Use of heated humidification during nasal CPAP titration in obstructive sleep apnoea syndrome

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ABSTRACT: Nasal symptoms associated with the use of nasal continuous positive airway pressure (nCPAP) in obstructive sleep apnoea (OSA) can adversely impact on patients' tolerance, acceptance and adherence to nCPAP therapy. Regular use of heated humidification is effective in alleviating these symptoms and improve patient comfort.

In a randomised, parallel, double-blinded, controlled study, the present authors examined the use of heated humidification during a single night laboratory nCPAP titration in untreated OSA patients and its effect on nasal symptoms, nasal airway resistance (NAR), effective pressure and treatment tolerability and acceptance.

Baseline characteristics of subjects (n=70) receiving placebo and humidification were (mean $\pm$ SEM): age 51.2 ± 2.2 versus 50.6 ± 1.6 yrs; body mass index 33.6 ± 0.9 versus 35.2 ± 0.9 kg·m⁻²; Epworth Sleepiness Scale 10.8 ± 1.0 versus 11.3 ± 0.7 ; and apnoea-hypopnoea index 43.5 ± 4.6 versus 44.4 ± 4.1 events·h⁻¹. Total inspiratory NAR, before (0.36 ± 0.09 (placebo) versus 0.33 ± 0.09 kPa·L⁻¹·s⁻¹) and after nCPAP (0.47 ± 0.11 versus 0.29 ± 0.04 kPa·L⁻¹·s⁻¹) were not significantly different between the groups. No difference was found in the frequency and severity of nasopharyngeal symptoms, therapeutic pressure and subjective response to nCPAP.

In conclusion, heated humidification during the initial nasal continuous positive airway pressure titration offers no additional benefit in nasal physiology, symptoms or subjective response to nasal continuous positive airway pressure, and, therefore, should not be routinely recommended.

KEYWORDS: Continuous positive airway pressure titration, heated humidification, nasopharyngeal side-effects, obstructive sleep apnoea syndrome, rhinomanometry, upper airway

Nasal continuous positive airway pressure (nCPAP) is currently the treatment of choice for symptomatic obstructive sleep apnoea syndrome (OSAS). Its effectiveness has been well documented [1–4], but the rate of acceptance and long-term adherence to this treatment remain suboptimal [5, 6]; namely, being compromised by unwanted psychosocial and physical side-effects [7–10].

Adverse symptoms of the upper airway are commonly reported with nCPAP [10, 11], which can be alleviated with the regular use of heated humidification [12–14]. Under experimental conditions, the administration of nCPAP in the presence of mouth leaks leads to the appearance of nasopharyngeal symptoms and a rise in nasal airway resistance (NAR). The latter was attenuated with heated humidification and is thought to form the physiological basis for the improvement in symptoms and compliance rates observed in clinical studies [15].

Since the early experience with nCPAP may influence acceptance and long-term adherence [3, 16–18], the aim of the present study was to investigate the benefit of adding heated humidification to nCPAP on the first night of titration. The current authors hypothesised that humidification would prevent a rise in NAR, significantly reduce the incidence and severity of nasal symptoms, and improve the efficiency of CPAP delivery to the collapsible (pharyngeal) airway segment, thereby lowering the therapeutic positive pressure required. As a result of these mechanisms, heated humidification during the first night might promote increased initial acceptance and potentially future adherence to therapy. Therefore, in a parallel, randomised, placebo-controlled, double-blinded study, the effect of heated humidification on: 1) total NAR; 2) effective CPAP; 3) the frequency and severity of nasopharyngeal symptoms; and 4) nCPAP tolerability and predicted future use were assessed.

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METHODS

Study design

A total of 70 untreated OSAS patients (aged ≥ 18 yrs) referred for a full overnight polysomnographic nCPAP titration were consecutively enrolled during the year 2001. The exclusion criteria were: 1) significant psychiatric, respiratory and cardiovascular co-morbidities; 2) supplementary oxygen; 3) significant nasal obstruction precluding nCPAP use; 4) previous surgical intervention for OSAS; and 5) inability to provide informed written consent. On the night of the titration, Epworth Sleepiness Scale (ESS) and NAR measurements were obtained. Randomisation to active (Sullivan HumidAire; Resmed, Sydney, Australia) or placebo treatment (HumidAire with a disabled heater, a perspex baffle with equivalent dead space, without water and a cover to mask the humidifier contents) was performed by a daytime technician who did not communicate between subjects or overnight staff. Humidifiers were connected to nCPAP (Sullivan Elite; Resmed) according to the manufacturer's recommendations and administered *via* a fitted Mirage nasal mask (Res Med Ltd, North Ryde, NSW, Australia). The humidifier setting was routinely set at six (out of eight), which in the experience of the present authors provided the optimal level of humidification without significant condensation. The following morning, NAR measurements were repeated and subjects filled out a questionnaire. The study was approved by the Repatriation General Hospital Ethics Committee, South Australia.

CPAP titration

The Sleepwatch (Compumedics, Melbourne, Australia) system was used to record electroencephalogram (EEG) (C_4A_1/C_3A_2), bilateral electro-oculogram, submental electromyogram, nasal airflow (pressure transducer), body position (mercury switch), and leg movements (piezo-electric sensors). ECG, oxygen saturation (OxiRadometer; Radiometer, Copenhagen, Denmark), mask pressure, ribcage and abdominal movements by respiratory inductance plethysmography were also monitored. Sleep stages were manually scored according to RECHTSCHAFFEN and KALES [19]. Obstructive apnoea was defined as $<20\%$ airflow lasting ≥ 10 s with ongoing respiratory efforts. Hypopnoea was defined as $>50\%$ diminution in the amplitude of two out of three respiratory channels (airflow, thoracic and abdominal) lasting ≥ 10 s. The severity of OSAS was expressed as the total apnoea and hypopnoea events per hour of sleep time. Overnight titration was performed by a sleep technologist. Starting with the lowest tolerated pressure (4 cmH₂O), increments of 1 cmH₂O were added for obstructive apnoea events or hypopnoea preceding EEG arousals. Subjects had to lie on their back for at least one rapid eye movement (REM) period during the study. An effective CPAP was reached when respiratory events, desaturation and respiratory event-related arousals were eliminated. Mouth leaks were monitored for by close observation for mouth opening, expiratory mouth air venting on video monitoring or spontaneous fluctuations (fall) in baseline CPAP level. If any of these changes occurred, a chinstrap was applied. The therapeutic CPAP was determined by a sleep physician (L. Jayaram) based on the pressure that controlled obstructive events during supine REM sleep. If supine REM sleep was not sampled, the pressure required to control respiratory events during non-supine REM sleep was determined. If obstructive events were

not completely controlled during REM sleep, 2 cmH₂O was added to the final pressure. In instances where the CPAP that controlled respiratory events during REM sleep did not exceed that for non-REM sleep, then the therapeutic non-REM CPAP level was recommended.

Questionnaire

A questionnaire was used to document baseline characteristics and the subjective responses following overnight nCPAP. Subjects were asked to rate: 1) their quality of sleep; 2) the feeling of morning freshness (1=worse, 2=same and 3=better than usual); 3) nCPAP tolerability (1=poor, 2=fair, 3=good and 4=very well); 4) predicted future use (1=refuse, 2=intermittent, 3=frequent and 4=all the time); and 5) the occurrence and severity of nasal side-effects (nasal stuffiness, discharge, burning, sore throat and dry mouth) on a 10 cm visual analogue scale (VAS).

Nasal airway resistance

Anterior active rhinomanometry (Masterscope Rhino; Jaeger, Hoechberg, Germany) was performed with a face-mask in accordance with the International Committee on Objective Assessment of the Nasal Airways [20]. Measurements were taken after 15 min in the seated and supine positions during quiet breathing with mouth closed. A minimum of three reproducible curves were recorded from each nostril and the average curve taken as representative. Inspiratory and expiratory NAR obtained from each nostril at a transnasal pressure of 150 Pa were used to calculate the total nasal resistance (R_{Total}):

$$1/R_{Total} = 1/R_L + 1/R_R \quad (1)$$

R_L and R_R are the left and right nasal resistances, respectively.

Statistical analysis

Data are expressed as mean $\pm$ SEM. Log transformation of data, which were not normally distributed, was performed prior to the analysis. Comparisons between group means were performed with the unpaired t-test and between proportions by the Chi-squared statistic. A two-tailed p-value <0.05 was accepted as significant.

RESULTS

Baseline characteristics were similarly distributed between groups (table 1). Up to half of the subjects reported allergic rhinitis with similar proportions admitted to using nasal corticosteroids in the previous 12 months. During this period, the most frequently reported nasosinus symptom was nasal stuffiness, followed by sore throat (23–28%) and runny nose (7–17%).

Two subjects (one placebo, one humidification) were intolerant to nCPAP and titration was stopped within 2 h of commencing therapy due to claustrophobia from the mask. Their data were excluded from subsequent analysis.

Nasal airway resistance

A total of 48 (70.6%) subjects had technically acceptable NAR data (*i.e.* free from nonzero baseline offset, and inspiratory and expiratory transnasal pressures achieved the requisite 150 Pa in both nostrils). Comparisons of baseline characteristics and outcome variables between subjects, with and without missing

TABLE 1 Subject characteristics

Variables	Placebo	Heated humidification [#]
Subjects n	36	34
Sex M:F	34:2	28:6
Age yrs	51.2±2.2 (20–72)	50.6±1.6 (28–67)
BMI kg·m⁻²	33.6±0.9 (25.3–44.6)	35.2±0.9 (27.2–48.7)
ESS[†]	10.8±1.0 (0–23)	11.3±0.7 (3–19)
AHI events·h⁻¹	43.5±4.6 (6.2–111.7)	44.4±4.1 (2.7–82.8)
Nadir Sa_{o2} %	82.4±1.2 (65–93)	80.6±1.8 (59–97)
History of oral-facial surgery %	17	33
History of allergic rhinitis %	37	50
History of nasal stuffiness[‡] %		
Never	9	10
Occasional	37	37
Frequent	54	53
History of runny nose[‡] %		
Never	6	21
Occasional	77	72
Frequent	17	7
History of sore throat[‡] %		
Never	27	17
Occasional	50	55
Frequent	23	28
Nasal steroids use[‡] %	46	40

Data are presented as mean±SEM (range), n or the percentage of subjects within the treatment group. M: male; F: female; BMI: body mass index; ESS: Epworth Sleepiness Scale; AHI: apnoea-hypopnoea episodes per hour of sleep; Nadir Sa_{o2}: lowest oxygen saturation during sleep. [#]: between group comparisons with unpaired t-test and Chi-squared test (all p-values >0.05); [†]: score ranges from 0–24, where 24 is the worst score attainable; [‡]: symptoms in the last 12 months.

data, did not demonstrate any significant differences, except for body mass index (31.3±0.86 (missing data subjects) *versus* 35.7±0.83 kg·m⁻²; p=0.002).

Total inspiratory NAR, performed in the seated and supine positions (both pm) prior to nCPAP application, were not significantly different between placebo and heated humidification groups (table 2; fig. 1). Similarly, measurements taken the following morning (supine; am) and the difference between the morning relative to evening (before and after nCPAP) measurements, calculated as a percentage change (am-pm % = am-pm/pm × 100), were not significantly different between groups (fig. 1). Analysis of the expiratory NAR data provided similar findings (table 2).

CPAP pressure

The mean effective CPAP levels for the two groups were not significantly different (table 2).

Nasosinus symptoms

A total of 64 subjects (94%) completed the questionnaire the following morning. Of these, 92% reported experiencing at least one upper airway symptom during the night. The frequency of reported nasal stuffiness, discharge, burning,

sore throat and dry mouth in the placebo group were 71%, 32%, 41%, 47% and 82%, respectively (fig. 2). This was similar and not significantly different to the humidification group (all Chi-squared statistic p-values >0.05). Also, the severity rated on VAS for each symptom and the composite score were not significantly different between the groups (table 2). In general, the symptoms were mild with the majority (>88%) of responses being rated ≤5 cm on a 10 cm VAS.

Subjective response

Over one-third of the subjects in this study reported an improvement in sleep quality and feeling refreshed with nCPAP (fig. 3), with no differences seen between treatment groups (Chi-squared statistic; p>0.05). The majority were able to tolerate nCPAP (≤10% reported poor tolerability) and, after the one night experience, >80% of subjects predicted that their use of the device would be on a frequent-to-regular basis. Again, the ratings for these responses were comparable between groups (Chi-squared statistic; p>0.05). No subjects who completed the titration study refused nCPAP therapy.

Post hoc subgroup analyses

Whilst the above results showed no benefit from heated humidification, there remained the possibility that some subgroups may benefit. Therefore, subgroup analyses were performed on subjects who reported, at baseline, a) “frequent or regular nasal stuffiness” (n=40); b) high inspiratory NAR (*i.e.* above the group median >0.20 kPa·L⁻¹·s⁻¹; n=26); and c) high CPAP (>10 cmH₂O; n=24). In none of these groups was any significant benefit shown for humidification *versus* placebo, on morning nasal symptoms, NAR and subjective responses, including tolerability and acceptability of treatment.

DISCUSSION

The findings from the present study indicate that the use of heated humidification during the initial titration study of nCPAP offers no additional benefit with respect to NAR, nasal symptoms, therapeutic CPAP level, subject response and the acceptance of therapy. This is in agreement with the only other randomised controlled study, which has examined the effects of heated humidification administered at the time of nCPAP initiation [21]. Contrary to these observations, the application of heated humidification in patients selected for chronic nasal/oral symptoms has been shown to improve nasal symptoms, patient comfort and compliance [12, 22, 23]. Even among unselected groups of patients, such as those included in the current study, heated humidification given over a longer duration (≥3 weeks) has been reported to reduce the incidence and severity of nasopharyngeal symptoms [13, 14, 24, 25]. However, in the latter case, the effect on nCPAP compliance and patient satisfaction has not consistently been in favour of heated humidification over placebo.

There are several potential reasons for the lack of positive findings in the present study. First, the application of heated humidification for one night may be insufficient to derive the benefits seen with more regular use. Systematic use of heated humidification over longer periods of time have been shown by other studies to offer advantages on patient comfort, acceptance and compliance to nCPAP [13, 14, 24, 25]. Secondly, the severity of nasopharyngeal symptoms in the subjects presented here was mild with generally low mean

TABLE 2 Results of the placebo and heated humidification group

Variables	Placebo	Heated humidification	p-value
Subjects n	26	22	
Total inspiratory NAR kPa·L⁻¹·s⁻¹			
Seated: pm	0.32±0.06 (0.1–1.61)	0.30±0.04 (0.08–0.83)	0.89
Supine: pm (before nCPAP)	0.36±0.09 (0.06–2.5)	0.33±0.09 (0.02–2.10)	0.66
Supine: am (after nCPAP)	0.47±0.11 (0.1–2.96)	0.29±0.04 (0.08–0.67)	0.29
am-pm difference %	278±221 (-81–5281)	27.5±13.3 (-93–139.5)	0.32
Total expiratory NAR kPa·L⁻¹·s⁻¹			
Seated	0.31±0.03 (0.07–0.8)	0.38±0.06 (0.07–1.2)	0.46
Supine: pm (before nCPAP)	0.38±0.06 (0.05–1.4)	0.53±0.27 (0.07–5.9)	0.85
Supine: am (after nCPAP)	0.41±0.10 (0.12–2.7)	0.34±0.05 (0.07–1.0)	0.77
Effective CPAP cmH₂O	9.95±0.58 (6.0–18.5)	10.16±0.74 (4.0–19.0)	0.91
Symptom score on VAS (worse=10 cm)			
Nasal stuffiness	2.68±0.45 (0.0–8.0)	2.33±0.53 (0.0–10.0)	0.81
Runny nose	0.33±0.14 (0.0–4.5)	0.47±0.18 (0.0–4.9)	0.38
Burning nose	1.06±0.36 (0.0–7.5)	0.86±0.26 (0.0–4.7)	0.84
Sore throat	0.68±0.19 (0.0–4.2)	1.40±0.38 (0.0–9.3)	0.15
Dry throat	2.45±0.38 (0.0–8.5)	3.88±0.54 (0.0–9.3)	0.23
Composite VAS (worse=50 cm)	7.20±1.02 (0.0–19.5)	8.95±1.27 (0.0–24.6)	0.48

Data presented as mean±SEM (range). NAR: nasal airway resistance; nCPAP: nasal continuous positive airway pressure; VAS: visual analogue score on a 10 cm scale (very severe=10 cm) am-pm difference %: (am-pm)/pm × 100. All p-values were obtained using unpaired t-test after log transformation of data.

scores in the placebo group. This may be related to the relatively brief exposure to nCPAP, which in this case was a single night application compared with longer exposures in patients already established on treatment. In the current scenario, any improvement in symptom severity from humidification (*i.e.* the effect size) would be expected to be quantitatively small and, therefore, may require a larger

sample size to detect a difference. In contrast, prolonged nCPAP use may give rise to more severe symptoms, where a greater benefit may be obtained from heated humidification. Indeed, if the current authors had examined the effect of humidification at a later time point or with longer nCPAP use, the findings might have been different. However, the focus of the present study was to address the effects of humidification during nCPAP therapy initiation; the motivation being that this strategy may potentially reduce the reported 20–42% refusal rate that follows the first night titration, for reasons

FIGURE 1. Total inspiratory nasal airway resistance (NAR) measured at different time points: pm before nasal continuous positive airway pressure (nCPAP) in the seated and supine positions; the next am after nCPAP; and the percentage increase in am relative to pm value for placebo and humidification groups. Data are expressed as mean±se am-pm difference (diff. %)=(am-pm)/pm × 100. □: placebo; ■: humidifier. NS: nonsignificant.

FIGURE 2. Number of subjects (presented as the percentage within each group) reporting nasopharyngeal symptoms related to nasal continuous positive airway pressure by treatment groups. □: placebo; ■: humidifier. Comparisons between proportions of subjects were performed using the Chi-squared test. All p-values > 0.05.

relating to nasal and mask intolerance [5, 26, 27]. Furthermore, anecdotal evidence suggests that subsequent trials with nCPAP following an unsuccessful first attempt often lead to further failure [26]. Finally, it is possible that the scales and the questionnaire used may lack sensitivity. This was considered unlikely, as similar scales and questionnaires have been used in other studies with positive results [13, 14, 24].

The relationship between the acceptance and adherence of nCPAP to adverse nasopharyngeal symptoms has previously been examined. Earlier studies which relied on patient-administered questionnaires were unable to demonstrate a correlation between the prevalence of nasal symptoms and the rates of nCPAP acceptance [26, 28]. The presented results are in keeping with these findings. However, patients who refused or eventually stopped therapy were reported to give nasal symptoms, along with other reasons, as a cause for treatment discontinuation [26, 27]. Without the consideration of potential confounders, such as OSAS severity, comorbidity, co-interventions, and patient's psychosocial background, this may have led to conclusions that overestimated the causal role of nasal symptoms in the refusal of therapy. Studies that have examined the relationship between nasal symptoms and nCPAP compliance have reported conflicting results. Using inbuilt CPAP monitors to quantify compliance and the pattern of use, some studies have demonstrated similar rates of nasal/

oral side-effects between compliant (>4 h·night⁻¹) and less compliant patients [7, 10]. In contrast, another study showed that patients who complained of nasal problems tended to use nCPAP less than those who reported no problems [9]. Furthermore, heated and cold pass-over humidification have been shown to be equally efficacious in reducing nasal symptoms, and yet have varying effects on nCPAP compliance [13, 14, 25]. These inconsistencies across different studies suggest that the relationship between nasal symptoms and compliance is unlikely to be straightforward. It needs to be considered in a framework that takes into account the dynamic interplay between physical and psychosocial factors. Although the present results are more relevant to the issue of therapy acceptance, some of the findings are informative regarding likely future therapy adherence, as it reflects on the patient's level of motivation and attitude towards therapy.

In the current cohort of untreated OSAS subjects, up to 92% reported experiencing at least one nasopharyngeal symptom during the night. This rate is higher than that expected for long-term nCPAP users [7, 10, 27, 28] and may reflect the difference in the current population and study design. Few studies have provided details of pre-existing nasal conditions prior to the commencement of nCPAP [7, 10, 27–29]. Half of the subjects in the present study indicated a history of allergic rhinitis and having experienced frequent nasal symptoms in

FIGURE 3. Number of subjects (presented as the percentage within groups) rating response to nasal continuous positive airway pressure (nCPAP) for a) sleep quality, b) feeling of freshness on awakening, c) nCPAP tolerance and d) predicted use of nCPAP. □: placebo; ■: humidifier. Comparisons between groups was performed using the Chi-squared test. All p-values >0.05 .

the past year. Disorders of the upper respiratory tract may increase the risk and severity of OSAS [30, 31] and, similarly, may contribute to the development of adverse symptoms with nCPAP [32]. Furthermore, the present authors administered the questionnaire immediately following nCPAP, which may have led to a higher rate of positive response compared with studies that have relied on patient recall over a period of time.

Whilst the overall prevalence of nasopharyngeal symptoms was high, the severity was mild and did not appear to adversely impact on subject tolerability or prediction of nCPAP use. Direct comparison of the current results to previous studies is difficult due to the paucity of data pertaining to the severity of nasal symptoms. However, based on reported percentages of patients requiring treatment for nasopharyngeal side-effects, the prevalence of distressing symptoms can be estimated to be 38–56% amongst long-term nCPAP users [23, 29]. In contrast, the authors found <20% of the responses being rated ≥ 5 on VAS (10 being the most severe) in this study. As previously mentioned, it is probable that a single night of nCPAP may result in milder symptoms, whereas higher rates of distressing symptoms are more likely associated with prolonged use.

In subjects with and without OSAS, the presence of mouth leaks during nCPAP leads to an excessive drying of the nasal mucosa, increase in NAR, release of inflammatory mediators and the development of upper airway symptoms. Heated humidification significantly attenuates these responses and alleviates symptoms [15, 22, 33]. In the present study, NAR tended to rise following overnight nCPAP, particularly in the placebo group. However, the difference in morning NAR did not reach statistical significance between the groups. Similarly, the mean NAR change with nCPAP was higher in the placebo group compared with the heated humidification group (278% *versus* 28%), but this result was heavily influenced by three subjects who experienced major rises in NAR. By their nature, NAR measurements are widely variable and large sample sizes are likely required to detect a small-to-moderate effect of humidification. Based on a night-to-morning coefficient of variation of NAR in the order of 40%, the current authors estimated that a sample size of 48 patients was sufficient to detect a real difference of 33% between treatment arms (80% power; two-tailed level 0.05). Differences of this magnitude or less would be unlikely to be of clinical significance. Consequently, the present authors believe that the absence of a NAR difference between groups is unlikely to reflect a type-II error. Furthermore, the rise in NAR that has been reported with nCPAP in the presence of mouth leaks [15, 22, 33] under experimental conditions has not been confirmed in unselected groups of patients in the setting of acute [34] or chronic nCPAP application [35]. Perhaps the practice of applying chinstraps in cases of suspected mouth leaks in the current study may have significantly affected the severity and proportion of subjects who would have otherwise had an adverse response to nCPAP.

While no benefit could be demonstrated for heated humidification in the overall group, subgroup analyses similarly did not confirm a benefit for subjects with significant pre-existing nasal symptoms, increased baseline NAR or those requiring high CPAP (possibly predisposing them to mouth leaks and more naso-sinus symptoms). However, it must be

acknowledged that smaller sample sizes in these groups increase the risk of a type-II statistical error.

In conclusion, the present authors found, in a group of unselected patients presenting for nasal continuous positive airway pressure initiation, a high rate of reported mild upper airway symptoms both preceding and following a single night of nasal continuous positive airway pressure treatment. Despite the relatively high frequency of nasopharyngeal symptoms, the application of heated humidification during the initial nasal continuous positive airway pressure titration did not confer any benefit over placebo in regards to nasal physiology, nasal/oral adverse events, patient tolerance and attitude to nasal continuous positive airway pressure therapy. The presented results do not support the routine use of heated humidification during first night nasal continuous positive airway pressure titration studies and suggest that, in instances where this might already be routine practice, significant savings in technicians' time might be possible.

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