Efficacy of neuromuscular electrical stimulation of calf muscles on nocturnal symptoms and quality of life in asthmatic children

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Abstract. – OBJECTIVE: To determine whether neuromuscular electrical stimulation of calf muscles could improve nocturnal symptoms and quality of life in asthmatic children.

PATIENTS AND METHODS: Sixty children (8-12 years) with moderate asthma were randomly allocated to three groups (A, B, and C). The three groups completed 12 weeks of supervised breathing exercises for 30 min. In addition, group A completed neuromuscular electrical stimulation of the calf muscles and group B completed aerobic exercise in the same period. The intervention was conducted five days a week for 12 consecutive weeks. Pre-and post-treatment evaluations involved pulmonary function tests, the Children's Asthma Control Questionnaire, calf muscle isometric muscle force, six-minute walk test, and Pediatric Asthma Quality of Life Questionnaire.

RESULTS: A significant increase in all measured variables was recorded in all groups in favor of group A ($p < 0.001$). However, calf muscle isometric muscle strength, and nocturnal symptoms were non-significant in group C ($p > 0.05$). There was a significant difference between groups A and C in all measured variables ($p < 0.001$) in favor of group A. Significant differences between groups B and C in all measured variables ($p < 0.001$) in favor of group B were also noted. No significant differences were seen between groups A and B ($p > 0.05$).

CONCLUSIONS: Neuromuscular electrical stimulation of calf muscles is an excellent adjunct to breathing exercise programs in improving nocturnal symptoms and quality of life in asthmatic children. Moreover, it can serve as a considerable alternative to traditional physical training in periods of disease exacerbation.

Key Words:
Asthma, Electrical stimulation, Nocturnal symptoms, Pulmonary function test, Quality of life.

Abbreviations

BMI: Body mass index; C-ACT: Childhood asthma control test; COPD: Chronic obstructive pulmonary disease; QoL: Quality of life; LLs: Lower limbs; FEV_1: Forced expiratory volume in 1 s; FVC: Forced vital capacity; HHD: Hand-held dynamometer; HR: Heart rate; HRQoL: Health-related quality of life; NMES: Neuromuscular electrical stimulation; PAQLQ: Pediatric Asthma Quality of Life Questionnaire; PEF: Peak expiratory flow; PFTs: Pulmonary function tests; 6MWT: Six minute walk test; 6MWD: Six minute walk distance.

Introduction

Asthma is a chronic inflammatory disease that affects a wide range of cells and cellular components in the airway. Intermittent or persistent diseases (mild, moderate, or severe) can be defined according to the existence of daytime and nocturnal symptoms, need for medication, frequency of exacerbations, pulmonary function, and physical activity limits[1]. Chronic inflammation causes airway hyper-responsiveness and blockage, resulting in recurrent attacks of wheezing, dyspnea, chest tightness, and coughing, especially at night or early morning, resulting in reduced quality of life (QoL), psychological well-being, and the ability to engage in everyday physical activities[2]. It affects approximately 19% of children, with 11% having inadequate asthma control[3]. School-aged children have a higher frequency of asthma symptoms[4]. Physical activity is the most frequently stated precipitating factor among school students[5], and this may also be a limiting factor[6].

Patients with asthma may have reduced muscle mass, which includes the respiratory muscles. Consequently, this could be a good target for

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training[7]. Dyspnea is due to the weakening of respiratory and peripheral muscles[8,9], resulting in a decreased pulmonary function not only by blocking airflow, but also by reducing the number of diaphragm muscle fibers[10]. A reduction in skeletal muscle performance is seen regardless of respiratory tract physical function[11]. Hypoxia, systemic inflammation, oxidative stress, malnutrition, disuse, reduced motor neuron activity, type I muscle fiber percentage, activity of oxidative enzymes, increased type IIb muscle fiber percentage, and long-term use of corticosteroids can all contribute to muscle weakness and fatigue, particularly in the lower limbs (LLs)[12]. Muscle deterioration is usually gradual, and subtle[13], leading to general fatigue and irritability[9], decrease in physical activity, sleep disturbances, psychosocial effects, school absenteeism[14], and a significant decrease in QoL[15]. Furthermore, due to the disease-related restrictions, children and adolescents with asthma often experience frustration, shame, and have low self-confidence[16]. They may also avoid physical activities because of parents' anxiety and protectiveness[17]. Reduced muscle strength, motor coordination, and exercise tolerance are all signs of exercise deprivation.

The presence of night-time symptoms is a key indicator of asthma control issues[18]. Despite breakthroughs in pharmacological treatments, a high percentage of patients with asthma have poor asthma control[19]. It has been documented that over two-thirds of asthma patients experience nocturnal worsening of symptoms[20], which are characterized by frequent awakening, chest tightness, increased airway hyper-responsiveness, usage of asthma medications, and reduced lung function. Anti-inflammatory medications and bronchodilators are frequently used to alleviate night-time asthma symptoms. However, nocturnal asthma remains a big issue[21]. The mechanisms that cause nocturnal asthma are multifactorial[22], including fluid accumulation in the thorax (rostral fluid)[23], overnight reduction in plasma cortisol levels, and increase in airway inflammation, which elevates cholinergic tone and promotes airway hyper-responsiveness. Nocturnal asthma causes sleep disruption, fatigue throughout the day, and poor cognitive performance, all of which contribute to a poor QoL[22].

Neuromuscular electrical stimulation (NMES) is routinely used in physical therapy to improve muscle strength and endurance, peripheral circulation, and to retrain motor functions[24]. Under identical technical conditions, NMES stimulates the muscles to a greater extent than voluntary muscular activities[25]. NMES of the LLs increases skeletal muscle mass, strength, exercise capacity, and overall health. Therefore, NMES may be beneficial in the treatment of dyspnea[26]. Based on previous studies[27], NMES can be safely used as an alternative to traditional physical exercises in patients with chronic obstructive pulmonary disease (COPD) during periods of aggravation of symptoms, in advanced stages of the disease, or even in patients receiving respiratory therapy. In comparison to typical physical training, another noteworthy element of NMES is that patients feel less worried during and after the exercise.

A systematic review[28] showed that exercise can reduce the prevalence and frequency of nocturnal symptoms in children and adults. A previous study[29] that compared the effects of breathing and aerobic exercises, concluded that though both are helpful, aerobic exercise is preferable. In individuals with COPD, both strength training and NMES have been shown to have a positive impact on health[26]. Recognizing that fluid accumulation in the thorax is one of the risk factors for poor asthma control has led to the discovery of new medications and a shift in clinical management. Simple treatments for reducing fluid accumulation in the legs, such as physical exercise, may be beneficial to asthma patients[28]. To our knowledge, no previous studies have assessed the effect of NMES on calf muscles in children with asthma. The hypothesis of this study was that NMES of the calf muscle could be as effective as aerobic training in improving nocturnal symptoms and QoL. Thus, the study aimed to determine whether NMES of the calf muscles could improve nocturnal symptoms and QoL in children with asthma.

Patients and Methods

Study Design, Ethics, and Consent

This was a prospective, randomized, parallel-group controlled trial with a planned duration of 12 weeks and conducted at the Abu El-Rish Pediatric Hospital, Faculty of Medicine, Cairo University. The trial was registered with the UMIN-CTR Clinical Trials platform (UMIN000046401). The study was approved by the Ethics Committee of the Faculty of Physical Therapy, Cairo University (NO: P.T.REC/012/003535), and all procedures complied with the Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans. Moreover, it also adhered to the Consolidated Standards of Reporting Trials (CONSORT) guidelines and Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT)[30,31]. The children's parents signed a consent form before the participation in the study. The intent of the study and its procedures were explained to all the parents.

Sample Size

Prior to initiating the study, sample size was calculated using G*POWER statistical software (version 3.1.9.2; Universitat Kiel, Germany). Based on data of forced vital capacity (FVC) from a pilot study conducted on five patients in each group, the required sample size for each group was estimated to be 20. The calculations were performed using alpha = 0.05, power 80%, and effect size 0.42.

Participants

Sixty asthmatic children ranging from 8 to 12 years (36 boys and 24 girls) were enrolled in the study. All the children were selected from the Abu El-Rish Pediatric Hospital. This age range was chosen because it is considered as a transitional time in the development of the respiratory system, marking the end of fast growth and structural changes in the peripheral lung unit[32]. The criteria for inclusion were as follows: persistent moderate asthma [60 < forced expiratory volume in 1 s (FEV_1) > 80% of the predicted value and absence of any exacerbation or change in medication in the preceding 30 days, peak expiratory flow (PEF) values of 60 ± 80% predicted at baseline, but normal after bronchodilator, and daily use of an anti-inflammatory agent at low or moderate][1], body mass index (BMI) within normal, and clinically-stable conditions (i.e., no changes in the medications for over one month and taking maintained doses of drugs in the past 3 months). None of the participants was involved in any other regular exercise program during the study period. The medical follow-up was performed by the same physician.

Exclusion criteria included exacerbation of asthma symptoms that required the use of systemic corticosteroids in the past month or during the study period, thoracic surgery, chronic sinusitis, cardiovascular diseases, musculoskeletal disorder, costovertebral fractures, spinal deformities, recent calf strains, compartmental leg syndrome, muscle relaxants and histamines, and inability to cope with the protocol for intervention and tests after the familiarity sessions.

Randomization, Allocation, and Blinding

Seventy children were examined for eligibility by the research coordinator. Ten children were excluded (eight did not meet the eligibility requirements, and parents of two did not allow participation), thus 60 children participated in the study. Following recruitment, the children were randomly allocated to one of three groups (A, B, or C) using a computer-generated randomization schema stratified through permuted blocks of randomly varying sizes. As the study was blinded, the block sizes were not revealed.

Following randomization (concealed allocation), the group allocation was revealed only to the non-blinded physiotherapist who was not involved in the study using computer software (Clean Web) after. The children were informed verbally by a physiotherapist. An independent statistician who was not part of the study created a randomization list before the investigation began. None of the children dropped out of the study. The study followed the CONSORT principles; Figure 1 depicts the experimental flow diagram[31].

Outcome Measurements

Medical history was used to assess eligible children and a preliminary assessment of body height (cm) and weight (kg), using a weight and height scale (health scale 70, made in China), was undertaken on those who met eligibility. Weight was calculated to the closest 0.1 kg, and the BMI was calculated.

All participating children in each group were measured under similar conditions, immediately before and after 12 weeks of treatment. A researcher who was blinded to the group allocations performed both the measurements. Pulmonary function tests (PFTs), asthma control, nocturnal symptoms, and calf muscle isometric muscle force were considered the primary outcomes, whereas the secondary outcome measures included the six-minute walk test (6MWT), and QoL. All evaluations were performed on a single day. The children did not use a bronchodilator for less than 12 h prior to the evaluation.

Pulmonary Function Tests

The PFTs was measured using a Master Screen IOS spirometer, 1999 (Jaeger, Würzburg, Germany). The percent-predicted values of FVC, FEV_1, FEV_1/FVC ratio, and PEF were measured. Each child was seated in a comfortable position. Initially, the child was instructed to breathe normally with the lips tightly closed on the mouthpiece.

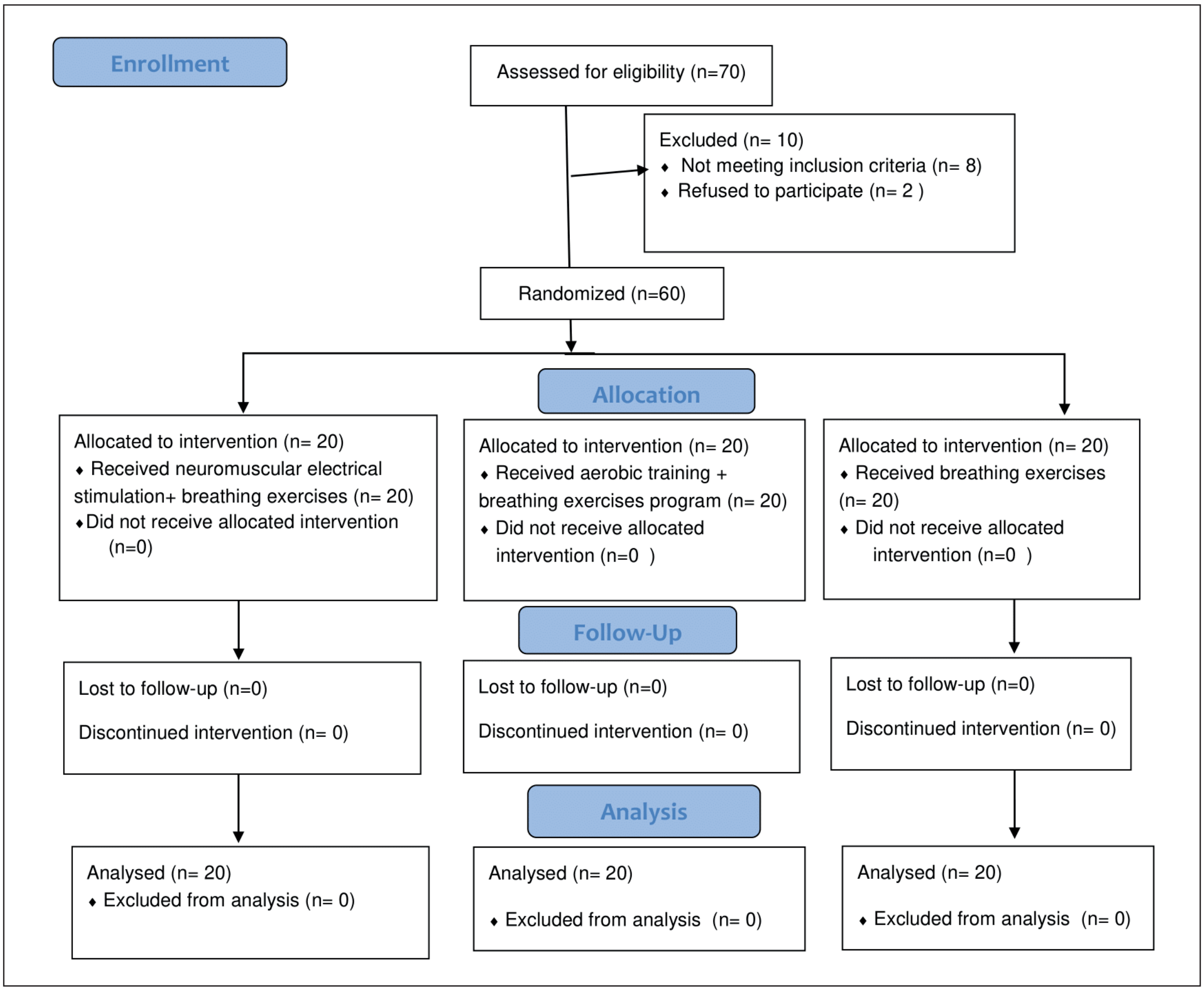

Figure 1. CONSORT flow diagram showing the experimental design of the study.

After a few breaths, each child was instructed to take several normal breaths. Following this, the child was instructed to breathe slowly and deeply as much as possible, followed by strong exhalations. The test was repeated thrice, and the most acceptable and repeatable data were taken[33]. The FVC and FEV_1 values from the three tests were within 10% of the highest values[34].

Asthma Control and Nocturnal Symptoms

The Childhood Asthma Control Test (C-ACT) was used to measure asthma control. This test includes seven items and is divided into two sections that were used in our study to evaluate asthma in the preceding 4 weeks[35]. The first section consists of four questions about the child's perception of asthma, activity limitation, coughing, and nocturnal awakening. Children are individually asked to select one answer from the four options for each question. A score is assigned to each response. The second section comprises three questions related to daily complaints, daytime wheezing, and night-time awakening. Each question has six response options, which are to be completed by the parents or caregivers[36]. The total scores from the sum of all seven items (0 = least asthma control, 27 = most asthma control; cutoff point ≤ 19 = poor asthma control). Furthermore, two C-ACT questions ($C\text{-}ACT_{3,7}$) linked to nocturnal symptoms were assessed separately.

Isometric Muscle Force

A handheld dynamometer (HHD, model 01165; Lafayette Instrument Company, Lafayette, IN, USA) was used to measure the isometric muscular force of the calf muscles. During a 5-s interval, the peak force in Newtons (N) was measured. The test was repeated thrice consecutively, and the greatest force was recorded. Ankle plantar flexion strength was measured while the child was in a long sitting position with the heel above the plinth edge. The HHD was placed on the plantar surface of the dominant leg, proximal to the first metatarsal head, with the force transducer being perpendicular to the metatarsals[37].

Six-Minute Walk Test

The 6MWT was used to assess the functional capacity of the children with lung disease-limited effort. Compared to healthy children, asthmatic children have a decreased six-minute walk distance (6MWD)[38]. The child was instructed to walk for 6 min at maximum speed on an unobstructed rectangular pathway while maintaining a steady pace without running. Monitoring pulse oximetry (SpO_2) was essential, then the child held a pulse oximeter on his or her hand. The test was conducted under the supervision of a researcher who stood at the center of the track, encouraging the child, and checking the pulse oximeter. The timer continued to run during any pause over the test. The distance was measured to the closest meter using track markings.

Quality of Life Assessment

The Pediatric Asthma Quality of Life Questionnaire (PAQLQ) was used to assess the QoL. This is a valid and reliable multidimensional asthma-specific and age-appropriate tool for assessing the health-related quality of life (HRQoL) of children and adolescents with asthma, aged 7-17 years[39]. It comprises 23 questions that span three domains: 5 about activity limits, 10 symptoms-related, and 8 related to emotional functions.

The PAQLQ rates the items on a 7-point Likert scale (1 = 'poor' and 7 = 'excellent' QoL). The mean response to all items in each domain was used to compute the domain score. The average of the mean scores for the three domains was used to calculate the overall score. The higher the score, the better the perception of the HRQoL.

Intervention

All children in the three groups performed breathing exercises for 30 min/5 days/week for 12 successive weeks. In addition, children in groups A and B underwent NMES of the calf muscles and aerobic training, respectively for 30 min/day, thrice a week. Each program was conducted by the same researcher. During the study, eligible children did not participate in any other activities or receive any injections or medication.

During treatment sessions, the researcher monitored and verified compliance. Before beginning the intervention, children were shown how to ensure that they could complete it appropriately. The adherence rate was approximately 98%, which depended on the attendance of the child and his/her completeness of the exercises. Child attendance was calculated by considering the total number of attended prescribed visits. The researchers checked the completeness of the interventions using the Template for Intervention Description and Replication (TIDieR) checklist and guide[40]. Dropout of the child from the study was considered when more than two sessions were missed, and the completeness was < 90% of the exercises.

Criteria for Discontinuation

Discontinuation was suggested if asthma symptoms or any other medical condition for which exercise was contraindicated worsened. Parents were therefore instructed to complete a training diary to record their medication, any side effects from therapy sessions (such as fatigue), and symptoms during the day and night. They were advised to contact the general practitioner and the study researcher if their child's symptoms worsened. During the 12-week treatment period, none of the children experienced any exacerbations.

Breathing Exercises

During the familiarization session, the children and their parents were taught about normal breathing patterns, such as nasal, diaphragmatic, quiet, slow, and regular breathing, as well as how diaphragmatic breathing, such as over-breathing, mouth breathing, and upper chest breathing, can affect asthma symptoms. Breathing exercises were conducted with the patients seated and in the supine position. Breathing exercises included diaphragmatic, lateral costal, and pursed-lip exercises. Each exercise was repeated in three sets of 10 repetitions for 10 min with a 5 min rest between each set.

Aerobic Training

Children in group A underwent supervised aerobic training using an electric treadmill (Pro-Form®, model 325i, São Paulo, Brazil) for 30 min (day-to-day), thrice a week for 12 weeks in an acceptable setting at a temperature of 22-25°C. The children wore sport shorts and shoes. The exercise included a 5 min warm-up, a 20 min training, and a 5 min cool-down. The warm-up and cool-down comprised of mild treadmill walking at 40-50% of maximal heart rate (HR). The intensity of the exercise was

Table I. Participants' characteristics.

		Group A	Group B	Group C	*p*-value
		mean ± SD	mean ± SD	mean ± SD	
Age (years)		10.05 ± 1.45	10.2 ± 1.39	10.47 ± 1.25	0.61
Weight (kg)		32.32 ± 6.04	32.47 ± 5.51	32.42 ± 5.32	0.79
Height (cm)		136.9 ± 8.56	137.7 ± 7.11	138.35 ± 6.83	0.83
BMI		17.07 ± 1.25	16.97 ± 1.17	17.33 ± 1.16	0.61
Sex	Boys	12 (60%)	13 (65%)	11 (55%)	0.81
	Girls	8 (40%)	7 (35%)	9 (45%)	

BMI: Body Mass Index; SD: standard deviation; *p*-value: level of significance; *: significant at $p < 0.05$.

managed by maintaining 70-80% of maximum HR with reference values derived using the Karvonen algorithm[41]. Before and after each exercise session, HR, respiratory rate, and SpO_2 were measured. The children were instructed to take β2 agonists before or during the session, if necessary.

Electrical Stimulation Protocol

A 4-channel neuromuscular stimulator (Compex Motion, Switzerland) was used to perform NMES of the gastrocnemius muscles. Electrodes (5 cm x 9 cm, StimTrode, Axelgaard Manufacturing, California, USA) were positioned over the approximate position of the motor points of calf muscle group of both legs[42]. The stimulation was conducted for 30 min (day-to-day) thrice per week for 12 weeks. An asymmetrical biphasic waveform, with a frequency of 40 Hz and pulse duration of 300 µs, was used at the maximally tolerated stimulation amplitude (typically between 20 and 40 mA) for 2 s on, followed by 2 s off. The calf muscles of both legs were stimulated out of sync, such that when the right gastrocnemius was contracted, the left leg got relaxed and vice versa[43].

Statistical Analysis

An ANOVA test for numerical data and a Chi-square test for categorical data were conducted to compare the participants' characteristics among the three groups. The normal distribution of data for all variables was checked using the Shapiro-Wilk test. Levene's test for homogeneity of variance was conducted to ensure homogeneity between the groups. To compare the within-and between-group effects on PFTs (FVC, FEV_1, FEV_1/FVC, PEF), C-$ACT_{3,7}$, C-ACT, calf muscle isometric muscle force, 6MWD, and PAQLQ (activity limitation, symptoms, emotional function, and overall score), a mixed-model multivariate analysis of variance (MANOVA) was performed. Post-hoc tests using the Bonferroni correction were carried out for subsequent multiple comparisons. Statistical Package for Social Studies (SPSS) version 25 for Windows (IBM Corp., Armonk, NY, USA) was used. For all statistical analyses, the level of significance was set at $p < 0.05$.

Results

Participants' Characteristics

Sixty children with moderately persistent asthma were included in this study. Table I shows the characteristics of the participants in the three groups. There was no significant difference in age, weight, height, BMI, and sex distribution between the groups ($p > 0.05$).

Effect of Treatment on Pulmonary Functions, C-$ACT_{3,7}$, C-ACT, Calf Muscle Isometric Muscle Force, 6MWD, and PAQLQ

There was a significant interaction between treatment and time (F = 47.14, $p = 0.001$, $\eta^2 = 0.92$). Additionally, there was a significant main effect of time (F = 1550.33, $p = 0.001$, $\eta^2 = 0.99$) and treatment (F = 34.51, $p = 0.001$, $\eta^2 = 0.9$).

Within Group Comparison

There was a significant increase in PFT_S (FVC, FEV_1, FEV_1/FVC, PEF), C-ACT, 6MWD, and PAQLQ (activity limitation, symptoms, emotional function, and overall score) in the three groups post-treatment compared with pre-treatment ($p < 0.001$). There was a significant increase in C-$ACT_{3,7}$ and calf muscle isometric muscle force in groups A and B post-treatment compared to pre-treatment ($p < 0.001$), while there were no significant changes in group C ($p > 0.05$, Table II).

Between Group Comparison

There were no significant differences among the three pre-treatment groups ($p > 0.05$) for all measured variables. Comparison between groups

Table II. Pre and post treatment mean values of the pulmonary functions, C-ACT$_{3,7}$, C-ACT, calf muscle isometric muscle force, 6MWD, and PAQLQ of the three groups.

	Group A					Group B					Group C				
	Pre	Post				Pre	Post				Pre	Post			
	mean ± SD	mean ± SD	*MD*	*% of change*	*p*- value	mean ± SD	mean ± SD	*MD*	*% of change*	*p*- value	mean ± SD	mean ± SD	*MD*	*% of change*	*p*- value
FVC (%)	73.90 ± 0.85	81.90 ± 1.25	8	10.83	0.001*	74.1 ± 1.07	82.5 ± 1.24	8.40	11.34	0.001*	73.60 ± 0.88	78.05 ± 1.19	4.45	6.05	0.001*
FEV_1 (%)	71.05 ± 0.83	82.35 ± 1.69	11.30	15.90	0.001*	70.6 ± 0.82	83.05 ± 1.76	12.45	17.63	0.001*	70.55 ± 0.69	75.45 ± 1.19	4.90	6.95	0.001*
FEV_1/FVC (%)	75.55 ± 0.83	83.55 ± 0.76	8	10.59	0.001*	75.65 ± 0.88	83.30 ± 0.73	7.65	10.11	0.001*	75.55 ± 0.83	77.85 ± 0.67	2.30	3.04	0.001*
PEF (%)	71.10 ± 0.91	81.35 ± 0.88	10.25	14.42	0.001*	71.65 ± 1.14	81.85 ± 1.18	10.20	14.24	0.001*	70.85 ± 0.88	75.10 ± 1.33	4.25	6.00	0.001*
C-ACT$_{3,7}$	2.15 ± 0.37	5.05 ± 0.51	2.90	134.88	0.001*	2.20 ± 0.41	5.30 ± 0.47	3.10	140.91	0.001*	2.25 ± 0.44	2.35 ± 0.49	0.10	4.44	0.42
C-ACT	13.70 ± 0.86	19.80 ± 1.24	6.10	44.53	0.001*	13.55 ± 0.89	19.30 ± 1.17	5.75	42.44	0.001*	13.45 ± 0.89	15.95 ± 1.00	2.50	18.59	0.001*
Calf muscle isometric muscle force (N)	142 ±1.68	179.60 ± 1.47	37.60	26.48	0.001*	141.55 ± 1.39	178.65 ± 1.87	37.10	26.21	0.001*	141.70 ± 1.72	141.95 ± 1.85	0.25	0.18	0.61
6MWD (m)	413.25 ± 5.15	457.70 ± 7.55	44.45	10.76	0.001*	412.30 ± 3.36	460.80 ± 9.01	48.50	11.76	0.001*	411.35 ± 5.25	435.95 ± 8.98	24.60	5.98	0.001*
Activity Limitation	4.60 ± 0.60	6.15 ± 0.67	1.55	33.70	0.001*	4.80 ± 0.70	6.50 ± 0.69	1.70	35.42	0.001*	4.65 ± 0.49	5.40 ± 0.50	0.75	16.13	0.001*
Symptoms	5.15 ± 0.59	6.95 ± 0.60	1.80	34.95	0.001*	5.25 ± 0.64	6.70 ± 0.47	1.45	27.62	0.001*	5.30 ± 0.57	6.05 ± 0.51	0.75	14.15	0.001*
Emotional function	4.95 ± 0.51	6.25 ± 0.55	1.30	26.26	0.001*	4.85 ± 0.49	6.50 ± 0.51	1.65	34.02	0.001*	4.85 ± 0.59	5.60 ± 0.50	0.75	15.46	0.001*
Overall score	5.10 ± 0.55	6.35 ± 0.49	1.25	24.51	0.001*	5.20 ± 0.52	6.55 ± 0.60	1.35	25.96	0.001*	5.05 ± 0.60	5.65 ± 0.67	0.60	11.88	0.001*

C-ACT: Childhood Asthma Control Test; MD: mean difference; FVC%: predicted forced vital capacity; FEV_1%: predicted forced expiratory volume in one second; PEF%: predicted peak expiratory flow; PAQL: Pediatric Asthma Quality of Life questionnaire; *p*-value: probability value; 6MWD: Six-minute walk distance; SD: standard deviation; *: significant at $p < 0.05$.

Table III. Comparison of post treatment mean values of the pulmonary functions, C-ACT$_{3,7}$, C-ACT, calf muscle isometric muscle force, 6MWD, and PAQLQ among the three groups.

	A *vs.* B	A *vs.* C	B *vs.* C
	MD (*p*-value)	MD (*p*-value)	MD (*p*-value)
FVC (%)	0.60 (0.38)	3.85 (0.001)*	4.45 (0.001)*
FEV_1 (%)	0.70 (0.49)	6.90 (0.001) *	7.60 (0.001)*
FEV_1/FVC (%)	0.25 (0.83)	5.70 (0.001) *	5.45 (0.001)*
PEF%	0.50 (0.52)	6.25 (0.001)*	6.75 (0.001)*
C-ACT$_{3,7}$	0.25 (0.33)	2.70 (0.001)*	2.95 (0.001)*
C-ACT	0.50 (0.51)	3.85 (0.001)*	3.35 (0.001)*
Calf muscle isometric muscle force (N)	0.95 (0.26)	37.65 (0.001)*	36.70 (0.001)*
6MWD	3.10 (0.76)	21.75 (0.001)*	24.85 (0.001)*
Activity Limitation	0.35 (0.24)	0.75 (0.001)*	1.10 (0.001)*
Symptoms	0.25 (0.42)	0.90 (0.001)*	0.65 (0.001)
Emotional function	0.25 (0.41)	0.65 (0.001)*	0.90 (0.001)
Overall score	-0.20 (0.87)	0.70 (0.001)*	0.90 (0.001)

C-ACT: Childhood Asthma Control Test; MD: mean difference; FVC%: predicted forced vital capacity; FEV_1%: predicted forced expiratory volume in one second; PEF%: predicted peak expiratory flow; PAQLQ: Pediatric Asthma Quality of Life Questionnaire; *p*-value: probability value; 6MWD: Six-minute walk distance; SD: standard deviation; *: significant at $p < 0.05$; *vs*.: versus.

post-treatment revealed that there were significant differences in all measured variables of groups A and B compared with those of C ($p < 0.001$), while there was no significant difference between groups A and B ($p > 0.05$, Table III).

Discussion

The treatment goal for children with asthma is to reduce the severity and frequency of symptoms to enable them to perform normal activities. The present study aimed to determine whether NMES of the calf muscles could improve nocturnal symptoms and QoL in asthmatic children.

There were significant improvements in the measured variables (PFT_S, C-ACT, QoL, and 6MWD) of the three groups in favor of the group that underwent combined treatment of breathing exercises and NMES of the calf muscle or aerobic training. Moreover, there was a significant reduction in nocturnal symptoms in the groups that underwent NMES of the calf muscle or aerobic training, while no significant improvement was recorded in the group that underwent only breathing exercises. No significant differences were recorded between the NMES and aerobic training for all measured variables.

The significant immediate improvements in PFT_S, C-ACQ, 6MWD, and QoL could be attributed to the improvement in respiratory muscle strength, chest wall mobility, and decrease in bronchospasm. The two most common measures for objective asthma evaluation are FEV_1 and PEF[44]. Both these measures reflect the degree of airway obstruction and lesions, as well as airway function and respiratory muscle strength[45,46]. PEF is commonly used as a reference for respiratory rehabilitation therapy assessment and is the most reliable measure to objectively evaluate an asthma episode[47,48]. Therefore, the significant improvements in FEV_1 and PEF might be due to an increase in respiratory muscle strength and a decrease in bronchospasms[48,49].

The significant effect of the breathing exercise program is consistent with a systematic review that concluded that respiratory exercises demonstrated benefits with regard to reducing symptoms and thus the need for bronchodilators provided[14], the use of medication[50], exacerbation episodes, the levels of anxiety and depression[51], and improved HRQoL[50].

Our results are in line with the findings of Evaristo et al[29] who documented that asthma control, asthma symptoms, airway inflammation, physical activity, psychological distress, and QoL improved similarly among outpatients with moderate-to-severe asthma who participated in aerobic training or breathing exercise programs. However, a higher percentage of aerobic exercise participants reported improved asthma control and less need for rescue medications. Additionally, it has been reported that aerobic training reduces exercise-induced bronchoconstriction[52], corticosteroid consumption, exacerbation episodes and asthma symptoms[53]. A recent study[54] compared the effects of NMES of the quadriceps with those of a conventional physical therapy program in patients with asthma. The findings revealed greater improvements in PFT_S, quadriceps strength, functional capacity, and QoL compared to the conventional physical therapy program alone.

The significant improvements in PFTs could be explained by the increased mechanical activity of the inspiratory muscles, especially the external intercostals, which has been demonstrated to have an accessory function in expiration, creating considerable thoraco-abdominal movement. All muscles involved in respiration were mechanically reorganized because of this. Respiratory muscles are both physically and functionally skeletal muscles. As a result, they might respond to training in the same way as the other skeletal muscles. These physiological adaptations improve muscle strength, endurance, and functional exercise capacity, resulting in a better QoL[55].

The physiological effects of breathing exercises include switching of muscle fiber type (increased proportion of type I fibers and size of type II fibers in the external intercostal muscles), diaphragm hypertrophy, improved neural control of the respiratory muscles, enhanced capillary blood flow[56], reduced work of breathing[57], improved respiratory muscle endurance[58], and attenuation of the respiratory muscle metaboreflex, which could increase blood flow to the LL muscles and partly lead to increased exercise tolerance and decrease in perceived breathlessness and exertion[59].

The effect of treadmill or NMES could be explained as follows: during the long-term muscle activity while muscle training, as the body needs to supply more oxygen to the working muscles, the lungs must provide extra oxygen to the working muscles via the blood stream by increasing the rate and depth of breathing, which can improve FVC, exchange of oxygen and carbon dioxide, O_2 intake and diffusion rate[60]. This occurs through widening of the respiratory tract and lowering of air flow resistance, stimulating inactive alveoli, increasing alveolar compliance, expanding the rib cage, and strengthening respiratory muscles, thus resulting in increased lung elasticity and lung expansion[61]. Treadmill training has the advantage of engaging a large number of muscles[62].

The significant improvement in nocturnal symptoms in children who underwent aerobic training or NMES is consistent with a previous systemic review by Francisco et al[28], which concluded that the studies investigating the effect of aerobic exercise on nocturnal symptoms in asthma revealed a reduction in the prevalence and frequency of nocturnal symptoms and improvement in QoL and asthma control. Only Westergren et al[63] found that the prevalence of nocturnal symptoms did not change following physical exercise training; however, it may be noted there were no participants with nocturnal symptoms at baseline in this study.

In both the upright and supine positions, asthmatic patients had greater respiratory resistance and stiffness than healthy subjects at baseline. As a result, the same amount of fluid deposition in the airway wall may produce a larger reduction in the diameter of small airways than in large airways, resulting in a higher increase in airway resistance in people with a narrower airway tree. Fluid overloading and rostral fluid, which shift from the legs to the thorax in the supine position, have been linked to poor asthma control and nocturnal symptoms. Accumulation of fluid in the thorax may result in a chain reaction that worsens airway constriction[23] as it increases blood volume and pressure in the bronchial circulation. As a result, the pressure gradient between the blood and interstitium increases, leading to increased fluid leakage and increasing airway wall edema, as well as peribronchial fluid cuffing resulting in excessive airway narrowing[64] and airway hyper-responsiveness that contribute to the severity of asthma[65]. Additionally, overnight rostral fluid increases fluid accumulation in the neck, narrowing the pharynx, resulting in increased resistance, collapsibility, and worsening of nocturnal symptoms[66]. It has been reported that compared to asthmatic patients, the effect of increased thoracic fluid volume on airway resistance is negligible[23].

Moreover, children with asthma have weakness in the lower limb muscles, which leads to a decrease in the pumping action of the muscles during the daytime, while increasing fluids in the lower limbs lead to increased amounts of rostral fluid during sleep. Additionally, patients with COPD have abnormalities in peripheral circulatory regulation[67]. Therefore, the significant improvement in nocturnal symptoms and in all measuring variables in the groups that underwent aerobic exercises or NMES, in comparison to the group that underwent the breathing exercises alone, might be due to improvements in the pumping action during the training and increasing the strength and reducing fatigue in the LL_S muscles, resulting in increased pumping action of the muscles during the daytime, thereby reducing the amount of rostral fluid. There is sufficient evidence to support that strengthening the calf muscle pump improves cardiovascular fitness and reduces fatigue. This could be attributed to a change in muscle fiber type in response to leg exercises[68]. Vena et al[43] concluded that calf muscle NMES is an effective method for reducing fluid accumulation during prolonged periods of inactivity and has the potential to be used as a device to prevent leg edema and treat health effects in at-risk groups. This observation is consistent with the findings of Neder et al[69], Hartkopp et al[70], and Thom et al[71], who found that NMES and treadmill improved muscle capillaries and oxidative capabilities, possibly enhancing overall aerobic capacity and exercise performance. Moreover, Kaymaz et al[72] concluded that high-frequency NMES (50 Hz) and aerobic training (treadmill walking and cycling) significantly enhanced quadriceps manual muscle testing scores in patients with severe COPD, with no significant differences between the groups.

The significant effect of calf stimulation on nocturnal symptoms could be explained by the greater effect of NMES of the skeletal pump in the legs, which reduces leg fluid by reducing capillary pressure and increasing tissue pressure. Muscle pumps in the foot, calf, and thigh are among the LLs pumps. The calf muscle pump is the most important of these pumps because it is the most efficient, has the highest capacitance, and produces high pressures[73]. A normal limb has a calf volume of 1500-3000 cm, a venous volume of 100-150 cm, and ejects more than 40-60% of the venous fluid with a single contraction[74]. In a previous study[75], the effectiveness of NMES and intermittent pneumatic compression of the calf muscles in improving the microcirculatory blood flow in the thigh of healthy individuals was compared. NMES was a more effective modality than pneumatic compression in reducing edema, as it increased microcirculation by more than a factor among three in comparison to pneumatic compression.

The NMES is less demanding for the heart and circulatory system than regular exercise. As a result, the ventilation demand is reduced, which lowers the risk of dyspnea. Owing to destabilization of the respiratory system, decompensation of the circulatory system, and other hazardous clinical signs, traditional training may be contraindicated during exacerbation periods. In prior research utilizing electrical stimulation, NMES has been shown to be safe for patients with exacerbations of the condition, patients with severe COPD, and even those undergoing respiratory therapy[54]. NMES might be especially beneficial for individuals with very low motivation for exercise because of low aerobic capacity[76]. Home-based NMES of leg muscle training in heart failure had similar advantages to conventional exercise in enhancing exercise capacity, making it an effective option for aerobic exercise training for patients who cannot participate in traditional exercise[77]; therefore, it can safely be performed at home.

Another important aspect of NMES use in comparison to conventional training sessions is the reduction in anxiety experienced by patients during and after therapy. Reduced anxiety allows patients to break through emotional barriers and eventually the spiral of inactivity, as in severe COPD cases, often leads to disability or death. Moreover, NMES does not induce muscle fiber damage or severe exhaustion[78].

Habib et al[79] concluded that in terms of physical functioning and social life, the QoL of asthmatic patients was significantly lower than that of healthy individuals. Therefore, the improvement in PFTs, asthma control, and nocturnal symptoms might explain the improvement in the 6MWD and QoL in this study. Reducing anxiety and depression, medication consumption, peak expiratory flow, asthma symptoms, and the levels of hyperventilation symptoms are reflected in improving the HRQoL[80] and normalizing the autonomic system[81]. The favorable impacts of increased exercise capacity are represented by psychological gains and better self-esteem, thus positively influencing HRQoL[82].

The lack of follow-up to monitor the long-term effects of the treatment methods is a limitation of this study. Nevertheless, it has several strengths, including the objective functional assessment of pulmonary function, patient perception of their problem, no drop out, and the lack of baseline discrepancies.

Conclusions

The NMES of calf muscles can serve as an excellent adjunct to the breathing exercise program in improving the nocturnal symptoms and QoL of asthmatic children. Moreover, it could be a considerable alternative to traditional physical training in periods of disease exacerbation and low-motivated children.

Authors' Contribution Statement

Conceptualization, Rasha A. Mohamed and Abeer M. Yousef; Data curation, Elsayed H. Mohamed; Formal analysis, Elsayed H. Mohamed; Methodology, Rasha A. Mohamed and Abeer M. Yousef; Software, Rasha A. Mohamed and Abeer M. Yousef; Validation, Rasha A. Mohamed, Abeer M. Yousef, Mohamed I. Mabrouk, and Mohamed M. Ragab; Investigation, Rasha A. Mohamed, Abeer M. Yousef, Elsayed H. Mohamed, Mohamed I. Mabrouk, and Mohamed M. Ragab; Writing-original draft; Rasha A. Mohamed and Abeer M. Yousef; Writing–review and editing, Rasha A. Mohamed; Approval of final manuscript, all authors.

Acknowledgements

The authors acknowledge the cooperation of all participating children and their parents.

Conflict of Interest

The authors declare no potential conflicts of interest. This research did not receive any specific grants from funding agencies in the public, commercial, or not-for-profit sectors.

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