

ADDITIONAL METHOD INFORMATION

Project promotion, centres, and internal organization

The project was initially promoted by the National Pulmonologist Society (SEPAR) through the Spanish Sleep Network and Spanish Noninvasive Ventilation Network. Both directing committees asked Dr. Juan F Masa to develop the project, to obtain grants, and to find centres with the following characteristics: 1) a complete sleep laboratory; 2) a home ventilation program; 3) at least three years of experience in the aforementioned areas; and 4) participation in at least one previous multicenter study promoted by the Spanish Sleep network or Spanish noninvasive ventilation network.

Successive versions of the protocol were discussed between the researchers in three consecutive official meetings of SEPAR and in continuous correspondence between researchers by email for 18 months. In 2008, the final version of the protocol and grant were available. The coordinator centre in Cáceres developed the following necessary tools to conduct a multicenter study: 1) a book collection; 2) electronic databases hosted on a website with a specific domain; 3) a notebook containing the project procedures (explained step-by-step) and the necessary questionnaires to standardize the work among centres; and 4) an external audit every three months to compare the operating variables between groups (dropouts due to medical causes and mortality) on which the continuity of the study depends. In 2009, the patient inclusion process was initiated, and one meeting was conducted with the researchers after the inclusion of the first five patients to make minor changes in the protocol if necessary.

The following actions were established a priori: 1) the preparation of monthly newsletters from the principal investigator to other researchers to report on the comparative inclusion results

between centres, encourage participant inclusion, and promptly communicate eventualities; 2) the establishment of an investigator meeting within the two annual official SEPAR meetings; and 3) policy publications with a forecast of the number of publications and authorship based on the number of patients included.

“Pickwick” project and present paper

The present paper reports the results of the “Pickwick” study, which was designed to understand the mid- and long-term efficacy of CPAP and NIV in obesity hypoventilation syndrome (OHS) and includes two parallel studies (see Figure S1). Patients with OHS and severe obstructive sleep apnoea (OSA) were randomized to continuous positive airway pressure (CPAP), noninvasive ventilation (NIV), or control group for two months of follow-up (first phase). Subsequently, for ethical reasons, patients included in the control group were re-randomized into the CPAP and NIV groups to complete a follow-up of 36 months (second phase). Patients with OHS without severe OSA (not clear candidates for CPAP treatment) were directly randomized to the NIV or control groups and followed-up for 36 months. The primary variable for the first phase was PaCO₂, and the primary variable for the second phase was days of hospitalization, with two independent sample size calculations performed.

In the present post-hoc analysis we used data obtained from 302 patients with OHS, with and without OSA, enrolled in the first phase of the randomized controlled trial.

CPAP/NIV treatment tolerance tests and explanation of treatments

Before randomization, we performed CPAP¹ and NIV tolerance tests. With the patient seated, we adjusted a ventilator in CPAP mode with a pressure of 7 cm H₂O for 15 minutes. Subsequently, the ventilator was switched to bi-level mode during spontaneous breathing, with the CPAP and

inspiratory positive airway pressure (IPAP) set at 16 cm H₂O for another 15 minutes. Patients who were unable to adapt, according to the investigator, were excluded.

Once randomized, we spent the necessary time with the patient to prioritize adaptation to treatment and explain the following to the patients: 1) the characteristics of their disease; treating their disease with NIV, CPAP, or lifestyle modifications (depending on the randomization treatment); and the importance of appropriate follow-up; 2) how lifestyle modifications, NIV, or CPAP devices work and the features of the mask and fastening systems; and 3) the potential short- and long-term benefits of the treatments and the associated consequences in daily life.

CPAP titration

This was the second of three PSGs performed by experiment technicians. The initial CPAP was 4 cm H₂O. When obstructive events appeared, the pressure was increased 1 cm H₂O every 5 minutes until apnea resolved. Subsequently, the CPAP was increased every 10 minutes to achieve the elimination of hypopnoea, thoracoabdominal paradoxical movement, flow limitations, and snoring. Once the respiratory events had disappeared, the CPAP was checked during the REM period and in the supine position, and the pressure was increased if respiratory events recurred. After a period without events and with normal sleep architecture, the CPAP was slowly reduced to 1 cm H₂O by 1-cm H₂O increments until the same event reappeared. Subsequently, the CPAP was augmented until no events and normal sleep architecture reappeared. At this point, the pressure was maintained or slightly increased, if necessary, until the end of the study.

A priori, nasal masks were proposed, but in cases of important oral leakage, full-face masks could be used. A humidifier was always added with a full-face mask and only if necessary with a nasal mask.

NIV adjustment

While the patient was awake, the expiratory positive airway pressure (EPAP) was set between 4 and 8 cm H₂O, and the inspiratory positive airway pressure (IPAP) was set between 18 and 22 cm H₂O (EPAP included). The pressures were adjusted to obtain normal oxygen saturation, if possible, as measured by pulse oximetry and patient tolerance. The respiratory rate was adjusted to 12-15 breaths/minute (close to the spontaneous respiratory rate, if possible), and the target volume was set at between 5 and 6 ml/kg of actual weight, allowing for an increase in the maximum pressure over the previously fixed IPAP, if necessary. A check of mechanical ventilation phases (trigger, pressurization, and ending) was also performed to avoid asynchronies and to refine the setting. After 30 minutes of continuous use, with patient adaptation and an adequate patient-ventilator interaction, an ABG was performed. The PaCO₂ result was used to adjust the ventilator parameters. The final adjustment was performed by means of conventional polysomnography (PSG), with the EPAP increased if obstructive apnoeas appeared and the IPAP increased if hypopneas, flow limitation, snoring, or non-apnoeic hypoventilation were present, until oxygen saturation normalization or the optimal pressure was reached. No changes were made in the assured volume during this nocturnal titration.

The ventilators used across the centres were as follows: Breas Vivo 40 (General Electric, England), BiPAP AVAPS (Philips-Respironics, Netherlands), Trilogy 100 (Philips-Respironics, Netherlands), VS Ultra (ResMed, Australia), Monal T50 (Air Liquide, France), and Puritan Bennett 560 (Puritan Bennett, USA).

Full-face masks were initially proposed, but for those who tolerated full-face masks poorly, a nasal mask could be used. A humidifier was always added with a full-face mask and only if necessary with a nasal mask.

Measurement of arterial blood gases

Arterial blood gases were measured following standard procedures². All tests were performed after at least 10 min of rest, at approximately 12 p.m., with the patient seated comfortably and breathing room air at least during 20 minutes before (except when the test was performed for NIV or oxygen titrations). The sample was analyzed immediately.

Dropout definition

Dropouts were defined as patients who decided to leave the study voluntarily or for one of the following medical reasons: 1) pH <7.33 at the first-month evaluation; 2) hospital admission requiring NIV treatment for more than five days, conventional mechanical ventilation for more than three days, or pH <7.33 while breathing room air at hospital discharge; or 3) death

PSG measurements and event definitions

We used the American Academy of Sleep Medicine's³ rule regarding configuration, filters, and sample signal rates. The neurological variables were measured using electroencephalogram, electrooculogram, and electromyogram (on the chin and both legs). Flow tracing was provided using a nasal cannula and thermistor for PSG in the absence of mechanical treatments and with flows from CPAP or ventilator devices for PSG performed using CPAP or NIV, respectively. Thoracoabdominal motion was measured by piezoelectric or inductance bands. Oxygen saturation was measured with a pulse oximeter (average time among centres varied from 2-4

seconds). An electrocardiogram and body position measurements were also collected. The PSG studies were analyzed manually at each participating centre according to the 2007 recommendations of the AASM³ and the respiratory scoring according to the Spanish Sleep Network rule⁴.

Apnea was defined as the absence of airflow ($\geq 90\%$ reduction) for ≥ 10 seconds, and hypopnea was defined as a discernible airflow or band reduction ($\geq 30\%$ and $< 90\%$) for at least 10 seconds with a $\geq 3\%$ drop in oxygen saturation or final arousal⁴.

A valid PSG recording required at least three hours of sleep time. In cases of an invalid recording, the test was repeated one additional time.

REFERENCES:

1. Masa JF, Jiménez A, Durán J, Capote F, Monasterio C, Mayos M, Terán J, Hernández L, Barbé F, Maimó A, Rubio M, Montserrat JM. Alternative methods of titrating continuous positive airway pressure: a large multicenter study. *Am J Respir Crit Care Med.* 2004;170(11):1218-24.
2. Baberà, JA. Giner J, Casan P, Burgos F. Manual SEPAR de Procedimientos. Módulo 3. Procedimientos de evaluación de la función pulmonar. 1ª ed. España: Luzán; 2002. Capítulo 4, Gasometría arterial; 67-78.
3. Iber C, Ancoli-Israel S, Chesson AL, Quan SF. The AASM manual of scoring of sleep and associated events. rules, terminology and technical specifications. Westchester, IL: American Academy of Sleep Medicine, 2007.
4. Grupo Español de Sueño (GES). Consenso Nacional sobre el síndrome de apneas-hipopneas del sueño. *Arch Bronconeumol* 2005;41(Suppl. 4):3–110.

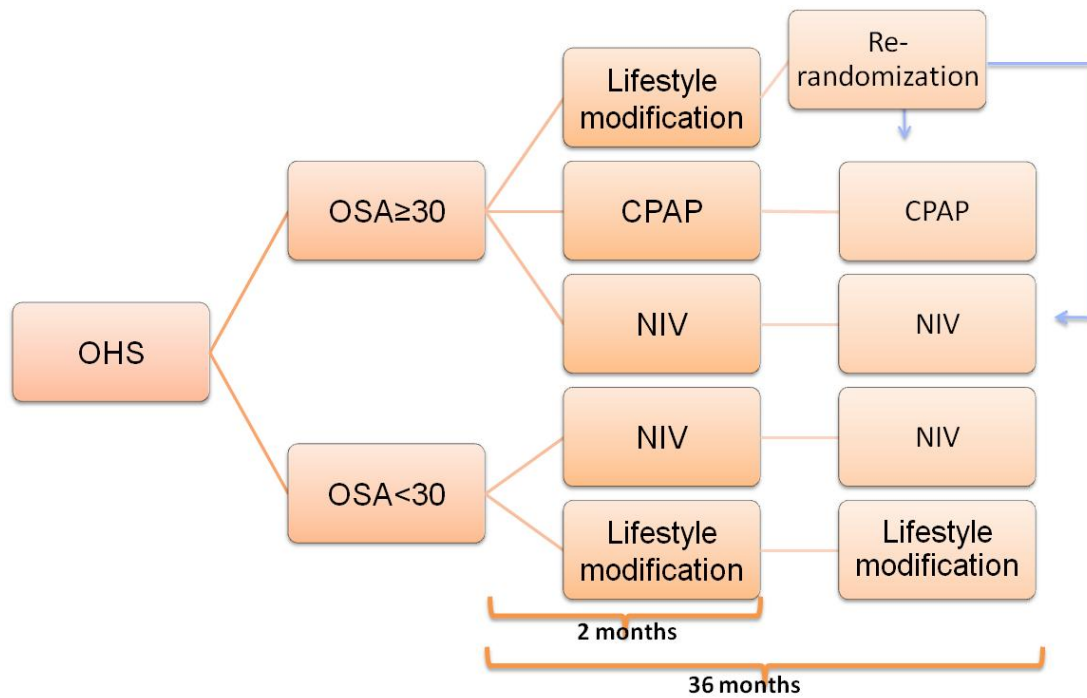


Figure S1—Flowchart of the Pickwick study. OHS, obesity hypoventilation syndrome; OSA, obstructive sleep apnea; NIV, noninvasive ventilation; CPAP, continuous positive airway pressure.