Supplementary Online Content


Trial protocol

This supplementary material has been provided by the authors to give readers additional information about their work.
Comparison of the effect of continuous positive airway pressure and mandibular advancement devices on blood pressure in patients with obstructive sleep apnea: a network meta-analysis

Protocol v1.0

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**Introduction and rationale**

Obstructive sleep apnoea (OSA) is characterised by recurring cessations or reductions in respiratory flow due to upper airway collapse during sleep. The condition is associated with oxygen desaturations and arousals from sleep which can lead to increases in blood pressure (BP) and cardiovascular disease.\(^1\)

Continuous positive airway pressure (CPAP) has been shown to be an effective treatment in improving the symptoms of OSA such as daytime sleepiness\(^2\) and recent meta-analyses have also shown it to reduce BP.\(^3\)–\(^7\) In 2007 a meta-analysis of 12 randomised controlled trials (RCTs) by Haentjens et al.\(^5\) estimated that CPAP reduced daytime systolic BP (SBP) and diastolic BP (DBP) by 2.3mmHg and 2.0mmHg respectively compared to a placebo treatment (sham CPAP or placebo tablet). In the same year a similar meta-analysis by Bazzano et al.\(^3\) of 16 RCTs which also included studies with control arms not using a placebo showed that CPAP reduced SBP by 2.5mmHg and DBP by 1.8mmHg. More recent meta-analyses by Montesi et al.\(^6\) and Fava et al.\(^4\) have shown similar decreases in diurnal BP. A meta-analysis by Schein et al.\(^7\) which only considered trials using sham CPAP for control showed reductions of around 3mmHg in SBP and DBP but no evidence of an effect on daytime BP.

Mandibular advancement devices are an alternative treatment to CPAP for treating OSA which work by protruding the mandible and tongue to keep airways open during sleep. A meta-analysis by Iftikhar et al.\(^8\) recently showed no evidence that MADs reduced BP relative to a control although the analysis included only two RCTs and may therefore have lacked power.

Despite most of the meta-analyses discussed above being published very recently, there has since been a considerable number of trials published which have investigated the effect of CPAP and/or MADs on BP in patients with OSA. In addition, no meta-analysis has yet made a thorough comparison of CPAP against MADs to determine which treatment, if any, is superior in lowering BP.

We aim to perform a broad network meta-analysis of trials investigating CPAP and/or a MAD against an inactive control arm (placebo or no treatment) or against each other. Such an analysis makes use of indirect comparisons to obtain better estimates of treatment effects and also allows the best treatment for a particular outcome to be identified.\(^9\) We also aim to explore the relationship between trial level characteristics and the reported effects on SBP.
and DBP. Due to the conflicting results of previous meta-analyses, we also aim to investigate whether trials reporting higher CPAP usage show greater reductions in BP.

Methods

Objective
To assess the effect of CPAP and MADs on BP in OSA patients against an inactive control arm and against each other using a network meta-analysis

Study eligibility criteria
Trials must have randomised patients aged 18 and over with a diagnosis of OSA (defined by an apnoea-hypopnoea index (AHI) of at least 5) to at least two of the following three sets of treatments: a) CPAP b) an MAD or c) an inactive control such as sham-CPAP, a placebo MAD, any other type of placebo (e.g. tablet) or no treatment. RCTs of patients with a concurrent disease (e.g. heart failure, hypertension etc.) will be considered eligible for inclusion. Trials must have measured and reported BP at a follow-up visit and preferably also at baseline or reported a treatment effect for this outcome. If two eligible studies contain a significant overlap in patients then the larger of the two studies will be used in the analysis. Both parallel and crossover RCTs and only trial reports published in English will be considered for eligibility.

Identification of trials
MEDLINE, Embase and Central will be searched using the Cochrane Highly Sensitive Search Strategy (sensitivity-maximising and precision-maximising version) for identifying RCTs. Search terms for each electronic database are shown in the appendix. Bibliographies of all eligible trial reports will be screened for further trials.

Endpoints
The primary outcomes will be the absolute change in SBP and DBP from baseline to follow-up in each of the following three treatment comparisons:

A. CPAP vs. inactive control
B. MAD vs. inactive control
C. CPAP vs. MAD

A secondary outcome will be the association between average treatment adherence measured in hours/night and the reported treatment effects on SBP and DBP in comparison A only.
The association between the following trial level characteristics and the reported treatment effects on ESS will be also investigated in exploratory analyses:

- Average baseline BP
- Average baseline AHI
- Length of follow-up
- Type of control arm (sham-CPAP, no treatment or other type of placebo)

**Data extraction**

The following data will be extracted from each study included in the meta-analysis:

- Trial characteristics: year of publication, trial design (e.g. crossover), inclusion criteria, experimental and control arms, sample size, analysis sample size, length of follow-up
- Overall average baseline patient characteristics: AHI, age, % male, BMI, ESS, BP
- Average treatment compliance over follow-up (hours/night)
- BP data reported in one of following ways along with corresponding SD or SE (in order of preference):
  1. Adjusted treatment effect for change in BP over follow-up
  2. Unadjusted treatment effect for change in BP over follow-up
  3. Mean change in BP from baseline to follow-up in each arm
  4. Mean BP for each arm at each visit
  5. Mean BP at follow-up visit only (if no baseline data available)

Data on daytime, morning or office BP measurements are preferable (in that order) otherwise 24 hour measurements will be used.

**Statistical methods**

Mean BP values for each arm at each visit (format (iv) above) will be used if available to estimate treatment effects for those studies not reporting data in formats (i)-(iii). To calculate the SE of the treatment effect in each study an estimate of the between-visit correlation is required. This correlation will be imputed from studies reporting ESS data in formats (i)-(ii) using the methods described by Elbourne et al. and the mean correlation will be used in the SE calculation. Sensitivity analyses will also be performed in which the minimum and maximum estimated correlations are used instead to impute missing SEs.

In crossover studies not reporting a treatment effect from an analysis specific to paired data the within-patient correlation will be assumed to be zero. This is a reasonable assumption when changes from baseline are of interest.
A network meta-analysis will be performed to assess treatment comparisons A, B and C on SBP and DBP. Multivariate random-effects meta-regression will be used as implemented through the network family of commands in Stata. A consistency model which assumes that treatment effects from direct and indirect comparisons are in agreement will first be used. An unstructured between-study covariance matrix will be used to allow for the possibility of unequal levels of heterogeneity in the different comparisons. To test for inconsistency, design-by-treatment interactions will be added to the consistency model where `design' refers to the set of treatments in a trial. To further investigate the plausibility of the consistency assumption we will also compare important trial and patient characteristics across different designs. Any differences may be a sign of inconsistency. Forest plots will be used to summarise study-level and pooled treatment effects and comparison-adjusted funnel plots will be used to assess publication bias.

Separate meta-analyses of direct evidence only (pairwise meta-analyses) will also be conducted for each treatment comparison using the metan command in Stata. Heterogeneity will be assessed in each analysis using Cochran's $\chi^2$ test and the I$^2$ statistic. Only random-effects models will be used to be consistent with the network meta-analysis. The purpose of this analysis is to determine how pooling only direct evidence differs to also incorporating indirect evidence. If evidence of inconsistency is found in the network meta-analysis then conclusions will be drawn from the pairwise analyses.

To assess the effect of trial and average patient characteristics on treatment effect, random-effects meta-regression will performed using the metareg command in Stata.

**Risk of bias assessment**

Each study included in the meta-analysis will be assessed for its risk of bias using the Cochrane Collaboration's tool. This tool assesses studies on several types of bias (e.g. selection bias, detection bias, attrition bias) and categorises studies by low, unclear or high risk of bias in each of six domains. Pooled treatment effects for each treatment comparison will then be compared between studies at low or high risk of bias in each domain using meta-regression as described above.

**References**


**Appendix – Search Strategies**

Terms specific to sleep apnoea:

- Apnea
- Apnoea
- OSA
- OSAS
- SAHS
- Hypopnoea
- Hypopnea
- Obstructive sleep apnea
- Obstructive sleep apnoea
Terms specific to the interventions:

CPAP

Continuous Positive Airway Pressure

Mandibular advancement

Oral appliance

Mandibular device

Dental appliance

Dental device

Oral device

Terms specific to the outcome:

Blood pressure