ORIGINAL ARTICLE

Long-term evaluation of phrenic nerve pacing for respiratory failure due to high cervical spinal cord injury

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Objectives: Phrenic nerve pacing (PNP) is a method of respiratory support that can replace mechanical ventilation (MV) in high-level cervical spinal cord injury (SCI) patients with diaphragmatic paralysis. Our objective was to evaluate survival and long-term quality of life in patients with external respiratory support by PNP vs volumetric respirator in patients with severe respiratory insufficiency due to a high-level spinal cord injury.

Design: This is a retrospective review study of a prospectively collected database for evaluate the survival and a questionnaire for quality of life has been collected face-to-face or by telephone at present.

Patients: Cervical SCI patients with permanent respiratory support (PNP or MV).

Methods: Long-term evaluation of a cohort of PNP-supported patients. We performed a comparison between these patients and volumetric respirator-supported patients. For survival analysis, we used the Kaplan–Meier method and Cox proportional hazards model. The health-related quality of life (HRQL) was assessed with SF-36 questionnaire, a general HRQL evaluation.

Results: One hundred twenty six patients on permanent respiratory support were evaluated during the study period. Of these, 38 were on PNP and 88 were mechanically ventilated. Paced patients were younger and had a longer survival, but in a multivariate analysis adjusted for age using a multiple logistic correlation we found that length of survival was greater for PNP patients. In terms of HRQL, the PNP-supported patients showed better results in terms of social functioning.

Conclusions: PNP is a stable and effective method of long-term respiratory support in this type of patients (SCI patients dependent on external respiratory support). In these patients it improves the length of survival and some social issues by quality of life when compared with patients under MV.

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INTRODUCTION

Spinal cord injury (SCI) is a devastating condition that causes high rates of morbidity and mortality. Injuries at high cervical spinal cord level interrupt the descending bulbospinal respiratory pathways, causing immediate paralysis of the respiratory muscles and severe respiratory insufficiency.^{1,2} The neurological consequences are often irreversible and so the patient cannot sustain sufficient ventilation; therefore, it is necessary to provide external respiratory support throughout mechanical ventilation (MV) for a prolonged or indefinite period.³ This fact interferes in a decisive way in family life and environment reintegration.⁴

Diaphragmatic pacing system by a portable phrenic nerve stimulator facilitates long-term artificial ventilation in patients who suffer respiratory muscle paralysis due to high cervical SCI. This portable system has no external tubes and provides intrathoracic pressures similar to physiological pressures, allowing patients' weaning from MV and facilitating hospital discharge.⁵ After an adaptation period to improve the muscle tone of the diaphragm, which is atrophied from disuse,⁶ permanent bilateral pacing is an effective method of definitive respiratory support.⁷

Moreover, phrenic nerve pacing (PNP) can diminish the incidence of respiratory infections and atelectasis, it improves patients' mobility

and lifestyle^{8,9} and, as a consequence of improved swallowing, mobility, comfort and sense of smell, also their verbal communication and quality of life.¹⁰ There are, however, strict criteria for its placement in order to maximize the chances of success after inability to wean from the respirator: (1) good pulmonary gas exchange, (2) good airway access, (3) indemnity of the phrenic nerve function (assessed by their conduction time and amplitude and fluoroscopic evaluation of diaphragmatic movement; trans-diaphragmatic pressure measurement being an optional test) and (4) no co-morbid conditions that may interfere.¹¹

We have tried to confirm our subjective impression that this device is not only effective but also well tolerated for many years performing a long-term evaluation. Therefore, the main purpose of this study is to evaluate the long-term outcome of PNP in our series of patients with severe chronic neuromuscular respiratory failure due to high cervical SCI by assessing their length of survival and the health-related quality of life (HRQL), and to compare these results with patients on MV.

METHODS

This is a retrospective review study in which clinical data were prospectively collected during hospital admission for SCI rehabilitation and during

successive visits. The local Research Committee and local Clinical Research Ethics Committee approved this study. The study group consisted of 38 spinal cord injured patients who had a phrenic nerve stimulator implanted. This cohort was compared with a second group of patients who have been mechanically ventilated with a volumetric mechanical respirator.

Inclusion criteria included respiratory failure due to high cervical SCI requiring external respiratory support (either PNP or volumetric mechanical respirator). Exclusion criteria included active pulmonary infections, cancerous disease or another underlying terminal concurrent illness. Mental disability or lack of family support was not considered exclusion criteria for device implantation. The study has been carried out at the Intensive Care Unit and the Intermediate Respiratory Care Unit in the National Paraplegics Hospital of Toledo, Spain. The selection of patients for each group did not follow a randomization process because of the strict criteria for PNP implantation.

Demographic and clinical data were prospectively collected at their first admission. Neurological examination to assess the level and severity of SCI was performed just before their transfer from the ICU to the rehabilitation ward in accordance with the International Standards for Neurological Classification of spinal cord injuries (ASIA impairment scale).¹² The respiratory, metabolic, cardiovascular or systemic co-morbidity was measured using the Charlson co-morbidity index.¹³ The length of stay was defined as the time (in days) from first admission to hospital discharge. Length of survival was defined as the time between SCI and the date of death, or 31st March, 2011, should they stay alive.

HRQL was assessed using the SF-36 questionnaire.¹⁴ This questionnaire has 36 questions and it covers 8 parameters: physical functioning, role limitations as a result of physical problems, physical pain, general health, vitality, social functioning and role limitations as a result of emotional problems and mental health. The higher the score, the greater the HRQL is regarded to be. This questionnaire was filled by a psychologist in face-to-face interviews or when this was impossible, in telephone interviews with all the surviving patients during the second half of 2010.

Statistics

Continuous variables have been expressed as mean $\pm$ s.d. Categorical variables have been expressed as absolute frequencies and percentages. We have used univariate analysis to evaluate the relationship between method of respiratory support and outcome. Length of survival has been expressed as the mean with 95% confidence interval. For continuous variables we have used Student's *t*-test if it was normal distribution, or the Mann–Whitney–Wilcoxon *U*-test for non-parametric comparisons. χ^2 -test (or Fisher's exact test if any of the sections of the table was less than 5) has been used to compare categorical variables. Survival has been estimated using Kaplan–Meier method and analysed with log-rank test, for which the censoring date was 31st March, 2011 (mortality status could be verified until that date). The Cox proportional hazard ratio model for continuous variables was used to perform a multivariate analysis for length of survival. *P* value ≤ 0.05 was considered statistically significant. Statistical analysis was performed using SPSS package, version 15.0 for Windows (SPSS Inc, Chicago, IL, USA).

RESULTS

We reviewed the medical records of all patients admitted in our Centre who required permanent respiratory support owing to respiratory failure because of diaphragmatic paralysis as a result of high cervical SCI above C3 level. We evaluated the data of 126 patients, 38 on PNP (PNP group) and 88 on the MV (MV group). As far as sex is concerned, 85 (67.5%) were male and 41 (32.5%) female. Injury mechanisms included traumas in 84 cases (66.7%), 61 of them road accidents, 15 falls at the workplace, 7 in sports and recreational activities and 1 penetrating injury during an aggression. Causes were non traumatic in 42 cases (33.3%): 9 tumours, 10 spinal cord ischaemia due to vascular disease, 8 infections, 6 degenerative spine disease and 9 cases of inflammatory myelitis. At hospital discharge, 81 patients (64.3%) returned to their homes, whereas 11

patients went to another hospital (8.7%) and 34 patients to a healthcare and community service centre (27%). When this study was carried out (along March, 2011), 67 patients (53.2%) were still alive and 59 (46.8%) had died.

PNP was implanted in 38 patients. All patients required permanent MV before the implantation of PNP from the moment of injury. The phrenic nerve stimulator facilitates long-term artificial ventilation in SCI patients by means of rhythmic contractions of the diaphragm. They are produced by trains of current pulses delivered to the phrenic nerves via electrodes attached to its thoracic portion and connected to a radio-frequency receiver implanted in a subcutaneous area. A circular antenna connected to the transmitter by wires is positioned over each receiver on the body surface. The transmitter generates a radio-frequency signal, which is coupled to the implanted receiver. Bipolar electrodes were implanted in the first six patients; after those we used four-pole electrodes. The phrenic nerve electrodes were implanted by open thoracotomy in all patients, but in seven who were operated on by thoracoscopic technique.

The average time interval from injury to PNP implantation was 20.76 ± 20.67 months (range 3.62–100.17 months). Implantation was done during the first year after their lesion in 14 patients, between 12 and 18 months in 9 patients and more than a year and a half in 15 patients. The post-implantation training protocol includes a slow and progressive replacement of respiratory support with the ventilator to the total support with the PNP. In general, the time with PNP support increases about 5% every 2 days. The mean time for this conditioning period (time for ventilator weaning after PNP implantation) was 47.33 ± 19.61 days (range 31–96 days). All PNP patients were provided with a portable volume ventilator on being discharged from the hospital as a security measure against possible breakdown of the device.

Eleven patients died during the follow-up period and 27 remain alive. Of these, 20 patients use it as their only respiratory support, while 5 cases use a mixed system in which the mainstay is PNP and the volumetric respirator is used during night time sleep. Two patients had to shift to MV during follow-up at 11.25 and 15.74 years, respectively: the first due to infection of the implanted device (from a wire that was inside a pressure ulcer) and the second due to severe deterioration of phrenic nerve conduction.

The demographic and clinical characteristics of both groups, PNP and MV, are shown in Table 1. There are not significant differences between both groups with respect to their distribution according to sex, cause of SCI, ASIA scale, Charlson co-morbidity index, causes of death and their destination after hospital discharge. By contrast, notable differences were evident in mean age, mortality rate (measured as the percentage of deaths over the total number of patients in each group) and length of survival according to Kaplan–Meier.

With the aim of comparing the length of survival and quality of life outcomes in PNP patients vs MV patients we analysed these variables using a multiple logistic correlation and we found that once age was controlled, the differences in co-morbidity, SCI level and mortality rate were not statistically significant, but length of survival was greater for PNP patients (see Table 2).

Overall, 44 patients completed the SF-36 questionnaire (65.7% of 67 survivors: 24 with PNP and 20 on respirator). To avoid selection bias we have analysed only the group of patients with C1–C2 level ASIA A grade of SCI (36 patients), and results are shown in Table 3. In the SF-36 questionnaire we have only observed significant differences ($P = 0.002$) in the social functioning dimension, with smaller differences in the areas of communication and external dependence.

Table 1 Demographic, clinical data and outcomes according to the mode of ventilatory support in C1–C2 SCI patients

	PNP	MV	P value
Patients (total: 126)	38 (30.16%)	88 (69.84%)	
Sex			
Male	23 (60.5%)	65 (73.9%)	0.20
Female	15 (39.5%)	23 (26.1%)	
Average age (in years)	17.8 ± 11.1	45.5 ± 21.9	<0.001
Cause of spinal cord lesion			
Traumatic	24 (63.2%)	61 (69.3%)	0.54
Medical	14 (36.8%)	27 (30.7%)	
SCI level			
C1 or higher (brain stem)	18 (47.4%)	27 (30.7%)	<0.001
C2	20 (52.6%)	25 (28.4%)	
C3 or lower		36 (40.9%)	
ASIA Grade			
A	24 (68.4%)	66 (75%)	0.55
B	6 (15.8%)	9 (10.2%)	
C	6 (15.8%)	13 (14.8%)	
Destination after 1st discharge			
Home	30 (78.9%)	51 (57.9%)	0.08
Another hospital	2 (5.3%)	9 (10.2%)	
Healthcare or community services centre	6 (15.8%)	28 (31.9%)	
Co-morbidity (Charlson index)	0.26 ± 0.60	0.65 ± 0.91	0.16
Mortality			
Living patients	28 (73.68%)	39 (44.32%)	0.003
Deaths	10 (26.32%)	49 (55.68%)	
Causes of death			
Respiratory	6 (60%)	41 (83.7%)	0.19
Others	4 (40%)	8 (16.3%)	
Time of death ^a			
0–5 years	6 (60%)	37 (75.5%)	0.15
5–10 years	1 (10%)	8 (16.3%)	
> 10 years	3 (30%)	4 (8.2%)	
Survival expectancy in years (mean with CI 95%) by Kaplan–Meier method	21.78 (17.95–25.61)	8.69 (6.37–11.02)	<0.001

Abbreviations: ASIA Grade, American Spinal Injury Association SCI severity scale; CI, confidence interval; ICU, intensive care unit; MV, mechanical ventilation; PNP, Phrenic nerve pacing; SCI, spinal cord injury.

^aTime from SCI to death, excluding first 6 months from injury.

DISCUSSION

This study sought to evaluate the long-term efficacy and quality of life following the use of PNP as method of artificial external respiratory support in high cervical spinal cord injured patients. As this procedure requires a stable neurological situation and proper functionality of the phrenic nerves, diaphragm and lungs, its implantation in practice is limited to a few patients.¹¹ Some authors recommend the use of PNP as the standard treatment for suitable candidates.¹⁵

Table 2 Cox regression analysis to evaluate the effect of covariables in the univariate analysis

Variable	OR	CI 95%	P value
Age	1.02	1.01–1.04	0.01
Sex	1.27	0.72–2.25	0.41
SCI level	1.06	0.79–1.42	0.68
Co-morbidity	0.81	0.57–1.14	0.23
Survival	0.98	0.97–0.99	0.04

Abbreviations: CI 95%: confidence interval for 95%; OR: odds ratio; SCI, spinal cord injury.

Table 3 Quality of life. Results of the SF-36 questionnaire in C1–C2 SCI-patient group

	PNP	MV	P value
Patients (total: 36)	21 (58.3%)	15 (41.7%)	
General health	5.9 ± 1.54	6.27 ± 1.28	0.70
Physical functioning	6.62 ± 1.7	6.60 ± 1.68	0.90
Role limitations as a result of emotional problems	4.85 ± 1.31	5.27 ± 1.22	0.39
Social functioning	7.67 ± 1.80	5.67 ± 1.17	<0.001
Physical pain	8.62 ± 2.82	8.87 ± 2.36	0.89
Vitality	35.76 ± 7.7	37.93 ± 11.7	0.17
Role limitations as a result of mental health	11.86 ± 3.12	12.2 ± 3.86	0.77
Total score	81.29 ± 13.82	82.80 ± 16.28	0.56

Abbreviations: MV, mechanical ventilation; PNP, Phrenic nerve pacing; SCI, spinal cord injury. The comparisons are analysed between the net scores and not between percentages.

The patients with cervical SCI who are ventilator dependent have reduced life expectancies and higher mortality rates compared with a general population of comparable age, sex and race.^{16,17} This study shows that patients in the PNP group have a greater mean length of survival vs a MV group in univariate comparison. However, we found a large age difference between both groups. Once the age adjustment had been made by multiple logistic analysis (Cox regression), we confirmed that the length of survival was greater in patients in the PNP group ($P = 0.04$). High-level SCI patients dependent on external respiratory support can often return to family life with good integration. Social integration after hospital discharge shows no significant differences after the univariate analysis.

HRQL can be defined as the subjective perception, influenced by our current state of health, of our capacity to perform those activities that are important to an individual, or as the perception that each person has of the consequences of his/her health on his/her physical, emotional or social well-being. Especially in patients with very high-level injuries, SCI reduces HRQL because of severe motor and vegetative disturbances. The improvement in the HRQL of SCI patients is an excellent indicator of the effectiveness of any rehabilitation programme.^{18,19}

It has been previously reported that PNP improves HRQL in respiratory-supported patients because of more natural breathing, better verbal communication, easier mobility and more comfort.^{3,20} However, this assumption has not been objectively demonstrated owing to a lack of appropriate measurement tools. We have not yet been able to define which questionnaires are best suited to calculate HRQL in cervical SCI patients.

The SF-36 questionnaire is an instrument to measure HRQL and it is widely used because of its good psychometric properties. It is a simple questionnaire that covers all the areas considered markers of HRQL. It is, however, a general method of evaluation that was not

designed to be used with SCI patients, as there is a section (nominated physical functioning) that regards capabilities that do not apply to this type of patients, such as climbing stairs, walking and so on. Notwithstanding this drawback, it has revealed itself useful in this particular population giving a zero value to the items that assess ambulation and using only subscales relevant to SCI.^{21–23} We consider that the SF-36 questionnaire is not the 'ideal' tool but it is a valid method to evaluate HRQL in numerous pathologies and also in our patients.

Despite the small sample sizes, we observed some relevant differences between both groups. Our results show a better HRQL in patients in the PNP group in the areas of social functioning according to the SF-36 score (Table 3). The activities involved in this subscale (such as going out to the street, travelling by car and chatting with family) can be interfered not only by their disability but also by the device of respiratory support that they need. Our study shows that the patients with PNP report fewer constraints related to these social activities vs the patients in the ventilator group. This improvement can be because of the greater mobility resulting from the use of PNP, given that this device can be transported more easily than the respirator and there are no tubes or connections to the tracheostomy tube,¹⁷ and provides a more physiological phonation.

The limitations of our study are principally associated to the small size of the sample, which renders difficult to demonstrate a statistical significance for the results regarding HRQL comparisons. We tried to minimize the biases linked to a retrospective study through the design of the statistical treatment of the data. As it is not possible to fully account for the age bias in who is offered the PNP, we tried to improve the multivariate analysis with a comparative analysis adjusting for age groups, obtaining quite similar results, which confer greater reliability to them. We are fully aware of all these limitations but we consider the following conclusions to be valid.

CONCLUSIONS

In patients with high-level SCI and severe respiratory insufficiency, PNP is an effective, safe and convenient respiratory support device, which can represent the weaning from MV. Our results show a prolonged survival in patients with PNP vs MV, although the difference is low. PNP patients experience a slightly better quality of life in the area of social functioning on the SF-36 questionnaire, probably as a result of being dependent upon a device which is safe, highly reliable, with improved portability, without tubes and with low maintenance requirements. In our criteria its implantation is justified in suitable patients. We consider that the main drawback is the strict inclusion criteria for its placement, which restricts it to young patients with high cervical SCI.

DATA ARCHIVING

There were no data to deposit.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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