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JOURNAL CLUB

Effect of CPAP on Blood Pressure in Patients with Obstructive Sleep Apnea and Resistant Hypertension

Commentary on Martínez-García M, Capote F, Campos-Rodríguez F, et. al. Effect of CPAP on blood pressure in patients with obstructive sleep apnea and resistant hypertension: the HIPARCO randomized clinical trial. JAMA 2013;310:2407-2415.

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SUMMARY OF MARTÍNEZ-GARCÍA ET AL.

Question

In individuals with resistant hypertension and obstructive sleep apnea (OSA), does the 12 week use of continuous positive airway pressure (CPAP) therapy vs. control (no CPAP) improve the 24-hour ambulatory mean blood pressure?

Methods

Design

Open label, multi-center, randomized, controlled trial; clinicaltrials.gov Identifier: NCT00616265.

Allocation

Randomization was conducted by site investigator, using specific software designed for the study that randomly assigned group allocation. Allocation was stratified by site. The randomization sequence was concealed by the software.

Blinding

The investigators and participants were not blinded to study arm assignment. The primary outcome measurement was blinded.

Follow-up period

3 months.

Setting

Participants were consecutively recruited from the Hypertension Clinical Units of 24 teaching hospitals in Spain.

Subjects

194 patients were randomly assigned to receive CPAP (n = 98) or no CPAP (control; n = 96).The mean age of participants was 56.0 ± 9.5 years, 69% were male, mean BMI was 34.1 ± 5.4 and the mean AHI was 40.4 ± 18.9. The mean number of years since diagnosis of resistant hypertension was 12.8 ± 8.6 and mean number of systemic anti-hypertensive medications used was 3.8 ± 0.9.

Inclusion Criteria: 1) primary resistant hypertension defined on 24-hour ambulatory blood pressure monitoring (24-ABPM) as blood pressure that remained above goal (i.e., average SBP ≥ 130 mm Hg, average DBP ≥ 80 mm Hg, or both) in spite of concurrent use of at least 3 antihypertensive medication agents prescribed at doses that provide optimal benefit, 2) age 18 to 75 years, 3) OSA, diagnosed by attended respiratory polygraphy (no EEG monitoring), defined as AHI of 15 or higher, 4) informed consent to participate.

Exclusion Criteria: 1) Secondary causes of resistant hypertension, 2) pregnancy, 3) disabling hypersomnia requiring urgent treatment (defined as an Epworth Sleepiness Scale ≥ 18), 4) current use of CPAP, 5) poor adherence with antihypertensive treatment, 6) long-term treatment with oral corticosteroids or nonsteroidal anti-inflammatory drugs, 7) renal insufficiency (creatinine ≥ 1.5 mg/dL), 8) a cardiovascular event in the month prior to the inclusion in the study, and 9) the regular use of sedatives, antipsychotics, and alcohol.

Intervention

Patients meeting eligibility criteria were randomized to either CPAP or no CPAP (control) for 12 weeks. Auto-titrating CPAP was used in the sleep laboratory within a period of less than 15 days after the diagnostic study to obtain a fixed CPAP pressure value (judged to be optimal by 2 blinded sleep experts). The fixed CPAP pressure was used for the remainder of the study. All patients were scheduled for follow-up 2 weeks after randomization and, subsequently, at 4, 8, and 12 weeks. During the follow-up visits, adherence to CPAP and anti-hypertensive medications were documented. At 12 weeks, a repeat 24-hour ABPM test was conducted in all patients.

Outcomes

The primary outcome was the change in the 24-hour ambulatory mean blood pressure from baseline to 12 weeks. Secondary outcome measures included changes in diurnal and nocturnal SBP, DBP, and changes in nocturnal blood pressure patterns.

The sample size (70 per group) was calculated to detect a reduction of 4 mm Hg or more in 24-hour mean blood pressure,

assuming a pooled standard deviation of 8.7 a Type I error of 5%, and a statistical power of 80%.

Patient follow-up

Intention to treat analysis with replacement of missing values by multiple imputations; 87 of 98 (88.7%) completed follow-up in CPAP arm, 87 of 96 (90.6%) completed follow-up in control arm.

Main results

The CPAP group achieved a statistically significant greater decrease in 24-hour mean blood pressure (3.1 mm Hg [95% CI, 0.6 to 5.6]; p = 0.02) and 24-hour DBP (3.2 mm Hg [95% CI, 1.0 to 5.4]; p = 0.005), but not 24-hour SBP (3.1 mm Hg [95% CI, -0.6 to 6.7]; p = 0.10) compared to the control group. The percentage of patients displaying a nocturnal blood pressure dipper pattern at the 12-week follow-up was greater in the CPAP group than in the control group (35.9% CPAP vs. 21.6% control; p = 0.02). Additionally, fewer patients in the CPAP group displayed a nocturnal riser pattern at the end of the study compared to the control group (adjusted OR, 0.45; p = 0.03).

There were no differences in the percentage of patients reaching a normotensive range in the 24-hour mean blood pressure (< 130/80 mm Hg) between the CPAP group and control group (18.4% CPAP vs. 13.8% control; p = 0.41).

The average CPAP use was 5 ± 1.9 hours per night, with 71 patients (72.4%) using it at least 4 hours per night. When comparing only those patients with complete data and 4 hours or greater average CPAP use versus controls (per protocol analysis), patients in the CPAP group showed a statistically significant decrease in 24-hour mean blood pressure of 4.4 mm Hg (95% CI, 1.8 to 7), p = 0.001; SBP, 4.9 mm Hg (95% CI, 1.2 to 8.6), p = 0.01; and DBP, 4.1 mm Hg (95% CI, 1.9 to 6.4), p < 0.001. This difference was more evident during the night, with a decrease of 7.1 mm Hg (p = 0.003) in nocturnal SBP and 4.1 mm Hg (p = 0.003) in nocturnal DBP. Moreover a small positive linear correlation between hours of CPAP use and improvement in mean blood pressure was noted (r = 0.29, p = 0.006); with an improvement of mean blood pressure of 1.3 mm Hg for each additional hour of CPAP use.

Conclusion

In adults with moderate to severe OSA and resistant hypertension despite optimal anti-hypertensive therapy, treatment of OSA with CPAP improved the mean 24 hour blood pressure after 12 weeks of therapy.

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COMMENTARY ON MARTÍNEZ-GARCÍA ET AL.

A strong body of research including both animal models and observational longitudinal studies implicates obstructive sleep apnea (OSA) as a causal risk factor for hypertension.[1,2] Randomized trials have demonstrated consistently that OSA therapy with CPAP lowers blood pressure by 2-3 mm Hg.[3] This effect is clinically significant in that it would be expected to reduce cardiovascular events by 5-10%,[4] but nevertheless, underwhelming when compared to the larger effects of antihypertensive medications. Many have suggested that these results may underestimate the true potential impact of CPAP because previous trials included patients with normal or only mildly elevated blood pressures, an inadequate severity of OSA, or who had poor adherence to CPAP. Small studies suggest the effect of OSA therapy may be much greater in patients with resistant hypertension.[5] If this were the case, this subgroup might benefit from routine OSA screening and treatment, particularly because OSA is highly prevalent in this population.[6]

The HIPARCO study represents the first high-quality clinical trial to specifically assess to what extent CPAP reduces blood pressure in patients with OSA and comorbid resistant hypertension. The investigators confirm the high prevalence of OSA in a resistant hypertension population—roughly 194/218 or 89%. The inclusion and exclusion criteria clearly identified a population with suboptimal blood pressure control despite 3 or more antihypertensive medications—a group most in need for novel blood pressure reduction strategies. The investigators carefully excluded the most common cause of resistant hypertension, medical noncompliance, to provide a homogenous population most likely to benefit from OSA treatment. The conservative definition of OSA, an apnea hypopnea index (AHI) > 15 based on a hypopnea definition requiring a 4% desaturation, ensured "real" disease, particularly since the mean AHI was 40.4. One minor criticism lies in determination of the effective CPAP pressure. The mean residual AHI was 4.1 ± 3.8 suggesting a number of patients may have had residual disease (particularly, given the strict rules for hypopnea scoring). The mean CPAP pressure of 8.5 cm H_2O seems low for a population of severe apneics, further raising concern of suboptimal treatment. Nevertheless, the mean CPAP compliance obtained, 5.0 h/night, is impressive considering this population was not recruited based on OSA symptoms. The outcome measure, 24-hour ambulatory blood pressure, is appropriately chosen to maximize sensitivity to the impact of OSA therapy. Some might criticize the lack of blinding to treatment allocation. However, there is little evidence of a placebo effect on blood pressure in prior OSA trials, so the use of sham CPAP seems unnecessary. Finally, the authors are to be commended for a fairly low dropout rate and use of multiple imputation to minimize bias from missing data.

The primary finding of the study, a 3.1 mm Hg reduction in mean blood pressure in the intent-to-treat analysis, is remarkably similar to prior trials and as such, simultaneously reassuring and disappointing. It is reassuring that OSA therapy has an additive effect on blood pressure control even when superimposed on to 3-4 antihypertensive medications. This confirms an earlier study of the additive effect of CPAP and valsartan.[7] For a population that is failing standard antihypertensive therapy, CPAP may provide a much better risk-benefit profile than a 4th or 5th line antihypertensive agent. Comparative effectiveness studies testing this hypothesis would clarify the role of CPAP in this setting. Despite the statistically significant reduction in blood pressure, the results are disappointing in that most sleep experts would have predicted a greater benefit in this popu-

lation. Certainly an 8-10 mm Hg benefit would have made it much easier to convince our hypertension colleagues to start routinely screening and treating OSA.

In addition to lowering mean blood pressure, the investigators found CPAP can alter the blood pressure profile to produce a normal nocturnal dipping pattern. While non-dipping has been shown to be an independent risk factor for cardiovascular disease,[8] there are no data on whether modifying dipping status alters cardiovascular risk. As a result, it is unclear whether the change in blood pressure profile has clinical significance beyond the reduction in mean blood pressure.

So, is this the final answer then—CPAP is never going to reduce blood pressure more than 3 mm Hg? Some have suggested that a greater effect may occur over a longer period of time to allow for vascular remodeling. However, there is no increase in CPAP effect on office blood pressure going from 3 months to 12 months.[9] The linear relationship of greater CPAP use with greater blood pressure effect, also seen in prior studies,[9,10] suggests the key to gaining a greater effect from OSA therapy may lie in developing techniques to enhance CPAP adherence or developing more tolerable treatments for OSA. Further investments in this area are clearly needed.

There also may exist subgroups that are more sensitive to the hypertensive effects of OSA and therefore to the anti-hypertensive effects of CPAP. These may relate to specific hypertensive pathways (e.g., hyperaldosteronism) or specific genetic backgrounds. For example, one study suggests African-Americans, a group at particularly high risk for hypertension and less responsive to standard antihypertensive medications, may have a greater blood pressure response to CPAP.[11]

In the end, however, despite all the interest in blood pressure, we must remember that blood pressure is merely a surrogate outcome. What our patients really care about and the question we need to strive to answer directly is whether CPAP therapy reduces cardiovascular events and mortality.

CITATION

Shafazand S, Patel SR. Effect of CPAP on blood pressure in patients with obstructive sleep apnea and resistant hypertension. *J Clin Sleep Med* 2014;10(3):341-343.

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DISCLOSURE STATEMENT

The authors have indicated no financial conflicts of interest.