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A novel intermittent negative air pressure device ameliorates obstructive sleep apnea syndrome in adults

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Abstract

Purpose Patients with obstructive sleep apnea syndrome (OSAS) have difficulties in compliance with continuous positive airway pressure (CPAP) and the treatment outcome is heterogeneous. We proposed a proof-of-concept study of a novel intermittent negative air pressure (iNAP®) device for physicians to apply on patients who have failed or refused to use CPAP.

Methods The iNAP® device retains the tongue and the soft palate in a forward position to decrease airway obstruction. A full nightly usage with the device was evaluated with polysomnography. Subgrouping by baseline apnea–hypopnea index (AHI) and body mass index (BMI) with different treatment response criteria was applied to characterize the responder group of this novel device.

Results Thirty-five patients were enrolled: age 41.9 ± 12.2 years (mean ± standard deviation), BMI 26.6 ± 4.3 kg/m^2, AHI 41.4 ± 24.3 events/h, and oxygen desaturation index (ODI) 40.9 ± 24.4 events/h at baseline. AHI and ODI were significantly decreased ($p < 0.001$) by the device. Patients with moderate OSAS, with baseline AHI between 15 to 30 events/h, achieved 64% response rate; and non-obese patients, with BMI below 25 kg/m^2, achieved 57% response rate, with response rate defined as 50% reduction in AHI from baseline and treated AHI lower than 20. There were minimal side effects reported.

Conclusions In a proof-of-concept study, the device attained response to treatment as defined, in more than half of the moderate and non-obese OSAS patients, with minimal side effects.

Keywords Obstructive sleep apnea syndrome · Sleep-disordered breathing · Apnea–hypopnea index · Intermittent negative air pressure · Intraoral device · Oral pressure therapy

Introduction

Obstructive sleep apnea syndrome (OSAS) therapies emphasize enhancing the activity or stiffening the upper airway muscles to prevent the collapse of the soft tissue during sleep [1, 2]. Continuous positive airway pressure (CPAP) is the standard treatment for OSAS. Despite its effectiveness, suboptimal adherence to CPAP is common

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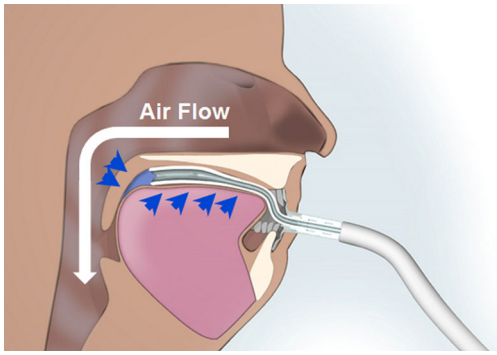

Fig. 1 The iNAP® sleep therapy system

[3]. The 5-year compliance rate in another report was as low as 17% [4]. Alternative treatment is in great demand for patients who have failed or refused to use CPAP. Hypoglossal nerve stimulation and oral appliances have been offered as potential treatments by driving the tongue forward or advancing the mandible [2, 5, 6]. Substantial weight loss and proper weight control are also suggested to manage OSAS. A body mass index (BMI) of 25 kg/m^2 or less is recommended [7].

The intraoral pressure gradient therapy by the intermittent negative air pressure (iNAP®) device used in this study has previously been suggested as a treatment approach for patients with mild to moderate OSAS [8]. Here, we performed a study to demonstrate the safety and efficacy of the device in patients with a broader spectrum of OSAS severity.

Methods

Participants

A convenience sample of adults with OSAS, defined as baseline apnea–hypopnea index (AHI) ≥ 5 events/h and presence of clinical complaints, were enrolled. Patients with any of the following conditions were excluded: pregnancy, history of OSAS surgical treatment (e.g., nasal cavity surgery, nasal plastic surgery, sinusitis endoscopic surgery, nasal airway obstruction surgery, uvulopalatopharyngoplasty), pulmonary or upper airway disease, cardiovascular comorbidities, or presence of any potential complications of sleep apnea.

Protocol design and study sequence

This was a single-center, prospective, feasibility study. After confirming the presence of OSAS, clinical evaluations of the upper airway were performed, followed by an oral interface fitting test and a negative pressure maintenance test. Imaging studies, including the Müller maneuver under a fiberscope and cephalometric X-rays, were then performed. Patients who met all entry criteria were treated and monitored during nocturnal polysomnography (PSG).

The recording and scoring of PSGs were performed following the 2007 recommendations of the American Academy of Sleep Medicine [9]. Specifically, hypopneas were required to have at least a 30% air flow reduction

Table 1 Demographics

		Enrolled ($N = 48$)	Efficacy analysis cohort ($N = 35$)	p value
Age (year)	Mean (SD)	41.67 (11.57)	41.89 (12.15)	0.500
	Median (min, max)	39.50 (21.00, 64.00)	40.00 (21.00, 64.00)	
	95% CI	(38.39, 44.94)	(37.86, 45.91)	
Height (cm)	Mean (SD)	169.56 (7.64)	168.94 (7.80)	0.500
	Median (min, max)	170.00 (150.00, 185.00)	169.00 (150.00, 184.00)	
	95% CI	(167.40, 171.72)	(166.36, 171.53)	
Weight (kg)	Mean (SD)	77.58 (13.68)	76.07 (14.91)	0.500
	Median (min, max)	76.00 (46.00, 108.00)	73.00 (46.00, 108.00)	
	95% CI	(73.71, 81.45)	(71.13, 81.01)	
Body mass index (kg/m^2)	Mean (SD)	26.94 (4.19)	26.55 (4.31)	0.209
	Median (min, max)	26.36 (17.75, 37.20)	25.62 (17.75, 37.20)	
	95% CI	(25.75, 28.12)	(25.12, 27.98)	
Gender	Male	44 (91.67%)	32 (91.43%)	0.484
	Female	4 (8.33%)	3 (8.57%)	

Table 2 The sleep architecture and the respiratory events

Efficacy analysis cohort ($N = 35$)	Mild group ($N = 3$)		Moderate group ($N = 14$)		Severe group ($N = 18$)	
	Baseline	Treated	Baseline	Treated	Baseline	Treated
TST (min)**	375.63 (75.90)	354.17 (68.56)	371.04 (79.23)	348.10 (56.06)	383.51(37.07)	340.02 (53.71)***
Sleep latency (min)	4.00 (0.50)	4.50 (0.50)	5.04 (5.66)	10.29 (12.95)	8.69 (10.38)	12.58 (17.42)
Sleep efficiency (%)	88.40 (11.78)	84.27 (12.84)	85.35 (14.83)	86.15 (11.82)	88.31 (6.64)	82.03 (11.16)**
Arousal index***	9.10 (3.65)	5.53 (3.04)	22.40 (3.55)	10.47 (5.33)***	61.08 (16.70)	50.02 (28.25)**
Stage N1%	22.87 (12.93)	24.90 (13.86)	21.79 (8.33)	22.05 (12.40)	31.98 (15.82)	29.71 (17.27)
Stage N2%*	34.80 (8.76)	37.73 (13.39)	38.44 (9.73)	32.68 (7.33)	39.45 (10.15)	36.79 (9.96)
Stage N3%*	26.87 (8.56)	23.13 (6.50)	20.62 (7.09)	25.31 (10.91)*	13.57 (9.76)	16.83 (10.89)
Stage REM (%)	15.43 (10.03)	14.27 (6.15)	19.16 (8.06)	19.94 (4.37)	14.98 (3.64)	16.66 (6.72)
Apnea index***	4.80 (5.2)	3.40 (2.17)	13.19 (5.6)	4.56 (3.31)***	52.45 (18.49)	42.41 (29.00)*
Obstructive apnea index**	4.77 (5.23)	3.27 (2.06)	14.56 (8.31)	7.87 (13.33)**	49.98 (18.54)	40.38 (29.55)*
Hypopnea index	4.43 (1.24)	2.23 (1.11)*	8.70 (6.33)	5.60 (3.90)	7.20 (6.20)	10.03 (8.87)
AHI***	9.27 (3.94)	5.63 (3.12)	22.56 (3.60)	10.59 (5.47)***	61.31 (16.49)	52.61 (25.52)**
ODI***	9.00 (3.73)	5.40 (3.10)	21.96 (3.85)	10.25 (5.46)***	60.95 (16.56)	52.35 (25.59)**
Mean SpO2 saturation (%)***	96.43 (0.99)	96.47 (0.12)	95.60 (0.97)	96.26 (1.00)*	91.51 (2.89)	92.74 (3.24)**
Lowest SpO2 saturation (%)**	81.33 (2.52)	83.00 (2.65)	80.93 (3.89)	84.43 (4.80)*	68.89 (7.39)	71.61 (8.43)
% TST SpO2 ≥ 90%***	99.04 (0.96)	99.89 (0.20)	98.34 (1.10)	99.22 (1.13)*	71.58 (16.51)	79.40 (18.57)***
% TST SpO_2 89–80%***	3.20 (3.37)	0.31 (0.54)	3.68 (2.15)	1.57 (1.60)***	31.31 (11.51)	22.51 (14.28)***
% TST SpO_2 79–70%	–	–	0.02 (0.07)	0.02 (0.08)	5.79 (7.91)	4.18 (7.01)
% TST SpO_2 69–60%	–	–	–	–	0.73 (2.22)	0.64 (1.60)

Values shown are mean (standard deviation, SD)

*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$. Paired t test of treated versus baseline

and a 4% desaturation. Mixed events were scored as obstructive events.

The lateral cephalometrics were performed on awake, supine patients. The angle between the Steiner's mandibular plane and the back of patients was set at 80°. The surface of the tongue, hard palate, soft palate, and tongue base were outlined by gargling the barium. The distance of the tongue or soft palate to the back wall of the upper airway, defined as T-P-D, was measured to examine if this device had succeeded in widening the upper airway.

Table 3 Safety comparison of ATLAST study and this study

	ATLAST study, no. of patients reported with any AE	This study, no. of patients reported with any AE
Total[a]	80/146 (54.79%)	20/35 (57.14%)
Occlusal change	1/146 (0.68%)	0/35 (0.00%)
Dental discomfort	19/146 (13.01%)	5/35 (14.29%)
Excessive salivation	3/146 (2.05%)	2/35 (5.71%)
Oral tissue discomfort	70/146 (47.95%)	7/35 (20.00%)[b]
Oral tissue irritation	27/146 (18.49%)	7/35 (20.00%)
Other AEs	21/146 (14.38%)[c]	6/35 (17.14%)[d]

[a] There was no severe or serious device-related AE that occurred in both studies

[b] Instances of oral tissue discomfort occurring in this study were all tongue discomfort

[c] Other AEs reported in ATLAST study include blood in mucous/saliva, headache, jaw discomfort, keratosis on tongue, leukoplakia, metallic taste in mouth, nasal congestion, nausea, and panic attack

[d] Other AEs reported in this study include breathing obstruction, heavy burden feeling of the heart, hyperplasia of prostate, bitten by dog with open wound at the posterior of the right knee, osteoarthrosis of the lower leg, pulpitis, and necrosis of the pulp

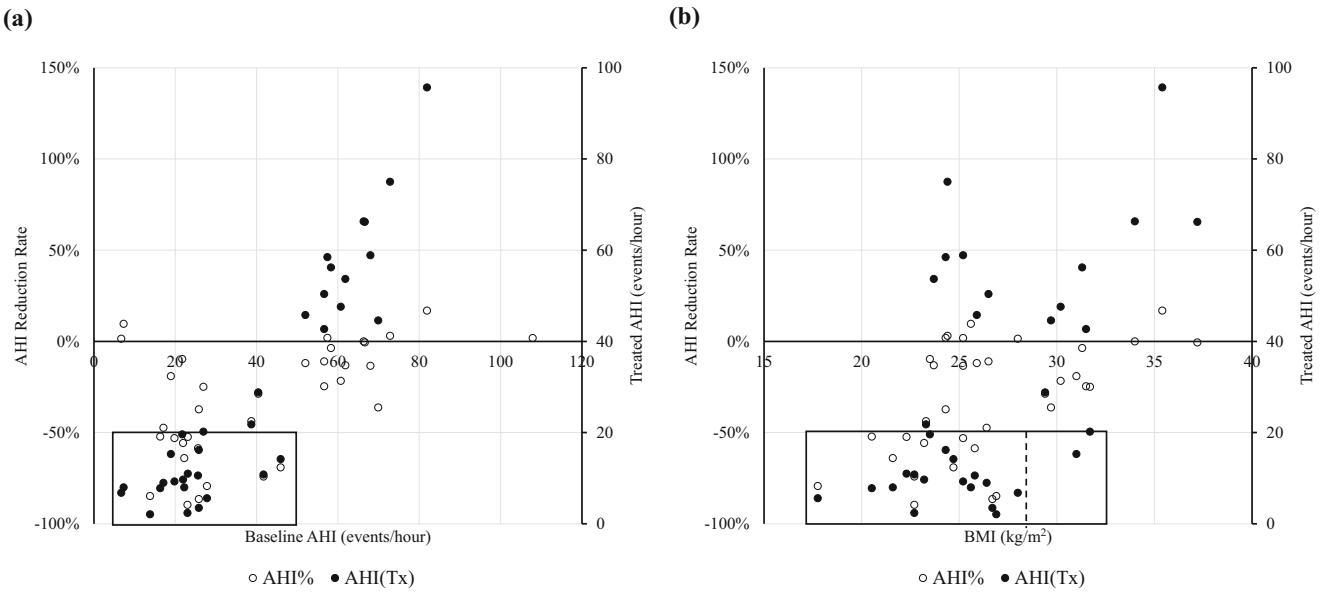

Fig. 2 Distribution diagram. **a** Scatter plot by patient's baseline AHI, and **b** scatter plot by patient's BMI

Device description

The iNAP® device is CE marked and has been cleared by the Taiwan Food and Drug Administration as "class II intraoral device for snoring and/or obstructive sleep apnea." The device is battery powered and is designed to prevent sleep-disordered breathing by providing negative pressure within the confined oral cavity to retain the tongue and the soft palate in a forward position, which enhances the patency of the pharyngeal upper airway without a mask and forced air (Fig. 1). The originality of the device is that when the targeted negative oral pressure is obtained, the air flow stops, restarting again only when air flow is needed to avoid a decrease in target pressure.

Results

Among the 48 subjects who consented to participate in the study, 35 patients (32 men, 91%) met all the enrollment criteria and were included in the efficacy analysis cohort. Of the 35 patients, age range was 22 to 63 years, body weight range 46 to 108 kg, and BMI range 17.8 to 37.2 kg/m^2. The demographics of all participants and of the efficacy analysis cohort were not significantly different (Table 1).

The sleep architecture and the respiratory events of the efficacy analysis cohort are listed in Table 2 according to the subgroups by baseline AHI severity (mild group, $5 \leq$ AHI < 15; moderate group, $15 \leq$ AHI < 30; and severe group, AHI ≥ 30 events/h). The mean ± standard deviation (SD) baseline AHI was 41.4 ± 24.3 and decreased significantly to 31.8 ± 28.5 events/h ($p < 0.001$) in the efficacy analysis cohort. The median of percentage change of AHI was −25% (interquartile −54%, −7%). The apnea index, obstructive apnea index, oxygen desaturation index (ODI), mean peripheral capillary oxygen saturation (SpO_2), lowest SpO_2, and percentage of total sleep time (TST) $SpO_2 \geq$ 90% were all significantly improved by the treatment. These changes were similarly seen in the moderate and the severe group. The TST was significantly reduced in the efficacy analysis cohort ($p < 0.01$) and the severe group ($p < 0.001$). The sleep efficiency was lowered in the severe group ($p < 0.01$). The arousal index was significantly decreased ($p < 0.001$); the stage N2% was significantly reduced ($p < 0.05$) while the stage N3% significantly increased ($p < 0.05$) in the efficacy analysis cohort.

Seven patients (20%) reported at least one oral tissue discomfort and/or one oral tissue irritation. These were the most frequently reported device-related adverse events (AEs) and were all mild in severity (Table 3). No severe device-related AE occurred during the study period and none of the patients or investigators stopped the trial due to safety concerns.

Responder grouping

We used treated AHI and the AHI reduction rate to draw the scatter plot of treatment outcome by each patient's baseline AHI and BMI (Fig. 2). The device responders had baseline AHI 5 to 50 events/h with BMI spanning

Table 4 Treatment response rate of the OSAS severity groups rated by three clinical treatment response criteria

		Criterion 1 < 50% initial AHI		Criterion 2 < 50% initial AHI and Tx AHI < 20		Criterion 3 Tx AHI < 10		Age	BMI
		Responder No.	%	Responder No.	%	Responder No.	%	Mean (SD) years	Mean (SD) kg/m^2
Efficacy analysis cohort	AHI ≥ 5 (N = 35)	12	34.29%	12	34.29%	11	31.43%	41.74 (11.94)	26.51 (4.29)
Mild group	5 ≤ AHI ≤ 15 (N = 3)	1	33.33%	1	33.33%	3	100.00%	34.13 (5.85)	26.83 (1.20)
Moderate group	15 ≤ AHI ≤ 30 (N = 14)	9	64.29%	9	64.29%	8	57.14%	42.78 (12.51)	24.48 (3.78)
Severe group	AHI > 30 (N = 18)	2	11.11%	2	11.11%	0	0.00%	42.19 (12.26)	28.03 (4.45)*
Mild–severe	5 ≤ AHI ≤ 60 (N = 26)	12	46.15%	12	46.15%	11	42.31%	40.72 (11.83)	25.49 (3.52)
Subgroup	5 ≤ AHI ≤ 50 (N = 21)	12	57.14%	12	57.14%	11	52.38%	39.77 (11.99)	24.92 (3.39)
	5 ≤ AHI ≤ 40 (N = 18)	10	55.56%	10	55.56%	11	61.11%	41.70 (11.76)	24.80 (3.47)
	5 ≤ AHI ≤ 30 (N = 17)	10	58.82%	10	58.82%	11	64.71%	41.25 (11.96)	24.89 (3.55)
Moderate–severe	15 ≤ AHI ≤ 60 (N = 23)	11	47.83%	11	47.83%	8	34.78%	41.58 (12.22)	25.32 (3.69)
Subgroup	15 ≤ AHI ≤ 50 (N = 18)	11	61.11%	11	61.11%	8	44.44%	40.71 (12.50)	24.50 (3.55)
	15 ≤ AHI ≤ 40 (N = 15)	9	60.00%	9	60.00%	8	53.33%	43.21 (12.17)	24.30 (3.65)
	15 ≤ AHI ≤ 30 (N = 14)	9	64.29%	9	64.29%	8	57.14%	42.78 (12.51)	24.48 (3.78)
Severe subgroup	30 ≤ AHI ≤ 60 (N = 9)	2	22.22%	2	22.22%	0	0.00%	39.72 (12.24)	26.62 (3.34)
	30 ≤ AHI ≤ 50 (N = 4)	2	50.00%	2	50.00%	0	0.00%	33.48 (11.45)	25.03 (3.03)
	30 ≤ AHI ≤ 40 (N = 1)	–	–	–	–	–	–	–	–

*BMIs of the severe group were statistically different ($p < 0.05$) with those of mild–severe subgroups and moderate–severe subgroups

mostly 18 to 28 kg/m^2 with two outliers at about 33 kg/m^2. In order to generate a more precise indication range of this novel device, we dissected the standard mild, moderate, and severe groups to mild–severe, moderate–severe, and severe subgroups (Table 4). We set lower bounds of the mild–severe subgroup with a baseline AHI of 5 events/h, thus resulting in ranges between 5 and 60, 5 and 50, 5 and 40, and 5 and 30 events/h, and so forth. Three different treatment response criteria were then applied: criterion 1, AHI reduction of more than 50% from baseline; criterion 2, treated AHI lower than 20 events/h and reduction of more than 50% from baseline; criterion 3, treated AHI lower than 10 events/h. The results of the first two response criteria were the same and the efficacy of this device for moderate patients was reached using all three criteria. The range of baseline AHI between 5 and 50 events/h seemed to be a proper patient pool for this novel device as more than half of the patients would gain benefits from the device using all three criteria. The treatment response rate of the mild group was positive in only about a third of the subjects when rated by the first two criteria while it was 100% when rated by criterion 3. On the other hand, for baseline AHI between 30 and 50 events/h, a positive 50% response rate was obtained using criteria 1 and 2 but was 0% as rated by criterion 3. These groups were also compared to each other using two important risk factors of OSAS, i.e., age and the BMI. While age showed no statistical difference among all subgroups, BMI was

Table 5 Treatment response rate of the BMI groups rated by three clinical treatment response criteria

		Criterion 1 < 50% initial AHI		Criterion 2 < 50% initial AHI and Tx AHI < 20		Criterion 3 Tx AHI < 10		Age	Baseline AHI
		Responder No.	%	Responder No.	%	Responder No.	%	Mean (SD) years	Mean (SD) events/h
Asia-Pacific Non-obese group	BMI < 25 kg/m^2 (N = 14)	8	57.14%	8	57.14%	5	35.71%	42.29 (14.20)	35.72 (17.77)
Asia-Pacific Obese group	25 ≤ BMI < 27.5 kg/m^2 (N = 10)	4	33.33%	4	33.33%	3	25.00%	43.10 (10.57)	39.39 (31.46)
WHO Non-obese group	27.5 ≤ BMI < 30 kg/m^2 (N = 3)	0	0%	0	0%	0	0%	35.33 (8.08)	39.00 (31.62)
WHO Obese group	BMI ≥ 30 kg/m^2 (N = 8)	0	0%	0	0%	0	0%	40.63 (11.38)	54.53 (21.12)

significantly higher in the AHI > 30 events/h subgroup. To complete the investigation of the indication range of this device, subjects were subdivided into four groups by their BMI following the obesity classification of WHO [10] and Asia-Pacific guidelines [11] (Table 5) as all subjects in this study were Taiwanese. The positive treatment response rate of the Asia-Pacific non-obese group, i.e., BMI lower than 25 kg/m^2, was about two thirds and the obese treatment response rate was about one third of subgroups when rated using the first two treatment response criteria. Criterion 3 did not allow a good differentiation of treatment response between non-obese and obese patients. To be noted, there was no statistical difference in age or baseline AHI among all BMI subgroups.

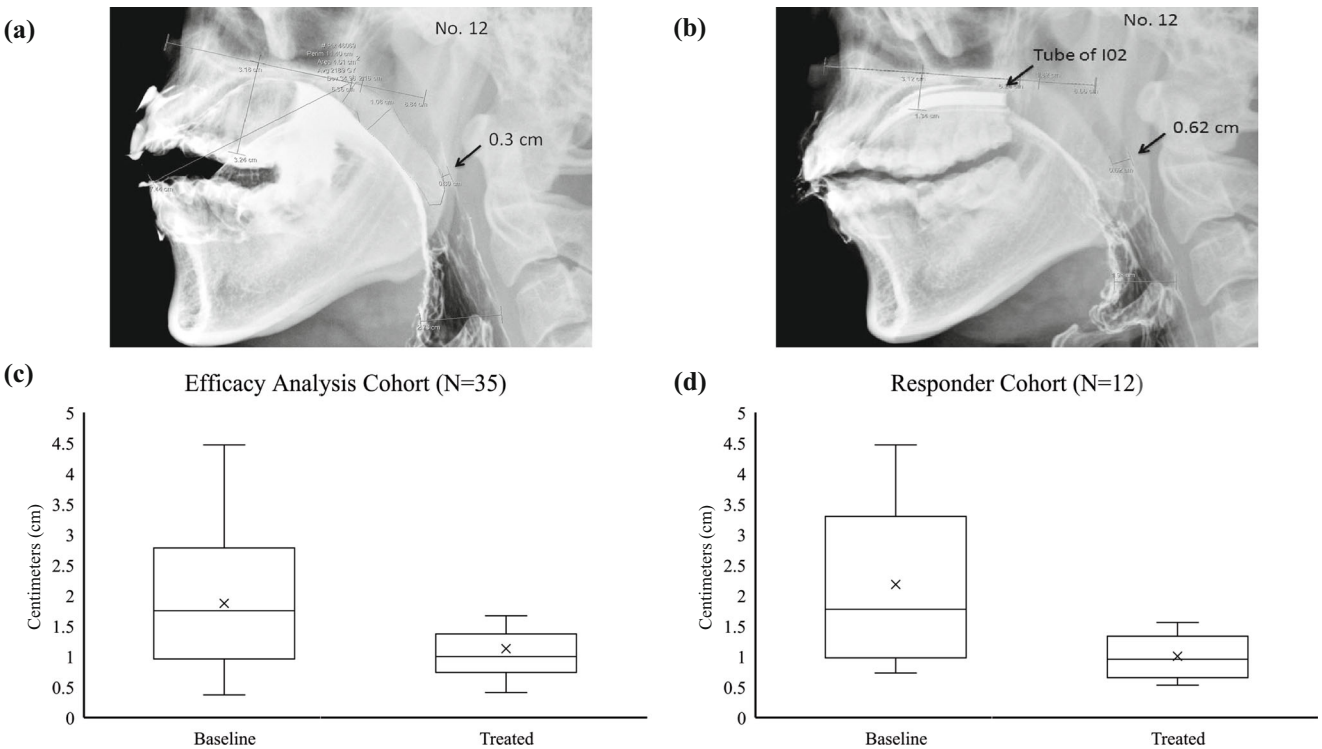

Fig. 3 Demonstration of the widening of the T-P-D by the iNAP®. **a** Untreated radiography of patient no. 12, **b** treated radiography of patient no. 12, **c** whisker plot of T-P-D (distance of the tongue or soft palate to the back wall of the upper airway) of efficacy analysis cohort, and **d** whisker plot of T-P-D of the responder cohort

Cephalometry

The device was suggested to form a closed space within the oral cavity and to bring tongue and/or soft palate forward. Therefore, the T-P-D as defined above was measured to find out if this device performed as suggested. Figure 3 shows X-rays of one patient before treatment (Fig. 3a) and during usage of device (Fig. 3b). A widening of 3.2 mm was noted during usage. The mean forward movement was 7.4 ± 10.0 mm ($p < 0.001$) in the efficacy analysis cohort (Fig. 3c) and 11.8 ± 12.5 mm ($p < 0.01$) in patients who showed a positive treatment response using criterion 2 (Fig. 3d).

Discussion

Our study aimed to investigate the full therapeutic spectrum of a new device for adults with OSAS. We enrolled patients with AHI of more than 5 events/h without setting an upper limit, achieving a study cohort with a broad spectrum of baseline AHIs ranging from 7 to 108 events/h. While not comparing the device with CPAP when evaluating a responder group, we aimed for a significant reduction of the AHI [12, 13]. We applied definitions of "treatment response" that have been used in studies assessing effectiveness surgical interventions and dental devices [14, 15] rather than "treatment cure" (i.e., AHI < 5 events/h). Despite the discrepancy of treatment response rates in the mild or the severe group as rated by the first two treatment response criteria or criterion 3, the respiratory events were statistically reduced for severe patients, especially in improving the blood oxygen saturation. Sleep latency showed a trend toward being longer in moderate and severe groups, and the arousal index was significantly reduced in the moderate ($p < 0.001$) and severe ($p < 0.01$) groups. This intermittent negative air pressure device may offer an alternative for non-obese patients with OSAS, especially those who are reported to be poorly adherent to CPAP or those with a low arousal threshold [16]. A longitudinal study with a larger population is necessary to determine longer term adherence to therapy with this device.

There is another intraoral negative pressure therapy device that has been previously approved for use by the US Food and Drug Administration [17–19]. However, the iNAP® differs from this device in two ways. Instead of compressing the tongue to form a clear space, the iNAP® merely reshapes the soft tissues into a forward-resting position. Second, without a "continuous" airstream with a vacuum, the iNAP® console stops air movement when the target negative oral pressure is reached, thereby avoiding local tissue discomfort and systematic dryness of the mouth. A favorable comparison of the two devices is shown in Table 3 (ATLAST vs iNAP®) [19]. In summary, the iNAP® device appears to be safe and has minimal side effects.

Conclusions

This feasibility study attempted to define responders to a novel intraoral negative pressure therapy device. The device increased the patency of the upper airway and was well tolerated. The study suggests that the best candidates for this device are non-obese subjects with baseline AHI between 5 and 50 events/h.

Author contributions Conception and design of this manuscript: T.C. Hung, C. Guilleminault
Acquisition of data: T.J. Liu, W. Y. Hsieh, B.N. Chen, W.K. Su
Analysis and/or interpretation of data: T.C. Hung
Drafting and revision of the manuscript: T.C. Hung
Revising and reviewing the manuscript for final releasing: K.H. Sun, C. Guilleminault

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Compliance with ethical standards

Ethical approval The study was approved by the MacKay Memorial Hospital Institutional Review Board and registered to the National Department of Health. The study was performed in accordance with applicable local regulations, International Conference on Harmonization Guidelines as well as the 1964 Declaration of Helsinki and its later amendments. All subjects were properly informed and consented to participate in this study.

Conflict of interest T.C. Hung is employed by Somnics, Inc., and is currently a PhD student at National Yang-Ming University. Besides T.C. Hung, the other authors declare that they have no conflict of interest.

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