CLINICAL SCIENCE

The use of nasal dilator strips as a placebo for trials evaluating continuous positive airway pressure

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OBJECTIVES: The aim of the current study was to compare the objective and subjective effects of continuous positive airway pressure to the use of nasal dilator strips in patients with acromegaly and moderate to severe obstructive sleep apnea.

METHODS: We studied 12 patients with acromegaly and moderate to severe obstructive sleep apnea (male/females = 8/4, age = 52 ± 8 ys, body mass index = 33.5 ± 4.6 Kg/m^2, apnea–hypopnea index = 38 ± 14 events/h) who had been included in a randomized, crossover study to receive three months of treatment with continuous positive airway pressure and nasal dilator strips. All patients were evaluated at study entry and at the end of each treatment by polysomnography, and Epworth Sleepiness Scale, Pittsburgh Sleep Quality Index and treatment satisfaction questionnaires. ClinicalTrials.gov: NCT01265121

RESULTS: The apnea–hypopnea index values decreased significantly with continuous positive airway pressure treatment but did not change with the use of nasal dilator strips. All of the subjective symptoms improved with both treatments, but these improvements were significantly greater with continuous positive airway pressure than with the nasal dilator strips.

CONCLUSION: The use of nasal dilator strips had a much smaller effect on the severity of obstructive sleep apnea in patients with acromegaly and moderate to severe obstructive sleep apnea in comparison to the use of continuous positive airway pressure. Moreover, the improvement in several subjective parameters without any significant objective improvement in obstructive sleep apnea resulting from the use of nasal dilator strips is compatible with a placebo effect.

KEYWORDS: Obstructive Sleep Apnea; Continuous Positive Airway Pressure; Nasal Dilator Strips; Acromegaly; Placebo.

INTRODUCTION

Obstructive sleep apnea (OSA) is a disease characterized by repeated episodes of complete (apneas) or partial (hypopneas) cessations of breathing during sleep, which lead to intermittent hypoxia and disrupted sleep (1). OSA is common among the general population and is associated with multiple health problems. Continuous positive airway pressure (CPAP) is the treatment of the choice for patients with moderate to severe OSA (2). CPAP can improve sleep architecture, reduce daytime sleepiness, improve mood, and reduce automobile accidents (3). There is growing evidence that the treatment of OSA with CPAP can also improve several cardiovascular and metabolic outcomes, and this treatment has been associated with a decrease in deaths due to cardiovascular issues (4). Data from observational studies highlight the necessity of randomized controlled trials (RCTs) to evaluate the effects of CPAP in patients with OSA in regards to several outcome measurements.

Numerous RCTs have compared the effectiveness of CPAP to that offered by various control therapies, including conventional care (5), placebo tablets (6), nasal dilator strips (NDSs) (7), and sham CPAP (8). Several authors have argued that sham CPAP should be the placebo intervention of choice in RCTs. Sham CPAP consists of a CPAP machine that is modified to contain a large hidden leak in the exhaust port of the mask to disperse the therapeutic pressure, resulting in a

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pressure level at the mask interface of generally less than 2 cm H_2O (9). However, the placebo effects of sham CPAP may be partially hampered by the discomfort and frustration caused by the necessity of wearing a mask every night with delivery of suboptimal pressure support (10). The Apnea Positive Pressure Long-Term Efficacy Study (APPLES) (11) randomized participants to receive six months of active or sham CPAP, and the results found that not only was adherence to sham CPAP significantly lower than the adherence to active CPAP (3.4 vs. 4.2 hours) but that overall study retention was lower in the sham group compared to the active CPAP group (S Quan, personal communication). These results suggest that sham CPAP may not only adversely influence sleep–related outcomes but may also adversely influence the integrity of a given study. Despite the need to understand the merits and limitations of using alternative control interventions in trials of CPAP, there has been a lack of research specifically focused on the impact of alternative control interventions on participant adherence, sleep quality, and other study outcomes.

NDSs have been designed to mechanically pull the lateral walls of the nasal vestibule outwards, which dilates the valve area of the nasal cavity and renders the vestibular wall stable and resistant to collapse. The strip is placed superior to the alar cartilage on either side of the nose, which enables the built–in elastic splints to pull the wall of the vestibule laterally and dilate the valve area (12). Similar to CPAP, NDSs are mechanical devices that can be prescribed for nightly use. However, the two types of devices look and feel much different, and NDSs are typically less intrusive than CPAP masks. Because NDSs are widely advocated for the prevention of snoring and the promotion of nasal breathing during exercise (13), they may serve as a potential control intervention for controlled trials evaluating CPAP. However, it is unclear the extent to which NDSs may influence study outcomes due to an active rather than a placebo effect, which would therefore attenuate the estimates of intervention effects associated with the use of CPAP. In this study, we tested the effects of NDSs in a particular group of patients with acromegaly and OSA, and we herein report the effects of a randomized crossover trial in which the objective and subjective effects of NDSs were compared to the effects of CPAP in patients with acromegaly and moderate to severe OSA.

METHODS

Subjects

We studied patients with acromegaly and OSA who had been recruited from out–patient clinics at the Division of Endocrinology and Metabolism of Clinics Hospital, Faculty of Medicine, University of São Paulo. The inclusion criteria consisted of men and women with acromegaly who were between 18–70 years of age, had experienced moderate or severe OSA (≥15 events of apnea and hypopnea per hour of sleep) as documented by polysomnography and who were naive to treatment. The exclusion criteria included the following: the presence of kidney or liver disease; malignancy; hypercortisolism; endocrinological diseases, such as hypothyroidism; uncontrolled diabetes mellitus (glycated hemoglobin greater than 9%); and a history of alcohol abuse, angina, acute myocardial infarction, or stroke. The study was approved by the local institutional review board, and all patients provided written informed consent.

Sleep Study

Overnight polysomnography was performed in the sleep laboratory (EMBLA; Flagra hf. Medical Devices, Reykjavik, Iceland) and included electroencephalography, electrooculography, electromyography, oximetry, measurements of airflow (oronasal thermistor and pressure cannula), and measurements of the rib cage and abdominal movements during breathing. Apnea was defined as the complete cessation of airflow for at least 10 seconds and associated with an oxygen desaturation of 3%. Hypopnea was defined as a significant reduction (>50%) in respiratory signals for at least 10 seconds and associated with an oxygen desaturation of 3%. The apnea–hypopnea index (AHI) value was calculated as the total number of respiratory events (apneas plus hypopneas) per hours of sleep (14).

Study Design

Following the diagnostic polysomnography confirmation of moderate to severe OSA, the patients were randomly assigned, according to a computer-generated list of random numbers to three months of treatment with NDSs (ClearPassage® A.K.C, Inc., Korea) or CPAP (REMStar Pro with C-Flex with humidifier; Respironics, Inc., Murrysville, PA). After three months, the treatment was discontinued for one week and then patients were crossed over to the alternative treatment. At the initiation of each treatment period, participants underwent full polysomnography to assess the effects of NDSs or CPAP. Therefore, all patients underwent a total of three polysomnographic studies including a diagnostic study, one using CPAP and other using NDSs. During each three month intervention period, participants were instructed to use NDSs or CPAP every night. In each treatment period, participants returned for evaluation once a week in the first month, and once a month in the second and third month. CPAP compliance was objectively measured by data collected on an adherence-monitoring card (Smart Card; Respironics, Inc.). Similar to a pill count approach, patients were given a limited number of NDSs, and adherence was measured by counting the NDSs that were returned at the next visit. After the conclusion of the study, CPAP was offered to all of the patients.

Evaluations

At the time of study entry and after the three-month intervention, the subjects were weighed and evaluated according to the questionnaires described below.

Epworth Sleepiness Scale

The Epworth Sleepiness Scale (ESS) was used to evaluate subjective excessive daytime sleepiness. Briefly, the patient rated the probability of dozing (from 0 to 3) in eight different situations, where a score above 10 points represented the presence of excessive daytime sleepiness (15).

Pittsburgh Sleep Quality Index

Subjective sleep quality was measured according to the Pittsburgh Sleep Quality Index (PSQI) (16), which is a self–report questionnaire that assesses sleep quality and disturbances over a one–month interval. The 19– item index generates the following seven component scores: subjective sleep quality, sleep latency, sleep duration, habitual efficient sleep, sleep disturbances, the use of sleeping medications,

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and daytime dysfunction. Each component score is equally weighed on a 0–3 scale. The sum of these seven component scores yields a global score ranging from 0 to 21. This questionnaire has been previously translated and validated in Brazilian Portuguese (17). Higher global scores indicate worse sleep quality. A cutoff score of 5 yielded a diagnostic sensitivity of 89.6% and a specificity of 86.5% for distinguishing between good and poor sleepers.

Treatment Satisfaction

A questionnaire was designed to evaluate the level of satisfaction with the given treatment and included questions regarding the impact of the treatment on sleep quality, feelings upon waking, difficulty falling asleep, and satisfaction with the treatment effect concerning daytime sleepiness. The patients were also asked to rate the treatment with a score from 0–10 (0 = poor, 10 = excellent).

At the end of the study, when the patients had been exposed to both treatments, they were again asked to rate each treatment. In addition, participants were asked to list the advantages and disadvantages of each treatment and were asked to select which treatment for OSA they preferred.

Statistical Analysis

The data were analyzed with the statistical software SigmaStat for Windows, version 2.0. A descriptive analysis was used to define the study population. The results are expressed as the means $\pm$ standard deviation, medians (interquartile range) or percentages, as appropriate. The Student's t test for independent samples and an ANOVA were used to compare the quantitative variables when appropriate. The χ^2 test was used for the qualitative variables. The potential explanatory variables used as independent variables consisted of demographic and clinical parameters. A p-value<0.05 was considered to be significant.

RESULTS

During a one-year period, we invited 19 patients with acromegaly to participate in this study. Seven patients were excluded after diagnostic polysomnography due to an AHI<15 events/h. Therefore, the total study sample comprised 12 patients with moderate to severe OSA. All of the patients had confirmed acromegaly (growth hormone (GH): 1.32 ± 0.9 ng/l; insulin–like growth factor 1 (IGF1): 337 ± 180 ng/l) and were receiving octreotide. The demographic and clinical characteristics of the population studied, including medications, are described in Table 1. The body mass index (BMI) values of the patients did not change during the intervention period (33.4 ± 4.8 Kg/m2 and 33.05 ± 4.9 Kg/m2 at the end of CPAP and NDS treatment, respectively ($p = 0.94$)).

The sleep parameters at baseline, during CPAP titration and with the use of NDSs are presented in Table 2. As expected, the administration of CPAP virtually abolished OSA. In contrast, the NDSs did not significantly alter OSA severity. The mean CPAP pressure was 10.1 ± 1.1 cm H_2O, and median use of the CPAP was 6.6 ± 1.6 h per night. The patients used the NDSs 98% of the nights studied. The subjective parameters at the time of study entry and following the use of CPAP and NDSs are presented in

Table 1 - The demographic and clinical characteristics of the patients.

(n = 12)	Mean $\pm$ SD
Age, ys	52 ± 8
Male/Female	8/4
Body mass index, Kg/m^2	33.5 ± 4.6
Caucasians/Mulatto/Black, n	5/4/3
Abdominal circumference, cm	102 ± 8
Neck circumference, cm	42 ± 3
Hypertension, n (%)	9 (75)
Diabetes, n (%)	4 (33)
Diuretics, n (%)	5 (42)
β–Blockers, n (%)	3 (25)
ACE inhibitors, n (%)	5 (42)
Calcium blockers, n (%)	3 (25)
ARBs, n (%)	4 (33)
Antiplatelet, n (%)	3 (25)
Oral hypoglycemic, n (%)	6 (50)
Antidepressants, n (%)	3 (25)

The values represent the numbers of patients (percentage) or the mean $\pm$ SD.
Abbreviations: ACE: angiotensin–converting enzyme; ARBs: angiotensin receptor blockers.

Table 3. The reported satisfaction with the use of CPAP and NDSs is shown in Table 4. The benefits of CPAP, as perceived by the patient and measured by the ESS, included improved sleep, less snoring, and a decrease in sleepiness. The disadvantages of CPAP were mainly related to the use of the mask and included the need to adjust the mask to prevent air leakage and the discomfort of using the mask, particularly related to the headgear. The advantages of the NDSs included their perceived practicality and comfort. At the end of the study, 10 patients considered CPAP and two patients considered NDSs to be the more effective treatment.

Table 2 - Sleep parameters of the participants at baseline, on nasal dilator strips and on CPAP.

Sleep Parameter	Baseline	CPAP	NDSs	p value
TST (min)	409 ± 51	378 ± 78	394 ± 55	0.49
Sleep efficiency (%)	86 ± 8	80 ± 16	88 ± 7	0.49
Sleep latency (min)	11 ± 13	16 ± 16	13 ± 15	0.71
REM latency (min)	91 ± 52	141 ± 90	110 ± 45	0.18
Stage 1 (%)	6 ± 3	7 ± 5	6 ± 5	0.58
Stage 2 (%)	64 ± 9	68 ± 11	61 ± 11	0.26
Stage 3 (%)	11 ± 5	12 ± 6	9 ± 6	0.35
REM (%)	20 ± 7	17 ± 10	18 ± 6	0.63
Arousal /h	27 ± 9	$17 \pm 10*$	27 ± 9	0.02
AHI (events/h)	38 ± 14	$8 \pm 6*$	39 ± 15	<0.01
Apnea index (events/h)	17 ± 14	$3 \pm 3*$	23 ± 18	<0.001
Hypopnea index(events/h)	22 ± 12	$5 \pm 4*$	$16 \pm 7^{\dagger}$	<0.001
Obstructive apnea, n	79 ± 79	$6 \pm 10*$	110 ± 99	<0.001
Central apnea, n	22 ± 42	14 ± 13	28 ± 59	0.82
SatO$_2$min,%	79 ± 7	$86 \pm 6*$	79 ± 6	<0.001

Abbreviations: CPAP: continuous positive airway pressure; NDSs: Nasal dilator strips; TST: total seep time; REM: rapid eyes movements; AHI: apnea-hypopnea index; SatO$_2$min: minimal oxygen saturation. * Different from CPAP whit baseline and NDSs. † Different from NDSs with baseline. Variables expressed as mean $\pm$ SD. Variables with skewed distribution are present as median (interquartile range).

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Table 3 - PSQI component scores and global score of the participants baseline, nasal dilator strips and CPAP.

	Baseline	CPAP	NDSs	p value
EES, score (0-24)	12±6	5±5*	9±7	0.016
Global PSQI score	12±3	4±2*	6±5 †	<0.001
PSQI >4, n (%)	12 (100)	5 (41)*	6 (50)	0.006
Subjective sleep quality	2 (1.5–2.5)	1 (0–1)*	1 (1–1.5) †	<0.001
Sleep latency	2 (1.5–3)	0 (0–1)*	0.5 (0–1.5) †	<0.001
Sleep duration	3 (2–3)	1 (0–1.5)*	1 (0–1.5) †	<0.001
Sleep efficiency	3 (1.5–3)	0 (0–1)*	0.5 (0–1.5)	0.003
Sleep disturbances	2 (1.5–2)	1 (1–1)*	1 (1–2)	0.009
Use of sleep medications	0 (0–0)	0 (0–0)	0 (0–0)	0.99
Daytime dysfunction	2 (2–2)	0 (0–1)*	1 (0–1) †	<0.001

Abbreviations: CPAP: continuous positive airway pressure; NDSs: Nasal dilator strips; EES: Epworth Sleepiness Scale; PSQI: Pittsburgh Sleep Quality Index.
Variables expressed as mean ± SD .Variables with a skewed distribution are presented as medians (interquartile range). *For the comparisons between CPAP with baseline; †For the comparisons between NDSs with baseline.

DISCUSSION

This crossover study tested the efficacy of NDSs to be used as a placebo by comparing the objective and subjective effects of CPAP versus NDSs in patients with acromegaly and moderate to severe OSA. In contrast to CPAP, the NDSs showed no effect on several polysomnographic parameters, including sleep structure, arousals, AHI, and minimal oxygen saturation. Despite the absence of objective effects, patients treated with NDSs reported significant improvements in several subjective measurements, including sleep quality, snoring intensity, and somnolence during the day. The subjective improvement associated with the use of NDSs was intermediate and significantly lower than the beneficial effects resulting from CPAP. The subjective comparison at the conclusion of the study showed that the vast majority of the patients (10 out of 12) considered CPAP therapy to be more effective than NDSs. The high level of adherence for the NDSs and the subjective improvements in sleep associated with their use support the concept that NDSs are an attractive control intervention for use in controlled clinical trials aimed at evaluating the effects of CPAP in patients with moderate to severe OSA in regards to objectively measured (physiological or biochemical) outcomes.

CPAP is the gold standard treatment for OSA and, although effective at relieving symptoms, its role in reducing long-term morbidities, such as cardiovascular disease, requires further evaluation in trials that also include proper control interventions. Because of its physical nature, an ''ideal placebo'' for CPAP likely does not exist. In this context, several alternatives, including pills, oral appliances, and conservative treatment, have been used in RCTs evaluating the effects of CPAP on different outcomes (5,6,18,19). However, there has been little research that has specifically evaluated the effectiveness of placebo candidates. Several studies have argued that sham CPAP is an appropriate control for CPAP, although sham CPAP may serve as a poor placebo due to its negative effects on sleep quality combined with the patients' ability to identify the sham treatment and secondary disappointment about being placed in an untreated control group. In contrast, NDSs are generally accepted by patients, many of whom perceive benefits and thus may be motivated to continue with long-term studies.

We reasoned that an ideal placebo should, similarly to CPAP, be used every night but not adversely influence sleep quality. Sleep apnea efficacy trials are typically designed to

Table 4 - Satisfaction treatment questionnaire of the participants with nasal dilator strips and CPAP.

Using the treatment over the last 3 months		CPAP	NDSs	p value
How was your sleep?	Much worse	0	0	NS
	Worse	0	0	
	Equal	1	2	
	Better	4	5	
	Much better	7	6	
How you felt upon waking?	Much worse	0	0	NS
	Worse	0	2	
	Equal	1	2	
	Better	5	6	
	Much better	6	2	
You had some trouble falling asleep?	Little difficult	1	1	NS
	No difficult	2	2	
	Much difficult	9	9	
How pleased was with the treatment?	Very discontented	0	1	NS
	discontented	0	1	
	Equal	1	1	
	Satisfied	4	3	
	Very satisfied	7	6	
Did the treatment helped in your daily activities?	No	0	2	NS
	Yes	12	10	
Rate the treatment (0–10) 0 = no effect 10 = maximal effect		9±1	7±3	0.01
Rate both treatments at the end of study (0 – 10) 0 = no effect 10 = maximal effect		9±1	5±3	0.007

Abbreviations: CPAP: continuous positive airway pressure; NDSs: Nasal dilator strips. Variable with normal distribution is express as mean ± SD.

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compare an active intervention, such as CPAP, with an inactive treatment. Thus, the use of NDSs as a ''placebo'' assumes that NDSs do not positively (or negatively) influence study outcomes. The effects of NDS are based on the assumption that nasal resistance may play a pivotal role in the genesis of OSA. Several studies have evaluated the effects of different strategies to decrease nasal resistance on OSA severity, and there have been controversial results (20). The beneficial effects of NDSs on perceived snoring and obstructed breathing are likely due to an active effect resulting from the increased cross–sectional area of the nasal cavity and the consequently reduced nasal airway resistance (21). The efficacy of NDSs, however, remains controversial. Although several studies have demonstrated beneficial effects of NDSs on snoring (22-24), sleep maintenance insomnia associated with sleep-disordered breathing (25), and AHI (21,26,27), others have not supported these findings (28,29). In our study, NDSs had no significant effect on the AHI and caused a small but significant decrease in the hypopnea index (Table 2). It is possible that NDSs may have a somewhat greater effect in patient groups besides this OSA–acromegaly patient sample. For example, the study by Redline et al. (7) reported that NDSs had a small beneficial effect on AHI in a subgroup of mildly affected OSA patients with sinus disease. It is likely that, among patients with moderate to severe OSA, neither the site of obstruction during apnea nor the site of generation during snoring is in the nose, and rather this location may be in the oropharynx or hypopharynx at the level of the soft palate or the velopharyngeal level (22). NDSs are therefore an attractive placebo because they offer high patient acceptability and a potential for minimal improvement in the AHI, although the level of improvement in OSA is much less than what can be achieved with CPAP.

The previously reported effects of sham CPAP (30), conservative treatment (5), and oral placebos (6) on subjective parameters have been extremely variable. For instance, Jenkinson et al. (30) found a 29% improvement in ESS associated with sham CPAP, whereas Engleman et al. (6) found no effect of oral placebos on ESS. In contrast to the overall lack of changes in objective measurements observed in our study, patients given NDSs reported significant improvements in several subjective measurements, including quality of sleep, perceived snoring, and symptoms of excessive daytime somnolence, as evaluated by the ESS. Compared to the baseline values, the ESS score decreased by 25% during NDS treatment, which is in line with previously reported studies that also reported positive effects of NDSs on ESS as high as 66% (21-24,31). We also evaluated sleep quality by PSQI, and whereas CPAP improved six out of seven PSQI items, NDSs improved four of these items.

Our study had several limitations. First, we studied patients with underlying acromegaly and OSA. Although unlikely, it is possible that NDSs are more effective for patients with OSA but without acromegaly. Second, the number of patients studied in this report was relatively small. However, the crossover nature of our study increased its statistical power and allowed us to evaluate differences between the CPAP and NDS arms not only for the objective parameters but also for the subjective parameters. Moreover, the study design enabled the comparison of the strengths and limitations of each treatment according to the

patients' perspectives. Finally, the long-term acceptability and use of this type of placebo requires further study.

In conclusion, this study demonstrated that NDSs did not appreciably affect objective measurements of sleep/OSA but were associated with modest improvements in subjective responses. Thus, NDSs may be an effective control intervention for trials aimed at evaluating the objective effects of CPAP in patients with OSA. The present study, however, evaluated patients with acromegaly, and it is possible that small beneficial effects may occur in other groups, such as patients with mild OSA and nasal obstruction. In those cases, the estimated differential effect of CPAP may be modestly underestimated.

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AUTHOR CONTRIBUTIONS

Amaro ACS and Lorenzi-Filho G participated in the study design, interpretation of results, analysis and collection of data, and preparation of the manuscript. Duarte FHG, Jallad RS, and Bronstein MD participated in the collection of data. Redline S contributed to the preparation of the manuscript.

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