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Inspiratory Muscle Training in Adults With Cerebral Palsy: Long Term Effects: A Double-Blind Randomized, Controlled Trial

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ABSTRACT

Respiratory disease is one of the main causes of morbidity and mortality in adults with cerebral palsy (CP). The main objective of the study was to investigate the maintenance over time of improvements in respiratory parameters achieved with inspiratory muscle training (IMT). This was a randomized, controlled, double-blind trial and with allocation concealment performed on 27 institutionalized CP patients randomly distributed in two groups: "high intensity training group" (HIT) trained with a load of 40% of the maximum inspiratory pressure (MIP) and "low intensity training group" (LIT) with 20%. Respiratory strength and pulmonary function were evaluated throughout the study. Four weeks after IMT most improvements persisted. Twelve weeks after IMT, only HIT maintained significant improvements ($p = 0.001$) in MIP; 24 weeks after IMT, in the HIT group, MIP was 10% higher than the initial results and pulmonary function parameters were 1% lower. In the LIT group, respiratory strength and pulmonary function were lower than at baseline. Improvements achieved with IMT are reduced over time once the treatment ends. During the first 4 weeks posttreatment, the benefits persist but from the 12th week there was a progressive loss of the improvement reaching a total loss at 24 weeks. To be most effective, a higher MIP load is suggested for respiratory treatment, which must be maintained over time and interruptions should not be longer than 4 weeks.

Clinical trial registration. The study was registered in the clinical trials database of the United States National Library of Medicine (www.clinicaltrials.gov) with the number of registration NCT04915170.

1 | Introduction

Cerebral palsy (CP) refers to a set of permanent alterations or disorders related to movement, posture, and balance (Patel et al. 2020). This disease appears in one out of every 500 births, accumulating a prevalence of 17 million people worldwide (United Nations, Department of Economics and Social Affairs, Population division. 2022). CP is a nonprogressive disorder. The respiratory system is one of the most affected as patients get older. Respiratory problems are an important cause of morbidity and mortality in CP populations (Boel et al. 2019). Adults with CP have a 14 times higher risk of dying from respiratory

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disease than the general population without disease (Ryan et al. 2019).

Respiratory muscle strength and chest mobility, which causes decreased lung expansion and compliance (restrictive pulmonary disfunction), are two parameters very reduced in CP patients. Adults with CP have a reduction of more than 50% of these parameters compared to healthy adult population (Lampe et al. 2014; Ezeugwu et al. 2013; Campbell et al. 2003). This has a negative impact on lung function due to the modification of the respiratory breathing pattern that will affect daily life activities and quality of life of people who suffer from it (Ersöz et al. 2006). Both respiratory muscle strength and chest mobility are qualities that can be improved with rehabilitation. The performance of respiratory exercises should be considered in patients with CP from early ages to avoid the deterioration of respiratory function.

Pulmonary rehabilitation has been proposed as an effective rehabilitation in children with CP to improve diaphragmatic work, chest mobility and quality of life, but there are no studies that analyse this training in adults with CP (Rutka et al. 2021; El Banna et al. 2020). Aerobic exercise and respiratory training are an essential part of physiotherapy treatment in patients with CP but there are no standardized protocols or consensus on the optimal training modalities (de Lima Crispim et al. 2023).

Due to the lack of knowledge regarding the most effective respiratory treatment in these patients, the need to carry out more studies in this regard arises. In this sense, inspiratory muscle training (IMT) can be a useful tool to improve the respiratory symptoms that occur in patients with CP (Keles et al. 2018). The effectiveness of IMT to improve pulmonary function has already been previously demonstrated in other adult population groups as elderly people (Martin-Sanchez et al. 2021; Seixas et al. 2020), multiple sclerosis patients (Martin-Sanchez et al. 2020; Huang et al. 2020) or Chronic Obstructive Pulmonary Disease patients (Figueiredo et al. 2020). IMT is feasible and effective to improve respiratory muscle strength, pulmonary function, trunk control, daily living activities, functional exercise capacity and quality of life. IMT can be considered as an adjuvant intervention in patients with respiratory disease (Martin-Sanchez et al. 2021; Seixas et al. 2020; Martin-Sanchez et al. 2020; Huang et al. 2020; Figueiredo et al. 2020). These benefits can lead to an improvement in the general condition of adult patients with CP that has not yet been studied.

IMT consists of performing inspirations through a device that opposes resistance to air flow with the consequent improvement of the respiratory muscles. However, the training load is not clearly established. Most authors and the manufacturer recommend working with a load of 30% of maximum inspiratory pressure (MIP), while other authors claim to achieve better results with high loads, 50% MIP (Abodonya et al. 2021; Craighead et al. 2021; McNarry et al. 2022). Recent studies recommend an adequate workload between 5% and 30% of MIP in population with severe disabilities and specifically in people with CP (Keles et al. 2018; Anand and Karthikbabu 2021; Varol-Kepenek et al. 2021).

In the previously mentioned studies, only the improvements achieved with IMT during the training period were analyzed, however there is little evidence in the general population of the maintenance of improvements after having finished the intervention, and there is no evidence in people with CP. The respiratory deficiencies experienced by people with CP determine their approach to respiratory training or treatment. The chronic or persistent nature of the disease requires knowing whether or not the effect of training continues over time and how long that time is, or whether these facts depend upon the type of training performed.

The main objective of this randomized, controlled trial was to investigate how the improvements achieved with IMT are maintained over time in adults with CP. For this, reassessments of respiratory parameters were carried out at 4, 12 and 24 weeks after completing the respiratory intervention. This study analyzed the effects of an 8-week IMT specific protocol on respiratory muscle strength and on pulmonary function in adults with CP.

2 | Materials And Methods

2.1 | Study Design

The research was conducted as a controlled, randomized, double-blind trial with allocation concealment. The Universidad de Salamanca Bioethics Committee confirmed that the study complied with ethical standards for its implementation (registry number 678, October 6, 2021). Additionally, the study was registered in the clinical trials database of the U.S. National Library of Medicine under the registry number NCT04915170.

2.2 | Participants

Institutionalized adults with CP aged between 35 and 64 years were included in the study; they were all members of ASPACE Salamanca. A score higher than 12 in Mini-Mental State Examination (MMSE) was established as an inclusion criterion. The exclusion criteria were the presence of a respiratory disease in the previous month, inability to understand assessment tests or intervention or hemodynamic alterations (heart rate > 150 beats per minute (bpm), systolic blood pressure > 140 millimeters mercury (mmHg) or diastolic blood pressure > 90 mmHg).

2.3 | Procedures and Measures of Outcomes

Adult people with CP were randomly allocated (computerized random assignment) to a HIT or LIT intervention group. Figure 1. The professional that collected the data and the participants were unaware of group assignment. Before (pre-intervention) and after (post-intervention) IMT, respiratory muscle strength and pulmonary function were evaluated. Once the intervention period ended, 3 more evaluations of the same parameters were made, the first at 4 weeks, the second at 12 weeks and the third at 24 weeks after finishing IMT. The revaluation points were determined to analyze the variations of the respiratory parameters in the short term (4 weeks), medium term (12 weeks) and long term (24 weeks). Figure 2.

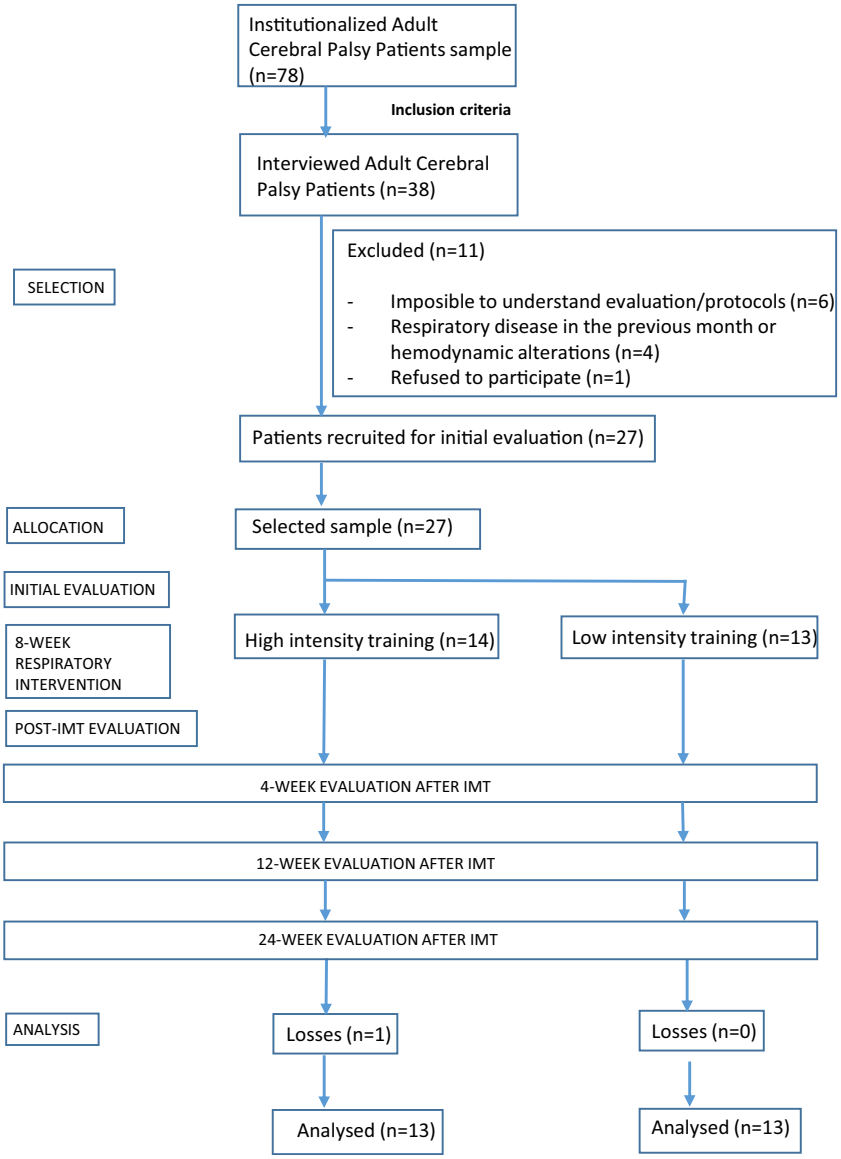

FIGURE 1 | Flowchart of participants. [Color figure can be viewed at wileyonlinelibrary.com]

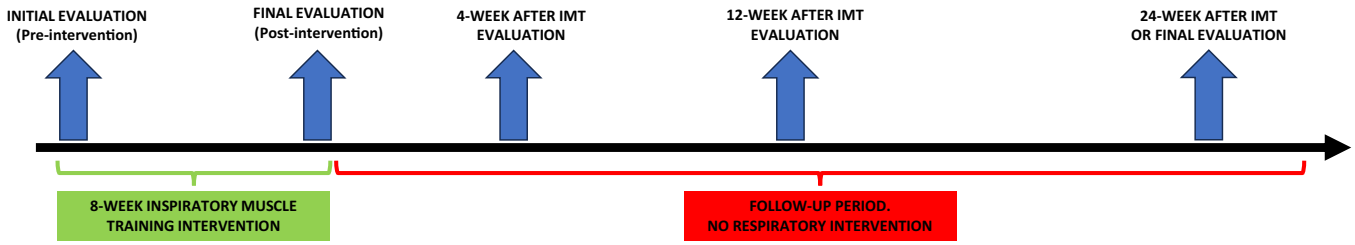

FIGURE 2 | Clinical trial progress. [Color figure can be viewed at wileyonlinelibrary.com]

2.3.1 | Primary Outcome

The primary outcome was respiratory muscle strength, measured pre-IMT, post-IMT and 4, 12 and 24 weeks after finishing the IMT intervention. It was evaluated through MIP and maximum expiratory pressure (MEP) using a pressure measurer (Elka PM-15, Laboliser, S.A., Barcelona, Spain), from residual volume and total lung capacity. Each measure was expressed in millibars and turned into centimeter of water, reference unit, (cm H_2O) (1 mbar = 1.01973 cm H2O), according to recommendations of the American Thoracic Society/European Respiratory Society (American Thoracic Society/European Respiratory Society 2002). The measurements were carried out with the patient sitting, back supported and in the same time slot. The same examiner did all the evaluations. Each test was repeated 3 times or until 2 valid results were obtained (difference less than 5%). A rest time of 1 min was respected between efforts to prevent short-term respiratory muscle fatigue. The highest value was selected. MIP was evaluated every 2 weeks to graduate the load of the device training.

2.3.2 | Secondary Outcome

The secondary outcome was pulmonary function, measured pre-IMT, post-IMT and 4, 12 and 24 weeks after finishing IMT intervention. The data collected were forced expiratory volume in 1 s (FEV_1) and peak expiratory flow (PEF). It was measured using the peak flow device (Asma-1, Vitalograph Ltd, Buckingham, England) that expresses the results of FEV_1 in liters (L) and PEF in liters per minute (L/min), according to the guidelines of the American Thoracic Society/European Respiratory Society (American Thoracic Society/European Respiratory Society 2002). The measurements were carried out with the patient sitting, back supported and in the same time slot. The same examiner did all the evaluations. Each test was repeated 3 times or until 2 valid results were obtained (difference less than 5%). A rest time of 1 min was respected between efforts to prevent short-term respiratory muscle fatigue.

The determination of inspiratory and expiratory muscle strength as well as pulmonary flow and volume provided global information about the respiratory system of adults with CP. In this way the strength of the respiratory muscles to introduce and expel air from lung and the capacity of the lungs and airway to perform their function can be analyzed. These respiratory parameters are a fundamental tool to detect, classify and follow the course of respiratory diseases.

2.4 | Experimental Protocol

IMT was carried out with a pressure threshold device (Threshold IMT, Philips-Respironics, Pittsburg, PA, USA). Threshold IMT provides consistent and specific pressure for inspiratory muscle strength and endurance training, regardless of how quickly or slowly patients breathe. This device incorporates a flow-independent one-way valve to ensure consistent resistance and features an adjustable specific pressure setting (in cm H_2O) to be set by a healthcare professional. When patients inhale through Threshold IMT, a spring-loaded valve provides resistance. Before training began, the participants and primary caregivers completed one-session familiarization with a specialist to learn how to operate the device.

Adults with CP participated in an 8-week training program, attending one session daily, 5 days a week. Each session consisted of 10 sets of 1 min of exercise, with 1 min of rest in between.

The HIT Group engaged in IMT at 40% of their MIP, with the training load adjusted every 2 weeks to maintain this intensity. The LIT Group performed IMT at 20% of MIP, following the same guidelines as HIT.

The training protocols for both groups were designed by a respiratory therapy specialist, and all IMT sessions were supervised by their primary caregivers. Caregivers provided the necessary help if any patient had difficulty controlling their head or arms to hold the device during the respiratory training session. This ensured adherence to the program and monitoring for any potential side effects, such as increased fatigue, breathing difficulties, dizziness, or nausea.

Throughout the intervention period, both groups continued their regular activities, receiving physiotherapy treatment for 45 min, twice a week. No participants received any other treatment during this time.

After finishing the 8-week intervention period with IMT, all the subjects who participated in the study stopped doing this training as part of their rehabilitation. CP patients continued with their daily normal activities and rehabilitation sessions without including IMT. During the following 24 weeks (without IMT), three evaluations of the respiratory parameters analyzed in the trial were made (MIP, MEP, FEV_1, PEF). The first evaluation was made 4 weeks after the intervention was completed, the second 12 weeks and the third 24 weeks after finishing IMT.

2.5 | Statistical Analysis

Given our limited sample size of 26 participants (13 in each group) who completed all 5 time points of the study, we were powered at 80% and 5% level of significance to detect only very large effect sizes for the group effect ($f = 0.574$), the time effect ($f = 0.715$), and the group-by-time interaction ($f = 0.715$), where $f = 0.1$ is considered "small", $f = 0.25$ is considered "medium" and $f = 0.40$ is considered "large" (Cohen 1988).

To test for the effects of the group differences over the 5 time points, a RM-ANOVA (Repeated Measures Analysis of Variance) was performed. This approach analyzes data where multiple measurements are taken on the same subjects, allowing for the evaluation of the influence of different conditions or treatments on a dependent variable over time. In our case, we performed four separate analyses, one for each of the dependent variables (MIP, MEP, FEV_1, and PEF). For each of these variables, five evaluation time points were studied (pre-intervention, post-intervention, 4 weeks, 12 weeks, and 24 weeks after the completion of the IMT treatment), and compared by the subjects' group membership (HIT group and LIT group). Before conducting the RM-ANOVA, normality assumptions were tested using the Shapiro-Wilk test and sphericity was tested using Mauchly's test. This test evaluates whether the variances of the differences between conditions (time points) are homogeneous. In more technical terms, it tests the null hypothesis that the covariance matrix is spherical (i.e., all variances are equal and covariances are equal among them). When Mauchly's test indicates a violation of sphericity (i.e., the null hypothesis is rejected), the Greenhouse-Geisser correction (when the violation is severe, p-value < 0.01) and Huynh-Feldt correction (when the violation is moderate, p-value between 0.01 and 0.05) are used to adjust the degrees of freedom in the ANOVA, using the epsilon (ε) index. Finally, Bonferroni adjustment was applied to adjust for multiple pairwise comparisons.

3 | Results

78 people with CP belonged to the association and were considered for the study sample. 38 patients with CP met the inclusion criteria and were selected to participate in the study. After applying the exclusion criteria, 27 participants were

voluntarily recruited to participate in respiratory training and randomly distributed in the HIT or LIT group. Figure 1. The sample size was small due to the diversity of affectation that exists in CP patients and the difficulty in recruiting patients who met the inclusion and exclusion criteria.

The study sample comprised 15 men and 12 women. None of the participants has worked during their lifetime, and all of them have received education in the association's various specialized centers at each stage of their lives (special education centers). There was a loss in a patient in the HIT group due to health problems unrelated to the training program. Training adherence was 100%, all the respiratory sessions were supervised by a professional. There were no adverse events in participants.

Gross Motor Function Classification System (GMFCS) and MMSE were evaluated at the beginning of the study. GMFCS: 3.66 ± 0.90; level I ($n = 0$), level II ($n = 3$), level III ($n = 8$), level IV ($n = 11$), level V ($n = 5$). MMSE: 17.96 ± 3.08. The baseline characteristics of the sample are shown in Table 1. Both groups had similar values at the beginning of the clinical trial, no differences were found between groups in the variables before starting the respiratory intervention.

Pre-intervention, post-intervention and 4, 12, 24 weeks after finishing the intervention primary outcomes results and comparison are shown in Table 2.

All the respiratory parameters evaluated presented very low values in the initial evaluation compared to the reference values for the healthy population. MIP was 19% of normal values for healthy population, MEP was 13%, FEV_1 was 56%, and PEF was 21% (Black and Hyatt 1969).

3.1 | Respiratory Muscle Strength

After verifying the normality assumption for all the data, we performed RM-ANOVA.

3.1.1 | Mip

We found statistically significant differences in the MIP measurements at the different time points analyzed (pre-intervention, post-intervention, 4 weeks, 12 weeks, and 24 weeks), with a large effect size: $F(1.55,37.33) = 82.030$, $p < 0.001$, η^2=0.774, $\beta - 1 = 1$. The initial scores ($\bar{X} = 20.88 \pm SD = 5.71$) were significantly lower than those obtained after the 8-week IMT training protocol ($\bar{X} = 27.31 \pm SD = 7.53$, $p < 0.001$ [95% CI −8.51, −4.34]). These differences remained significant 4 weeks after the IMT ended (27.15 ± 7.53, $p < 0.001$ [95% CI −8.50, −4.04]). The evaluation at 12 weeks showed a notable loss in the improvements gained from the IMT, but the results remained statistically significant compared to the baseline values (23.96 ± 6.38, $p < 0.001$ [95% CI −4.49, −1.67]). Finally, at the 24-week evaluation, almost a complete loss of the improvements was observed; the mean value remained higher than the initial value, but only at the sample level, with no significant differences found (21.65 ± 5.88, $p = 0.434$ [95% CI −1.88, 0.35]).

A significant interaction between the evolution of MIP over time and the training group (HIT and LIT) was found, with a large effect size: $F(1.55,37.33) = 6.064$, $p = 0.009$, $\eta^2 = 0.202$, $\beta - 1 = 0.794$. Both groups showed a similar trajectory across the five time points, with a slightly greater improvement observed in the HIT group, which showed significant differences at all time points compared to baseline values (20.38 ± 6.63). At 8 weeks with IMT (28.77 ± 9.04, $p < 0.001$ [95% CI −11.33, −5.43]); at 4 weeks after finishing IMT (28.62 ± 8.78, $p < 0.001$ [95% CI −11.38, −5.08]); at 12 weeks (25.08 ± 7.41, $p < 0.001$ [95% CI −6.69, −2.70]); and at 24 weeks after the intervention (22.38 ± 6.96, $p = 0.006$ [95% CI −3.58, −0.42]). In the LIT group, the observed improvement was slightly lower, even leading to a complete loss of the improvement obtained during the treatment, with some cases showing values lower than those obtained in the initial evaluation. Thus, statistical significance was only found between baseline values (21.38 ± 4.84), at 8 weeks with IMT (25.85 ± 5.62, $p < 0.001$ [95% CI −7.41, −1.51]), and at 4 weeks after finishing IMT (25.69 ± 6.01, $p = 0.003$ [95% CI −7.46, −1.15]). No differences were found at 12 weeks (22.85 ± 5.23, $p = 0.329$ [95% CI −3.46, 0.533]) or at 24 weeks after the intervention (20.92 ± 4.73, p = 1 [95% CI −1.12, 2.04]).

3.1.2 | Mep

We found statistically significant differences in the MEP measurements at the different time points analyzed (pre-intervention, post-intervention, 4 weeks, 12 weeks, and 24 weeks), with a large effect size: $F(2.38,57.23) = 83.88$,

TABLE 1 | Baseline characteristics of the sample (mean ± SD).

Parameters	High intensity training ($n = 3$)	Low intensity training ($n = 13$)	Full sample ($n = 26$)
Age (years)	44.31 ± 12.15	47.31 ± 6.52	45.81 ± 9.67
MIP (cm H2O)	20.38 ± 6.63	21.38 ± 4.84	20.88 ± 5.71
MEP (cm H2O)	25.08 ± 5.82	25.46 ± 5.08	25.27 ± 5.36
FEV1 (liters)	1.26 ± 0.34	1.25 ± 0.25	1.26 ± 0.29
PEF (liters/minute)	69.23 ± 19.70	64.23 ± 15.56	66.73 ± 17.58

MIP: Maximum inspiratory pressure; MEP: Maximum expiratory pressure; cm H2O: centimeters of water; FEV1; Forced Expiratory Volume in 1 s; PEF: Peak Expiratory Flow.

TABLE 2 | Pre-intervention, post-intervention and 4, 12, 24 weeks after intervention primary and secondary outcomes. Mean, Standard deviation, percentage and *p*-value.

Variable	Group	Pre-Intervention X(SD)	Post-Intervention			4 weeks			12 weeks			24 weeks		
			X(SD)	%	*p*	X(SD)	%	*p*	X(SD)	%	*p*	X(SD)	%	*p*
MIP	HIT	20.4 (6.6)	28.8 (9.0)	41	< 0.001	28.6 (8.8)	40	< 0.001	25.1 (7.4)	23	< 0.001	22.4(7.0)	9.8	0.006
	LIT	21.4 (4.8)	25.8 (5.6)	21	< 0.001	25.7 (6.0)	20	0.003	22.8 (5.2)	7	0.329	20.9(4.7)	−2.2	1.000
MIP Model: Time effect $F(1.55, 37.33) = 82.030$, $p < 0.001$, $\eta^2 = 0.774$; Group-by-Time effect $F(1.55, 37.33) = 6.064$, $p = 0.009$, $\eta^2 = 0.202$; Group effect $F(1, 24) = 0.447$, $p = 0.510$, $\eta^2 = 0.018$.														
MEP	HIT	25.1 (5.8)	30.8 (6.6)	23	< 0.001	29.6 (5.9)	18	< 0.001	27.2 (5.8)	9	< 0.001	25.2(5.8)	1	1.000
	LIT	25.5 (5.1)	27.5 (5.2)	8	0.010	26.7 (5.5)	5	0.196	25.4 (5.1)	−0.3	1.000	24.4(5.1)	−4	0.028
MEP Model: Time effect $F(2.38,57.23) = 83.88$, $p < 0.001$, η^2=0.778; Group-by-Time effect $F(2.38,57.23) = 14.212$, $p < 0.001$, η^2=0.372; Group effect $F(1, 24) = 0.632$, $p = 0.435$, $\eta^2 = 0.026$.														
FEV1	HIT	1.26 (0.34)	1.37 (0.33)	9	0.001	1.35 (0.33)	7	0.021	1.28 (0.32)	1	1.000	1.25(0.32)	−1	1.000
	LIT	1.26 (0.25)	1.30 (0.24)	4	0.648	1.29 (0.25)	2	1.000	1.23 (0.25)	−2	0.809	1.20(0.26)	−4	0.021
FEV1 Model: Time effect $F(1.33,31.99) = 39.82$, $p < 0.001$, η^2=0.624; Group-by-Time effect $F(1.33,31.99) = 2.54$, $p = 0.112$, η^2=0.096; Group effect $F(1, 24) = 0.165$, $p = 0.688$, $\eta^2 = 0.007$.														
PEF	HIT	69.2 (19.7)	79.1 (19.5)	14	< 0.001	77.4 (19.5)	12	0.002	71.0 (18.4)	3	1.000	68.6(18.3)	−1	1.000
	LIT	64.2 (15.6)	66.1 (16.0)	3	1.000	64.1 (15.9)	−0.2	1.000	59.5 (17.2)	−7	0.055	58.2(17.3)	−9	< 0.001

PEF Model: Time effect $F(1.52,36.46) = 40.62$, $p < 0.001$, $\eta^2 = 0.629$; Group-by-Time effect $F(1.52,36.46) = 7.86$, $p = 0.003$, η^2=0.247; Group effect $F(1, 24) = 2.379$, $p = 0.136$, $\eta^2 = 0.090$.
FEV1: Forced expiratory volume in first second; HIT: High intensity training group; LIT: Low intensity training group; MIP: Maximum inspiratory pressure; MEP: Maximum expiratory pressure; PEF: Peak expiratory flow; p: *P* value Bonferroni correction; SD: Standard deviation; X: Mean; %: Percentage of change.

$p < 0.001$, $\eta^2 = 0.778$, $\beta - 1 = 1$. The initial scores (25.27 ± 5.36) were significantly lower than those obtained after the 8-week IMT training protocol (29.15 ± 6.06, $p < 0.001$ [95% CI −5.05, −2.72]). This improvement was maintained 4 weeks after the IMT ended (28.15 ± 5.78, $p < 0.001$ [95% CI −3.96, −1.81]), but it lost much of its strength over time, showing significant differences at 12 weeks (26.31 ± 5.43, $p < 0.032$ [95% CI −2.02, −0.06]). Finally, at the 24-week evaluation, a complete loss of the improvements obtained was observed (24.81 ± 5.37, $p = 0.548$ [95% CI −0.24, 1.17]).

A significant interaction between the evolution of MEP over time and the training group (HIT and LIT) was found, with a large effect size: $F(2.38,57.23) = 14.212$, $p < 0.001$, $\eta^2 = 0.372$, $\beta - 1 = 0.999$. Both groups showed a similar trajectory over time, but with notable differences during the first month, with better results in the HIT group. The HIT group (25.08 ± 5.82) showed significant differences at 8 weeks with IMT (30.85 ± 6.55, $p < 0.001$ [95% CI −7.41, −4.12]), at 4 weeks after finishing IMT (29.62 ± 5.92, $p < 0.001$ [95% CI −6.06, −3.02]), and at 12 weeks (27.23 ± 5.81, $p < 0.001$ [95% CI −3.54, −0.77]), but lost this improvement by 24 weeks after the intervention (25.23 ± 5.82, $p = 1$ [95% CI −1.15, 0.85]). In the LIT group, the observed improvement was considerably lower, with almost a complete loss of the improvement 1 month after treatment, showing values even lower than the baseline evaluation at 3 months. Thus, statistical significance was only found between baseline values (25.46 ± 5.08) and the measurement at 8 weeks with IMT (27.46 ± 5.22, $p = 0.010$ [95% CI −3.64, −0.36]). No statistical significance was found at 4 weeks after finishing IMT (26.69 ± 5.47, $p = 0.196$ [95% CI −2.75, 0.29]) or at 12 weeks (25.38 ± 5.09, p = 1 [95% CI −1.31, 1.46]). However, it is worth noting that at 24 weeks post-intervention, significant differences were observed (24.38 ± 5.07, $p = 0.028$ [95% CI 0.08, 2.08]), with values lower than those at pre-intervention.

These results, corresponding to respiratory muscle strength, can be visualized in Figure 3, using parallel coordinates accompanied by box plots and the improvements expressed as percentages relative to the baseline values.

Changes in MIP during the clinical trial.

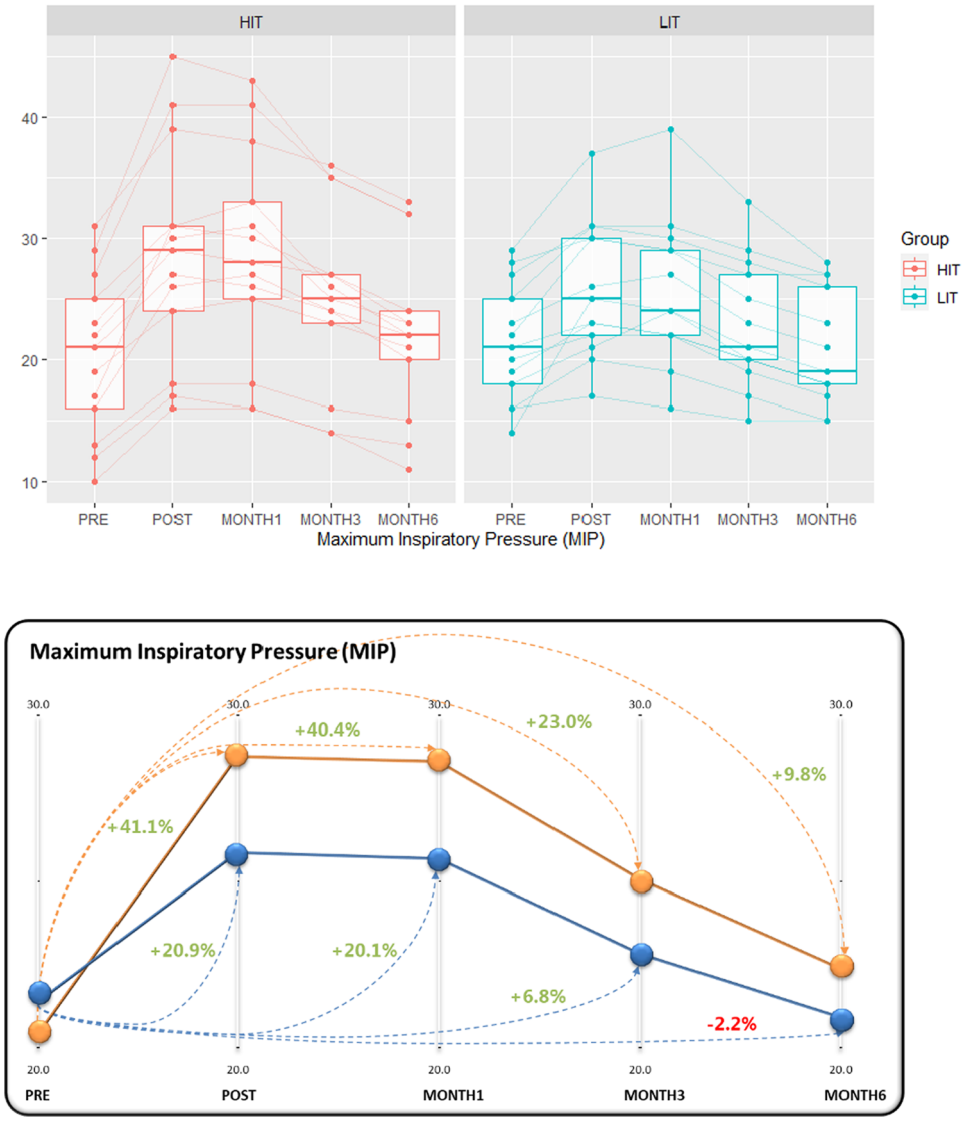

FIGURE 3 | Changes in respiratory strength during the clinical trial. [Color figure can be viewed at wileyonlinelibrary.com]

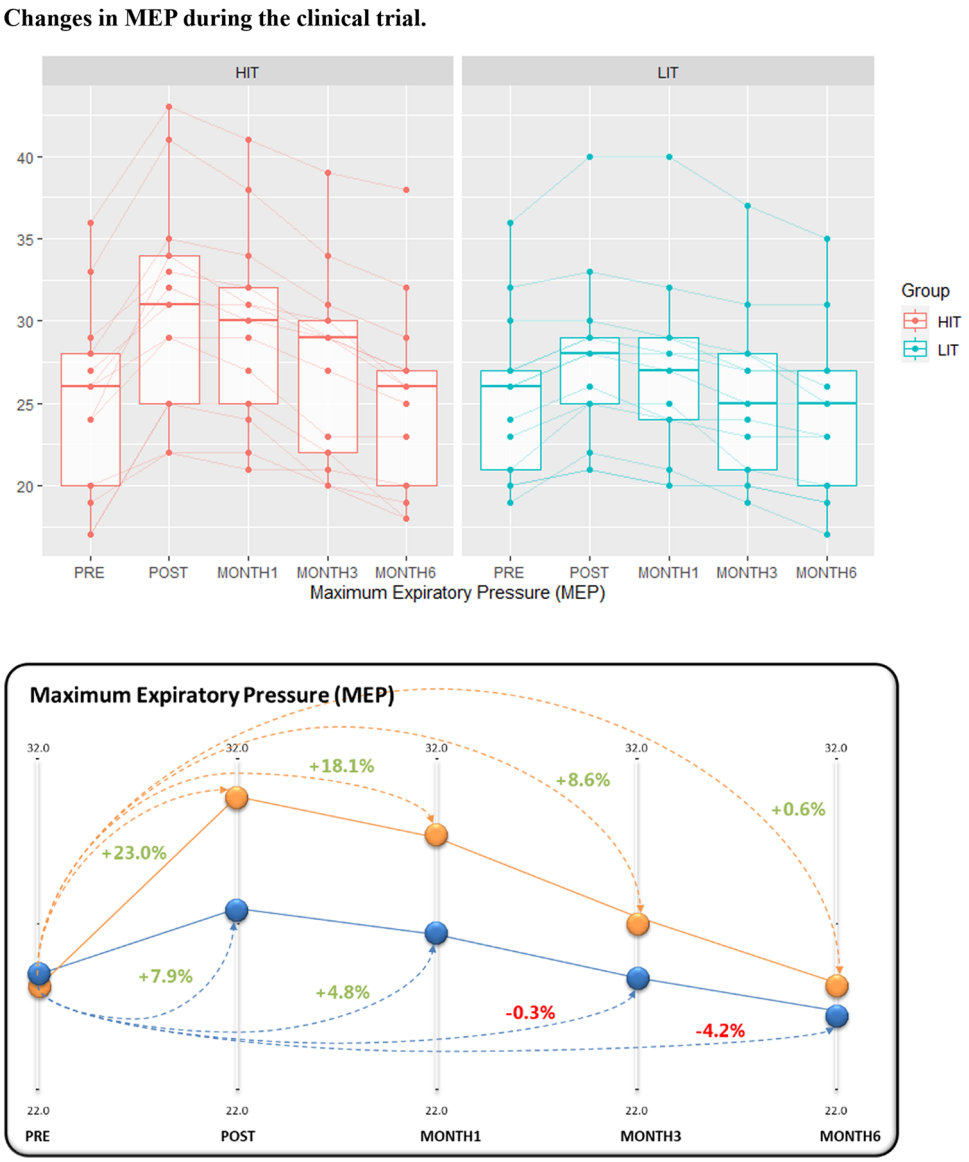

FIGURE 3 | (Continued)

3.2 | Pulmonary Function

3.2.1 | FEV_1

Regarding FEV_1, we found statistically significant differences at the different time points analyzed (pre-intervention, post-intervention, 4 weeks, 12 weeks, and 24 weeks), with the following results: $F(1.33,31.99) = 39.82$, $p < 0.001$, $\eta^2 = 0.624$, $\beta - 1 = 1$. IMT significantly improved FEV_1 (baseline values of 1.26 ± 0.29) after 8 weeks of treatment (1.34 ± 0.29, $p = 0.001$ [95% CI −0.131, −0.025]). The evaluations after completing the intervention showed a continuous loss of the benefits achieved in these parameters. At 4 weeks posttreatment, there was a slight loss, but the results remained above the baseline values (1.32 ± 0.29, $p = 0.030$ [95% CI −0.109, −0.004]). At 12 weeks, the decline was more noticeable, with results below the initial values (1.25 ± 0.28, p = 1 [95% CI -0.028, 0.046]). Finally, at 24 weeks, the decrease in values continued, reaching statistical significance when compared to the baseline values (1.23 ± 0.28, $p = 0.048$ [95% CI 0.000, 0.071]).

We did not find a significant interaction between the evolution of FEV_1 over time and the training group (HIT and LIT), $F(1.33,31.99) = 2.54$, $p = 0.112$, $\eta^2 = 0.096$, $\beta - 1 = 0.387$. However, it is worth noting better results in the HIT group (baseline values 1.26 ± 0.34), with significant improvements after 8 weeks of treatment (1.37 ± 0.33) and at 4 weeks posttreatment (1.35 ± 0.33); values declined at 12 weeks (1.28 ± 0.32) and at 24 weeks (1.25 ± 0.32), falling below the initial values. In the LIT group (baseline values 1.26 ± 0.25), the observed improvement was notably lower, and the decline over time was more pronounced, with measurements at 8 weeks of treatment (1.30 ± 0.24), 4 weeks posttreatment (1.29 ± 0.25), 12 weeks (1.23 ± 0.25), and 24 weeks (1.20 ± 0.26).

3.2.2 | PEF

Finally, we found statistically significant differences in the PEF at the different time points analyzed (pre-intervention, post-intervention, 4 weeks, 12 weeks, and 24 weeks), $F(1.52,36.46) = 40.62$, $p < 0.001$, $\eta^2 = 0.629$, $\beta - 1 = 1$. In relation to the baseline

values (66.73 ± 17.58), improvement was only significantly noticeable at 8 weeks of treatment (72.58 ± 18.67, $p = 0.001$ [95% CI −9.73, −1.96]). This improvement lost strength over time, becoming nonsignificant at 4 weeks posttreatment (70.73 ± 18.80, $p = 0.058$ [95% CI −8.08, 0.08]), and continued to decrease, showing values below the baseline at 12 weeks (65.27 ± 18.41, p = 1 [95% CI −1.90, 4.82]) and 24 weeks (63.38 ± 18.21, $p = 0.008$ [95% CI 0.658, 6.034]).

There was a significant interaction between the evolution of PEF over time and the training group (HIT and LIT), with a large effect size $F(1.52,36.46) = 7.86$, $p = 0.003$, $\eta^2 = 0.247$, $\beta - 1 = 0.883$. However, PEF only significantly increased in the HIT group (baseline values 69.23 ± 19.70) at 8 weeks of IMT (79.08 ± 19.46, $p < 0.001$ [95% CI −15.34, −4.35]) and at 4 weeks posttreatment (77.38 ± 19.46, $p = 0.002$ [95% CI −13.93, −2.38]). This improvement was nearly completely lost at 12 weeks (71.00 ± 18.41, $p = 1$ [95% CI −6.53, 2.99]) and fully lost at 24 weeks (68.62 ± 18.28, p = 1 [95% CI −3.19, 4.42]).

In the LIT group (baseline values 64.23 ± 15.56), no significant changes were observed over time, as the improvement at 8 weeks of IMT was minimal (66.08 ± 15.99, p = 1 [95% CI −7.34, 3.65]). Furthermore, patients worsened, showing values below the baseline at 4 weeks posttreatment (64.08 ± 15.89, $p = 1$ [95% CI −5.62, 5.93]) and continued to decline at 12 weeks (59.54 ± 17.21, $p = 0.055$ [95% CI −0.064, 9.45]), with significant results at 24 weeks post-intervention due to the deterioration of the patients (58.15 ± 17.25, $p < 0.001$ [95% CI 2.28, 9.88]).

A very interesting result of this study was that 24 weeks after the respiratory intervention all the variables evaluated were reduced with respect to the initial values in both groups. While in HIT the reduction was minimal or even remained very similar to the initial values, in LIT the loss was more considerable, even this decrease became significant in PEF and FEV_1. Pulmonary function changes are shown in Figure 4.

4 | Discussion

This is the first randomized, controlled trial that studies the long-term effects (once the respiratory training has finished) of

Changes in FEV_1 during the clinical trial.

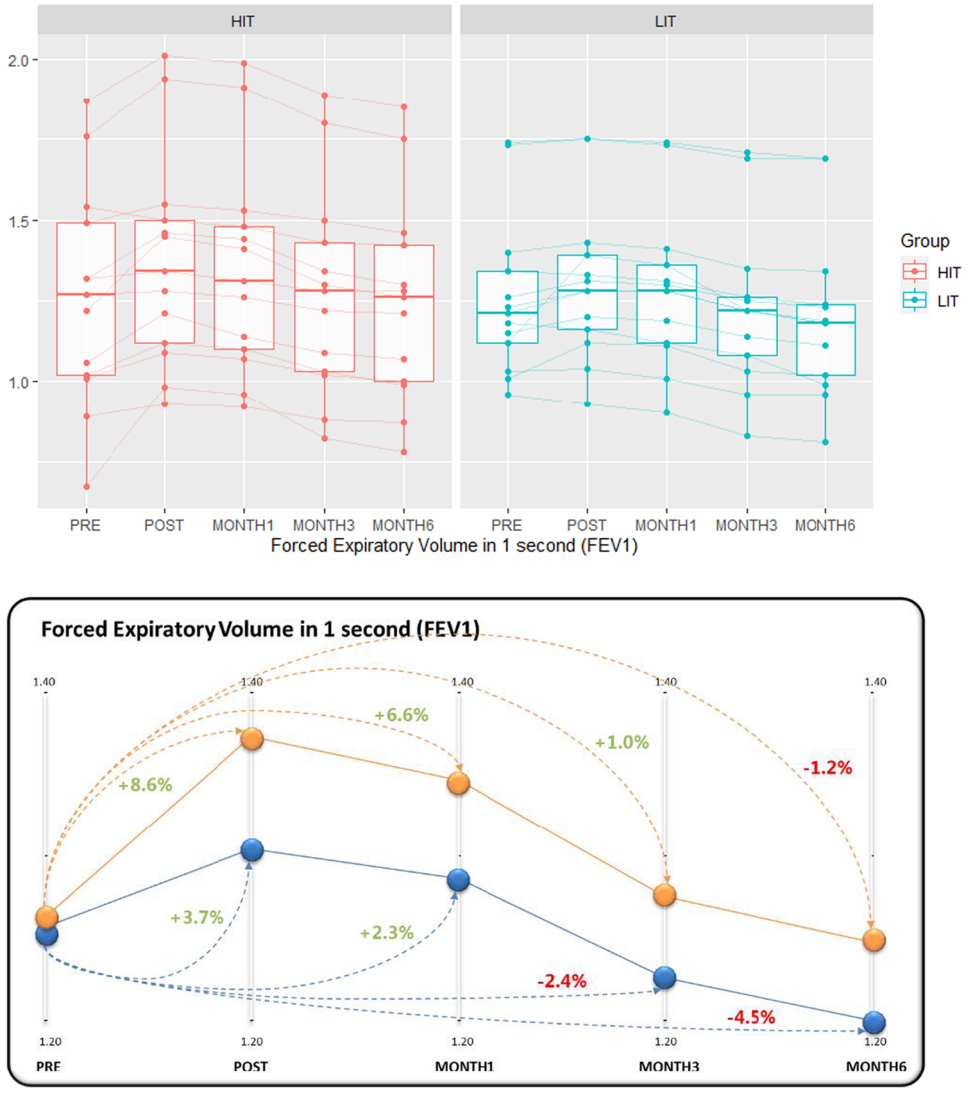

FIGURE 4 | Changes in pulmonary function during the clinical trial. [Color figure can be viewed at wileyonlinelibrary.com]

Changes in PEF during the clinical trial.

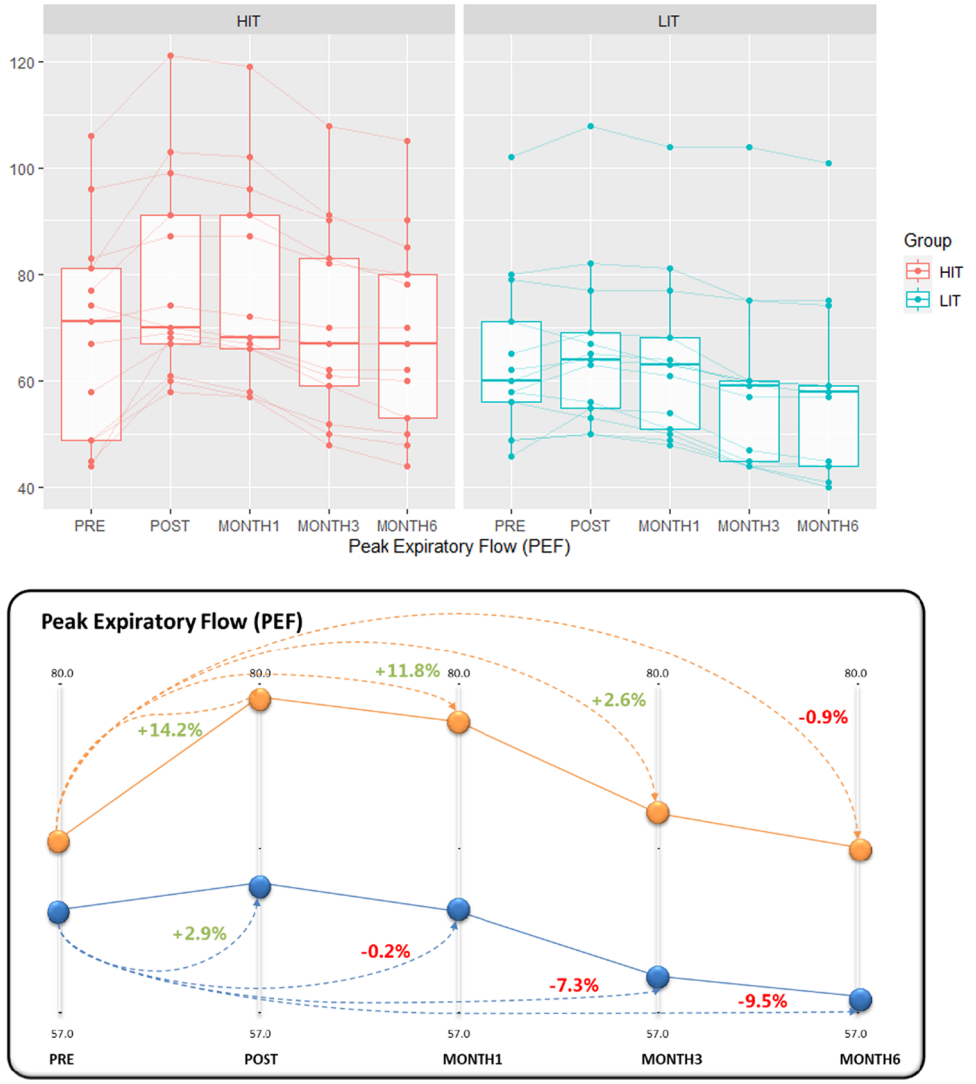

FIGURE 4 | (Continued)

a supervised IMT program in adult people with CP. While there was an improvement in respiratory parameters after 8-week of IMT, the results of the present study showed that most of these benefits were maintained 4 weeks after the end of the intervention then progressively decreased, losing part of the benefits at 12 weeks and almost all of them at 24 weeks. To be more informative, two IMT programs were analyzed, one with a high load (40% MIP; HIT) and the other low (20% MIP; LIT). We conclude that high loads were more effective to improve respiratory parameters in this population and to maintain the effects over time.

The analyzed sample was adult institutionalized people with CP with an average age of 46 years and a very important limitation at the respiratory level, with greatly decreased values with respect to the reference values for a healthy population.

Considering the limitation in the respiratory parameters presented by this population, it was decided to train the inspiratory muscles with low to medium loads. Participants had GMFCS levels between II and V, all of them preserved cognitive and cooperative function to effectively perform the training protocol. Those patients who had some physical limitation in the control of the head or arms to hold the device during the training sessions received the necessary help from their primary caregiver. Previous studies have only included population classified with GMFCS levels I-IV, with no inclusion of people with level V (Cayeiro-Marín et al. 2024). In this case, patients had better respiratory function and mobility than our sample. Therefore, this study will provide new information on respiratory therapy in most affected people with CP.

Life expectancy in people with CP generates controversy, and there are no exact data today. Some specialized agencies claim that life expectancy is between 30 and 60 years (ASPACE 2020; Birth Injury Center 2022) and a recent study stated that 22% of people with CP lived 58 years or older (Blair et al. 2019). In this way, our study sample would be included within adult people with CP.

4.1 | Effects of IMT on Respiratory Muscle Strength

Previous studies have shown that IMT improves respiratory muscle strength (MIP and MEP) in CP patients. When performing training of the inspiratory muscles, the most benefitted parameter is usually MIP, and the improvements obtained are greater training with higher loads (Abodonya et al. 2021; Lee et al. 2014; Kepenek-Varol et al. 2022). However, improvements in MEP are also observed with IMT, also greater in patients trained with higher loads. This happens due to repeated exposure to the same stimulus (learning effect), a mechanism that develops an increase in respiratory muscle strength by improving neuromuscular recruitment pattern (Kamen 2005).

The main objective of this clinical trial was to evaluate the maintenance of effects obtained with IMT in CP people. There are currently no studies analyzing these effects in patients with CP.

The results presented in this study reveal that the improvements obtained after 8-weeks of IMT are maintained during the first 4 weeks after the intervention, presenting results like those obtained in the post-intervention evaluation. In the second evaluation carried out at 12 weeks, a significant loss of the improvements obtained in respiratory strength between 10% and 20% was already observed. In the last evaluation, performed at 24 weeks, respiratory strength was close to the values before the IMT intervention or even lower. This is explained by the constant loss in muscle mass suffered by adult people, affecting the respiratory muscles among others. There is an established link between inactivity and losses of muscle mass and strength, this suggests that physical activity should be a protective factor for the prevention but also the management of sarcopenia (Santilli et al. 2014). Therefore, proper training of the respiratory muscles is essential in CP patients who tend to lose functionality in all their muscles over time. IMT is presented as one of the best options for respiratory treatment in this population. It is necessary to find a specific work protocol (time and load of training with the device) that achieves the best results in this aspect.

Analyzing the data individually, high loads achieved greater improvements during the intervention period and managed to maintain these improvements for longer than low loads. Respiratory strength (MIP and MEP) was the only variable that remained above the initial values 24 weeks after the intervention, and only in patients trained with high loads. Therefore, a higher training load was more effective in maintaining the improvements obtained with IMT in CP patients.

4.2 | Effects of IMT on Pulmonary Function

FEV_1 and PEF were measured to evaluate the pulmonary function. Both parameters improved after IMT, however this improvement was more noticeable in high intensity group.

Although the benefits obtained after IMT were lower in the pulmonary function than in the respiratory strength, part of these improvements were maintained over time. Training with high loads again achieved greater improvements and a longer maintenance time of these results.

Four weeks after IMT, pulmonary function was like post-intervention evaluation in HIT but there was a loss about 10% in LIT.

Twelve weeks after intervention, the decrease of all parameters was important, and the results were like those of preintervention evaluation. Training with high loads managed to keep PEF and FEV_1 values above initial values. However, those patients who trained with low loads suffered a small loss in these parameters.

Twenty-4 weeks after the respiratory intervention all the variables evaluated were reduced with respect to the initial values in both groups. While in HIT the reduction was minimal or even remain very similar to the initial values, in LIT the loss was more important, even this decrease became significant.

In the same way that it happened with respiratory muscle strength, pulmonary function improvements were greater with high loads, and these improvements were maintained for a longer period than with low loads. A load of 40% MIP (high intensity) was well tolerated by all participants and the results obtained were better than with a 20% MIP load. A load of 20% MIP manages to improve respiratory strength. However, the improvements obtained are insufficient, and their loss over time is faster. Respiratory training with threshold devices in people with CP must be carried out with a minimum load of 40% MIP to achieve the greatest improvements and to maintain them over time.

The loss of the benefits obtained after IMT begins to be remarkable from 12 weeks without training.

Although this intervention is not usually part of a rehabilitation program in patients with CP, it can help to improve the situation of this population group. Analyzing the situation of respiratory rehabilitation in CP patients in our country, Spain, we realized that respiratory intervention was performed based on traditional exercises aimed at improving mobility and helping to mobilize secretions. This is a very important part in the treatment of CP patients, but better results can be achieved by trying to improve respiratory parameters. People with CP have many problems in their daily lives associated with poor respiratory function, mainly due to weakness of the respiratory muscles, accumulation of secretions, alterations in chest, ineffective coughing, or shortness of breath.

IMT has been shown to improve respiratory muscles and lung function in different population groups, but so far there is no study in adult people with CP. Showing the benefits that this training can achieve, it could become part of the treatment. The improvement of respiratory strength and pulmonary function enhances respiratory function and combats all the respiratory problems mentioned above that patients with CP may suffer.

On the other hand, IMT serves as feedback to improve the respiratory pattern and train oral inspiration and expiration, difficult to find in most patients.

Carrying out a novel exercise as part of their rehabilitation improves adherence to treatment.

Using a resistometer for respiratory training can help make more complete respiratory evaluations. The determination of respiratory muscle strength, volumes and pulmonary flows (spirometry) is necessary in this type of patient; currently it is something that is not routinely done in this population. It would help to know the state of the respiratory system of our patients and to measure the progression and effectiveness of treatments.

Our aim was to show that IMT is safe and effective in adults with CP and that it can be a great complement for rehabilitation and more specifically for respiratory rehabilitation. The results obtained in the study support this type of intervention as a promising treatment in patients with CP.

4.3 | Clinical Implications

There is currently no clinical trial that studies the maintenance of the benefits obtained with respiratory training in patients with CP. This study confirms that respiratory training is useful in this population and that this treatment must be maintained over time. There is no clear consensus regarding the training protocol and its maintenance in this population. The benefits achieved with the respiratory intervention are progressively lost once it ends. This study increases knowledge in respiratory training in patients with CP and guidance in the parameters to use as well as the treatment time.

4.4 | Trial Limitations and Future Implications

A limitation of this trial was the lack of inclusion of another group of similar characteristics that did not carry out any respiratory training above their normal daily activity, and that served as a control group.

The duration of the intervention is another limitation, as there are no other similar studies in this population group; we followed the IMT guidelines for other groups. Specialists in respiratory physiotherapy in neurological patients have designed all aspects of the protocols that have been implemented.

Future clinical trials seeking to study the benefits of IMT in institutionalized cerebral palsy patients should evaluate quality of life, trunk control or dyspnea to obtain a better understanding of the effects obtained.

This is the first respiratory study of its kind carried out in adults with CP; it is necessary to continue the investigation in the adult population with CP due to the health problems suffered by people with this disease and the increasing life expectancy appreciated in this population group.

5 | Conclusion

The present study showed that improvements achieved with IMT are reduced over time once the treatment ends. During the first 4 weeks after treatment the benefits persist but from the 12th week there is a progressive loss of the improvement reaching a total loss at 24 weeks and even values lower than the initial ones in some variables. High loads were more effective to improve and to maintain these improvements over time for a longer period than low loads.

Respiratory treatment must be maintained over time and interruptions should not be longer than 4 weeks so as not to lose part of the benefits achieved with training.

Author Contributions

Carlos Martin-Sanchez has been responsible for the design of the protocol, the experimental part and the redaction of the manuscript. Corresponding author and responsible for the integrity of manuscript. Fausto Jose Barbero-Iglesias has collaborated in the project to advise in the main themes of the study and to carry out the evaluation material. Victor Amor-Esteban has collaborated in the project to complete statistical evaluation. Marta Martin-Sanchez has collaborated in the experimental part and the revision of the manuscript. Ana Maria Martin-Nogueras has collaborated in the project to advise and guide in the redaction of the manuscript, the statistical evaluation and the proper elaboration of the complete manuscript.

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Ethics Statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines. This randomised trial complies with internationally-accepted standards for research and practice reporting. All the subjects signed an informed consent. The study protocol was approved by the Bioethics Committee of the University of Salamanca (number of registry 678, 6th October 2021).

Consent

All subjects have been informed and have signed the inform consent before their inclusion in the study.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Further enquiries can be directed to the corresponding author. All the data collected in the study will be shared. Individual deidentified participant data are available. Additional and related documents such as study protocol or statistical analysis are available. The data will be available from publication and for as long as necessary. The data will always be shared with the approval of the corresponding author analyzing the purpose which they are going to be used. The data that support the findings of this study are available from the corresponding author upon reasonable request.

Permission to Reproduce Material From Other Sources

Available.

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