e-ISSN: 2807-7970

AKSONA

Volume 4 Number 2, July 2024

Blood Pressure in Patients Obstructive Sleep Apnea and Resistant Hypertension with Continuous Positive Airway Pressure (CPAP) Therapy: A Systematic Review and Meta-Analysis

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Article info

Article History:
Received Dec 18, 2023
Revised Apr 9, 2024
Accepted May 7, 2024
Published Jul 31, 2024

Keywords:
Blood pressure
Cardiovascular disease
CPAP
Obstructive sleep apnea
Resistant hypertension

ABSTRACT

Introduction: Obstructive sleep apnea (OSA) is an upper respiratory tract disorder that is often associated with cardiovascular diseases, one of which is resistant hypertension (RH). On the other side, Continuous Positive Airway Pressure (CPAP) is a medical treatment that is often used for patients with OSA and RH. **Objective:** This meta-analysis aimed to determine the effectiveness of CPAP in patients with OSA and resistant hypertension by measuring systolic and diastolic blood pressure at diurnal, nocturnal, and 24 hours. **Methods:** We conducted a systematic review using a PRISMA flowchart, utilizing sources such as PubMed, Scopus, Science Direct, and ClinicalTrials.gov with MeSH. We then reviewed these sources for quality studies using RoB2, and analyzed the data using the Revman website version. 5.4. **Results:** The five studies included in the analysis found that CPAP, while maintaining conventional drugs, significantly affected the blood pressure of patients with OSA and RH. The significant results were made clearer by obtaining data for nocturnal SBP pressure, mean -3.89 mmHg (95% CI: -7.03 to -0.76) with a p-value < 0.02, and then nocturnal DBP obtained a mean of -2.34 mmHg (95% CI: -4.70 to 0.02) with a p-value < 0.05. Meanwhile, the 24-hour results for SBP obtained a mean of -2.97 mmHg (95% CI: -5.88 to -0.06) with a p-value < 0.05, and the 24-hour results for DBP obtained a mean of -2.39 mmHg (95% CI: -4.62 to -0.16) with a p-value < 0.04. **Conclusion:** CPAP, while maintaining conventional treatment according to indications, can reduce 24-hour and nocturnal blood pressure in patients with OSA and resistant hypertension.

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Available at https://e-journal.unair.ac.id/index.php/aksona

INTRODUCTION

Obstructive Sleep Apnea (OSA) is a respiratory disorder commonly caused by recurrent airway blockages during sleep that last 10 seconds to 1 minute and result in temporary drops in oxygen levels. Its prevalence stands at around 3-7% in men and 2-5% in women, with daytime sleepiness, while approximately 24% of men and 9% of women have OSA without such symptoms.[1] Obesity, central body fat accumulation, enlarged neck circumference, gender, age, craniofacial abnormalities, and upper airway issues are all risk factors for OSA. Regardless of the respiratory classification, OSA leads to severe cardiovascular complications such as hypertension, ischemic heart disease, stroke, irregular heart rhythms, and metabolic disruptions.[2]

Research findings from a study involving 99 hypertensive patients revealed that 56% of them were diagnosed with OSA. This findings suggests a link between the increasing prevalence of OSA and the emergence of resistant hypertension, which ultimately affect the severity of OSA itself.[3] Another cross-sectional study indicated that the occurrence of resistant hypertension among individuals with OSA ranges from 60% to 71%.[4] Additionally, a separate investigation highlighted a higher percentage of hypertension in severe OSA cases, around 53%, compared to moderate OSA at 46%. Unfortunately, 30–50% of OSA patients tend to ignore the presence of hypertension, despite the fact that the risk of developing resistant hypertension is around 83%.[5]

Research spanning the last 30 years reveals a failure to improve awareness, treatment, and control rates for blood pressure treatment targets. Resistant hypertension, which frequently requires three or more antihypertensive medications or four simultaneously, is associated with OSA complications, including upper airway function failure, hypoxemia, hypercapnia, and negative intrathoracic pressure development.[6] Epidemiologically, resistant hypertension affects 12-15% of the global hypertensive population, varying by gender and age.[7]

Adopting a healthy lifestyle in addition to pharmacological and non-pharmacological treatments can lessen the severity of OSA with hypertension and avoid recurrence. The use of specific antihypertensive medications for OSA is based on limited clinical evidence. However, drugs inhibiting the sympathetic nervous and Renin-angiotensin aldosterone systems show potential in lowering excessive aldosterone in OSA.[8] Non-pharmacological treatment can be administered using positive airway pressure as the gold standard or other alternative methods, such as behavioral interventions, negative pressure interventions, and surgical procedures.[9] Studies evaluating CPAP therapy for OSA and resistant hypertension offer varying opinions on its efficacy in reducing cardiovascular disease risk.[10] As a result, more comprehensive research is needed to understand CPAP's specific impact on blood pressure, which is crucial in most cardiovascular cases.

OBJECTIVE

This analysis study was intended to determine and compare the effectiveness of CPAP therapy to the use of antihypertensive drugs alone for patients with OSA and resistant hypertension.

METHODS

a. Selection and Screening

This review selection used the PRISMA flowchart sourced from PubMed, Scopus, Science Direct, and ClicicalTrial.gov, with Boolean operators (AND/OR/NOT) and review adjustments according to MeSH.

b. Eligibility Criteria

The inclusions chosen for this study were: i) studies using RCT methods, ii) study populations consisting of adult OSA and resistant hypertension patients, iii) studies comparing CPAP therapy to the use of conventional drugs alone according to indications, iv) full text literature, and v) studies that provide results on the effect of CPAP therapy for patients with OSA and resistant hypertension.

c. Data Quality Analysis

Study quality was assessed using Risk of Bias 2 (RoB2), which has five main domains and a low risk of bias assessment category for all studies.

d. Data Analysis

Data extraction was first collected in Microsoft Excel format and then entered into analysis via the RevMan website version 5.4 with the fixed effect model used in the study, and the heterogeneity was calculated and presented by I^2. Meanwhile, the outcomes are described according to the respective results, with the assessment category being significant for ($p < 0.05$) or not ($p > 0.05$).

RESULTS

The study was determined using the PRISMA flowchart in Figure 1 and obtained through 4 databases totaling 1,649 journals. The studies were then filtered based on the inclusion criteria, and small groupings were created so that five studies were used in the

journals used in this research. Furthermore, assess the quality of the study done with a risk of bias of 2, and all studies performed the assessment results with low risk of bias.

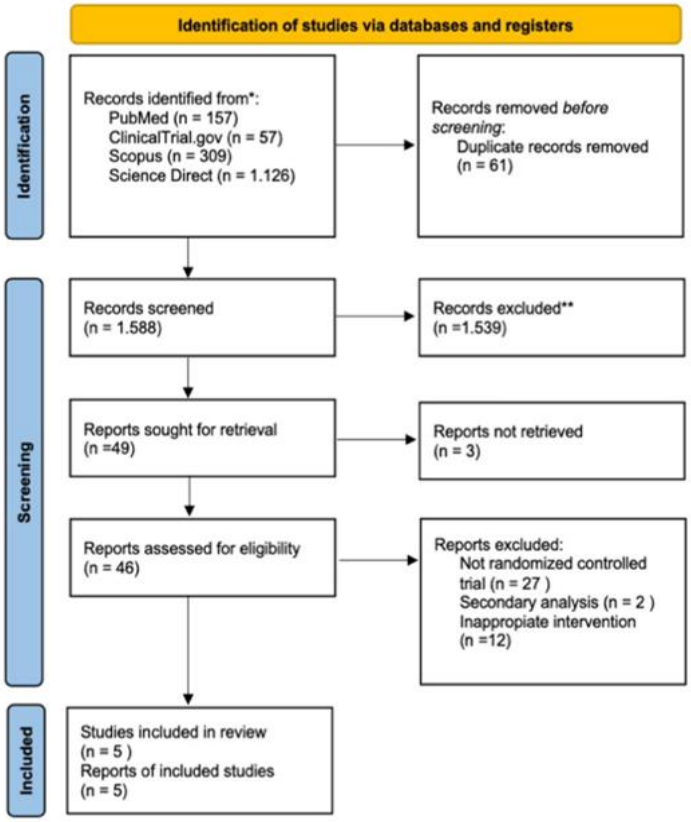

Figure 1. PRISMA flowchart

Table 1 displays the study characteristics, including the author's name, the year of publication, the country of origin, the length of study, the number of participants receiving CPAP therapy and conventional medicine, the course mean Apnea-Hypopnea Index (AHI), the mean 24-BP, the CPAP compliance, etc. The study was conducted for three months with CPAP compliance >4 hours/night. In contrast, others observed compliance >4 hours/night for six months.

Table 1. Study characteristics meta-analysis

Studies	Study design	Country	Duration (month)	Comparison	Participant (CPAP/ Control)	BMI	CPAP Compliance	Mean 24-h SBP (CPAP/ Control)	Mean 24-h DBP (CPAP/ Control)	Mean AHI (CPAP/ Control)
Muxfeldt et al. 2015	RCT	Rio de Janeiro, Brazil	6	CPAP + drugs/drugs	106(46/60)	33.4(5.3)	127(16) /130(16	75(11) /76(12)	44(24) / 39(18)	75(11) /76(12)
Lloberes et al. 2014	RCT	Barcelona, Spain	3 months	CPAP+drugs/drugs	56(27/29)	31.4 ±4.9	5.6 ± 1.5	139.2 ± 11.5*	83 ±11.1*	50 ± 20.3*
Martinez-Gracia et al. 2014	Parelel, RCT	Valencia, Spain	3 months	CPAP+drugs/drugs	194 (98/96)	34.1(5.4)	5 (1.9)	144.9(11.7)/143.5 (13.2)	83.4(11.1)/82.6 (10)	41.3(18.7) / 39.5(19.2)
Pedrosa et al. 2013	RCT	São Paulo, Brazil	6 months	CPAP+drugs/drugs	35 (19/16)	32(28-39)	6.01 ± 0.20	163 ± 4/161 ± 7	97 ± 3/96 ± 3	36(24-51) /28(22-38)
Lozano et al. 2010	Paralel, RCT	Barcelona, Spain	3 months	CPAP+drugs/drugs	41(20/21)	30.8 ± 5	5.6 ± 1.52	130.5 ± 14.9 /129.4 ±12.9	76.7 ± 9.6/75.4 ± 10.5	59.79±19.71 / 46.78±21.43

Note: *Numerical values use true-hypertension based on study.
Numbers between brackets shown the number of populations for each category.

The analysis is displayed on a forest plot with a fixed effect model, which is then divided into systolic blood pressure (SBP) and diastolic blood pressure (DBP) result groups. The diurnal SBP results were shown in Figure 2. The result was -1.95 mmHg (95% CI: -4.78 to 0.88), I^2 = 25%, p > 0.18.

On the other hand, for diurnal DBP, as shown in Figure 3, the results were -1.72 mmHg (95% CI: -3.96 to 0.53), I^2 = 0%, p > 0.13. The analysis revealed no significant results in CPAP therapy used at night in terms of its effectiveness on the patient's condition during the day.

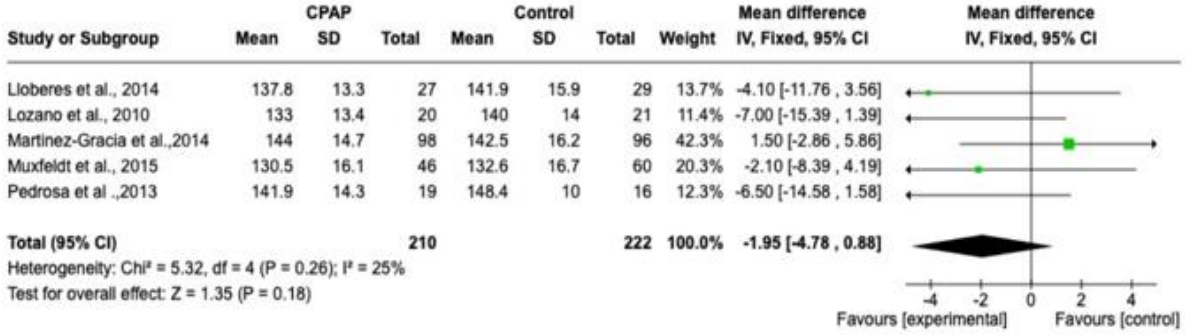

Figure 2. Diurnal SBP Meta-analysis

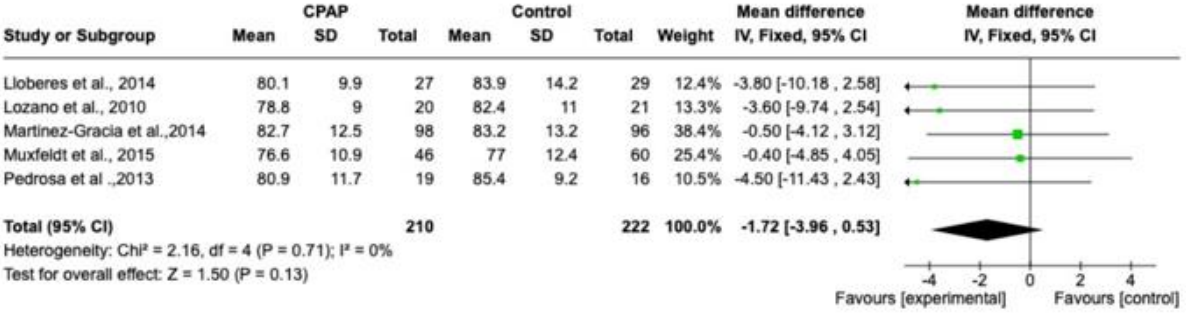

Figure 3. Diurnal DBP Meta-analysis

Then, another analysis was carried out on nocturnal blood pressure. In Figure 4, the results for SBP were -3.89 mmHg (95% CI: -7.03 to -0.76), I^2 = 0%, p < 0.02. Figure 5 displays DBP results of -2.34 mmHg (95% CI: -4.70 to 0.02), I^2 = 18%, p < 0.05. Both showed significant results regarding the effects of CPAP therapy on nocturnal blood pressure.

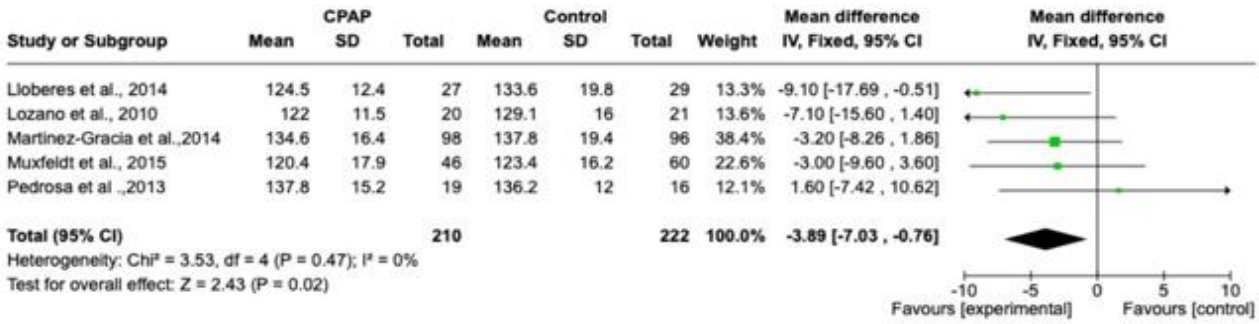

Figure 4. Nocturnal SBP Meta-analysis

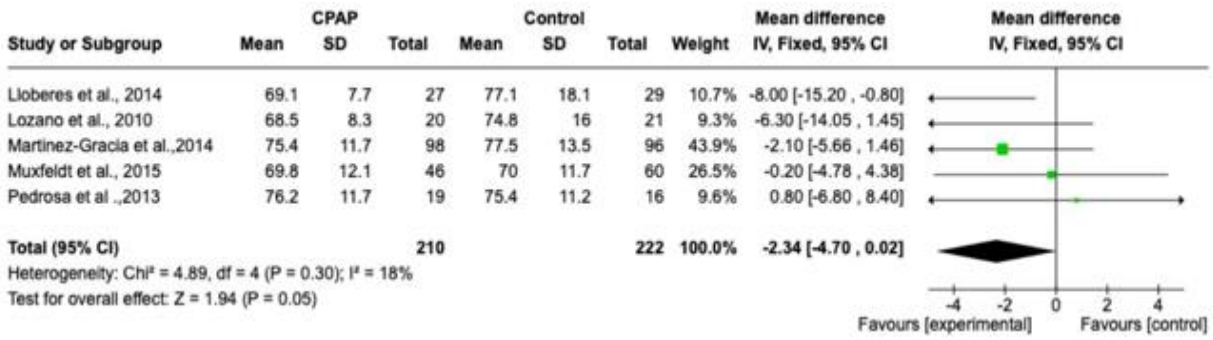

Figure 5. Nocturnal DBP Meta-analysis

Finally, overall analysis was carried out to get a 24-hour picture of the effect; SBP in Figure 6 shows -2.97 mmHg (95% CI: -5.88 to -0.06), I^2 = 0%, p < 0.05. Then, DBP in Figure 7 shows -2.39 mmHg (95% CI: -4.62 to -0.16), I^2 = 0%, p < 0.04. In other words, the overall results 24-hours blood pressure was significantly affected by CPAP, use in OSA patients with resistant hypertension.

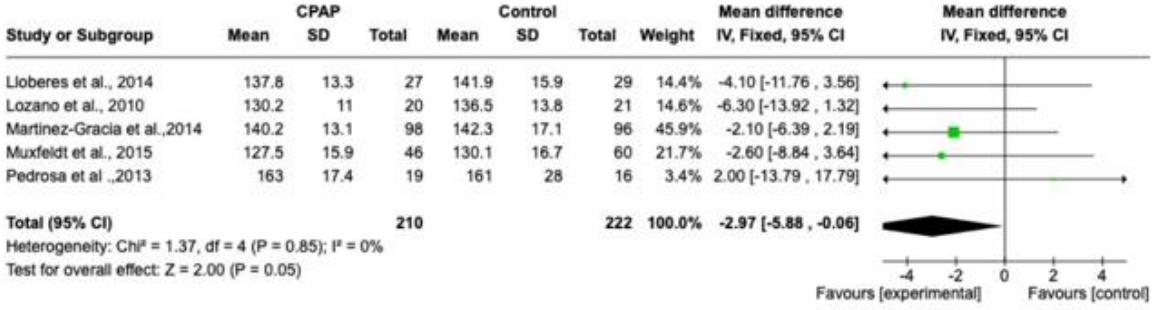

Figure 6. 24-Hours SBP Meta-analysis

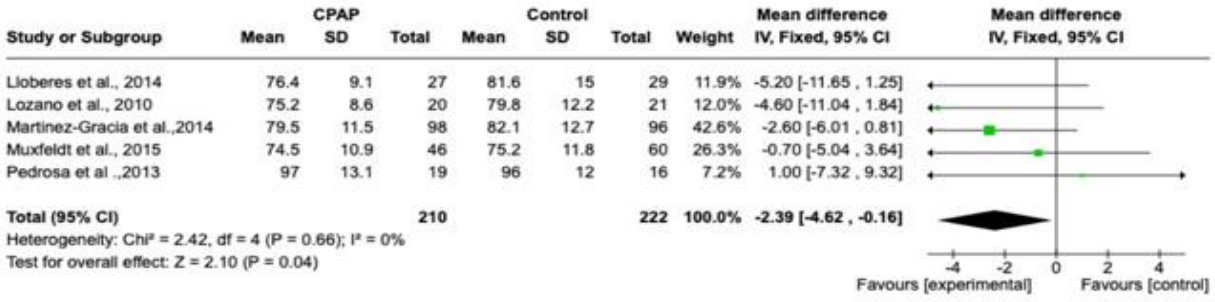

Figure 7. 24-Hours DBP Meta-analysis

DISCUSSION

This group of patients with OSA and resistant hypertension is characterized as severe AHI (≥30) and uncontrolled blood pressure (≥140/90 mmHg).[11,12] In this meta-analysis, the mechanism of CPAP therapy for patients with OSA and resistant hypertension is given for 5.4 hours/night with a period of 3 to 6 months through these categories. According to the American Thoracic Society's recommendations, CPAP compliance should be maintained for a minimum of 4 hours per night for 70% of the time and at least a 3-month period.[13] However, studies from Thailand suggest that better results with CPAP therapy can be achieved with a compliance of at least 6 hours per night; in addition, other factors affecting compliance, such as long-term usage, age, patient habits, and accompanying comorbidities, should be considered.[14]

The relationship between CPAP adherence and therapy duration influences CPAP therapy's effectiveness as a treatment for OSA and resistant hypertension patients. Long-term and continuous CPAP treatment can effectively lower blood pressure. However, data suggest that around 30-80% of OSA

patients who use CPAP for 4 hours/night have a low level of compliance, while compliance is still higher in the severe category.[13] Low compliance shows that the relationship between duration and effectiveness is also decreasing. CPAP treatment significantly reduces 24-hour diastolic and systolic blood pressure; if CPAP use exceeds the median duration, use >4 hours/night.

CPAP therapy compliance is also affected by the severity of OSA, which can be found using the AHI, Body Mass Index (BMI), and Epworth Sleepiness Scale (ESS) among populations who are more likely to develop OSA. This means that the severity of OSA can have an impact on hypertension treatment.[15] The effect of CPAP therapy on administration compliance, duration (long term), and severity of OSA influence the effectiveness of outcomes for patients with OSA and resistant hypertension. Therefore, CPAP therapy can be given and effectively reduces 24-ho BP, especially at night, while considering additional factors, such as compliance with the duration of use of >4 hours/night for patients with OSA and resistant hypertension.

All of them have their advantages and disadvantages. CPAP does indeed have an impact on individuals with moderate to severe OSA, including lowering blood pressure in patients with resistant hypertension. However, the most frequently reported side effects affecting therapy compliance are patients' complaints, such as dry mouth, congested nose, and frequent nighttime awakenings due to mask pressure or leakage.[16] CPAP use can sometimes cause cerebrospinal fluid to leak because it affects intracranial pressure, especially after surgery or in other situations, like aerophagy, which can make gastroesophageal reflux disease worse.[17] Nevertheless, the emergence of CPAP side effects ultimately depends on the individual. This statement is deduced from the data obtained on long-term side effects, which surprisingly are unrelated to equipment leakage, the primary cause in many cases.[18]

The benefits of administering CPAP therapy can also help Indonesian society reduce the incidence of OSAS among hypertensive patients. Survey results indicate that approximately 64% of Indonesians suffer from hypertension.[19] A study conducted in Depok, Indonesia, revealed that those at risk of OSA had 57.3% higher rates of hypertension than those who were not at risk.[20] This statistic underscores the importance of considering CPAP therapy, which has been shown to lower blood pressure by 2-3 mmHg. However, there is still a need to assess CPAP therapy duration and compliance, particularly among patients with OSA and resistant hypertension. Therefore, providing positive airway pressure therapy to OSA and hypertension patients in Indonesia could be a viable solution, considering the ease of equipment use and the availability in the country.

CONCLUSION

In conclusion, CPAP therapy, as an additional treatment with antihypertensive drugs for patients with OSA and resistant hypertension, significantly influences the reduction of blood pressure over 24 hours, including nocturnal BP. CPAP therapy is also effective when used for at least >4 hours/night, so it can be regarded as supportive treatment for patients with OSA and resistant hypertension. Further research on providing CPAP therapy to patients with OSA and resistant hypertension should be conducted with a longer observation period.

Acknowledgment
None

Conflict of Interest
All authors have no conflict of interest.

Funding
This research was not funded by any affiliations or other funding sources.

Author Contributions
MRR contributed to systematizing this research, data processing, extraction, preparation, and administration. BSP and PL reviewed articles and provided guidance. All authors who have read and approved the research results.

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