from independent T-test

^b P-values were obtained from Mann-Whitney test

^c Significant differences after Bonferroni correction

Table 3 Comparison of the effects of MADs between positional and non-positional OSA patients

Effect of MADs	Positional OSA	Non-positional OSA	P-value
% change of overall AHI	71.22 ± 20.86	50.38 ± 35.94	0.004 ^{a, c}
% change of supine AHI	75.51 ± 18.34	51.33 ± 39.05	0.002 ^{b, c}
% change of non-supine AHI	35.18 ± 88.59	55.01 ± 39.88	0.896 ^b
Change of % time with snoring >40dB	12.82 ± 14.01	10.90 ± 17.62	0.591 ^a
Change of % of time with SpO ₂ <90%	0.69 ± 6.37	3.15 ± 8.39	0.748 ^b

^a P-values were obtained from independent T-test

^b P-values were obtained from Mann-Whitney test

^c Significant differences after Bonferroni correction

Table 4 Multiple linear regression analysis of the risk factors on the effect of MRD on AHI (percent change of overall AHI)

Explanatory variables	β	Coefficient	95% CI ^b	P-value
Age	-0.225	-0.675	-1.386, 0.036	0.062
BMI	-0.170	-1.093	-2.546, 0.360	0.138
Gender (Male)	0.162	10.965	-4.846, 26.775	0.171
Positional OSA	0.448	27.646	12.630, 42.662	<0.001
% of time in supine ^a	0.032	0.039	-0.233, 0.312	0.775

^a Average value in pre- and post-treatment sleep study

^b Confidence interval

Multivariate ANOVA F-test p=0.003, R square=0.225

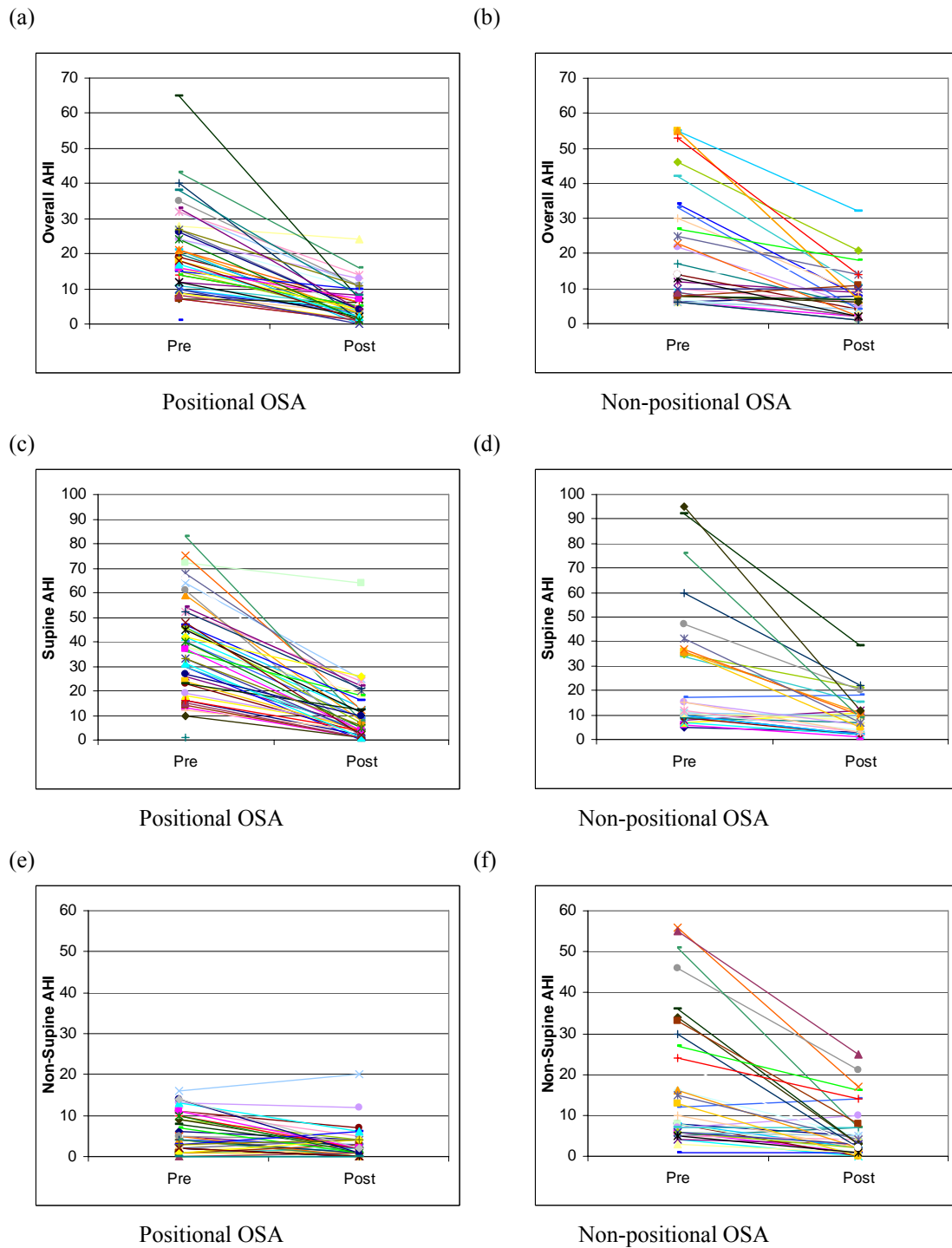


Figure 1 These six graphs show the pre-post MRD changes for positional subjects (left side figures) and non-positional subjects (right side figures). The two top figures (a and b) show the overall AHI data, the middle two figures (c and d) show the supine AHI data and the bottom two figures (e and f) show the Non-Supine AHI data.