Original Article

Preoperative parameters and their prognostic value in amyotrophic lateral sclerosis patients undergoing implantation of a diaphragm pacing stimulation system

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Abstract

Introduction: Amyotrophic lateral sclerosis (ALS) is a progressive neuromuscular disease with devastating and fatal respiratory complications. Diaphragm pacing stimulation (DPS) is a treatment option in diaphragm insufficient ALS patients. Ventilatory insufficiency depending on diaphragmatic failure is treated by the present study aimed to investigate prognostic value of preoperative clinical and functional characteristics of ALS patients undergoing implantation of a DPS system and to determine appropriate indications for the DPS system. **Methods:** The study included 34 ALS patients implanted with DPS system. All patients underwent multidisciplinary and laboratory evaluations before the surgery. The laboratory examinations included pulmonary function tests and arterial blood gas analysis. Survival rates were recorded in a 2-year follow-up after the surgery. **Results:** Twenty-eight of 34 patients with ALS survived after a 2-year follow-up. These patients were younger than those who died and had the disease for a longer time; however, the differences were not significant. Both right and left hemidiaghragms were thicker in the survived patients ($P < 0.0001$ for each). Pulmonary function tests revealed no significant differences between the patients who survived. Arterial blood gas analysis demonstrated lower partial pressure of carbon dioxide in the survived patients ($P = 0.025$). **Conclusions:** DPS implantation was more efficacious in ALS patients with mild respiratory failure and thicker diaphragm. Predictors of long-term effectiveness of DPS system are needed to be addressed by large-scale studies.

Key Words

Amyotrophic lateral sclerosis, diaphragm pacing, respiratory failure

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Introduction

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease with unknown etiology that results in death of upper motor neurons in the brain as well as lower motor neurons in the brainstem and spinal cord.[1] The incidence of ALS is largely uniform across most parts of the world. ALS incidence during the last decades has been increased.[2] Many studies from Europe and North America reported the incidence of ALS to be 1–3/100,000 and the prevalence of ALS to be 4–6/100,000 per year.[2] It is estimated that there are approximately 90,000–100,000 ALS patients in the world and 3500–5000 ALS patients in Turkey.[3] About 10–15% of ALS patients have a familial form of the disease. If no family history is identified, it is diagnosed ass sporadic ALS. Sporadic spinal ALS is slightly more frequent in males.[2]

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Respiratory symptoms in ALS appear in further stages when the skeletal and bulbar muscles are involved. However, respiratory failure may be seen even at the beginning of disease in some ALS patients because of phrenic motor neuron involvement. Patients that fail to perform coughing function efficiently due to the involvement of respiratory muscles frequently develop community-acquired pneumonia, aspiration pneumonia, and ventilator-related pneumonia, which particularly occurs in the inferior lobes in the mechanical ventilator-dependent patients.[4] Progressive weakness of respiratory muscles leads to carbon dioxide retention and hypercarbic respiratory failure, which accounts for at least 84% of deaths from ALS.[5] Respiratory failure is the most important morbidity and mortality factor influencing the progression of disease.[6-8] Dyspnea and sleep alterations occur, and survival is influenced due to diaphragmatic involvement, particularly in the degenerative process.

There is no definite treatment for the disease. Riluzole, a tetrodotoxin-sensitive sodium channel blocker, may delay the need for ventilator and prolong survival for several months; however, it has a limited therapeutic effect.[5] Disease duration from the onset of symptoms to death is 30 months in average; however, 1/5 of patients survive up to 5 years and 1/10 of patients survive up to 10 years.[2] Noninvasive ventilation (NIV) is a part of standard care for patients who have advanced respiratory failure.[5] The most widely used one is bi-level positive airway pressure. NIV reduces dyspnea, improves sleep, and prolongs survival. In further stages, mechanical ventilation is performed via tracheostomy.[5]

Studies have demonstrated that low-frequency electric stimulation of lower extremity muscles improves muscle functions in Duchenne myopathy. Moreover, it is suggested that diaphragm may also be stimulated ALS patients.[5] Diaphragm pacing stimulation (DPS) system was first developed to control lower motor neuron involvement of phrenic nerve in patients with spinal cord injury. DPS system has substantially improved the quality of life by making patients with spinal cord injury free of mechanical ventilator and reduced cost of care. From this point of view, it has been suggested that decrease in vital capacity, which is the most important problem in ALS, can be prevented via low-frequency electrical stimulation of diaphragm. DPS system for ALS was first implanted in 2005.[9] Implantation of a DPS system in ALS patients converts Type IIB (fast-contracting) muscle fibers into better functioning Type I (slow-contracting) muscle fibers by reversing nonuse atrophy, as in tetraplegic patients.[1]

Purpose

This study aimed to investigate prognostic value of preoperative clinical and functional characteristics of ALS patients who underwent implantation of a DPS system and to determine appropriate indications for DPS system.

Methods

The present study comprised of 34 ALS patients who underwent implantation of a DPS system in our clinic between April 2012 and 2014. All patients were examined before DPS system implantation by thoracic surgeons, neurologists, chest diseases specialists, anesthesiologists, respiratory physiotherapists, psychiatrists, nurses, and DPS system technical team members.

Patients

All patients who were followed-up at the Neuromuscular Diseases Outpatient Clinic of Neurology Department for ALS and underwent implantation of a DPS system for respiratory failure were included in the present study. Demographic characteristics of the patients were recorded retrospectively. In addition, results of preoperative pulmonary function tests and arterial blood gas analysis were reviewed.

The patients were evaluated between 08:30 and 10:30 am using a standard protocol. Simple spirometry was performed by the same technician in all patients excluding those who failed to perform respiratory function tests due to tracheostomy using Jaeger Lab Manager V452I. Forced vital capacity (FVC), forced expiratory volume in 1 s (FEV1), and FEV1/FVC were evaluated according to the American Thoracic Society and the European Thoracic Society guidelines.[10] Arterial blood gas analysis is actualized in all patients and spirometry is only nontracheostomised patients. The patients with tracheostomy were only evaluated with arterial blood gas analysis.

Measurement of diaphragm thickness

Diaphragm thickness was evaluated by thorax computerized tomography in the preoperative period. Radiological images were reconstructed in three dimensions, and diaphragmatic thickness was measured from the medial one-third part of the diaphragms over thoracal 11–12 (T11, T12) in the coronal sections by a single physician.

Surgical procedure

DPS system was implanted by the same thoracic surgery team. The patients underwent four laparoscopic incisions in the supine position, and primarily, the motor points of the diaphragms effectively responding to the electrical stimulation were detected. Two electrodes were implanted in each diaphragm (NeuRx, Synapse Biomedical, Oberlin, OH, USA). The implanted electrodes were connected to the system by passing out from the right hypochondrium through the subcutaneous tunnel. The fifth electrode under the skin was used as anode. The system was tested at the end of surgery. It was observed that DPS system provided a tidal volume between 100 and 400 mL in the patients who were under anesthesia.

After all patients were followed-up in the Intensive Care Unit for 1 day during the postoperative period, they were then followed-up by all team members in the clinic.

Statistical analysis

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL, USA) version 15.0 for windows program. Demographic data were expressed as mean and standard deviation or median (interquartile range) according to the distribution of data. Continuous variables were compared using Mann–Whitney U-test between the patients who died and survived within the 2-year period after DPS implantation. Categorical variables were compared using Chi-square and Fisher's exact tests, where appropriate. A $P < 0.05$ was considered statistically significant.

Results

Of the patients (n = 34), 12 (35%) were female and 22 (65%) were male. Before DPS system implantation, 8 patients had tracheostomy and 9 patients had percutaneous endoscopic gastrostomy (PEG). Five of these patients had both tracheostomy and PEG. Eight patients had a concomitant disease; one had atelectasis, three had pneumonia, and four had chronic obstructive pulmonary disease. Six (three females and three males) patients died during the 2-year follow-up period [Table 1].

Twenty-eight patients who survived were younger than the patients who died and had the disease for a longer time; however, the differences were not significant. Both the right and left diaphragma were found to be thicker in the survived patients as compared to those who died ($P < 0.0001$ for each) [Table 2].

Evaluation of the blood gas concentrations revealed that PaO_2 and oxygen saturation was found to be higher in the survived patients; however, the difference was not significant. Contrarily, $PaCO_2$ value was significantly lower in the survived patients than in those who died ($P < 0.01$) [Table 3]. Evaluation of pulmonary function tests revealed similar FVC, FEV1, and FEV1/FVC in both groups ($P > 0.05$ for each) [Table 4].

Cox regression analysis for potential confounders such as disease duration, the presence of comorbid diseases, FVC, and $PaCO_2$ demonstrated no significant effect of these parameters [Table 5].

Discussion

ALS is a progressive neurodegenerative disease with unknown etiology that primarily involves the motor cortex, brain stem, and motor neuron cell population in the spinal cord. Low-frequency electrical stimulation of diaphragm is suggested as the first-line treatment of respiratory failure in ALS patients.[1] Based on this information, the present study aimed to determine the parameters having prognostic value by evaluating clinical and demographic data in ALS patients who underwent implantation of a DPS system due to respiratory failure. Despite limited number of patients evaluated, we determined that preoperative diaphragm thickness was high and carbon dioxide concentration, which is the indicator of alveolar ventilation, was low in the survived patients.

Although ALS may appear in the second decade of life, an early period, it peaks at the age of 64–75 years.[2] Among the patients with an implanted DPS system for ALS, the youngest patient was a female at the age of 30 years. The mean age of the patients who died during the 2-year follow-up period was higher than that of those who survived.

Indicators of poor prognosis for ALS include a disease onset after the age of 65 years, the short time between the disease onset and diagnosis, rapid progression, low body mass index, presence of frontotemporal dementia-ALS picture, dyspnea at the disease onset, and rapid decrease in pulmonary functions.[2] Mean survival in bulbar-onset ALS is 12-26 months. In this study, while the time elapsed from diagnosis to the implantation of DPS system was 2.25 years for patients who survived; it was 1.1 years for those who died. This indicated that the disease was more progressive in the patients who died. Although only three patients died of respiratory reasons, all patients who died had comorbid diseases.

Respiratory failure develops in all forms of ALS. While NIV was the most commonly preferred therapeutic method in the past; recently, DPS system can be considered in selected patients. Bi-level positive airway pressure ventilation slows

Table 1: Demographic characteristics of the patients who died

Patient number	1	2	3	4	5	6
Age (year)	62	74	58	57	62	50
Gender	Female	Male	Male	Female	Female	Male
Disease duration (year)	3	1	1	1	1	3
Tracheostomy	-	-	-	-	-	+
PEG[a]	-	-	-	-	+	+
Cause of death	MI[b]	MI	Pneumonia	Respiratory failure	Pneumonia	UTI[c]
Postoperative death (day)	115	105	101	193	41	214

[a]PEG = Percutaneous endoscopic gastrostomy, [b]MI = Myocardial Infarction, [c]UTI = Urinary tract infection

Table 2: Demographic data and diaphragm thickness of the patients

	Survived patients (n=28)	Died patients (n=6)	*P*
Age (year)	56.00 (46.50-63.00)	60 (55.25-65.00)	0.175
Disease duration (year)	2.00 (1.00-3.00)	1.00 (1.00-3.00)	0.254
Right diaphragm thickness (mm)	0.49 (0.42-0.60)	0.305 (0.295-0.325)	0.001
Left diaphragm thickness (mm)	0.445 (0.39-0.60)	0.29 (0.2775-0.31)	0.001

Data are presented as median (interquartile range)

Table 3: Arterial blood gas values of the patients

	Survived patients (n=28)	Died patients (n=6)	*P*
PaO_2[a]	94.50 (75.25-103.00)	70.00 (64.75-87.75)	0.154
$PaCO_2$[b]	35.50 (32.00-39.00)	41.50 (38.50-47.25)	0.025
Oxygen saturation	96.50 (94.00-98.00)	95.00 (91.50-98.00)	0.282

Data are presented as median (interquartile range). [a]PaO_2 = Partial pressure of oxygen, [b]$PaCO_2$ = Partial pressure of carbon dioxide

Table 4: Pulmonary function test results of the patients

	Survived patients (n=28)	Died patients (n=6)	*P*
FVC[a] (L)	1.40 (0.94–1.99)	1.42 (1.14–2.50)	0.720
FVC (%)	49.00 (33.00–62.00)	62.00 (38.00–77.50)	0.379
FEV1[b] (L)	1.24 (0.86–1.81)	0.98 (0.85–2.03	0.720
FEV1 (%)	50 (26.50–56.00)	56.00 836.00–74.00)	0.473
FEV1/FVC (%)	91.00 (80.50–95.00)	77.00 (67.00–84.50)	0.068

Data are presented as median (interquartile range). [a]FVC = Forced vital capacity, [b]FEV1 = Forced expiratory volume 1 s

Table 5: Cox regression analysis of the patients for potential confounders

	OR	95% CI	*P*
FVC	1.008	0.955-1.041	0.887
Duration of illness	0.464	0.133-1.619	0.464
PaO_2	0.983	0.927-1.043	0.577
Comorbidities	1.645	0.170-15.890	0.667

FVC = Forced vital capacity, PaO_2 = Partial pressure of oxygen, OR = Odds ratio, CI = Confidence interval

down pulmonary worsening, improves symptoms, and prolongs survival.[2] Although DPS system shows the same effect, it prolongs the time for patients to become mechanical ventilation-dependent or enhances the time for mechanical ventilator-dependent patients to wean from the ventilator.[11] Patients are directed to NIV when dyspnea appears indicating that FVC decreased below 50%.[2] Likewise, patients with an FVC of 50–85% at the time of diagnosis or of 45% before surgery may be directed to implantation of a DPS system. In this study, no significant differences were determined between the patients who died and survived in terms of FVC, FVC%, FEV1, and FEV1%. Eight patients had tracheostomy before DPS implantation due to advanced dyspnea, and they were on mechanical ventilator support. While five of these eight patients completely weaned from mechanical ventilator support approximately 8 weeks after implantation of a DPS system, three patients weaned partially. This suggested that DPS might be effective even in advanced dyspnea based on proper patient selection and preoperative patient evaluation.

Evaluation of the preoperative blood gas values revealed that PaO_2 did not significantly differ between the patients who died and survived, whereas a significant difference was determined in terms of $PaCO_2$. Although the median $PaCO_2$ value was within the normal ranges in the patients who died, we are in the opinion that preexisting hypercapnia might be a limitation for implantation of a DPS system.

In ALS, diaphragm thickness is reduced due to nonuse atrophy. DPS system reverses atrophy in the diaphragm and converts Type IIB (fast-contracting) muscle fibers into better functioning Type I (slow-contracting) muscle fibers.[12] In 2014, Onders *et al*. determined a significant increase in the diaphragm thickness, which they measured via ultrasonography before and after implantation of a DPS system.[1] In the present study, the diaphragm thickness was measured using computed tomography before implantation of a DPS system in ALS patients. Accordingly, DPS system was not implanted in the patients with diaphragm thickness <0.2 cm. Both the right and left diaphragm thickness of the patients who died were significantly lower than that of those who survived. We think that implantation of a DPS system would be more reasonable before nonuse atrophy develops and diaphragm becomes thinner.

The limitations of this study included limited number of patients and the lack of evaluation of inspiratory muscle pressure during the preoperative examination. Besides mortality rate was observed low indicating a selection bias although all DPL patients were consecutively assigned.

Conclusions

The present study suggested that DPS system in ALS was more beneficial for patients without reduced diaphragm thickness and severe respiratory failure. However, the facts that ALS is a progressive disease and even early-diagnosed patients with dyspnea alone at the disease onset may be lost rapidly remain valid. Series with higher patient number and with longer follow-up period are needed to establish appropriate patient selection criteria.

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Conflicts of interest
There are no conflicts of interest.

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