A multicentre randomised controlled trial and economic evaluation of continuous positive airway pressure for the treatment of obstructive sleep apnoea syndrome in older people: PREDICT

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Scientific summary

CPAP for the treatment of obstructive sleep apnoea syndrome

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Scientific summary

Background

Obstructive sleep apnoea syndrome (OSAS) is a disorder which gives rise to breathing difficulties during sleep as a result of repetitive closure of the pharyngeal airway. The resulting sleep disruption sometimes leads to severe daytime sleepiness, high blood pressure (BP) and a possible increased risk of heart attack, stroke and neurocognitive dysfunction. OSAS is the third most common respiratory disorder, after asthma and chronic obstructive pulmonary disease. In its severe form it affects from 2–4% of middle-aged people. In older people, the prevalence is much greater, with up to 20% of older people having OSAS.

Obstructive sleep apnoea syndrome can be treated with continuous positive airway pressure (CPAP), which stops the pharyngeal airway closure, thereby normalising breathing. A recent report by the National Institute for Health and Care Excellence concluded that CPAP is clinically effective at reducing sleepiness and is a cost-effective treatment for OSAS in middle-aged people. However, these beneficial effects of CPAP are not generalised across all groups with OSAS, including older people. This is because older patients with OSAS appear to experience fewer symptoms of sleepiness and therefore may receive less benefit from treatment. In the older population there are also likely to be many other causes of sleepiness, making it more difficult to know what symptoms are a result of OSA. Prior to the publication of this report, very little information was available for clinicians and health-care professionals regarding the best way to treat OSAS in older people, and even less information was available about how CPAP treatment impacted on quality of life and about its cost-effectiveness in this population.

Objectives

Positive Airway Pressure in Older People: a randomised controlled trial (PREDICT) aimed to determine the clinical efficacy of CPAP in older people with OSAS by way of reducing subjective sleepiness and to establish its cost-effectiveness. A number of secondary outcomes, focusing on the important consequences of untreated OSAS, were also measured, including neurocognitive function, road traffic accidents (RTAs), changes in BP and metabolism. More general aspects thought to reflect successful treatment of a chronic condition, such as improvements in mobility, quality of life overall and the use of health-care resources such as visits to a general practitioner or hospital for treatment, were also measured. Adherence to CPAP treatment was the tertiary outcome measure. Patients also recorded any side effects of CPAP treatment. The specific outcomes are listed below.

Coprimary outcomes

1. Subjective sleepiness at 3 months was assessed using the Epworth Sleepiness Scale (ESS) mean score at months 3 and 4, answering the question ‘Is CPAP clinically effective at 3 months?’ The ESS is a well-established and validated scale for measuring subjective sleepiness; a reduction in ESS score reflects symptom improvement.
2. Cost-effectiveness over 12 months was assessed using the European Quality of Life-5 Dimensions (EQ-5D), and health-care resource use was measured monthly over the duration of the trial. Costs were evaluated from the NHS perspective, and health outcomes were expressed as quality-adjusted life-years (QALYs).

Secondary outcomes

1. Subjective sleepiness at 12 months: the ESS mean scores at months 10, 11 and 12 were used to answer the question 'Is CPAP cost-effective at 12 months?'

The following outcomes were measured at 3 and 12 months:

1. objective sleepiness, measured using the Oxford Sleep Resistance (OSLER) test
2. quality of life and mood, assessed using the Short Form questionnaire-36 items (SF-36), the Sleep Apnoea Quality of Life Index (SAQLI; a disease-specific sleep apnoea questionnaire which included CPAP side effects) and the Hospital Anxiety and Depression Scale
3. functionality, as measured using the Townsend Disability Scale
4. nocturia, as self-reported frequency
5. mobility according to Timed Up and Go test
6. self-reported road accidents
7. cognitive function determined by the Mini-Mental State Examination, Trail Making Test Part B, Digit Symbol Substitution test and simple and four-choice reaction time test
8. cardiovascular risk factors, such as systolic and diastolic BPs and fasting blood profile
9. new cardiovascular events, including myocardial infarction, stroke, transient ischaemic attack, angina, atrial fibrillation and peripheral vascular disease.

Tertiary outcome

Treatment compliance was measured objectively, by downloading data from the CPAP machines at 3- and 12-month assessments.

Methods

Design

This was a randomised, parallel, investigator-blinded multicentre trial over 12 months. Consecutive eligible patients were offered trial entry. Patients had to be 65 years or older with newly diagnosed OSAS at enrolment. The diagnosis of OSAS was based on a routine clinical sleep study performed in the recruiting centres. The severity of OSAS was defined as oxygen desaturation index (ODI) at $\geq 4\%$ desaturation threshold level for > 7.5 events/hour and an ESS score of ≥ 9. All enrolled patients also underwent a domiciliary overnight respiratory polygraphy (Embletta® GOLD™, Embla®, Amsterdam, the Netherlands).

Setting and team

The trial took place in NHS sleep clinics across the UK: Scotland (Edinburgh), Wales (Newport) and England (12 centres). These centres had expertise in the assessment and treatment of OSAS. The cost-effectiveness analysis was carried out by the Centre for Health Economics, York. The Medical Research Council Clinical Trials Unit (MRC CTU) allocated the randomisation codes and carried out the clinical analysis. The trial was managed by the Oxford Respiratory Trial Unit and Imperial College London and monitored by Trial Steering and Data Monitoring Committees. An industrial partner [ResMed (UK) Ltd] supported the trial by providing the CPAP machines and loaning the equipment required for the sleep studies.

Interventions

Patients were randomised (1 : 1) to CPAP with best supportive care (BSC) or BSC alone for 12 months. Patients assigned to CPAP were established on autotitrating CPAP delivered using the standard clinical protocols in the recruiting centres. BSC was defined as advice on minimising daytime sleepiness through improved sleep hygiene, using naps or caffeine as required and weight loss if appropriate, which was summarised in a booklet format. A booklet containing this information was compiled by the trial

management team and provided to all patients. This could also be supplemented with information routinely given at each centre.

Patients were randomised centrally by the MRC CTU using computer-generated randomisation. The allocation group was revealed by telephone to the person initiating the intervention once baseline data collection was complete. Structured assessments were performed at baseline, 3 and 12 months. All patients received a telephone call at 1 week, 1 month and 6 months to record symptoms and side effects and to optimise CPAP adherence. Patients also completed monthly diaries recording symptoms, side effects, health-care resource use, change in medications, functionality and quality-of-life questionnaires. Domiciliary overnight pulse oximetry was performed at 3 and 12 months.

Analysis

All analyses were pre-specified in the analysis plan. Analysis was by intention to treat with adjustment for treatment allocation, minimisation factors and the corresponding baseline variable of the outcome using standard statistical techniques and incorporating multiple imputation analysis.

Cost-effectiveness analysis took the perspective of the UK NHS over a time horizon of 1 year. Health outcomes were expressed as QALYs using EQ-5D and Short Form-6 dimensions (SF-6D) derived from the SF-36.

Results

From February 2010 to May 2012, 278 patients were randomised. Follow-up visits were conducted in 245 (88%) and 231 (83%) patients at 3 and 12 months, respectively. Overall, 231 (83%) patients completed the trial. Mean (standard deviation; SD) age was 70.6 years (SD 4.7 years; range 65–89 years), ODI 28.7 (SD 19.1) events/hour (range 0.4–120.4 events/hour) and ESS score of 11.6 (SD 3.7; range 4–22).

In total, 140 patients were randomised to CPAP and 138 to BSC. Baseline ESS score was similar between groups, mean (SD) 11.5 (SD 3.3) CPAP and 11.4 (SD 4.2) BSC. The demographics and clinical characteristics were broadly similar between the two groups.

Coprimary outcomes

1. Subjective sleepiness at 3 months: there was a significant reduction in ESS score at 3 months in patients allocated to CPAP was –3.8 (SD 0.4) compared with BSC –1.6 (SD 0.3), with a difference of –2.1 [95% confidence interval (CI) –3.0 to –1.3; $p < 0.001$]. The treatment effect was significantly greater in patients with higher baseline ESS score or higher CPAP use.
2. Cost-effectiveness at 12 months: the average QALYs obtained using the EQ-5D were 0.680 (95% CI 0.638 to 0.722) QALYs for CPAP and 0.666 (95% CI 0.627 to 0.705) QALYs for BSC. The relative increase in QALYs with CPAP was 0.005 (95% CI –0.034 to 0.044). The average cost per patient allocated to CPAP was £1363 (95% CI £1121 to £1606) and for BSC was £1389 (95% CI £1116 to £1662).

Overall, the CPAP group accrued on average –£35 (95% CI –£390 to £321) lower costs. The results were not sensitive to different assumptions regarding missing data, although they were sensitive to different scenarios regarding the cost of equipment. In addition, the probability of CPAP being cost-effective was more certain in patients with higher baseline ESS scores. The probability that the intervention was cost-effective at the thresholds conventionally used in the NHS (£20,000 per QALY gained) was 0.61.

Secondary outcomes

1. The improvement in the ESS score on CPAP was maintained at 12 months [treatment effect –2.0 (95% CI –2.8 to –1.2; $p < 0.001$)].
2. When cost-effectiveness was assessed using SF-6D, CPAP improved QALYs by 0.018 (95% CI 0.003 to 0.034) and the probability of CPAP being cost-effective was 0.96.
3. Objective sleepiness was significantly reduced at 3 months ($p = 0.02$) but less so at 12 months ($p = 0.06$).
4. Mobility was reduced at 3 months ($p = 0.03$) but not at 12 months ($p = 0.8$).
5. The energy/vitality domain of the SF-36 improved at 3 months ($p = 0.001$) and 12 months ($p = 0.004$); this was also the case for the disease-specific quality-of-life SAQLI (3 months $p = 0.005$; 12 months $p = 0.001$).
6. CPAP improved total and low-density lipoprotein cholesterol at 3 months [treatment effect –0.2 mmol/l (95% CI –0.3 to 0.0 mmol/l; $p = 0.05$) and –0.15 mmol/l (95% CI –0.29 to –0.01 mmol/l; $p = 0.04$), respectively], but the effect was not sustained at 12 months.
7. There was a treatment effect on systolic BP, which was 3.7 mmHg (95% CI 0.2 to 7.3 mmHg; $p = 0.04$) lower at 12 months, which was entirely attributable to a fall in systolic BP in the BSC group.
8. The incidence of new cardiovascular events did not differ between groups at 3 ($p = 0.48$) or 12 months ($p = 0.72$). Atrial fibrillation was the predominant new pathology.
9. Measures of mood, functionality, nocturia, accidents and cognitive function were unchanged at 3 and 12 months.

Tertiary outcome

Of the 140 patients randomised to CPAP, 120 (86%) at 3 months and 99 (71%) at 12 months reported they were still using CPAP. CPAP usage data were obtained in 117 patients at 3 months [median duration of use 1 hour 52 minutes/night; interquartile range (IQR) 0 hours 19 minutes to 5 hours 12 minutes/night] and in 102 patients at 12 months (median usage 2 hours 22 minutes/night; IQR 0 hours 10 minutes to 5 hours 9 minutes/night).

Serious adverse events

There were 37 serious adverse events, all of which were independently classified as unrelated to the trial: in the CPAP group there were 15 serious adverse events (including one death) in 12 patients and in the BSC group there were 22 serious adverse events (including one death) in 13 patients. CPAP was associated with several common self-reported side effects, such as dry mouth. There was no clinically important harm from CPAP use.

Conclusions

This trial found that CPAP reduced subjective sleepiness in older people with OSAS at 3 months, despite low overall CPAP usage. The beneficial effects were maintained at 12 months and the magnitude of the improvements was similar to that seen in middle-aged patients treated with CPAP.

The reduction in subjective sleepiness was corroborated by a significant improvement in objective sleepiness measured by the OSLER test at 3 months. Quality of life, assessed using the SAQLI and SF-6D, was significantly improved by CPAP.

Overall, the economic benefit of CPAP was linked to potential reduction in health-care use, offsetting the cost of the CPAP equipment, although the EQ-5D may not have been the appropriate measure to use in this disease group.

Secondary outcomes related to cognitive function did not differ between the two groups despite reductions in sleepiness in the CPAP group. In addition, mood, which may impact on cognitive function, did not change. Nor were other secondary outcomes, nocturia and RTAs, improved with CPAP, which may reflect their multifactorial aetiologies.

In terms of the cardiovascular outcomes, there was a significant reduction in total cholesterol at 3 months in the CPAP group, but this was not sustained at 12 months. CPAP produced no improvement in BP. In the BSC group, systolic BP fell, an observation previously reported and difficult to explain.

The mean CPAP usage was low at 3 and 12 months, although similar to other trials in minimally symptomatic OSAS patients. Adopting a standard clinical approach rather than an intensive trial approach may have resulted in lower CPAP use. In addition, other factors, such as reduced social support, may have contributed to lower CPAP adherence, since 50% of the patients reported sleeping alone.

Limitations and strengths

A possible limitation of this trial was that sham CPAP was not used as a comparator, although any placebo effect there might have been in the CPAP group is very likely to have disappeared by 12 months. In addition, the objective OSLER test and the dose–response relationship between the treatment effect and CPAP usage support a real effect.

One of the strengths of this trial was that patients were drawn from geographically diverse areas, with treatment in a real-life clinical setting. PREDICT has also been the longest randomised CPAP treatment trial in OSAS, assessing both clinical and economic benefits. In addition, it is one of the first trials specifically aimed at older people ($\geq$ 65 years).

Generalisability

The trial did not focus on asymptomatic older people with OSA and, although it could be argued that the patients studied had a relatively low mean ESS score at baseline, they were sufficiently symptomatic to seek treatment. At the other end of the disease spectrum, exclusion of highly symptomatic OSAS patients (20%) in whom CPAP was considered mandatory is likely to have diminished the effect size. The exploratory analyses revealed that the treatment effect was larger in patients with a higher baseline ESS score or more frequent CPAP use. Equally, the marginal improvement in cost-effectiveness was more favourable in the more symptomatic patients.

Recommendations

Based on the results of this trial, we suggest that future research:

- focus on how best to optimise CPAP delivery especially in the older patient
- aim to stratify older patients with OSAS according to comorbidities and to assess the effectiveness of CPAP treatment
- define patient-centred outcomes for treatment of OSAS in women and ethnic groups, both of whom are currently under-represented in clinical trials
- explore the hypothesis that OSA in different groups may have different causes anatomically and physiologically, with different consequences.

This last point remains to be investigated and is fundamental to the understanding of OSAS.

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