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ORIGINAL ARTICLE

A clinical pilot study: High frequency chest wall oscillation airway clearance in patients with amyotrophic lateral sclerosis

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Abstract

Respiratory complications are common in patients with amyotrophic lateral sclerosis (ALS) with respiratory failure representing the most common cause of death. Ineffective airway clearance resultant from deficient cough frequently contributes to these abnormalities. We sought to evaluate the effectiveness of high frequency chest wall oscillation (HFCWO) administered through the Vest^{TM} Airway Clearance System when added to standard care in preventing pulmonary complications and prolonging the time to death in patients with ALS. This is a single center study performed at the Penn State Milton S. Hershey Medical Center (HMC). Nine patients with a diagnosis of ALS and concurrently receiving non-invasive ventilatory support with bi-level positive airway pressure (BiPAP) were recruited from the outpatient clinic at HMC. Four patients were randomized to receive standard care and five patients to receive standard care plus the addition of HFCWO administered twice-daily for 15 min duration. Longitudinal assessments of oxyhemoglobin saturation, forced vital capacity (FVC), and adverse events were obtained until time of death. Pulmonary complications of atelectasis, pneumonia, hospitalization for a respiratory-related abnormality, and tracheostomy with mechanical ventilation were monitored throughout the study duration. No differences were observed between treatment groups in relation to the rate of decline in FVC. The addition of HFCWO airway clearance failed to improve time to death compared to standard treatment alone (340 days +/− 247 vs. 470 days +/− 241; p=0.26). The random allocation of HFCWO airway clearance to patients with ALS concomitantly receiving BiPAP failed to attain any significant clinical benefits in relation to either loss of lung function or mortality. This study does not exclude the potential benefit of HFCWO in select patients with ALS who have coexistent pulmonary diseases, pre-existent mucus-related pulmonary complications, or less severe levels of respiratory muscle weakness.

Key words: *Amyotrophic lateral sclerosis, high frequency chest wall oscillation airway clearance*

Introduction

Amyotrophic lateral sclerosis (ALS) is a chronic, progressive neurological disease process affecting motor neurons located in the cerebral motor cortex, brain stem and spinal cord (1). ALS causes severe and irreversible weakness of functional groups of skeletal muscles, including the respiratory muscles necessary for ventilation and cough. Respiratory complications are common in patients with ALS including atelectasis, pneumonia, hypoxemia, and respiratory failure; the latter complication representing the most common cause of death with a range of survival 2–5 years after diagnosis. Non-invasive ventilatory support with bi-level positive airway pressure (BiPAP) has demonstrated benefit in relieving symptoms of dyspnea and prolonging life in patients with ALS but remains non-curative (2,3).

For any disease process the development of respiratory failure represents an imbalance between the strength and endurance of the respiratory muscles and the requisite work of breathing required to achieve adequate gas exchange. This relationship becomes even more important as neurological disease activity progresses. In patients with neuromuscular disease and involvement of the respiratory muscles, any concomitant pulmonary disorder worsening pulmonary function can severely compromise existent respiratory muscle weakness and precipitate respiratory failure. In fact the development of atelectasis secondary to ineffective airway mucus clearance and retained secretions has been shown to be a direct contributing factor to both respiratory failure and infectious pneumonia in patients with ALS, and the prevention of atelectasis has been reported as a major priority in avoiding respiratory

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failure in patients with various neuromuscular disorders (4,5).

As opposed to clinical states associated with mucus hyper-secretion, mucus related abnormalities in these patients are thought to result from defective airway clearance. Effective cough mechanisms involve multiple coordinated actions of the respiratory system including near maximal inspiration, closure of glottis and contraction of the expiratory muscles on the anterior-lateral wall of the abdomen. All necessary functions are frequently impaired in patients with ALS; although significant impairment of cough effectiveness only becomes evident at severe levels of muscle weakness usually in association with forced vital capacity (FVC) measurements less than 30% predicted normal values (6). Thus any clinical benefit from efforts at improved mucus clearance would be expected to be most prominent at mild to moderate levels of respiratory muscle weakness and a waning of benefit as weakness progresses to severe degrees of impairment (7). Similar clinical evolution has also been demonstrated in relation to non-invasive ventilatory support with BiPAP which nevertheless has proven efficacy in prolonging survival in the disease ALS (2,3).

As disease severity progresses, a number of cough assistance maneuvers and devices are available as assistance in these areas but are designed principally to assist the mechanical aspects of cough efficiency such as cough augmentation techniques and insufflator-exsufflator machines (8). However, cough alone is ineffective in clearing mucus from the more distal peripheral airways where mucociliary function becomes the most important airway clearance mechanism.

High frequency chest wall oscillation (HFCWO) has demonstrated efficacy in assisting mucus clearance in patients with disorders associated with mucus hyper-secretion but preserved muscle function such as cystic fibrosis (CF) (9). HFCWO is an external non-invasive respiratory modality proven effective in mobilizing airway secretions from the small peripheral airways and improving mucus rheology in patients with CF and has become an important modality in the airway clearance techniques (ACT) of this group of patients (10,11). These beneficial effects upon both mucus clearance and clinical parameters are evident in both the outpatient and inpatient settings with durations of HFCWO only 20–30 min per treatment at frequency of only three times per day (12,13). However, the proven value of HFCWO in patients with relatively normal mucus composition and characteristics but neuromuscular weakness is still under investigation, especially as a long-term treatment modality. The Vest^{TM} Airway Clearance System utilizes an inflatable cloth-like vest that covers the entire thorax (front and back) and the upper abdomen (Hill-Rom, Batesville, IN). Vest^{TM} device is inflated to a constant pressure so as to maximize the surface area over which high-frequency (5–20 Hertz [Hz]) small-volume pressure impulses are transmitted externally to the entire chest area. In this study we investigated the potential clinical benefit of the addition of HFCWO to patients with ALS who were concomitantly receiving BiPAP for defined indications in terms of reducing respiratory-related complications and prolonging the time until death. This particular well-defined endpoint was selected because of its extreme clinical relevance and because a belief that avoidance of mucus-related respiratory complications could potentially impact survival (4).

Materials and methods

Patient selection

This study was performed in accordance with the recommendations found in the Helsinki Declaration of 1975 and was approved by the Institutional Review Board (IRB) and Human Subjects Protection Office (HSPO) of the Penn State Milton S. Hershey Medical Center (HMC) (14). Prior to enrollment all patients provided informed consent. Patients were prospectively enrolled from the pool of patients with ALS receiving care at HMC beginning 1 March 2003. Consecutive patients satisfying eligibility criteria were recruited for study participation. Study enrollment was terminated on 1 July 2004, but enrolled patients were continued in follow-up until 18 June 2005. Inclusion and exclusion criteria are detailed in Table I. At the time of enrollment patients were considered clinically stable and without immediate risks for respiratory failure as evidenced by adequate measurements of both FVC and oxyhemoglobin saturation, and were deemed capable of participating with the study-specific therapeutic interventions. Although direct measurements of cough function were not assessed, based upon FVC measurements, respiratory muscle function was projected to be of sufficient strength to attain some degree of cough effectiveness with most FVC measurements greater than 30% predicted (6). In addition all patients were instructed and capable of performing cough augmentation maneuvers. Finally, non-invasive ventilatory support with BiPAP was either already instituted within the previous three months or initiated at time of study enrollment based upon recommendations of clinical practice guidelines and not because of signs or symptoms of respiratory insufficieny (16).

Patient interventions

Randomization was achieved using blind-sealed envelopes. Eligible patients were randomly allocated to receive standard therapy and care or standard

Table I. Patient selection criteria.

Inclusion criteria:
•Adults 18 years of age or older
•Established diagnosis of ALS based upon El Escorial World Federation of Neurology criteria for definite or probable ALS (15)
•Mental capacity to provide informed consent
•Life expectancy greater than three months
•Institution of BiPAP within three months of study enrollment or at time of study visit 1-based upon following objective criteria:
Forced vital capacity (FVC) $<50\%$ predicted
Arterial partial pressure of oxygen (PaO_2) <50mmHg
Arterial partial pressure of carbon dioxide ($PaCO_2$) >45 mmHg
Nocturnal oxyhemoglobin saturation $<88\%$ (either sustained for 5 min or 10% of the monitored time)
Exclusion criteria:
•Dementia or mental/physical incapacity to comply with study requirements
•Head and/or neck injury which has not yet been stabilized
•Active hemorrhage with hemodynamic instability

therapy and care plus initiation of HFCWO using the Vest^{TM} Airway Clearance System (Hill-Rom, Batesville, IN). Vest^{TM} device was fitted according to chest size, delivered to the patient's home, followed shortly by a visit from the company representative/therapist who instructed the patient and care-givers on proper use and directions. External pressure was adjusted to attain tight-secure fit and oscillation frequencies were increased beginning at 5Hz to a maximum of 20Hz as tolerated at recommended 5-min increments. Patients were instructed to utilize the Vest^{TM} device twice daily at a minimum duration of 15 min per treatment. In addition, all enrolled patients received instruction and coaching on cough augmentation maneuvers including breath stacking and abdominal thrust. Following initial orientation and verification of appropriate utilization, no additional compliance evaluations were performed during the course of study participation. However following completion of study, family members of deceased participants were contacted by telephone and asked to estimate HFCWO compliance based upon memory recall.

Patient outcome assessments

The primary outcome measure was the time (survival days) from study enrollment until death. Secondary outcome measures included: forced vital capacity (FVC) measurements, oxyhemoglobin percent saturation measured by digital pulse oximetry, pneumonia, atelectasis, hospitalizations for a respiratory-related abnormality, and requirement for tracheostomy and mechanical ventilation. FVC was measured according to standards and criteria of the American Thoracic Society and percent predicted values as per Knudson et al. (17,18). All study-related assessments were obtained at times of routine clinical care visits approximately once every three months.

Statistical analyses

Data are reported as mean, standard deviation (SD) and range. Statistical analyses were performed using a paired *t*-test for matched variables on an intent-to-treat basis. The log-rank test was used to compare the survival profiles of the two study groups. The analysis was carried out using the PROC LIFETEST application of SAS statistical software version 9.1. A p value less than 0.05 was considered to represent statistically significant differences.

Results

A total of nine patients were recruited and enrolled in this study. Five patients were randomly assigned to standard care plus the addition of HFCWO and four patients were allocated to standard care alone. Eight patients continued study participation until death; one patient in HFCWO treatment group withdrew after 35 days but was included in data analyses until study termination.

Demographic characteristics and physiological variables (FVC and percent oxyhemoglobin saturation) upon study entry are listed in Table II. Patient groups were matched according to gender and pulmonary physiological parameters at study entry. The group of patients receiving both standard therapy plus HFCWO was statistically older than the standard treatment group alone. The preservation of oxyhemoglobin saturations greater than 90% is consistent with the characteristics of the oxygen dissociation curve and previously published clinical results, demonstrating that in the absence of concomitant intrinsic lung disease there was no significant degree of gas exchange abnormalities evident until severe levels of respiratory muscle weakness were present as evidence by FVC measurements consistently less than 30% predicted normal values. (6,19,20–22)

The study was terminated at the time of death of final active-study participant. Eight patients died with death being a study-defined endpoint. No device-related adverse events or study-defined respiratory complications were identified. Eight of nine patients enrolled had at least two longitudinal measurements of FVC over a defined time period to allow calculation of a rate of decline in FVC

Table II. Patient demographic and outcome data.

	Standard Care	Standard Care + HFCWO
Age (years)	53.5+/−6.2 (46–61)	64.0+/−4.6* (57–69)
Male/Female	3/1	4/1
Entry FVC (1)	1.70+/−0.37 (1.37–2.20)	1.93+/−0.83 (1.20–3.28)
Entry FVC (% predicted)	40%+/−8.1% (31%–48%)	47%+/−13.9% (26%–65%)
Entry O_2 % Sat.	96.0%+/−1.8%	94.4%+/−1.9%
Respiratory complications**	None	None
Rate of decline in FVC (ml/day)	3.2+/−2.6 (1.4–7.0)	4.0+/−2.5 (1.8–7.1)
Survival days	470+/−241 (282–821)	340+/−247 (88–737)

Data reported as mean +/− standard deviation (SD) and (range); HFCWO- High frequency chest wall oscillation; FVC- Forced vital capacity; O_2 Sat.- Oxyhemoglobin saturation (measured by digital pulse oximetry); * Statistically significant differences between treatment groups ($p<0.05$); ** Pneumonia, atelectasis, hospitalization for respiratory-related abnormality, and tracheostomy with mechanical ventilation.

(reported as ml/day). Most FVC measurements were obtained relatively early during the course of study participation since as patient clinical status deteriorated, diagnostic tests were obtained less frequently as most patients chose hospice care in a familiar and comforting setting. Although mean value of rate of decline in FVC was greater in patients assigned to standard care plus HFCWO treatment group, these values did not attain statistical significance.

Retrospective data accrual obtained from telephone conversations with family members of four deceased study participants who completed study participation generated estimated HFCWO compliance values based upon memory recall equaling 10%, 50%, 85%, and 90% for each study participant assigned to the HFCWO treatment group.

In relation to the primary outcome measure, the addition of HFCWO using the Vest^{TM} Airway Clearance System failed to improve survival compared to standard care alone (340 days +/− 247 vs. 470 days +/− 241; $p=0.26$).

Discussion

The management of respiratory related abnormalities is a critical component of the overall care of patients with chronic and progressive neuromuscular disorders, including ALS. Dependent upon level of severity and the specific muscle groups affected, a number of respiratory system abnormalities can be anticipated. In addition, respiratory failure remains the most common cause of death (23). Although patients with ALS do not commonly have abnormalities of mucus hyper-secretion, because of reduced cough efficacy they frequently develop complications of mucus retention due to defects in airway clearance. A number of mechanical devices are available to assist in airway mucus clearance with potential clinical benefit for patients with ALS. The Vest^{TM} Airway Clearance System is an external device with proven efficacy in mobilizing retained secretions from the peripheral airways of the lung and improving mucus rheology, both mechanisms highly efficacious in promoting mucus clearance from the respiratory tract. In this study, the addition of Vest^{TM} HFCWO to randomly selected patients with ALS failed to achieve any significant clinical benefits in relation to the primary study endpoint of time to death (survival days). In addition, HFCWO failed to modify the rate of decline in FVC given the progressive nature of this chronic neurodegenerative disease process. No predefined study-respiratory related complications occurred, thus precluding the ability of addition of Vest^{TM} therapy in this study to prevent or reduce the frequency of atelectasis, pneumonia, hospitalization for a respiratory related abnormality, or requirement for tracheostomy and mechanical ventilation. The small number of patients studied may have prevented the identification of differences in study-defined respiratory-related complications. However, the results of this study do not exclude the potential clinical efficacy of the addition of HFCWO to standard care of selective patients with ALS who either have concomitant pulmonary disease, pre-existent mucus-related pulmonary complications or with less severe levels of respiratory muscle weakness.

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