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Diaphragm Pacing Could Have Efficacy for Sleep Condition in Patients with Amyotrophic Lateral Sclerosis

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Abstract

Background: To investigate the efficacy of electrical diaphragm pacing (DP) for sleep condition in patients with amyotrophic lateral sclerosis (ALS).

Method: We investigated 5 Japanese ALS patients without positive-pressure mechanical ventilation (3 men and 2 women, aged 59.6 ± 9.6 years). All of them were implanted NeuRx RA/4 Diaphragm Pacing System R (NeuRx) in the diaphragm laparoscopically. We assessed physical status and polysomnographic recordings before implantation and after 6 months of conditioning with DP turned on.

Results: 4 patients completed the evaluation. Sleep condition showed the tendency to improve far from getting worse despite of deterioration of physical status and respiratory function.

Conclusion: DP with NeuRx might assist the sleep condition in ALS patients at least in 6 months of follow up.

Keywords: Amyotrophic lateral sclerosis; Respiratory insufficiency; Diaphragm pacing

with spinal cord injury and ALS [3,4]. We have reported the efficacy and safety of DP for Japanese ALS patients and pathological findings of the autopsied case [5-7]. In this article, we focused on the ancillary impact of DP on sleep condition in ALS patients.

Patients and Methods

This study was ancillary to a prospective, open-labeled, non-randomized trial for 5 Japanese ALS patients without positive pressure mechanical ventilation (3 men and 2 women, aged 59.6 ± 9.6 years). Eligibility criteria were as for the main study, namely that patients had to be 21 years or older, familial or sporadic ALS diagnosed with laboratory-supported probable, probable, or definite according to the World Federation of Neurology El-Escorial criteria; with bilateral phrenic nerve function clinically acceptable as demonstrated by bilateral diaphragm movement with fluoroscopic sniff test or electrophysiological study; chronic hypoventilation was documented by at least one of the following: FVC less than 50% predicted, or MIP (maximal inspiratory pressure) less than 60 cm H₂O, or PaCO₂ greater than or equal to 45 mmHg or nocturnal SaO₂ less than or equal to 88% for at least 5 continuous minutes; suitable surgical candidate, and negative pregnancy test in female participants of childbearing potential. Patients were excluded if they had cardiac or pulmonary disease that would increase the risk of general anesthesia, or diaphragm abnormality such as a hiatal hernia or paraesophageal hernia. Additionally, we excluded those who were implanted electrical device such as cardiac pacemaker or defibrillator, and had severe psychological problem including dementia [5,6].

We started DP with NeuRx RA/4 Diaphragm Pacing System R (NeuRx, Synapse Biomedical, Ohio, USA). We did not restrict the concomitant use of other NIV and 2 patients had already been administered NIV at inclusion (Table 1). We implanted DP electrodes into the diaphragm close to the phrenic motor

Introduction

Respiratory insufficiency is a critical problem in patients with amyotrophic lateral sclerosis (ALS). Earlier administration of non-invasive ventilation (NIV) prolongs the survival in ALS patients and is regarded as the standard care [1,2]; however, its effect on quality of life remains to be elucidated. Diaphragm pacing (DP) is used to augment respiration when patients have intact diaphragm motor units and has been applied to patients

point laparoscopically under general anesthesia according to previous reports [3,8]. In brief, the diaphragm was exposed, the phrenic nerve motor point was mapped, pacing electrodes were implanted, and finally the wires were routed to the external pulse generator. Two pacing electrodes were placed

on the motor points of the diaphragm on each side and intraperitoneal electrode. We continued DP for 24 hours a day. Diaphragm contractions were induced by delivering trains of stimuli with the conditions of: frequency, < 20 Hz; pulse width, < 200 μ sec; and intensity, < 25 mA, as tolerated.

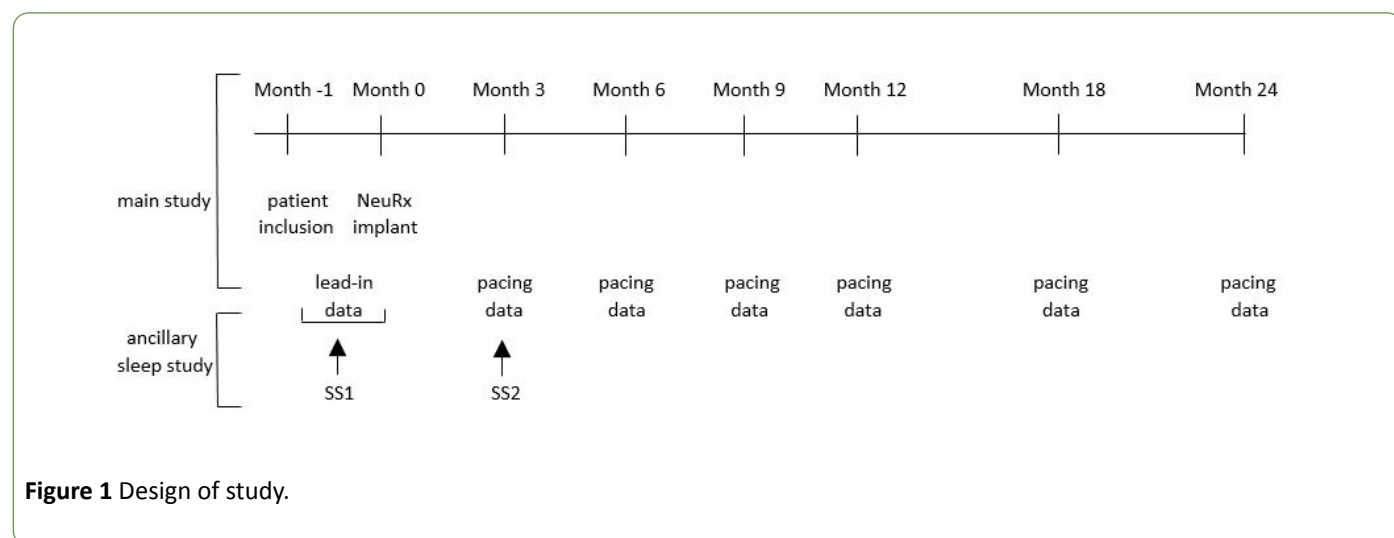
Table 1 Demographics and disease characteristics of patients at inclusion.

No.	Age/Gender	Criteria	Initial symptom	Duration *** (months)	ALSFRS-R	Bulbar score ****	Use of NIV
1	70/F	probable	LMNs* in lower limb	20	33	12	(-)
2	63/M	definite	LMNs* in upper limb	32	42	9	(-)
3	60/M	probable	LMNs in lower limb	26	28	11	Nasal CPAP Cough Assist
4	44/F	probable	UMNs** in lower limb	28	14	6	(-)
5	61/M	definite	LMNs in lower limb	14	43	12	BiPaP

*Lower motor neuron sign; **Upper motor neuron sign; ***Disease duration from the onset to inclusion; ****Mild: 9–12, Moderate: 5–8, Severe: 0–4

The primary study data was collected within one month before implantation. Repeat evaluations were performed 3, 6, 9, 12, 18, 24 months post implant in the main study [6]. Collected data comprised ALS functional rating scale (ALS-FRS-R); spirometric variables including predicted vital capacity (%,

sitting); blood gas; fluoroscopic diaphragm evaluation; tolerance and safety information. These assessments were performed with NIV other than DP turned off. The study design is summarized in **Figure 1**.



For the ancillary sleep study, reported here, one-night laboratory polysomnographic recordings (PSG, Philips Respironics GK, Japan) within 1 month before (SS1) and 6 months of DP (SS2) were performed. At SS1 the sleep study was performed with NIV for those patients using NIV. As SS2 the sleep study was again performed with NIV for those patients using NIV (there was no change in the patients using NIV at SS1 to SS2).

Additionally, DP was used during the PSG for all patients at SS2. Statistical analysis was performed using paired t-test and significance was set up $p < 0.05$. This study was approved by the Review Board of Tokushukai Medical Alliance, and the patients provided written informed consent in accordance with the Declaration of Helsinki before implantation.

Results

4 patients (2 men and 2 women, aged 59.5 ± 11.0 years) completed to evaluate sleep condition because one patient (No. 3) withdrew because he was introduced mechanical ventilation with tracheostomy triggered by an accidental aspiration. All patients met the inclusion criteria for chronic hypoventilation and demonstrated bilateral phrenic nerve function as demonstrated by electrophysiological studies.

The use of DP after 6 months was as follows; frequency 12Hz pulse width 63.1 ± 26.3 μ sec (20 to 80 μ sec), intensity 10 ± 1.6 mA (6 to 11 mA). Neither modification of already administered NIV nor new administration of NIV were observed in a follow up period. Riluzole, a tetrodotoxin-sensitive sodium channels blocker, had been administered for at least three months before the implantation in all patients.

According to the progression of ALS, motor function and vital capacity deteriorated with significance, however, PaCO₂ did not elevate significantly. Regarding sleep condition, total sleep time (TST, min), sleep latency (min), Stages 1-2 duration (% TST), REM sleep duration (% TST), and time spent with SpO₂ under 90% (min) showed no significant difference between the

couple of polysomnographic studies, which indicated that the first-night effect was negative. On the other hand, arousal index (AI, per hour) declined in all patients. In addition, apnea-hypopnea index (AHI, per hour) and wake after sleep onset (WASO, min) declined in 2 patients and was similar in other 2 patients (**Table 2 and Figure 2**).

Table 2 ALSFRS-r, respiratory variables, and sleep condition in before DP (SS1) and after 6 months of DP(SS2).

Variables	SS1(within 1 month before DP)	SS2(6 months after DP)	p-value
ALSFRS-r	34.0 ± 11.6 (18 ~ 43)	22.3 ± 0.7 (14 ~ 31)	0.0353 < 0.05
VC (% pred)	68 ± 11.4 (57.7 ~ 83.4)	29.9 ± 16.2 (7.3 ~ 42.1)	0.0314 < 0.05
PaCO ₂ (mmHg)	37.9 ± 0.7 (37.3 ~ 38.9)	41.7 ± 3.3 (38.0 ~ 45.9)	0.0667
Total sleep time (TST), min	344.6 ± 75.9 (231.5 ~ 393.5)	371.5 ± 40.5 (343.5 ~ 431.0)	0.2549
Wake after sleep onset, min	220.6 ± 108.0 (128.5 ~ 374.0)	144.5 ± 44.0 (86.5 ~ 193.0)	0.1006
Sleep latency, min	36.1 ± 10.2 (26.0 ~ 49.5)	33.4 ± 43.0 (0.0 ~ 96.0)	0.4603
Stages 1-2 duration, % TST	77.7 ± 4.6 (72.0 ~ 83.2)	74.2 ± 8.3 (64.0 ~ 81.3)	0.2201
REM sleep duration, % TST	21.6 ± 5.1 (16.5 ~ 28.0)	25.0 ± 7.9 (18.2 ~ 34.0)	0.2337
Arousal index, per hour	29.4 ± 17.7 (5.8 ~ 48.2)	16.0 ± 11.6 1.9 ~ 30.2)	0.0717
Apnea-hypopnea index, per hour	16.8 ± 12.4 (2.1 ~ 29.0)	6.8 ± 4.6 (2.1 ~ 12.8)	0.1083
Time spent with SpO ₂ <90%, min	1.6 ± 3.1 (0.0 ~ 6.2)	3.9 ± 6.0 (0.0 ~ 12.6)	0.1119

Discussion

This is the first study of the efficacy of DP with NeuRx on sleep condition in ALS patients from Japan. Our study was small; however, our results confirmed the previous research

with a longer period of evaluation [9]. Additionally, this is the first study, worldwide, to beneficial effect of active DP for sleep. The previous research compared sleep before and after diaphragm conditioning, but without DP active during the PSG.

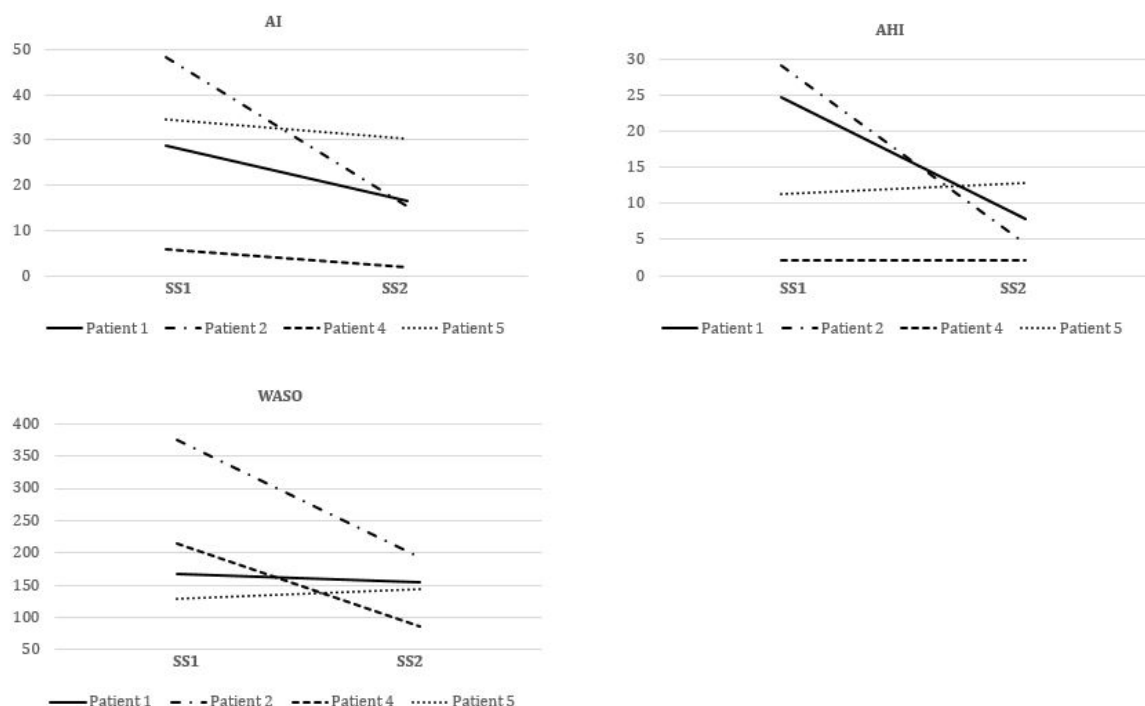


Figure 2 AI, AHI, and WASO before DP (SS1) and after 6 months of DP (SS2).

This study showed a trend toward improvement in sleep with active DP, despite continued progression of ALS. As CO₂ expiration depends mainly on internal intercostal muscles, DP has little relation with CO₂ level and the compensation with respiratory rates might prevent CO₂ accumulation. Therefore, the combination uses of BiPaP and DP may be optimum to prolong the survival.

Based on the results of a multicenter study compared with published historical data for NIV as the control [1], the US food and Drug Administration approved NeuRx for humanitarian device exemption in 2011 [10]. To the contrary, the combination of NIV and DP with NeuRx was less effective than NIV alone for survival in randomized-controlled trial in the UK [11]. Another trial in France showed that DP with NeuRx had no benefit on quality of life and improvement of survival [12].

The heterogeneity of clinical features and course of ALS might influence the different results observed in these clinical trials. In addition, the difference of the percentage of bulbar palsy or definite ALS patients, and the average age between groups could attribute to this discrepancy [11,12]. We have to identify the suitable clinical form of ALS, appropriate timing of introduction, and proper condition of stimulation for DP with NeuRx in future.

Conclusion

DP with NeuRx could prevent worsening of sleep condition at least 6 months from DP. Further investigation should be necessary to identify the optimal target patient of ALS and way of pacing with NeuRx.

Conflicts of Interest

There are no conflicts.

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