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Evaluation of Inspiratory Muscle Training Effect Compared With Diaphragmatic Breathing in Respiratory Parameters in Amyotrophic Lateral Sclerosis Patients: A Randomized Controlled Trial

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Abstract

Background: Many patients with amyotrophic lateral sclerosis (ALS) experience respiratory failure. The use of respiratory muscle training exercises can improve the respiratory function of these patients. This study aimed to evaluate the effect of inspiratory muscle training (IMT) on respiratory muscle function in ALS patients.

Methods: In the current randomized controlled clinical trial study, 22 patients were randomly divided into intervention (n = 11) and control groups (n = 11). In the control group, patients used only chest-opening training and diaphragm exercises. Patients in the intervention group used IMT in addition to controlled exercises (chest opening training and diaphragm exercises). Respiratory function by spirometry and monitoring of maximum inspiratory and expiratory pressure, functional capacity with a 6-minute walk test, and arterial blood gases were also assessed by ABG analysis at baseline and after 8 weeks. A comparative analysis of variables was performed with a student t-test, considering type 1 error ($\alpha = 0.05$) using SPSS 27 software.

Results: The indexes included maximal inspiratory pressure (PImax) ($P = 0.000$) and maximal expiratory pressures PEmax ($P = 0.002$). The strength of breathing muscles index (S-index) ($P = 0.002$) had a significant increase before and after rehabilitation in both groups ($P < 0.05$). In intergroup analysis, the only factor with a significant increase was PImax ($P = 0.019$).

Conclusion: The use of IMT, along with chest opening training and diaphragm exercises, can cause a relative improvement of the respiratory muscles' function indexes, especially PImax in ALS patients. More clinical trials are required.

Keywords: Amyotrophic lateral sclerosis, Inspiratory Muscle training, Maximal Inspiratory Pressure, Maximal Expiratory Pressure, Respiratory Muscle Strength

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↑What is "already known" in this topic:
Amyotrophic lateral sclerosis (ALS) is a rare disease for which there is still no definitive cure. Respiratory dysfunction is one of the most important complications of ALS, which reduces quality of life and increases mortality. Respiratory muscle strengthening exercises play a significant role in improving the respiratory status of patients with various chronic respiratory diseases.

→What this article adds:
The present clinical trial study demonstrates the role of an inspiratory muscle training (IMT) device intervention in patients with ALS. Overall evidence from this study showed that IMT can improve respiratory muscle strength and pulmonary function in patients with ALS.

Introduction

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease involving the upper and lower motor neurons, which annually results in the death of 30,000 patients worldwide (1). Unfortunately, despite extensive research into the treatment of this disease, no definitive cure for this disease has been provided yet (2).

Various studies have shown that about 3% to 5% of these patients suffer from respiratory failure, which can lead to reduced quality of life and increased mortality rates in these patients at advanced levels (3). Therefore, evaluating the respiratory function of these patients and paying attention to the symptoms reported by the patient, such as shortness of breath and pre-sleep hypoventilation, can play an important role in controlling respiratory failure and increasing patient survival (4). Evaluation of these symptoms is possible by monitoring the factors involved in the respiratory function of these patients.

Previous studies have shown that the vital capacity of ALS in 26 patients studied showed lower values than expected. In patients exhibiting symptoms of the disease, the partial pressure of carbon dioxide (PCO_2) showed a significant correlation with inspiratory muscle strength. Additionally, those with pronounced ALS symptoms demonstrated elevated PCO_2 levels and reduced pH levels (5).

In patients with ALS, spontaneous breathing is affected by damage to the anterior horn neurons that are responsible for the diaphragm nerve. The diaphragm can be reinforced like other skeletal muscles in the body, which can improve lung parameters and, ultimately, respiratory status in ALS patients (6, 7). However, there is no specific protocol for how to do the exercises. Nowadays, strengthening of inspiratory muscles is a part of pulmonary rehabilitation in different respiratory patients, which used to increase the respiratory capacity of athletes. Also, the benefits of employing this method to enhance the strength and functionality of respiratory muscles in patients with chronic obstructive pulmonary disease, spinal cord injury-related disorders, Duchenne muscular dystrophy, and myasthenia gravis have been demonstrated (8-11).

The inspiratory muscle training (IMT) device, by applying controlled current resistance, strengthens the respiratory muscles and prevents the progression of respiratory failure (12). This device can store pressure and respiratory flow data, and therefore, the physician can monitor IMT home programs (13).

Despite the widespread use of the IMT system in recent years, its use in ALS patients has been less studied. The present study was performed to investigate the role of this method on respiratory muscle function in these patients.

Methods

Study Design and Participants

The present study was performed as a non-blind, randomized clinical trial in parallel groups from April to September 2019 in Masih Daneshvari Hospital, Tehran, Iran. There was no communication between patients participating in each group when visiting the relevant clinic. Since ALS is a rare disease and our access to patients was very limited, sampling was conducted using total population sampling. In this study, a total of 30 patients diagnosed with ALS were referred by a neurologist. Following the acquisition of informed consent and the application of inclusion criteria—which required the ability to perform exercises, a maximal inspiratory pressure (PImax) of <60 cm H_2O, no surgical history within the past 12 months, absence of severe osteoporosis, and a dyspnea score of <6 on the Borg Scale—22 patients were subsequently assigned to 2 treatment groups through Block Randomization. A random number table was used for randomization, and binary treatment blocks were considered. A person unaware of the group assignment randomly assigned patients to 2 separate groups based on patient code and case number. Then, another person randomly moved the patients in these blocks, and a random list of the 2 treatment groups was obtained.

Patients performed controlled exercise therapy (including diaphragm exercises and chest opening exercises) in the control group, and in the intervention group, patients used the IMT in addition to exercise-controlled therapy (similar to the control group). Both groups performed these exercises twice a day for 8 weeks.

Inspiratory Muscle Training

Inspiratory muscle training was performed using a mechanical IMT device (POWER breath, United Kingdom), and the patients in the intervention group performed deep, powerful inhalations to reach the desired threshold. This threshold is set at 30 % PImax initially. In the morning and afternoon, the patients followed the prescribed regimen of 30 repetitions of these exercises, taking a 2-minute break after each ten repetitions. Within two weeks, the severity of IMT increased gradually to 60% PImax.

Assessments

Patients in both groups were tested for the first time at the beginning of the training programs and then 8 weeks after exercise. Factors affecting lung function were evaluated by pulmonologists, and an experienced physical therapist evaluated patients' ability to perform a 6-minute walk test.

Pulmonary Function Assessment

To measure spirometry variables, the patient is in a calm position and places her lips firmly around the mouth of the spirometry device. The patient then inhaled and exhaled forcefully, telling the patient to breathe as much as possible and then rest for a minute. This procedure was repeated 3 times, and the best performance was considered for each patient. The patient was referred to the pulmonary function test (PFT) unit to measure PImax and PEmax. In addition, a computer-based IMT device (Power breath K5) was used to measure the strength of breathing muscles index (S-index). For this purpose, the patient learns to perform deep breathing after complete or relatively complete exhaustion. It then drains the lungs as far as possible while the patient's nostrils are closed and performs a sud-

den inhalation while holding the device with both hands. This procedure is repeated at least 3 times, and the patient rests 30 seconds between each repetition. The best performance is considered for each patient. The procedure was performed once on the first day and once at the end of the eighth week.

Six-Minute Walk Test

The 6-minute walk test reveals the patient's exercise capacity and can provide patients with greater safety and comfort than methods such as the shuttle test (14). This test was performed based on the guideline provided by the American Thoracic Society and asked the patient to walk as fast as possible in the 30-meter corridor. Heart rate, oxygen saturation, walking distance, and Borg scale were recorded (15). To minimize sample loss and ensure patient attendance at treatment sessions, the treatment team conducted regular follow-up calls to remind patients of the scheduled session times.

Arterial Blood Gas Analysis

Arterial blood gas analysis was used to assess the condition of ventilation and acid-base disorders in patients. Blood samples obtained from patients were transferred to the laboratory and interpreted.

Statistical Analysis

A post hoc power analysis was performed for the primary outcome using a paired-sample t-test. The calculated power for detecting the specified effect size was 0.95. This indicates that the study had a very high probability of detecting the effect size, assuming the true effect size and significance level provided are accurate. Because ALS is a rare disease and the number of patients referred by the neurology clinic is very low, we examined all patients referred by a neurologist to Masih Daneshvari Hospital who met the inclusion criteria. To present our data, we applied both descriptive and analytic statistics. Quantitative variables were presented as relative frequencies, and qualitative data were presented as the mean ± standard deviation. To compare quantitative variables between the 2 groups, we utilized a student t-test. Type 1 error was put at $P \leq 0.05$. All statistical analyses were performed using SPSS 27 software.

Results

Out of 30 ALS patients who were referred to Masih Deneshvari Hospital in Tehran by a neurologist, 22 patients—13 men and 9 women, with an average age of 51.45 years who fulfilled the requirements to be included in this clinical research—took part in the study (Table 1).

Figure 1 shows the flowchart of participants and excluded patients. The comparison of the baseline values of the studied variables showed that at the beginning of the study and before the pulmonary rehabilitation, there was no significant difference between the mean variables of the 2 groups (Table 1).

Examining the values obtained from arterial blood gas analysis of ALS patients showed that the average PCO_2 in the control group was significantly reduced ($P = 0.015$). In contrast, there was no significant difference in PCO_2 in the intervention group before and after pulmonary rehabilitation ($P = 0.231$). Examining the HCO_3 values of the patients showed that using pulmonary rehabilitation with the 2 methods we investigated does not create any significant difference in the HCO_3 values of the patients in the control group and the intervention group ($P = 0.267$ and $P = 0.068$, respectively). In addition, although the pH changes in both groups after the intervention were not physiologically significant, the mean pH was 7.36 ± 0.06 before rehabilitation, and it was 7.35 ± 0.05 after rehabilitation in the intervention group. Therefore, a significant decrease in pH was observed in the group of patients using the IMT ($P = 0.021$) (Table 2).

Table 1. Demographic Characteristics of the Patients

Variable	PR Group	PR + IMT Group	*P* Value
characteristics			
Age, year (Mean ± SD)	56.82 ± 7.06	58.54 ± 6.17	0.548
Weight, kg (Mean ± SD)	57.45 ± 5.22	54.73 ± 5.55	0.249
Height, cm (Mean ± SD)	167.09 ± 4.50	169.09 ± 5.08	0.341
Gender, Female/Male (Frequency (percent))	4 (36.40)/ 7 (63.60)	5 (45.50)/ 6 (54.50)	0.665
NIV, Yes/No (Frequency (percent))	3(27.30)/ 8 (72.70)	1 (9.1)/ 10 (90.90)	0.586
Difference between the baseline variables			
FVC, ml (Mean ± SD)	80.45 ± 20.09	76.54 ± 16.23	0.621
FEV1, mL(Mean ± SD)	78.00 ± 19.30	76.18 ± 15.52	0.810
FEV1/FVC, % (Mean ± SD)	86.37 ± 12.52	88.64 ± 4.34	0.576
TLC, L (Mean ± SD)	90.28 ± 14.37	82.36 ± 10.23	0.154
RV (Mean ± SD)	94.73 ± 19.26	101.00 ± 26.07	0.529
PCO_2, mmHg(Mean ± SD)	46.00 ± 10.28	47.07 ± 6.78	0.776
PH(Mean ± SD)	7.35 ± 0.02	7.37 ± 0.06	0.614
HCO_3, mmol/L(Mean ± SD)	29.36 ± 3.90	30.02 ± 4.23	0.706
PEmax, cm H_2O (Mean ± SD)	28.73 ± 4.51	24.91 ± 7.88	0.183
PImax, cm H_2O (Mean ± SD)	42.54 ± 5.68	49.64 ± 10.33	0.06
SIndex, (Mean ± SD)	45.04 ± 20.97	49.81 ± 16.78	0.563
6MWTD, m (Mean ± SD)	255.36 ± 95.93	266.64 ± 71.24	0.758

Abbreviations: PR, Pulmonary rehabilitation; IMT, Inspiratory Muscle Training; NIV, Non-Invasive Ventilation; FVC, Forced Vital Capacity; FEV1, Forced Expiratory Volume in the first second; TLC, Total Lung Capacity; RV, Residual Volume; PCO_2, Partial Pressure of Carbon Dioxide; PEmax, Maximal Expiratory Pressures; PImax, Maximal Inspiratory Pressures; 6MWTD, Six Minute Walk Test Distance. Independent T-TEST analysis of significance difference and descriptive statistics of characteristics with Chi-Square ($\chi 2$). For all analyses, $P < 0.05$ was considered statistically significant (*).

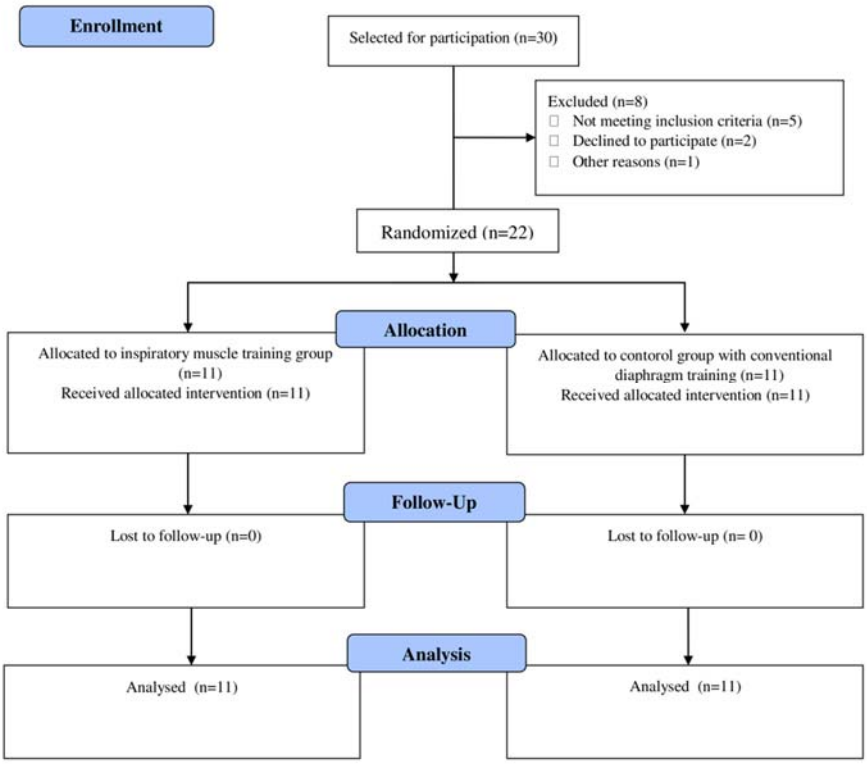

Figure 1. Flowchart of the study

Table 2. Average Variables of Control and Intervention Groups Before and After Pulmonary Rehabilitation Training

Variable	PR Group (Mean ± Standard deviation)		Mean Difference	SE	P Value	PR + IMT Group (Mean ± Standard division)		Mean Difference	SE	*P* Value
	Before	After				Before	After			
FVC, Ml (Mean±SD)	80.45±20.09	83.18±20.10	-2.73	1.31	0.065	76.54±16.23	79.73±15.04	-3.18	1.05	0.013*
FEV1, mL (Mean±SD)	78.00±19.30	76.64±21.62	1.36	1.65	0.427	76.18±15.52	74.00±25.33	2.18	4.84	0.662
FEV1/FVC, % (Mean±SD)	86.36±12.52	89.73±11.18	-3.36	1.37	0.035*	89.90±4.43	90.40±6.31	-1.5	1.23	0.254
TLC, L (Mean±SD)	90.27±14.37	83.00±28.26	7.27	8.41	0.408	82.36±10.23	84.45±9.86	-2.09	1.47	0.186
RV (Mean±SD)	94.73±19.26	96.00±19.53	-1.27	0.47	0.022*	101.00±26.07	102.18±20.51	-1.18	2.38	0.631
PCO_2, mmHg (Mean±SD)	46.00±10.28	43.27±8.33	2.73	0.93	0.015*	47.07±6.78	46.45±7.65	0.62	0.48	0.231
PH (Mean±SD)	7.35±0.03	7.34±0.02	0.006	0.007	0.404	7.36±0.06	7.35±0.05	0.02	0.007	0.021*
HCO^3, mmol/L (Mean±SD)	29.36±3.90	29.00±3.43	0.36	0.31	0.267	30.03±4.23	27.82±4.02	2.20	1.08	0.068
PEmax, cm H_2O (Mean±SD)	28.73±4.54	33.18±7.14	-4.45	1.07	0.002*	24.91±7.87	31.91±9.38	-7.00	3.04	0.044*
PImax, cm H_2O (Mean±SD)	42.54±5.68	47.00±6.71	-4.45	0.98	0.001*	49.64±10.33	58.27±7.96	-8.64	1.29	<0.001*
S-index, % (Mean±SD)	45.04±20.97	51.21±18.35	-6.17	1.95	0.01*	49.81±16.78	55.45±19.52	-5.64	2.06	0.021*
6MWTD, cm (Mean±SD)	255.36±95.93	271.73±120.03	-16.36	9.16	0.104	266.64±71.24	279.45±70.67	-12.82	11.54	0.293

Abbreviations: PR, Pulmonary rehabilitation; IMT, Inspiratory Muscle Training; NIV, Non-Invasive Ventilation; FVC, Forced Vital Capacity; FEV1, Forced Expiratory Volume in the first second; TLC, Total Lung Capacity; RV, Residual Volume; PCO_2, Partial Pressure of Carbon Dioxide; PEmax, Maximal Expiratory Pressures; PImax, Maximal Inspiratory Pressures; 6MWTD, Six Minute Walk Test Distance. Descriptive Statistics and paired t-test results. For all analyses, $P < 0.05$ was considered statistically significant (*).

Examining the results obtained from the pulmonary function test of the 2 groups of patients examined in this study showed that the mean FEV1 in the 2 groups before and after pulmonary rehabilitation had no statistically significant difference ($P = 0.427$ and $P = 0.662$, respectively). Moreover, no significant difference was observed in the average total lung capacity (TLC) in the control group and the intervention group before and after rehabilitation ($P = 0.408$ and $P = 0.186$, respectively). The general process of improving breathing in these patients can be traced by examining forced vital capacity (FVC). The FVC in the control group, which did not employ IMT, was 80.45 ± 20.09 before pulmonary rehabilitation using IMT, according to the results shown in Table 2, which displays the difference in the mean of the variables under investigation in the 2 groups.

Table 3. Intergroup Differences of Study Indicators

Variable	PR Group	PR + IMT Group	Mean Difference	*P* Value
FVC, ml (Mean ± SD)	-2.72 ± 4.36	-3.18± 3.49	0.45	0.790
FEV1, ml (Mean ± SD)	1.36 ± 5.46	2.18 ±16.07	-0.82	0.876
FEV1/FVC, % (Mean ± SD)	-3.36± 4.57	-1.50 ± 3.89	-1.86	0.326
TLC, L (Mean ± SD)	7.27 ± 27.91	-2.09 ± 4.88	9.36	0.286
RV (Mean ± SD)	-1.27 ± 1.55	-1.18 ± 7.91	-0.09	0.971
PCO_2, mmHg (Mean ± SD)	2.73 ± 3.10	0.62 ± 1.61	2.11	0.069
PH (Mean ± SD)	0.006 ± 0.02	0.02 ± 0.05	-0.02	0.233
HCO_3, mmHg (Mean ± SD)	0.36 ± 1.03	2.21 ± 3.58	-1.84	0.127
PEmax, cm H_2O (Mean ± SD)	-4.45 ± 3.56	-7.00 ± 10.09	2.54	0.445
PImax, cm H_2O (Mean ± SD)	-4.45 ± 3.26	-8.64 ± 4.29	4.18	0.019*
SIndex,% (Mean ± SD)	-6.17 ± 6.46	-5.64 ± 6.84	-0.53	0.854
6MWTD, cm (Mean ± SD)	-16.36 ± 30.38	-12.81 ± 38.28	-3.54	0.812

Abbreviations: PR, Pulmonary rehabilitation; IMT, Inspiratory Muscle Training; NIV, Non-Invasive Ventilation; FVC, Forced Vital Capacity; FEV1, Forced Expiratory Volume in the first second; TLC, Total Lung Capacity; RV, Residual Volume; PCO_2, Partial Pressure of Carbon Dioxide; PEmax, Maximal Expiratory Pressures; PImax, Maximal Inspiratory Pressures; 6MWTD, Six Minute Walk Test Distance. Independent T-TEST analysis of significance difference between the variables by test and control group. For all analyses, $P < 0.05$ was considered statistically significant (*).

After rehabilitation, the mean of this variable was 83.18 ± 20.10, which indicated no significant increase in FVC in the control group ($P = 0.065$). Meanwhile, in the intervention group, where the patients used the IMT in addition to pulmonary rehabilitation exercises, FVC showed a significant increase compared to before rehabilitation ($P = 0.013$).

Maximum expiratory pressure (PEmax) in the control group increased significantly after pulmonary rehabilitation compared to before rehabilitation ($P = 0.002$). Similarly, maximum inspiratory pressure (MIP) (PImax) was associated with a significant increase compared to the mean values before rehabilitation ($P = 0.001$). In the intervention group, the comparison of the results obtained from the mean of PEmax and PImax showed a significant increase in these variables ($P = 0.044$ and $P < 0.001$, respectively). Examining the results obtained from the S-index of the patients showed that the mean S-index in the control group increased from 20.97 ± 45.04 to 51.21 ± 18.35, indicating a significant increase in this variable as a result of performing lung expansion exercises ($P = 0.01$). Similarly, in the intervention group, the mean of the S-index of patients using the IMT increased significantly ($P = 0.021$).

The results obtained from the 6-minute walking test of patients with ALS in the 2 groups under investigation showed that the mean of the 6-minute walking test of patients in both groups increased after pulmonary rehabilitation. However, this difference was not statistically significant ($P = 0.104$ in the control group and $P = 0.293$ in the intervention group) (Table 2).

Examining the relationship between the average variables under investigation between the 2 groups of patients undergoing breathing exercises (control) and the group of patients undergoing breathing exercises with IMT, using independent t-test analysis, showed a significant difference between the average PImax of the 2 groups ($P = 0.019$). However, no significant differences were observed in other variables under investigation in the 2 groups (Table 3).

Discussion

ALS is a rare disease, and few studies have investigated the strengthening of inspiratory muscles in these patients. Management of the changes in the respiratory muscles of ALS patients can play a potential role in improving their quality of life (15). The main focus of our study was the use of inspiratory muscle-strengthening exercises to improve the respiratory function of ALS patients. In ALS patients, due to the damage of the neurons related to the diaphragm nerves, it is essential to maintain the function of the respiratory muscles. Examining the MIP or PImax is one of the useful tests introduced to evaluate the function and strength of respiratory muscles, especially the diaphragm in neuromuscular diseases (16). In our study, a significant improvement in PImax was observed in intragroup and intergroup analysis ($P < 0.05$). On the other hand, since in the intergroup analysis, the mean changes of PImax were in favor of the group of patients using IMT compared to the control group, it can be said that the use of IMT helped to strengthen the lung rehabilitation of ALS patients participating in our study. Previous studies have shown that, like skeletal muscles, respiratory muscles can also adapt to exercise through structural and neural adaptation by hypertrophy using additional motor units and increasing the contraction frequency of muscle fibers (17).

Our study results are consistent with those of the previous studies. Previously, the role of respiratory muscle training in improving pulmonary function in similar cases of ALS has been confirmed. Plowman et al examined the performance of 12-week inspiratory and expiratory muscle training in ALS patients and showed that the use of this program is associated with a significant increase in the maximal expiratory pressure, but not maximal expiratory pressure; however, these results may be due to the long study period (18). In line with our results, Vicente-Campos et al showed that a month-long combined training program of IMT can improve the respiratory function of ALS patients (19). In a similar study, breathing exercises with the IMT therapeutic tool in ALS patients showed that this method caused a significant increase in PImax and increased the inspiratory strength of the patients (19).

Even if a small number of ALS patients were the subject of numerous similar studies in the past, it is possible to comprehend the beneficial impact of IMT in enhancing inspiratory strength and respiratory function based on the findings.

Neves et al also found that the use of IMT along with expiratory muscle training can lead to increased PEmax and PImax in chronic obstructive pulmonary disease patients (20). Similar findings in a study by Laohachai et al showed that using IMT can increase PImax and PEmax in patients with a Fontan circulation (21). The effectiveness of IMT on the improvement of PImax of ALS patients has been confirmed before (19).

Examining the results obtained from the arterial gas analysis of the patients participating in this study showed that the average pH values, despite a slight decrease in both groups, were significant only in the intervention group before and after rehabilitation, and no significant difference was observed in the intergroup analysis. Also, PCO_2 was significant only in the control group. In patients with ALS, the pulmonary function to excrete carbon dioxide is impaired due to neuromuscular damage, and therefore, blood bicarbonate increases significantly. This situation can lead to respiratory acidosis in these patients (22). Therefore, reducing arterial blood gases can control these patients' respiratory acidosis conditions. In our study, there was no significant decrease in the results of intergroup blood gas analysis of ALS patients undergoing pulmonary rehabilitation. Previous studies have shown that the average amount of arterial blood gases decreases significantly after using inspiratory muscle exercises in patients with cervical spinal cord injury (23, 24).

The study by Rahmy et al in patients with interstitial pulmonary fibrosis presented similar results to our findings on the reduction of arterial blood carbon dioxide pressure after using IMT (25). The results showed that patients who used the inspiratory muscle trainer for 8 weeks had significant improvements in blood gases.

On the other hand, the pulmonary function of patients who used IMT did not increase significantly compared to the control group. The results of our study showed that the use of IMT does not make much difference in the lung function components of ALS patients; however, the mean of FVC in the intervention group that benefited from this method was significantly higher than the conditions at the beginning of the study. Since the decrease in FVC level can indicate pulmonary abnormalities, the mean increase of this factor in patients who used inspiratory muscle exercises in this study indicates the positive effect of these exercises on their pulmonary function. Several studies have been designed to investigate the role of IMT in the pulmonary function of different patients (26, 27).

Dos Santos et al showed that the use of IMT combined with short-term aerobic and resistance exercise (combined training) can significantly improve peak oxygen uptake, distance covered in the 6-minute walk test, respiratory function, and quality of life in patients after coronary artery bypass graft surgery (26). Previous studies that have examined the effect of IMT in patients with ALS have confirmed the positive effect of these exercises on improving FVC in these patients (19). Khoshkhabar et al have also reported the positive role of IMT in improving these factors (9).

In our study, the mean of respiratory muscle strength (S-index) showed a significant increase in intragroup analysis; in contrast, no significance was observed in intergroup analysis. The general evidence from this randomized controlled study has shown that IMT can improve respiratory muscle strength and pulmonary function in patients with ALS. Because patients with ALS have progressive weakness in the respiratory muscles, these findings can be considered a valuable step in improving their respiratory status.

Most research on the IMT technique has been conducted in patients with conditions including COPD, Duchenne muscular dystrophy, and others; each of these conditions necessitates a different rehabilitation regimen (27-31).

However, due to the limitations of studies that have used this method in patients with ALS, the results of the present study have been compared with the results of similar studies.

Our study demonstrated a considerable increase in the strength and function of the inspiratory and expiratory muscles in patients with ALS, despite the limited sample size. Patients with ALS frequently avoid frequent medical center visits because of their physical limitations. To keep the treatment process organized and prevent loss to follow-up, we used video conferences or daily contact to interact with patients in our study.

Limitations

Our study had a small sample size, and the breathing exercises were done over 8 weeks. A greater sample size and a comparison of the duration of various treatments may yield different outcomes. The patients were randomly selected for the study based on the inclusion criteria, however, we did not distinguish between the various phases of ALS or the length of the illness in our study. Comparing patients' spinal and bulbar symptoms relative to their respiratory function and nerve involvement may be an intriguing topic for future research.

Conclusion

The present study investigated the role of IMT with chest expansion exercises and diaphragmatic exercises. Our results showed that both types of training protocols can lead to relative improvement in respiratory muscle function. However, access to an optimal and generalizable training protocol for patients with different levels of ALS requires further studies.

Authors' Contributions

The study was conceived, organized, and managed by M.M., A.F., M.V., M.A., S.S., R.Z., B.H., and B.Z. Also, A.F. was the corresponding author and the main executor of this study. All authors have contributed to the preparation and analysis of the present manuscript.

Ethical Considerations

This study was conducted following the approval of the

Ethics Committee of Shahid Beheshti University of Medical Sciences, Tehran, Iran, with the code IR.SBMU.NRITLD.REC.1397.073. This study was also registered in the Iranian Clinical Trial System with the code IRCT20200611047727N2. Before entering the study, all patients signed an informed consent form.

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Conflict of Interests

The authors declare that they have no competing interests.

References

1. Chiò A, Mora G, Lauria G. Pain in amyotrophic lateral sclerosis. Lancet Neurol. 2017 Feb 1;16(2):144-57.
2. Petrov D, Mansfield C, Moussy A, Hermine O. ALS clinical trials review: 20 years of failure. Are we any closer to registering a new treatment?. Front Aging Neurosci. 2017 Mar 22;9:68.
3. Lechtzin N, Cudkowicz ME, de Carvalho M, Genge A, Hardiman O, Mitsumoto H, Mora JS, Shefner J, Van den Berg LH, Andrews JA. Respiratory measures in amyotrophic lateral sclerosis. Amyotroph. Lateral Scler Front Degener. 2018 Jul 3;19(5-6):321-30.
4. Rinchetti P, Rizzuti M, Faravelli I, Corti S. MicroRNA metabolism and dysregulation in amyotrophic lateral sclerosis. Mol Neurobiol. 2018 Mar 1;55(3):2617-30.
5. Hogden A, Foley G, Henderson RD, James N, Aoun SM. Amyotrophic lateral sclerosis: improving care with a multidisciplinary approach. J Multidiscip Healthc. 2017;10:205.
6. Rinchetti P, Rizzuti M, Faravelli I, Corti S. MicroRNA metabolism and dysregulation in amyotrophic lateral sclerosis. Mol Neurobiol. 2018 Mar 1;55(3):2617-30.
7. Hogden A, Foley G, Henderson RD, James N, Aoun SM. Amyotrophic lateral sclerosis: improving care with a multidisciplinary approach. J Multidiscip Healthc. 2017;10:205.
8. Karsten M, Ribeiro GS, Esquivel MS, Matte DL. The effects of patients exhibiting symptoms of the disease with linear workload devices on the sports performance and cardiopulmonary function of athletes: A systematic review and meta-analysis. Phys Ther Sport. 2018 Nov 1;34:92-104.
9. Khoshkhabar M, Mirenayat M, Abedi M, Karimzade S, Rizehbandi M, Fakharian A. The effect of inspiratory muscle training on spirometry parameters of patients with chronic obstructive pulmonary disease. J Clin Physiother Res. 2020 Jan 1;5(1):e2-.
10. Human A, Corten L, Jelsma J, Morrow B. Inspiratory muscle training for children and adolescents with neuromuscular diseases: A systematic review. J Neuromuscul Dis. 2017 Jun 1;27(6):503-17.
11. Taya M, Amiya E, Hatano M, Maki H, Hosoya Y, Ishida J, Bujo C, Tsuji M, Konishi Y, Yokota K, Haga N. Inspiratory muscle training for advanced heart failure with lamin-related muscular dystrophy. J Cardiol Cases. 2019 Dec 1;20(6):232-4.
12. Jung JH, Kim NS. Relative activity of respiratory muscles during prescribed inspiratory muscle training in healthy people. J Phys Ther Sci. 2016;28(3):1046-9.
13. Aktuğ ZB, Kurt S, Pişkin NE, Yavuz G, İbiş S. Effect of inspiratory muscle training with the device on respiratory functions. Mediterr J Sports Sci. 2022 Sep 28;5(3):571-81.
14. Corcia P, Couratier P, Blasco H, Andres CR, Beltran S, Meininger V, Vourc'h P. Genetics of amyotrophic lateral sclerosis. Rev Neurol. 2017 May 1;173(5):254-62.
15. Agarwala P, Salzman SH. Six-minute walk test: clinical role, technique, coding, and reimbursement. Chest. 2020 Mar 1;157(3):603-11.
16. Schoser B, Fong E, Geberhiwot T, Hughes D, Kissel JT, Madathil SC, Orlikowski D, Polkey MI, Roberts M, Tiddens HA, Young P. Maximum inspiratory pressure as a clinically meaningful trial endpoint for neuromuscular diseases: a comprehensive review of the literature. Orphanet J Rare Dis. 2017 Dec;12:1-2.
17. Hariza O, Lasmitasari B, Widjanantie SC, Nusdwinuringtyas N. the Effects of inspiratory muscle training in Neuromuscular disorders. Indones J Phys Med Rehabil. 2018;7(01):57-66.
18. Plowman EK, Gray LT, Chapin J, Anderson A, Vasilopoulos T, Gooch C, Vu T, Wymer JP. Respiratory strength training in amyotrophic lateral sclerosis: A double-blind, randomized, multicenter, sham-controlled trial. Neurology. 2023 Apr 11;100(15):e1634-42.
19. Vicente-Campos D, Sanchez-Jorge S, Chicharro JL, Becerro-de Bengoa-Vallejo R, Rodriguez-Sanz D, García AR, Rivoire M, Benet A, Boubekeur S, Calvo-Lobo C. POWERbreathe® inspiratory muscle training in amyotrophic lateral sclerosis. J Clin Med. 2022 Nov 9;11(22):6655.
20. Neves LF, Reis MH, Plentz RD, Matte DL, Coronel CC, Sbruzzi G. Expiratory and expiratory plus inspiratory muscle training improves respiratory muscle strength in subjects with COPD: systematic review. Respir Care. 2014 Sep 1;59(9):1381-8.
21. Laohachai K, Winlaw D, Selvadurai H, Gnanappa GK, d'Udekem Y, Celermajer D, Ayer J. Inspiratory muscle training is associated with improved inspiratory muscle strength, resting cardiac output, and the ventilatory efficiency of exercise in patients with a Fontan circulation. J Am Heart Assoc. 2017 Aug 21;6(8):e005750.
22. Alarcan H, Cotet C, Lépine N, Morel J, Vourc'h P, Andres C, Corcia P, Blasco H. Evaluation of arterial blood gas parameters as prognostic markers in amyotrophic lateral sclerosis. Eur J Neurol. 2023 Jun;30(6):1611-8.
23. Abd El-Kader SM. Impact of respiratory muscle training on blood gases and pulmonary function among patients with cervical spinal cord injury. Electron J Gen Med. 2018 Jan 1;15:15-20.
24. Hassan AK, Elnahas NG, Abdeen HA, Elkatatny AA. Effect of respiratory strengthening exercise on arterial blood gases in post-cervical spinal cord injury patients. Ejpmr. 2019;6(9):161-165.
25. RAHMY AF, ESRAA N, MOHAMED SHENDY PD. Inspiratory Muscle Training Versus Diaphragmatic Breathing Exercise on Maximal Inspiratory Pressure and Blood Gases on Interstitial Pulmonary Fibrosis. Med J Cairo Univ. 2020 Dec 1;88(December):2295-301.
26. Dos Santos TD, Pereira SN, Portela LO, Cardoso DM, Dal Lago P, dos Santos Guarda N, Moresco RN, Pereira MB, de Albuquerque IM. Moderate-to-high intensity inspiratory muscle training improves the effects of combined training on exercise capacity in patients after coronary artery bypass graft surgery: A randomized clinical trial. Int J Cardiol. 2019 Mar 15;279:40-6.
27. Duruturk N, Acar M, Doğrul MI. Effect of inspiratory muscle training in the management of patients with asthma: a randomized controlled trial. J Cardiopulm Rehabil Prev. 2018 May 1;38(3):198-203.
28. Elmorsi AS, Eldesoky ME, Mohsen MA, Shalaby NM, Abdalla DA. Effect of inspiratory muscle training on exercise performance and quality of life in patients with chronic obstructive pulmonary disease. Egypt J Chest Dis Tuberc. 2016 Jan 1;65(1):41-6.
29. Williamson E, Pederson N, Rawson H, Daniel T. The effect of inspiratory muscle training on duchenne muscular dystrophy: a meta-analysis. Pediatr Phys Ther. 2019 Oct 1;31(4):323-30.
30. de Medeiros AI, Fuzari HK, Rattesa C, Brandão DC, de Melo Marinho PÉ. Inspiratory muscle training improves respiratory muscle strength, functional capacity and quality of life in patients with chronic kidney disease: a systematic review. J Physiother. 2017 Apr 1;63(2):76-83.
31. Hoffman M. Inspiratory muscle training in interstitial lung disease: a systematic scoping review. J Bras Pneumol. 2021 Sep 6;47(04):e20210089.