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Effect of Continuous Positive Airway Pressure versus Supplemental Oxygen on Sleep Quality in Obstructive Sleep Apnea: A placebo-CPAP controlled study

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ABSTRACT

Study Objectives: We investigated the short term effectiveness of CPAP and O_2 in improving sleep quality in patients with OSA.

Design: Randomized, double blinded, placebo-CPAP controlled, parallel study.

Setting: General Clinical Research Center at a University Hospital

Patients: Seventy-six untreated OSA patients

Interventions: Patients were randomized to one of three treatments (CPAP, placebo-CPAP, nocturnal O_2 at 3 L/min) for 2-weeks. Sleep quality was assessed at baseline, and after one and 14 days of therapy. Repeated measures ANOVA was used to evaluate treatment and time effects, and their interaction.

Measurements and Results: Sixty-three patients completed the protocol. When compared to placebo-CPAP and nocturnal O_2, CPAP increased REM sleep and significantly reduced stage 1 sleep, number of stage shifts ($p \leq 0.003$). CPAP improved to within normal limits apnea hypopnea index, total arousal index, and mean oxyhemoglobin saturation ($p \leq 0.001$). The effects of CPAP were apparent during the first night of therapy. Oxygen improved only mean nocturnal saturation ($p = 0.009$). CPAP had no significant effect on stage 2 sleep or slow wave sleep.

Conclusions: CPAP was associated with an improvement in sleep quality in OSA patients by consolidating sleep, reducing stage 1 sleep, and improving REM sleep. CPAP was effective in correcting the respiratory and arousal abnormalities of OSA. The effectiveness of supplemental oxygen was limited to oxyhemoglobin desaturation.

Key Words: Continuous positive airway pressure; Obstructive sleep apnea; Sleep quality; Oxygen; Placebo-CPAP.

INTRODUCTION

Continuous positive airway pressure (CPAP) is considered the most effective and the preferred therapy for obstructive sleep apnea syndrome (OSA). In placebo-controlled and uncontrolled studies CPAP has been shown to correct the elevated apnea hypopnea index (AHI) and the transient desaturations associated with respiratory events during sleep.[1-4] In uncontrolled studies, CPAP has also been shown to improve daytime sleepiness,[5,6] mood,[7] cognitive function,[8] quality of life,[9] and to improve cardiovascular function in OSA patients.[10] In one sub therapeutic CPAP controlled study CPAP was effective in reducing excessive daytime somnolence and improving self-reported well being.[11]

However, the effects of CPAP in improving sleep quality in OSA have been less consistent,[1,12] Obstructive sleep apnea patients generally have poor sleep quality, characterized by short sleep latency, increased stage 1 sleep, decreased rapid eye movement (REM) and slow wave sleep (SWS), poor sleep efficiency, and frequent sleep fragmentation caused by transient arousals. We were surprised to find that only two randomized placebo controlled trials have evaluated the effectiveness of CPAP in improving sleep quality. We previously reported that in severe OSA patients, a one-week trial of CPAP was not different than placebo-CPAP (CPAP at a sub-therapeutic pressure) in improving sleep architecture, except for improvement in arousal index.[1] More recently, McArdle and Douglas reported improvements in stage 1, SWS, and arousal index, after 4 weeks on CPAP, but reported no improvement in REM sleep in a randomized cross over study utilizing an oral capsule as placebo.[12] In 1997, in a systematic review of the sleep literature, the effectiveness of CPAP as a treatment for OSA was called into question because of the dearth of studies using adequate placebo-CPAP controls.[13] This review highlights the need for rigorously controlled studies, which are still all-too-few in the field of

sleep medicine. We therefore designed a study to further evaluate the effects of CPAP on sleep quality in OSA patients comparing it to a placebo CPAP that delivered virtually no CPAP pressure.

The effect of supplemental oxygen on sleep architecture in OSA has not been rigorously studied against CPAP or placebo-CPAP controls. In some OSA patients who cannot tolerate CPAP and are not candidates for a surgical procedure, supplemental oxygen therapy has been used in an attempt to reverse the harmful effects of the transient hypoxemia during sleep.[14,15] Nocturnal supplemental oxygen has been suggested by some as an alternative therapy in the non-somnolent or the CPAP non-compliant OSA patient.[15,16] Most studies evaluating supplemental oxygen in OSA have included only a few patients, the results have been mixed, have used nasal cannulas to deliver oxygen, and few have evaluated the effect of supplemental oxygen on sleep architecture in OSA.[15-18] To our knowledge, the combination of placebo-CPAP with oxygen, to allowed for a more precise and needed comparison to CPAP therapy has not been reported.

The aim of this study was to evaluate the effectiveness of CPAP or supplemental oxygen, delivered via placebo-CPAP set-up, on sleep quality in obstructive sleep apnea patients in a randomized double-blinded placebo-CPAP controlled trial after one day and after 2 weeks of treatment.

METHODS

Subjects

All subjects gave informed consent, which was approved by the University of California San Diego Institutional Review Board. Seventy-six adult subjects suspected of having OSA were studied at the University of California San Diego General Clinical Research Center Gillin Laboratory of Sleep and Chronobiology (GCRC LSC) between 2000 and 2004. Subjects suspected

of having OSA were recruited from the community and from local sleep laboratories by advertisement. Screening criteria included a history of chronic loud snoring with or without excessive daytime somnolence, age 30 to 65 years, and weight between 1.0 and 2.0 times the ideal body weight as determined from Metropolitan Life tables.[19] Inclusion criteria also included having an AHI $\geq$ 15. Subjects were excluded if they were receiving medications known to affect sleep, if they had congestive heart failure, symptomatic obstructive pulmonary, coronary or cerebral vascular disease, history of life threatening arrhythmias, cardiomyopathy, history of psychosis, narcolepsy, current alcohol or drug abuse, if they had previous surgery for the treatment of OSA, or if they had a periodic limb movement index (number of leg kicks per hour of sleep) $\geq$ 15 on baseline polysomnography (PSG). In the study interval 413 subjects were screened for this study, 337 were ineligible, and 76 agreed to participate. Subjects received a modest honorarium for their participation.

Experimental design

Potential OSA subjects were prescreened with an unattended overnight home sleep study using the Stardust (Respironics Inc., Marietta, GA) home sleep recording system. Subjects who were suspected of having significant obstructive sleep apnea based on the home recordings were evaluated for sleepiness with the Epworth Sleepiness Scale (ESS),[20] and were admitted to the GCRC LSC for a confirmatory overnight full PSG sleep recording. If the PSG recording revealed an AHI $\geq$ 15, they were admitted to the GCRC LSC for two additional nights. The same team of nighttime technicians and daytime technicians performed and scored the polysomnograms under the direction of the lead author.

On the second night of admission qualifying subjects were randomized in a double-blinded fashion to receive traditional nasal CPAP, placebo-CPAP, or supplemental oxygen at 3 L/min,

delivered via placebo-CPAP set-up. The technicians who scored the sleep studies and the investigators were blinded to the randomization assignments.

Equipment for all treatment arms was similar, consisting of a CPAP generator, CPAP mask and tubing, heated humidifier (Fisher and Pykel HC100, Aukland New Zealand), and oxygen concentrator (Alliance, Healthdyne Technologies Model 505, Marietta Georgia) that could be switched to produce room air with the flick of hidden switch as indicated. The supplemental gas was introduced into the CPAP system at the level of the humidifier.

Subjects randomized to CPAP received active CPAP plus an oxygen concentrator that provided room air. Those assigned to placebo-CPAP received sub-therapeutic CPAP (CPAP < 1 cm H_2O at the mask) plus an oxygen concentrator that provided room air. Finally, those assigned to nocturnal supplemental oxygen received sub-therapeutic CPAP plus an oxygen concentrator delivering oxygen at 3 L/min. Supplemental oxygen with placebo-CPAP produced an FiO_2 of 32-34% at the CPAP mask.

A modified version of the sham-CPAP system reported by Farre et at.[21] was used for the placebo-CPAP. A modified CPAP mask containing ten ¼ inch drill holes to allow for adequate gas exchange with room air was used while the CPAP pressure was set at a constant 3 cm H_2O. A pressure reducer, with a 3 mm orifice, was placed in the CPAP tubing between the CPAP unit and the modified CPAP mask. With this system the pressure at the CPAP mask was 0.5 cm H_2O at end-expiration and 0 cm H_2O during inspiration, and the patient was able to feel a gentle breeze at the nose. The noise level of real CPAP plus the oxygen concentrator was not perceptibly different than that of placebo-CPAP and oxygen concentrator.

In the CPAP treated group, optimal effective nasal CPAP pressure to minimize sleep apnea was obtained by conventional manual overnight CPAP titration during monitoring with

PSG as previously described.[1] The patient was fitted with an appropriate sized CPAP mask (Respironics Profile Light). After generic orientation, the patient was allowed to fall asleep at a CPAP of 4 cm H_2O. CPAP was increased in 1 to 2 cm H_2O increments until the respiratory events and snoring were abolished. The titration was considered ended when most respiratory events were controlled while the patient was in the supine position and in the second or third REM sleep period, or until a CPAP of 20 cm H_2O had been reached. If the AHI was > 10/hr., the CPAP therapy was considered sub-optimal and the patient was discharged from the study (all subjects randomized to CPAP had an effective titration, and none reached a CPAP of 20 cm H_2O).

Placebo-CPAP and supplemental oxygen subjects were oriented to the mask and equipment in the same way as the CPAP group, and underwent a mock titration.

Polysomnography was repeated on the third night of admission as subjects slept with their assigned treatment. During this time the patients had time to adjust to CPAP in an observed environment and had their questions answered. The next morning subjects were discharged home and instructed to use their assigned treatment (CPAP, placebo CPAP, or supplemental oxygen) during sleep for two weeks. Research staff was in frequent telephone contact with subjects to answer questions, and check and encourage compliance with the therapy. All CPAP units (Aria LX CPAP System, Respironics Inc., Murrysville, Pennsylvania) had a hidden compliance clock.

After two weeks of treatment, the subjects were readmitted to the GCRC LSC to undergo a fourth overnight PSG with their assigned treatment. The ESS was repeated. To verify the effectiveness of the blinding process, before discharge from the study, the subjects were asked what they thought their treatment assignment was.

Sleep recordings and sleep quality variables

Sleep was recorded using the Grass Heritage, (model PSG36-2, West Warwick, RI) sleep recording system, which recorded central and occipital electroencephalogram (EEG), bilateral electro-oculogram, submental and tibialis anterior electromyogram (EMG), electrocardiogram, nasal airflow (nasal cannula and pressure transducer), oral airflow (thermistor), respiratory effort (chest and abdominal piezoelectric belts), and oxyhemoglobin saturation (SpO_2).

Sleep staging was scored according to the criteria of Rechtshaffen and Kales.[22] Sleep architecture variables included the percent of total sleep time for stage 1 (stage 1%), stage 2 (stage 2%), slow wave sleep (SWS%), and stage REM sleep (REM%). Other variables included total sleep time, sleep latency to first epoch of sleep, sleep efficiency, the number of sleep stage shifts occurring during the sleep study, and total arousal index (TAI).

Arousal definition was based on the criteria published in the 1992 ASDA Report on EEG arousals.[23] An arousal from sleep was defined as a sudden rise in EEG frequency to alpha or theta for ≥ 3 seconds but < 15 seconds whether or not associated with a rise in EMG activity, except for arousals during REM sleep which required also a rise in EMG activity. The abrupt appearance of K-complexes or a burst of delta activity before an arousal was scored as part of the arousal only if accompanied by superimposed alpha EEG frequency. The TAI was calculated by dividing the total number of arousals by the total sleep time.

Apneas were defined as decrements in airflow ≥ 90% from baseline for a period ≥ 10 seconds. Hypopneas were defined as decrements in airflow ≥ 50% but < 90% from baseline for a period ≥ 10 seconds. Airflow was measured using a pressure transducer and thermistor simultaneously. The pressure transducer was used as the primary channel to score apneas and hypopneas. The thermistor was used primarily to detect oral breathing, and served as a confirmatory adjunct to the pressure transducer measurement. The apnea hypopnea index (AHI)

and mean SpO_2 during the total time in bed were also used to assess the effectiveness of CPAP and supplemental oxygen therapy.

Statistical analysis

Eleven commonly measured variables from polysomnography were used to describe sleep quality (Table 2). The ESS score was evaluated as a secondary outcome. Data not normally distributed underwent natural log transformation before analysis. Differences between and within the three treatment groups over time were assessed using repeated measures analysis of variance (Two-way-ANOVA). Daily average treatment duration was included as a covariant to control for compliance. An alpha value of 0.05 was considered significant. This analysis allowed us to test for a main effect of treatment (CPAP vs. placebo-CPAP vs. oxygen), time effect (prior to treatment, after 1 day of treatment and after 14 days of treatment) and the interaction of time by treatment. A time effect alone would imply that the treatment itself had no specific effect on the variable of interest. A treatment by time interaction would imply that subjects responded to a specific treatment over time with a significant response. Post hoc analyses were done using independent sample t-tests, 2-tailed significance, with Bonferroni adjustment for multiple comparisons between treatments. A $p \leq 0.017$ was considered significant. We performed a posteriori power calculation for SWS% and stage 2%. Given our sample size and the observed distribution, we had 80% power to detect differences of 5 percentage points in SWS and 9 percentage points in stage 2 sleep over time between placebo and the treatment groups. Statistical analyses were performed using the SPSS statistical software packages (SPSS for Windows 11.0; SPSS Inc.; Chicago).

RESULTS

Of the 76 subjects admitted for testing, two were excluded from the study due to medical illnesses and two were excluded because of an AHI less than 15/hr. Three subjects were removed from the study due to inability to sleep with or intolerance of CPAP equipment. One subject was excluded because of a periodic limb movement during sleep index > 15. Five subjects were removed from the analysis because they did not complete the study protocol. The final sample included 63 subjects with an AHI ≥ 15.

Baseline measurements

Table 1 provides the subjects' characteristics. The subjects were predominantly men (79%), and were obese with an average body mass index (BMI) of 31.8± 6.1. On average, subjects had significant excessive daytime somnolence at baseline as reflected by the ESS score of 12.2± 5.4. There were no significant differences at baseline between groups in age, BMI, Sleepiness Scale score, or screening blood pressure.

There were no significant differences in the baseline sleep quality characteristics for the three treatment groups (Table 2). On overage, the subjects had severe obstructive sleep apnea with severe sleep fragmentation as noted by severely elevated AHI and TAI.

Compliance with therapy

Compliance with the treatment assignment was similar for all treatment groups (6.61 ± 1.19 hours, 5.98 ± 1.27 hours, and 6.60 ± 1.19 hours for the CPAP, placebo-CPAP and oxygen groups respectively). The mean effective titrated CPAP was 11.0 ± 3.7 cm H_2O (range 7 to 19 cm H_2O) for the CPAP treated group. Approximately one third of the subjects on placebo or supplemental oxygen felt they were receiving CPAP or subjectively felt better. Approximately one third of the subjects had no opinion as to their therapy assignment, and one third were able to correctly guess their treatment assignment at completion of the study.

Effect of treatment on sleep architecture and arousals

On repeated measures ANOVA, there was a significant group by time interaction for stage 1% ($p= 0.001$), REM% ($p < 0.001$), TAI ($p < 0.001$) and number of sleep stage shifts per night ($p = 0.032$). There was no group by time interactions for stage 2%, SWS% (Table 3), sleep latency, total sleep time, or sleep efficiency.

On post hoc analyses CPAP, as compared to the placebo-CPAP or supplemental oxygen, significantly reduced stage 1% ($p \leq 0.006$), number of stage shifts per night ($p \leq 0.004$), TAI ($p \leq 0.001$), and significantly increased REM% ($p \leq 0.003$), both after one and 14 days of therapy (See Figure 1).

Effect of treatment on respiratory parameters during sleep

On repeated measures ANOVA, there was a significant group by time interaction for AHI ($p <0.001$) and mean nocturnal SpO_2 ($p = 0.002$).

On post hoc analyses CPAP, as compared to the placebo-CPAP or supplemental oxygen, significantly reduced AHI ($p < 0.001$) both after one and after 14 days of therapy. CPAP and supplemental oxygen significantly increased mean nocturnal SpO_2 ($p \leq 0.01$) (See Figure 2).

Effect of treatment on daytime somnolence

On repeated measures ANOVA, there was a borderline significant time effect on the ESS score before and after therapy ($p = 0.076$), suggesting that excessive daytime sleepiness decreased with time for all treatment groups. There was no significant treatment effect or time by treatment interaction on ESS. However, only the CPAP group had a mean ESS score that was less than nine after two weeks of therapy (8.2 ± 4.4, 10.0 ± 4.5, 10.6 ± 6.4, for CPAP, placebo-CPAP, and oxygen respectively).

DISCUSSION

The effects of CPAP or supplemental oxygen in improving sleep quality in OSA have not been rigorously tested against an adequate placebo-CPAP as required by an evidenced based approach.[13] The lack of rigorously controlled studies is a decided limitation for advancing the knowledge base in sleep medicine. In this study we looked at the short term changes in sleep architecture with CPAP an supplemental oxygen and present evidence that in a randomized, prospective, placebo-CPAP controlled, double blinded trial, CPAP was associated with an improvement in sleep quality by decreasing stage 1 sleep and stage shifts, increasing REM sleep and reducing the total number of arousals. Surprisingly, CPAP had no effect on SWS, stage 2 sleep, or other sleep parameters, suggesting that CPAP was only partially effective in improving sleep architecture in our OSA patient sample population. As previously shown by controlled and uncontrolled studies, CPAP was completely effective in correcting AHI and mean nocturnal SpO_2 in subjects with severe OSA (Figure 2).[1-4] Supplemental oxygen, as a therapy for OSA, was only effective in correcting mean nocturnal SpO_2, and had no significant effect on any other sleep variable (Figure 1 and 2).

CPAP is considered the most effective therapy for obstructive sleep apnea. It is not unusual to encounter reported cases of remarkable improvements in excessive daytime somnolence and well-being after just one night of CPAP.[2,24] However, the strength of the evidence on the effectiveness of CPAP in correcting the sleep physiological derangements caused by OSA have been questioned.[1,13] There is a general lack of well designed and carefully controlled prospective studies to determine the true effectiveness of CPAP in improving sleep quality. In the current study we used extreme care to insure blinding and compliance with the treatment arms, allowing us to determine the effectiveness of both CPAP and supplemental oxygen in correcting sleep quality and respiratory physiology.

Effects of treatment on sleep architecture and arousals

Only the CPAP treated group demonstrated significant improvements in sleep architecture and arousals. CPAP significantly reduced stage 1% and the number of sleep stage shifts. CPAP also improved REM% to the normal range (Figure 1). These changes were noted after one day of therapy and were maintained at two weeks of therapy. The effect of CPAP on stage 1 and REM sleep appears to be the result of its effectiveness in correcting AHI and arousals. Apneic events are known to result in sleep fragmentation by increasing the number of arousals, which leads to greater proportions of stage 1 sleep and less REM sleep. We previously reported no significant improvement in sleep architecture after a one week CPAP trial compared to a sub-therapeutic CPAP control (CPAP at 2 cm H_2O), in a study with a similar design as the current one.[1] It is unclear why we did not see improvements in sleep architecture with CPAP in our prior study. However, a possible explanation is that the sub-therapeutic placebo-CPAP was not sufficiently sub-therapeutic and rather had a significant therapeutic effect on sleep architecture. In the current study, the placebo-CPAP used provided < 0.5 cm H_2O pressure at the nasal interface at end-expiration and 0 cm H_2O pressure during inspiration.

McArdle and Douglas published the only other placebo-controlled trial in the literature that specifically studied the effectiveness of CPAP in correcting sleep architecture in OSA.[12] They used an oral capsule-placebo versus CPAP for one month in a cross-over design. Similar to the current study, they found that CPAP reduced stage 1 sleep and arousal index, and had no effect on sleep efficiency. However, opposite to our findings, they found improvement in SWS and no improvement in REM sleep. These differences are not likely explained by duration of treatment trial, since in the current study and in uncontrolled studies,[4,25] CPAP was effective in improving REM sleep and various other measures of sleep architecture even after one single

night of therapy. Compliance with CPAP was more than 6 h/night in the current study as compared to 4.5 h/night in the McArdle and Douglas study. Greater total sleep time allowing for more REM sleep cycles could explain the correction of REM% in the current study. Conversely, a shorter total sleep time in the McArdle and Douglas study could have overestimated SWS, since it primarily occurs in the first third of the sleep period. Another factor that could be contributing to the differing results in SWS include the crossover design in the McArdle and Douglas study that may have provided greater statistical power than our parallel design with a similar sample size. Regrettably, placebo studies in this area are extremely rare and inconsistencies across these few studies will only be resolved by further replication.

Stage 2 sleep is the most abundant stage during normal sleep, ranging from 45 to 55% of total sleep time in young adults.[26] Stage 2 sleep has recuperative effects on alertness, mood, and performance.[27] In untreated sleep apnea patients stage 1 and stage 2 sleep rise in an apparent compensation for the reduction in REM sleep and SWS. Therefore, with the correction of apneas with CPAP, we expected a reduction in stage 2 sleep. The lack of reduction in stage 2 sleep in this study was probably related to the lack of improvement in SWS. However, in our CPAP and placebo groups, (mean age 48 years), SWS and stage 2 sleep percentages before and after treatment were low, but within their age-related normative values (Table 3).[26] Therefore, it is possible that a significant change in SWS and stage 2 sleep with CPAP may only be seen in younger OSA patients, and thus explain the lack of response to CPAP in our population. Further research with age stratification is needed to clarify this point. This study looked at sleep architecture changes based on in-laboratory polysomnography measurements. Therefore, the low SWS% noted in our population could have been due to a laboratory effect. It is possible that sleep quality patterns may be different when the patients sleep in their own homes and beds.

Effect of treatment on daytime somnolence

In the current study, the effect of CPAP in decreasing the ESS score over time was not statistically different from placebo-CPAP or supplemental oxygen. Our results differed from those of Monserrat et al. and Jenkinson et al., both of whom used a sub-therapeutic placebo-CPAP similar to ours.[6,11] They reported improvement in daytime sleepiness and function with a 6 and 4-week course of CPAP respectively. Our findings also differ from those of McArdle and Douglas who reported improvement in ESS score after 6-12 months of CPAP.[12] The significant difference in design between these studies and ours is the longer duration of CPAP therapy. It is possible that the ESS score takes longer than 2 weeks of CPAP to improve, or conversely, that the beneficial effects of placebo-CPAP attenuate over time.

The effect of supplemental oxygen

Supplemental oxygen therapy for OSA has been recommended for those who are not able to tolerate CPAP and who are not surgical candidates.[15] Several small uncontrolled or non-blinded studies (n = 4 – 21) that used supplemental oxygen to treat OSA had mixed results in overnight oxygenation and AHI.[15,16,28,29] In general, supplemental oxygen given at a flow ranging from 2-4 L/min, improved nadir saturation and in some cases also improved mean saturation. In two studies, transtracheal oxygen decreased AHI,[28,29] and in one study, supplemental oxygen was reported to be more effective in improving oxygenation and hypopneas than CPAP.[16]

In the current study, supplemental oxygen given at a fixed flow of 3 L/min through a placebo-CPAP set-up, was highly effective in correcting mean nocturnal oxyhemoglobin saturation only (Figure 2). Supplemental oxygen had no effect on AHI, TAI, or on any other sleep architecture variable (Figures 1 and 2). Our findings are consistent with the hypothesis that

increased respiratory effort and not transient hypoxemia causes arousals in OSA. The best example of such phenomena is the upper airway resistance syndrome, a variant of OSA, were the patient presents classically with frequent arousals but no transient hypoxemia.[30] Also, hypoxia is a poor arousal stimulus in humans, both in NREM and REM sleep.[31] We chose a commonly used flow of supplemental oxygen (3 L/min) used as initial therapy for a number of illnesses including OSA. It is unclear if a greater flow of oxygen would have resulted in improvements in other sleep quality parameters. The variability of the outcomes in prior reports,[15,16,28,29] is most likely due to small study sample populations, widely different study protocols, and lack of adequate blinding or controls, making it difficult to compare with our current findings. The combination of supplemental oxygen with placebo-CPAP, instead of the usual nasal cannula utilized in other studies, allowed for a more rigorous comparison between CPAP and supplemental oxygen.

The specific role of oxyhemoglobin desaturation in the pathophysiology of OSA has not been well elucidated. It is unclear if drops in SpO_2 have any pathologic additive or synergistic interactions with apneas or arousals. However, there is strong evidence that intermittent hypoxemia is the primary mediator for sympathetic nervous system activation and hypertension seen in OSA.[14,32,33] In the current study, supplemental oxygen effectively improved to within normal range mean SpO_2 without affecting AHI or TAI (see Figures 1 and 2). Our data suggest that supplemental oxygen could be used as a tool to separate the individual pathophysiological effects of hypoxemia from those of apneas and arousals in OSA. The effectiveness of supplemental oxygen alone in preventing OSA related cardiovascular complications is not known.

Weaknesses and strengths of the study

In this study, we carefully controlled for CPAP by using a placebo-CPAP set-up that was

well accepted by the patient and provided less than 0.5 cm H_2O pressure at the nose. Patients using placebo-CPAP or placebo-CPAP plus oxygen supplementation experienced a gentle breeze from the CPAP mask, which we feel is critical for a true placebo-CPAP model. We felt that such a placebo set-up would replicate the actual experience that the CPAP patient undergoes, minus the continuous positive airway pressure. The placebo-CPAP was well tolerated, and on exit questioning approximately one third of the subjects receiving placebo-CPAP or supplemental oxygen felt subjectively better or felt that they had received real CPAP. Approximately one third of the participants had no opinion as to what they had received. In the current study, the compliance with all treatments arms was excellent (6.4 ± 1.2 hrs/night), increasing the level of confidence in our findings.

A potential weakness in the current study was the relative short duration of therapy (2 weeks). CPAP can often take longer than two weeks for proper adjustment. However, we purposely worked closely with the patients to insure compliance and trouble shoot any problems arising with the various component of CPAP resulting in a high level of compliance.

We used a parallel design in this study which can be viewed as less powerful than a crossover design as used by McArdle and Douglas.[12] However, a crossover design would not have been appropriate when using placebo-CPAP, since going from real CPAP to placebo would potentially be quite obvious to the patient.

In a study such as ours, it would have been interesting to explore the changes produced by CPAP or oxygen on hypopneas of various definitions, i.e. with or without an associated oxyhemoglobin desaturation. However, our definition of hypopneas did not allow for such an analysis.

Another limitation in the study design was the use of a fixed flow of oxygen to correct

OSA induced desaturations. In retrospect, titration of the supplemental oxygen to achieve a certain predetermined level of SpO_2 during respiratory events would have been more appropriate, since the degree of desaturation will vary with obesity, REM sleep, and pulmonary function.[34,35]

CONCLUSIONS

In conclusion CPAP therapy when compared to placebo-CPAP was associated with a rapid improvement in sleep quality by decreasing sleep stage shifts, reducing stage 1 sleep, and improving REM sleep, which persisted throughout a 2-week treatment trial. CPAP also improved to within normal limits the respiratory and arousal abnormalities characteristic of OSA patients. The effectiveness of supplemental oxygen as a therapy for OSA was restricted to oxyhemoglobin saturation during sleep.

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FIGURE LEGENDS

Figure 1. Time plots of the effectiveness of continuous positive airway pressure (CPAP, closed circles), supplemental oxygen (opened squares), and placebo-CPAP (opened circles), on correcting sleep architecture sleep-quality variables. Values represent mean ± standard error of the mean. (A) Stage 1 sleep percent (Stage 1 %) is improved to near normal by CPAP. (B) Stage REM sleep percent (REM %) is improved to normal limits by CPAP. (C) Number of stage shifts/night is significantly reduced by CPAP. (D) Total arousal index (TAI) improved to within normal limits with CPAP. Supplemental oxygen at 3 L/min had no effects on sleep architecture. The effects of CPAP were apparent during the first night of therapy. * Denotes statistically significant change from placebo-CPAP.

Figure 2. Time plots of the effectiveness of continuous positive airway pressure (CPAP, closed circles), supplemental oxygen (opened squares), and placebo-CPAP (opened circles), on correcting respiratory sleep-quality variables. Values represent mean ± standard error of the mean. CPAP improved to within normal limits (A) apnea hypopneas index (AHI). CPAP and supplemental oxygen at 3 L/min improved to within normal limits (B) Mean oxyhemoglobin saturation (SpO_2). The effects of CPAP and oxygen were apparent during the first night of therapy. * Denotes statistically significant change from placebo-CPAP.

511 Table 1. Characteristics of subjects by treatment group prior to randomization (mean ± SD,

512 range)*

Variables	***Placebo***	***CPAP***	***Supplemental O_2***
N	19	22	22
Men/ women	16/3	18/4	16/6
Age	48.3 ± 11.2 (31 – 65)	48.2 ± 10.9 (29 – 65)	43.4 ± 8.6 (30 – 56)
BMI (kg/m^2)	31.8 ± 6.8 (23.4 – 50.2)	31.8 ± 5.5 (23.1 – 44.0)	32.0 ± 6.4 (23.4 – 52.0)
ESS	12.3 ± 6.7 (0 – 23)	11.6 ± 4.9 (2 – 22)	12.8 ± 4.5 (0 – 21)
Mean SBP (mmHg)	126.7 ± 16.6 (102 – 161)	134.8 ± 15.7 (111 – 163)	132.3 ± 13.3 (113 – 162)
Mean DBP (mmHg)	77.2 ± 10.3 (57 – 96)	79.7 ± 8.8 (61 – 96)	78.8 ± 9.7 (64 – 105)

513 * There was no statistically significant difference between treatment groups
514 BMI: Body mass index (weight in kg/height in m^2)
515 ESS: Epworth Sleepiness Scale score
516 SBP: Systolic blood pressure
517 DBP: Diastolic blood pressure

Table 2. Baseline Sleep Characteristics by Treatment Group (mean ± SD)*

Variables	***Placebo***	***CPAP***	***Supplemental O_2***
Total sleep time (min)	338.2 ± 38.7	347.8± 47.8	358.4± 53.6
Sleep efficiency (%)	83.1 ± 7.2	80.7 ± 11.4	83.8 ± 11.3
Sleep latency (minutes)	9.7 ± 6.9	7.7 ± 5.2	9.3 ± 14.5
Stage 1%	17.9 ± 11.4	19.5 ± 9.3	19.0 ± 12.4
Stage 2%	62.7 ± 8.2	61.3 ± 9.2	58.4 ± 11.6
SWS%	4.1 ± 5.1	5.0 ± 6.9	5.7 ± 7.4
REM%	15.3 ± 4.8	14.3 ± 6.9	15.1 ± 4.7
Total arousal index	43.8 ± 32.6	41.0 ± 28.4	47.8 ± 34.2
Stage shifts/night	194 ± 68	200 ± 75	206 ± 65
AHI	57.5 ± 32.1	65.9 ± 28.6	64.9 ± 33.7
Mean SpO_2 (%)	92.9 ± 4.4	93.2 ± 4.0	92.6 ± 5.0

* There was no statistically significant difference between treatment groups
Stage% = percent of total sleep time spent at a specific sleep stage. SWS = slow wave sleep (stage 3 + stage 4 sleep). AHI = apnea hypopnea index. SpO_2 = Oxyhemoglobin saturation during total time in bed by pulse oximeter.

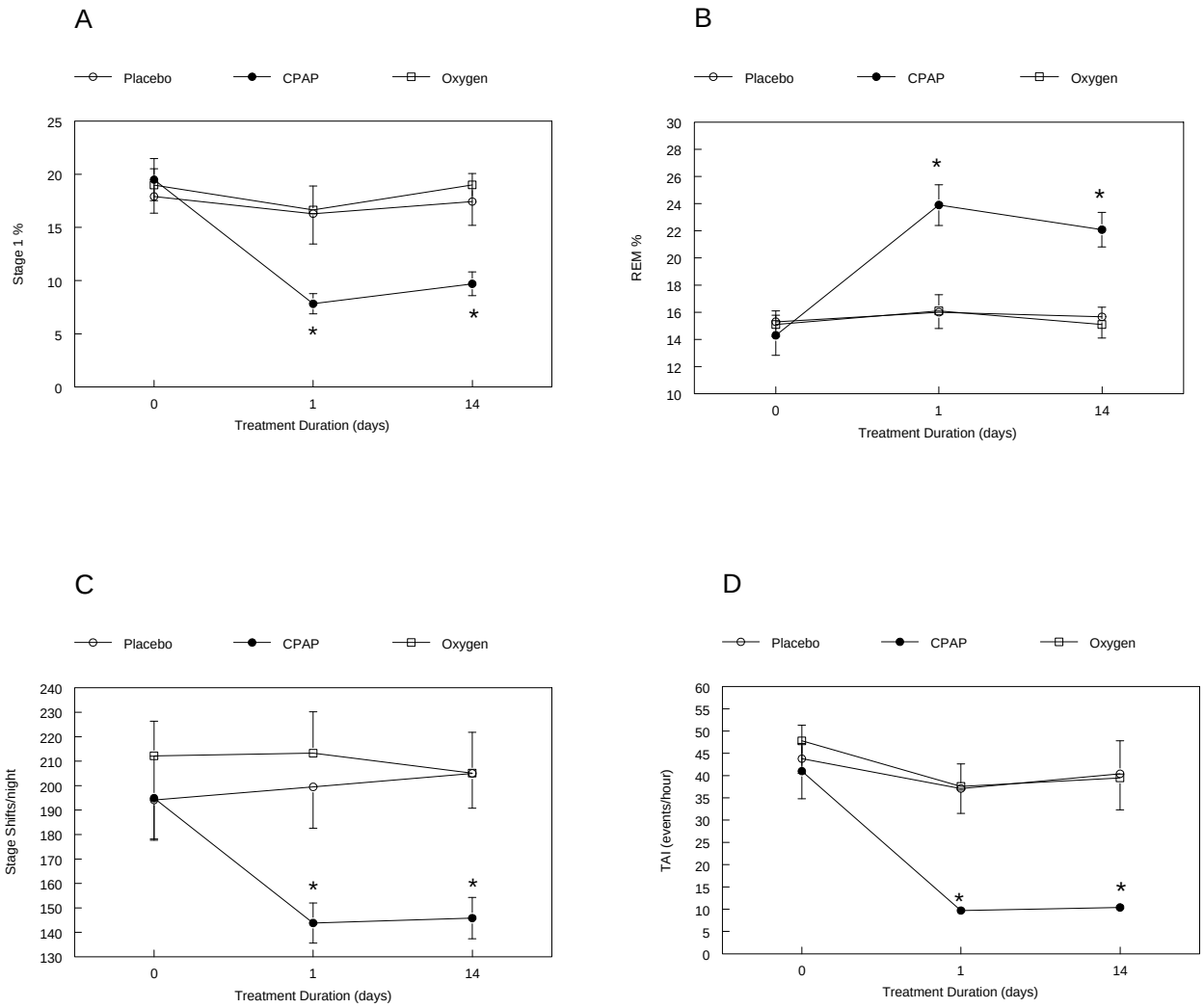
Table 3. Changes noted in SWS% and stage 2% with continuous positive airway pressure (CPAP), supplemental oxygen, and placebo-CPAP.

SWS% ± SD	**baseline**	**After one day**	**After 2 weeks**
placebo	4.1 ± 5.1	5.9 ± 6.4	4.7 ± 5.8
CPAP	5.0 ± 6.9	11.5 ± 10.0	7.1 ± 6.2
Oxygen	7.3 ± 11.3	7.8 ± 9.2	6.9 ± 9.5

Stage 2% ± SD	**baseline**	**After one day**	**After 2 weeks**
placebo	62.7 ± 8.2	61.9 ± 10.1	62.2 ± 9.0
CPAP	61.3 ± 9.2	56.8 ± 10.8	61.1 ± 9.2
Oxygen	58.6 ± 12.1	59.0 ± 14.8	59.0 ± 14.4

* There was no statistically significant difference between treatment groups over time.

531 Figure 1
532



533 Figure 2
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