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Original Article

Title

Diurnal mouthpiece ventilation and nocturnal non-invasive ventilation versus tracheostomy invasive ventilation in patients with Amyotrophic Lateral Sclerosis

ABSTRACT

Background Respiratory disorders are a major cause of morbidity and mortality in Amyotrophic lateral sclerosis (ALS).Current guidelines suggest the provision of noninvasive ventilation (NIV) for symptomatic hypoventilation in patients with ALS. Inspite of these results the proportion of ALS patients on tracheostomy invasive ventilation (TIV) is relatively high.

Methods 32 patients were included in the study: 16 patients were treated with nocturnal NIV associated with diurnal mouthpiece ventilation (MPV) and 16 with TIV .The primary endpoint of the study was to evaluate survival in the two groups. Secondary endpoints were to evaluate differences in the two populations in terms of clinical outcomes and quality of life (HRQoL).

Results Cox analysis survival data shows no statically difference in the hazard function of the two groups.
The comparison between the two groups showed a significant improvement in the average value of gas indices (paO_2, $paCO_2$) in the group treated with TIV in comparison to the group treated with MPV/NIV. Conversely, the evaluation of the questionnaires on HRQoL showed a higher score in patients treated with MPV/NIV compared to those treated with TIV.

Conclusions Ventilatory treatment with MPV and TIV did not demonstrate significant differences in survival. Patients treated with MPV reported a better HRQoL, although TIV group showed higher ventilatory parameters improvement than MPV group.

key words

amyotrophic lateral sclerosis ,non invasive mechanical ventilation,mouthpiece ventilation, tracheostomy mechanical ventilation, survival time,respiratory outcomes,quality of life

Introduction

Amyotrophic Lateral Sclerosis (ALS) is a neurodegenerative progressive and multifactorial disease with a poor prognosis, which selectively affects motor neurons, both central and peripheral. The main clinical manifestations consist of generalized asthenia, fasciculations and progressive limitation of all motor activities to cause dysphonia, dysphagia, paralysis and difficulty in breathing [1-3].

There is evidence that mechanical ventilation (MV) techniques ,non-invasive (NIV) or invasive (IMV) improve resistance to stress and ventilatory functions and prolong survival [4-8]; therefore the functional respiratory evaluation is particularly relevant in patients with ALS, above all to optimize their therapeutic-rehabilitative program[1,9,10].

NIV proves to be an excellent alternative to IMV [11] and also a means of weaning from it, even though there are cases in which IMV is the only possible technique in the ALS patient approach because of its performances with regard to respiratory parameters. NIV offers numerous advantages among which the decreased need for oro-tracheal intubation, associated with side effects such as: upper airway trauma, impaired speech and swallowing and ventilator-associated pneumonia (with incidence of 30% and mortality equal to 40 -80%)[12].

Finally, NIV is less disabling compared to IMV via tracheostomy and allows a wider ability to manage daily activities for the patient and a reduced difficulty of assistance from family members and health personnel, thus reducing rehabilitation costs and improving Health Related Quality of Life (HRQoL) [9-14]. NIV is possibly effective in raising HRQoL for patients with ALS who have respiratory insufficiency [15-17]. Tracheostomy invasive ventilation (TIV) is possibly effective in preserving HRQoL for patients with ALS, but possibly with a greater burden for their caregivers[18].TIV may be considered to preserve HRQoL in patients with ALS who need long-term ventilatory support [18,19].

The main objective of this observational study was to describe and evaluate the use of daytime NIV using Mounthpiece ventilation (MPV) in association with conventional nocturnal NIV, compared to TIV in ventilator-dependent patients affected by ALS; the secondary objectives was to evaluate differences in the two populations in terms of clinical outcomes, and HRQoL.

Material and Methods

An observational study was carried on at ALS Multidisciplinary Centre and Respiratory Diseases Unit of Hospital of Sestri Levante,Rehabilitation Pulmonology,Don Gnocchi Foundation,Milan and Pulmonary Department,San Martino Hospital,Genova .This included ALS patients for whom mechanical ventilation was prescribed from January 2014 to December 2018 . Written informed consent was obtained from all participants and procedures were conducted according to the Declaration of Helsinki .The study was approved by each Ethics Commitee ,and registered at Chinese Clinical Trial Registry as ChiCTR1800014772.

Study population and study design

All patients were enrolled with a diagnosis of ALS according to the revised criteria of El Escorial [20] at the regional Neurological Center of Reference. From the time of their first respiratory evaluation patients were evaluated every two to six months (based on the level of progression of their disease). The tests performed routinely were as follows: Forced Vital Capacity (FVC), Forced Expiratory Volume at the first second (FEV_1), Maximal Inspiratory Pressure (MIP), Maximal Expiratory Pressure (MEP), Sniff Nasal Inspiratory Pressure (SNIP), Peak expiratory flow after coughing (PCF), arterial blood gas analysis (ABG), oxygen saturation ($SatO_2$).Pulmonary function tests were performed with a computerized body plethysmography (VMAX 20 PFT Sensor Medics, Yorba Linda, CA,US),

according to the ATS/ERS Guidelines [21-25] .HRQoL has been assessed every 6-12 months by mean of SAT- P [26]. The SAT-P is a self-administered, generic questionnaire that evaluate daily life satisfaction, a component of subjective HRQoL. It consists of 32 items. The patient is asked to rate his satisfaction by mean of a 10 cm horizontal visual analogue scale (VAS). The tool provides individual scores about each single item and 5 factor scores, all ranging from 0 (lowest level of satisfaction) to 100 (highest level of satisfaction) [27].

Moreover, some laboratory parameters were evaluated every three to six months : albumin, pre-albumin,alfa-1 acid glycoprotein and C reactive protein (a panel used to evaluate patient's nutritional status)[28] .

NIV was administered when the vital capacity (FVC) , fell below 50% of predicted or clinical signs of nocturnal hypoventilation appeared and / or MIP was found to be below -60 cmH2O or SNIP below -40 cmH_2O[9]. Cough assistance with physiotherapeutic techniques started if the PCEF had fallen below 270 l / min, the Mechanical Cough Assistor (MAC) under 160 l/m [14]. With the progression of the muscle weakness and because of the increasing of use NIV ,MPV was added during the day. The clinical conditions for starting MPV are reported in table 1 [9] .

When NIV plus mechanical assisted cough were not able to mantain an adequate ventilation ($satO_2 \leq 94\%$) , TIV has been offered [29]. The ventilator was set in volumetric controlled assisted mode (VCV) during MPV and in pressure (bilevel -spontaneous/timed -ST or assisted pressure control ventilation -APCV) or volumetric mode (VCV) during the NIV.For these patients a double program provided ventilator was used.Theventilator setting was determined in outpatient clinic. Further adjustments were made based on comfort,symptoms and overnight oximetry or diurnal ABG. Patients with severe bulbar deficiency were treated with TIV .For these patients APCV mode was used. The other patients were treated at the beginning with NIV.Patients who showed deficiency of bulbar fuction during the course of the disease or a suddend and/or severe deterioration were switched to TIV group .The ventilators used were : Resmed Stellar 150,Resmed Astral 150,Resmed Eliseè 150.Angled mouthpieces 15 mm or 22 mm[1] were used to

deliver MPV.Nasal mask,oronasal mask and full face mask were used to deliver nocturnal NIV following the choice of the patient and the progression of the ventilatory failure.

The patients when it needs underwent percutaneous endoscopy gastrotomy (PEG) for enteral nutrition.

Every patient was provided of airway clearance technique (cough assistor) as complementary techniques of mechanical ventilation [1].Every patient was follow at multidisciplinary clinic team which have enanbled and facilitated the coordination of all procedures ,reinforced good practices with early and complete care of their needs.Furthermore,a medical and nursing care care team integrated into the hospital team have taken care for the patients to verify the correct functioning and to ensure correct management of ventilatory treatment by the caregivers.

Demographic data, disease phenotype,age at the time of diagnosis were recorded as they were noted also the beginning of the NIV, the beginning of mechanical ventilation for more than 12 hours, the beginning of MPV, tracheostomy and death. All tests of respiratory function and quality of life were reviewed by dividing the examination period into 3 phases :

- disease diagnosis phase;
- start of mechanical ventilation phase;
- last three months of life of the patients phase.

.*Statistical analysis*

For statistical analysis was used the R-Project software version 2.13.2. The results obtained were expressed as mean and standard deviation and evaluated by efferving the p-Value (a measure of evidence against the null hypothesis, i.e. the level of significance assigned to that particular value) that was calculated with the Student's test every step.

For the comparison between the various parameters of the two different groups, the univariate analysis regression

test was used. A level of variation greater than 0.05 was statistically significant. Regarding the survival analysis, this was performed using the Kaplan-Maier method; the Log-rank test (Logarithmic Ranks Test) was used to compare the survival of the two groups.To guarantee a blindness for lower risk of bias for clinician-assessed outcomes such as HRQoL the questionnaires were administered by two different nurses and the data were evaluated by an independent statistician blinded to patients' treatment assignment.

Results

80 patients with ALS were screened in the study; 48 of them were excluded from the analysis for limited data or for lack of consent to the publication of data or inability to perform respiratory function measurements. 32 patients were included in the analysis: 27 patients were initially treated with nocturnal NIV associated with daytime MPV and 5 with TIV.Eleven patients switched to TIV owing to severe deterioration of bulbar or respiratory function. Finally 16 patients were included into MPV + nocturnal NIV group and 16 into TIV group (see study flow chart)(fig.1). .Baseline characteristics of the patients in the two groups are presented in the table 2a-2b .

The time elapsed from the time of diagnosis to the beginning of the NIV varies from 12 days to 1218 days with an average of 267 days. 22 patients (70%) had more than one indication for NIV: FVC below 50% predicted for 21 patients (65%), followed by 7 patients with MIP less than -40 cmH_2O (22%) and 5 with SNIP less than -60 cmH_2O (10%), diurnal hypercapnia for 3 patient (16%); 2 patients (6.%) reported ortopnea and symptoms of respiratory disorders during sleep.The time between the introduction of the NIV and the start of the MPV varies between 20 days to 390 days with an average of 139 days. The MPV was introduced following previously described criteria.Eleven patients,when severe bulbar dysfunction and/or severe respiratory failure happened were switched from MPV/NIV to TIV.Instead, patients who chose not to undergo TIV continued with NIV. In addition, all patients (with the exception of

2 patients) underwent PEG for enteral nutrition.

Six patients of the MPV/NIV group were treated with VCV + ST mode,eight patients with VCV + APCV and two with VCV .Fourteen patients belonging to TIV group were treated with APCV mode and two with VCV mode.

The average days of ventilatory treatment for each group of patients: 617.56 days for the MPV/NIV patient group vs 782.69 days for the TIV group .The median days for MPV group were 487.19. No patient died from decision to withdraw mechanical ventilation.Mortality analysis is showed by Kaplan-Maier curves diagram (fig.2). The Kaplan Meier survival analysis has reported here is a monovariable analysis where the "outcome" variable of interest is the failure time. Graphically the failure is represented by a "step / step" of the line: with each step corresponds the death of a patient. Finally, total MPV/NIV survival time was 1131.69 days in MPV/NIV group compared to the 1088.06 days for TIV group (CI 0.30-0.81) . No statistical difference regarding survival in the group treated with MPV/NIV compared to the group treated with TIV has been shown. No correlation was found between survival and any ALS phenotype.

The comparison between the two groups showed a significant improvement over the time in some respiratory parameters (paO_2, $paCO_2$,), in the group treated with TIV compared MPV/NIV ($p>0.001$,$p>0.001$ respectively) . The evaluation of the HRQoL showed a higher score profile in patients treated with MPV/NIV compared to TIV ($p>0.001$)(fig.3a-b and fig.4).No statistical differences was found in the other parameters evaluated (albumin,pre-albumin,C-reactive protein,α1-glicoprotein, ,MIP,MEP,SNIP,PCF and ventilation days) (table 2).

Discussion

In the two last decades the natural history of neuromuscular diseases (NMDs) changed : it is due particularly to improvements in the diagnosis and treatment of the respiratory complications which can lead rapidly to death [30].The

increasingly widespread application of ventilatory support and assisted coughing as well as the progressive change in the approaching to these patients with early application of NIV and management of multidisciplinary teams has resulted in a considerable improvement in the quality and expenctancy of life for these patients [31-34]. However, there are few studies that have demonstrated the efficacy of MPV associated with other different interfaces in the treatment of ventilatory insufficiency in NMDs [14,35-38]. This is one of the first studies describing the use of MPV in patients with ALS associated with traditional nocturnal NIV and MAC in a population of completely depending patients ventilated until 24 h per day.No randomized controlled study comparing NIV and TIV is available in medical literature [37,38].However,some evidences from observational studies suggest that NIV should be trailled in all patients except for those with bulbar dysfunction [38].

NIV has demonstrated to prolong survival in ALS [39,40].Early initiation of NIV should produce a protective role for survival ,as well as tracheostomy which showed a lower probability of death [8,41].An interesting study which has evaluated decision-making factors and survival analysis in a Japanese Hospital observed that in a population of 190 people with ALS the use of MV prolonged median survival compared to natural course (75 months for TIV,43 months for NIV,32 months natural course).TIV was the preferred choice in younger patients ,in higher progression of the illness and preserved motor functions [42].

The results obtained in our study confirm the effectiveness of the use of MPV/ NIV until the patient is able to maintain an adequate bulbar function[43] . In patients with severe bulbar impairment, in fact, NIV improves sleep-related symptoms, but it is unlikely to increase survival: therefore, its efficacy is related to the severity of bulbar dysfunction [6,8,9]. In a recent review by Heritier Barras et al. on MV in patients with ALS, they claimed that the use of MV 24 hours a day had become a common and well tolerated practice in patients with ALS [33]. On the other hand the use of MPV in the recent years has been increasing in patients with NMDs with promising results [44-46].To our knowledge our

observational study is the first which has compared 24 h MPV /NIV with TIV .Surprisingly, a similar mortality was observed in the two groups,although TIV improved respiratory parameters (paO_2 and $paCO_2$ more than MPV/NIV).

We are aware that the study present some limitations :

1.This is a real life study , with a limited number of patients.

2.The choice of the treatment was not blinded and exchangeable over the study .

3.The choice of treatment was according to the physician's clinical judgement : this can be a possible bias.

Conversely,its strenght is to be a real life study,where ALS patients were treated with NIV (if possible) and only later TIV was offered.Every patient had chosen if continuing MPV/NIV or switching to TIV.

Conclusions

MPV/NIV has been a safe and effective fashion to treat patients with ALS requiring continuous ventilatory support.

It has not demonstrated significant differences in survival compared to TIV. Patients treated with MPV/NIV reported a better HRQoL despite lower respiratory values (ABG,MIP,MEP,SNIP,PCF) over time .Therefore, NIV/MPV should be offered as an alternative to TIV for patients with mantained bulbar timely. It has prolonged free time from diagnosis to death similarly to TIV .These results may be as a starting point for future larger randomized controlled trials.

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Conflicts of interest

The authors declare no financial or other conflicts of interest.

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Table 1 Criteria to start day time non invasive ventilation

- Persistent diurnal hypercarbia > 50 mmHg and or when SpO_2 < 92% while awake
- Daytime dyspnoea
- Non invasive ventilation use > 12 h /day

Table 2a Characteristics of the patients at baseline

Parameter	MPV group	TIV group	p-value
age	67,6 ± 4,0	71,6 ± 3,0	0,3432
BMI	24,9 ± 4,7	23,6 ± 2,6	0,3298
prealbumin	16,5 ± 3,0	18,8 ± 1,9	0,0886
albumin	3.771 ± 304	3.876 ± 236	0,4414
α1 acid glic	88,4 ± 19,7	90,3 ± 15,6	0,8239
C-RP	0,7 ± 0,2	0,7 ± 0,2	0,9448
FVC	84,8 ± 9,2	85,9 ± 9,2	0,8114
FEV_1	81,3 ± 10,8	77,6 ± 10,7	0,4902
MIP	69,9 ± 10,5	69,8 ± 7,1	0,9602
MEP	66,4 ± 7,1	65,4 ± 8,1	0,7385
SNIP	67,1 ± 8,0	64,1 ± 5,8	0,3219
PCF	370,0 ± 32,9	355,6 ± 53,8	0,5316
$satO_2$	95,7 ± 1,1	95,9 ± 1,2	0,6932
paO_2	79,3 ± 3,4	83,0 ± 4,4	0,2059
$paCO_2$	38,6 ± 2,2	39,3 ± 2,6	0,4999
Ph	7,4 ± 0,0	7,4 ± 0,0	0,0940
AHI	10,1 ± 2,8	9,6 ± 4,3	0,7630
ODI	16,1 ± 5,4	15,6 ± 3,1	0,7732
Sat-P	72,8 ± 7,7	71,9 ± 7,6	0,8066

MPV .mouthpiece + nocturnal non-invasive ventilation group
TIV tracheostomy invasive ventilation group
ALS amiotrphyc lateral sclerosis

BMI Body mass index α1-glic alfa-1 acid glycoprotein C-RP C-reactive protein FVC Forced vital capacity FEV_1 Forced expiratory pressure at first second MIP Maximal inspiratory pressure MEP Maximal expiratory pressure SNIP Sniff nasal inspiratory pressure PCF Peak cough flow $satO_2$ oxygen saturation paO_2 Oxygen arterial pressure $paCO_2$ carbon dyoxide arterial pressure AHI Apnea-hypopnea index ODI Oxygen desaturation index Sat-P Satisfaction Profile

Table 2b ALS phenotypes in the two groups

Phenotype	MPV group	TIV group
Bulbar	0	5
Classic	8	7
Flail arm	2	4
Flail leg	1	0
Pure lower motor neuron	2	0
Pyramidal	3	0

Table 3 Laboratory, respiratory and HRQoL parameters over time

Parameter	T0		T1		T2		p-value
	MPV	TIV	MPV	TIV	MPV	TIV	
Prealbumin	16.5±3.0	18.8±1.9	14.7±2.4	15.0±1.3	13.1±1.8	12.2±0.4	0.08
Albumin	3.771±304	3.876±236	3.542±277	3.425±181	3.465±±242	3.415±121	0.23
C -RP	0.7±0.2	0.7±0.2	0.6±0.2	0.7±0.4	0.6±0.2	0.8±0.2	0.26
MIP	69.9±10.5	69.8±7.1	49.9±7.0	46.5±4.7	34.0±5.7	33.4±5.3	0.31
MEP	66.4±7.1	65.4±8.1	49.9±5.3	45.5±7.1	37.1±4.2	36.2±4.0	0.12
SNIP	67.1±8.0	64.1±5.8	48.9±5.0	39.9±9.0	34.5±4.2	30.9±5.2	0.06
PCF	370.0±32.9	355.6±53.8	270.1±21.0	257.5±24.8	193.1±19.7	186.3±23.5	0.14
paO_2	79.3±3.4	83.0±4.4	63.9±5.4	59.3±4.9	51.8±3.0	61.3±2.5	0.001
$paCO_2$	38.6±2.2	39.3±2.6	44.6±6.2	43.9±3.9	54.3±0.5	42.0±0.8	0.001
SAT-P	72.8±7.7	71.9±7.6	55.3±10.0	53.7±7.2	42.9±5.1	30.7±1.4	0.001
Time ventilation (days)					617.56	782.69	0.09
Survival days					1131.63	1088.06	0.27

T0 Disease diagnosis phase T1 Starting mechanical ventilation T2 Last three months
MPV : mouthpiece non- invasive ventilation group TIV tracheostomy invasive ventilation group

C-RP C reactive protein MIP maximal inspiratory pressure MEP maximal expiratory pressure SNIP PCF satO2 : oxygen saturation paO2 paCO2 SAT-P satisfaction Profile HRQoL Health related quality of life

Legends

Table 1 Criteria to start day time non invasive ventilation

Table 2a Characteristics of the patients at baseline

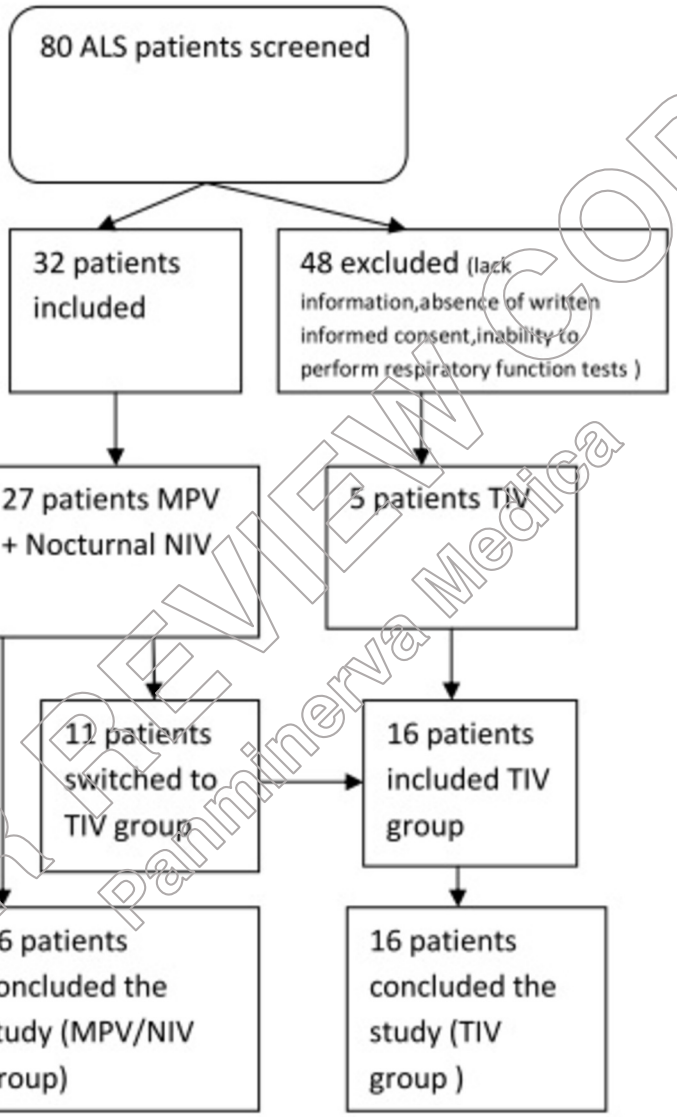
Table 2b ALS phenotypes in the two groups

Figure 1 Study flow chart

Figure 2 Survival of patients in Kaplan-Meier model.Blue,patients treated with tracheostomy invasive ventilation (TIV);red,patients treated with diurnal mouthpiece ventilation and nocturnal non invasive ventilation (MPV)

Figure 3a-3b Trend over time of PaO_2 and $PaCO_2$ in the three examination phases (1.diagnosis phase; 2.start of mechanical ventilation phase;3. last three months of life) in the two groups

Figure 4 Trend over time of Sat-P in the three examination phases



MPV Mouthpiece ventilation

NIV non invasive ventilation

TIV tracheostomy invasive ventilation