DATA SUPPLEMENT

Title: Noninvasive ventilation in obesity hypoventilation syndrome without severe obstructive sleep apnoea

Subtitle: A randomised clinical trial from the Pickwick project

Authors:

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ADDITIONAL METHOD INFORMATION

Project promotion, centres, and internal organisation

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 Caceres 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 standardise 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 continuous positive airway pressure (CPAP) and noninvasive ventilation (NIV) in obesity hypoventilation syndrome (OHS) and includes two parallel studies (see Figure E1). Patients with OHS and severe sleep apnoea (OSA) were randomised to CPAP, NIV, or control group for two months of follow-up (first phase). Subsequently, for ethical reasons, patients included in the control group were re-randomised 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 randomised to the NIV or control groups and followed-up for 36 months (first and second phases). The primary variable for the first phase was $PaCO_2$, and the primary variable for the second phase was days of hospitalisation, with two independent sample size calculations performed.

The present paper contains the results of two months of follow-up of 86 OHS patients without severe OSA who received two treatment alternatives, namely, NIV, and lifestyle modification (control). The second phase of the Pickwick study is ongoing at this time.

NIV treatment tolerance tests and explanation of treatment

Before randomisation, we performed a NIV tolerance tests. With the patient seated, we adjusted a ventilator in bi-level mode during spontaneous breathing, with the expiratory positive airway pressure (EPAP) and inspiratory positive airway pressure (IPAP) set at 7 and 16 cm H_2O, respectively, for 15 minutes. Patients who were unable to adapt, according to the investigator, were excluded.

Once randomised, we spent the necessary time with the patient to prioritise adaptation to treatment and to give explanation on: 1) the characteristics of their disease; treating their disease with NIV or lifestyle modifications (depending on the randomisation treatment); and the importance of appropriate follow-up; 2) how lifestyle modifications or NIV device 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.

NIV ventilators and masks

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 procedures.[1] 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 (except when the test was performed for NIV or oxygen titrations). The sample was analysed immediately.

Polysomnographic measurements and event definitions

We used the American Academy of Sleep Medicine's (AASM)[2] 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 polysomnography (PSG) in the absence of mechanical treatments and with flows from ventilator devices for PSG performed using NIV. 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 analysed manually at each participating centre according to the 2007 recommendations of the AASM[2] and the respiratory scoring according to the Spanish Sleep Network rule.[3]

Apnoea was defined as the absence of airflow (≥90% reduction) for ≥10 seconds, and hypopnoea was defined as a discernible airflow or band reduction (≥30% and <90%) for at least 10 seconds with a ≥3% drop in oxygen saturation or final arousal.[3]

ADDITIONAL RESULTS

See Figure E2.

ADDITIONAL DISCUSSION COMMENTS

Our polysomnographic NIV titration is somewhat different than several prior randomised clinical trials.[4,5,6] EPAP was used only to eliminate obstructive apnoeas, and IPAP was adjusted to treat the rest of the respiratory events. Other studies [5,6] have used EPAP to eliminate apnoeas and hypopnoeas and IPAP only for hypoventilation. Our minimum IPAP value was 18 cm H_2O, although the real IPAP could have been higher due to our use of the assured volume mode, which would result in a higher IPAP than that reported in the other randomised studies without assured volume mode (18 cm H_2O in Borel's study and 16 cm H_2O in Piper's study [5,6]. However, this minimum IPAP was lower than in our parallel randomised clinical trial which included only patients with OHS and severe OSA (20 cm H_2O) using the same NIV adjustment protocol. This can be explained by the necessity of controlling greater number of hyponoeas or more severe central hypoventilation associated with different phenotypes. We used a backup respiratory rate (close to the spontaneous respiratory rate) instead of spontaneous bilevel positive airway pressure ventilation to assure a "normal" respiratory rate during sleep. This setting could have introduced some patient-ventilator asynchronies, although they were checked and corrected during the daytime titration trial. A randomised clinical trial [7] demonstrated that in patients with OHS both a low backup respiratory rate (10-12 breaths/minute) or a high backup respiratory rate (18 to 22 breaths/minute) were more effective in reducing the number of central and mixed respiratory events than spontaneous bilevel PAP ventilation.

Two randomised studies [8,9] evaluated the efficacy of adding an assured volume to bilevel pressure support mode. Clinical, functional, and PSG improvement was observed in one study [9] but not in the study that included "super-obese" patients [9]. Our patients exhibited similar characteristics to those of the first study, and we obtained improvements similar to those achieved in both studies. An additional non-randomised study also reported nocturnal improvement but impairment in sleep quality [10].

Clinical series have reported subjective dyspnoea improvement, [11-13] although some series included patients who were not completely in stable conditions. [8] Similarly to the parallel randomised study including only OHS patients with severe OSA, in the present study no statistical significant change in the dyspnoea scale was observed. We believe that obesity could play a role in this subjective perception.

Although we found significant improvement in ESS with NIV treatment (Table 3), the change was lower than the studies including patients with significant OSA severity, [4-6] NIV improved other clinical symptoms but with statistical significance only for unrefreshing sleep and tiredness (Figure 3). In comparison with the parallel study including only patients with severe OSA, [4] the symptoms frequency after two month of NIV treatment were not very different to the present study, however the baseline frequency was higher. Therefore the poorer improvement observed in clinical symptoms in the present study may be caused by the absence of severe OSA and perhaps also due to the lower sample size.

Heath related quality of life (HRQL) tests improved with NIV treatments in some studies[8,9,13,14] even with shorter periods of follow-up as that was utilised in our study.[8,14] In the present study, only some of the test used achieved improvement in the NIV group related to the control group (Table 3). This intermediate improvement was also observed in our parallel randomised study, despite in severe OSA patients sleepiness and other clinical symptoms improved more than in the present study.[4] We believe that, in contrast to what occurred with CPAP treatment in patients with pure OSA (without OHS), the potential clinical improvement caused by NIV treatment could have been masked by the persistence of dyspnoea and the higher frequency of comorbidities, thereby resulting in a lower magnitude of HRQL improvement. Other potential reason to explain the absence of intergroup differences is the mild improvement obtained by implementing lifestyle changes in the control group, especially in the FOSQ questionnaire.

We have not used transcutaneous CO_2 measurement during the PSG test due to the need to incorporate a lot of centres to obtain a large sample size. Transcutaneous CO_2 is an important measurement to determine sleep hypoventilation although it is expensive. Variability and accuracy limitation compared with $PaCO_2$ have been recognised.

Oxygen therapy is frequently supplemented to NIV or CPAP treatment regimens in clinical practice to increase the residual hypoxemia during sleep or in the daytime. An observational study showed that supplementary oxygen therapy was an independent factor for mortality,[15] although another study[16] did not find an association between supplemental oxygen and mortality. Other studies have reported an increase in daytime $PaCO_2$[17-19] or nocturnal transcutaneous PCO_2[20] in stable OHS patients treated with oxygen, although low concentrations did not change the pH.[19] Thus, we did not effectively suppress the oxygen in any patients for this reason. We did not add oxygen in our PSG studies to enable comparison of the real oxygenation levels with treatments; therefore, we could not determine the effect of this treatment during sleep. Moreover, all of our arterial blood gases were obtained at 12 p.m. and after 20 minutes without oxygen. The percentage of patients with oxygen therapy and the oxygen flow were similar between groups. Although we do not totally reject some influence of oxygen therapy on the daytime $PaCO_2$ results (particularly in the control group), it seems no very important although future large studies must establish the role to supplemental oxygen to NIV treatment.

Although we used the same ventilator mode across centres, the ventilator was not the same. Despite not finding statistical differences in the evolution of daytime $PaCO_2$ among the ventilator brands, we cannot totally exclude this bias because the study was not designed for this objective and our sample size may be insufficient to obtain statistical significant differences.

Given that the prevalence of non-severe OSA (AHI<30) in OHS was only 28%, it took more than 5.5 years to enrol the necessary number of subjects across 16 tertiary sleep centres in Spain. Patients were referred for consultation to our clinics for both OHS and OSA. However, the vast majority of referrals were due to suspicion of OSA. We also believe that enrolment took longer than expected since OHS patients without severe OSA exhibit less of the clinical characteristics of patients with classic severe OSA and may not be referred as frequently for consultation.

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FIGURE LEGENDS

Figure E1: Flowchart of the Pickwick study.

Figure E2: PaCO2 evolution during the follow-up in the two groups. PaCO2 improvement was obtained in the NIV group early in the first month. The P value was adjusted by baseline values (PaCO2, age, gender, body mass index, and AHI baseline values).

Figure E1

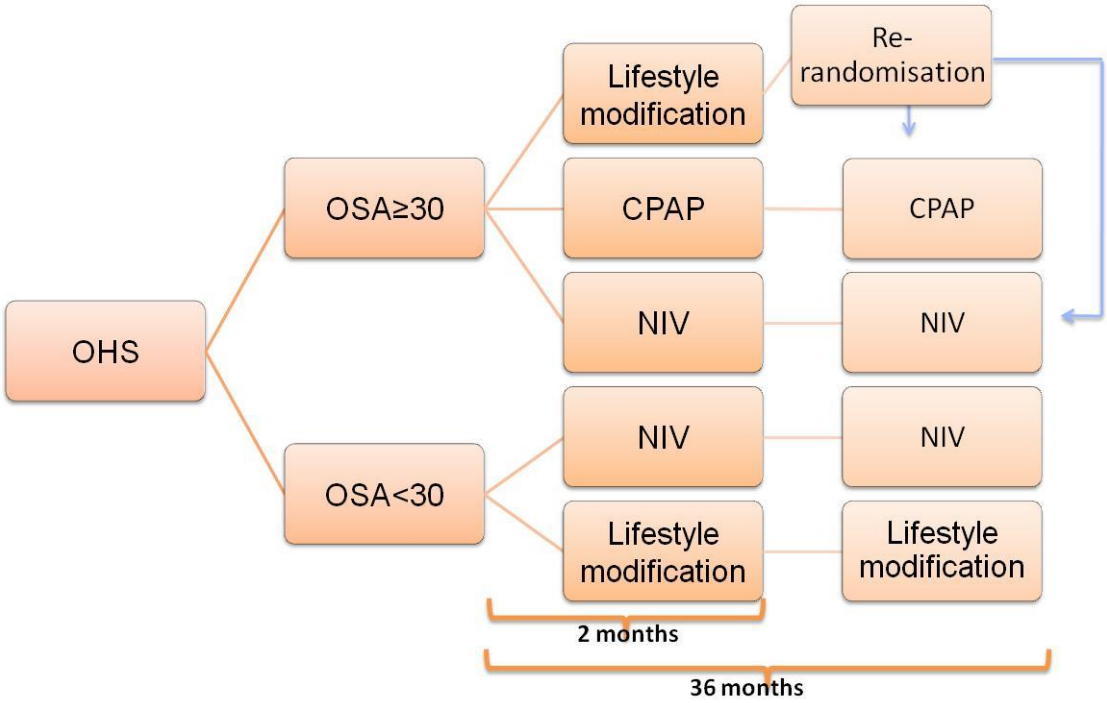
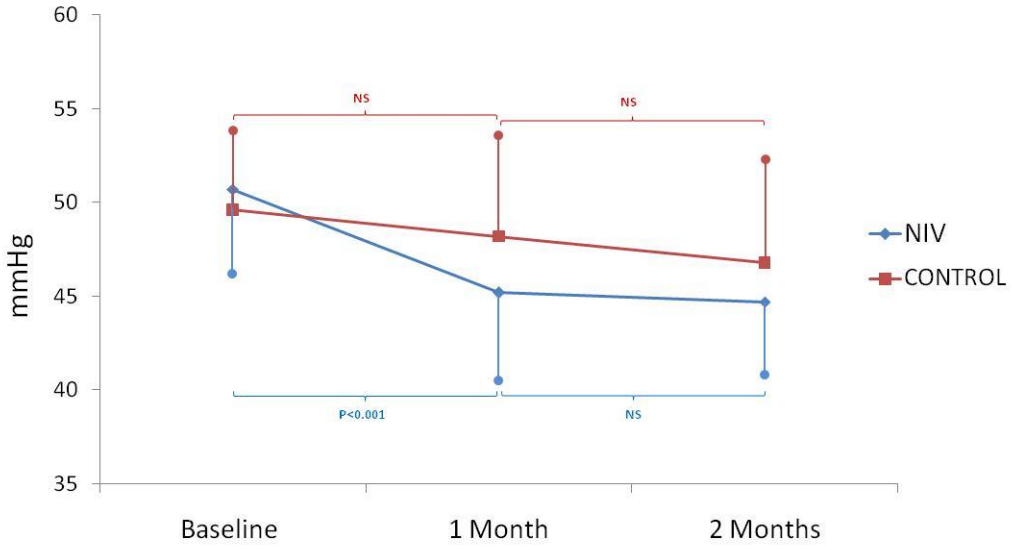

OHS
OSA≥30
OSA<30
Lifestyle modification
CPAP
NIV
NIV
Lifestyle modification
Re-randomisation
CPAP
NIV
NIV
Lifestyle modification
2 months
36 months

Figure E2


60
55
50
45
40
35
mmHg
NS
NS
P<0.001
NS
Baseline
1 Month
2 Months
NIV
CONTROL