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Commentary on CPAP vs. Oxygen for Treatment of OSA

Commentary on Gottlieb DJ, Punjabi NM, Mehra R, et al. CPAP versus oxygen in obstructive sleep apnea. N Engl J Med 2014;370:2276-2285.

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SUMMARY OF GOTTLIEB ET AL.

Question

In individuals with cardiovascular (CV) disease or multiple CV risk factors and obstructive sleep apnea (OSA), does the 12 week use of continuous positive airway pressure (CPAP) therapy vs. nocturnal oxygen vs. sleep and lifestyle education (control) improve the 24-hour ambulatory mean blood pressure?

Methods

Design

Multi-center, randomized, controlled trial; clinicaltrials.gov Identifier: NCT01086800.

Allocation

Randomization was performed centrally via a web-based system, using a stratified permuted block design. The randomization sequence was concealed. Allocation was stratified by recruitment site and by the presence of coronary artery disease.

Blinding

The investigators and participants were not blinded to study arm assignment. Clinical site staff, performing ambulatory blood pressure testing, and coordinating center staff, editing and scoring the blood pressure recordings, were blinded to group assignment.

Follow-up period

3 months.

Setting

Participants were recruited from cardiology clinics at four participating US medical centers and were screened for OSA using the Berlin questionnaire, followed by home sleep testing for eligible patients.

Subjects

318 participants were randomly assigned to healthy lifestyle and sleep education alone (HLSE – control; n = 106), or CPAP and HLSE (n = 106) or nocturnal oxygen (NSO) and HLSE (n = 106). The mean age of participants was HLSE: 63.1 ± 7.7, CPAP: 63.5 ± 7.0, and NSO: 62.9 ± 7.3. More than 69% of participants were male and white, mean BMI range was 33.0 to 34.7 and the mean AHI range was 24.0 ± 8.1 (NSO) to 25.5 ± 8.8 (HLSE). Majority of patients were on an Ace-inhibitor or ARB or β blocker, more than 50% had a history of coronary artery disease (CAD), 88% had hypertension. Blood pressure was generally well controlled at baseline.

Inclusion Criteria: 1) Age 45-75 years; 2) High risk for CVD event, defined by: a) established stable CAD or b) 3 or more established CVD risk factors, e.g., hypertension (treated by a physician or systolic BP > 140 or diastolic BP > 90), diabetes mellitus, BMI > 30, total cholesterol > 240 or LDL cholesterol > 160 or being treated for dyslipidemia; 3) Berlin score ≥ 2; 4) Home sleep study confirmed OSA defined as AHI ≥ 15.

Exclusion Criteria: 1) Congestive heart failure with a cardiac ejection fraction of < 35% or NYHA class ≥ 2; 2) poorly controlled HTN (> 170/ > 110), poorly controlled diabetes, stroke with functional impairment or other poorly controlled co-morbidities; 3) severe chronic insomnia or circadian rhythm disorder; 4) severe sleepiness with an Epworth Sleepiness Score of ≥ 16; 5) resting oxygen saturation < 90%; 6) pregnancy; 7) using oxygen or past use of prescribed CPAP or BiPAP for sleep apnea; 8) Had upper airway surgery (UPPP) for snoring or sleep apnea; 9) AHI > 50, central sleep apnea index > 5, nocturnal oxygen saturation < 85% for > 10% of sleep record.

Intervention

Patients meeting eligibility criteria were randomized to HLSE (control), CPAP and HLSE, or NSO and HLSE for 12 weeks. Auto-titrating CPAP was used for treatment of OSA in CPAP study arm and then set within 7 days to a fixed 90th percentile delivered pressure obtained from recorded machine data. The fixed CPAP pressure was used for the remainder of the study. Nocturnal oxygen was delivered via a stationary concentrator at 2LPM using nasal cannula. Phone follow-up and remote transmission of PAP adherence were completed at regular intervals. At 12 weeks, the primary and secondary outcome measurements were repeated.

Outcomes

The primary outcome was the adjusted 24-hour ambulatory mean blood pressure (MAP) at 12 weeks (adjustments were

made for study site, presence or absence of coronary artery disease, and blood pressure as measured at baseline). Secondary outcome measures included blood draws for glucose, insulin, low-density lipoprotein cholesterol (LDL), high-density lipoprotein cholesterol (HDL), total cholesterol, triglycerides, N-terminal pro–brain (B-type) natriuretic peptide (BNP), and high-sensitivity C-reactive protein. Endothelial function was also assessed using the EndoPAT device (Itamar Medical) after an overnight fast.

This was designed as a Phase II study with a conservative assumption that 12 week data will only be available for 85% of subjects and the coefficient of variation of the response in each arm would be either 0.1 or 0.5; a sample size of 100 per arm would have 80% power in detecting an effect size (ratio of the mean response between any 2 of the 3 arms) of at least 1.04 and 1.21 respectively, based on a two-sample t-test and a two-sided significance level of 0.05.

Patient follow-up

Per protocol analysis for those who had complete data for primary outcome at 12 weeks. However, all patients received the assigned intervention. Some patients were lost to follow-up (95% completed study), withdrew or did not complete primary outcome; 97 of 106 (91.5%) included in MAP analysis in HLSE arm, 90 of 106 (84.9%) included in MAP analysis in CPAP arm, and 94 of 106 (88.7%) were included in primary outcome analysis in NSO arm. A sensitivity analysis using multiple imputation techniques to assess the effect of missing data did not change the results of the primary analysis.

Main results

The CPAP group achieved a statistically significant decrease in adjusted 24-hour mean blood pressure compared with education alone (2.4 mm Hg; P = .04) and compared with nocturnal oxygen (2.8 mmHg; p = 0.02). No significant difference was noted in the primary outcome in the oxygen group vs. control. Analysis of the reactive hyperemia index (endothelial function) at 12 weeks revealed no significant differences among the three groups. CPAP was associated with a significantly lower adjusted level of C-reactive protein at 12 weeks than was education alone; no significant difference in other lab measurements.

The mean duration of nocturnal supplemental oxygen use was 4.8 ± 2.4 hours per night which was significantly greater than the mean CPAP use of 3.5 ± 2.7 hours per night

(P = 0.001). There was no significant association between hours of CPAP use and 24-hour mean arterial pressure, however nocturnal systolic pressure improved more with each additional hour of CPAP used.

Conclusion

In predominately male adults with mildly symptomatic, moderate to severe OSA and stable cardiovascular disease or risk factors, treatment of OSA with CPAP improved the mean 24 hour blood pressure after 12 weeks of therapy. Nocturnal supplemental oxygen did not show an improvement. The results were achieved in a population of subjects with relatively well controlled blood pressure, on anti-hypertensive medications, and despite the exclusion of those with very severe OSA.

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COMMENTARY ON GOTTLIEB ET AL.

Obstructive sleep apnea (OSA) is a common disease with significant cardiovascular adverse health consequences. Epidemiologic studies published in the last century.[1-5] indicated that moderate to severe sleep-disordered breathing affected an estimated 4% of middle-aged women and 9% of middle-aged men. Current prevalence is likely higher given the burgeoning obesity epidemic in the US. A recent study estimated current prevalence of moderate to severe SDB (AHI ≥ 15) at 13% of middle-aged men and men and 6% of middle -aged women.[6]

Sleep-disordered breathing (SDB) is a recognized risk factor for cardiovascular disease including hypertension, coronary artery disease, and cardiac mortality.[7-10] Effective treatment of SDB may have significant public health implications. Unfortunately, CPAP adherence remains suboptimal, especially in asymptomatic individuals.[11-13] The study by Gottleib et al. explores an alternative approach in patients who were less likely to use PAP therapy, individuals seen in a cardiology practice, who were not a priori diagnosed with SDB. The authors demonstrated convincingly that treatment with CPAP improved the mean 24 hour blood pressure after 12 weeks of therapy in patients with moderate to severe OSA and stable cardiovascular disease or risk factors.

The salutary response to CPAP therapy in this population may have significant implications for the diagnosis and management of SDB. The investigators followed the scoring guidelines published by the American Academy of Sleep Medicine.[14,15] Specifically, the investigators used a desaturation threshold of 3% or more (rather than 4% or more) as indicative of hypopnea in the presence of 50% reduction of flow. Therefore, a portion of participants in this study would have been missed if the current CMS threshold of 4% reduction in oxyhemoglobin saturation had been used. The improvement in BP in this study further corroborates several studies that have demonstrated an association between respiratory events; even those associated with modest desaturation, and increased risk of cardiovascular consequences.[16]

The lack of reduction in blood pressure in the supplemental oxygen arm suggests that elimination of chronic intermittent hypoxia was not sufficient to decrease blood pressure. This finding contrasts with multiple studies demonstrating that episodic hypoxia contributes to the breathing instability,[17,18] carotid body sensitization[19] and persistent sympathetic excitation.[20,21] However, it is unclear whether supplemental oxygen *eliminated* episodic oxyhemoglobin desaturation or *blunted* its magnitude. It is plausible that cycles of deoxygenation-reoxygenation may have persisted, albeit at a higher nadir oxyhemoglobin saturation. Evidence in the literature suggests that the consequences of episodic hypoxia may be determined by the frequency, rather

than the magnitude of oxyhemoglobin desaturation.[22,23] It is also possible that CPAP was more effective in eliminating episodic hypoxia than the fixed flow of supplemental oxygen. Further studies are required to ascertain the potential role for supplemental oxygen in patients with SDB and high loop gain or those with high propensity to breathing instability.[18,24,25]

The study by Gottlieb et al. poses a few unanswered questions that would require a larger sample size to address. For example, the study population consisted predominantly of white men (80% and 75% respectively). The multitude of consequences of intermittent hypoxia may be influenced by age and gender, depending on the experimental paradigm and the specific physiologic consequence.[26-28] Whether the results are representative of the findings in women or in other races cannot be determined from the study. The lack of improvement in any of the secondary outcomes, including reactive hyperemia index was intriguing. It is unclear if the duration of treatment was insufficient for such an effect to manifest. Alternatively, vascular and endothelial changes may be irreversible following prolonged exposure to chronic episodic hypoxia.

Finally, the study demonstrated a significant reduction in blood pressure following CPAP therapy, even in patients with well-controlled hypertension at baseline. It is possible that the response to PAP therapy may be more pronounced in patients whose hypertension is less controlled. The key element is adherence to PAP therapy.

In Summary, the study by Gottlieb et al. reaffirms the benefits of CPAP therapy for the treatment of sleep apnea, even in patients with modest degree of sleepiness. Until we discover a cure, CPAP therapy remains the treatment of choice for sleep apnea.

CITATION

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DISCLOSURE STATEMENT

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