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DEPARTMENTS

JOURNAL CLUB

Effects of CPAP and Weight Loss on OSA Outcomes

Commentary on Chirinos et al. CPAP, weight loss, or both for obstructive sleep apnea. N Engl J Med 2014;370:2265-75.

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SUMMARY OF CHIRINOS ET AL.

Question

In individuals with obesity and moderate to severe obstructive sleep apnea (OSA), does the 24 week use of continuous positive airway pressure (CPAP) therapy and weight loss vs. CPAP alone vs. weight loss alone improve the CRP level?

Methods

Design

Two center, randomized, controlled trial; ClinicalTrials.gov identifier: NCT0371293.

Allocation

Randomization was conducted with a permuted-block design, with stratification according to sex, status with respect to statin use, and enrollment site. The randomization sequence was concealed.

Blinding

The investigators and participants were not blinded to study arm assignment. Research staff, measuring primary and secondary outcomes (except for blood pressure), were blinded to group assignment.

Follow-up period

24 weeks.

Setting

Participants were recruited from sleep medicine, general medicine clinics, and through radio advertisements. They were screened for OSA using a home based sleep monitor (ApneaLink, Resmed).

Subjects

181 participants were randomly assigned to weight loss alone (n = 61), or CPAP and weight loss (n = 62) or CPAP alone (n = 58). The mean age of participants: Weight loss alone 48.3 years, CPAP and Weight loss 49.0 years, and CPAP alone 49.8 years. More than 53% of participants were male and white, mean BMI range was 38.1 to 39.8 and the mean AHI range was 39.7 ± 20.3 (weight loss group) to 47.1 ± 26.86 (CPAP and weight loss). Median baseline CRP levels ranged from 4.3 to 4.7 mg/liter. Hypertension was diagnosed in 39-41% of participants and less than half were on anti-hypertensive medication.

Inclusion Criteria: 1) Age 18 to 80, 2) Moderate to severe OSA (AHI > 15 events/hour), diagnosed by in lab polysomnography, 3) Body mass index of > 30 kg/m^2, 4) Baseline CRP > 1.0 mg/dl, 5) Informed consent.

Selected Key Exclusion Criteria: 1) Predominant central sleep apnea, 2) Type 1 Diabetes, 3) Type 2 Diabetes that was poorly controlled or associated with recent medication changes, 4) Use of supplemental oxygen, 5) Acute coronary syndrome or stroke within 3 months of study onset, 6) A high-risk occupation necessitating treatment of OSA, 7) Blood pressure > 160/95 mmHg, 8) Active infection, malignancy or chronic inflammatory disorders, or systemic steroid use, 9) Medical conditions that were unstable or would compromise the safety of the subject, 10) Severe depression, 11) Significant left ventricular dysfunction, arrhythmia, 12) Evidence of severe untreated restless leg syndrome or chronic pain syndrome that gave rise to frequent awakenings at night.

Intervention

Patients meeting eligibility criteria were randomized to the three study arms for 24 weeks. An in laboratory CPAP titration study was performed and subjects in the study arms with CPAP received a fixed pressure CPAP or auto-adjusting CPAP device. Adherence to CPAP therapy was monitored weekly by a wireless router attached to the CPAP machine. Participants in study arms requiring weight loss received weekly counseling sessions with a caloric intake goal set at 1200-1500 kcal/day for those weighing < 114 kg and 1500-1800 kcal/day for those weighing ≥ 114 kg. Unsupervised exercise was initiated at week 4, starting at four, 15 minute weekly sessions, and increasing to four, 50 minute weekly sessions by week 15. Primary and secondary outcomes were measured at baseline, weeks 8, and 24.

Outcomes

The primary outcome was the 24 week change in the CRP level. Secondary outcome measures included insulin sensitivity and dyslipidemia (determined by measuring serum levels of triglycerides, high density lipoprotein [HDL] cholesterol, low-density lipoprotein [LDL] cholesterol, and LDL-particle concentration).

Exploratory end points included systolic blood pressure, mean arterial pressure, pulse pressure, and HDL-particle concentration.

A modified intention to treat analysis was performed for the primary analysis, defined as all participants who were randomly assigned to a study group and for whom at least one follow-up observation was available. Additional per protocol analyses (defined as those participants who had a minimum of 5% of baseline weight loss and for whom adherence to CPAP therapy was at least 4 hours/night on at least 70% of total number of nights) were performed.

On the basis of previous studies evaluating the effects of CPAP therapy alone and weight loss alone on CRP levels, the study had 90% power to detect standardized between-group differences in the change from the baseline CRP level of at least 0.53 mg/liter in the modified intention to treat population and at least 0.79 mg/liter in the per-protocol population, allowing for a type I error rate of 0.05.

Patient follow-up

A total of 136 participants completed the study (35 dropped out before the 8 week follow-up and an additional 10 participants dropped out after 8 weeks). The modified intention to treat analysis included 146 participants who had at least one study endpoint measurement after initiation of therapy.

Main Results

Baseline characteristics were similar in all three groups. The decline in body weight was similar in the weight-loss and combined-intervention groups (6.8 kg and 7.0 kg, respectively); there was no observable decline in body weight in the CPAP group. The average duration of CPAP use was 4.0 hours per night, with no significant differences between the CPAP alone and combined intervention groups. Of the 146 participants with at least one endpoint measurement, only 90 met the adherence criteria determined a-priori for the per protocol analysis.

The combined intervention group did not have a significant incremental improvement (between group differences) on CRP levels, as compared with either weight loss alone or CPAP alone, in either the modified intention-to-treat or the per-protocol analyses. In both the modified intention-to-treat population and the per-protocol population, the CRP level was significantly reduced at 24 weeks (compared to baseline; within group difference) in the weight-loss and combined-intervention groups but not in the CPAP group, and the reduction in the CRP level was significantly greater ($p = 0.01$) in the weight-loss group than in the CPAP group.

For the secondary outcomes, the weight loss only and the combined interventions groups had reductions in insulin resistance, and serum triglyceride levels; but there were no significant differences in these values between the combined-intervention group and the weight-loss group. None of these changes were observed in the group receiving CPAP alone. Blood pressure was reduced in all three groups. In per-protocol analyses, the combined interventions resulted in a larger reduction in systolic blood pressure and mean arterial pressure than did either CPAP or weight loss alone.

Conclusion

In predominately male adults with severe OSA, treatment of OSA with CPAP and weight loss for 24 weeks did not show a significant incremental improvement in CRP when compared with CPAP alone, or weight loss alone. However, the CRP levels did significantly change from baseline in the combined interventions arm and the weight loss alone arm with no significant change noted in the CPAP alone arm. For the secondary outcomes, treatment with CPAP and weight loss had an incremental effect on insulin resistance and serum triglyceride levels, compared with CPAP alone, but no significant incremental effects of combined therapy were observed compared with weight loss alone. In exploratory analyses, combination therapy was associated with a larger reduction in blood pressure among participants who adhered to the therapeutic regimen.

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COMMENTARY ON CHIRINOS ET AL.

Kudos to Chirinos and colleagues for designing a pragmatic and clinically relevant study in an attempt to understand the individual importance of obstructive sleep apnea (OSA) and obesity on cardiovascular risk. The study has increased our understanding and should inform practice going forward.

First, one comment on the study design. The authors chose to focus on C-reactive protein (CRP) both as an inclusion criteria and as the study's primary outcome, as a proxy for cardiovascular risk. The decision to use CRP was likely another practical one, in that a much longer and expensive study would be needed to assess the impact of the interventions on cardiovascular health if a hard outcome, such as incident myocardial infarction, were used. Thus, in order to see differences in CRP, only subjects with an elevated CRP could be admitted into the study—which might have limited the generalizability of the results. Thankfully then, in some ways, the study was negative in terms of the primary outcome, yet still revealed much useful information in other physiologically important parameters. Additionally, although CRP has been used in other large and practice-changing trials, there are problems with its use as a proxy: it is not clear that CRP is on the causal pathway to improved cardiovascular health; different studies have used different thresholds to define high risk; what level of CRP reduction might be considered clinically significant is not known; nor can it be assumed that any reduction achieved via CPAP use would have had the dramatic benefits seen in CRP reduction achieved with statins (HMG-CoA reductase inhibitors).[1,2] Other recent studies in the field, such as by Gottlieb and colleagues, have instead used blood pressure changes after 3 months of intervention.[3]

The study reminds us how hard it is to get subjects motivated enough to either wear CPAP or lose weight through diet and exercise. About 20 percent of enrolled subjects choose not to continue with the study (and most of the analysis was either modified intention-to-treat or per-protocol). Since the subset of patients who volunteer for research are likely to be more

adherent than patients who do not, this is likely an underestimate of the number of "real world" patients who would not continue with OSA/obesity treatment. Conversely, it is encouraging that the medical weight loss intervention was associated with substantial weight loss (~7 kg, or 15 pounds), and robust improvements in blood pressure and insulin sensitivity. It would be important to learn which patients successfully lose weight. Are these patients who are most adherent to CPAP, or are these the patients most fearful of CPAP?

Surprising to me were the average blood pressure changes seen with weight loss, which dwarf those of CPAP alone. Given these dramatic improvements, and that weight gain that is sometimes seen with CPAP use,[4] it will no longer be sufficient to focus on metrics of CPAP adherence alone when determining quality of care in a Sleep Medicine clinic. Efforts at weight loss must also be emphasized. In fact, I do think that the authors accomplished their goal of determining the individual importance of obesity and OSA for patients. Based on the results, there are two possible paradigms for the management of such patients. First, that OSA is a disease with neurocognitive and cardiovascular consequences. The study by Chirinos and colleagues support the use of CPAP for the former, and weight loss for the latter. Alternatively, CPAP may be thought of as a stop gap measure in the short term, with efforts at weight loss the appropriate long term therapy for obese patients with OSA.

CITATION

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DISCLOSURE STATEMENT

The authors have indicated no financial conflicts of interest.