Study protocol

The effect of antihypertensive agents over Sleep Apnea: protocol for a randomized controlled trial

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Abstract

Background

Obstructive sleep apnea (OSA) and hypertension are well-known cardiovascular risk factors. Their control could reduce the burden of heart disease across populations. There are several drugs to control hypertension, but the only consistently effective treatment of OSA is continuous positive airway pressure. The identification of a drug capable to improve at the same time OSA and hypertension would provide a novel approach in the treatment of both diseases.

Methods/design

This is a randomized, double-blind, clinical trial, comparing the association of Chlorthalidone and Amiloride with Amlodipine as first drug option in patients older than 40 years of age with Stage I hypertension (140-159/90-99 mmHg) and moderate OSA (15-30 apneas/hour of sleep). Variation of the number of apneas per hour and blood pressure measured by Ambulatory Blood Pressure monitoring are the primary outcomes. Adverse events, somnolence scale (Epworth), ventilatory parameters and C reactive protein are the secondary outcomes. The follow up will last 8 weeks. The sample size will be of 29 participants per group.

Discussion

The role of fluid retention in OSA is known for several decades. The role of diuretics is well established in hypertension but was never appropriately tested in sleep apnea. Besides to test the efficacy of these drugs, this study will help to
understand the mechanisms that link hypertension and sleep apnea and its treatment.

ClinicalTrials.gov: NCT01896661

Keywords

Sleep apnea, hypertension, treatment, diuretics, Chlorthalidone, Amlodipine
Background

Obstructive Sleep Apnea (OSA) is a well known cardiovascular risk factor and a major cause of secondary hypertension [1, 2]. About 30% of the population has OSA, which is moderate to severe (more than 15 apneas/hour of sleep) in 16.9% of the adults [3]. OSA is present in 30-80% of the hypertensive patients [4]. We demonstrated that 38% of the patients with controlled hypertension have OSA, in contrast to 71% of the patients with resistant hypertension [5]. Each episode of apnea/hour increases the risk of hypertension by 4% [6].

The association between OSA and hypertension has been disregarded by clinicians and even by researchers of hypertension [7]. The cost and low availability of the golden standard method to diagnose OSA, full polysomnography, may be one of the reasons [8, 9]. The use of portable devices, which were validated in our laboratory, could circumvent such limitation, since they have reasonable sensitivity (96%) and specificity (64%) [10].

The standard treatment of OSA is with continuous positive airway pressure device (CPAP), with 46 clinical trials showing benefits [11]. It was also showed in randomized clinical trials that CPAP lowers blood pressure, particularly in patients with hypertension [12]. Blood pressure decreased by 7.8/5.3 mmHg in the 24h in patients with OSA and hypertension, but did not decreased in those without OSA [13]. The efficacy of CPAP in patients with milder forms of OSA is still unproven [14], which could be secondary to the low adherence to the use of the device. Other therapies could be beneficial in such patients [15].

A Cochrane review, which identified 26 clinical trials of 21 drugs, totaling 394 patients, failed to identify any pharmacological treatment with consistent
efficacy. Some drugs, like fluticasone, mirtazapine, physostigmine and nasal lubricant, seem to reduce the number of apneas, but trials were small and presented methodological limitations, precluding the use of these drugs in clinical practice [15]. It has been suggested that drug therapy must be tailored to the mechanism of OSA identified in each patient [15].

Extravascular fluid shift has been implicated in the physiopathology of OSA. During the night, shift of fluids from legs led to increasing neck circumference, peripharyngeal pressure and upper airway collapsibility [16-19]. Sixty years ago it was described an increase of 0.5 cm in earlobe increases during the sleep [20]. The application of lower body pressure of 40 mmHg with antishock trouser reduces leg fluid volume and increases neck circumference and resistance of the pharynx [18].

Patients with controlled hypertension had a reduction of 175 mL in leg volume and an increase of 1.0 cm in neck circumference after sleep, in comparison with a leg volume reduction of 346.7 mL and an increase in the neck circumference of 1.5 cm in patients with resistant hypertension [21]. The leg volume shift is positively correlated to the number of apneas (R²=0.56) [21]. CPAP reduced the neck increase proportionally to the reduction of apneas, but it did not prevent leg volume shift [19].

Sympathetic renal ablation with radiofrequency reduced blood pressure by 33/11 mmHg in six months [22]. It also reduced the number of apneas per hour of 16.3 to 4.5 in 10 patients with resistant hypertension and OSA [23], an effect that was attributed to the promotion of salt excretion and total body fluid reduction [23]. Spironolactone led to a reduction of 39.8 to 22.0 apneas per hour after 8 weeks of
treatment in 12 patients with resistant hypertension [24]. There is no controlled study exploring the concept that these drugs may act through total body fluid reduction.

In the ALLHAT trial, chlorthalidone, lisinopril and amlodipine had comparable efficacy in the prevention of coronary heart disease [25]. The diuretic, however, was superior to lisinopril in the prevention of stroke prevention and amlodipine in the prevention of heart failure [25]. There is evidence that the efficacy in prevention of events is related to the magnitude of the blood pressure reduction [25, 26].

The main adverse event of chlorthalidone is hypokalemia, which blunted the efficacy of the treatment in the SHEP trial [27] and increased the serum glucose [28]. The use of amiloride, a physiological aldosterone antagonist, could ameliorate this adverse effect. This potassium sparing diuretic was effective and well tolerated in a randomized trial performed by our group [29].

Amlodipine was most effective than valsartan, an angiotensin receptor blocker, in the prevention of myocardial infarction and stroke in the VALUE trial [30]. In the ACCOMPLISH trial, the combination benazepril-amlodipine was more effective in the prevention of composite cardiovascular events than the combination benazepril-hydrochlorothiazide [31]. There is no evidence that amlodipine influences the balance of fluids, and edema is one of its main adverse effects.

The sum of the evidences shows that chlorthalidone and amlodipine are the most effective drugs for the initial treatment of hypertension. Their use in OSA was not appropriately tested t date. Thus, a trial testing the efficacy of these drugs to
control both blood pressure and sleep apnea is warranted. Such trial could contribute for the understanding of the relationships between hypertension, fluids, hypoxia and OSA.

**Rationale**

OSA has been associated to fluid retention, which accumulates in the pharynx facilitating its collapse, generating intermittent hypoxia, increasing sympathetic activity and blood pressure. CPAP reduce apneas, which reduces sympathetic activity, reducing blood pressure and increasing salt and water excretion. Sympathetic renal ablation promotes salt and water excretion, reducing systemic sympathetic activity and total body water (including the pharynx), reducing apneas. Diuretic could represent a new way to abort this vicious cycle promoting the direct excretion of salt and water.

**Research Question**

Is clortalidone with amiloride effective in the treatment of OSA comparatively to amlodipine in patients with OSA and hypertension?

**Methods**

Design

Randomized, double-blind, clinical trial, controlled by an active treatment.

Eligible participants
Patients older than 40 years of age with Stage I hypertension (140-159/90-99 mmHg) and moderate OSA (15-30 apneas/hour of sleep).

Exclusion criteria

- Low life expectancy
- Other indications for the use of diuretics or calcium channel blocker
- Intolerance or contraindications to the study drugs, pregnancy, cardiovascular disease (heart failure or recent – three months - myocardial infarction or stroke),
- Use of more than one drug for hypertension
- Secondary hypertension
- Participation in other clinical trial in previous 6 months.

Random allocation

Randomization will be done by a computer generated list, using a validated software (Random allocator), with block size of four.

Interventions

Chlorthalidone plus amiloride 25 and 5 mg daily, versus amlodipine 10 mg daily taking in the morning.

Outcomes

Primary

1. Number of apneas/hour (Apnea-Hypopnea Index).

2. Blood pressure.

Secondary
1. Adverse events.

2. Somnolence scale (Epworth) and respiratory parameters.

3. C reactive protein.

Follow-up and duration of the study

Outpatient clinical visits for evaluation and enrollment and 8th week of treatment. Figure 1 shows flow-chart of selection, interventions, follow-up and outcomes.

Assessment of outcomes

Apneas per hour will be measured at the baseline and follow-up by type III portable polysomnography (Sonmocheck - Weinmann GmbH, Hamburg, Germany), which was validated in our service [10]. Blood pressure will be measured at the baseline and follow-up by average blood pressure (two measurements by a validated automatic electronic device) and ambulatory blood pressure monitoring (Spacelabs 90207 - Spacelabs, Redmond, WA).

Epworth somnolence scale will also be applied at the baseline and follow-up. It measures the possibility of sleep in 8 daily activities (sitting and reading, watching television, sitting in public space, being passenger in a car for 1 hour, laying down in the afternoon, sitting and talking to someone, sitting after a meal without alcohol, stopped in the car for few minutes).
Adverse events will be investigated by open questions and by a semi-structured questionnaire including general symptoms and the presumed adverse effects of the drugs used in the trial. Standard laboratory tests will be done to search for adverse events, such as hypokalemia and elevated glucose. C-reactive protein will be determined as well.

Wash out

Patients using one antihipertensive drug will need to stop it for 2 weeks to be confirmed for eligibility, when most of the effect of BP drugs vanishes [32].

Control of adherence

The checking for adherence will be done by pill counting.

Sample size calculation

For a mean of 20 apneas/hour at the baseline and a reduction of 7 apneas/hour, with a standard deviation of 9 apneas/hour, power of 80% and P alpha of 5%, 26 patients will be required per group. The sample will be increased in 10% to account for possible losses in follow up, resulting in 58 patients to be randomized.

Statistics
Differences between groups variables will be analyzed with Chi-square for categorical and Student t test for continuous variables. Confounding will be controlled with logistic regression and multiple linear regression models.

Ethical approval

The project and the informed consent form were approved by the Ethics committee of the Hospital de Clínicas de Porto Alegre, which is accredited by the Office of Human Research Protections as an Institutional Review Board. All participants will be asked to sign the informed consent to participate in the study.

Trial status

Recruiting patients.

List of abbreviations

OSA: Obstructive Sleep Apnea; CPAP: continuous positive airway pressure device; ACE: angiotensin converting enzyme; ALLHAT: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; SHEP: Systolic Hypertension in the Elderly Program; VALUE: Valsartan Antihypertensive Long-term Use Evaluation; ACCOMPLISH: Avoiding Cardiovascular Events in Combination Therapy in Patients Living with Systolic Hypertension

Competing interests

The authors declare that they have no competing interests.
Authors' contributions

FTC: conceived the study, revised the background, prepared the planning for data collection and prepared the draft of the Ms.

DM: participate in the revision of the background, participate in planning for data collection and contributed for the draft of the Ms.

SCF: participate in planning for data collection and contributed for the draft of the Ms.

MG: participated in the revision of background, and revised the draft of the Ms.

LBM: participate in planning for data collection and revised the draft of the Ms.

FDF: conceived the study, participate in planning for data collection and prepared the final version of the Ms.

All authors read and approved the final version of the manuscript.

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Legend for Figure 1:

Flow chart of participants’ selection, interventions and outcomes.
58 patients

Exclusion criteria:
- Age > 40 years
- Blood pressure 140-159/90-99 mmHg
- 15-30 apneas/hour of sleep

58 patients

Chlorthalidone 25 mg
Amiloride 5 mg

Amlodipine 10 mg

8 weeks

Primary endpoints: Apnea-Hypopnea Index and Blood Pressure

Secondary endpoints: Adverse events, Somnolence scale (Epworth), respiratory parameters, C reactive protein