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ORIGINAL ARTICLE

Nasal insufflation treatment adherence in obstructive sleep apnea

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Abstract
Background Nasal insufflation (NI) is a novel treatment method that has been introduced for improving respiration during sleep. NI's warmed and humidified nasal airflow provides ventilatory assistance delivered as a rapidly dispersed pressure head, with minimal side wall pressures, that may affect treatment tolerability. The aim of the current study was to investigate objective and subjective adherence rates for NI therapy in mild to moderate obstructive sleep apnea (OSA).
Methods Ten patients (three men and seven women; age, 51.3 ±9.6 years; BMI, 32.2±7.7 kg/m^2 [mean±sd]) with recently diagnosed mild to moderate OSA (10.9±5.8 events/h) were investigated. A crossover design was used to compare adherence to NI and continuous positive airway pressure (CPAP) therapy using a range of objective and subjective measurements. Objective (sleep efficiency (%) and arousal indices (arousal/h)) and subjective evaluations of sleep quality were carried out each night in the laboratory. During in-home treatment, adherence for both therapies was assessed objectively (time on therapy) and subjectively (self-reported sleep diary).
Results Objectively derived adherence values were comparable for CPAP and NI, with both treatment devices sharing similar usage per night (3.5±2.5 vs. 3.6±1.6 h/night; respectively) and the number of nights with at least 4 h of treatment (5.5±4.3 vs. 6.8±3.3 nights/trial, respectively). Self-reported adherence was significantly higher than objectively assessed adherence ($p<0.03$).
Conclusions This study showed similar adherence to NI and CPAP over a short period of usage. A randomized clinical trial is now essential for determining the comparative effectiveness of NI therapy in relation to treatment with CPAP.

Keywords Nasal cannula · Humidification · Randomized crossover design · Sleep apnea · Home therapy

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Introduction

Consequences of obstructive sleep apnea (OSA) include sleep fragmentation, metabolic dysfunction, cardiovascular disease, and increased mortality rates [1–4]. The gold standard of treatment for OSA is continuous positive airway pressure (CPAP) therapy. Various interface options are available for CPAP delivery, including nasal masks, oro-nasal masks, oral masks, and total face masks. The type of interface prescribed is likely to influence patients' acceptance of CPAP therapy and adherence to treatment [5]. Treatments such as surgery, mandibular advancement splints, and weight loss have been tried in settings where CPAP adherence is suboptimal; however, alternatives require investigation as they emerge. Nasal insufflation (NI) is a novel open cannula system that has been introduced to improve respiration during sleep; however, how

it is perceived in comparison with CPAP treatment is not known [6]. NI delivers warm, humidified air into the nasal airway at a continuous high flow rate and low pressure through a simple cannula [7]. Its primary mechanism of action is believed to occur through slight increases to end-expiratory pharyngeal pressure, thereby lowering the overall pressure levels necessary for alleviating airway obstruction [8]. The findings of McGinley et al. and Jose Haba-Rubio et al. suggest that NI could be an alternative where other methods of OSA therapy are not well tolerated [9]. To date, there have been no studies examining NI acceptability in the home setting. This study examines objective and subjective adherence to NI compared with CPAP use. We hypothesize that adherence to NI would be similar to CPAP over a short period of usage in the home setting. This study sets the foundation for randomized clinical trials that would examine the effectiveness of long-term NI use.

Methods

Ten subjects were recruited with mild to moderate OSA. Subjects were excluded if they were already receiving treatment for OSA or concurrent sleep disorders. The study was approved by the Human Research Ethics Committees of Sir Charles Gairdner Hospital and The University of Western Australia.

Study procedures

Polysomnography

Overnight assessments were conducted by a standard, full-montage in-laboratory nocturnal polysomnographic recording. Signals collected and analyzed were as follows: electroencephalograms (EEG; C3-A2, O1-A2 & Fz-A1), electrooculogram (EOG; right [ROC] and left [LOC]), submental electromyogram (EMG), electrocardiogram (ECG), inductance plethysmography (chest and abdomen), and leg EMG (left and right). Airflow signals were collected using a nasal pressure cannula or lightweight pneumotachograph.

Standard polysomnographic scoring techniques were used to stage sleep, respiratory events, and arousals which were scored according to the AASM guidelines [10]. Values of sleep efficiency, sleep latency, and arousals/hour were determined for each polysomnographic recording.

Continuous positive airway pressure

Participants used an auto-titrating nasal CPAP (6–16 cm H_2O) for the in-laboratory overnight studies and the 2-week at-home CPAP trial period. Each subject was fitted for the most appropriate size CPAP mask (ultra-mirage, ResMed Ltd, Bella vista, Australia). Each participant completed a standard training session for use of the pressure generator (S8 AutoSet Spirit ResMed, Bella vista, Australia) and CPAP mask prior to first use. Heated humidification was set at a standard level for all participants for use with the CPAP. For the home trials, an electronic data recording unit was attached to the machine to record the time spent at therapeutic pressure.

Nasal insufflation

A custom nasal airflow system was used to deliver constant flow of between 10 and 35 L/min at the nose through a nasal cannula. The airflow system was custom designed to have the outward appearance of an off-the shelf CPAP machine (S8, ResMed Inc, Bellavista, Australia). The main differences in the appearance of the nasal airflow system compared to the CPAP system were as follows: (a) the outer diameter of the tubing was smaller (11 mm), (b) the nasal CPAP mask was replaced with a custom soft silicon nasal prong interface (similar to a nasal cannula), and (c) an additional water reservoir was attached to the humidification chamber. A built-in heating pad and humidifying chamber regulated the temperature and humidity of the air delivered via the nasal prongs. A heated wire incorporated into the lumen of the nasal cannula tubing yielded a temperature of 30 to 35 °C and relative humidity of up to 90 % at the nasal outlet. Delivered airflow, temperature, humidity, and pressure were recorded by sensors located at the cannula outlet. In order to optimize user experience, we did not include instrumentation to capture nasal airflow measurement and pressure on the polysomnograph recording. An electronic data recording unit captured the airflow, temperature, humidity, and pressure delivered by the nasal airflow system while in use during the at-home trial.

Treatment adherence

There were two measures of adherence to treatment: the average usage over the 2-week home-based trial period and the number of nights with more than 4 h of treatment application.

Treatment adherence was recorded automatically on memory cards embedded within each treatment device. Participants also recorded their sleep times and treatment times using a sleep diary.

Subjective measures

Sleep quality over the 2-week trial period was assessed with the Pittsburgh Sleep Quality Index (PSQI) [11]. Quality of life was assessed using the Functional Outcomes of Sleep Questionnaire (FOSQ) [12], a 30-item OSA-specific measure of health-related quality of life. Both were modified for use across a 2-week measurement period rather than the standard

1-month period of assessment. Following each overnight sleep assessment, a morning questionnaire assessed self-reported sleep quality (SRSQ), treatment acceptability, self-efficacy, and outcome expectations. A score for overnight perceived sleep quality was derived from five items that measured perceived total sleep time, sleep latency, and arousals. Treatment acceptability was measured using a four-item questionnaire developed for the present study.

Study protocol

Each patient completed two home trials and five sleep polysomnography studies: a baseline PSG and a pair of treatment studies (Fig. 1). The first PSG, absent of any treatment devices, served as a baseline to assess initial sleep characteristics. A sleep study with concurrent treatment was conducted before each home trial period, assessing the particular device's initial treatment effects, and a follow-up treatment study was conducted after each home trial period.

Baseline sleep study

All participants first underwent baseline overnight polysomnography (PSG) to assess disease severity and initial sleep characteristics. Participants completed baseline measurements of quality of life and perceived sleep quality prior to initial treatment assessments.

Initial treatment assessment

Following baseline assessment, the order of treatments was randomized; participants returned to the sleep laboratory on two separate nights to undergo initial treatment with either CPAP or NI therapy. Each overnight study included 8 h under full treatment with concurrent PSG to assess initial treatment effects. During this time, patients were familiarized with the treatment devices and instructed by the research technician on proper usage. After each treatment night, the participants completed questionnaires assessing SRSQ, treatment acceptability, self-efficacy for treatment usage, and treatment outcome expectations.

Home trial

After initial treatment assessments and training, patients underwent 2 weeks of in-home treatment with either CPAP or NI. Patients were instructed to use their treatment device nightly and complete a sleep diary recording their device usage. Additionally, each treatment device automatically recorded and stored adherence rates over the 2-week trial. At the end of the 2 weeks, participants returned to the sleep laboratory for a post-treatment overnight evaluation with polysomnography. The following morning, the participants completed post-treatment questionnaires assessing perceived sleep quality, treatment acceptability, self-efficacy, and outcome expectations. The participants were then given the alternative treatment device (CPAP or NI) for a second 2-week home treatment period. At the end of this period, a second post-treatment overnight evaluation was conducted with the respective morning questionnaires. At the end of each 2-week trial period, the participants completed the sleep quality (PSQI) and quality of life (FOSQ) questionnaires to assess overall experiences with the treatment device.

Statistical analysis

Data are reported as means±standard deviation. Paired *t* tests were performed to compare pre-and post-treatment differences and differences between the treatment conditions, with *p* values less than 0.05 considered significant. Repeated measures factorial ANOVA was used to compare adherence rates between the treatments across the 2-week trial periods, with treatment devices (CPAP, NI) and report type (self-reported, auto-recorded) as the independent variables. Post hoc comparisons were made with Bonferroni corrections.

Results

Subject demographics

Ten subjects (three men and seven women; age, 51.3± 9.6 year; BMI, 32.2±7.7 kg/m^2) completed the study (Table 1). Our study mainly consisted people with mild disease, with mean apnea-hypopnea index (AHI) of 10.9±5.8 events/h. In general, events were predominantly obstructive, and subjects had no prior treatment exposure to any therapy for sleep apnea.

Nasal insufflation versus continuous positive airway pressure in the home setting

The objective and subjective pre- and post-treatment assessments for CPAP and NI are shown in Table 2. There was no treatment order effect. After the 2-week in-home trial period, NI therapy demonstrated an improvement in perceived sleep quality (15.6±5.4 vs. 21.9±5.1 a.u.; pre- vs. post-treatment; p=0.02) and with no change in sleep efficiency (86.8±8.8 vs. 80.5±11.3 %; p=0.18). Whereas, CPAP demonstrated no such improvements in perceived sleep quality (18.4±5.3 vs. 17.1±7.0 a.u.; p=0.65) also with no change in sleep efficiency (80.3±13.4 vs. 81.0±8.2 %; p=0.89). NI and CPAP had similar values for all other objective and subjective measurements.

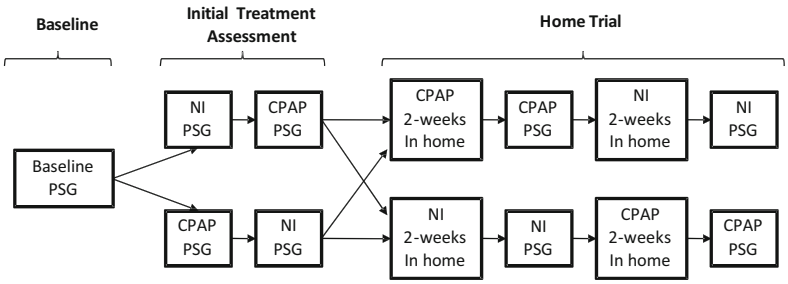

Fig. 1 Pre = PSG with therapy prior to in-home treatment period; Post = PSG with therapy following in-home treatment period. The randomized crossover study design included five overnight polysomnographic sleep study (*PSG*). Initially subjects performed a baseline diagnostic PSG and then were randomized for PSG with either CPAP or NI (nasal insufflation) treatment. On the following night, a PSG study was conducted with the alternate treatment. Each subject then had 2 weeks at home with the first treatment and then subsequently 2 weeks with the alternate treatment. There was a post-treatment PSG following each at home treatment period

Following the home trial period, NI therapy demonstrated no changes in sleep latency (11.1±10.3 vs. 7.1±8.6 %; pre- vs. post-treatment; p=0.35), hourly arousals (19.2±10.9 vs. 19.7±12.9 arousals/h; p=0.93), treatment acceptability (15.8 ±2.4 vs. 14.8±3.2 a.u.; p=0.44), self-efficacy (20.5±3.8 vs. 18.9±5.5 a.u.; p=0.46), and outcome expectations (15.5±4.4 vs. 13.8±4.5 a.u.; p=0.40). These findings are comparable to CPAP, which demonstrated no changes in sleep latency (10.8 ±13.1 vs. 9.2±10.4 %; pre- vs. post-treatment; p=0.77), hourly arousals (15.1±11.3 vs. 21.4±10.5 arousal/h; p=0.21), treatment acceptability (16.1±1.9 vs. 15.7±3.5 a.u.; p= 0.75), self-efficacy (21.2±4.0 vs. 20.7±5.1 a.u.; p=0.81), and outcome expectations (17.1±3.3 vs. 16.5±3.0 a.u.; p= 0.68).

The values for both long-term subjective sleep measurements and treatment adherence for both therapies are presented in Table 3. CPAP and NI had similar values for the PSQI (11.9±4.8 vs. 10.2±4.0

a.u., respectively) and FOSQ (14.8±3.7 vs. 14.0±3.1 a.u., respectively). Objectively derived adherence values were comparable for CPAP and NI, with both treatment devices sharing similar usage per night (3.5±2.5 vs. 3.6±1.6 h/night, respectively) and the number of nights with at least 4 h of treatment (5.5±4.3 vs. 6.8±3.3 nights/trial, respectively).

Table 1 Participant demographics and baseline sleep characteristics

Demographics	
Age (year)	51.3±9.6
Sex	3 M:7 F
BMI(kg/m$_2$)	32.2±7.7
Sleep characteristics	
TST (min)	363.8±75.2
Sleep latency(min)	30.1±30.7
Sleep efficiency	76.3±13.5
AHI (events/h)	10.9±5.8
Arousals/h	17±8.1
PSQI	11.6±4.0
FOSQ	13.8±2.8

N=10 subjects

TST total sleep time, *AHI* apnea-hypopnea index, *PSQI* Pittsburgh Sleep Quality Index, *FOSQ* Functional Outcomes of Sleep Questionnaire, *F* females, *M* males

Self-reported adherence was significantly higher than objectively assessed adherence (p<0.03).

Discussion

This study is the first of its kind to investigate adherence rates and subjective experiences for mild to moderate sleep apnea patients using NI therapy in the home setting. In our study, NI had comparable objective sleep characteristics and subjective user assessments to CPAP. Adherence rates over the 2-week trial period were similar between the two treatment devices. Previous studies have shown that the interface used, how well it fits the patient, and the air pressure level delivered are all important factors that determine adherence to treatment [6].

In this study, both treatment options used appropriately fitted nasal delivery interfaces: an ultra-mirage nasal mask for the CPAP treatment and a custom fit silicon nasal prong for the NI treatment. For CPAP, the nasal mask requires a tight seal to maximize air pressure delivered and to minimize air leak [13]. This is necessary to provide the sustained air pressure essential to splinting the airway, increasing the pharyngeal cross-sectional area, and thereby reducing supraglottic resistance [14]. NI achieves similar reduction in inspiratory resistance by providing nasopharyngeal flows that either match or exceed patient's inspiratory flow [7]. The physiological effect of NI is mediated in part through positive pressure support of the airways similar to CPAP, improvements in conductance, pulmonary compliance, and reducing energy expenditure for gas conditioning. The high gas flow, in combination with gas leak around the nostrils, contributes to dead space washout of CO_2 [15].

We did not explore treatment effectiveness in this study; however, there is work that indicates NI could be a potential treatment option for sleep apnea. Nilius et al. [16] showed that NI could be used to treat a subgroup of patients across a spectrum from mild to severe sleep apnea, particularly if their

Table 2 Objective and subjective measures for CPAP and NI treatment CPAP Nasal insufflation

	Pre	Post	Pre	Post
Objective				
Sleep Efficiency (%)	80.3±13.4	81.0±8.2	80.5±11.3	86.8±8.8
Sleep Latency (min)	10.8±13.1	9.2±10.4	11.1±10.3	7.1±8.6
Arousals/hr	15.1 ± 11.3	21.4 ± 10.5	19.2 ± 10.9	19.7 ± 12.9
Subjective				
Sleep quality (a.u.)	18.4±5.3	17.1±7.0	15.6±5.4	21.9±5.1
Treatment acceptability (a.u.)	16.1±1.9	15.7±3.5	15.8±2.4	14.8±3.2
Self-efficacy (a.u.)	21.2±4.0	20.7±5.1	20.5±3.8	18.9±5.5
Outcome expectations (a.u.)	17.1±3.3	16.5±3.0	15.5±4.4	13.8±4.5

Pre PSG with therapy prior to in-home treatment period, *Post* PSG with therapy following in-home treatment period

sleep-disordered breathing events predominantly consist of obstructive hypopneas or REM-related events but not obstructive and central apneas. In another study, Nilius et al. [17] demonstrated that high flow NI improved efficiency of breathing and may be used as an adjunct to low flow oxygen for preventing hypercapnic respiratory failure in severely ill COPD patients. Overlap syndrome which is defined as co-existence of COPD and OSA could be investigated as a therapeutic target for NI. CPAP, on the other hand, has also been shown to reduce mortality in overlap syndrome [18, 19]. While these results are still preliminary, this patient population could serve as an interesting subgroup on which to investigate and compare the treatment effects of CPAP and NI.

Humidification is an established factor that contributes to CPAP adherence [20]; therefore, it is possible that the humidity delivered by NI may also have added to treatment acceptance. Nasal dryness and/or stuffiness with CPAP use are traditional complaints associated with suboptimal humidification [21]. While ambient conditions and personal preferences contribute, the established range of humidification for CPAP is from 0 to 90 % relative humidity. NI allows for tightly controlled high level of humidification (85–95 %) at airflow rates of ≥30 L/min with pressure of between 2 and 3 cm H_2O. The delivery mode of NI and CPAP thus provide different levels of humidification at lower pressures, which may in turn lead to differences in perception and explain the higher positive subjective feedback noticed with NI use albeit not statistically significant. In this study, both CPAP and NI humidity levels were standardized for all participants; however, individual humidification optimization may be a factor that contributes to higher comfort levels and better adherence.

Table 3 Treatment comparison CPAP vs. NI

	CPAP	NI
Subjective Measures		
PSQI	11.9±4.8	10.2±4.0
FOSQ	14.8±3.7	14.0±3.1
Adherence		
Self-reported		
Usage (h/night)	4.3±2.1	5.0±2.2
Nights >4 h	8.3±4.8	9.0±4.1
Auto-recorded		
Usage (h/night)	3.5±2.5	3.6±1.6
Nights >4 h	5.5±4.3	6.8±3.3

Values are means +/- SD

PSQI Pittsburgh Sleep Quality Index, *FOSQ* Functional Outcomes of Sleep Questionnaire

Treatment adherence was also likely to be modified by psychological factors [22]. Hoffstein [23] found that the perception of treatment benefit did not relate to actual objective findings, highlighting the importance of patients' experiences and beliefs. Our study examined the subjective experiences associated with each treatment device. Sawyer et al. [24] identified self-efficacy and outcome expectancies as important psychological factors, which, along with AHI, mediated the relationship of 3-month CPAP adherence. Self-efficacy, defined as the confidence that one has that he/she can make a given health behavior change during times when such a change is difficult, in particular, was measured to be significantly influential on 1 week and 1 month of CPAP use. This is hardly surprising as health psychologists have previously shown self-efficacy to be one of the primary predictors of behavior change and a target for intervention [25].

Objectively derived adherence values were comparable for CPAP and NI, with both treatment devices sharing similar usage per night. CPAP adherence studies have shown that of those who do initially accept the treatment and take it home, 25–50 % fail to adhere optimally to the treatment, and in the long-term, up to 25 % of patients stop using the CPAP treatment by the third year [26, 27]. Given the similarities of adherence rates in this study, NI long-term use may be estimated, if short-term adherence is a predictor. Factors such as disease severity, insurance requirements, and cost may be important considerations in such projections.

NI had comparable measurements to CPAP in self-efficacy and outcome expectancies, a result consistent with the similar

adherence rates observed for NI therapy and CPAP. Few studies have successfully established prediction factors for adherence. Although it has been shown that correlations exist between CPAP adherence and clinical variables, such as disease severity and sleepiness [28–31], these relationships consistently suffer from inadequate robustness and thus are limited in their predictive power. Further investigations into the efficacy and side effect profile of NI are required; a randomized clinical trial is now essential for determining the comparative effectiveness of NI therapy in relation to treatment with CPAP.

Limitations

The study was limited by several factors. In the current study, we did not include a second nasal pressure cannula to the polysomnographic recording during the overnight studies with NI. While the setup of the nasal cannula reflected the long-term use configuration, this prevented the detection of sleep-disordered breathing events. We believe our results would have approached greater significance with a larger sample size. Post hoc power calculations revealed that a sample size of N=25 would be adequate to detect statistical significance in the observed improvements in sleep efficiency, PSQI, and the changes in the FOSQ. Larger sample size would also allow the use of further regression analyses for determining factors that may be predictors of adherence and PSQ. The FOSQ and PSQI have been validated for a 4-week period and may not be sensitive to changes within a 2-week period. Tsara et al. [32] showed that quality of life improvements are greater in more severe OSA, suggesting that the disease severity of our participants may not have been severe enough to exhibit QOL improvements. Participants were not immediately recruited following their diagnostic sleep study, preventing us from controlling for possible maturation effects.

Implications

CPAP and NI work via distinct mechanisms; however, NI provides the closest visual resemblance to CPAP among existing alternatives. Following better characterization of its efficacy profile, NI could be used as a therapeutic placebo in double-blinded crossover trials designed to determine isolated effects of both treatment options. In selected patient populations such as those with overlap syndrome, NI presents the possibility of a unique treatment choice owing to its physiologic effects of lowering CO_2 and increasing end expiratory pressure [17].

Subsequently, physiologic studies investigating gender-specific effects of NI variation on upper airway critical closing pressure (Pcrit), ventilatory instability, and sleep architecture may broaden our understanding of the pathophysiology of sleep-disordered breathing.

Conclusions

This study showed similar adherence to NI and CPAP over a short period of usage. A randomized clinical trial is recommended as the next step in determining the comparative efficacy of NI therapy in relation to treatment with CPAP and also to characterize the side effects of NI since those of CPAP are already well known. Following more robust studies, we suggest that NI could be considered in the setting of mild to moderate OSA, as it may suit a subset of patients with characteristic treatment or tolerance problems.

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Conflict of interest In the past 12 months, Dr. Kirkness has served as a scientific consultant for in Sleep Technologies and received grant and study support from the American Heart Association 12SDG8100000, NIH NHLBI-HL105546, and ResMed Science Center that are managed by the Johns Hopkins School of Medicine Office of Policy Coordination. No other conflicts.

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