

Original Article

Continuous positive airway pressure and cardiovascular outcomes in obstructive sleep apnoea patients: a systematic review and meta-analysis of randomized controlled trials

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Abstract: Background: Continuous positive airway pressure (CPAP) has been utilized to reduce blood pressure in obstructive sleep apnea (OSA) patients, but few studies are available in terms of mortality data and other cardiovascular outcomes. Methods: This study systematically searched PubMed, Embase, and Cochrane Library databases for studies investigating the effects of CPAP on OSA patients. Basic characteristics and outcomes were extracted. A random effects model was used to pool the overall size. Q and I² statistics were employed to quantify between-group heterogeneity. Egger's and Begg's tests were employed to identify small-study effects. Results: Of 590 primary records, 9 randomized controlled trials, including 5,923 patients, were finally included in the meta-analysis. CPAP was not associated with all-cause mortality (relative risk [95% confidence interval]: 0.92 [0.65-1.30], I² = 0.0%) or cardiovascular mortality (0.70 [0.27-1.80], I² = 36.3%) in OSA population. Incidence of myocardial infarction (0.95 [0.53-1.70], I² = 25.8%) or strokes (0.91 [0.68-1.24], I² = 0.0%) was not significantly different between the CPAP group and non-CPAP group. Neither Egger's nor Begg's tests indicated any small-study effects. Conclusion: CPAP was not significantly associated with all-cause mortality, cardiovascular mortality, or occurrence of myocardial infarction and strokes in the OSA population.

Keywords: Continuous positive airway pressure, all-cause mortality, cardiovascular mortality, obstructive sleep apnea, randomized controlled trial

Introduction

Obstructive sleep apnea (OSA) is present in around 15% of men and 5% of women aged 30-70 years, based on apnea-hypopnea indexes measured as events/hour ≥ 15 [1]. OSA is characterized by oxygen desaturation and sleep disruption. It has been markedly associated with occurrence of hypertension [2]. It also results in numerous cardiovascular diseases through increased sympathetic activity, systemic inflammation, and metabolic anomalies [3]. Continuous positive airway pressure (CPAP) has been used as an important therapy for OSA patients, especially for moderate-to-severe OSA patients [4].

However, the effects of CPAP on OSA patient cardiovascular outcomes remain debatable [4].

A meta-analysis of 27 cohorts and 3,162,083 participants concluded that all-cause mortality increases with OSA severity, while CPAP markedly reduces all-cause mortality and cardiovascular mortality [5]. However, since it mainly included observational studies, the meta-analysis failed to establish a reliable causal relationship between CPAP use and mortality outcomes. Interestingly, another earlier meta-analysis of randomized controlled trials (RCTs) suggested that CPAP was not associated with death, cardiovascular events, or strokes in OSA patients [6]. Recently, the Sleep Apnea Cardiovascular Endpoints (SAVE) study showed that the addition of CPAP to usual care was not associated with all-cause mortality or cardiovascular outcomes in 2,717 eligible adults aged 45-75 years with moderate-to-severe OSA and

cardiovascular or cerebrovascular disease [7]. The SAVE study, along with recent publications of other RCTs, warranted a reanalysis of the effects of CPAP on cardiovascular outcomes [7-9].

The present systematic review and meta-analysis was conducted to investigate the effects of CPAP on all-cause mortality, cardiovascular mortality, myocardial infarction, and strokes in OSA patients.

Methods

This study complied with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statements [10].

Literature search

On April 6, 2017, this study searched MEDLINE (since 1946), Cochrane Library (since inception), and Embase (since 1947) databases, with the combination of MeSH terms and free words of “obstructive sleep apnea”, “continuous positive airway pressure”, and “mortality”. The search was restricted to English. Reference lists of all eligible studies were searched to identify relevant publications.

Study selection and data extraction

Two investigators (H.X.L. and H.Z.L.) independently screened the studies based on SPICO (study design, participants, intervention, controls, and outcomes) principle, with the following inclusion criteria: 1) Randomized controlled trials; 2) OSA participants diagnosed with polysomnography; 3) CPAP as an intervention; 4) Control group, given usual care without CPAP; and 5) Mortality data reported. Primary outcomes were all-cause mortality and cardiovascular mortality. Secondary outcomes were occurrence of myocardial infarction and strokes. Baseline characteristics and outcome data were independently extracted by two investigators (J.L.Z. and J.T.W.). Disagreements were resolved by discussion with a third investigator (S.Q.W.).

Quality assessment

Risks of bias of eligible RCTs was classified as low, unclear, or high, with these 5 specific domains recommended by Cochrane Collaboration: randomization generation, allocation concealment, blinding of participants and person-

nel, incomplete outcome data addressed, and free of selective reporting [11].

Statistical analysis

Relative risk (RR) and corresponding confidence intervals (CI) were synthesized with a random effects model. Q statistic and I^2 statistic were used to identify between-group heterogeneity [12]. I^2 statistic represents the percentage of overall variability attributable to heterogeneity, with a value of lower than 50% indicating mild heterogeneity of bias. Egger's and Begg's tests were used to identify small-study effects [13, 14]. This study did not visually examine publication bias with funnel plots, as it is indicated for meta-analyses of more than 10 studies [15]. Sensitivity analyses were performed to show how effect sizes changed after the removal of each individual study. All statistical analyses were performed with Stata 14.0 software (Stata, College Station, Texas, USA).

Results

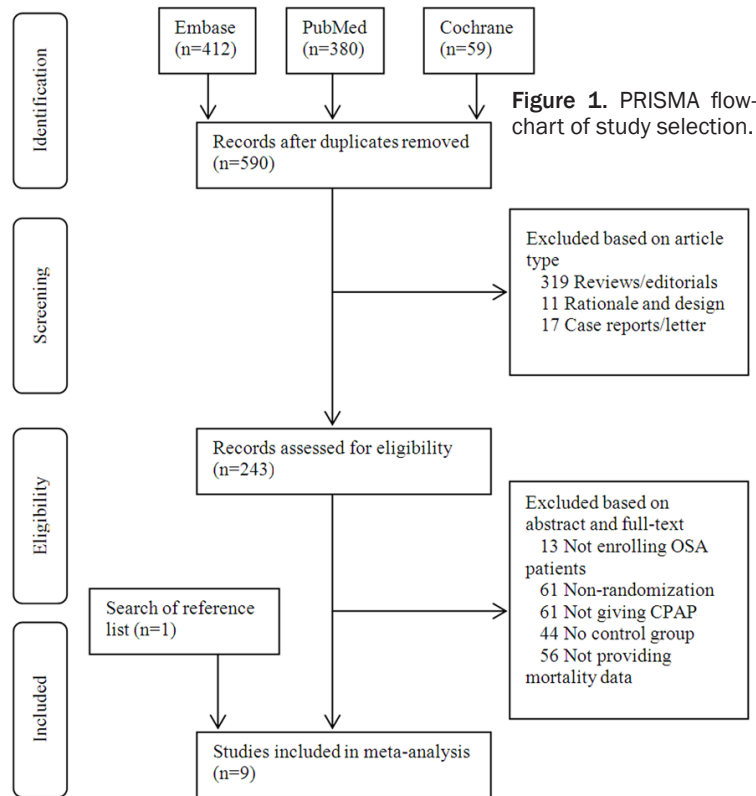
Study selection

Figure 1 shows the PRISMA flowchart of study selection. This study primarily retrieved 412, 380, and 59 records from Embase, PubMed, and Cochrane databases, respectively. After removal of duplicates, 590 records were screened by publication type. Thus, reviews, case reports, and rationale and design articles were excluded. The remaining 243 records were screened by abstracts and full-texts. Therefore, 13 records not enrolling OSA patients, 61 not performing randomization, 61 not having CPAP as an intervention, 44 not establishing control groups, and 56 not providing mortality data were excluded. Eight studies were included in meta-analysis. Later, 1 additional study was identified by examining the references of included studies [16]. Therefore, 9 RCTs were finally eligible for this systematic review and meta-analysis [7-9, 16-21].

Basic characteristics

Table 1 summarizes basic characteristics of the 9 eligible studies. Overall, a total of 5,923 OSA patients, including 2,961 in the control group and 2,962 in the intervention group, were studied. Patient characteristics, such as age, sex, body mass index, and blood pressure,

CPAP for OSA patients



were very similar and comparable between the control group and intervention group in all eligible studies. They were predominantly old men with a relatively high body mass index, along with normal systolic blood pressure and diastolic blood pressure. Eight studies administered conventional medications to the control group, while 1 study allocated the OSA patients to a sham group [16]. The OSA patients were followed up for 6 to 68 months.

Quality assessment

Figure 2 shows the risk of bias in 5 different domains. Overall, risk of bias was low in the 9 eligible RCTs but blinding of participants and personnel was only reported in 3 RCTs [16, 19, 21]. Incomplete outcome data were well addressed in all studies. Generation of randomized sequence was reported in most studies. Selective reporting and allocation concealment were observed in low risk.

All-cause mortality and cardiovascular mortality

All studies reported all-cause mortality for 5,923 OSA patients. CPAP was not associated with all-cause mortality and statistical hetero-

geneity was very low (RR [95% CI]: 0.92 [0.65-1.30], $I^2 = 0.0\%$, $P > 0.05$; **Figure 3A**). Five studies reported cardiovascular mortality for 3,883 OSA patients. CPAP was not associated with cardiovascular mortality and mild heterogeneity was observed (0.70 [0.27-1.80], $I^2 = 36.3\%$, $P > 0.05$; **Figure 3B**) [9, 18, 19, 21]. Although no significant benefits were observed for CPAP, there appeared to be a tendency favoring its beneficial effects.

Myocardial infarction and strokes

Five studies reported myocardial infarction for 3,883 OSA patients. CPAP was not associated with occurrence of myocardial infarction, with mild heterogeneity observed (0.95 [0.53-1.70], $I^2 = 25.8\%$, $P > 0.05$; **Figure 4A**) [9, 18, 19, 21]. Six studies reported occurrence of strokes for 4,274 OSA patients. CPAP was not associated with occurrence of strokes (0.91 [0.68-1.24], $I^2 = 0.0\%$, $P > 0.05$; **Figure 4B**). The effects of CPAP on myocardial infarction and strokes were quite consistent among various studies, with all 95% CI of OR crossing the null line of 1.00.

Sensitivity analysis

Neither Begg's test nor Egger's test showed small-study effects for all-cause mortality, cardiovascular mortality, myocardial infarction, or strokes (all $P > 0.05$). Most heterogeneity of this meta-analysis arose from changes of the magnitude rather than the direction of individual OR. Since all study results of primary outcomes and secondary outcomes crossed the null effect line 1.00, the removal of any study could not significantly change the overall effect size.

Discussion

The present systematic review and meta-analysis of 9 RCTs and 5,923 patients showed that CPAP was not associated with all-cause mortality, cardiovascular mortality, and occurrence of

CPAP for OSA patients

Table 1. Baseline characteristics of the 9 included randomized controlled trials

| First author | Year | CPAP/ Control | Age (yrs) | Male | Follow-up (month) | Treatment of control group | CPAP duration (h/night) | BMI | SBP | DBP | AHI | ESS |
|-----------------|------|------------------|--------------|-----------|----------------------|-------------------------------|----------------------------|-----------|---------|-------|-----------|-------------|
| McEvoy RD [7] | 2016 | 1346/1341 | 61/61 | 1092/1082 | 44 | Usual care | 3.3 | 28.8/28.5 | 132/131 | 80/79 | 29.0/29.6 | 7.3/7.5 |
| Craig S [20] | 2012 | 195/196 | 58/58 | 153/152 | 6 | Standard care | 2.7 | 32.2/32.5 | 130/130 | 81/81 | 10 | 7.9/8.0 |
| Parra O [18] | 2014 | 57/69 | 64/66 | 41/48 | 68 | Conventional treatment | 5.3 | 30.2/28.8 | NA | NA | NA | 8.3/7.3 |
| Schlatzer C [8] | 2016 | 152/151 | 58/58 | 123/127 | 6 | Standard care | 2.7 | 32.0/32.6 | NA | NA | NA | 8.5/8.4 |
| Peker Y [9] | 2016 | 122/122 | 66/67 | 105 | 57 | Non-CPAP | 6.6 | 28.4/28.5 | NA | NA | 28.3/29.3 | 5.5/5.5 |
| Huang Z [19] | 2014 | 36/37 | 62/63 | 28/32 | 36 | Non-CPAP | 4.5 | 27.9/27.5 | 148/146 | 83/83 | 28.3/28.7 | 9.3/8.3 |
| Barbe F [21] | 2012 | 357/366 | 52/52 | 313/306 | 48 | No active intervention | NA | 31.3/31.1 | 132/131 | 80/80 | 42/35 | 6.5/6.5 |
| McMillan A [17] | 2014 | 140/138 | 71/71 | 120/109 | 12 | Best supportive care | 2.4 | 33.9/33.6 | 138/140 | 78/78 | NA | 11.6/11.6 |
| Kushida CA [16] | 2012 | 556/542 | 52/51 | 363/356 | 6 | Sham CPAP | 4.2/3.4 | 32.4/32.1 | NA | NA | 39.7/40.6 | 10.07/10.09 |

CPAP = continuous positive airway pressure, BMI = body mass index, SBP = systolic blood pressure, DBP = diastolic blood pressure, AHI = apnea-hypopnea index, EES = Epworth sleepiness score, NA = not available.

CPAP for OSA patients

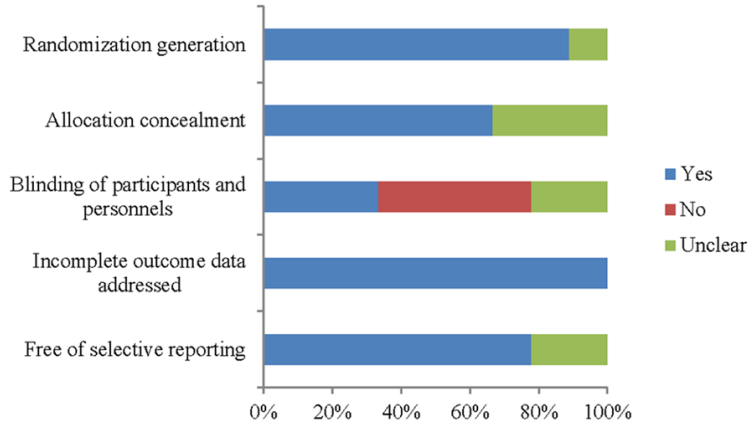


Figure 2. Risk of bias table.

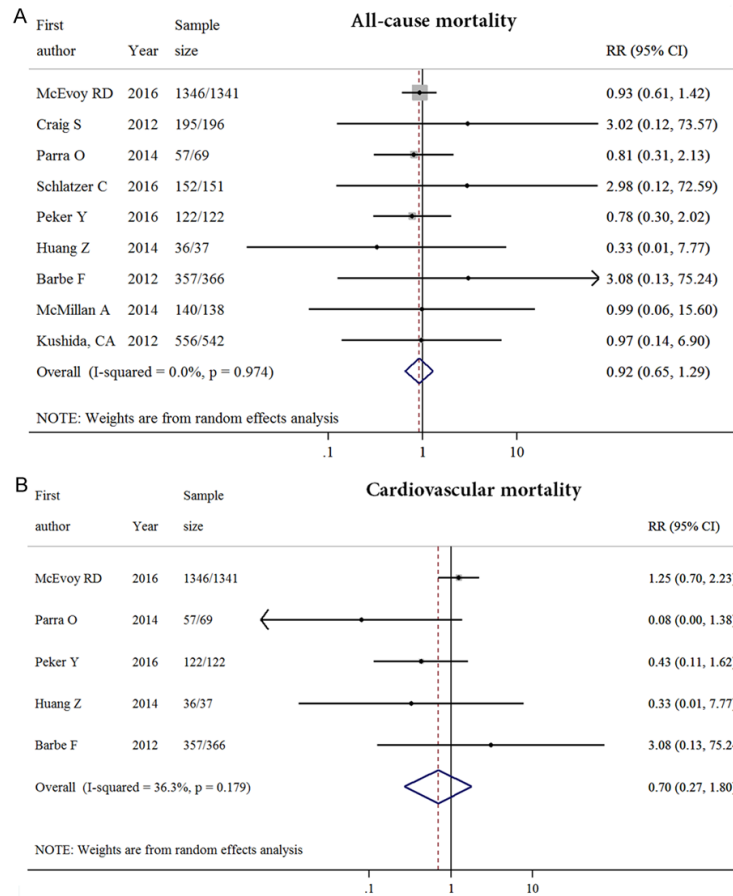


Figure 3. Effects of continuous positive airway pressure on all-cause mortality and cardiovascular mortality.

myocardial infarction and strokes in OSA patients. These results are unlikely to change in future observational studies or RCTs, as nearly all eligible studies showed similar trends. Of no-

te, most eligible patients in this meta-analysis had pre-existing cardiovascular disease (mostly from SAVE study). Thus, this meta-analysis mainly looked at CPAP for secondary prevention. Given that impaired endothelial function is found in OSA and that this is an early step in the development of cardiovascular diseases, it is possible that CPAP may have an effect only in primary prevention. The Multicentre Obstructive Sleep Apnea Interventional Cardiovascular (MOSAIC) trial showed that CPAP does not improve the calculated vascular risk in patients with minimally symptomatic OSA [20]. McEvoy RD et al. reported similar trends in patients with moderate-to-severe OSA [7]. Recently, an analysis of national registry data showed that patients receiving CPAP treatment had more comorbidities before and after diagnosis, compared with nontreated patients [22]. However, present results indicate that comorbidities may not contribute to the effects of CPAP on patient outcomes. Parra O et al. showed that CPAP did not significantly improve cardiovascular event-free survival in patients with acute strokes and OSA during a 68-month follow-up period [18]. The Randomized Intervention with Continuous Positive Airway Pressure in CAD and OSA (RICCADSA) trial showed that CPAP was not associated with better outcomes in patients with coronary artery disease and OSA [9]. Huang Z et al. found that long-term CPAP did not improve the prognosis of hypertensive patients with coronary heart diseases [19]. In consecutively enrolled older patients with OSA and unspecified comorbidities, CPAP did not have extra benefits when compared with the best

CPAP for OSA patients

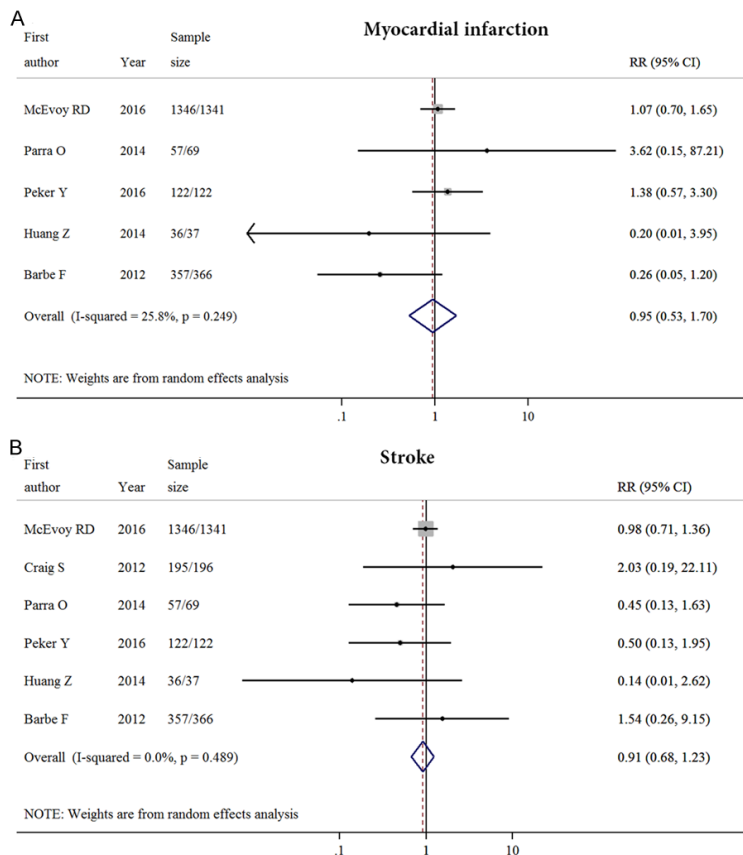


Figure 4. Effects of continuous positive airway pressure on incidence of myocardial infarction and strokes.

supportive care alone [17]. However, given the clinical benefits and few harms of CPAP therapy on the reduction of blood pressure and daytime sleepiness, it may be worthy to conduct future RCTs to further validate the effects of CPAP on patients with severe OSA and hypertension.

Both anatomically imposed mechanical loads and compensatory neuromuscular responses are responsible normal function of the upper airway. OSA occurs when the genioglossus muscle relaxes and the tongue falls back during sleep to obstruct the upper airway [23]. It is characterized by recurrent hypoxia, oxidative stress, sympathetic activation, and endothelial dysfunction, all of which are important risk factors of cardiovascular diseases [24]. OSA also causes other major sequelae, such as cognitive deficits and behavioral abnormalities [25]. Recent studies have shown that OSA accelerates the progression of mild Alzheimer's disease and Parkinson's disease and manifests as recurrent headaches in the morning in some

patients [26]. The impairment of multiple organs by OSA suggests the need for effective treatments to improve oxygen inhalation during sleep.

Theoretically, the reduction of hypoxic episodes during sleep is likely to contribute to lower incidence of events. Negative results of currently available RCTs and meta-analysis may be associated with the following factors. First, overall cardiovascular events were low in both the CPAP group and non-CPAP group. For example, it was found that all-cause mortality occurred in 2.0% (59/2908) and 2.2% (65/2901) of OSA patients receiving CPAP and non-CPAP, respectively. Considering the low incidence of cardiovascular outcomes, it may be reasonable to enlarge sample sizes in future trials. Second, a relatively high non-compliance rate has been observed in trials of CPAP. In the Randomized Intervention with Continuous Positive Airway Pressure in CAD and OSA (RICCADSA) trial, of 122 patients assigned to CPAP, 30 (24.6%) and 45 (36.7%) returned to CPAP within the first 3 and 12 months, respectively.

Great inconsistencies between low outcome events and high non-compliance rates indicate that current trials might have been influenced by various biases. Although other treatments, such as mandibular advancement device, exercise-training, and dietary weight loss, have been proposed to improve health-related quality of life in OSA patients, CPAP remains the most effective treatment in decreasing apnea-hypopnea index and oxygen desaturation indexes [27, 28]. A recently published systematic review confirmed that CPAP is the only choice for improving patient mental component scores and physical component scores of the 36-Item Short Form Health Survey [28]. The failure of CPAP in reducing "hard outcomes", such as mortality and adverse events, does not necessarily prevent it from being used in routine clinical practice to relieve patient symptoms. Future clinical trials

may compare the effects of CPAP with other treatments on improving patient quality of life.

In conclusion, according to the present meta-analysis, CPAP is not associated with all-cause mortality, cardiovascular mortality, strokes, or myocardial infarction in OSA patients. More research is warranted to confirm the current evidence on this topic.

Disclosure of conflict of interest

None.

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