Amyotrophic Lateral Sclerosis. 2009; 10: 384–392

informa
healthcare

ORIGINAL ARTICLE

INSPIRATIonAL – INSPIRAtory muscle training in amyotrophic lateral sclerosis

BENJAMIN C. CHEAH[1,2], ROBERT A. BOLAND[1], NINA E. BRODATY[2], MARGIE C. ZOING[1,2], SANDRA E. JEFFERY[2], DAVID K. MCKENZIE[1,2] & MATTHEW C. KIERNAN[1,2]

[1]*Prince of Wales Medical Research Institute & Prince of Wales Clinical School, University of New South Wales, Sydney, New South Wales, and* [2]*Multi-Disciplinary ALS Clinical Service, Prince of Wales Hospital, Sydney, New South Wales, Australia*

Amyotroph Lateral Scler Downloaded from informahealthcare.com by 94.30.44.221 on 11/20/12
For personal use only.

Abstract

Respiratory impairment, due to respiratory muscle weakness, is a major cause of morbidity and mortality in patients with amyotrophic lateral sclerosis/motor neuron disease (ALS/MND). Threshold loading may strengthen the inspiratory muscles and thereby improve patient prognosis. A phase II, double-blind, randomized-controlled trial was undertaken to determine whether a 12-week inspiratory muscle training programme attenuated the decline in respiratory function and inspiratory muscle strength in patients with ALS/MND. Nine patients were randomized to inspiratory muscle training and 10 to sham training. Primary endpoints were respiratory function (forced vital capacity, vital capacity), lung volumes and inspiratory muscle strength. Patients were assessed before, during and immediately after a 12-week training period, and at eight weeks follow-up. While improvements in inspiratory muscle strength were observed in both treatment arms, there was a non-significant increase in maximum inspiratory pressure of 6.1% in the experimental group compared to controls (standard error of mean, 6.93%; 95% confidence interval −8.58–20.79; $p = 0.39$). The gains in inspiratory muscle strength were partially reversed during a period of training cessation. In conclusion, inspiratory muscle training may potentially strengthen the inspiratory muscles and slow the decline in respiratory function in patients with ALS/MND.

Key words: *Amyotrophic lateral sclerosis, breathing exercises, clinical trial, respiratory function tests, respiratory muscles*

Introduction

Amyotrophic lateral sclerosis (or motor neuron disease; ALS/MND) is a fatal neurodegenerative disease of the human motor system, involving progressive weakness of voluntary muscles. Diagnosis requires evidence of upper and lower motor neuron impairment (1,2). Prognosis is generally poor with 50% of patients surviving up to three years from diagnosis (3,4). Irrespective of the site of disease onset, respiratory muscle weakness culminates in respiratory failure and related pulmonary complications. Non-invasive ventilation remains the best therapy for managing this component of the disease (5).

The role of exercise in ALS/MND has been the subject of great debate, particularly given epidemiological studies that suggested ALS/MND may be triggered by a history of intense physical activity (6). Furthermore, compensatory overuse of surviving muscle groups to preserve function may exacerbate neural dysfunction, and thereby potentially accelerate the loss of motor units (7). On the other hand, promising studies of resistance exercise in ALS/MND patients have suggested that such training is safe and efficacious in reducing the decline in muscle strength (8,9). In addition, aerobic training of ALS/MND patients with non-invasive respiratory support may have a positive impact on global disease progression and respiratory function (10).

Inspiratory muscle training (IMT) has been utilized in patients with chronic obstructive pulmonary disease to improve inspiratory muscle strength and endurance (11), enhance exercise performance (12) and alleviate dyspnoea (13). Similar effects have also been observed in various neurological disorders including myasthaenia gravis (14) and spinal cord injury (15). Studies of IMT in Duchenne muscular dystrophy have demonstrated improvements in inspiratory muscle strength and endurance (16,17). It

Correspondence: M. C. Kiernan, Prince of Wales Medical Research Institute, Barker Street, Randwick, NSW 2031, Australia. Fax: 61 2 93822437. E-mail: m.kiernan@unsw.edu.au

(Received 27 February 2009; accepted 29 May 2009)

ISSN 1748-2968 print/ISSN 1471-180X online © 2009 Informa UK Ltd. (Informa Healthcare, Taylor & Francis AS)
DOI: 10.3109/17482960903082218

RIGHTSLINK

may not seem appropriate, however, to extrapolate these findings to ALS/MND patients, given the different pathophysiology and the more rapid progression of muscle weakness in ALS/MND.

The first study of IMT in six ALS/MND patients reported a non-significant increase in forced vital capacity (FVC) after a three-month training programme (18). A separate study involving eight ALS/MND patients infused with theophylline breathed through a resistive apparatus, noted objective reductions in respiratory muscle fatigue and concomitant increases in inspiratory and expiratory muscle strength (19). Neither of these studies incorporated a control group, thereby relying on measuring within-subject changes, thereby rendering the findings indeterminate. Control groups are clearly warranted, particularly given concerns that intense physical activity may exacerbate weakness in patients with chronic partial denervating disorders (20). Consequently, the present study describes a double-blind, randomized-controlled trial that was undertaken to determine whether IMT was safe and efficacious in improving respiratory function in ALS/MND patients.

Amyotroph Lateral Scler Downloaded from informahealthcare.com by 94.30.44.221 on 11/20/12
For personal use only.

Patients and methods

Eligibility criteria

Patients with a clinical diagnosis of ALS/MND, aged 18–75 years, were eligible for study enrolment (1). Exclusion criteria included tracheostomy ventilation or non-invasive ventilation for greater than 14 h/day, diagnosis of a coexisting respiratory or neurological illness, or history of an unstable medical condition in the preceding three years. Patients were recruited from the multidisciplinary ALS/MND clinical service at the Prince of Wales Hospital, with the study approved by the South-Eastern Sydney Area Health Service Human Research Ethics Committee (Eastern Section). Written informed consent was obtained from all patients who enrolled in this study, and the trial was registered with the Australian New Zealand Clinical Trials Registry (ACTRN012607000258459). The first patient enrolled in the study in February 2007 and the last patient completed the study in February 2008.

Trial endpoints

The primary outcomes comprised measures of respiratory muscle strength and function. Spirometric measures (vital capacity (VC) and forced vital capacity (FVC)) were obtained using standard techniques (21). Lung volumes were determined using whole-body plethysmography (22). All measures of respiratory function were performed in accordance with the American Thoracic Society and European Respiratory Society guidelines (Vmax 22; Sensormedics; Yorba, Linda, California, USA). A flanged rubber mouthpiece was used to overcome the inability of some patients to create a tight lip seal due to facial muscle weakness. Maximum inspiratory pressure (MIP) and maximum expiratory pressure were measured from residual volume and total lung capacity (TLC), respectively (23). Sniff nasal inspiratory pressure (SNIP; MicroRPM; Micromedical, Rochester, Kent, UK) was performed using conventional methodology (24). All pulmonary function data were expressed as percentage predicted values. Given that no internationally accepted guidelines for calculating percentage of predicted values exist, percentage predicted values for SNIP were calculated using previously derived formulae (25). Arterialized blood was sampled from ear-lobe capillaries (ABL77; Radiometer Medical; Copenhagen, Denmark; 26).

Patients were assessed with the ALS/MND Functional Rating Scale-Revised (ALSFRS-R), an established marker of disease progression in ALS/MND (27) that has been used as a primary endpoint in recent ALS/MND treatment trials (28). The Short Form-36 is a self-administered, generic measure of health-related quality of life, sensitive to changes in ALS/MND patient functional status following the initiation of non-invasive ventilation (5). The 6-minute walk test (6MWT) was used to evaluate functional exercise capacity (29), with data only collected from patients who could ambulate (with or without walking aids). Hand-held dynamometry, a reproducible quantitative assessment of grip strength, was assessed using a Jamar dynamometer (Asimow Engineering Co., Los Angeles, CA, USA; 30). Standard nerve conduction studies (Synergy Version 12.0; Viasys Healthcare, Surrey, UK) were obtained from the ulnar nerve, with compound responses recorded from the abductor digiti minimi at all visits to calculate the neurophysiological index, a measure of the number of remaining motor units comprising abductor digiti minimi, as follows (31): neurophysiological index equals compound muscle action potential (mV) multiplied by F-wave frequency, all divided by distal motor latency. the F-wave frequency is supposed to be on the same level as the compound muscle action potential.

Procedures

Randomization and allocation. After completion of baseline assessment, patients were allocated to the experimental (i.e. IMT) or control (i.e. sham IMT) groups using permuted block randomization. A randomization schedule was prepared for 20 patients at the outset of the study by an independent researcher who had no direct contact with the patients. Randomly generated permuted blocks of

RIGHTSLINK

two, four and six were used to allocate 10 patients to each treatment arm (i.e. experimental or control groups). Patients were divided equally between treatment arms within each block. Consecutively numbered opaque envelopes were then prepared and sealed containing group allocation. As each training group was filled, a staff member of the hospital physiotherapy department, independent of the study, randomized patients to the control or experimental groups according to the next envelope in the sequence. The same member of staff then allocated the appropriate IMT device (Threshold IMT, Inspiratory Muscle Trainer; Respironics; Cedar Grove, NJ, USA; Figure 1A) or sham IMT device for each patient.

Investigators and patients were blinded to group allocation (i.e. active vs. sham). Given that all patients had the opportunity to interact with each other during group-training sessions, they were discouraged from discussing their own training experiences to prevent unblinding. To ensure blinding among hospital staff, the widened ends of the IMT devices were covered with duct tape to conceal the spring-loaded valve, which was removed in sham IMT devices.

Trial structure and training programme. Patients commenced the 12-week training programme at the second visit to hospital (Table I). Patients returned to hospital on two further occasions during the 12-week training period and again immediately after the training programme. A follow-up visit was scheduled eight weeks after completion of the training programme to assess the sustainability of the training effect following a period of training cessation (Figure 1B).

The second visit to hospital involved patients receiving uniform instructions on IMT in a personal session with a physiotherapist. All patients (irrespective of group allocation) were instructed to slowly exhale to residual volume, followed by quick inhalation to TLC through the IMT device. Once patients

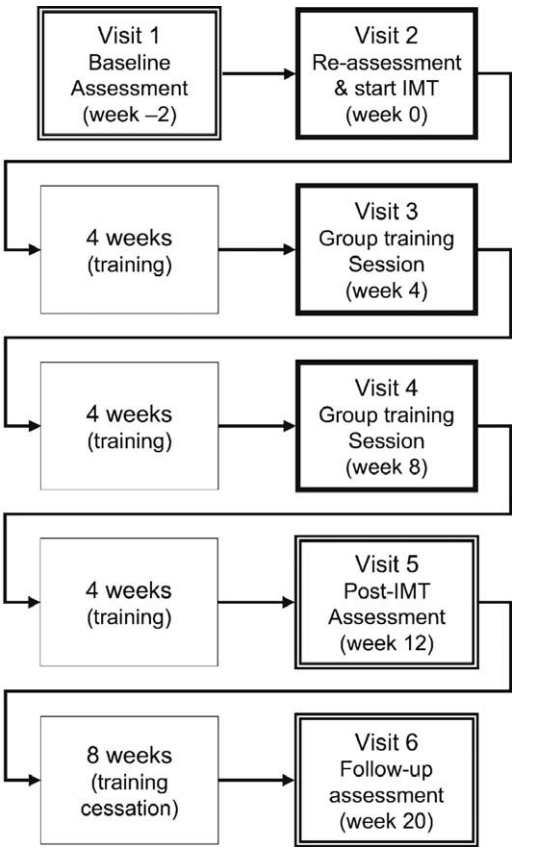

Figure 1. (A) The threshold inspiratory muscle training device used in this study. With the use of a nose clip, the patient inhaled through the mouthpiece (arrowhead) to generate a negative pressure within the plastic cylinder. A spring-loaded valve, located at the top of the device (arrow), opened once the pressure within the cylinder (i.e. mouth pressure) overcame the compression in the spring. The valve opened when mouth pressure ranged from -9 to -41 cm H_2O. The threshold load imposed was set to a percentage of the maximal sniff nasal inspiratory pressure attained by the patient at the second-fourth visits. (B) Flowchart illustrating the trial structure. Patients attended the first visit for baseline assessment. Re-assessment of effort-dependent measures, including maximum inspiratory pressure and sniff nasal inspiratory pressure, were undertaken at the second visit. At the second visit, patients also received instructions on how to use the inspiratory muscle training device and participated in a group-training session. Patients later returned on a four-weekly basis for further re-assessment and participation in two more group-training sessions. Once patients had completed 12 weeks of inspiratory muscle training, they returned to hospital for post-training assessment at the fifth visit. At this visit, patients also returned their training devices to the investigators. Patients returned eight weeks later to assess the effects of training cessation at the sixth visit.

Amyotroph Lateral Scler Downloaded from informahealthcare.com by 94.30.44.221 on 11/20/12
For personal use only.

RIGHTSLINK

Table I. Trial structure illustrating measures collected at each visit.

Endpoint	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6
Respiratory function tests	✓				✓	✓
Whole-body plethysmography	✓				✓	✓
MIP, MEP & SNIP	✓	✓	✓	✓	✓	✓
Ear-lobe capillary blood sampling	✓				✓	✓
6-min walk test	✓				✓	✓
Grip strength	✓				✓	✓
Neurophysiological index		✓	✓	✓	✓	✓
Short Form-36		✓	✓	✓	✓	✓
ALSFRS-R		✓	✓	✓	✓	✓

Definition of abbreviations: ALSFRS-R: Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised; MEP: maximum expiratory pressure; MIP: maximum inspiratory pressure; SNIP: sniff nasal inspiratory pressure.

Amyotroph Lateral Scler Downloaded from informahealthcare.com by 94.30.44.221 on 11/20/12
For personal use only.

understood how to operate the IMT device and completed all necessary respiratory muscle strength testing, they participated in group-training sessions, lasting 10 min. At the end of the second visit to hospital, patients were instructed to continue training at home for 10 min, three times a day, seven days a week, for 12 weeks. The third and fourth visits to hospital also concluded with group-training sessions.

The IMT device was initially set to 15% of the maximal SNIP obtained at the patient's second visit to hospital. The setting was subsequently increased to 30%, 45% and 60% of the maximal SNIP at the beginning of the second, third, and fourth weeks of training, respectively. Thereafter, the SNIP measurements were repeated and the device setting was re-adjusted to 60% of the value obtained at each subsequent visit (i.e. the third and fourth visits; the device setting increased or decreased, depending on the maximal SNIP value). The maximum threshold load of 60% SNIP used in the present study was derived from the use of high-intensity IMT in patients with chronic obstructive pulmonary disease in a separate study (12). If 60% of maximal SNIP exceeded the maximum opening pressure of the standard IMT device (i.e. -40 cm H_2O), the patient was provided with a modified device. This involved replacing the internal spring with a less compliant device, as previously reported by Hill et al. (9). The modified IMT devices were subsequently re-calibrated by connecting them to a pneumotachometer (Hans Rudolph, Kansas City, MO, USA) and a pressure transducer proximal to the device (range ± 200 cm H_2O). The pressure at which the internal valve opened was determined at onset of airflow through the device at four different settings. Signals were sampled to a computer (Spike2, CED, Cambridge, UK) for subsequent measurement. A linear relationship was established between these results and the numerical settings on the device. Consequently, a graph was generated and the settings on the modified devices were adjusted accordingly. Patients continued training with the modified IMT devices at the appropriate setting.

The sham IMT devices were created by removing the spring-loaded valves from original IMT devices. If a patient in the control group had a maximum SNIP that was high enough to warrant the use of a modified device, the internal valve was removed after the new spring had been inserted and the IMT device recalibrated.

Compliance. All patients were assigned training diaries to monitor compliance, which was defined as the amount of time spent training (in minutes) over the 12-week period divided by the maximum amount of time a patient could have spent training over the training programme (i.e. 2520 minute). The principal investigator contacted all patients by telephone on a weekly basis to promote compliance and address any issues regarding the training programme. IMT devices were returned to the investigators when patients returned to hospital for post-training assessment (i.e. visit 5) to ensure that patients were unable to train during the period of training cessation.

Statistical analysis

All endpoints were analysed by intention-to-treat. Missing values were imputed using the 'last observation carried forward' approach. An observer independent of data collection and patient interaction performed statistical analysis on de-identified data using repeated measures analysis of covariance. The analysis adjusted for baseline values, reducing the variance of the data and increasing study power. A repeated measures analysis was conducted in preference to separate hypothesis tests to compare between-group differences at each study visit because it is associated with a lower type 1 error. Statistical analyses were performed using SPSS for Windows (release 15.0; SPSS Inc., Chicago, IL, USA). Given the novelty and exploratory nature of this study, it was not possible to calculate the sample size required a priori. Results are presented as mean $\pm$ SEM (standard error of mean), unless otherwise specified.

RIGHTSLINK

Results

Of 37 consecutive patients who were eligible for trial enrolment, 19 agreed to participate in the study (Figure 2). The main reason for patients declining involvement in the trial related to difficulties with attending hospital on six occasions. The baseline demographics of each group are summarized in Table II. All patients were referred to a specialized multidisciplinary ALS/MND clinic, and reflected a range of clinical phenotypes. Compliance with the training regimen was high (experimental group, 81.7 ± 28.0%; control group, 85.2 ± 24.9%; mean ± SD). Forty-one protocol violations occurred over the trial. These consisted of seven visits not completed on the scheduled date (6.1%), 33 measures not performed due to physical disability (3.9%), and two missed visits (1.8%). One patient died soon after completion of the training period. The cause of death was ill defined, as this patient complained of chest pain before dying in her sleep. There were no serious adverse effects reported by patients. A single patient was prescribed non-invasive ventilation prior to commencing the clinical trial due to symptoms of nocturnal hypoventilation. During participation in the trial, this patient did not develop dyspnoea. This patient was randomized to the experimental group (Table II) and tolerated IMT.

Primary endpoints

There was an overall trend for improvement in respiratory function in the experimental group, with a mean difference in FVC of 4.59 ± 3.02% (95% CI −1.85–11.02; $p = 0.15$). Accordingly, mean VC was higher in the experimental group than in the control group (1.44%; 95% CI −4.24–7.13; $p = 0.60$). Consistent with the natural history of ALS/MND, VC decreased significantly over the period of training cessation by 3.03 ± 1.34% (95% CI 0.18–5.89; $p < 0.05$) in both treatment arms. Whole-body plethysmography extended a non-significant difference between mean TLC in the experimental compared to the control group of 7.93 ± 4.66% (95% CI −2.07–17.93; $p = 0.11$) over the duration of the clinical trial (Figure 3A). There

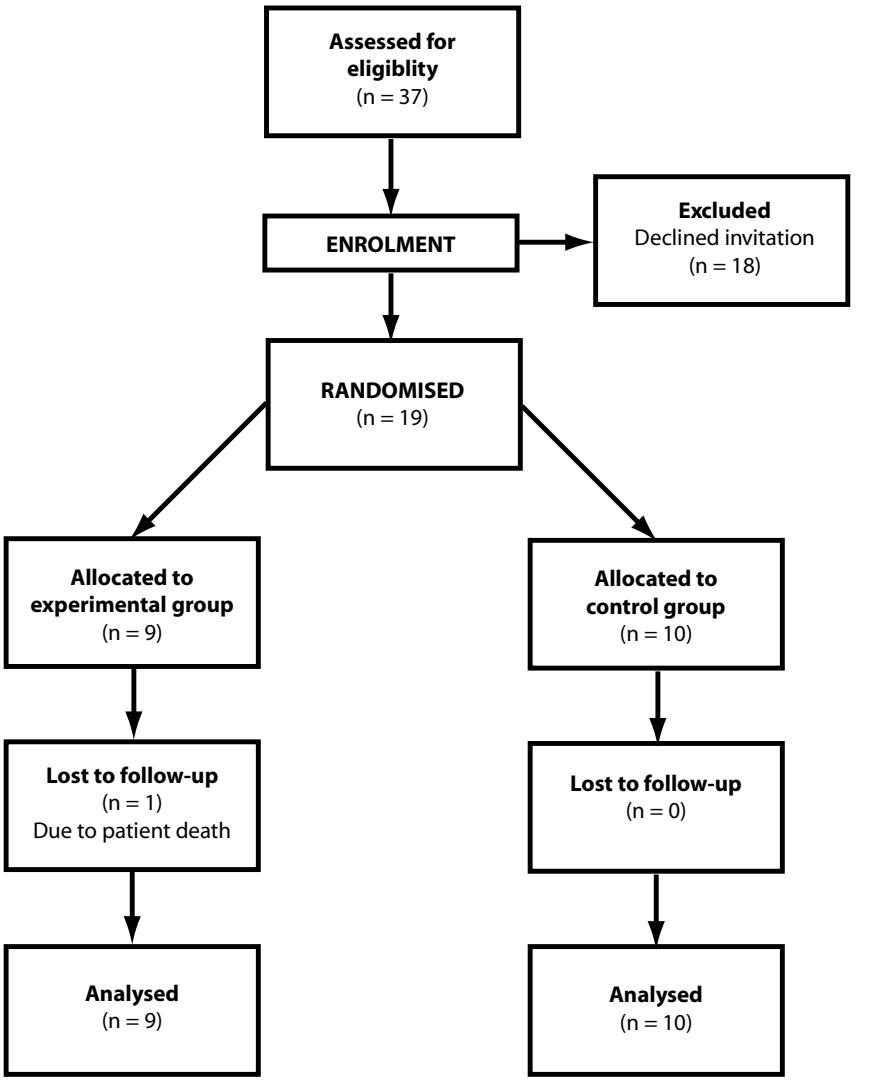

Figure 2. Flow chart illustrating the movement of patients through the clinical trial.

Amyotroph Lateral Scler Downloaded from informahealthcare.com by 94.30.44.221 on 11/20/12
For personal use only.

RIGHTSLINK

Table II. Summary of baseline characteristics of each treatment arm.

Characteristic	Experimental group ($n=9$)	Control group ($n=10$)	p-value
Males (females)	6 (3)	6 (4)	0.76
Age (years; mean ± SD)	54.2 ± 9.8	53.4 ± 9.5	0.85
Diagnosis	ALS (6), PBP (1), PLS (2)	ALS (9), PLS (1)	0.47
Disease duration (months; mean ± SD)	29.8 ± 15.7	34.6 ± 33.8	0.69
Site of disease onset	Limb (7), Bulbar (2)	Limb (9), Bulbar (1)	0.47
Bulbar involvement	7	5	0.21
Use of riluzole	8	9	0.94
ALSFRS-R (mean ± SD)	38.2 ± 6.5	38.9 ± 2.7	0.62
Use of non-invasive ventilation	1	0	0.28
Forced vital capacity	85.8 ± 20.2	83.6 ± 16.7	0.86
Vital capacity (% predicted; mean ± SD)	83.8 ± 18.1	80.3 ± 15.2	0.64
Sniff nasal inspiratory pressure (% predicted; mean ± SD)	78.5 ± 35.6	78.0 ± 9.3	0.85
Maximum inspiratory pressure (% predicted; mean ± SD)	81.3 ± 35.2	70.6 ± 29.0	0.71

Definition of abbreviations: ALS: amyotrophic lateral sclerosis; ALSFRS-R: Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised; PBP: progressive bulbar palsy; PLS: primary lateral sclerosis; SD: standard deviation.

Amyotroph Lateral Scler Downloaded from informahealthcare.com by 94.30.44.221 on 11/20/12
For personal use only.

was little change in TLC (0.40 ± 1.06%; 95% CI −1.87–2.67; $p=0.71$) over the period of training cessation. In contrast, TLC declined progressively in the control group throughout the study period.

Improvements in inspiratory muscle strength were observed in both treatment arms over the training period, although the effect was less marked in the control group. This magnitude of effect was more pronounced on MIP testing, which although non-significant, was 6.10 ± 6.93% greater in the experimental group than the control group (95% CI −8.58–20.79; $p=0.39$). Inspiratory muscle strength subsequently declined following withdrawal of the training device in both treatment arms (SNIP: 6.55 ± 1.88%; 95% CI 2.55 −10.54; $p<0.05$; MIP: 4.53 ± 2.15%; 95% CI −0.03–9.08, $p=0.05$), although the values obtained at the end of the study still remained above baseline levels (Figure IIIB). Maximum expiratory pressure was similar over the whole study in both treatment arms (mean difference, 1.13 ± 3.33%; 95% CI −6.07–8.34; $p=0.74$). As may be expected, the decline in maximum expiratory pressure continued over the period of training cessation (4.30 ± 1.52%; 95% CI 1.02 −7.59; $p<0.05$). In terms of metabolic and biochemical parameters, there were no significant differences between treatment arms in pH (mean difference, −0.01 ± 0.01; 95% CI −0.03–0.02; $p=0.44$), capillary oxygen saturation (mean difference, −0.84 ± 1.17; 95% CI −3.34–1.67; $p=0.49$), partial pressure of oxygen (mean difference, 1.11 ± 4.22; 95% CI −7.87 –10.10; $p=0.80$), partial pressure of carbon dioxide

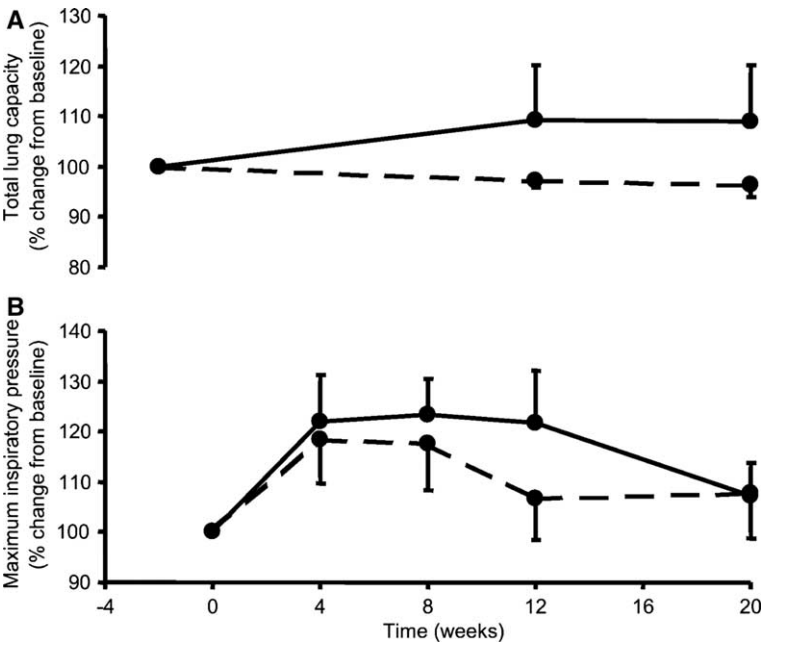

Figure 3. (A) Total lung capacity versus time. (B) Maximum inspiratory pressure versus time. Note that the x-axis begins at week −2, because patients underwent whole-body plethysmography at the first visit, which occurred, on average, two weeks prior to the first training session (or second visit; at week 0, i.e. inspiratory muscle training took place between weeks 0 and 12). The continuous lines represent the experimental group; the dotted lines represent the control group. Error bars denote the standard error of mean.

RIGHTSLINK

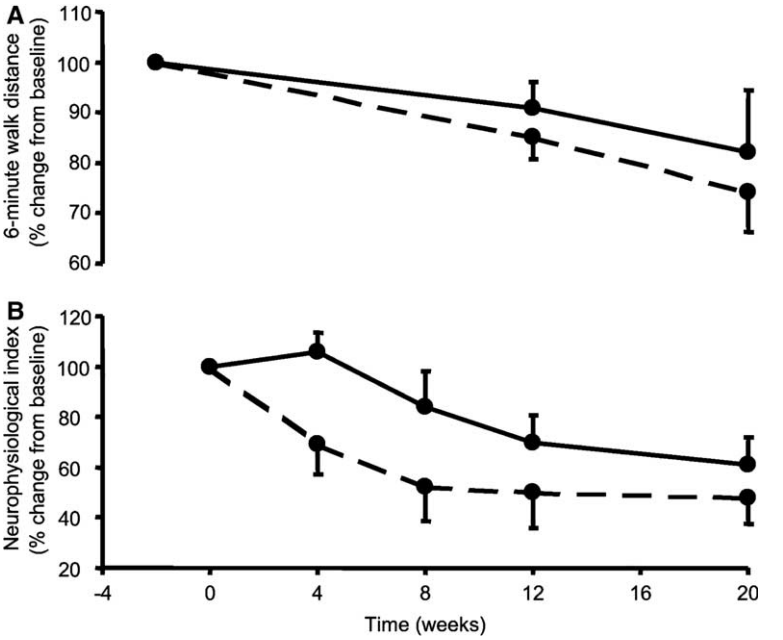

Figure 4. (A) 6-min walk distance versus time. (B) Neurophysiological index versus time. Note that the *x*-axis begins at week −2, because the 6-min walk test was administered at the first visit, which occurred, on average, two weeks prior to the first training session (or second visit; at week 0, i.e. inspiratory muscle training took place between weeks 0 and 12). The continuous lines represent the experimental group; the dotted lines represent the control group. Error bars denote the standard error of mean.

Amyotroph Lateral Scler Downloaded from informahealthcare.com by 94.30.44.221 on 11/20/12
For personal use only.

(mean difference, 1.27±3.76; 95% CI −9.29 –6.76; $p=0.74$), and bicarbonate levels (mean difference, 0.84±1.11; 95% CI −1.53–3.21; $p=0.46$).

Secondary endpoints

There were no significant differences in the psychological components of the Short Form-36 between treatment arms: mental component summary (mean difference, −0.01±0.01; 95% CI −0.03 −0.02; $p=0.44$), role emotional (i.e. role limitations because of emotional problems; mean difference, −1.27±3.76; 95% CI −0.29 −6.76; $p=0.74$), mental health (−0.84±1.17; 95% CI −0.29 −6.76; $p=0.49$), vitality (mean difference, 2.46± 5.89; 95% CI −9.39 −14.30; $p=0.67$) and social functioning scores (mean difference, −1.03±1.29; 95% CI −3.79 −1.73; $p=0.44$).

Total ALSFRS-R declined over the entire study period for both treatment arms. There was little difference between the experimental and control groups in total ALSFRS-R (mean difference between experimental and control groups, 0.04±0.73; 95% CI −1.51–1.60; $p=0.95$). While performance in the 6MWT was grossly below normal in both treatment arms at baseline and declined at a linear rate over the study, patients in the experimental group walked comparatively further than those in the control group at the fifth and sixth visits (mean difference in the distance walked, 6.00±3.61%; 95% CI −1.80 –13.80; $p=0.12$; Figure 4A). Neurophysiological index (Figure 4B) and grip strength demonstrated linear decline over the trial in both treatment arms. Although results did not reach statistical significance, both neurophysiological index (0.24±0.26 units; 95% CI −0.30–0.79; $p=0.36$) and grip strength (1.48±1.24 kg; 95% CI −1.15–4.10; $p=0.25$) were consistently higher in the experimental group than in the control group over the entire study. These combined findings suggest that patients in the experimental group may have deteriorated at a slower rate than controls. Muscle weakness (1.86±0.55 kg reduction in grip strength; 95% CI 0.70 −3.03; $p<0.01$) and lower motor neuron dysfunction (0.19±0.11 reduction in neurophysiological index; 95% CI −0.04 −0.42; $p=0.09$) progressed over the period of training cessation. Accordingly, patient functional exercise capacity also declined during the eight-week period of training cessation (3.62% reduction in distance walked during 6MWT; 95% CI 0.97–6.26; $p=0.01$).

Discussion

The present clinical trial is the first to evaluate the effects of IMT in ALS/MND patients in the context of a double-blind, randomized-controlled trial. Consistent trends for improvement were demonstrated across all respiratory parameters over multiple occasions (i.e. FVC, VC, TLC, MIP and SNIP). Measures of respiratory function suggested that IMT may have partially ameliorated the restrictive defect that develops in ALS/MND. In addition, measures of inspiratory muscle strength suggested that IMT was efficacious in strengthening the inspiratory muscles. As such, the results of the present trial would tend to support the hypothesis that despite an environment of ongoing denervation, the inspiratory muscles of ALS/MND patients

RIGHTSLINK

are capable of responding favourably to a strength-training programme.

Prior to interpreting findings from the present study, a potential limitation was that the sham training protocol may have compromised study power, given that patients in the control group also demonstrated improvements in inspiratory muscle strength over the first eight weeks of the training programme. Of relevance, a previous study of IMT in healthy volunteers established that repeated inhalations to TLC and holding for 10 s was sufficient to strengthen the inspiratory muscles and significantly increase VC (32). The fact that MIP in the control group returned to baseline levels over the last four weeks of the training period indicates that although sham training was efficacious in strengthening the inspiratory muscles, it alone was a weaker training stimulus than training with an active IMT device.

Another potential limitation of the present study was the involvement of patients with normal baseline levels of respiratory muscle strength. Although the inclusion of such patients may seem to have hindered the interpretability of the results of this study, sub-clinical respiratory muscle involvement was, in retrospect, clearly present in most patients who demonstrated apparently normal respiratory muscle strength at the commencement of the clinical trial. Although needle electromyography of the diaphragm was considered to confirm respiratory muscle involvement, invasive testing was deferred on the basis that it was not standard practice and potentially may have deterred patients from participating in this trial. Given that the aim of the present study was to provide preliminary evidence that IMT was safe and efficacious in ALS/MND, the inclusion of such patients would seem justified.

In terms of assessing the effectiveness of blinding in this study, it became evident to investigators during the study that the noise made by performing IMT and sham IMT was different. Patients in this study, however, remained oblivious to their group allocation. As such, given the exploratory nature of the INSPIRATIonAL trial, the difficulty in maintaining adequate investigator blinding would not be considered a serious methodological flaw.

Separately, it is unlikely that the changes observed in the present study were attributable to a learning effect, given that patients were instructed to perform maximally during respiratory muscle strength testing at both baseline visits (i.e. visits 1 and 2). Furthermore, the methodologies employed in the present study were validated in the original studies (21,22,23,25). In combination, these measures ensured that a learning effect did not bias the outcomes of this study.

Nardin et al. recently completed a study of diaphragmatic training in 10 ALS/MND patients with respiratory impairment, with the aim to strengthen inspiratory muscles (33). Instead of using an IMT device, patients in that study engaged in diaphragmatic training, a breathing technique that required conscious awareness of diaphragmatic contractions. Although the results of the study were largely non-significant, patients who successfully engaged in diaphragmatic training demonstrated a trend towards reduced rates of decline in FVC. In addition to the presence of a control group and more comprehensive respiratory muscle strength evaluation, the present study has methodological advantages over the study conducted by Nardin et al. The use of a training device in the present study enabled patients to conceptualize the performance of IMT and thus successfully perform training with high levels of compliance. By contrast, only 40% of patients enrolled in the study conducted by Nardin et al. could master diaphragmatic training. This discrepancy between both studies highlights the importance of simple IMT techniques.

Conclusions

In total, findings from the present study would tend to suggest that a 12-week IMT programme has the potential to strengthen the inspiratory muscles and delay progression of the restrictive defect in ALS/MND patients. However, these findings should not be over-interpreted due to the small sample size, the likelihood of a sham training effect and the short training period. Given the potential benefits of IMT in ALS/MND patients suggested in the present study, a phase III clinical trial has recently commenced (www.anzctr.org.au; ANZCTRN12608000238370). Data collected from the present study and the investigators' experiences with IMT have played an important role in the design and execution of the phase III trial.

Acknowledgements

The assistance of Jane Butler and Anna Hudson from the Prince of Wales Medical Research Institute for re-calibrating the modified IMT devices, and Renae Macnamara for input into the study design and assistance with manuscript preparation are gratefully acknowledged. Finally, the authors would like to acknowledge all ALS/MND patients who participated in this trial.

This trial was an investigator-driven study with support from the Australian Rotary Health Research Fund (Mary Jane Douglas Award). Benjamin Cheah was awarded the University of New South Wales BrainSciences PhD scholarship.

Competing interests

The manufacturers of the training device and custom-made springs played no role in financing this project, nor were they involved in the study design, data analysis, data interpretation or preparation of this report.

Amyotroph Lateral Scler Downloaded from informahealthcare.com by 94.30.44.221 on 11/20/12
For personal use only.

RIGHTSLINK

References

1. Brooks BR, Miller RG, Swash M. Munsat TL: World Federation of Neurology Research Group on Motor Neuron Diseases. El Escorial revisited: revised criteria for the diagnosis of amyotrophic lateral sclerosis. Amyotroph Lateral Scler Other Motor Neuron Disord. 2000;1:293–9.
2. Vucic S, Burke D, Kiernan MC. In: Kiernan MC, editor. The Motor Neurone Disease Handbook. Sydney: Australasian Medical Publishing Company Limited, 2007. p. 89–104.
3. Kiernan MC. Motor neuron disease: a Pandora's box. Med J Aust. 2003;178:311–2.
4. Winhammar JMC, Rowe DB, Henderson RD, Kiernan MC. Assessment of disease progression in motor neuron disease. Lancet Neurol. 2005;4:229–38.
5. Bourke SC, Tomlinson M, Williams TL, Bullock RE, Shaw PJ, Gibson GJ. Effects of non-invasive ventilation on survival and quality of life in patients with amyotrophic lateral sclerosis: a randomized controlled trial. Lancet Neurol. 2006;5:140–7.
6. Chio A, Benzi G, Dossena M, Mutani R, Mora G. Severely increased risk of amyotrophic lateral sclerosis among Italian professional football players. Brain. 2005;128:472–6.
7. Vucic S, Krishnan AV, Kiernan MC. Fatigue and activity dependent changes in axonal excitability in amyotrophic lateral sclerosis. J Neurol Neurosurg Psychiatry. 2007;78: 1202–8.
8. Drory VE, Goltsman E, Reznik JG, Mosek A, Korczyn AD. The value of muscle exercise in patients with amyotrophic lateral sclerosis. J Neurol Sci. 2001;191:133–7.
9. Bello-Haas VD, Florence JM, Kloos AD, Scheirbecker J, Lopate G, Hayes SM, et al. A randomized controlled trial of resistance exercise in individuals with ALS. Neurology. 2007;68:2003–7.
10. Pinto AC, Alves M, Nogueira A, Evangelista T, Carvalho J, Coelho A, et al. Can amyotrophic lateral sclerosis patients with respiratory insufficiency exercise? J Neurol Sci. 1999;169:69–75.
11. Lotters F, van Tol B, Kwakkel G, Gosselink R. Effects of controlled inspiratory muscle training in patients with COPD: a meta-analysis. Eur Respir J. 2002;20:570–6.
12. Hill K, Jenkins SC, Philippe DL, Cecins N, Shepherd KL, Green DJ, et al. High-intensity inspiratory muscle training in COPD. Eur Respir J. 2006;27:1119–28.
13. Harver A, Mahler DA, Daubenspeck JA. Targeted inspiratory muscle training improves respiratory muscle function and reduces dyspnoea in patients with chronic obstructive pulmonary disease. Ann Intern Med. 1989;111:117–24.
14. Fregonezi GA, Resqueti VR, Guell R, Pradas J, Casan P. Effects of eight-week, interval-based inspiratory muscle training and breathing retraining in patients with generalized myasthaenia gravis. Chest. 2005;128:1524–30.
15. Liaw MY, Lin MC, Cheng PT, Wong MK, Tang FT. Resistive inspiratory muscle training: its effectiveness in patients with acute complete cervical cord injury. Arch Phys Med Rehabil. 2000;81:752–6.
16. Koessler W, Wanke T, Winkler G, Nader A, Toifl K, Kurz H, et al. Two years' experience with inspiratory muscle training in patients with neuromuscular disorders. Chest. 2001;120: 765–9.
17. Gozal D, Thiriet P. Respiratory muscle training in neuromuscular disease: long-term effects on strength and load perception. Med Sci Sports Exerc. 1999;31:1522–7.
18. Gross D, Meiner Z. The effect of ventilatory muscle training on respiratory function and capacity in ambulatory and bedridden patients with neuromuscular disease. Monaldi Arch Chest Dis. 1993;48:322–6.
19. Schiffman PL, Belsh JM. Effect of inspiratory resistance and theophylline on respiratory muscle strength in patients with amyotrophic lateral sclerosis. Am Rev Respir Dis. 1989;139: 1418–23.
20. Bennett RL, Knowlton GC. Overwork weakness in partially denervated skeletal muscle. Clin Orthop. 1958;12:22–9.
21. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardization of spirometry. Eur Respir J. 2005;26:319–38.
22. Wanger J, Clausen JL, Coates A, Pedersen OF, Brusasco V, Burgos F, et al. Standardization of the measurement of lung volumes. Eur Respir J. 2005;26:511–22.
23. Black LF, Hyatt RE. Maximal respiratory pressures: normal values and relationship to age and sex. Am Rev Respir Dis. 1969;99:696–702.
24. Fitting JW, Paillex R, Hirt L, Aebischer P, Schluep M. Sniff nasal pressure: a sensitive respiratory test to assess progression of amyotrophic lateral sclerosis. Ann Neurol. 1999;46: 887–93.
25. Uldry C, Fitting JW. Maximal values of sniff nasal inspiratory pressure in healthy subjects. Thorax. 1995;50:371–5.
26. Pitkin AD, Roberts CM, Wedzicha JA. Arterialized earlobe blood gas analysis: an underused technique. Thorax. 1994;49:364–6.
27. Cedarbaum JM, Stambler N, Malta E, Fuller C, Hilt D, Thurmond B, et al. The ALSFRS-R: a revised ALS functional rating scale that incorporates assessments of respiratory function. BDNF ALS study group (phase III). J Neurol Sci. 1999;169:13–21.
28. Bhatt JM, Gordon PH. Current clinical trials in amyotrophic lateral sclerosis. Expert Opin Investig Drugs. 2007;16: 1197–207.
29. Butland RJ, Pang J, Gross ER, Woodcock AA, Geddes DM. Two-, six-, and 12-min walking tests in respiratory disease. Br Med J (Clin Res Ed). 1982;284:1607–8.
30. Goonetilleke A, Modarres-Sadeghi H, Guiloff RJ. Accuracy, reproducibility, and variability of hand-held dynamometry in motor neuron disease. J Neurol Neurosurg Psychiatry. 1994;57:326–32.
31. de Carvalho M, Swash M. Nerve conduction studies in amyotrophic lateral sclerosis. Muscle Nerve. 2000;23: 344–52.
32. Fanta CH, Leith DE, Brown R. Maximal shortening of inspiratory muscles: effect of training. J Appl Physiol. 1983;54:1618–23.
33. Nardin R, O'Donnell C, Loring SH, Nie R, Hembre K, Walsh J, et al. Diaphragm training in amyotrophic lateral sclerosis. J Clin Neuromuscul Dis. 2008;10:56–60.

Amyotroph Lateral Scler Downloaded from informahealthcare.com by 94.30.44.221 on 11/20/12
For personal use only.

RIGHTSLINK