STUDY PROTOCOL

Clinical trial of a rehabilitation device based on electrical stimulation for patients with obstructive sleep apnoea (OSA): a study protocol [version 1; peer review: awaiting peer review]

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Abstract

Obstructive sleep apnoea-hypopnoea syndrome (OSA) is a respiratory disorder characterised by repetitive obstruction of the upper airway, leading to several interruptions during sleep. It is currently one of the main public health problems worldwide and one of the main cardiovascular risk factors in developed and intermediate developing countries, whose populations are increasing in rates of obesity and age. One of the common treatments for OSA is a continuous positive airway pressure (CPAP) device, which pumps air through a hose, reaches a mask that the patient has over his or her nose and travels the airway, keeping the upper airway open during sleep and avoiding episodes of airway collapse. The problem is that CPAP is not accepted by some patients due to a lack of adaptation, so alternative treatments may be needed. For some years, there have been explorations of treatments related to electrical stimulation of the muscles of the upper airway as therapy to reduce the number of episodes of apnoea (measured through the apnoea-hypopnoea

index) during the night, strengthening these muscles through stimulation. This is the protocol of the first clinical study of a rehabilitation device for home use that not only provides functional stimulation of the upper-airway dilator muscles but also provides sensory stimulation. This device works by strengthening the dilating muscles of the upper respiratory tract and improving the sensory capacity of the laryngo-pharyngeal tract and is based on existing publications on the effectiveness of functional and somatosensory neurostimulation through neuroplasticity in the recovery of neurological deficits.

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Keywords

Rehabilitation device, Electrical stimulation, Obstructive Sleep Apnea, Genioglossus muscle, Laryngopharyngeal sensory test.

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Competing interests: This project will evaluate a electrostimulation device which will be potentially protected by a patent. The financial rights of such a patent will belong to the institutions participating in this project (Universidad de La Sabana, Universidad de Navarra, Universidad Central and Fundacion Neumologica Colombiana) and the following authors of this protocol would have intellectual rights in the invention: William D. Moscoso-Barrera, Luis Mauricio Agudelo-Otalora, Javier Burguete, Secundino Fernández, Elena Urrestarazu Bolumburu, María Angélica Bazurto, Natalia Gelvez, Carolina Bermúdez, Luis F. Giraldo-Cadavid.

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Introduction

Sleep apnoea is a significant cardiovascular risk factor. Its consequences include systemic high blood pressure, pulmonary hypertension, myocardial infarction and cerebrovascular disease [(Caples *et al.*, 2005), (Rangel-León *et al.*, 2015)]. It also produces metabolic alterations related to the control of glycemia and lipids (Caples *et al.*, 2005). Additionally, it is linked to obesity, which creates a vicious cycle: obesity causes sleep apnoea, and sleep apnoea worsens obesity by altering the response to hormonal mediators of satiety (Romero-Corral *et al.*, 2010).

Despite representing a pathology with multiple complications, there are limited treatments for obstructive sleep apnoea-hypopnoea syndrome (OSA). The adherent use of continuous positive airway pressure (CPAP) has been shown to have beneficial effects on OSA outcomes, including avoiding further deterioration in the airway (Maurer *et al.*, 2012); however, the adherence rate for this device is low (even less than 40% in some cases), forcing researchers to look for alternatives (Kezirian *et al.*, 2010). Surgical procedures related to the treatment of OSA have variable results, with high mortality rates (Maurer *et al.*, 2012) and effectiveness ranging from 20% to 60% (Maurer *et al.*, 2012).

Recent research was investigated electrical stimulation of the upper airway in animals and humans with OSA. Animal studies have consisted of inserting needle electrodes orally into the genioglossus muscle of awake dogs or stimulating the hypoglossal nerve in anaesthetised and non-anaesthetised felines, checking the response of the airway muscles in stimulations with frequencies up to 50 Hertz (Hz) (Kezirian *et al.*, 2010). Similarly, rats were stimulated on the upper laryngeal nerve with frequencies between 30 Hz and 40 Hz for 50 seconds, causing swallowing reflexes, which shows the effects of the action on the muscles (Tsuji *et al.*, 2015).

Human studies for the management of OSA began with the intraoral electrical stimulation of the upper airways carried out by Guilleminault in the 1970s (Guilleminault *et al.*, 1978). These early interventions did not detail the muscle groups on which electrostimulation was exerted, nor did they have diagnostic methods for determining whether the stimulation was taking place on dilating muscles or airway constrictors. Any of these reasons could explain a simultaneous stimulation of dilating and constrictor muscles of the airway, which could be responsible for the failure of such interventions.

Around ten years later, research focused specifically on the main dilating muscle of the airway, the genioglossus, showing that genioglossus stimulation reduced the apnoea-hypopnoea index (AHI) (Schwartz *et al.*, 1993) and daytime sleepiness. However, the successful stimulation of upper airway muscles and relief from upper airway obstruction still has problems, such causing the patient to wake during sleep and the need to implant electrodes invasively on the hypoglossal nerve (Yoo & Durand, 2005).

More recently, a device has been developed that seeks to stimulate the hypoglossal nerve by electric current (Maurer *et al.*, 2012). This device performs functions similar to a pacemaker,

generating an electrical stimulus synchronously with breathing (Kezirian *et al.*, 2010; Maurer *et al.*, 2012). Several studies have shown that electrical stimulation in the hypoglossal nerve through this device improves the airspace of the oropharynx and hypopharynx, thus decreasing obstructive episodes during sleep by up to 68% (Kezirian *et al.*, 2010; Lorenzi-Filho *et al.*, 2017; Maurer *et al.*, 2012). However, the implantation of this device is done in an invasive way and is highly irreversible.

Furthermore, there is a new therapeutic horizon that until now has not been explored in OSA: the use of sensory recovery interventions based on the concepts of neuroplasticity that are the basis of neurological rehabilitation (Gillick & Zirpel, 2012; Howlett *et al.*, 2015; Page *et al.*, 2015; Robbins *et al.*, 2006). In fact, there is already preliminary information on the effectiveness of such interventions in the recovery of the sensitivity of patients with oropharyngeal dysphagia (Gallas *et al.*, 2010; Pauloski *et al.*, 2013; Rofes *et al.*, 2013).

The evidence provided by previous research on the effectiveness of electrostimulation in OSA supports the potential of such interventions for the treatment of this entity, as long as stimulation is applied on the dilating muscles of the airway and stimulation of the constrictor muscles is avoided. Likewise, there is evidence that supports the potential benefit of electrostimulation in the recovery of sensory alterations of the laryngopharyngeal tract, which may have a role in the OSA pathogenesis. However, there are a number of problems with this treatment that have yet to be solved, including the development of a non-invasive, effective device; the alteration in sleep architecture by micro-arousals, or awakenings caused by the electric current; and the lack of a device for that a patient can use with minimal level training, on an outpatient basis.

Methods

Research question

How effective a new electrostimulation device is in dilating the upper airway, improving AHI, desaturation indices and quality of life in patients with obstructive sleep apnea

General objective

To evaluate in a first clinical trial a rehabilitation device for patients with OSA based on oropharyngeal electrical stimulation, which strengthens the dilating muscles of the upper airway, improves mechanical laryngopharyngeal sensitivity and improves OSA.

Specific objectives

Perform experimental electrotherapy, nasoendoscopy, polygraphy and polysomnography tests with the device in order to calculate thresholds of functional and sensory intensities on the dilating muscles of the upper airway in patients with OSA. These tests also include the detection of signals that measure breathing events during sleep in patients with OSA in order to use them in the control mechanisms of the electrostimulation device.

Assess the effects and safety of the device in a group of five healthy volunteers for preliminary results.

Evaluate in a small group of patients with OSA the device capacity to stimulate the upper-airway dilating muscles and to reduce the AHI and oxygen desaturation indices when the electrostimulation device is used over a medium-term period (eight weeks) with morning and evening therapy sessions.

Population, selection process and setting

A feasibility clinical study of a medical device (Abdel-Aleem, 2009; CDHR *et al.*, 2013) will be performed in patients prospectively recruited at the Sleep Medicine Service of Fundacion Neumologica Colombiana a tertiary care referral university medical centre specialized in respiratory and sleep medicine, located at Bogota. Patients will initially be evaluated by the Pulmonary and Sleep Medicine Service of Fundacion Neumologica Colombiana to confirm the diagnosis of OSA, for which the presence of symptoms of the disease plus a basal overnight polysomnogram with an AHI greater than 5 will be required.

In total, 12 patients with OSA will be recruited from those referred for full overnight polysomnography: four with mild, four with moderate and four with severe OSA. Patients will be recruited prospectively and consecutively after explaining the study and signing the informed consent. They will be evaluated by a pulmonary and sleep medicine doctor to confirm the diagnosis of

OSA. For diagnosing OSA it will be required the presence of symptoms of the disease plus a baseline polysomnogram with an apnea-hypopnea index (AHI) greater than 5/h. Their general medical condition will also be evaluated and their admission to the protocol defined in accordance with the inclusion / exclusion criteria. Afterwards, the patients will undergo a clinical evaluation by a speech language pathologist trained in myofunctional therapy for OSA (see Figure 1). The study will also include a group of 5 healthy volunteers. The standard clinical evaluation of all patients and healthy volunteers will include the application of a standardized questionnaire assessing for the comorbidities of the Charlson Comorbidity Index (Charlson *et al.*, 1994). Candidates for participating as healthy volunteers will also be screened with the STOP-BANG questionnaire (Baldini *et al.*, 2017; Chung *et al.*, 2016). A healthy volunteer will be defined by the absence of signs and symptoms of acute conditions and comorbidities, and a STOP-BANG score < 3 (Baldini *et al.*, 2017; Chung *et al.*, 2016).

The classifications of the subjects in each category of OSA and as healthy controls will be done by pulmonary and sleep medicine physicians after the standard clinical evaluation. If it is considered that the subject applies as a control, they will be included in the study after signing the informed consent

Figure 1. Process of selecting candidates for intervention.

The definition of mild, moderate or severe OSA will depend on the presence of symptoms plus an AHI (measured during a full overnight polysomnography) between 5 and 15 in the case of mild OSA, >15 to <30 in the case of moderate OSA and ≥ 30 in the case of severe OSA.

Sample size calculation. Considering that this will be the first and pilot study of the electrostimulation device, there are no previous studies to make precise sample size calculations. Therefore, we considered it more appropriate to calculate the sample size using the effect size, that is, how large is the difference in the AHI before and after the intervention in terms of the standard deviation (SD) of the AHI (Cohen, 1988; Machin *et al.*, 2009; Rosenthal, 1996). This method avoids the requirement of knowing the precise values for the means and SDs of the variables under study. For this pilot study, in which the priority is assessing feasibility, we considered that the AHI difference before and after the intervention should correspond to a large effect size to be considered significant. Future studies looking for smaller differences will use the results of this pilot study for sample size calculations. Effect size larger than 0.8 are considered large (Cohen, 1988; Rosenthal, 1996).

Therefore, the sample size was calculated looking for an effect size of 1.0 (a decrease in the AHI after the intervention of 1.0 SD of the AHI, which could correspond to about 15 apnoea-hypopnoea events per hour (Butler *et al.*, 2019)), assuming a significance of 95%, a power of 80% for comparing repeated measures (Machin *et al.*, 2009). With such assumptions, we calculated a minimum sample size of 10 subjects to detect statistically significant differences in the repeated measures comparison of pre-and post-intervention AHI (Machin *et al.*, 2009), and two subjects were added to compensate for the potential loss to follow-up, for a total of 12 subjects.

Inclusion criteria for patients. Patients over 18 years of age with confirmed OSA (four with mild OSA, four with moderate OSA and four with severe OSA) who sign their informed consent to participate in the study.

Inclusion criteria for controls:

Subjects over 18 years of age

Exclusion criteria for patients and controls:

1. Pregnancy
2. Basal polysomnography that does not meet validity criteria to be interpreted.
3. Anticoagulation (although not a contraindication for laryngopharyngeal sensory endoscopic testing, anticoagulation is an exclusion criterion for this study to maintain the lowest level of risk).
4. Haemorrhagic diathesis (to avoid risk of severe epistaxis during nasal endoscopy).
5. Glasgow scale less than 15 (to avoid confusion with sensory or motor laryngopharyngeal involvement

due to neurological disease that compromises the state of consciousness).

6. Basal oxygen saturation by awake pulse oximetry below 88%.
7. Patients with more than 5% of the total apnoea events being of central origin measured during a full overnight polysomnography (to avoid including patients with central sleep apnoea in whom laryngopharyngeal electrostimulation would have no effect).
8. Inflammatory or infectious lesions on the face or neck
9. Skin hypersensitivity
10. Anaesthetic areas, burns, bruises or recent wounds in the area of electrical stimulation
11. Cardiac pacemakers or other telemetry-controlled devices,
12. History of maxillofacial or pharyngeal surgery.
13. Active cancer
14. Tumours of the laryngopharyngeal tract.
15. Significant mental and/or behavioural conditions or inability of the patient to cooperate during the examination/intervention.
16. Epilepsy
17. Central nervous system (CNS) surgery in the last three months (to avoid confusion with muscle or sensory laryngopharyngeal compromise).
18. Brain trauma in the last three months (to avoid confusion with muscle or sensory laryngopharyngeal compromise).
19. Neurological sequelae of any cause compromising the head and neck muscles (to avoid confusion with muscle or sensory laryngopharyngeal compromise).
20. Underlying neuromuscular diseases affecting the head and neck muscles (to avoid confusion with muscle or sensory laryngopharyngeal involvement due to neuromuscular disease).
21. Chronic use of systemic corticosteroids at doses greater than or equal to 20 mg daily of prednisone or equivalent (to avoid confusion with corticosteroid myopathy that compromises the laryngopharyngeal region).
22. Bone prostheses or osteosynthesis (with polarized currents there is danger of chemical burn and bone resorption)
23. Acute febrile processes
24. Chronic decompensated diseases

25. Diseases in terminal states
26. Refusal to participate in the study.

Additional exclusion criteria for controls: The following exclusion criteria will apply to controls in order to ensure that they do not have significant comorbidities:

1. Previous diagnosis of OSA
2. STOP-BANG score >3 (Baldini *et al.*, 2017; Chung *et al.*, 2016)
3. Age > 60
4. Body mass index > 30
5. Any comorbidity of the Charlson Comorbidity index (Charlson *et al.*, 1994) determined by the physician evaluating the selection criteria.

Procedures

Anthropometric variables, including weight in kilograms, size in metres, body mass index in kilograms/squared meters (BMI), and the neck's circumference in centimetres, will be measured. In addition, the Epworth Sleepiness Scale (Johns, 1991), the Sleep Apnoea Quality of Life Index (SAQLI) (Coman *et al.*, 2016) including the CPAP tolerance domain, will be applied for OSA patients and the STOP-BANG questionnaire for controls (Baldini *et al.*, 2017; Chung *et al.*, 2016). A full list of variables is provided in Table 1.

Candidates to be enrolled (patients and controls) will receive detailed information about the study and will sign their informed consent to participate in it.

Electrostimulation. Experimental tests with transcutaneous electrical stimulation at different intensities and at the points of the submandibular region previously explored by this and other research groups (Rangel-León *et al.*, 2015) will be conducted first of all on the five healthy volunteer subjects. For the electrostimulation, the experimental device will be used. The stimulation with the electrode will be carried out on the upper airway dilator muscles, starting with the extralaryngeal muscles and then stimulating facial muscles. Electrostimulation will be performed in specific facial and extralaryngeal muscles, using a current type Biphasic Symmetric TENS, with a phase duration of 100 microseconds (μ s), a frequency of 40 Hertz (Hz), an intensity of about 12 milliamps (mA) and a constant voltage, during a time of 15 minutes. The current intensity will be titrated to the tolerance of the patient or until obtaining visible muscle contraction. During stimulation, the region corresponding to the carotid sinus and the stellate ganglion will be avoided. During these tests, the neuromuscular functional and sensory thresholds of the upper airway, the most effective points of electrostimulation and the tolerance of intervention will be determined. The determination of the functional threshold will be made by clinical evaluation of the subject during stimulation (determining the current intensity required to induce contraction of the stimulated muscle).

Electrostimulation begins with electrodes placed on the skin in the submentonean and submandibular triangles (Figure 2), making sure not to place electrodes on the carotid sinus. The goal of this stimulation will be topographical closeness of the genioglossus, geniohyoid, mylohyoid, platysma and digastric muscles. For this purpose, symmetrical biphasic transcutaneous electrical nerve stimulation type (TENS-type) currents will be used, with a phase duration of 100 microseconds (μ s), a frequency of 40 Hz and an intensity between 9–12 milliamps (mA), until the patient cannot tolerate electrostimulation or until visible muscle contraction (Rangel-León *et al.*, 2015).

The functional threshold corresponds to the smallest current intensity capable of obtaining contraction of the airway's dilating muscles. The presence of contraction of the stimulated muscles will be determined by asking the patient about the sensation they feel, as well as by external and endoscopic inspection. These thresholds will be measured using the experimental device, which provides real-time information of the current characteristics (including intensity, voltage and frequency). The sensory threshold corresponds to 75% of the functional threshold's current intensity (Robbins *et al.*, 2006; Rofes *et al.*, 2013). The degree of opening of the upper airway obtained on these thresholds will be determined by conventional video-flexible-nasolaryngoscopy measuring the upper airway diameters using software designed ad hoc and previously validated.

After characterizing the electrostimulation thresholds in healthy volunteers (functional and sensory thresholds), as well as their desired and secondary effects, the 12 subjects with OSA will undergo electrostimulation at the same area of the neck using similar current characteristics and titrating the current intensity to determine the functional and sensory thresholds for each patient. The neuromuscular thresholds of the upper airway and the most effective points of electrostimulation will be determined during these tests. Again, the determination of the functional threshold will be made by clinical evaluation of the subject during stimulation, and the degree of opening of the upper airway based on these thresholds will then be evaluated by conventional video-flexible-nasolaryngoscopy.

We will conduct an analysis of the correlation of the signals obtained in experimental tests, elaborate a map of more effective points for electrical stimulation and determine the intensities required for each patient. We will assess the possibility of using the same standard point map for all patients.

Afterwards, the 12 OSA patients will receive an eight-week therapeutic intervention, using a protocol similar to that used by our group (Rangel-León *et al.*, 2015). The effects of the intervention will be evaluated looking for improvement of the AHI, the desaturation indices, the Epworth Sleepiness Scale (ESS) (Johns, 1991) and the Sleep Apnoea Quality of Life Index SAQLI. (Coman *et al.*, 2016). The improvement of the AHI and desaturation indices will be determined by comparing full overnight polysomnograms conducted before and after the intervention and looking at the changes in such indices. Polysomnograms will include standard electroencephalography,

Table 1. Variables.

Name	Definition	Type	MEASUREMENT SCALE	Values
Age	Years from birth to date of study	Quantitative	Continuous	Years
Sex	Patient sex	Qualitative	Dichotomous	Male 1 Female 2
Weight	Patient's weight	Quantitative	Continuous	Kg
Size	Patient height	Quantitative	Continuous	Cm
Body mass index (BMI)	Body Mass Index: Weight in kg/Size in meters ²	Quantitative	Continuous	Kg/m ²
Pre-rehabilitation neck perimeter	Neck perimeter prior to starting rehabilitation, in cm	Quantitative	Continuous	Cm
Comorbidities	Associated concomitant diseases	Qualitative	Nominal	0. None 1. Myocardial Infarction 2. Congestive Heart Failure 3. Peripheral Vascular Disease 4. Cerebrovascular Disease 5. Dementia 6. Chronic Obstructive Pulmonary Disease (COPD) 7. Connective Tissue Disease 8. Peptic Ulcer Disease 9. Diabetes Mellitus (1 point uncomplicated, 2 points if end-organ damage) 10. Moderate to Severe Chronic Kidney Disease (2 points) 11. Hemiplegia (2 points) 12. Leukemia (2 points) 13. Malignant Lymphoma (2 points) 14. Solid Tumor (2 points, 6 points if metastatic) 15. Liver Disease (1 point mild, 3 points if moderate to severe) 16. Acquired Immunodeficiency Syndrome (AIDS) (6 points)
Obstructive sleep apnoea (OSA) Evolution Time	Years completed from the diagnosis of pathology to admission to protocol	Quantitative	Discreet	Years
Start date	Start date in protocol	Quantitative	Discreet	day-month-year
Date of basal polysomnogram	Date of polysomnogram prior to the start of the rehabilitation protocol	Quantitative	Continuous	day-month-year
Apnoea-hypopnoea index (AHI) basal	Apnoea hypoapnoea Index during sleep obtained from basal polysomnogram	Quantitative	Discreet	Number of events/hours
Rapid eye movement (REM) vs non-REM sleep AHI	Number of apnoeas and hypopnoea per hour of REM vs. Non-REM sleep reported in polysomnography according to American Sleep Academy criteria.	Quantitative	Continuous	Number of events/hour per hour of REM vs non-REM sleep

Name	Definition	Type	MEASUREMENT SCALE	Values
index of desaturation	Number of desaturation episodes per hour determined by pulse-oximetry (decrease >3% in SpO2%) during sleep reported in polysomnography according to american Sleep Academy criteria.	Quantitative	Continuous	Number of desaturations per hour of sleep
T90	Percentage of sleep time spent under 90% oxygen saturation	Quantitative	Continuous	Percentage of sleep time spent under 90% oxygen saturation
SpO2 nadir	Lowest oxygen saturation by pulse oximetry	Quantitative	Continuous	Lowest SpO2
Mean SpO2	Mean oxygen saturation by pulse oximetry	Quantitative	Continuous	Mean SpO2
Severity of OSA	Mild OSA: 5 to 15/hour IAH Moderate OSA: IAH >15/hour <30/hour Severe OSA: IAH ≥ 30/hour	Qualitative	Ordinal	0. No OSA 1. OSA mild 2. Moderate OSA 3. Severe OSA
Date of polysomnogram for Continuous Positive Airway Pressure (CPAP) titration	Date of completion of the polysomnogram with CPAP titration	Quantitative	Discreet	day-month-year
Therapeutic pressure (apnoea-hypopnea and snoring abolition)	Pressure with abolition of apnoea, hypopnea and snoring in polysomnogram	Quantitative	Continuous	Centimeters of H2O
Pre-intervention sleep apnoea quality of life index (SAQLI)	Score obtained in the application of the Spanish version of SAQLI before the start of the intervention	Quantitative	Continuous	Score obtained on the scale
Tolerance to pre-rehabilitation CPAP	Degree of tolerance by the patient to CPAP used prior to qualified rehabilitation on a scale of 1 to 10	Qualitative	Ordinal	1: No tolerance 10: Excellent tolerance
Pre-intervention Epworth scale	Score obtained on the application of the Epworth scale at the start of rehabilitation	Quantitative	Continuous	Score obtained on the scale
Hours using CPAP	Number of hours the patient used CPAP overnight	Quantitative	Continuous	Hours
Post-rehabilitation control polysomnogram date (basal, i.e. without CPAP)	Date of study after completion of rehabilitation protocol	Quantitative	Discreet	day-month-year
Post-rehabilitation AHI	Hypoapnea apnoea index obtained from post-rehabilitation polysomnogram	Quantitative	Discreet	Number of events/hours
Post-intervention quality of life scale	Score obtained in the application of the Spanish version of SAQLI	Quantitative	Continuous	Score obtained on the scale
Epworth Scale post-intervention	Score obtained on the application of the Epworth scale at the end of rehabilitation	Quantitative	Continuous	Score obtained on the scale
Therapeutic CPAP pressure in post-rehabilitation polysomnogram	Pressure with abolition of apnoea, hypoapnea and snoring in post-rehabilitation polysomnogram	Quantitative	Continuous	Cm of H2O
Post-rehabilitation weight	Patient's weight at completion of rehabilitation	Quantitative	Continuous	Kg

Name	Definition	Type	MEASUREMENT SCALE	Values
Post-rehabilitation neck perimeter	Perimeter of the neck after completion of rehabilitation	Quantitative	Discreet	Cm
Neck triangles	Submentonean, anterior submandibular and posterior submandibular triangles	Qualitative	Nominal	1: Submentonean triangle. 2: Right anterior submandibular triangle 3: Right posterior submandibular triangle. 4: Left anterior submandibular triangle 5: Left posterior submandibular triangle
Functional threshold: Minimum intensity of electrostimulation capable of generating muscle contraction	Intensity of electric current capable of generating externally visible contraction or by endoscope for each triangle of the stimulated neck	Quantitative	Continuous	Milliampere (mA)
Sensory Threshold: Current intensity corresponding to 75% of the functional threshold	Intensity of electric current capable of generating sensory stimulation without muscle contraction by each triangle of the stimulated neck	Quantitative	Continuous	Milliampere (mA)
Psychophysical sensitivity threshold	Minimal stimulus perceived by the patient during the sensory test performed using the LPEER at the following levels: 1. Upper surface of the soft palate 2. Lateral wall of the hypopharynx at the level of the base of the epiglottis 3. Aryepiglottic folds, between the corniculated and cuneiform cartilages	Quantitative	Continuous	Millinewtons (mN)

Figure 2. Electrostimulation area. The electrodes for electrostimulation will be placed in the red area.

electrooculography, mandible and leg electromyography, nasal and oral airflow, and electrocardiography; respiratory effort will be measured by diaphragmatic excursion, and oxygen saturation will be measured by pulse oximetry. Polysomnograms will be performed, read and interpreted in the sleep laboratory of the Colombian Pneumological Foundation by certified personnel blinded to the patient intervention. The person in charge of reading and interpreting the polysomnograms will be blinded to the patient's intervention. Sleep stages and respiratory events (including apnoea-hypopnoea and desaturation events) will be scored according to the rules of the American Academy of Sleep Medicine (AASM) Manual for Scoring of Sleep and Associated Events (Berry *et al.*, 2012). The clinical diagnosis of OSA will be defined by an apnoea-hypopnea index (AHI) > 5 events/hour of sleep, with symptoms of sleep fragmentation and daytime somnolence according to the American Academy of Sleep Medicine. The severity of OSA will be determined according to the AHI as follows: mild, 5–14.9; moderate, 15–30; and severe > 30 events/hour (Takegami *et al.*, 2009).

Patients will undergo a conventional video-flexible-nasolaryngoscopy in which the degree of obstruction and the laryngopharyngeal sensitivity during wakefulness will be determined in accordance with the protocol previously validated by our research group (Giraldo-Cadavid *et al.*, 2017; Giraldo-Cadavid *et al.*, 2017). Briefly, the upper airway mucosa is stimulated at precise points (aryepiglottic folds, lateral pharyngeal walls and soft palate) using air-pulses of different intensities, the sensory thresholds correspond to the lower air-pulse intensity perceived by the patient (Giraldo-Cadavid *et al.*, 2017; Giraldo-Cadavid *et al.*, 2017). This test is performed using a thin flexible endoscope with a working channel of 1.2 mm. The endoscopist introduces the endoscope through the patient's nasal cavity. It is lubricated with water-soluble gel to decrease discomfort. The endoscopist does not use anesthetics because the test only produces mild to moderate discomfort, it is infrequently associated with pain, and anesthetics might alter the laryngopharyngeal tract reflexes and the measurements of their thresholds.

The sensory evaluation consists of administering pulses of air at different intensities to the patient to stimulate and determine the reflex thresholds of the laryngeal adductor (LART), cough (CRT), gag reflexes (GRT) and psychophysical sensitivity thresholds.

Effectiveness assessment will also include video-flexible-nasolaryngoscopies with measurement of laryngopharyngeal sensitivity as previously detailed, and Drug-induced sleep endoscopy (DISE) each performed before the intervention and a second of each test performed after the intervention. During DISE the level and degree of upper airway obstruction will be determined at the soft palate, tonsils, tongue base and the epiglottis using software designed ad hoc for measuring the airway diameter and perimeter and previously validated.

The image processing software is made in Python and determines the airway obstruction degree as follows:

The system takes the video made during DISEs, divides it into image format frames for edition. Subsequently, the rater selects the frames with the airway region where he wants to make the measurements while there are not OSA events, usually in the initial phase of sedation (in light sleep), he also selects frames with the same airway regions to make the measurements during the OSA events, usually in more profound stages of sleep. In each frame, the rater delimits the areas and diameters to be measured in the image using the computer's mouse. The software processes the images to calculate the areas' and diameters' size in pixels and displays their corresponding values in a graph. To calculate the percentage of obstruction the computer divides the measures of the areas and diameters during OSA events by the corresponding measures taken at the beginning of the DISE (during the lightest stage of sleep) when there are not obstructive sleep apnoeas.

The pre-intervention tests, including clinical evaluation (history, anthropometric measures and physical exam), basal polysomnogram, SAQLI, ESS, STOP-BANG, and DISE will be performed a maximum of one month before the start of the intervention, and the post-intervention tests will be performed a maximum of one month after the intervention.

During the study, patients will continue with the therapy ordered by their treating physician for the management of OSA, including CPAP and lifestyle changes.

Any adverse event will be notified to the institutional review board and competent authorities in the expected time according to its severity: less than 24 hours in case of serious adverse events.

Statistical analysis

The effectiveness assessment will be based on the improvement of the following outcomes:

- AHI during sleep.
- AHI during rapid eye movements (REM) sleep.
- AHI during non-REM sleep.
- Desaturation index: number of desaturations per hour during sleep.
- T90: percentage of sleep time spent under 90% oxygen saturation.
- SpO2 nadir: lowest oxygen saturation measured by pulse oximetry.
- Mean SpO2: mean oxygen saturation measured by pulse oximetry.
- Number of patients who lower one or more categories in the severity of OSA (moving from severe to moderate, severe to mild or moderate to mild OSA or normalising the AHI).

- Number of patients who climb one or more categories in the severity of OSA (moving from mild to moderate, mild to severe or moderate to severe OSA).
- Improvement in the quality of life as measured by SAQLI.
- Improvement in daytime sleepiness as measured by the ESS.

Qualitative variables will be described with absolute and relative frequencies, and comparisons between before and after the intervention will be made by the McNemar test.

Quantitative variables will be evaluated for assumptions of normality by the Shapiro-Wilk test. If they have normal distribution, they will be described with means and standard deviations; otherwise, they will be described with medians and interquartile ranges. Comparisons of before and after the intervention will be made by student t-tests for paired measurements if the distribution is normal or by the Wilcoxon signed range tests otherwise.

Statistical analysis will be performed using Stata version 16.1 (StataCorp, Lakeway Drive, USA).

Ethics

The type of electric current that will be used in this study is safe in its application with a low probability of causing burns or adverse events in deep tissues. Electrostimulation is an invention widely used today for pain management for cancer, precordial pain, herpes, vertebral pain and immediate postoperative pain (Rodríguez, 2004). However, because new and experimental equipment not yet approved by regulatory bodies will be used, there is a higher than minimum risk present. This protocol was approved by the ethics committee (IRB) of Fundación

Neumológica Colombiana with act number 234 of March 2, 2018 any modification in this protocol will be submitted to the IRB for approval before its implementation.

The study will be explained to each patient verbally and in a written document that summarises the objectives and characteristics of the study. Informed written consent will be obtained from patients who agree to enter the study.

The database with patient information will be anonymised to preserve patient confidentiality. Insurance will be taken out to cover the risks of side effects in patients.

This protocol was registered with ClinicalTrials.gov on 29th October 2020 (NCT04607343).

Plan for dissemination of study results

The study results will be summarized and presented in at least one international and one national medical conference. Afterwards a final report in the form of a scientific original article will be submitted to an international peer review journal.

Study status

Not yet recruiting.

Data availability

Underlying data

No data are associated with this article.

Reporting guidelines

Open Science Framework: Clinical trial of a rehabilitation device based on electrical stimulation for patients with obstructive sleep apnoea (OSA): a study protocol. <https://doi.org/10.17605/OSF.IO/AU8F4> (Giraldo-Cadavid *et al.*, 2021)

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