

The Effect of Intermittent Negative Air Pressure, iNAP® on Subjective Daytime Sleepiness in Middle-aged Patients with Moderate Obstructive Sleep Apnea

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ABSTRACT

Background: In a previous study, we have demonstrated that intermittent negative air pressure (iNAP®) therapy improves the apnea severity in patients with mild-to-moderate obstructive sleep apnea syndrome (OSAS).

Purpose: This study was conducted to evaluate the effect of subjective daytime sleepiness for patients with moderate OSA.

Methods and Materials: A total of seven men and one woman with moderate OSA were enrolled in this single-center, prospective, non-randomized clinical study. All patients used the iNAP® devices in their home during sleep between the diagnostic and second polysomnography assessment. To determine the changes in the subjective sleepiness between the diagnostic and iNAP®-treated PSGs, the Epworth Sleepiness Scale (ESS) score was estimated immediately before the first and second PSG.

Results: At baseline the mean (standard deviation) age and body mass index of the study participants were 41.5 (\pm 6.3) years and 23.2 (\pm 2.6), respectively. The baseline apnea-hypopnea index (AHI) was 22.2 \pm 2.2, and decreased to 15.6 \pm 5.3 after the iNAP® therapy ($p=0.007$). The arousal index improved from 29.8 \pm 9.2 at baseline to 19.3 \pm 5.1 with the iNAP® device ($p=0.0025$). With the improvement of apnea severity, the ESS decreased from 14.0 \pm 3.8 to 9.1 \pm 4.4 ($p=0.0076$).

Conclusions: The negative pressure therapy with the iNAP® Sleep Therapy System ameliorated both the apnea severity and the subjective daytime sleepiness in middle-aged patients with moderate OSA.

Keywords: Intermittent negative air pressure (iNAP®); Subjective daytime sleepiness; Epworth Sleepiness Scale (ESS)

INTRODUCTION

The obstructive sleep apnea syndrome (OSA) is characterized by recurrent obstruction of the upper airway during sleep, and it is estimated that 13% and 6% of middle-aged men and women, respectively, suffer from moderate to severe OSA, which is defined as a score of more than 15 on the apnea-hypopnea index (AHI) [1]. The intermittent hypoxia in OSA that is associated with airway obstruction often leads to transient arousals that results in sleep-state fragmentation throughout the night. These pathophysiologic changes result in excessive daytime sleepiness and have serious consequences with regard to the quality of life.

For patients with moderate to severe OSA, continuous positive airway pressure (CPAP) is the gold standard for treatment [2,4]. However, for patients with mild to moderate OSA, therapeutic options include oral appliances, prosthetic mandibular advancement (PMA), and it is an established alternative treatment. However, adherence to CPAP is frequently low [5-8]. Studies on the adherence to positive airway pressure (PAP) have wide variations (30%-80%) in the reported percentages of OSA patients with successful PAP adherence [9,10]. Moreover, PMA treatment may not be effective for patients with severe OSA, with reported success rates in the range of 51-81% and 14-61% in mild-to-moderate and severe OSA, respectively [11]. There are several side effects of PMA, such as tooth pain, pain in the temporomandibular joint, gum diseases, and dry mouth [11,12].

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We have demonstrated that an intermittent negative air pressure (iNAP®) device improved the apnea severity in patients with mild to moderate OSA, despite a marginal but significant degree of amelioration that was indicated by the AHI score [13]. Recently, Hung et al. reported that the iNAP® device generated a good response in more than half of their non-obese patients with moderate OSA with minimal adverse effects [14]. The iNAP® system involves a console and a device which provides negative pressure that is powered by two AA-sized batteries, which have a running life of approximately 7 days.

This study was conducted to evaluate the effect of subjective daytime sleepiness for middle-aged patients who had only moderate OSA.

MATERIALS AND METHODS

Participants

This study enrolled eight adults' patients, 7 men and 1 woman with moderate OSA, who visited the Fukuoka Urasoe Clinic between September, 2017 and March, 2019. The chief complaints of each patient were daytime sleepiness, witnessed apnea, and/or loud snoring. All of the patients were required to undergo diagnostic polysomnography (PSG). We excluded patients with a history of cardiovascular diseases, cerebrovascular diseases, or diabetes mellitus, for avoiding the potential confounding factors.

Study Design and Interventional Device

This single-center, non-controlled, non-randomized, proof-of-concept study undertook nighttime monitoring and evaluation of participants who were prescribed monotherapy for OSA. All study participants underwent a diagnostic PSG that was followed by a second PSG after the use of the iNAP® Light Sleep Therapy System. All patients used the specified devices at their home during sleep between the first and second PSGs. The device detects the air pressure within the oral cavity and automatically adjusts the pressure gradient that is applied to the airway as needed, as previously described [13]. The Epworth Sleepiness Scale (ESS), which is a reliable patient self-assessment method to measure excessive daytime sleepiness (EDS), is the most widely used clinical tool for the evaluation of the subjective trait of sleepiness based on a questionnaire that ascertains the individual's tendency to doze off [15]. To determine the subjective sleepiness between the diagnostic PSG and iNAP®-treated PSG, the ESS score was determined immediately before the first and second PSGs.

Polysomnography

As shown in our previous study [16], standard overnight PSG included continuous monitoring with a central electroencephalogram (EEG), electrooculogram (EOG), submental and anterior tibial electromyogram (EMG), and electrocardiogram (ECG) by using conventional leads. The airflow was monitored with oral and nasal thermistors, and the respiratory effort was measured by respiratory inductance plethysmography through transducers that were placed over the

chest and the abdomen. The oxyhemoglobin saturation was continuously recorded through a pulse oximeter (3900P, Datex-Ohmeda Co., Louisville, CO, USA). All of the abovementioned parameters were continuously recorded by using RemLogic version 3.2 (Embla, Thornton, CO, USA). All recordings were scored directly on the screen by polysomnographers who were certified by the Japanese Society of Sleep Research based on the 2014 guidelines from the American Academy of Sleep Medicine (AASM) [17]. Obstructive apnea was defined as near-complete (>90%) cessation in airflow for more than 10 seconds during sleep, despite ventilatory effort. Hypopnea was defined as a reduction in the airflow of more than 30%, with concurrent reductions in the oxyhemoglobin saturation of at least 3% or arousals from sleep [18].

Statistical Analysis

All participants with moderate OSA were included in the data analysis. A paired t-test was used to examine the change from the baseline to after the treatment in each patient. Results are expressed as median \pm standard deviation, and all p-values are 2-tailed with statistical significance set at <0.05 . Statistical analyses were performed using StatMate version 5.01 (Atoms, Tokyo, Japan).

RESULTS

Study Population

This study included seven men and one woman (age, mean \pm SD [range] 41.5 ± 6.3 [29-50] years; body mass index (BMI) 23.2 ± 2.6). In a previous paper [12], we have reported that the iNAP® therapy might be more effective in younger rather than elderly OSA patients. Therefore, the middle-aged patients were enrolled to investigate the effect of subjective daytime sleepiness with the iNAP® device. The average interval from the first diagnostic PSG to the PSG after the use of the iNAP® device was 58.3 ± 27.4 days. In addition, it has been considered that a subset of OSA patients with good response to the iNAP® therapy might be patients with moderate OSA in the previous study [12]. Thus, patients with moderate OSA were recruited in this study. The demographics and baseline data for the patients who completed the protocol are presented in Table 1.

Effectiveness of iNAP® Therapy

The baseline AHI was 22.2 ± 2.2 , whereas the AHI with iNAP® device was 15.6 ± 5.3 , which indicated a significant reduction as shown in Figure 1. With the improvement of apnea severity, a reduction of the ESS score for subjective sleepiness from 14.0 ± 3.8 to 9.1 ± 4.4 was observed (Figure 2). However, with regard to the other PSG markers, no significant differences in sleep efficiency and wakefulness after sleep onset (WASO) (77.6 ± 9.6 to 83.6 ± 5.6 , $p=0.167$ and 93 ± 41 to 65 ± 29.7 , $p=0.18$, respectively), were observed. However, the arousal index

improved from 29.8 ± 9.2 at baseline to 19.3 ± 5.1 with the iNAP® device ($p=0.0025$; Figure 3).

Table 1: Patients characteristics at baseline (n=8).

Sex (male:female)	7:1
Age (years)	41.5 ± 6.3
Baseline AHI	22.2 ± 2.2
Body mass index (BMI) (kg/m ²)	23.2 ± 2.6
Epworth Sleepiness Scale (ESS)	14.0 ± 3.8

Data are presented as mean \pm standard deviation.

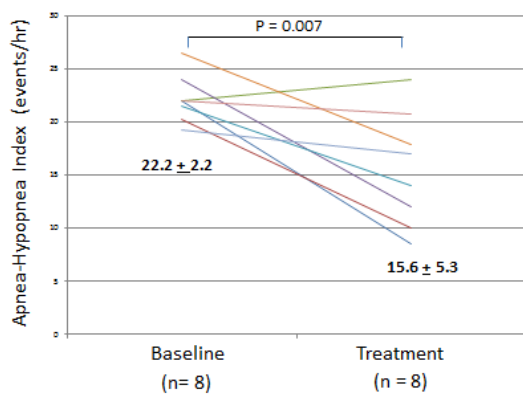


Figure 1: Diagram showing effect of the Intermittent Negative Air Pressure (iNAP®) therapy on the apnea severity in middle-aged patients with moderate obstruction sleep apnea. The apnea-hypopnea index (AHI) at baseline and after the treatment with iNAP® in 8 patients with moderate OSA is presented.

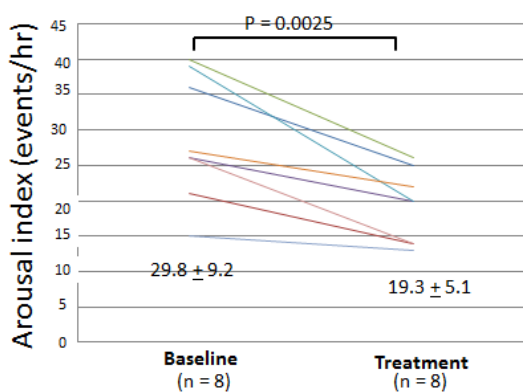


Figure 2: Effect of the Intermittent Negative Air Pressure (iNAP®) therapy on the arousal index of middle-aged patients with moderate obstructive sleep apnea.

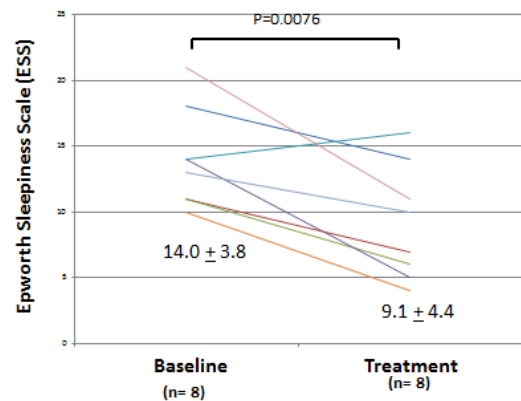


Figure 3: Effect of Intermittent Negative Air Pressure (iNAP®) therapy on the subjective daytime sleepiness, Epworth Sleepiness Scale (ESS), in middle-aged patients with moderate obstructive sleep apnea.

DISCUSSION

This study confirmed that the iNAP® therapy was effective in the reduction of both apnea severity and subjective daytime sleepiness in middle-aged patients with moderate OSA. The improvement of the arousal index in PSG was observed in all study participants. It has been reported that the arousal index is a more potent contributory factor than apnea severity for sympathetic overactivity in OSA patients [19]. Consequently, the amelioration of increased sympathetic overactivity with iNAP® device might contribute to the prevention of cardiovascular comorbidity through the reduction of systolic pressure. Therefore, the iNAP® therapy might be useful for the prevention of cardiovascular events. In studies of adherence to oral appliances (OAs) treatment, the objective data on the adherence to OAs has proven difficult to estimate because of the limited subjective adherence monitor for OAs to date. However, there are several reports that indicate the rate of patient use of an OA at the 3-year follow-up was 50% [20] and the adherence at the 4-year follow-up was 62% [21]. However, the adherence of the iNAP® device used in this study remained unknown, although all of the study participants could use the device in their homes every night for nearly 2 months.

This study found that the iNAP® improved the subjective daytime sleepiness, as evaluated by ESS. The underlying physiological mechanisms that cause EDS in patients with OSA remain unresolved. However, the severity of OSA measured by AHI does not correlate well with the presence of daytime sleepiness. Nonetheless, CPAP has proved to be an effective treatment for EDS, especially for individuals with a high AHI or severe sleepiness [22]. It has been suggested that this effect may be due to the amelioration of sleep fragmentation, rather than the elimination of intermittent nocturnal hypoxemia [23]. Accordingly, the improvement of daytime sleepiness in our study with iNAP® device may have been a result of the decreased arousal index rather than a decline in apnea severity, as OSA is a heterogeneous disorder and multiple pathophysiologic causes are presently recognized. The anatomical characteristics of the upper airway, such as obesity or a small jaw, remains a

fundamentally important pathophysiological factor for OSA [24-26]. However, non-anatomical factors, such as impaired muscle responsiveness [27-29], low arousal threshold [30,31], high loop gain [32,33], rostral fluid shift [34], and lung volume [35,36], play a variable role. One of the pathophysiological actions of the iNAP® device leads to the anterior displacement of the tongue, which is followed by an anatomical increase in the upper airway volume. The negative pressure reflex (NPR) has been reported to be the main mechanism of genioglossal muscle activation [37]. As another mechanism of action of the device, it was assumed that negative pressure-sensitive mechanoreceptors located within the mucosa of the upper airway are activated by the negative pressure induced by the iNAP® device and may contribute to the maintenance of the patency of the upper airway.

Despite the abovementioned features, this study has some limitations. The main limitation of this study was the small study sample size, similar to that in a previous study [13]. A large number of participants in this study could not be recruited because of the dearth of manpower and economic limitations at the study center. In this study, all patients used the iNAP® device therapy for 55.3 ± 27.4 days prior to the repetition of the study assessments. However, it has been difficult to determine whether all patients used the device with the same adherence. There are several treatments for patients with OSA, including behavioral interventions (weight loss, positional therapy, alcohol avoidance, and cessation of hypnotic therapy), oral appliances, positive airway pressure therapies, surgical therapy (tonsillectomy, maxillomandibular advancement, bariatric surgery), and pharmacotherapy [38,39]. On the other hand, several clusters, “disturbed sleep group (cluster 1)”, “minimally symptomatic group (cluster 2)”, and “excessive daytime sleepiness group (cluster 3)”, have been identified [40]. However, more personalized therapy for the heterogeneous population of OSA patients has not been established. From the results of our study, treatment with iNAP® device might be suitable for middle-aged patients with moderate OSA among “excessive daytime sleepiness group (cluster 3)”.

CONCLUSIONS

This study demonstrated that negative pressure therapy by using the iNAP® Sleep Therapy System improved both the apnea severity and the subjective daytime sleepiness in middle-aged patients with moderate OSA. Despite the small study sample, this study is the first research attempt to demonstrate on the effectiveness of the iNAP® device for the treatment of subjective daytime sleepiness. Further large-scale, controlled studies are needed to validate the findings of this research.

COMPLIANCE WITH ETHICAL STANDARDS

This study received no funding.

CONFLICTS OF INTEREST

The author declares that there are no conflicts of interest with regard to this study.

ETHICAL APPROVAL

This study was approved by the Institutional Ethic Committee at the Nakamura Clinic, Urasoe, Okinawa in Japan. In addition, informed consent was obtained from all the patients before enrollment in this study, which was performed in accordance with the principles of the Declaration of Helsinki and its later amendments.

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