A randomized controlled trial of resistance exercise in individuals with ALS

V. Dal Bello-Haas, PT, PhD
J.M. Florence, PT, DPT
A.D. Kloos, PT, PhD, NCS
J. Scheirbecker, MPT
G. Lopate, MD
S.M. Hayes, PT, MS
E.P. Pioro, MD, PhD, FRCPC
H. Mitsumoto, MD, DSc

Address correspondence and reprint requests to Dr. V. Dal Bello-Haas, School of Physical Therapy, University of Saskatchewan, 1121 College Dr., Saskatoon, SK, Canada S7N 0W3
vanina.dalbello-haas@usask.ca

ABSTRACT **Objective:** To determine the effects of resistance exercise on function, fatigue, and quality of life in individuals with ALS. **Methods:** Subjects with a diagnosis of clinically definite, probable, or laboratory-supported ALS, forced vital capacity (FVC) of 90% predicted or greater, and an ALS Functional Rating Scale (ALSFRS) score of 30 or greater were randomly assigned to a resistance exercise group that received a home exercise program consisting of daily stretching and resistance exercises three times weekly or to a usual care group, who performed only the daily stretching exercises. ALSFRS, the Fatigue Severity Scale (FSS), and Short Form-36 (SF-36) were completed at baseline and monthly for 6 months. FVC and maximum voluntary isometric contraction (MVIC) were monitored monthly throughout the study. **Results:** Of 33 subjects screened, 27 were randomly assigned (resistance = 13; usual care = 14). Eight resistance exercise subjects and 10 usual care subjects completed the trial. At 6 months, the resistance exercise group had significantly higher ALSFRS and SF-36 physical function subscale scores. No adverse events related to the intervention occurred, MVIC and FVC indicated no negative effects, and less decline in leg strength measured by MVIC was found in the resistance exercise group. **Conclusion:** Our study, although small, showed that the resistance exercise group had significantly better function, as measured by total ALS Functional Rating Scale and upper and lower extremity subscale scores, and quality of life without adverse effects as compared with subjects receiving usual care. **NEUROLOGY 2007;68:2003-2007**

ALS is a rapidly progressive neurodegenerative disease with an unknown etiology, except in the small number of cases caused by a mutation in the Cu/Zn superoxide dismutase gene. In more than 70% of patients, the presenting symptom is focal upper (U/E) or lower extremity (L/E) muscle weakness.[1] The role of exercise in people with ALS has been controversial, and the possibility of inducing overwork damage through excessive exercise or strengthening exercises is a concern. Highly repetitive or heavy resistance exercise can cause prolonged loss of strength in weakened or denervated muscle,[2,3] and some epidemiologic data have shown a higher incidence of ALS in individuals performing intense work or leisure physical activity before disease onset.[4,5,6] A rise in creatine kinase has been linked to strenuous exercise in patients with muscular dystrophy or chronically denervated muscles,[7] suggesting that weakened muscle fibers may degenerate with excessive exercise. Excessive exercise may also impair recovery of degenerated muscle fiber, and animal studies suggest muscle fiber degeneration may exacerbate motor neuron denervation.[7]

Two early case studies reported resistance exercises had positive effects in people with ALS,[8,9] and significantly less decline in ALS Functional Rating Scale (ALSFRS) and Ashworth Spasticity Scale scores was found in patients who engaged in a 15-minute, twice-daily exercise program consisting of "moderate range of motion training" designed "to improve muscle endurance."[10] More recent animal findings suggest that high-intensity endurance exercise may be detrimental, whereas low- or moderate-intensity endurance exercise may be of some benefit.[11-13]

Supplemental data at www.neurology.org

With the dearth of controlled studies, the effects of resistance exercise are not well under-

From the School of Physical Therapy (V.D.B.-H.), University of Saskatchewan, Saskatoon, Canada; and Department of Neurology (J.M.F., J.S., G.L.), Washington University School of Medicine, St. Louis, MO, Division of Physical Therapy (A.D.K.), Ohio State University, Columbus, Department of Neurology (S.M.H.) and Eleanor and Lou Gehrig MDA/ALS Research Center (H.M.), Neurological Institute, Columbia University, New York, and Department of Neurology (E.P.P.), Cleveland Clinic, OH.

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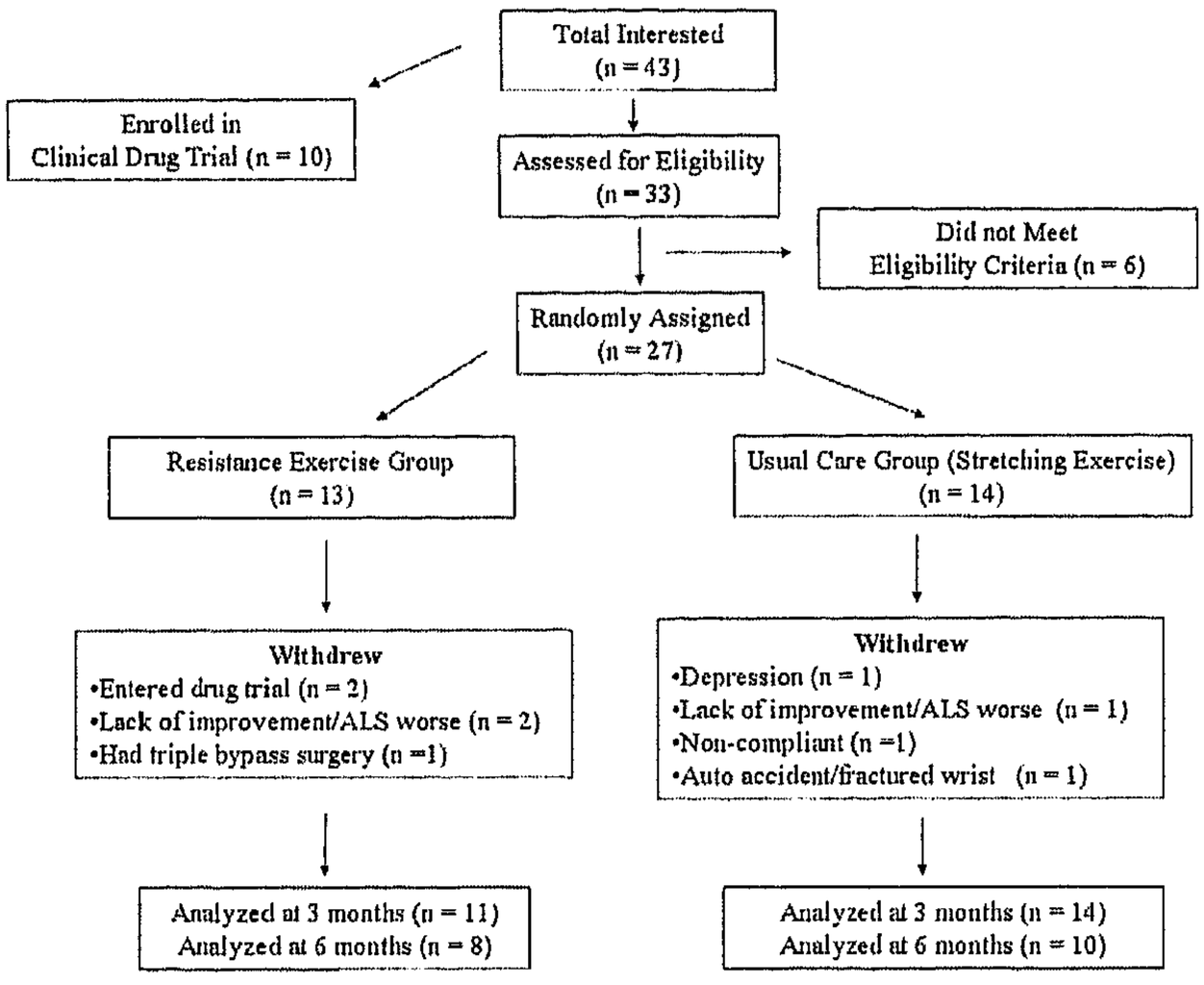
Figure Flow of participants through each trial stage



Shown are numbers of subjects who were screened, enrolled in study, randomized, dropped out of the study, and analyzed.

stood in this population, and whether exercise is beneficial or detrimental in patients with ALS remains unsolved. We conducted a controlled trial of resistance exercises in patients with early-stage ALS and compared them with patients receiving usual care (stretching exercises).

METHODS We conducted a 6-month, parallel-group, randomized study of adults with early stage ALS. A detailed description of the study procedures is found in appendix E-1 on the *Neurology* Web site (www.neurology.org). The study protocol was approved by the institutional review boards of the participating institutions, and all subjects provided written informed consent.

Initial statistical analysis consultation determined that 20 subjects per group were needed to determine with 95% confidence that a within-group population SD was no more than 1.4 times the observed sample SD. The study was stopped prior to reaching this target because of the difficulty in finding participants who met the inclusion criteria. In particular, the increasing availability of ALS pharmaceutical trials made recruiting for this study problematic.

Twenty-seven eligible, consecutive subjects were randomly assigned, by selecting an opaque envelope that contained group assignment, to either the resistance exercise group or the usual care (stretching exercise) group, which served as the control (figure). Participants were prescribed an exercise program by a research physical therapist who was unblinded to group assignment. Subjects in the usual care group received a program consisting of once-daily U/E and L/E stretching exercises. Subjects in the resistance exercise group were also given the stretching exercise program, and in addition, each subject was prescribed an individualized U/E and L/E moderate-load and moderate-intensity resistance exercise program. Resistance exercise protocols were developed according to patient tolerance and limitations. For example, if the subject could not move the limb through available range of motion against gravity (e.g., muscle strength grade less than 3), no exercise was prescribed for that muscle group. Compliance and adverse effects were monitored throughout the study period.

Subjects were assessed at baseline and monthly thereafter for 6 months. All monthly evaluations were performed by a second research physical therapist who had extensive ALS clinical trial testing experience and who was blinded to group assignment. The subjects were not blinded to the type of exercise program they performed and were instructed not to reveal their group assignment to the evaluating physical therapist. Even with these precautions, there were some rare instances of unblinding. The blinded evaluating physical therapist did not discuss potential results of the study outcomes with the subjects, and data analysis was conducted without knowledge of group identities.

The primary endpoint was the change in global function at 6 months, as measured by the ALSFRS, a widely used and extensively validated functional scale for ALS.[14] The ALSFRS evaluates bulbar and breathing function, in addition to extremity function; thus, we also analyzed the combined U/E and L/E subscale score (ALSFRS items 4 to 9), in addition to total ALSFRS score. Secondary outcome measures included fatigue, as measured by the Fatigue Severity Scale (FSS),[15] and quality of life was measured using the Short Form-36 (SF-36).[16]

Because resistance exercise has not been extensively studied in patients with ALS, at each monthly visit, we also evaluated muscle strength using maximum voluntary isometric contraction (MVIC)[17] and forced vital capacity (FVC) to monitor for signs of adverse effects of the prescribed exercise.

Data analysis. The available case analysis used all subjects who completed the study at 3 and 6 months. Kolmogorov–Smirnov test of normality was nonsignificant for all variables, except for baseline SF-36 role disability due to physical health problems (R-P) subscale score. Usual care and resistance exercise group mean data for primary, secondary, and safety outcome measures were compared at 3 and 6 months using the *t* test. For the R-P subscale score, comparisons between the two groups' median scores were made using the Wilcoxon rank sum test. Baseline characteristics were analyzed using *t* test, χ^2, or Fisher exact test. $p < 0.05$ was considered to be significant for all tests.

We examined data trends post hoc. We did not expect a bias in favor of the resistance exercise group, as dropout rates and reasons for dropouts did not differ significantly between groups. Regardless, we completed a stringent intention-to-treat analysis and imputed usual care group means at month 6 for missing data points for both the resistance exercise and the usual care group subjects.[18]

RESULTS Recruitment began in October 1999 and ended in June 2005. Characteristics of the enrolled subjects are shown in table E-1, and results are summarized in table E-2. There were no differences in demographic and other variables between groups, although there was a trend toward a worse SF-36 physical functioning score (P-F) in the usual care group ($p = 0.06$).

Four usual care group subjects and five resistance exercise group subjects did not complete the study

($p = 0.70$). Two subjects in each group who withdrew were taking riluzole. Usual care group subjects who discontinued had significantly lower SF-36 R-P sub scale scores, and resistance exercise group subjects who discontinued had significantly lower FSS scores and significantly higher SF-36 R-P and vitality sub scale scores (data not shown).

Of the subjects who discontinued, none of them did so because they believed the exercise program itself was resulting in a worsening of their condition, although three withdrew because they felt the disease was progressing. No subjects reported that excessive soreness, cramping, or fatigue precluded performing either exercise protocol. The subject who was dropped because of bypass surgery had a history of cardiac problems including a previous myocardial infarction, hypercholesteremia, and hypertension controlled with medication. He was given initial clearance to participate in the study by his cardiologist.

Typically compliance was high or moderate for the most subjects, although it fluctuated in individual patients, ranging from high to non compliant in any given month. The exception was one subject in the usual care group, who did not comply with the protocol and dropped out at the 4-month visit. The four subjects who withdrew because of depression, perceived disease progression, or perceived lack of benefit from the study did not follow the protocol in the month before withdrawing.

Differences between groups were found at 3 months for the combined U/E and L/E ALSFRS score ($t = -2.05$, $df = 23$, $p = 0.05$). At 6 months there was a difference between groups for total ALSFRS score ($t = -2.48$, $df = 16$, $p = 0.02$) and combined U/E and L/E extremity ALSFRS score ($t = -3.03$, $df = 16$, $p = 0.01$). At 6 months, only the SF-36 P-F subscale score differed between groups ($t = 2.58$. $df = 16$, $p = 0.02$). FSS score did not differ at 3 or 6 months between groups.

At month 6, the MVIC lower extremity megascore was lower in the resistance exercise group ($t = -2.32$, $df = 16$, $p = 0.03$), indicating less decline in L/E. Baseline to month 6 % change in raw MVIC data ranged from −0.80 to −37.15% in the usual care group and −47.22 to +35.34% in the resistance exercise group. There was a greater than 10% positive change in raw MVIC values for four L/E muscle groups in the resistance exercise group (data not shown).

No differences were found at 3 or 6 months in FVC.

All subjects who withdrew were lost to follow-up. Total ALSFRS score and combined U/E and L/E ALSFRS score remained different between groups at 6 months ($t = -2.143$, $df = 25$, $p = 0.04$; $t = -2.426$, $df = 25$, $p = 0.02$) with intention-to-treat analysis, and there were still trends toward less decline in the MVIC L/E megascore and improved P-F subscale scores for the resistance exercise group (data not shown). No other significant differences were found between groups with intention-to-treat analysis.

DISCUSSION We found that a home-based 6-month moderate-load and moderate-intensity resistance exercise program resulted in significantly less decline in global function in patients performing resistance exercise, as measured by the total ALSFRS score. Because a decision was made to end the study early and the dropout rate was high, the study is powered at approximately 71% (ALSFRS) and the effect size is 0.53 (Cohen $d = -1.23$). Our findings are encouraging, as the exercise program did not have detrimental effects and subject adherence was generally good, with most subjects completing the prescribed exercise sessions on a month-to-month basis.

The resistance exercise group had significantly less decline in the SF-36 P-F subscale score at 6 months compared with the usual care group, a finding that may have been influenced by baseline differences that were clinically but not statistically significant as well as by differences in subjects who remained in the study and those who withdrew. Although intention-to-treat analysis failed to show a difference in P-F subscale scores between the two groups at 6 months, the usual care group had a linear decline in P-F subscale scores over time, and the resistance exercise group had a weak trend toward less decline over time.

Among patients who completed the study, fatigue scores at 6 months did not differ between the groups. As there are no validated ALS-specific fatigue scales, we used the FSS to measure fatigue, a scale developed for patients with multiple sclerosis.[17] The FSS may not be sensitive enough to detect change in our ALS population; however, both groups had higher fatigue scores by 6 months. ALS-related fatigue may have a central origin[19] in addition to peripheral components, which may or may not be affected by exercise.

Safety outcomes demonstrated a trend toward a linear decline over time in the usual care group and a trend toward less decline over time or maintenance in the resistance exercise group. Three U/E and eight L/E muscle groups demonstrated a positive change in muscle strength, as measured by MVIC, over the study period. The L/E MVIC scores declined significantly less in the resistance exercise

group at 6 months, indicating that L/E muscle strength declined less over time. The intention-to-treat analysis did not show a difference between the groups.

Our protocol emphasized safety to minimize risk and maximize adherence, as subjects were completing the exercise program at home without the benefit of physical therapy supervision. Studies with larger sample sizes are needed to confirm our results. Different and more aggressive exercise protocols combined with closer monitoring of ALS muscle changes using electrophysiologic measures need to be examined. It remains to be seen whether the use of high-resistance programs and aerobic exercise provide benefits in people with ALS without undue risks. Ideal resistance exercise prescription for patients with ALS has not yet been established and the safety of using of a one repetition maximum testing protocol to prescribe exercise warrants investigation.

A subset of people with ALS may respond more positively to resistance exercises, both physically and psychologically. The extent and areas of involvement, the stage and severity of ALS, the rate of disease progression, and the severity of respiratory and bulbar manifestations can interfere with the ability to participate in an exercise program. Exercise may not have any ultimate influence on disease progression and mortality, and although exercise may improve function, increase strength temporarily, and decrease the effects of disuse atrophy, especially in the earlier stages of the disease, a patient who is hoping for a cure may not deem these effects critical. Engaging in exercise may not be a priority for some individuals. Others may believe participating in an exercise program will lead to permanent strength increases and may stop exercising when they realize that despite the program strength is decreasing because the disease is progressing.

An important limitation in this study is the sample size. Because the study participants completed their exercise program at home, to ensure safety we set the ALSFRS and FVC inclusion criteria quite high, which limited the number of eligible participants. Clinically, we have found that those with an FVC of less than 90% predicted or an ALSFRS score of less than 30 tend to have more advanced disease. We thought these patients might not be physically able to complete a 6-month exercise protocol, thus they were excluded.

Despite achieving a reasonable initial sample size for this patient population and type of research, we had difficulty retaining subjects. Over the study period, withdrawal increased: usual care group 0% and resistance exercise group n = 2 (15.4%) at 3 months; usual care group n = 4 (28.6%) and resistance exercise n = 5 (38.4%) at 6 months. High dropout rates are not unusual in ALS clinical studies, particularly those requiring longer follow-up.[10] It was not feasible to have patients attend the three tertiary care study centers to complete the exercise programs. Home exercise programs do not have any elements of socialization, and although the socialization aspect of exercise is thought to contribute positively to attendance and compliance,[20] it is unlikely that a high attendance rate for a group exercise program would be sustainable long term for people with ALS, as the disease progresses.

We excluded subjects who were enrolled in a concurrent ALS clinical drug trial. This decision also substantially limited the number of potential subjects and contributed to the subject dropout. It is reasonable for patients faced with a devastating, life-threatening illness to choose a pharmaceutical trial that may slow disease progression rather than a study that may influence function in the short term. However, it is also imperative to conduct well-designed, well-powered nonpharmaceutical clinical studies to develop care plans based on the best available evidence. The difficulties we encountered in recruiting and retaining subjects are not uncommon and highlight the need to re-examine the best way to conduct ALS studies and the need for innovative clinical designs and approaches. Adequate and cost-effective data collection methods and appropriate intervention time frames and follow-up intervals need to be balanced with the burden of data collection. The utility and feasibility of collecting data during home visits rather than clinic visits and using self-report measures that can be mailed to the study center or that can be collected via the telephone need to be explored. Although randomized control trials are the gold standard, alternative study designs such as Comprehensive Cohort Design[21] or Two-Stage Randomized Design,[22,23] with or without cross-over could be utilized. These designs consider that randomization might not be acceptable to patients and their families and take into account patient preferences. Outcomes of these nonrandomized studies do approximate those of randomized studies.[24]

Despite the poor prognosis of ALS, resistance exercises may be an essential component of the overall care of patients with this disease. Patients with ALS should be encouraged to engage in individualized resistance programs that are nonfatiguing. We have observed clinically that moderate resistance exercise programs implemented early can reduce the complications associated with disuse atrophy. Avoiding

these complications may maintain the patient's mobility and function for a longer period, thereby decreasing the patient's need for assistance with activities of daily living and transfers. Patients who participate in an exercise program may have a greater sense of control over what is happening to their bodies. These psychological benefits may enable patients to better maintain optimal functional independence and enhance their quality of life and well-being throughout all stages of the disease.

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