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Original Article

Continuous positive airway pressure treatment impact on memory processes in obstructive sleep apnea patients: a randomized sham-controlled trial

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ABSTRACT

Objective: The aim of this study was to investigate the changes in a large panel of memory processes after six weeks of continuous positive airway pressure (CPAP) in obstructive sleep apnea (OSA) patients. This randomized controlled trial compared the influence of effective CPAP to sham CPAP over six weeks on different memory processes in OSA patients.
Methods: The study took place in a sleep laboratory and outpatient sleep clinic in a French tertiary-care university hospital. A total of 36 patients with OSA were randomized to receive either CPAP ($n = 18$) or sham CPAP ($n = 18$) for six weeks. Interventions were either effective CPAP or non-effective sham CPAP, for six weeks. All patients underwent an extensive battery of tasks evaluating three separate memory systems, before and after treatment. Verbal episodic memory was tested after forced encoding, procedural memory was tested using simplified versions of mirror drawing and reading tests, and working memory was examined with validated paradigms based on a theoretical model.
Results: The study subjects were 55 ± 11 years of age and 72.2% were male. The mean body mass index was 29.5 ± 4.1 kg/m^2 and the apnea–hypopnea index was 37.1 ± 16.3/h. Prior to treatment, memory performances of OSA patients were altered. In an intention-to-treat analysis, memory deficits were not significantly improved after six weeks of effective CPAP compared to sham CPAP treatment. Verbal episodic, procedural, and working memory scores were comparable between both groups.
Conclusion: Using cautious methodology in comparing effective CPAP to sham CPAP and a well-defined set of memory assessments, we did not find improvement in memory performance after six weeks of treatment.

1. Introduction

Patients with obstructive sleep apnea (OSA) exhibit neuropsychological impairment such as cognitive dysfunctions [1,2] that could be due to sleep fragmentation as well as intermittent nocturnal hypoxia [3–5]. Indeed, we and others have previously demonstrated that OSA patients had mild but significant memory impairment affecting episodic, procedural, and working memories [6–10]. The memory system is divided into short-term and long-term memories, which, in turn, can be separated into different processes. Long-term memory includes episodic memory (which refers to the recollection of specific experiences) and procedural memory (which refers to learning skills) [11]. Short-term memory is a multicomponent working-memory system that allows the temporary maintenance of limited information available for immediate access by other cognitive processes [12]. The negative impact of OSA on short-term memory is still unclear [10,13]. Working memory also includes many cognitive processes such as storage, processing, supervision, and coordination. Thus, the different memory systems can be affected independently of one another by OSA and could be differently affected by its treatment.

The effect of continuous positive airway pressure (CPAP) treatment, the first-line therapy for OSA, on cognitive decline in OSA patients is still debated. About half the studies report that CPAP improves, at least partially, memory impairment in OSA patients. Two randomized controlled trials (RCT) have shown that two to three

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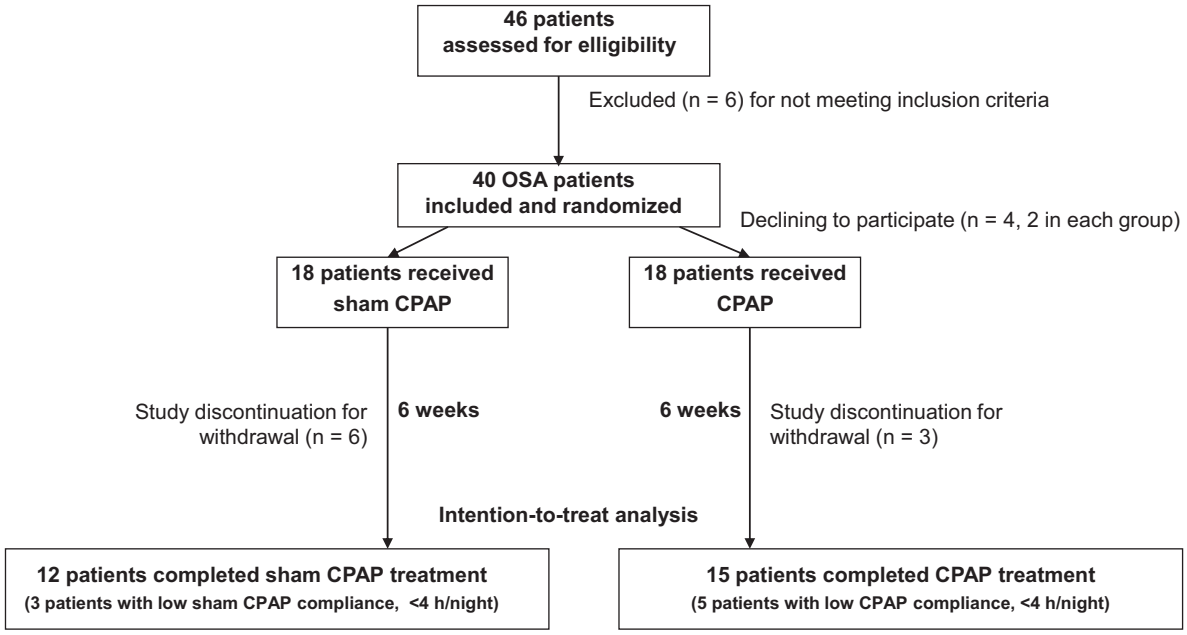

Fig. 1. Study flow chart. CPAP, continuous positive airway pressure; OSA, obstructive sleep apnea.

weeks of CPAP is insufficient to show a beneficial effect on overall cognitive dysfunction [14,15]. A more recent RCT [16] suggests that two months of CPAP-use in severely obese sleep apnea patients results in only mild improvement of working memory (executive functions).

On the other hand, one study showed that 15 days of CPAP treatment is sufficient to normalize attentive, visuospatial learning, and motor performances [17], and in another study, six months of CPAP normalized most neuropsychological deficits in the areas of memory, attention, and executive tasks [18]. We also showed in ten OSA patients that four to six months of CPAP treatment normalized most of the cognitive executive and learning disabilities without modifying short-term memory impairment [19].

However, the variability in study design (and, in particular, the inclusion or exclusion of a control group receiving sham CPAP), sampling methodology, OSA severity, and comorbidities across studies makes their analysis difficult [20,21]. Consequently, a definite demonstration of the CPAP efficacy on memory dysfunction in OSA is still lacking. Moreover, there is a strong variability in tests used across studies, and few studies have explored more than one aspect of memory processes. To test the hypothesis that patients with OSA syndrome would improve memory performances after effective CPAP treatment, we compared verbal episodic memory, visual–motor and reading procedural memory, auditory and spatial working memory, and the capacity to allocate attentional resources in OSA patients randomized to receive either effective or sham CPAP.

2. Methods

2.1. Design and setting

This study performed at Grenoble University Hospital, France, was a randomized, double-blind, parallel-group, sham-controlled trial. It was conducted in accordance with applicable good clinical practice requirements in Europe, French law, ICH E6 recommendations, and ethical principles of the Declaration of Helsinki (South Africa 1996 and Edinburgh 2000). The study was approved by an independent Ethics Committee (Comité de Protection des Personnes, Grenoble, France, IRB0005578) and registered on the ClinicalTrials.gov site (NCT00464659). Written informed consent was obtained from all patients. An external data quality control was performed systematically for the following criteria: informed consent, complications, adverse events, and case report forms.

The primary endpoint was the change in memory function of OSA patients after six weeks of CPAP treatment, in comparison with sham CPAP treatment.

2.2. Patients

Patients were recruited from the Sleep Laboratory at University Grenoble Hospital and the Outpatients Sleep Clinic in a French tertiary-care university hospital (Grenoble, France). Subjects more than 18 years of age who were diagnosed with OSA (apnea–hypopnea index [AHI] > 15/h) on polysomnography (PSG), were naive of CPAP treatment, and gave written informed consent were eligible. The study was conducted following the Consolidated Standards of Reporting Trials (CONSORT) recommendations [22].

Patients were excluded if they declined to participate or were unable to give informed consent. Patients with any of the following were also excluded: severe depressive disorders (Hospital Anxiety and Depression [HAD] score >16), mild intellectual deterioration (Mini Mental State [MMS] score <28), functional failure of the dominant upper limb to achieving graphomotor task, associated oxygen therapy, current pregnancy or lactation, history of stroke, or uncontrolled cancer (Fig. 1).

2.3. Procedures

2.3.1. Patient visits and treatments

At the baseline visit, patients underwent an overnight sleep study. The Epworth Sleepiness Scale (ESS) was completed, and arterial blood gases analysis was performed to exclude obesity hypoventilation syndrome in subjects with a body mass index above 30 kg/m^2. Memory evaluation was then performed, and clinical office blood pressure (BP) was measured.

Patients were then randomized by an independent statistician to be treated by CPAP or sham CPAP for six weeks. This treatment duration was similar to that used in a previous RCT [23]. Patients