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A Pilot Study Assessing Adherence to Auto-Bilevel Following a Poor Initial Encounter with CPAP

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SCIENTIFIC INVESTIGATIONS

Study Objectives: We hypothesized that early intervention with an auto bilevel device would improve treatment adherence compared to CPAP among OSA patients with a poor initial experience with lab-based CPAP titration.

Methods: Patients with a poor initial CPAP experience were recruited for this parallel group, randomized, double-blind, controlled pilot study. After an in-lab titration, patients were randomized with either an auto-bilevel device or CPAP. Treatment adherence and functioning were assessed at 90 days.

Results: We enrolled 51 subjects, with 47 completing the protocol. Groups were equally matched for gender, age, education, and OSA severity. There was no significant difference in the proportion of compliant subjects (≥ 4 h/night) between the auto bilevel and CPAP groups (62% vs. 54%; p = 0.624) after 90 days of use. Functional outcomes significantly improved in both groups during treatment use (p < 0.001) but did not differ between groups.

Conclusions: There was no statistically significant difference in adherence between the auto bilevel and CPAP groups in this study. Patients with a poor initial CPAP exposure may still achieve an acceptable long-term clinical outcome. Both groups demonstrated comparably significant improvements in functional outcomes, sleepiness, and fatigue complaints over the treatment period.

Clinical Trials Information: NCT00635206 ClinicalTrials.gov

Keywords: Treatment compliance, obstructive sleep apnea, continuous positive airway pressure, bilevel positive airway pressure, lung

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Despite the well-established consequences of OSA, treatment is challenging due to suboptimal adherence or variable efficacy of established therapies. Given the fact that some patients tolerate CPAP poorly, clinicians frequently expend considerable efforts to improve CPAP usage. Up to 50% of patients who are recommended treatment with nasal CPAP are not using the therapy a year later.[1]

A commentary on this article appears in this issue on page 49.

The individual long-term pattern of CPAP therapy usage is likely due to multiple factors, such as severity of OSA, amount of pressure applied, perceived benefit, and the ability to use the therapy. However, a key factor in long term compliance is the timing of good usage patterns. Several studies have indicated that the critical window to determine long-term usage occurs within the first month of usage, possibly sooner.[2,3] Other data have suggested that variables such as sleep efficiency during in-lab CPAP titration may predict treatment adherence.[4] Since perceived benefit is prognostic regarding long-term CPAP adherence, patients who are initially intolerant of CPAP may be a group in whom early intervention has benefit.

Bilevel or auto-titration devices have been used to improve patient comfort in those with treatment intolerance related to expiratory pressure discomfort. However, the vast majority of trials using these devices show no clinically important usage benefit over standard CPAP therapy,[5-8] despite some preference for the adjustable pressure devices versus standard CPAP.

In concert with addressing pressure discomfort related to standard therapy, some clinical trials have demonstrated the efficacy of flexible bilevel positive airway pressure. A randomized trial demonstrated equivalent adherence compared with standard CPAP in the initial treatment of OSA, as well as comparable efficacy.[9] Another large study assessing existing non-adherent users after more than 9 months of therapy and an additional 2 weeks of standard interventions demonstrated significantly greater adherence rates using a flexible bilevel pressure device compared to standard CPAP therapy.[10]

Based on the notion that early treatment usage predicts sustained adherence, we sought to determine whether an alterna-

BRIEF SUMMARY

Current Knowledge/Study Rationale: Despite the challenges by clinicians to maintain adequate treatment adherence, nasal CPAP therapy continues to be the primary treatment option for obstructive sleep apnea (OSA). CPAP adherence is likely related to multiple factors, such as disease severity, nasal symptoms, and pressure discomfort. It is unclear if early intervention with an auto-bilevel device would improve adherence after a poor initial in-lab encounter with CPAP.

Study Impact: Comparable and overall compliant adherence rates between the auto-bilevel and CPAP groups limited the effect size and clinical significance interpretation of this pilot study. However, poor initial experiences to PAP therapy can still lead to positive treatment outcomes through use of various device types and appropriate support.

tive flow delivery device would be better tolerated than standard nasal CPAP. We performed a randomized controlled pilot study to test the hypothesis that early intervention with an alternative device (auto-titrating, bilevel, and pressure flexing) would improve therapy outcomes as compared with standard CPAP among OSA patients with a poor initial experience with lab-based CPAP titration. More specifically, our primary hypothesis was to test if a greater proportion of participants were adherent to treatment (at h of usage for all nights) in the auto-bilevel group compared to the CPAP group after 90 days of treatment.

METHODS

Participants

Potential participants were adult patients (ages 21-75 yr) referred for diagnostic evaluation of OSA at the participating sleep centers. Eligible patients had a confirmed OSA diagnosis (baseline apnea/hypopnea index [AHI] ≥ 15/h) by either full-night diagnostic polysomnography (PSG) or split-night PSG, and had to have had a suboptimal facility-based attended CPAP titration according to standard clinical protocol with ≥ 3 h of attempted titration data. To be classified as a suboptimal titration, one of the following clinical criteria had to be met: (1) poor sleep efficiency index (SEI) ≤ 70% during titration period; (2) ≥ 20 arousals/h (excluding leg movement related arousals); (3) CPAP titration aborted by the patient; or (4) persistent sleep disruption despite therapeutic CPAP therapy and low probability of CPAP compliance in the judgment of the reviewing physician. In order to represent "real world" clinical practice, clinical PSG recordings were independently scored at each facility according to established criteria[11] by blinded experienced registered technologists and reviewed/verified by investigators at each site.

Exclusion criteria included major uncontrolled medical or psychiatric conditions; prior CPAP or bilevel use; chronic respiratory failure or insufficiency; surgery on the upper airway, nose, sinus, or middle ear within 90 days of participation; the presence of any untreated and diagnosable non-OSA sleep disorder (e.g., restless legs syndrome, insomnia); current shift workers; known history of alcohol or drug abuse within the past 3 years; chronic nightly hypnotic use for < 3 months; and periodic limb movement (PLM) arousal index ≥ 10/h. Also excluded were patients who refused to consider further interventions to standard CPAP or unwilling to return within 90 days, those for whom PAP therapy was otherwise medically complicated or contraindicated, and who had a diagnosis of complex sleep apnea or persistent central apneas during clinical CPAP titration. Three fully accredited sleep facilities enrolled participants in the trial, one located in the northeast (Site A), and 2 located in the Midwestern United States (Sites B and C). The study was approved by participating sites' institutional review boards, and all participants provided informed consent prior to initiation of any study procedures.

Procedures

Following a suboptimal CPAP titration, patients underwent a screening visit to determine subject eligibility and obtain informed consent. Demographic data, vital signs, and current medications were recorded. One week after screening, participants were randomly assigned to either standard CPAP or automatically titrated auto-bilevel nasal positive pressure (auto-bilevel; Auto BiFlex, Respironics, Inc.) and underwent a full-night titration (Baseline Study Visit). Due to the small sample size and to maintain balanced group placement, a restricted randomization procedure (Urn randomization)[12] was used for treatment group placement using the variables of gender, age, diagnostic AHI, and education.

All-night titration PSG was performed using standard parameters of electrooculogram, electroencephalogram (C4A1/C3A2, O2A1/O1A2), submental and anterior tibialis electromyogram, electrocardiogram, snoring microphone, airflow as measured by internal pressure transducer from bilevel device, respiratory effort, and oxygen saturation. Each participant was required to have ≥ 6 h of time in bed during the research titration. The CPAP group was titrated according to standard clinical practice of titration, with an optimal pressure determined once an AHI < 5/h during supine REM sleep was achieved. The auto-bilevel group was initiated and maintained with a comfort setting of 3, maximum inspiratory positive airway pressure (IPAP) of 25 cm H_2O, maximum pressure support of 8 cm H_2O, and an expiratory positive airway pressure (EPAP) of 4 cm H_2O (EPAP = 6 cm H_2O for patients who required ≥ 10 cm H_2O support on CPAP). All study PSG data were scored manually by blinded registered technologists. Sleep stages and arousals were analyzed per established criteria.[11] Apneas were defined as a cessation of airflow ≥ 10 sec. Hypopneas were defined as a reduction in airflow ≥ 30% compared to baseline, lasting ≥ 10 sec, and associated with an oxygen desaturation ≥ 4%.

Following titration PSG and determination of optimal pressure settings for each group, all participants received their devices for usage in the home for the next 90 days. The participant, investigator, respiratory therapist, and research staff were all blinded to the therapy group. To maintain the blind, the display screen on the device was blinded to therapy settings. Education and counseling were standardized to all participants to optimize compliance to therapy, which included verification of proper mask fit. Participants were permitted to change masks during the trial if mask comfort was determined as a tolerance issue as per standard of care. Heated humidification was allowed to be used and adjusted as needed. Patients returned at days 30 and 90 for follow-up visits.

Outcome Measures

Adherence data were monitored via each device's compliance tracking capabilities. These data were continuously collected over the entire 90-day home trial period, but were downloaded around days 7, 30, and 90. Data were reported as minutes of therapy usage per night.

Subjective estimates of daytime functioning and the functional impact of sleepiness were assessed at baseline and the follow-up visits at 30 and 90 days. The Epworth Sleepiness Scale (ESS)[13] and the Fatigue Severity Scale (FSS)[14] were used to assess subjective estimates of sleepiness and fatigue, respectively. The Functional Outcomes of Sleep Questionnaire (FOSQ)[15] was used to assess impact on daily living as a result of sleepiness.

Statistical Analysis

To assess the primary endpoint and other results related to CPAP usage data, an adherent patient was operationally defined

Table 1—Demographic and baseline measures for the auto bilevel group (N = 26) and the CPAP group (N = 22)*

Variable	Auto-Bilevel Group (N = 26)	CPAP Group (N = 22)	*t*-test	p-value
% Male	81%	73%	-0.65	NS
Age, yr	54.1 (12.5)	56.6 (9.8)	-0.764	NS
Education, % College	62%	54%	0.907	NS
BMI	34.9 (6.5)	31 (4.4)	2.345	0.023
Neck Circum (cm)	43.3 (4.6)	40.2 (10.0)	1.414	NS
Nicotine, #/day	1 (4.0)	1.9 (4.7)	-0.688	NS
Alcohol, drinks/wk	2 (3.2)	3.8 (6.6)	-1.219	NS
% Split Night PSG	65%	86%	-1.687	NS
Diagnostic AHI/h	41.1 (22.5)	39.4 (24.5)	0.242	NS
ESS	9.8 (3.9)	8.2 (4.5)	1.302	NS
FSS	4.6 (1.4)	4 (1.2)	1.593	NS
Global FOSQ	84.3 (20.5)	88.5 (21.6)	-0.688	NS
ATU-A, Self-Efficacy	20.4 (3.2)	19 (4.7)	1.278	NS
TAT Titration	27.9 (Range 6-97 d)	26.7 (Range 6-54 d)	0.232	NS

*Values given as means (SD), unless otherwise indicated. NS, not significant; ESS, Epworth Sleepiness Scale; FSS, Fatigue Severity Scale; FOSQ, Functional Outcomes Sleep Questionnaire; TAT Titration = time, in days, between in-lab titration failure and baseline study visit titration.

as average therapy usage ≥ 4 h/night during the defined treatment period. Our primary hypothesis was that across 90 days, the proportion of participants adherent with therapy would significantly differ between the CPAP and auto-bilevel groups. To our knowledge, this is the first trial to investigate the impact of therapy pressure variations on adherence in a population of patients who experienced in-lab titration failures. Thus, the study was not powered to any endpoint, as it represented a pilot study to determine primary endpoint effect sizes and statistical power for potential future trials. Proportions of overall adherence at 90 days were compared using a χ^2 test. To account for dropouts, the primary endpoint was analyzed on an intent-to-treat basis. Secondary assessments included a comparison of cumulative adherence data between the groups by day up to day 90 as well as at average usage for the first 7 days and first 30 days to account for an early pattern of use. These assessments were each compared using a χ^2 test. Remaining subjective estimates of daytime functioning and FOSQ scores were compared from baseline to each follow-up visit using repeated-measures ANOVA. Demographic, clinical, PSG data, and baseline measures were also reported and compared using a *t*-test. All data are reported as mean ± standard deviation (SD), unless otherwise noted. For all statistical analyses, the α level was set to 0.05. All data analyses were performed using SPSS for Windows v. 17 (SPSS, Inc, Chicago, IL).

RESULTS

Demographics and Baseline Assessments

A total of 51 patients completing clinical polysomnography with CPAP was assessed for study eligibility and consented to study participation. In regards to meeting suboptimal titration inclusion criteria, 3 patients aborted their titration, one was enrolled due to persistent arousals despite therapeutic CPAP, and the remaining 47 patients had poor SEI, increased arousal index, or met multiple suboptimal titration criteria. Two patients were excluded for not meeting study inclusion/exclusion criteria, and one patient withdrew at the baseline visit. A total of 48 participants were randomized into the trial, 26 into the auto-bilevel group and 22 into the CPAP group. A total of 48 participants were analyzed for the primary endpoint on an intent-to-treat basis. All secondary analyses were performed using the 47 participants who completed all study visits. There were no significant differences in enrollment nor group placement among the 3 study sites (Enrollment: Site A: 19, Site B: 10, Site C: 19, $\chi^2 = 1.382$, $p = 0.501$), but there was a significant difference in compliance proportions among the sites ($\chi^2 = 6.469$, $p = 0.039$).

Table 1 shows the demographic data for the 2 study groups. There were an equal proportion of males in each group (81% males auto-bilevel group, 73% males CPAP group). The 2 groups also did not differ according to age, education, neck circumference, OSA severity, or baseline subjective measures. There was a significant difference in BMI between the groups (34.9 kg/m^2 auto-bilevel group vs. 31.0 kg/m^2 CPAP group, $p < 0.05$); however, subsequent ANCOVA analysis demonstrated that BMI did not significantly co-vary with compliance data. In summary, the typical participant was a middle-aged male, college educated, with an elevated BMI, who had severe sleep apnea and a mild degree of daytime functioning impairment based on the FOSQ.

Treatment Adherence

One randomized participant discontinued the study early (auto-bilevel Group). One participant in the CPAP group used therapy the first night and failed for the remainder of the study but completed all study visits. There was no significant difference in the proportion of adherent users between the treatment groups over the 90 day treatment period ($\chi^2 = 0.240$, $p = 0.624$), although a slightly higher percentage of participants met adherent criteria in the auto-bilevel group (62% vs. 54%). Of note, the cumulative average usage for both groups over the entire 90

Table 2—Compliance data during the treatment period*

Variable	Auto-Bilevel Group	CPAP Group	p-value
Days 1-30			
Proportion Group Compliant	73%	59%	0.306
Avg Use/Night	293.2 min (107.1)	265.4 min (128.1)	0.422
%Nights > 4 h Use	66.0% (29.1)	59.3% (35.0)	0.48
Days 1-90			
Proportion Group Compliant	62%	55%	0.624
Avg Use/Night	284.7 min (110.9)	255.1 min (116.9)	0.377
%Nights > 4 h Use	63.8% (29.6)	56.9% (29.4)	0.429

*Values given as means (SD), unless otherwise indicated. NS, not significant.

Table 3—Subjective measure outcomes for the auto bilevel and CPAP group for each visit*

	Auto Bilevel Group			CPAP Group			
Variable	Baseline	Day 30	Day 90	Baseline	Day 30	Day 90	Interaction p-value†
ESS	9.7 (3.9)	8.2 (3.2)	8.1 (3.8)	8.2 (4.6)	6.6 (4.6)	6.9 (4.4)	NS
FSS	4.6 (1.4)	4.0 (1.2)	3.7 (0.9)	3.9 (1.0)	3.7 (1.2)	3.4 (1.2)	NS
FOSQ, Global	84.0 (20.9)	97.5 (13.8)	100.0 (11.3)	91.4 (17.3)	96.6 (16.6)	100.1 (15.4)	NS

*Values given as means (SD), unless otherwise indicated. NS, not significant. †ESS, FSS, and FOSQ scores significantly changed from baseline ($p < 0.001$), but no interaction by group. ESS, Epworth Sleepiness Scale; FSS, Fatigue Severity Scale; FOSQ, Functional Outcomes of Sleep Questionnaire.

days would be considered as adherent (284.7 min/night auto-bilevel group vs. 255.1 min/night CPAP group). A goal of this pilot trial was to collect data on a small sample of participants to determine statistical power for a larger trial. Post hoc sample size estimation using average usage/day in each group would require a sample size of 426 participants to detect a 30-min significant difference in treatment adherence. Given the comparable and overall compliant adherence rates between the groups, effect size estimates were relatively small ($d = 0.260$), limiting a clinically significant interpretation of this pilot data.

To consider whether long-term treatment adherence could be determined within the first 30 days of usage, the proportion of adherent users by group was assessed for the first 7 days and first 30 days of therapy. Adherence rates were comparable between the groups during the first 7 days of treatment (31% auto-bilevel group vs. 32% CPAP group; $\chi^2 = 0.006$, $p = 0.938$). Although there was still no significant difference in adherence rates, a larger difference was observed over the first 30 days of therapy (73% auto-bilevel group vs. 59% CPAP group; $\chi^2 = 1.049$, $p = 0.306$). Refer to **Table 2** for adherence data during the treatment period.

Subjective Estimates

Means and SD for each measure and visit are shown in **Table 3**. Subjective estimates of daytime functioning as measured by the ESS were significantly improved at the day 30 visit compared to baseline for the entire sample ($F = 13.147$, $p < 0.01$), whereas the FSS was most improved at the day 90 visit ($F = 21.968$, $p < 0.001$). However, there were no significant differences between groups over the treatment period. Global FOSQ scores also significantly improved from baseline to the day 90 visit for the entire sample ($F = 25.805$, $p < 0.001$); however, there once again were no significant differences between groups over the treatment period. Of note, participants in the auto-bilevel group demonstrated a larger improvement in global FOSQ scores throughout the treatment period and a much more rapid increase by day 30 visit than the CPAP group.

DISCUSSION

Our findings suggest that intervening with the auto-bilevel device immediately after a poor initial laboratory exposure instead of standard CPAP did not result in significantly improved adherence rates over the entire treatment period. Both groups demonstrated comparable improved daytime functioning and functional outcomes during the course of treatment.

Despite efforts to compare the auto-bilevel device to standard CPAP in a population susceptible to poor treatment adherence, both groups were surprisingly adherent on average during the treatment period (284.7 vs. 255.1 min use/night). High adherence rates across the sample have been reported in other studies which have attempted to initiate a comparison of devices at the beginning of therapy.[9,16] Based on our experiences as well as previous report,[4] we had anticipated fairly poor adherence among patients who had a poor initial CPAP experience. The cumulative benefit of participating in the trial may have improved population adherence rates by providing intense support and maintenance of the therapy, along with proper mask adjustments and humidification. Such findings may be important clinically, since the outcome of patients with poor initial CPAP adherence is quite good regardless of the therapy provided.

There were potential limitations to our study. As this was a pilot study, the sample size was limited and not powered to assess a significant difference between the treatment groups. Significant variance in compliance rates in the CPAP group likely contributed to a small effect size of the primary endpoint. As with all multicenter trials, there is a risk of population differ-

ences within the sample. Groups were equally randomized to groups by site, but there were minor differences in compliance rates by site. Even though education and support procedures throughout the study were consistent among the sites, there could have been differences in referral patterns and patient populations to each center.

A primary goal of our pilot study was to determine the benefit of both intervening immediately after a poor initial encounter with CPAP during in-lab titration and an alternative pressure delivery device to make a positive impact on treatment adherence. Although aspects of our methodology were novel and could have been a factor related to our limited effect size, we felt it necessary to explore the potential of early intervention given our clinical experiences. It could also be argued that our selection criteria to identify those patients having a suboptimal initial exposure to CPAP were not ideal and perhaps other parameters should have been used. In addition, it is well documented that treatment adherence may be determined within the first 30 days of use—maybe as few as three days.[2,3] Data also exist supporting poor sleep efficiency during in-lab CPAP titration as a factor impacting adherence.[4] Previous studies have attempted to either demonstrate improvement in adherence by early interventions or the use of variable pressure devices. Other studies attempting to utilize novel therapies at initiation of treatment have also failed to demonstrate clinically significant improvements in adherence rates compared to CPAP[9,17]; despite some preference differences, most studies using bilevel devices also fail to demonstrate different clinically significant usage patterns.[5-8] Comparable to these studies, our study failed to demonstrate a significant improvement in adherence rates, regardless of improved daytime functioning and functional outcomes.

These results may not be generalizeable to all populations who experience tolerance difficulties with CPAP. In fact, a previous study has demonstrated that an auto-bilevel device can improve compliance in those who have already demonstrated longer term failure using CPAP.[10] Without prior established adherence patterns, one night of experience during titration may not fully determine these patterns in the population chosen. However, groups were comparable according to typical predictive variables such as age, OSA severity, and sleepiness measures at baseline.

In conclusion, the use of an auto-bilevel device after a poor initial encounter with CPAP resulted in nonsignificant and only marginally improved adherence rates compared to standard CPAP therapy, although the entire sample demonstrated favorable adherence rates. The auto bilevel device was just as efficacious as CPAP therapy in improving functional abilities. Further work is needed to understand the true benefits (if any) of multiple interventions to improve treatment adherence (e.g., auto-bilevel, humidification, mask comfort, and education) and who may benefit the most with this type of device for treatment of their OSA. Patients with a poor initial experience with CPAP are still good candidates for PAP therapy with appropriate support.

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