ORIGINAL ARTICLE

Efficacy of Oral Appliance Therapy in the Treatment of Severe OSA in CPAP-Resistant Cases

Deepak Shrivastava[1] · John K. Bixby[2] · Douglas S. Livornese[2] · Felix Urena[2] · Michael J. Bixby[2] · Vikrum Jain[1]

Abstract

Purposes Continuous positive airway pressure (CPAP) is the current standard of care for the treatment of obstructive sleep apnea (OSA). It is known that there is a low rate of adherence in many patients. Oral appliance therapy (OAT) is effective in patients with mild-to-moderate OSA. The efficacy of OAT in severe patients is unknown. The aim of this study is to evaluate treatment using an in-laboratory titration method to determine whether OAT might be appropriate for patients with severe OSA.

Methods This is an IRB approved, retrospective study of 41 adults (mean age 51 years; 73% male) with severe OSA who were intolerant of CPAP therapy. All patients were treated with OAT (OASYS Oral–Nasal Airway System™). The sample was sub-divided into severe [Apnea–Hypopnea Index (AHI > 30 < 50)] and very severe (AHI > 50) groups. Informed consent was obtained from all patients included in the study. The device was custom fit by a dentist. After patients reported subjective symptom improvement, titration polysomnography was performed. If obstructive events were still noted after 90 min of the sleep study, an attending sleep technologist titrated the device in vivo in 1 mm increments for a maximum of 3 mm to optimize effectiveness.

Results For severe cases, almost half (46%) were resolved with a post-treatment AHI < 5, while two-thirds (66%) had an AHI < 10. For very severe cases, 43% were resolved with a post-treatment AHI < 5, while 64% had an AHI < 10. All findings were statistically significant ($p < 0.001$).

Conclusions This preliminary study supports the notion that oral appliance therapy using the OASYS Oral–Nasal Airway System™ may be effective in severe cases of OSA.

Keywords Obstructive sleep apnea treatment · Mandibular advancement · Removable orthodontic appliances · Polysomnography

Abbreviations

AHI	Apnea–Hypopnea Index
AASM	American academy of sleep medicine
BMI	Body mass index
CPAP	Continuous positive airway pressure
ENT	Ear nose throat
ECG	Electrocardiogram
EEG	Electroencephalogram
EMG	Electromyography
EOG	Electrooculogram
FDA	Food and drug administration
OSA	Obstructive sleep apnea
OAT	Oral appliance therapy
PSG	Polysomnography
REM	Rapid eye movement
RDI	Respiratory distress index

✉ Deepak Shrivastava
dshrivastava@sjgh.org

1 SJGH Sleep Center, ACGME Accredited Sleep Medicine Fellowship Program UC Davis School of Medicine, San Joaquin General Hospital, 500 W. Hospital Road, French Camp, CA 95231, USA

2 Sleep Dynamics – Center for Diagnosis of Sleep Disorders – An AASM Accredited Center, Neptune City, NJ 07753, USA

1 Introduction

Epidemiological studies have suggested a high prevalence of obstructive sleep apnea (OSA) in the general population [1–3]. Despite the availability of effective screening instruments and diagnostic testing, OSA remains underdiagnosed [4–8]. The severity of OSA is defined by the pre-treatment apnea–hypopnea index (AHI), which is the total number of apnea and hypopnea events that occur per hour of sleep. A higher AHI corresponds to more severe disease. At all levels of severity, OSA is associated with significant cardiovascular, neurocognitive, and metabolic morbidity [4–9]. In addition, OSA is independently associated with an increased likelihood of motor vehicle accidents, increased on-the-job accidents and other occupational hazards, and a diminished quality of life. Therefore, effective management of OSA is imperative to mitigate its sequelae and prevent long-term complications.

The currently recommended, first-line treatment of OSA is the use of continuous positive airway pressure (CPAP), which is highly efficacious. CPAP provides pneumatic splinting of the upper airway and prevents its collapse during inspiration [10]. In contrast, surgical management of OSA includes upper airway reconstruction and bypass procedures. The choice of surgical procedure depends on the severity of the condition and patient preference. On the other hand, oral appliances are the most accepted and clinically proven alternatives to CPAP. These appliances cover the upper and lower dental arches and are designed to keep the lower jaw in a protruded position during sleep [11]. Oral appliance therapy (OAT) that utilizes mandibular advancement, increases the pharyngeal airway space, and reduces upper airway collapsibility. In fact, results with OAT can be comparable to CPAP in some patients [12]. A recent 2-year follow-up study involving OAT suggested that mild-to-moderate cases could be effectively treated with an adjustable oral appliance, while severe OSA should be initially treated with CPAP [10]. However, it is known that there is a low rate of compliance in some patients being treated with CPAP [13–16]. Singh and Abramson [17] investigated the use of the OASYS Oral–Nasal Airway System™ for mild-to-moderate cases of OSA. Therefore, the aim of this study is to test the hypothesis that OAT using a novel in-laboratory titration method might be appropriate for patients with severe OSA that have been unable to tolerate CPAP therapy.

2 Materials and Methods

This retrospective, observational study was reviewed and approved by IRBco, an accredited organization which provides IRB oversight for studies. We included patients with severe levels of OSA who declined or were unsuccessful with CPAP therapy. The sample received treatment with an OASYS Oral–Nasal Airway System™ adjustable oral appliance (OAT). The OASYS Oral–Nasal Airway System™ is approved by the US Food and Drug Administration (FDA) as a mandibular advancement device (MAD). It is a custom-fabricated oral device (Fig. 1) used for the treatment of snoring, mild-to-moderate OSA, and upper airway resistance syndrome. In addition, the OASYS Oral–Nasal Airway System™ has been reviewed by the ENT division of the FDA, and has been approved as a nasal dilator for upper airway resistance. In view of these approvals, its use could be extended to treating severe cases of OSA. The device works by ameliorating obstruction in the posterior pharyngeal space as an MAD, but it also lowers nasal upper airway resistance by opening the nasal valves and stretching the nasolabial folds from within the mouth [18]. The device also incorporates an extension that projects to the root of the tongue (Fig. 1) to prevent the tongue from falling back by guiding it towards the palate.

This preliminary study comprised 41 subjects (30 men; 11 women) with severe OSA who were unable to tolerate CPAP therapy. The total sample was sub-divided into severe cases (AHI > 30 < 50) and very severe cases (AHI > 50). After obtaining informed consent from the patients in this study, a qualified dentist custom fit each device. All patients received the same custom-fitted device


Fig. 1 OASYS Oral–Nasal Airway System™. Note that the device incorporates an extension (arrowed) that projects to the root of the tongue to prevent it from falling back and guiding it towards the palate

(OAT) to eliminate potential effects of variable appliance designs. Study participants were required to demonstrate that they tolerated and complied with the use of the device. After this assessment, when participants reported subjective improvement in symptoms, a PSG titration was performed in a sleep laboratory to fine-tune the appliance [19, 20] and establish the most accurate setting.

Data Collection from Titration PSG: a standard overnight PSG was performed using Phillips Respironics Alice 5 computerized monitoring software, with a sleep technologist in attendance. Measured parameters included: frontal EEG (F4–M1, F3–M2); central EEG (C4–M1, C3–M2); occipital EEG (01–M2, 02–M1); left and right EOG; ECG; chin EMG; left and right anterior tibialis EMG; combined oral–nasal thermistor airflow, and nasal pressure. The equipment included abdominal and thoracic movement piezo-respiratory effort belts: a pulse oximeter and a transducer microphone to quantify snoring intensity. Body position was also monitored, as well as standard audio–video recording. The recorded signal tracings, including apneas and hypopneas, were scored using the American Academy of Sleep Medicine (AASM) scoring manual [21].

The sleep technologist used the protocol of CPAP titration as per AASM guidelines [21]. For example, titration was done by gradually adjusting the device to resolve any residual snoring, apneas, hypopneas, oxygen desaturations, and arousals. If obstructive events were still noted after 90 min of the PSG study, the attending sleep technologist titrated the device in vivo in 1 mm increments in a protrusive direction for maximum of 3 times or 3 mm, for optimal effect and to minimize sleep disturbance, using titration strips (Fig. 2). This procedure ensured that the appliance was effective in various body positions and during the different sleep stages. An attending dental sleep specialist also reviewed the data to determine the most appropriate position for the device. An attending board-certified sleep physician then interpreted the final PSG results, and determined the efficacy of the oral appliance according to AASM guidelines [21].

After completion of the titration PSG, the oral appliance was returned to its original position by removing the titration strips. The final summary report included the supervising and interpreting physician's assessments and any significant observations, such as REM-dominant OSA, snoring, or any other events that occurred during sleep. In addition, the summary included tabulated data from each titration, post-titration AHI, REM sleep duration, and oxygen saturation. After receiving the summary report, the referring dentist determined the final mandibular position of the device, and adjusted it to the position determined by the results of the PSG study. The dentist continued to follow up with periodic examinations for about 4 months as recommended by the Clinical Practice Guideline for the Treatment of OSA and
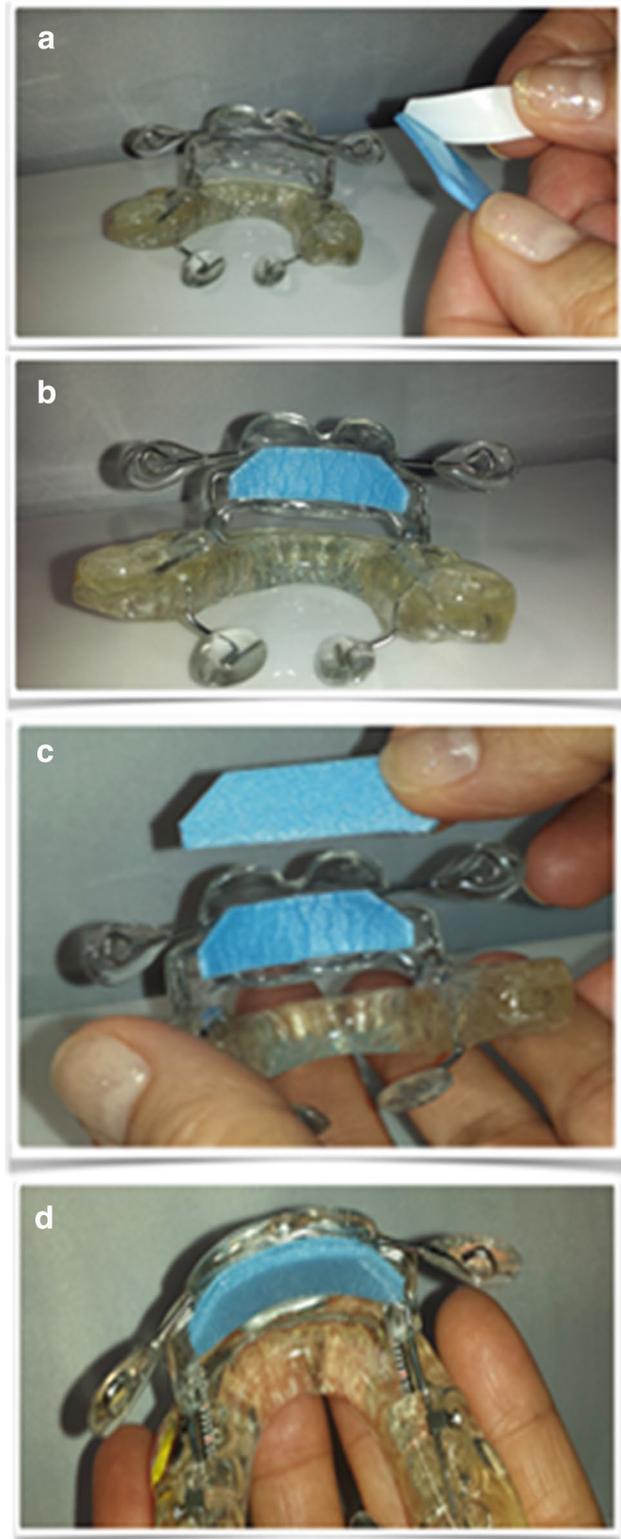
Fig. 2 a–d In-laboratory titration strips. These were used to gradually adjust the device to resolve any residual respiratory events. If events were still noted after 90 min of the PSG study, the attending sleep technologist titrated the device in vivo in 1 mm increments, using the titration strips
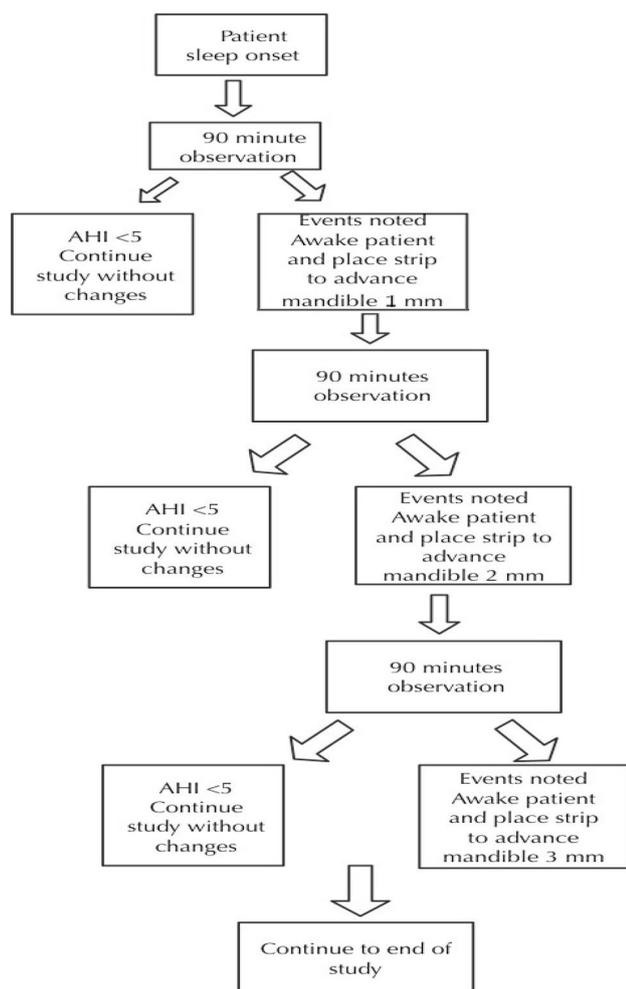
Fig. 3 Flow chart summarizing the in-laboratory PSG titration technique. Note that if obstructive events were noted after 90 min of the PSG study, the attending technologist titrated the device in 1 mm increments in a protrusive direction for maximum of 3 times, using titration strips

Snoring with Oral Appliance Therapy Update 2015 [22]. Figure 3 summarizes the workflow.

The attending physician was responsible for the overall decisions regarding the need for supplemental oxygen therapy, central sleep apnea management, and any other implicating conditions discovered during the titration PSG. Finally, the physician determined whether the OSA had been adequately treated according to the AASM criteria.

Statistical analysis was performed on the PSG data using matched, paired t tests (SAS University Edition).

3 Results

The mean treatment time of the study was 4 months. No significant side effects were reported either during the overnight titration PSG or during the study period. The total sample was sub-divided into severe cases (AHI > 30 < 50; $n = 25$) and very severe cases (AHI > 50; $n = 16$). The average age of the severe cases was 50.5 years (37–73) and average age of the very severe cases was 46.8 years (21–62). The average BMI of the severe cases was 32.2 (21.8–46.4) and 34.6 (27–43) for the very severe cases. Table 1 summarizes these results.

Treatment success was determined by a resolution of symptoms as defined by AASM criteria [23]. Indeed, the PSG data showed significant improvements for the major measures of OSA. For the severe cases, the average baseline AHI was 37.5 h^{-1} (31.6–49.7), while it was 73.4 h^{-1} (51.9–120.3) in very severe case. Specifically, for the severe subjects (18 males and 7 females), optimum resolution with an AHI of < 5 was achieved for 16 of the 25 subjects. Thus, 64% of the severe OSA sub-sample showed optimal resolution. For this sub-sample, the average AHI fell from 37.5 h^{-1} (31.6–49.7) to 7.5 h^{-1} (1.0–26.9) ($p < 0.001$), while the SpO_2 nadir improved from 80 to 88% ($p < 0.001$). Similarly, the percentage of sleep time with SpO_2 saturation < 90% improved from about 40–21% of the night. These findings are summarized in Table 1 and Fig. 4.

In addition, there were 16 subjects with very severe OSA (AHI > 50): 12 males and 4 females. An optimum resolution with AHI of < 5 was achieved for 10 of the 16 subjects. Thus, 63% of the very severe OSA sub-sample showed optimal resolution. For this sub-sample, the average AHI fell from 73.4 h^{-1} (51.9–120.3) to 13.4 h^{-1} (0.5–55.3) ($p < 0.001$), while the SpO_2 nadir improved from 76 to 85% ($p < 0.001$). Similarly, the percentage of sleep time with SpO_2 saturation < 90% improved from about 40% (0.0–82) to 21% (0.0–100) of the night. These findings are summarized in Table 1 and Fig. 5.

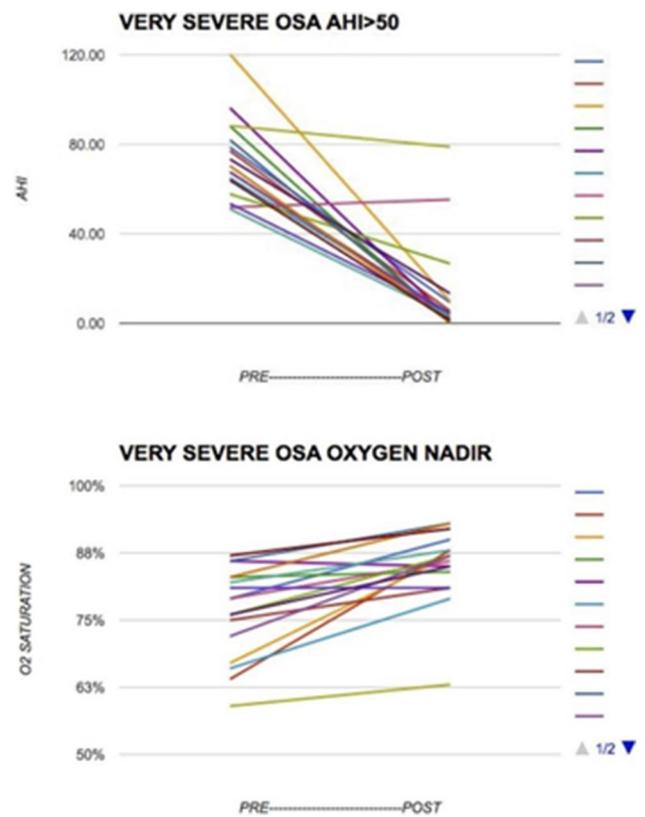**Table 1** Summary of parameters used in this study

	Average age	Average BMI	Males–females	Pre-treatment AHI	Post-treatment AHI	Pre-treatment O$_2$ nadir < 90%	Post-treatment O$_2$ nadir < 90%
Severe OSA AHI > 30 < 50	50.5	32.2	18–7	37.5	7.5	80% −37.9 min	88% −20 min
Very severe OSA AHI > 50	46.8	34.6	12–4	73.4	13.4	76% −47.2 min	85% −10.6 min
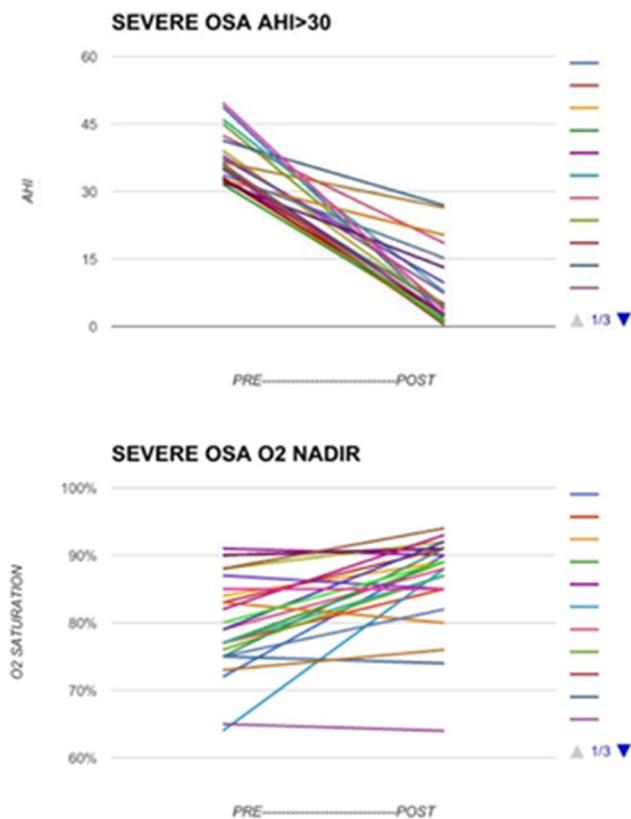
Fig. 4 Plots showing changes in the AHI and SpO_2 nadir for the severe OSA group. For this sub-sample, the average AHI fell from 37.5 h^{-1} (31.6–49.7) to 7.5 h^{-1} (1.0–26.9) ($p < 0.001$), while the SpO_2 nadir improved from 80 to 88% ($p < 0.001$)

Fig. 5 Plots showing changes in the AHI and SpO_2 nadir for the very severe OSA group. For this sub-sample, the average AHI fell from 73.4 h^{-1} (51.9–120.3) to 13.4 h^{-1} (0.5–55.3) ($p < 0.001$), while the SpO_2 nadir improved from 76 to 85% ($p < 0.001$)

4 Discussion

The current treatment of choice in patients diagnosed with OSA is continuous positive airway pressure (CPAP). However, this approach is prone to intolerance, and compliance is sometimes less than optimal [24]. Indeed, although some cases of OSA are thought to be disorders of craniofacial anatomy, oral appliance therapy (OAT) is not typically recommended for severe or very severe cases of OSA unless the patient is refractory to CPAP [25]. However, in some preliminary studies, OAT has been used to treat cases of severe OSA[25, 26] without an overnight titration PSG. Our present study suggests that a follow-up titration PSG is an effective method of demonstrating the efficacy of OAT in the treatment of severe OSA. Just as CPAP devices are titrated to find the best pressure setting for the subject, oral appliances can be titrated in the sleep laboratory to find the most efficacious setting and position of the mandible. A titration PSG study involves fine-tuning the device in vivo to ensure maximum resolution of OSA. In our study, a nighttime attending technologist performed the adjustments, while the subject slept wearing the customized and adjustable oral appliance.

Therefore, the goal of in-laboratory titration in this study was to optimize the efficacy of OAT. While the nighttime PSG technologist made every effort to eliminate obstructive events and airflow limitations to improve breathing during sleep, a board-certified sleep physician used AASM guidelines to interpret the PSG results, establish the efficacy of OAT, and prepare the summary report. The main variable used to determine the PSG titration outcomes in this study was the apnea hypopnea index (AHI).

We attempted to minimize selection bias in this study in a number of ways. First, all pre- and post-treatment polysomnographic studies were completed consecutively during the study period. Second, we only included patients who: strictly adhered to the OAT protocol; used a single type of appliance, and we required the use of expert sleep technologists to complete the titration PSG. Finally, all results, such as the AHI, were reviewed and interpreted by board-certified sleep specialists following established AASM guidelines. The AHI is the most accepted measurement at this time to determine effective titration during a PSG study [27], even though the Respiratory Distress Index (RDI) values are not included. Nevertheless, the

results of this present study showed robust improvements in both severe and very severe categories of OSA studied, and we found that most of the study subjects showed significant improvement in AHI.

Specifically, when the pre-treatment, baseline AHI was compared with the post-treatment AHI over a 4-month period (Figs. 5, 6), our analysis revealed a most remarkable effect in subjects with severe and very severe OSA (Table 1). Our findings are notable in that they demonstrated that the OASYS Oral–Nasal Airway System™ oral appliance was highly efficacious. We found little or no relationship between device efficacy and a range of confounding variables, such as gender, age, and BMI (data not shown). Interestingly, our results differ somewhat from other previously published data in the literature. For example, our data demonstrated significant improvement in OSA in older individuals, in contrast to data previously reported by Liu and Lowe, which suggested that OAT was restricted to younger patients [28]. Similarly, Otsuka and colleagues found that patients with lower BMIs were more likely to respond to OAT [29], which also contrasts with our findings. Importantly, however, we also found that OAT was effective in the treatment of both severe and very severe OSA (Table 1, Figs. 5, 6). These findings are in accord with a review by Hoffstein [30], which concluded that OAT constitutes a relatively heterogeneous group of devices for the treatment of OSA. This heterogeneity likely accounts for the variability in their benefit and side effects, at least in part, and supports our findings. Indeed, according to the current evidence, OAT successfully resolves mild-to-moderate OSA in 40–50% of patients, and significantly improves it in an additional 10–20% [30–32]. The results of our current study appear to extend this range into severe and very cases of OSA.

We also reviewed the changes in post-treatment SpO_2 nadir, using the oxygen saturation nadir as a surrogate marker of oxidative stress that perpetuates the detrimental process of atherosclerosis [33–35]. We found that the use of OAT significantly increased the lowest post-treatment SpO_2, regardless of disease severity ($p < 0.001$: Table 1; Figs. 5, 6). Moreover, a review of the desaturation data indicated that treatment significantly reduced the percentage of total oxygen desaturation sleep time by about − 7% ($p < 0.001$; Table 1). Other studies have shown more variable results in improvement in the oxygen saturation, especially in cases of severe OSA [36]. Therefore, our results are encouraging, but are limited by the study's retrospective design and modest sample size. There is now a clear need for well-controlled, prospective trials with larger sample sizes to determine the overall efficacy of OAT with overnight PSG titration in the treatment of severe OSA. Future studies are also needed to evaluate the effect of nasal dilation in conjunction with mandibular advancement versus mandibular advancement alone.

Compliance with ethical standards

References

1. Punjabi NM. The epidemiology of adult obstructive sleep apnea. Proc Am Thorac Soc. 2008;5(2):136–43.
2. Franklin KA, Lindberg E. Obstructive sleep apnea is a common disorder in the population—a review on the epidemiology of sleep apnea. J Thorac Dis. 2015;7(8):1311–22.
3. Garvey JF, Pengo MF, Drakatos P, Kent BD. Epidemiological aspects of obstructive sleep apnea. J Thorac Dis. 2015;7(5):920–9.
4. Martinez D, Klien C, Rahmeier L, et al. Sleep apnea is a stronger predictor for coronary heart disease than traditional risk factors. Sleep Breath. 2012;16:695–701.
5. Dimitri H, Ng M, Brooks AF, et al. Atrial remodeling in obstructive sleep apnea and the risk of sudden cardiac death. Heart Rhythm. 2012;9:321–7.
6. Gami AS, Olson EJ, Shen WK, et al. Obstructive sleep apnea and the risk of sudden cardiac death. J Am Coll Cardiol. 2013;62:610–6.
7. Aronsohn RS, Whitmore H, Vauter EV, et al. impact of untreated obstructive sleep apnea on glucose control in type 2 diabetes. Am J Respirt Crit Care Med. 2010;181(5):507–13.
8. Vgontzas AN, Papanicolaou DA, Bixler EO, et al. Sleep apnea and daytime sleepiness and fatigue: relation to visceral obesity, insulin resistance, hypercytokinemia. J Clin Endocrinol Metab. 2000;85:1151–8.
9. Redline S, Yenokyan G, Gottlieb DJ, et al. Obstructive sleep apnea-hypopnea and incident stroke. Am J Respir Crit Care Med. 2017;182:269–77.
10. Doff MHJ, Hoekema A, Wijkstra PJ, et al. Oral appliance versus continuous positive airway pressure in obstructive sleep apnea syndrome: a 2-year follow-up. Sleep. 2013;36:1289–96.
11. Karatayli-Ozgursoy S, Demireller A. Hyoid suspension surgery with UPPP for the treatment of hypopharyngeal airway obstruction in obstructive sleep apnea. Ear Nose Throat J. 2012;91:358–64.
12. Hochban W, Brandendurg U, Peter JH. Surgical treatment of obstructive sleep apnea by maxillomandibular advancement. Sleep. 1994;17:624–9.
13. Engleman HM, Asgari-Jirhandeh N, McLeod AL, et al. Self-reported use of CPAP and benefits of CPAP therapy. A patient survey. Chest. 1996;109:1470–6.
14. Reeves-Hoché MK, Meck R, Zwillich CW. Nasal CPAP: an objective evaluation of patient compliance. Am J Respir Crit Care Med. 1994;149:149–54.
15. Kribbs NB, Pack AI, Kline LR, et al. Effects of one night without nasal CPAP treatment on sleep and sleepiness in patients with obstructive sleep apnea. Am Rev Respir Dis. 1993;147:1162–8.
16. Hussain SF, Irfan M, Waheed Z, et al. Compliance with continuous positive airway pressure (CPAP) therapy for obstructive sleep apnea among privately paying patients—a cross sectional study. BMC Pulm Med. 2014;14:188. https://doi.org/10.1186/1471-2466-14-188.

17. Singh GD, Abramson M. Effect of an intra-oral nasal dilation appliance on 3-D nasal airway morphology in adults. Sleep Breath. 2008;12(1):69–75.

18. Hoekema A, Stegena B, Wijkstra PJ, et al. Obstructive sleep apnea therapy. J Den Res. 2008;87:882–7.

19. Almeida FR, Parker JA, Hodges JS, et al. Effect of a titration polysomnogram on treatment of success with a mandibular repositioning appliance. J Clin Sleep Med. 2009;5:198–204.

20. Holley AB, Lettieri CJ, Shah AA. Efficacy of an adjustable oral appliance and comparison with continuous positive airway pressure for the treatment of obstructive sleep apnea syndrome. Chest. 2011;140:1511–6.

21. Berry RB, Brooks R, Gamaldo CE et al; for the American Academy of Sleep Medicine. The AASM manual for the scoring of sleep and associated events: rules, terminology and technical specifications, scoring manual version 2.4. American Academy of Sleep Medicine;2017.

22. Ramar K, Dort LC, Katz SG, Lettieri CJ, Harrod CG, Thomas SM, Chervin RD. Clinical practice guideline for the treatment of obstructive sleep apnea and snoring with oral appliance therapy: an update for 2015. J Dent Sleep Med. 2015;2(3):71–125.

23. American Sleep Disorders Association. Practice parameters for the treatment of snoring and obstructive sleep apnea with oral appliances. Sleep. 1995;18:511–3.

24. Gulati A, Oscroft N, Chadwick R, Ali M, Smith I. The impact of changing people with sleep apnea using CPAP less than 4 h per night to a bi-level device. Respir Med. 2015;109(6):778–83.

25. Ferguson KA, Cartwright R, Rogers R, Schmidt-Nowara W. Oral appliances for snoring and obstructive sleep apnea: a review. Sleep. 2006;29:244–62.

26. Singh GD, Griffin TM, Cress SE. Biomimetic oral appliance therapy in adults with severe obstructive sleep apnea. J Sleep Disord Ther. 2016;5:1–5.

27. Kushida CA, Morgenthaler TI, Littner MR, et al. Practice parameters for the treatment of snoring and obstructive sleep apnea with oral appliances: an update for 2005. Sleep. 2006;29:240–3.

28. Liu Y, Lowe AA. Factors related to the efficacy of an adjustable oral appliance for the treatment of obstructive sleep apnea. Chin J Dent Res. 2000;3:15–23.

29. Otsuka R, Almeida FR, Lowe AA, Ryan F. A comparison of responders and nonresponders to oral appliance therapy for the treatment of obstructive sleep apnea. Am J Orthod Dentofac Orthop. 2006;129:222–9.

30. Hoffstein V. Review of oral appliances for treatment of sleep-disordered breathing. Sleep Breath. 2007;11:1–22.

31. Ozturk O, Tuna SH, Hayri U. The efficacy of oral appliance in patients with severe obstructive sleep apnea: a cohort study. Oral Dis. 2015;21:386–92.

32. Haviv Y, Bachar G, Aframian DJ, et al. A 2-year mean follow-up of oral appliance therapy for severe obstructive sleep apnea: a cohort study. Oral Dis. 2015;21:386–92.

33. Vasdev S, Gill VD, Singal PK. Modulation of oxidative stress-induced changes in hypertension and atherosclerosis by antioxidants. Exp Clin Cardiol. 2006;11(3):206–16.

34. Kattoor AJ, Pothineni NVK, Palagiri D, Mehta JL. oxidative stress in atherosclerosis. Curr Atheroscler Rep. 2017;19(11):42. https://doi.org/10.1007/s11883-017-0678-6.

35. Jezovnik MK, Poredos P. Oxidative stress and atherosclerosis. E-journal Cardio Practice. [Internet]. 2007 [cited 2018 Feb 1];6(6). https://www.escardio.org/Journals/E-Journal-of-Cardiology-Practice/Volume-6/Oxidative-stress-and-atherosclerosis-Title-Oxidative-stress-and-atheroscleros.

36. Fukuda T, Tsuiki S, Kobayashi M, et al. Selection of response criteria affects the success rate of oral appliance treatment for obstructive sleep apnea. Sleep Med. 2014;15:367–70.