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Noninvasive respiratory muscle aids during PEG placement in ALS patients with severe ventilatory impairment

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ABSTRACT

Although no clear recommendations are given about when percutaneous endoscopic gastrostomy (PEG) should be placed in amyotrophic lateral sclerosis (ALS) patients, some experts underline the risk of respiratory complications when patients had severe ventilatory muscle impairment (SVMI).
Aim: To evaluate the efficacy of noninvasive ventilation (NIV) and mechanically assisted cough (MAC) to avoid respiratory complications related to PEG placement in ALS patients with SVMI.
Material and methods: Prospective study including ALS patients who had chosen to have PEG placement timed by swallowing dysfunction with the aid of NIV and MAC if needed. PEG was carried out under volume-cycled NIV through a nasal mask. MAC was applied prior to and at the end of the procedure.
Results: Thirty ALS patients (60.43 ± 12.03 years) were included. Prior to PEG placement: BMI 25.0 ± 4.6 kg/m^2, ALSRFS-R 19.5 ± 5.0, Norris bulbar sub-score 15.1 ± 6.6, %FVC 35.9 ± 18.1%, PCF 2.3 ± 1.2 L/s, PImax −35.6 ± 24.6 cm H_2O, and PEmax 40.5 ± 23.9 cm H_2O. Three patients had PEG placement under tracheotomy ventilation because NIV SpO_2 was below 88%. No patient died during the procedure nor did any have respiratory complications. Survival at 1 month was 100%.
Conclusion: Respiratory support provided by volume-cycled NIV and MAC permits successful PEG placement in most ALS patients with SVMI.

1. Introduction

Around 80% of amyotrophic lateral sclerosis (ALS) patients, independent of the site of onset, develop progressive bulbar dysfunction (BD) [1]. As a consequence, a progressive swallowing impairment appears, causing malnutrition, weight loss, and dehydration. These problems can also be accompanied by recurrent episodes of choking, aspiration, respiratory infections, and pneumonia [1]. As malnutrition is an independent prognostic factor for survival in ALS patients [2], and respiratory problems due to aspiration decrease effectiveness of noninvasive respiratory muscle aids, it is important to manage dysphagia [3].

Initial control of dysphagia in ALS is based on strategies to maintain nutritional intake by altering food consistency [4]. However, as BD progresses and these measures become ineffective, enteral nutrition delivered via percutaneous endoscopic gastrostomy (PEG) permits adequate feeding [4]. This feeding method stabilizes body weight and is probably effective in prolonging survival in ALS [5].

When this study started, international guidelines argued that the risks of respiratory complications related to the procedure increased when FVC was lower than 50% of predicted [6], and they recommended PEG placement before this moment [7]. However, these recommendations were based on studies that were methodologically deficient, in which, moreover, pulmonologists did not participate in the prevention and management of potential respiratory problems. Recently, when such guidelines were up-dated [4], a specific time for PEG placement was not recommended, although the existence of

Abbreviations: ALS, Amyotrophic lateral sclerosis; ALSFRS-R, Revised Amyotrophic Lateral Sclerosis Rating Scale; BD, Bulbar dysfunction; BMI, Body mass index; FVC, Forced vital capacity; FVC%, Predicted FVC; FVCdif%, % of difference between FVC in sitting and supine position; FVCs, FVC in supine position; FEV_1, Forced volume expired in 1 s; FEV_1%, Predicted FEV_1; MAC, Mechanically assisted cough; MI–E, Mechanical insufflation–exsufflation; MIC, Maximum insufflation capacity; NBS, Norris bulbar sub-score; NIV, Noninvasive mechanical ventilation; PCF, Peak cough flow; PCF_{MIC}, Manually assisted PCF; PCF_{MI-E}, Mechanically assisted PCF; PEmax, Maximal expiratory pressure at mouth; PEmax%, Predicted PEmax; PEG, Percutaneous endoscopic gastrostomy; PImax, Maximal inspiratory pressure at mouth; PImax%, Predicted PImax; PRG, Percutaneous radiologic gastrostomy; SpO_2, Pulse oxyhaemoglobin saturation; TMV, Mechanical ventilation by tracheostomy.

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complications was stressed when FVC<50%. Guidelines established by endoscopists do not mention the lowering of FVC as an absolute or relative contraindication of PEG placement [8].

In view of the potentially positive effect of noninvasive mechanical ventilation (NIV) to prevent and manage respiratory problems in ALS patients when respiratory muscles become weak [9], NIV has been proposed as a respiratory muscle support during PEG placement in order to reduce the related respiratory complications in those patients with FVC lower than 50% [10,11]. At present, evidence of the usefulness of NIV for this purpose originates from a limited body of data, but the available results could make it possible to assume that, if NIV can be provided, the choice of the time of PEG placement can be decided in clinical practice in accordance with the seriousness of the patient's swallowing impairment and not necessarily on the fall in FVC. Based on this assumption, the aim of this study was to assess the efficacy of noninvasive respiratory muscle aids, NIV and mechanically assisted cough (MAC), to allow successful PEG placement in a cohort of ALS patients who already had severe ventilatory muscle impairment (SVMI) at the time at which PEG placement was decided.

2. Material and methods

This prospective study was performed between January 2005 and December 2009 at two university hospitals, and included all ALS patients diagnosed according to the revised El Escorial criteria [12] who, at the time of needing a PEG due to impaired oral food intake or progressive weight loss (>10%), had a FVC lower than 50% of the predicted value or who used home NIV [4,13]. All the patients had received clear information about PEG (its usefulness, placement procedure, and maintenance measures) beforehand, so that they could make their own decisions regarding when to have PEG placement. Such information included the risks and advantages of our proposal of choosing the point in time of PEG placement depending on swallowing impairment and not the fall in FVC. The alternative procedures when PEG placement was impossible with the aid of NIV were percutaneous radiologic gastrostomy (PRG) or PEG with mechanical ventilation by tracheostomy (TMV).

Exclusion criteria were refusal to participate or the presence of pulmonary or airway disease. Informed consent was obtained and the protocol approved by the Hospital's Ethics Committee.

3. Pulmonary function assessment

Pulmonary function assessments were made prior to PEG placement. Spirometry was assessed with a pneumotachograph spirometer (MS 2000; Schatzman; Madrid, Spain) in accordance with the European Respiratory Society's guidelines [14] as described in previous studies [15]. FVC was measured both in sitting and supine positions.

Maximum inspiratory pressure (PImax) and maximum expiratory pressure (PEmax) were measured (Electrometer 78.905[a]; Hewlett-Packard; Andover, MA, USA) according to the Black and Hyatt technique [16].

Cough capacity was assessed with a pneumotachograph spirometer (MS 2000; Schatzman; Madrid, Spain) and a sealed oronasal mask (Martin Vecino, Madrid, Spain) as described in previous studies [15]. The highest peak cough flow (PCF) measurement obtained from at least three maximal cough manoeuvres after a deep inspiration with less than 5% variability was recorded. Maximum insufflation capacity (MIC) by air stacking was achieved by the patient taking a deep breath, holding it, and then air stacking consecutively delivered volumes of air from a manual resuscitator (Revivator; Hersill, Madrid, Spain) through the oronasal mask to the maximum volume that could be held with a closed glottis. The patient then exhaled the maximally held volume of air into the pneumotachograph for volume measurement. Manually assisted PCF (PCF_{MIC}) was measured with a pneumotachograph connected to the mask and the manual resuscitator in order to achieve MIC; a thoracoabdominal thrust was applied during the cough effort. Mechanically assisted PCF (PCF_{MI-E}) was measured with a pneumotachograph connected to the mask and the MI–E device (Cough-Assist; JH Emerson; Cambridge, MA). It was set at 40 cm H2O of insufflation pressure, −40 cm H2O of exsufflation pressure with an insufflation/exsufflation ratio of 2/3, and a pause of 1 s between each cycle. A thoracoabdominal thrust was applied during the exsufflation cycle.

Functional impairment was evaluated using the Revised Amyotrophic Lateral Sclerosis Rating Scale (ALSFRS-R) [17] which ranges from 44 (normal functioning) to 0, and bulbar involvement was assessed in accordance with the Norris scale bulbar sub-score (NBS) [18], which ranges from 39 (normal functioning) to 0.

4. NIV-PEG protocol

Patients were admitted to hospital 24 h before the procedure, and from then on followed a protocol-based management [19].

A trained pulmonologist provided respiratory care measures. Before the patient was transferred to the endoscopy unit, MAC was applied with an in-exsufflation device (Cough-Assist™, Philips-Respironics International Inc., Murrysville, Pa, USA) through an oronasal mask (Martin Vecino, Madrid, Spain); 6–8 cycles (insufflation pressure +40 cm H_2O, exsufflation pressure −40 cm H_20, insufflation/exsufflation ratio 2/3, pause 1 s) with a thoracoabdominal thrust during the exsufflation time were applied as described in previous studies [15].

NIV was delivered in volume-cycled assist-control mode (PV 501 and PV 403, Breas Medical, Mölndal, Sweden; Legendair, Airox, Pau, France) through a nasal mask (Healthdyne, Marietta, GA, USA). Before transfer to the endoscopy unit, the necessary ventilatory changes were made at the respiratory ward to change from the oronasal mask to the nasal mask for those patients using NIV at home and the appropriate adjustments were made for the use of a nasal mask for those who had not been treated with NIV before. The effectiveness of nasal-NIV was checked via subjective tolerance and the clinical and gasometric response [20].

In the endoscopy unit, sedoanalgesia with midazolam and fentanyl was started, and clinical variables (level of sedation, thoracoabdominal respiratory movements, and air-leaks through the mouth) and biological variables (SpO_2, heart rate, respiratory rate, and blood pressure) (Spot Vital Sings, Welch Allyn Inc., Skaneateles Falls, NY, USA) were monitored continuously. Due to the increase in mouth air-leaks during the PEG placement procedure, previous ventilator parameters were readjusted by the pulmonologist for patient comfort and to maintain $SpO_2 \geq 95\%$ at a FiO_2 of 0.21. Making use of complementary clinical information for ventilation adjustment, the pulmonologist checked that the thoracoabdominal movements were appropriate and synchronic with the ventilator, generating a peak inspiratory pressure around 20 cm H_2O Fig. 1.

In the NIV protocol during the PEG procedure, the use of oxygen was only to be employed if there was a low flow (≤2 L/min, connected to the mask) in those cases where the increases in tidal volume to compensate for mouth air-leaks did not obtain a SpO2≥92%, despite the ventilator generating visible and synchronic thoracoabdominal movements. If SpO2≥92% could not be reached with nasal-NIV plus low flow O2 (≤2 L/min), then PEG placement was cancelled and, following the patient's previously expressed wishes, it was replaced with a PRG or a PEG placement with TMV.

PEG was performed by two endoscopists experienced in this technique, using the pull through method ("pull" technique) [19]. During PEG placement, mouth secretions were managed with conventional aspiration.

When the procedure was finished, NIV was adjusted via an oronasal mask (Mirage, Resmed, Madrid, Spain) and MAC was applied again. Repeated sessions (6 to 8 cycles) every 5 min of MAC were applied until signs of retained respiratory secretions (pathological

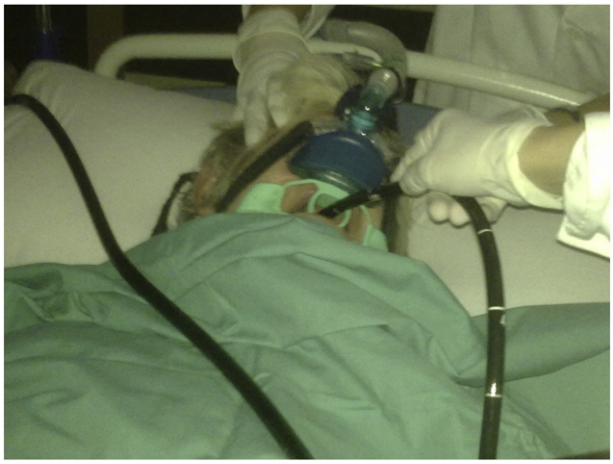

Fig. 1. Noninvasive ventilation during percutaneous endoscopic gastrostomy in a patient with amyotrophic lateral sclerosis.

respiratory sounds, SpO_2 lower than 95% without supplementary oxygen, and PIP greater than 30 cm H_2O) were no longer presented.

The patients were transferred to the respiratory ward and NIV was maintained for 2 h. Subsequently, patients used NIV and MAC as they did before PEG placement. Patients were discharged from the hospital and sent home if enteral feeding via PEG was tolerated without complications 24–48 h after PEG insertion. Complications and survival at 1 month were recorded.

5. Results

All the patients chose swallowing impairment, and not the state of their respiratory muscles, as the point at which PEG was to be performed, and they all agreed to participate in this study.

PEG under NIV and MAC was indicated for 30 patients with SVMI during this study. Fourteen of them had bulbar onset (46.7%), and at that time all of them had severe BD. Data on demographics, respiratory function, and cough capacity assessment are shown in Table 1. The mean loss of BMI during the previous 6 months was 4.2 ± 4.2%.

Twenty-five patients used home NIV (83.3%) for 11.0 ± 5.6 h per day (range: 8–24 h), 20 of them (80%) with volume-cycled ventilators (delivered tidal volume 822.9 ± 132.5 mL) and five (20%, all of them from the Hospital Universitari Sant Joan) with pressure cycled ventilators (IPAP 16.6 ± 1.3 cm H_2O, EPAP 5.4 ± 0.9 cm H_2O). All 30 patients used MAC to clear airway secretions at home and all those with continuous ventilation had volume-cycled ventilators.

Twenty-seven of the 30 patients underwent successful PEG placement with NIV assistance delivered with a volume-cycled ventilator. Mean SpO_2 during the procedure was 96.0 ± 1.5%. The mean tidal volume needed to maintain an effective ventilation was 1557.5 ± 164.8 mL (range 1200 to 1800 mL), and in five patients oxygen was added to the nasal mask due to sporadic falls in SpO_2 produced by excessive air-leaks through the mouth despite increased ventilatory assistance. After the procedure, respiratory secretions were successfully managed with MAC in all of these patients. Early minor complications arose in two patients (7.4%), both cases of local wound infection which were resolved successfully with medical treatment. Twenty-five patients (92.6%) were discharged with home NIV. No patient died during the procedure nor during the first month after PEG placement.

In three patients PEG placement could not be performed with NIV, because nasal-NIV did not maintain effective alveolar ventilation. When trialling nasal-NIV prior to PEG procedure in two of them, who had nocturnal home NIV through an oronasal mask, SpO_2 remained lower than 85% (FiO_2 0.21), the respiratory thoracoabdominal movements were almost unnoticeable and $PaCO_2$ was higher than 55 mm Hg, despite the tidal volume being increased up to 1800 mL.

Table 1
Demographic and lung function parameters of ALS patients for whom percutaneous endoscopic gastrostomy was indicated.

	Total population $n = 30$
Male/Female	13/17
Age (years)	60.4 ± 12.0
BMI (kg/m^2)	25.0 ± 4.6
Time from ALS onset to PEG (months)	39.6 ± 30.3
Bulbar/spinal onset	16/14
FVC (L)	1.1 ± 0.5
FVC%	35.9 ± 18.0
FVCs (L)	0.6 ± 0.4
FVCdif	35.4 ± 18.8
MIC (L)	1.5 ± 0.6
PCF (L/s)	2.3 ± 1.2
PCF_{MIC} (L/s)	2.9 ± 1.5
PCF_{MI-E} (L/s)	3.4 ± 0.6
PImax (cm H_2O)	−35.6 ± 26.6
%PImax	35.2 ± 22.5
PEmax (cm H_2O)	40.5 ± 23.9
%PEmax	27.7 ± 17.5
ALSFRS-R	19.5 ± 5.0
NBS	15.1 ± 6.6

ALSFRS-R = Revised Amyotrophic Lateral Sclerosis Rating Scale; BMI = body mass index; FVC = forced vital capacity; FVC% = % of predicted FVC; FVCdif% = % of difference between FVC in sitting and supine positions; FVCs = FVC in supine position; MIC = maximum insufflation capacity; NBS = Norris bulbar sub-score; PCF = peak cough flow; PCF_{MIC} = manually assisted PCF; PCF_{MI-E} = mechanically assisted PCF; PEmax = maximal expiratory pressure at mouth; PEmax% = % of predicted PEmax; PEG = percutaneous endoscopic gastrostomy; PImax = maximal inspiratory pressure at mouth; and PImax% = % of predicted PImax.

In these two patients the failure of nasal-NIV was due to excessive air-leaks through the mouth; in the other one (without home NIV ventilation) the failure of nasal-NIV was due to episodes of glottic closure. All three preferred PEG with TMV to PRG as an alternative procedure. All three were discharged with nocturnal home TMV and any of them have complications or die in the following month.

6. Discussion

If explicit or consistent guidelines are not available, the decision to place a PEG tube should focus mainly on the patient's inability to ingest food or water by mouth [21]. However, the fact that respiratory muscle weakness in ALS may appear before severe dysphagia has led some authors to consider that the evolution of FVC outweighs dysphagia when deciding on the timing for PEG. In contrast to this current opinion, this study supports the feasibility and safety of PEG timed by swallowing impairment in most of the patients with ALS and SVMI, when the procedure is carried out with noninvasive muscle aids. The fact that PEG placement with NIV was not possible in the case of three patients stresses the need to inform patients beforehand so that they can participate actively in making decisions.

The risk of complications in patients undergoing PEG, despite the illness that motivates the placement of a PEG, arises mainly from the associated comorbidity [8], and sedation is the foremost cause of cardiopulmonary complications [22]. PEG procedure-related mortality has been reported to range from 0% to 2%, with a 30-day mortality in the range of 6.7 to 26% [8]. In ALS patients, respiratory complications of PEG placement are related to the risk of aspiration due to the increased upper airway secretions, the passage of the gastroscope and the patients' impaired cough capacity, in this case worsened by sedation [23]. In addition, RC are related to the impaired respiratory muscle strength associated with a supine position and stomach insufflation [5,24], and to abolished respiratory output due to sedation [5,24]. Moreover, due to BD, PEG placement in ALS can be complicated by laryngeal spasms [5,24].

Some authors associate the appearance of respiratory problems related to PEG with the decrease in FVC and to avoid such problems, they recommend PEG placement before FVC falls below 50% of

Table 2
Trends on percutaneous endoscopic gastrostomy tube placement in amyotrophic lateral sclerosis patients.

	Type of study	FVC%	NIV during procedure	NIV at home	Mortality (24 h)	Mortality (30 days)
Mathus-Vliegen,[24] 1994	P	45.8 ± 14.4	N	N	3.6%	11.5%
Mazzini,[5] 1995	P	30.6 ± 28	N	N	0.0%	9.7%
Chio,[28] 1999	P	68.9 ± 19.1	N	N	0.0%	2%
Kasarkis,[6] 1999						
CNTF study	R	39.1	N	N	0.0%	6.3%
BDNF study	R	52.5	N	N	0.7%	9.3%
Thorton,[23] 2002	R	53	N	N	9.09%	–
Boitano,[11] 2001	P	33.4 ± 9.55	Y	Y	0%	0%
Gregory,[10] 2002	R	35.7 ± 11.25	Y	N/Y	0%	6.0%
Present study	P	35.9 ± 18.0	Y	Y	0%	0%

FVC = forced vital capacity; N = no; NIV = noninvasive ventilation; P = prospective study; R = retrospective study; and Y = yes.

predicted, without taking into account how important swallowing impairment is at that time [4,13]. Nevertheless, the studies this recommendation is based on should be viewed with caution. Two are retrospective [6,23] and in one of them, moreover, patients from other protocols were used [6]. In one of the three prospective studies, the patients participated simultaneously in a study evaluating a drug [25]. No pulmonologists intervened in any of the five studies.

Reviewing the early complications after PEG in ALS (Table 2), one patient died during the procedure because of a respiratory insufficiency related to midazolam [25], and during the first 24 h, one died due to a mucus aspiration [23] and another due to "sudden respiratory insufficiency caused by weakness of respiratory muscles"[25].

From the scant information regarding longer-term deaths, it seems that respiratory problems were the first cause. Nonetheless, it is impossible to attribute the deaths to PEG placement and not to the poor respiratory condition of the patients (with or without PEG) which is, in itself, a predictive factor of short-term death in ALS [26]. For instance, Chio et al. [24] do not attribute to PEG placement the deaths which appeared in their study, and they call for more studies "to settle generally acceptable guidelines for establishing the best timing for PEG execution". It is striking that when the American Academy of Neurology stresses the increase in the risk for patients with FVC <50% [4], the basis for this are the results reported in a retrospective article designed for other objectives [6]. It seems more logical to tackle potential respiratory problems by means of specific prevention and management procedures than by scheduling PEG depending on an FVC value.

The articles by Boitano et al. [11] and Gregory et al. [10] incorporated experts in respiratory problems among the staff in charge of PEG placement. Although the number of patients included by Boitano et al. [11] is clearly insufficient to come to conclusions, their NIV pilot study using pressure support reported promising results: the five patients were sedated and there were no immediate deaths nor after thirty days [27]. The five had home NIV. The study by Gregory et al. [10] was retrospective and does not give the method of NIV used. Forced vital capacity impairment was similar to other studies, the patients were sedated and there were no intrahospital deaths either, but during the first 30 days there were 6% deaths caused by severe respiratory insufficiency. The authors do not say whether the patients had ventilatory support or cough aids at home.

Our study does not have a control group. Clinical research involving ALS patients must find a balance between the scientific method and ethical concerns [9]. Given the dramatic effect that the use of NIV had for the safety of PEG placement in ALS patients with SVMI – albeit in a pilot study –[27] and in the light of our own clinical experience in the use of NIV on ALS patients, the principle of beneficence meant that we could not deprive a group of randomly chosen patients of NIV.

In order to tackle potential complications related to a decrease in respiratory output associated with sedoanalgesia and to increased muscular weakness due to the drugs – along with the additional problem of potentially important air-leaks related to the need to maintain the mouth open during the PEG placement – we choose volume-cycled NIV as it requires no inspiratory effort and is easier to adjust to compensate for air-leaks. Our results show that, with the exception of three patients, the use of volume-cycled NIV and the close vigilance of the clinical and pulse oxymetry data allowed us to provide effective NIV during PEG.

In order to prevent the potentially life-threatening problems related with upper airway secretions during the passage of the gastroscope [28], mechanically assisted cough has been used in our study to avoid complications related to respiratory secretions. These measures, which were complementary to NIV, may have been useful, but our protocol did not make it possible to differentiate the relative value of NIV and that of the assisted cough in the success of the procedures.

Although we had neither deaths nor major complications during the PEG placement, it could not be performed on three patients due to the ineffectiveness of the NIV. Consequently, it is necessary to reach a joint decision on the programming of PEG with the patients and offer them the most exact and clear information possible well enough in advance for them to be able to take decisions. The absence of sound recommendations in the experts' guidelines is another factor that reinforces the necessity to establish an arrangement with the patients.

In conclusion, respiratory support provided by volume-cycled NIV and MAC permits successful PEG placement in most ALS patients with SVMI. The decisions related to the moment of PEG placement JNS, JM should be jointly agreed with the patients.

Conflict of interest statement

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