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Protocol

Cognition and obstructive sleep apnoea in Parkinson's disease, effect of positive airway pressure therapy (COPE-PAP trial): protocol of a randomized controlled trial

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ABSTRACT

Background: Parkinson's disease (PD) is the second most frequent neurodegenerative disease and is associated with cognitive dysfunction. Obstructive sleep apnea (OSA) has been linked with cognitive dysfunction in the general population and in PD. Treatment with positive airway pressure (PAP), can improve cognition in the general population and in patients with other neurodegenerative diseases. However, the effect of PAP therapy on cognitive function has not been well studied in PD.
Methods: This randomized controlled trial will assess the effect of 6 months of PAP therapy versus placebo on global cognitive function in PD patients with OSA and reduced baseline cognition. Secondary outcomes will include quality of life and other non-motor symptoms of PD. Exploratory outcomes will be specific domains of neurocognitive function and symptoms of REM sleep behaviour disorder.
Conclusions: PD-related cognitive dysfunction often evolves towards dementia and has substantial personal, social and healthcare costs. Few interventions have been shown to improve cognition in PD to date. If positive, results from our study could prove OSA to be a new therapeutic target relevant to cognition and would support more systematic screening for OSA in PD patients with cognitive decline.
Trial Registration: Trial registration number is NCT02209363.

Keywords: Parkinson's disease, Neurodegenerative disorders, Obstructive sleep apnea, Sleep-disordered breathing, Cognitive function

INTRODUCTION

Parkinson's disease (PD) is the second most frequent neurodegenerative disorder.[1] It is characterized by degeneration of dopaminergic neurons in the substantia nigra.[2] In addition to the classic motor symptoms, non-motor symptoms (NMS), including cognitive dysfunction and sleep disorders, greatly impair quality of life.[3] Cognitive dysfunction is found in 20-40% of patients with early PD.[4] PD-related dementia affects up to 80% of patients, leading to major personal, societal and health-care burden.[3,5]

Obstructive sleep apnea (OSA) is a highly prevalent and treatable sleep disorder characterized by recurrent upper airway obstruction with intermittent hypoxemia and sleep fragmentation. It is associated with cognitive impairment in the general population and with cognitive decline in aging.[6,7] OSA affects 20-60% of PD patients.[8]

Sleep disorders are associated with worse HRQoL in PD.[9] Evidence suggests that OSA in PD has deleterious effects on motor symptoms and NMS, including cognitive function.[10,11] Previous work from our group found lower global cognition in PD patients with OSA.[11]

Positive airway pressure (PAP) therapy is the recommended first-line therapy for symptomatic OSA.[12] In the general population, response to PAP therapy has been variable and incomplete regarding cognitive function.[13–17] In PD patients with OSA, PAP therapy successfully corrected sleep apnea and reduced excessive daytime sleepiness.[18] In a prospective observational study, we observed significant improvement in cognitive function and NMS after 12 months of PAP treatment.[19] The effect on cognitive function was more marked in the subgroup with reduced baseline cognition. However, in the only published randomized cross-over trial (RCT), no improvement in cognitive function was observed after 3 nor 6 weeks of PAP therapy despite improved OSA, daytime sleepiness and sleep quality.[18] No medium-long-term RCTs assessing the effect of OSA treatment in PD have been conducted.

The present study aims to evaluate the effect of OSA treatment on cognitive function in PD patients with OSA and reduced cognition. We postulate that, when already affected by a degenerative process like PD, the brain is more vulnerable to OSA and treatment is more likely to be effective.

Objectives

The primary objective of this study is to assess the effects of six months of PAP therapy in PD patients who have OSA and evidence of mild cognitive impairment (MCI), on the Montreal cognitive assessment (MoCA), compared to placebo (nasal dilator strips or NDS). The secondary objectives are to assess the effect of six months of PAP therapy on MoCA scores in a per protocol (efficacy) analysis, on quality of life and on overall PD NMS burden. In addition, we will explore the effect of PAP on specific domains of neurocognitive function and on symptoms of REM sleep behaviour disorder (RBD).

METHODS

Trial design and setting

This is a single-blind, parallel group, randomized controlled trial (RCT) of auto-PAP (treatment) versus nasal dilator strips (control).

All testing is performed at sites of a single centre – the McGill University Health Centre (MUHC, Glen site and Montreal neurological institute) in Montreal, Canada.

Participants

Eligibility criteria

Inclusion criteria included patients with clinical diagnosis of PD based on the movement disorder society (MDS) criteria, clinical impression of MCI and a MoCA score ≤27, presence of moderate to severe OSA on screening in-laboratory polysomnography, as defined by an RDI≥15/hour, and adequate knowledge of English or French for completion of study assessment.[20]

Exclusion criteria included patients with oxygen saturation <75% for >10% of the diagnostic PSG; other major neurological disorder; unstable cardiac disease, uncontrolled hypertension, or diabetes; active cancer or other disorder with an expected survival <6 months; active OSA treatment (prior diagnosis of OSA will constitute an exclusion criterion only if the patient is currently being treated for the OSA); significant vision or hearing impairment that could affect performance on neurocognitive assessment tasks; stable medication regimen prior to inclusion in the study; and latex allergy.[15]

Elevated sleepiness score with or without a safety-critical occupation is sometimes considered an exclusion criterion in OSA trials in the general population due to the potential risk of not treating OSA in this context. In the context of PD, hypersomnolence is frequent and can be related to both the disease and medication.[21] Additionally, OSA has not, to date, been considered an important factor in PD clinically. Therefore, there is sufficient equipoise regarding treatment of OSA in both sleepy and non-sleepy PD patients not to exclude either from this trial.

Study protocol

PSG

Subjects will undergo standard overnight PSG (Nihon Kohden) at the sleep laboratory of the Research Institute of the MUHC. Standard full PSG channels will be recorded, including 6 EEG channels (C3, C4, F3, F4, O1, O2), bilateral tibialis anterior EMG and digital video.[22] Respiratory inductance plethysmography will be used for thoracoabdominal motion, nasal pressure for airflow and pulse oximetry for oxygen saturation. Data will be scored manually using standard American academy of sleep medicine (AASM) clinical criteria by a certified technologist, with expert physician review.[23]

Measures will include standard variables for sleep quality and respiratory disturbance. Subjects with total sleep time <2 hours will be convened for a second study to improve diagnostic accuracy of OSA.

Interventions

After completing a screening PSG, questionnaires and baseline neurocognitive testing, subjects are randomized in a 1:1 ratio to treatment (auto-adjusting PAP or APAP) or control (NDS) interventions (Figure 1).

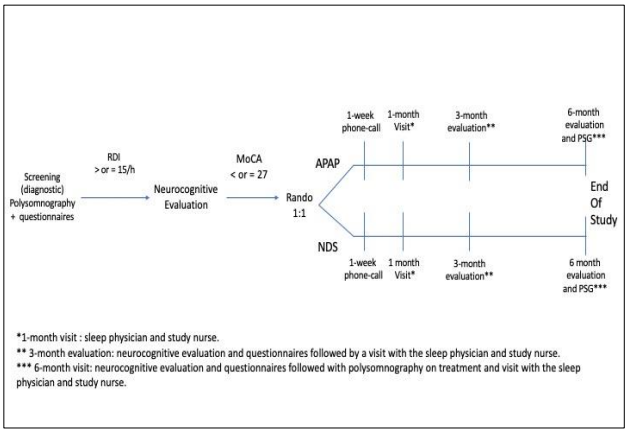

Figure 1: Summary of study procedures Legend: APAP: automatic positive airway pressure; MoCA: Montreal Cognitive Assessment test; NDS: Nasal dilator strips; PSG: polysomnography. RDI: respiratory disturbance index.

APAP

Standard APAP therapy is initiated for consenting subjects with OSA. APAP is a well-established treatment for OSA and has become the standard of care in many places. These devices automatically deliver the required pressure through an algorithm based on detected upper airway obstruction. This allows for initiation of therapy without delay, in contrast to traditional "fixed" PAP that requires in-laboratory titration. Hence, APAP will reduce burden on study participants, by avoiding an additional PSG night for PAP titration, and to maximize comfort and compliance.

Patients randomized to PAP therapy will be referred to our partner PAP provider (VitalAire Inc.) who will provide specific teaching, follow-up and troubleshooting of technical issues related to PAP use via standardized protocols, in cooperation with the PI and study staff. After the initiation visit, subjects will be contacted again by the experienced sleep nurse by phone at 1 week. For patients who remain unable to use APAP, a home visit can be performed by the sleep nurse for interested participants. A respiratory therapist from the PAP provider company will remain available and in contact with the participants and study staff as needed to change equipment or optimize mask fit and comfort with therapy.

Reports from a modem attached to the patients' PAP device will be obtained remotely and reviewed by an expert sleep physician after 1, 3 and 6 months to assess treatment efficacy and adherence, at the time of a clinical patient interview in person, over the phone or via videoconference. Adjustments of APAP settings will be made as necessary. An additional report of the device will be reviewed at 4.5 months by the study sleep nurse, to encourage adherence as needed. Close follow-up will allow optimizing therapy to maximize compliance. However, we expect that up to 20% of individuals may not be able to use PAP.

NDS

NDS is a form of placebo control to PAP and has been successfully used previously in RCTs.[24,25]A placebo effect was notable in that subjective sleep quality improved, without improvement in OSA parameters on PSG. NDS are safe, with minimal adverse reactions (skin irritation or localized allergic reaction). While sham PAP has been used in PAP trials, it has numerous drawbacks, and there is still debate as to whether this is the best control intervention.[15,18,26] Sham PAP tends to be associated with lower compliance and, in one trial, a majority of subjects correctly guessed their assignment, suggesting that true blinding is difficult with sham PAP.[15,27] The small pressure generated by sham PAP may have some physiologic effect on OSA, such that it would not be a true placebo but rather a partially effective intervention.[26] Additionally, although PAP is well-tolerated in the majority of patients, it can be difficult for some individuals. Sham PAP has been shown to decrease sleep quality on PSG.[26] In our proposed study, subjects randomized to NDS will be given a labelled supply of strips and participate in a teaching session on their proper use. Participants will be called at 1 week to evaluate any issues with NDS. Subjects will also see the sleep physician and research nurse at 1, 3 and 6 months, mimicking visits for the PAP group. A strip count will be done at the time of these visits to assess adherence.

Treatment duration and follow-up

The treatment period will be 6 months, with follow-up outcome assessments occurring at 3 and 6 months in both groups. We have included a 3-month assessment in case drop-out rate beyond 3 months is greater than expected and our primary analysis is inconclusive. Towards the end of the 6 months period, participants will undergo a PSG using their respective treatment. Randomization to placebo of individuals with severe OSA, thus delaying treatment by up to 6 months, has been considered ethically acceptable.[15] At least part of the delay is compensated by accelerated diagnosis via the research protocol compared to the usual clinical pathways, where long delays exist. Moreover, cardiovascular risk associated with OSA is primarily related to severe hypoxemia. For this reason, we have excluded patients with severe hypoxemia on PSG. However, longer trials are difficult to justify as withholding effective treatment in patients with moderate-to-severe OSA could yield some undesirable effects.

Outcomes

Primary outcome measure

The primary outcome measure is the mean change in the MoCA test score from baseline to 6 months. The MoCA test is a widely-used screening tool for cognitive impairment addressing multiple domains of cognitive function in a brief practical format.[28] The MoCA has good psychometric properties, can be used for serial assessments and was found to be reproducible in PD as well as sensitive to deterioration over time in other neurodegenerative diseases.[29,30]

Secondary outcomes measure

Quality of life

The PDQ-39 is a validated PD-specific quality of life measure containing 39 questions and eight domains: mobility, activities of daily living, emotional well-being, stigma, social support, cognition, communication, and bodily discomfort.[31] This scale is recommended by the MDS Task Force on assessment of quality of life in PD.[32]

NMS of PD

The MDS-UPDRS part 1 subscale (non-motor aspects of experiences of daily living) will be used as a global measure of PD NMS.[33] A higher score implies greater symptoms. The MDS-UPDRS is a standardized and widely used scale, recommended for the assessment of motor and NMS in PD.[33]

Exploratory outcome measures

Patients will undergo a complete neurocognitive assessment at baseline, 3 and 6 months to assess 5 domains of cognitive function: attention/working memory, executive function, language, memory and visuospatial function. Our battery has been chosen based on the MDS task force paper on MCI in PD.[34] A list of this battery is provided in the supplemental material. This battery should take approximately 90 minutes with breaks. These assessments will be conducted in-person with the neuropsychologist at the Montreal neurological hospital. In exceptional circumstances (primarily related to the COVID 19 pandemic), certain 3 months assessments could be conducted remotely.

In our preliminary study, PAP therapy resulted in improvement in RBD symptoms.[35] We will use the RBDQ1 to screen for RBD.[36] In those with positive responses, we will use our own questionnaire of intensity and severity of RBD. Standard features of RBD on PSG will also be evaluated.[23]

Other covariates

We will obtain comprehensive anthropomorphic data, medical and PD history (including medication and schedule, Hoehn and Yahr stage and complete MDS-UPDRS), history of sleep disorders, daytime sleepiness (Epworth sleepiness scale) and mood (Beck depression inventory II or BDI-II).[33,37,38]

Statistical analysis

Sample size

In our pilot observational work in PD patients, the change in MoCA score with 6 months of PAP treatment was 2.5 (SD 2.4), whereas the change in those untreated for OSA (with or without OSA) was 0.14 (SD 2.6), yielding a between-group difference of 2.36. Our sample size was calculated using a conservative estimate for difference in change in MoCA between groups of 2.2, SD for change of 2.7, and assuming intention to treat. Using 1:1 randomization, we would need 25 subjects per group (α=0.05, power 80%). In order to account for a 20 % non-compliance and 5% loss to follow-up (according to our previous cohort study), we have adjusted the sample according to Lachin.[39,40] The total required sample size will therefore be 90, or 45 per group. In our pilot work, 74% of PD patients with MoCA <27 had OSA. Thus, if we conservatively estimate that 65% of screened individuals with MoCA <27 will have OSA, we will need to screen 138 individuals to yield 90 eligible subjects.

Given the number of subjects we will recruit to address our primary objective, we will have 77% power to detect a difference of 7 for the PDQ-39 (SD=9, α=0.05). Regarding the MDS-UPDRS part 1, we will have 74% power to detect a difference of 3.3 (SD=4.4, α=0.05). Exploratory analyses will assess change in specific neurocognitive measures, for which, with the planned samples size, we will be able to detect a difference between groups of about 0.8×SD (SD for change from baseline). Our sample size is not adjusted for multiple comparisons because there is only a single primary outcome.

Statistical methods

The primary outcome will be the difference between groups in change in MoCA score from baseline to 6 months. This outcome will be compared between groups using a t-test under intention to treat; subjects randomized but lost to follow-up will be included, with the last measurement carried forward or using multiple imputation. In sensitivity analyses, we will adjust for potentially unbalanced confounders such as age, sex, depression scores and levodopa medication dose via linear regression. A subgroup analysis of patients with or without medication change throughout the study will be performed for the primary outcome.

In per protocol (efficacy) analyses, we will compare the change in MoCA score from baseline to 6 months in subjects who complied with treatment (PAP use ≥3 hour/night ≥70% nights) and adjust for confounders as above, via linear regression. We will also estimate the

causal average complier effect. This effect may more closely estimate treatment efficacy in trials with imperfect compliance. Secondary and exploratory outcomes will be analysed similarly.

Randomization

Randomization will be obtained through the database software (Dacima Software Inc.) after inclusion/exclusion data and data for stratification are entered by study staff. Blocked randomization will be performed, stratified by severity of cognitive dysfunction (MoCA<24 versus 24-26 versus 27) to avoid imbalance between groups. Treatment allocation will be communicated by the software directly to the unblinded research nurse, who will arrange treatment initiation.

Blinding

Complete subject blinding is not possible, but subjects are not aware that NDS are a placebo, as they are told that two treatments for OSA are being compared. Subjects will be asked not to disclose their treatment to the outcome assessor.

Treatment initiation and follow-up will be ensured by the research nurse (NDS) or the VitalAire respiratory therapist and sleep nurse (PAP), and clinical follow-up by an expert physician, neither of whom will be involved in outcome assessment. Outcome assessments will be performed by a single well-trained and blinded assessor.

Data collection, management, and analysis

Data collection methods

Outcomes will be measured at 3 and 6 months. Care will be taken to repeat measurements in the "ON" state (when motor symptoms are controlled) and at the same time of day at each time point to avoid circadian variations in performance. Although MoCA scores have been shown to be reproducible in PD, we will use alternative versions between visits (version 2 at 3 months, and version 3 at 6 months). Remaining outcome measures will be reproduced at each visit.

Data management

All data will be entered blindly in an electronic database software (Dacima software Inc., Montreal, Qc). Periodic data cleaning will be performed to promote data quality, and final data cleaning will be done by the research team, in collaboration with the PI. The database software tracks all data changes and extractions. The study statistician and research fellow will have access to the database and be able to query and extract forms for statistical analysis.

Steering committee

The steering committee, including the four co-investigators (MK, AB, GL, ALL), will meet regularly. The PI, and co-investigators, will meet regularly with study personnel to review progress and troubleshoot any issues as they arise. Since no interim analyses are planned and no major safety issues are expected to arise during this study, there will be no data safety and monitoring committee. All adverse outcomes will be reported to our research ethics board (MUHC).

DISCUSSION

Cognitive dysfunction and other NMS are increasingly recognized as early major detrimental factors affecting health-related quality of life in PD.[3] Recent evidence has demonstrated that OSA is associated with cognitive dysfunction in PD.[11,19,41] Prospective data is mixed, with our observational data suggesting PAP therapy can improve cognition, whereas others find no benefit.[19,41] OSA could be a reversible and treatable risk factor for the development of PD-related cognitive dysfunction, but further data are needed.[41,42] With this study, we aim to evaluate the effect of 6 months of PAP therapy, compared with placebo (NDS) on global cognition and other NMS in PD patients with OSA and reduced cognitive function.

In the general OSA population, PAP therapy trials assessing global and specific neurocognitive function have been inconsistent.[13,15,17] In 2013, a systematic review and meta-analysis evaluating patients with varying degrees of OSA found an association between OSA and impairment in executive functions, which improved with PAP.[43] However, the APPLES trial, a large multicentre RCT evaluating 6 months of PAP versus sham-PAP, found no apparent benefits in three domains of cognitive function (attention/psychomotor function, learning/memory, executive/frontal lobe function), despite improvement in daytime sleepiness.[15] Inclusion of younger patients with high baseline functioning in this study could have selected patients with higher cognitive reserve and consequently less likely to respond to treatment.

Moreover, the effects of PAP on cognition could be more prominent in cognitively vulnerable populations, such as in the elderly or patients with neurodegenerative diseases.[17,44] A RCT of patients >65 years old showed that treatment with PAP improved episodic and short-term memory, executive functions and mental flexibility.[17] Consistent with these results, a study found that one year of PAP therapy improved cognition and slowed cognitive decline in patients with OSA and MCI.[45] A recent systematic review and meta-analysis of 4 studies conducted in patients >65 years old found mild improvement in memory tasks with PAP therapy but not in executive functions nor vigilance. However, findings were undermined by lack of power and low quality evidence.[46]

PAP therapy has been studied in Alzheimer's disease (AD).[44,47,48] In a three-week sham-controlled PAP trial conducted in patients with mild-moderate AD, PAP had no significant effect on global cognition or on the composite

neuropsychological score, though planned sample size was not attained.[44] However, there was improvement in neurocognitive function from baseline in combined therapeutic periods of active PAP. Moreover, in the open-label follow-up, patients with sustained PAP use (mean 13.3 months) showed less deterioration of their global cognition and had improvements in depressive symptoms, daytime sleepiness and subjective sleep quality, compared with the untreated group.[47]

Most studies emphasize that treatment duration can be a key factor in the cognitive response to PAP therapy. Studies that found improvement in cognition were conducted over more than 1 to 3 months.[49,50] In our preliminary work in PD patients, cognitive function was improved after 6 and 12 months of PAP treatment.[19] However, it remains unclear for how long treatment needs to be maintained before benefits can be observed, or whether benefits are sustained over longer periods. Consequently, in this study, we opted for a longer treatment period of 6 months; a longer placebo-controlled study would have been ethically unjustifiable.

In exploratory analyses, we will look at the impact of PAP therapy on specific domains of neurocognitive function, as targeted by the MDS Task Force publication on MCI in PD.[34] This will allow us to better characterize the profile of cognitive dysfunction in PD, and to identify areas of cognitive function susceptible to treatment. This will be especially important in the event that global cognition remains unchanged with treatment, as improvement in certain specific domains of cognitive function might be related to increased functionality and quality of life in PD. We will also assess the effect of PAP therapy on RBD manifestations, as our observational work suggests these symptoms may improve with treatment of OSA.[35]

CONCLUSION

In conclusion, PD-related cognitive dysfunction and dementia are almost inevitable over the course of the illness and interventions aimed at preventing cognitive decline in this population are currently lacking. OSA has been proposed as a contributor to cognitive decline and impaired quality of life in PD. However, robust RCTs are needed to validate the benefits and feasibility of PAP therapy in PD patients with OSA. If positive, results from our study will favour a more systematic screening for OSA in PD patients and suggest PAP therapy as new non-pharmacological disease modifying therapy for the prevention, and perhaps treatment, of cognitive decline in this population.

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Conflict of interest: MK receives unrestricted research support for this study from VitalAire Inc and Phillips Respironics, as well as unrelated unrestricted research grant from Fisher Paykel. She is a member of the Advisory Board for Biron Soins du Sommeil. The other authors have no competing interests to declare

Ethical approval: The study was approved by the MUHC research ethics board (REB) [MP-37-2015-1195 (14-187-GEN), July 8th, 2015]. All protocol amendments have been submitted and approved by the REB and published in clinicaltrials.gov

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