Complementary Therapies in Medicine 57 (2021) 102673

Contents lists available at ScienceDirect

Complementary Therapies in Medicine

journal homepage: www.elsevier.com/locate/ctim

Potential impacts of Acu-TENS in the treatment of adolescents with moderate to severe bronchial asthma: A randomized clinical study

Ragab K. Elnaggar [a,c,*], Samah A. Moawd [b,c], Shaimaa E. Ali [d], Abeer M. Yousef [d], Alshimaa R. Azab [a,c]

[a] Department of Physical Therapy for Pediatrics, Faculty of Physical Therapy, Cairo University, Giza, Egypt
[b] Department of Physical Therapy for Cardiovascular/Respiratory Disorder and Geriatrics, Faculty of Physical Therapy, Cairo University, Giza, Egypt
[c] Department of Health and Rehabilitation Sciences, College of Applied Medical Sciences, Prince Sattam Bin Abdulaziz University, Al-Kharj, Saudi Arabia
[d] Department of Basic Sciences, Faculty of Physical Therapy, Cairo University, Giza, Egypt

ARTICLE INFO

Keywords:
Chronic respiratory diseases
Adolescents
Acu-TENS
Immune response
Pulmonary function
Quality of life

ABSTRACT

Objective: The purpose of this study was to evaluate the efficacy of transcutaneous electrical nerve stimulation over the acupuncture points (Acu-TENS) on total serum immunoglobulin E (IgE_{total}), pulmonary function, and quality of life in adolescents with asthma.

Methods: In a double-blind randomized clinical trial, 32 adolescents (age; 12–16 years) with asthma participated and were assigned randomly to receive either the breathing retraining program (control group) or the breathing retraining program plus Acu-TENS application (Acu-TENS group). Acu-TENS was applied for 40 min' day-after-day session for two successive months, with no side-effects reported. Serum IgE_{total}, pulmonary function [forced vital capacity (FVC), forced expiratory volume at one second (FEV_1), and FEV_1/FVC], and quality of life were evaluated pre- and post-treatment.

Results: Serum IgE_{total} ($P = 0.028$, $\eta_p^2 = 0.15$), Pulmonary function [FVC ($P = 0.043$, $\eta_p^2 = 0.13$), FEV_1 ($P = .046$, $\eta_p^2 = 0.12$)], and quality of life ($P < .001$, $\eta_p^2 = 0.17$) increased significantly in the Acu-TENS group when compared to the control group.

Conclusion: This study demonstrates that the Acu-TENS is an impending asthma treatment that may be used to reinforce the immune system response, ameliorate lung function, and increase the quality of life in adolescents with asthma.

1. Introduction

Bronchial asthma is a long-term inflammatory condition affecting the pulmonary airways. It is associated with intrapulmonary hyper-responsiveness, which lead to recurring episodes of breathlessness, coughing, wheezing, and chest tightness. Such episodes are commonly accompanied by diffuse airflow obstruction that is often reversible with treatment or even spontaneously.[1] The world asthma prevalence is estimated to be about 4.3 %.[2] There are approximately 334 million asthma patients of all ages worldwide, which is expected to increase by more than 100 million by 2025.[3] The data regarding asthma prevalence among adolescents continue to generate a worrisome picture. Previous reports indicated that diagnosed asthma in the United States has increased from 3 % to 6.2 % between 1995 and 2003 among those who are 10–13 years of age.[4] According to a recent nationwide study in Saudi Arabia, the prevalence of asthma has currently reached 8.2 % among adolescents.[5]

Patients with allergic conditions such as asthma usually have high levels of total serum immunoglobulin (IgE_{total}) that interact with antigens and triggers a variety of immunological responses.[6,7] During the acute attack, lungs and airways react to allergens, and breathing becomes more difficult .[8] More explicitly, the airway resistance increases dramatically during asthma exacerbations, leading to entrapment of a large amount of air inside the lungs and increases all static lung volumes. It also reduces the dynamic lung volumes and airway conductance, all of which indicate an impaired pulmonary function.[9] Patients diagnosed with bronchial asthma have also been reported to have a significant decline in the health-related quality of life, which is likely associated

* Corresponding author at: Department of Physical Therapy for Pediatrics, Faculty of Physical Therapy, Cairo University, 7 Ahmed Elzayat St. Bein Elsarayat, PO 12624, Dokki, Giza, Egypt.
E-mail address: rke_pt2001@yahoo.com (R.K. Elnaggar).

https://doi.org/10.1016/j.ctim.2021.102673
Received 2 June 2020; Received in revised form 20 November 2020; Accepted 19 January 2021
Available online 26 January 2021

with the compromised physical activities, sleep disturbances, and consequent psychosocial effects.[10]

Although the use of asthma medications such as inhaled corticosteroids, β_2 agonists, and their combination have been widely regarded as effective therapies for controlling symptoms, various types of physical therapy have been used besides medical treatment to optimize the outcomes.[11,12] Several breathing re-training techniques like diaphragmatic breathing, nasal breathing, slow breathing, controlled breath holds, and simple relaxation exercises have been suggested to enhance lung function, augment diaphragm, and rib-cage mobility, and boost immune function in asthmatic patients.[7,13–16] Besides, complementary and integrative therapies as massage, yoga, and bioenergetics approaches like acupuncture, are recommended as adjunct treatments for bronchial asthma.[17]

Based on traditional acupuncture, the acupoint transcutaneous electrical nerve stimulation (Acu-TENS) has emerged as an integrative intervention. It involves stimulation of the acupuncture points using electrical signals by applying surface electrodes over the acupoints instead of needles, which makes it non-invasive and easy-to-apply with no adverse effects. The Acu-TENS has been proved to ameliorate pulmonary functions, reduce breathlessness during exercise, and improve quality of life in patients with chronic obstructive pulmonary disease (COPD).[18–20] It has also been shown that Acu-TENS can improve the expiratory flow rates post-exercises in healthy subjects.[21] Evidence on the use of Acu-TENS in patients with asthma is lacking. There barely exists one randomized placebo-controlled trial, which reported improvements in some aspects of pulmonary function in patients with moderate asthma following the application of Acu-TENS for 45 min, three sessions/week for four weeks.[22] Nevertheless, the findings from a single clinical trial remain non-conclusive.

This randomized clinical study purposed to evaluate the Acu-TENS effect on asthma biomarkers (IgEtotal), pulmonary functions, and quality of life in adolescents with asthma. We hypothesized that the conjunction of Acu-TENS and breathing retraining would be superior at 8 weeks compared with breathing retraining alone.

2. Methods

2.1. Study design

This was a double-blinded, randomized clinical trial carried out between December 2018 and February 2020. It was carried out at the Outpatient Clinic of College of Applied Medical Sciences, Prince Sattam bin Abdulaziz University (PSAU), Saudi Arabia. Ethical approval was obtained from the Ethics Committee at the Physical Therapy Department at PSAU (No: RHPT/0018/0027). All procedures were in compliance with the ethical standards of the 1964 Declaration of Helsinki. Parents or legal guardians of the participants signed a consent form before the baseline evaluation.

2.2. Blinding procedure

To avoid bias, this study was double-blinded. Examiners were kept unaware of which treatment group participants have been allocated to. Also, the adolescents being treated were not knowledgeable of the treatment allocation. To achieve blindness, two therapists were other than the examiners assumed the responsibility of conducting the treatments.

2.3. Subjects

This study was conducted on 32 adolescents with asthma attending for the care of asthma in the central hospital in the region. The criteria for inclusion were as follows: moderate to severe asthma as per the Global Initiative for Asthma (GINA) recommendations for asthma diagnosis, which integrates the present pattern of respiratory symptoms with the corroborating evidence from comprehensive history/examination and spirometry – that is if children experience more than one of the typical asthma symptoms; occur variably over time and vary in intensity; often worse at night or on waking, and often triggered by exercise, laughter, allergens, and cold air; show positive bronchodilator reversibility; a spirometry test indicating a forced expiratory volume at one second (FEV_1) = 60–80 % (moderate) or < 60 % (severe) of the predicted values,[23] age between 12 and 16 years; body mass index (BMI) < 25 kg/m2, and clinically-stable conditions (i.e., no changes in the medications were advised by the attending physician for > one month and taking maintained doses of drugs in the past 3 months). Exclusion criteria were aggravation of asthma symptoms that necessitate the use of systemic corticosteroids in the past month or during the study time, chronic sinusitis, history of thoracic surgery, respiratory co-morbidities that pose further ailments than asthma, and impairment of the cognitive function.

2.3.1. Allocation technique

Included adolescents were distributed randomly to a breathing retraining program (control group' n = 16) and a breathing re-training program in addition to an Acu-TENS application (Acu-TENS group; n = 16). We followed a simple randomization method, where an independent subject picked up a non-transparent sealed envelope containing a code for either of the study groups (control or Acu-TENS).

2.3.2. Sample size

A power analysis was conducted before data collection to identify the proper sample size and to nullify the effect of type II error using G-Power software, V3.0.10 (Neu-Isenburg, Germany). Estimates of the mean difference and standard deviation of forced vital capacity (MD = 6.15 and SD = 4.56) were attained from a small pilot study consisting of 6 adolescents and were used for the analysis. Assuming an alpha error of 5% and the desired power of 90 %; an overall sample of 26 participants (13 subjects for each group) was required. The sample was increased to 32 participants, accounting for an approximate dropout rate of 20 %.

2.4. Assessment

2.4.1. Serum IgE_{total} estimation

The serum IgE_{total} level was estimated from a blood sample (15 mL) collected from each adolescent in a vacutainer (Becton Dickinson, Plymouth, UK) from the median cubital or dorsal metacarpal veins. Thirty minutes later, when the blood was clotted, plasma was separated from the blood sample by centrifugation and stored at –20 °C until analysis. Estimation of the serum IgE_{total} was performed by means of enzyme-linked immunosorbent assay kits and the Organon Teknika Microwell system (Organon Teknika, Boxtel, the Netherlands).[7]

2.4.2. Pulmonary function

A pulmonary function test was applied to determine the percent-predicted values of the forced vital capacity (FVC), FEV_1, and the FEV_1/FVC ratio. The measurement was performed in a standing position using a spirometry analyzer (Autospiro-507; Minato Medical Science; Osaka. Japan) by a well-trained technician. First, each adolescent was asked to breathe in and out normally several times with their lips closed tightly on the mouthpiece, and a soft caliper applied to the nose. After that, he/she was asked to breathe in slowly as deeply as possible and then to breathe out vigorously. In conformity with the American Thoracic Society/European Respiratory Society (AST/ERS) recommendations for a standardized pulmonary function report, data from three acceptable and repeatable tests were collected – that is the FVC and FEV_1 values from the three tests were within 0.150 L or 10 % of the highest values, whichever is greater.[24] The highest values were recorded and employed for data analysis.[16]

2.4.3. Quality of life

The translated version of the pediatric asthma quality of life questionnaire (PAQLQ) was used. It has been shown to be valid and reliable as a multidimensional asthma-specific and age-appropriate instrument for the assessment of the health-related quality of life of children and adolescents with asthma aging from 7 to 17 years.[25] It consists of 23 questions covering 3 domains: 5 questions reflecting the (activity limitations), 10 questions identifying the (symptoms), and 8 more questions determining the (emotional function). The PAQLQ uses a 7-point Likert scale to rate the items; 1 indicates "poor" quality of life, while 7 expresses a "good" quality of life. The score of each domain was calculated as the mean response to all its items. The overall score was represented by the average of the mean scores of the three domains. The higher the score the better health-related quality of life perception.

2.5. Interventions

2.5.1. Breathing retraining

Participants in both groups underwent a breathing re-training program aiming at improving asthma and hyperventilation symptoms and promoting the strength of respiratory muscle. The program consisted of the following steps: (1) regularize the breathing pattern to reduce the variability of rate and depth by deep diaphragmatic breathing, (2) lessening the impact of asthma with a reduction in night-time episodes by nasal breathing, (3) maximizing the use of collateral ventilation in patients with reduced ventilation through breath holds/pauses (4) increase strength of inspiratory muscle through increasing inspiratory efforts and slowly decrease the rest period by inspiratory muscle training technique, and (5) muscle relaxation to release tension and so alleviating asthma symptoms by relaxation technique.[7,15,16,26–28]

2.5.2. Acu-TENS application

First, the acupoints Dingchuan (EX-B1) has been identified bilaterally (0.5 cm lateral to the spinous process of the seventh cervical vertebra which is equal to the distance between the medial ends of the creases of the interphalangeal joints and the participant's middle finger), this acupoint was selected because it is a commonly used point by acupuncturists for alleviating dyspnea symptom,[29] and has also been documented in previous literature to positively impact several aspects of the cardiorespiratory functions in healthy subjects and in patients with asthma or COPD.[21,22,30–32] To minimize skin resistance and ensure maximal current transmission, the acupoints Ex-B1 area on both sides were cleaned with alcohol before attaching TENS electrodes. The electrodes (5×5 cm^2) were fitted into their position by a plastic film to ensure the restriction of electrical stimulation to the selected acupoint. Attaching the electrodes to a dual-channel portable TENS unit (ITO 320; ITO Company Ltd; Tokyo, Japan), with the following parameters (frequency was adjusted to 2 Hz, pulse-width of 200 μs. and intensity according to participants' durability without feeling discomfort); durability means that the participants ask the therapist to discontinue the increase in the stimulation. Once the participants feel accommodated with the stimulation from TENS, the intensity of the current was increased and every time the participants reported any accommodation to the stimulation, it was increased. Receiving TENS over the acupuncture points (EX-B1) by participants in the Acu-TENS group for 40 min three times/week for 8 consecutive weeks. While participants in the control group got placebo-TENS for 40 min with similar electrodes' placement as the Acu-TENS group, but with zero intensity. To achieve blindness in the trail, one physiotherapist was assigned for Acu-TENS application or placebo TENS and another physiotherapist for recording the outcome measures.[33,34] None of the participants reported any adverse effects of the Acu-TENS application.

2.6. Data analysis

The statistical analysis was based on the intension-to-treat approach to compare the control and Acu-TENS groups. To approach missing data, we used a multiple imputation method (regression model). The Shapiro-Wilk test showed symmetrical distributions of the measured variables and thus permitted the use of parametric analysis. We used the two-way repeated-measure analysis of variance (ANOVA) test to estimate the difference between the study groups and the group-by-time interaction. The treatment-effect has been decided by the group-by-time interaction because the correlations associated with repeated measures are taken into account. Where the ANOVA test was significant, the pre-to-post changes in each group were calculated through the paired *t*-test. Effect-sizes for the significant between- and within-group differences were calculated using partial eta-squared (η_p^2) and Cohen's *d* formulae, respectively. All analyses were performed in statistical software Stata version 15.1 (Stata Corp, College Station, TX), and *P*-value <.05 was considered statistically significant.

3. Results

A diagram illustrating the participants' flow in the study is shown in Fig. 1. Fifty-seven adolescents were initially screened. Of them, 32 adolescents were eligible and were randomized to the study groups. However, three adolescents (9% overall; one from the control group and two from the Acu-TENS group) were lost during the study, while 29 participants completed the assigned treatment and follow-up measurements.

The demographic and clinical characteristics of the children are demonstrated in Table 1. The control and AcuTENS groups were similar in age, weight, height, BMI, and gender distribution ($P > 0.05$). Additionally, both groups were matching regarding asthma duration, severity, drug use and dose, and baseline peak expiratory flow rate (PEFR) ($P > 0.05$).

The immune responses (i.e., total serum IgE level) of the control and AcuTENS groups are presented in Table 2. The mixed ANOVA test revealed a significant group-by-time interaction in favor of the Acu-TENS group [F (1, 31) = 5.32; $P = 0.028$; $\eta_p^2 = 0.15$]. However, the within-group analysis indicated that the serum IgE_{total} decreased significantly in the control group ($P = 0.045$; $d = 0.6$) and the Acu-TENS group ($P < 0.001$; $d = 1.4$).

The pulmonary function measures of both groups are described in Table 3. There was a significant group-by-time interaction in favor of the Acu-TENS group concerning FVC [$F(1, 31) = 4.49$; $P = 0.043$; $\eta_p^2 = 0.13$] and FEV_1 [$F(1, 31) = 4.32$; $P = 0.046$; $\eta_p^2 = 0.12$]. However, the pre-to-post changes in FEV_1FVC were equivalent in the control and Acu-TENS groups [$F(1, 31) = 0.22$; $P = 0.65$]. The within-group analysis revealed that the FVC increased significantly in the control ($P = 0.018$; $d = 0.7$) and Acu-TENS ($P < 0.001$; $d = 1.1$) groups, as was the case regarding the FEV_1 in the control ($P = 0.001$; $d = 1.1$) and Acu-TENS ($P < 0.001$; $d = 2.0$) groups.

The subscale scores of PAQLQ and the overall score are summarized in Table 4. There was a significant group-by-time interaction in favor of the Acu-TENS group for the following measures: activity limitation [$F(1, 31) = 5.26$; $P = 0.029$; $\eta_p^2 = 0.15$] and emotional function [$F(1, 31) = 5.42$; $P = 0.027$; $\eta_p^2 = 0.15$] subscales, as well as the overall PAQLQ score [F (1, 31) = 5.94; $P = 0.021$; $\eta_p^2 = 0.17$]. However, changes in the symptom's subscale were similar among the control and Acu-TENS groups [F (1, 31) = 2.56; $P = 0.12$]. The within-subject analysis showed that the control and Acu-TENS groups achieved a significant increase in the activity limitation ($P = 0.004$; $d = 0.9$ and $P < 0.001$; $d = 1.7$ respectively), emotional function ($P = < 0.001$; $d = 1.2$ and $P < 0.001$; $d = 1.9$ respectively), and overall PAQLQ scores ($P = < 0.001$; $d = 2.2$ and $P < 0.001$; $d = 2.3$ respectively).

4. Discussion

This double-blind randomized controlled study purposed to assess the effect of Acu-TENS besides breathing re-training on serum IgE_{total},

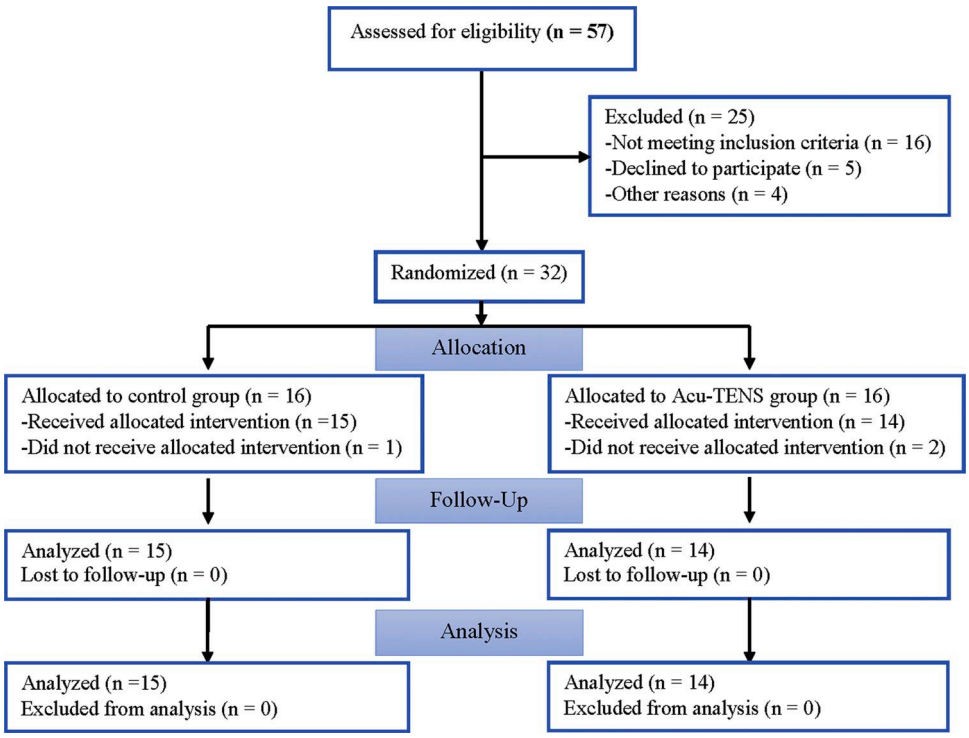

Fig. 1. Participants' flowchart.

Table 1
Demographic characteristics of asthmatic adolescents in the control and Acu-TENS group.

Children characteristics	Control group (n = 16)	AcuTENS group (n = 16)	Sig.
Age, *years*	13.4 ± 2.3	12.6 ± 1.6	0.29†
Gender (b/g), *n*	9 (56.3 %) / 7 (43.7 %)	11 (68.8 %) / 5 (31.2 %)	0.72‡
Weight, *kg*	46.2 ± 8.2	44 ± 7.3	0.43†
Height, *m*	1.48 ± 0.1	1.44 ± 0.1	0.26†
BMI, kg/m^2	21.1 ± 2.7	21.2 ± 1.9	0.98†
Duration of asthma, *years*	7.2 ± 2.3	6.6 ± 1.3	0.39†
Severity of asthma (moderate/severe), *n*	13 (81.3 %) / 3 (18.7 %)	10 (62.5 %) / 6 (37.5 %)	0.22‡
Inhaled steroids (Budesonide, *mg/day*)	0.79 ± 0.12	0.82 ± 0.11	0.45†
Short β_2 agonist dose, *μg*	477.1 ± 73.9	438.1 ± 63.7	0.12†
Montelukast sodium use (yes/no), *n*	5 (31.3 %) / 11 (68.7 %)	3 (18.7 %) / 13 (81.3 %)	0.34‡
Baseline FEV_1, % of predictive values	51.8 ± 4.6	54.4 ± 4. 7	0.11†
Degree of asthma control through ACT	17.31 ± 1.92	18.25 ± 2.44	0.24†

Continuous variables are listed as mean ± standard deviation categorical variables which are described as frequency (percentage).
Sig: Significance at $P<0.05$, b/g: boys/girls, BMI: body mass index, FEV_1: forced expiratory volume at the first second, ACT: asthma control test.
† Independent *t*-test.
‡ Fishers' exact test.

Table 2
Immune response (total serum immunoglobulin level, IU/mL) to treatment control and Acu-TENS group.

	Control group	AcuTENS group	Group-by-time interaction	
			Sig.	η_p^2
Pre-treatment	307.4 ± 47.9	327.2 ± 46.9	0.028*	0.15
Post-treatment	273.5 ± 70	243.2 ± 35.1		
Sig.	0.045*	< 0.001*		
Cohen's *d*	0.6	1.4		

Sig: Level of significance at $P < 0.05$, η_p^2: partial eta-squared, * significant.
Notes: Change differences between both groups is decided y the group-by-time interaction significance level; $d = 0.2$ represent a "small", 0.5 "medium" and 0.8 a "large" within-group effect-size of the difference within groups. While, $\eta_p^2 = 0.01$ considered a "small", 0.09 "medium" and 0.25 a large" effect-size of the difference between groups.

pulmonary functions, and quality of life in adolescents with asthma. The results confirmed the hypothesis that Acu-TENS added to the breathing-re-training program can induce more significant effects on immune system response, pulmonary functions, and quality of life and so it is regarded as a beneficial therapeutic approach for adolescents' asthma.

Acu-TENS, a new technique used in pulmonary rehabilitation programs but not broadly mentioned in the previous literature, so it was not easy to find comparable results regarding its effect on adolescents with asthma. A recent randomized placebo-controlled study by Elnozhe and Rifaat investigated the efficacy of Acu-TENS for 4 weeks on the Ding Chuan acupoints in patients with asthma and demonstrated meaningful improvement of the pulmonary functions.[22] In agreement with these results, the present study showed a prominent effect of Acu-TENS on the pulmonary functions where the FVC and FEV1 significantly improved. An earlier randomized controlled trial by Ngai et al. evaluated the influence of Acu-TENS applied on FEV_1, over acupoints in subjects with asthma, immediately after and at 20-min intervals post-exercise for one hour and concluded that Acu-TENS therapy can decrease FEV1 following exercises in patients with asthma.[35]

The results demonstrated herein may also extend evidence on Acu-TENS in children with COPD, who have important similarities such as chronic inflammation, airflow limitation, and bronchoconstriction.[36] Liu et al. explored the effect of 4 weeks of Acu-TENS over the EX-B-1 (Dingchuan), BL-13 (Feishu), BL-23 (Shenshu), and ST-36 (Zusanli) acupoints in patients with stable COPD and stated that the Acu-TENS enhanced the predicted FEV_1%, reduced the severity of dyspnea, and attenuated the impact of COPD symptoms on the overall health.[34] Another study by Lau and Jones evaluated the outcomes of a single session lasting 45-minute of Acu-TENS on dyspnea and pulmonary

Table 3
Changes in pulmonary function measures in the control and Acu-TENS group.

Variable		Control group	AcuTENS group	Group-by-time interaction	
				Sig.	η_p^2
FVC, %	Pre-treatment	72.6 ± 3.1	73 ± 5.2	0.043*	0.13
	Post-treatment	76.5 ± 4.6	82.4 ± 4.7		
	Sig.	0.018*	< 0.001*		
	Cohen's *d*	0.7	1.1		
FEV_1, %	Pre-treatment	51.8 ± 4.6	54.4 ± 4. 7	0.046*	0.12
	Post-treatment	61.5 ± 7.6	70.4 ± 6.1		
	Sig.	0.001	< 0.001*		
	Cohen's *d*	1.1	2.0		
FEV_1/FVC	Pre-treatment	71.2 ± 7.3	73.9 ± 6.8	0.65	–
	Post-treatment	80.4 ± 8.3	84.8 ± 6.7		
	Sig.	–	–		
	Cohen's *d*	–	–		

FVC: forced vital capacity, FEV_1: forced expiratory volume at one second, FEV_1/FVC: the ratio of the forced expiratory volume at one second to the forced vital capacity.
Sig: Significance at $P < 0.05$, η_p^2: partial eta-squared, * significant.
Notes: Change differences between both groups is decided y the group-by-time interaction significance level; $d = 0.2$ represent a "small", 0.5 "medium" and 0.8 a "large" within-group effect-size of the difference within groups. While, $\eta_p^2 =$ 0.01 considered a "small", 0.09 "medium" and 0.25 a large" effect-size of the difference between groups.

Table 4
Quality of life scores for the control and Acu-TENS group.

Variable		Control group	AcuTENS group	Group-by-time interaction	
				Sig.	η_p^2
Activity limitation	Pre-treatment	4.9 ± 0.9	5.3 ± 0.6	0.029*	0.15
	Post-treatment	5.4 ± 0.8	6.3 ± 0.4		
	Sig.	0.004*	< 0.001*		
	Cohen's *d*	0.9	1.7		
Symptoms	Pre-treatment	5.2 ± 0.5	5.5 ± 0.4	0.12	–
	Post-treatment	5.7 ± 0.4	6.3 ± 0.3		
	Sig.	–	–		
	Cohen's *d*	–	–		
Emotional function	Pre-treatment	5.0 ± 0.4	5.3 ± 0.5	0.027*	0.15
	Post-treatment	5.5 ± 0.5	6.2 ± 0.5		
	Sig.	< 0.001*	< 0.001*		
	Cohen's *d*	1.2	1.9		
Overall score	Pre-treatment	5.0 ± 0.3	5.4 ± 0.3	0.021*	0.17
	Post-treatment	5.6 ± 0.4	6.2 ± 0.3		
	Sig.	< 0.001*	< 0.001*		
	Cohen's *d*	2.2	2.3		

Sig: Significance at $P < 0.05$, η_p^2: partial eta-squared, * significant.
Notes: Change differences between both groups is decided y the group-by-time interaction significance level; $d = 0.2$ represent a "small", 0.5 "medium" and 0.8 a "large" within-group effect-size of the difference within groups. While, $\eta_p^2 =$ 0.01 considered a "small", 0.09 "medium" and 0.25 a large" effect-size of the difference between groups.

functions in patients with COPD and proved that Acu-TENS may be a valuable non-invasive complementary intervention in the management of COPD, recommending the use of Acu-TENS in the treatment of patients with asthma.[37] There is also additional evidence on Acu-TENS in healthy individuals. A pilot study by Chan et al. examined the effect of a single session of Acu-TENS for 45 min on the post-exercise airway resistance, FEV_1, and FVC in healthy individuals. They found that the airway resistance reduced remarkably in the Acu-TENS group when compared with the placebo-TENS group ($P = .029$) and this was also associated with immediate enhancement of the FEV_1.[38]

To our knowledge, the immunomodulatory effect of Acu-TENS has not yet been examined in patients with asthma. The results of the present study revealed a favorable improvement in the immune responses in the Acu-TENS group as reflected by the greater decline in the serum IgE_{total}. Supportive of this, are the findings from previous studies that employed traditional acupuncture for treating asthma, especially since the Acu-TENS has the same basis as traditional acupuncture. An early study by Guan and Zhang investigated the immunologic effects of acupuncture on patients with asthma. They reported a significant reduction in the serum IgE_{total} levels, suggesting that acupuncture can exert modulation action on the immunoglobulins by reinforcing the immunological function.[39] Also, another study by Yang et al. examined the clinical and immunomodulatory effects of acupuncture in patients with allergic asthma. Their results implied that acupuncture has a regulatory effect on the adaptive immune system as the level of IgE_{total} in the sera decreased significantly 5 weeks of acupuncture therapy.[40] Further, a very recent study by Nurwati et al. reviewed the current evidence on the role of acupuncture in ameliorating asthma symptoms concluded that acupuncture can induce anti-asthmatic effects through multiple pathways, from which is the regulation of the secretion of IgE_{total}.[41]

The results of the present study showed meaningful enhancements in the quality of life in the Acu-TENS group as the overall and subscales scores of PAQLQ increased significantly as compared to the control group. In line with these results, a pragmatic randomized trial carried out by Brinkhaus et al. investigated the effectiveness of acupuncture along with routine care in patients with asthma. The results demonstrated clinically significant improvements in disease-specific and general quality of life in the acupuncture group when compared to the control group.[42] Improved adaptive immune responses and pulmonary functions (the ameliorative signs of asthma symptoms) in the Acu-TENS group may have motivated patients to engage more in physical and social activities and helped them to achieve general wellbeing, which in turn conferred benefits to the quality of life of those patients.

Although the changes in the Acu-TENS group were superior to the control group, the breathing re-training program yielded significant improvements in all measured variables. These come along with the results of previous studies that proved the positive effects of breathing-re-training techniques on pulmonary functions and quality of life in asthmatic patients. However, previous studies on the effect of these techniques on immune response are very limited. A study was conducted by Elnaggar and Shendy on children with asthma.[7] The results showed significant improvements in pulmonary functions, without changes in the serum IgE_{total} levels. Thus, the significant effect of Acu-TENS may have related to the effect of acupuncture stimulation that produces immediate bronchodilation effect by reducing the resistance of airways and releasing endorphins and other neurohumoral factors.

The findings of the present study may be somewhat limited by the lack of prior research studies on the topic. These findings, therefore, need to be interpreted with caution and additional studies are needed to lay the foundation for understanding and substantiating the effect of Acu-TENS in the treatment of asthma. Another source of uncertainty is that the study sample comprised adolescents with moderate or severe asthma. It could be argued that responses may differ according to asthma severity. Future studies on the current topic are therefore recommended to analyze the effect of Acu-TENS in subsamples representative of different asthma severity to draw a definite conclusion. A further note of caution is due here because this study only assessed the short-term effect of Acu-TENS and cannot assure the sustainability of this effect. Thereby, further research should be undertaken to investigate the long-term effect define the extent to which it would be maintained.

5. Conclusion

Summarily, the present study demonstrated that Acu-TENS could be used as an adjunct to respiratory re-training programs to reinforce adaptive immunological response, ameliorate pulmonary functions, and enhance the quality of life in adolescents with moderate to severe asthma. Further investigations are warranted to substantiate the results of this study.

Funding

None.

Author statement

Ragab K. Elnaggar: Had full access to all the data in the study and takes the responsibility for the integrity and accuracy of the data, was involved in all stages of this study (concept and design, study supervision, analysis, and interpretation of data, drafting the manuscript and revision.

Samah A. Moawd: Study supervision, acquisition, analysis, and interpretation of data, drafting the manuscript, editing, and revision.

Shaimaa E. Ali: Statistical analysis and interpretation of data, drafting the manuscript, editing, and revision.

Abeer M. Yousef: Analysis and interpretation of data, editing and revision.

Alshimaa R. Azab: Study supervision, acquisition, analysis, and interpretation of data, drafting the manuscript, editing, and revision.

Declaration of Competing Interest

The authors report no declarations of interest.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ctim.2021.102673.

References

1 Agarwal R, Dhooria S, Aggarwal AN, et al. Guidelines for diagnosis and management of bronchial asthma: Joint ICS/NCCP (I) recommendations. *Lung India*. 2015;32 (Suppl 1):S3–s42.
2 Loftus PA, Wise SK. Epidemiology of asthma. *Curr Opin Otolaryngol Head Neck Surg*. 2016;24(3):245–249.
3 Behera D, Sehgal IS. Bronchial asthma–issues for the developing world. *Indian J Med Res*. 2015;141(4):380–382.
4 Clark NM, Dodge JA, Thomas LJ, Andridge RR, Awad D, Paton JY. Asthma in 10- to 13-year-olds: challenges at a time of transition. *Clin Pediatr (Phila)*. 2010;49(10): 931–937.
5 Musharrafieh U, Tamim H, Houry R, AlBuhairan F. A nationwide study of asthma correlates among adolescents in Saudi Arabia. *Asthma Res Pract*. 2020;6(1):1–8.
6 Oettgen HC, Geha RS. IgE in asthma and atopy: cellular and molecular connections. *J Clin Invest*. 1999;104(7):829.
7 Elnaggar RK, Shendy MA. Efficacy of noninvasive respiratory techniques in the treatment of children with bronchial asthma: a randomized controlled trial. *Bull Fac Phys Ther*. 2016;21(1):1–10.
8 Niven AS, Argyros G. Alternate treatments in asthma. *Chest*. 2003;123(4): 1254–1265.
9 Madan D, Singal P, Kaur H. Spirometric evaluation of pulmonary function tests in bronchial asthma patients. *J Exer Sci physiother*. 2012;6(2):106.
10 Nalina N, Chandra MS. Assessment of quality of life in bronchial asthma patients. *Int J Med Public Health*. 2015;5(1).
11 Janssen I, Leblanc AG. Systematic review of the health benefits of physical activity and fitness in school-aged children and youth. *Int J Behav Nutr Phys Act*. 2010;7:40.
12 Bruurs ML, van der Giessen LJ, Moed H. The effectiveness of physiotherapy in patients with asthma: a systematic review of the literature. *Respir Med*. 2013;107(4): 483–494.
13 Salvi D, Agarwal R, Salvi S, Barthwal BM, Khandagale S. Effect of diaphragmatic breathing on spirometric parameters in asthma patients and normal individuals. *Indian J Physiother Occup Ther*. 2014;8(3):43.
14 Karam M, Kaur BP, Baptist AP. A modified breathing exercise program for asthma is easy to perform and effective. *J Asthma*. 2017;54(2):217–222.
15 Elnaggar RK. A randomized placebo-controlled study investigating the efficacy of inspiratory muscle training in the treatment of children with bronchial asthma. *J Asthma*. 2020:1–9.
16 Elnaggar RK, Shendy MA, Mahmoud MZ. Prospective effects of manual diaphragmatic release and thoracic lymphatic pumping in childhood asthma. *Respir Care*. 2019;64(11):1422–1432.
17 McClafferty H. An overview of integrative therapies in asthma treatment. *Curr Allergy Asthma Rep*. 2014;14(10):464.
18 Yu M, Gao L, Kong Y, et al. Safety and efficacy of acupuncture for the treatment of chronic obstructive pulmonary disease: A systematic review protocol. *Medicine*. 2019;98(37), e17112.
19 Wang J, Li J, Yu X, Xie Y. Acupuncture therapy for functional effects and quality of life in COPD patients: a systematic review and meta-analysis. *Biomed Res Int*. 2018; 2018, 3026726.
20 Ngai SP, Spencer LM, Jones AY, Alison JA. Acu-TENS reduces breathlessness during exercise in people with chronic obstructive pulmonary disease. *Evid Based Complement Alternat Med*. 2017;2017.
21 Ngai SP, Jones AY, Hui-Chan CW. Acu-TENS and postexercise expiratory flow volume in healthy subjects. *Evid Based Complement Alternat Med*. 2011;2011.
22 Elnozhe FM, Rifaat N. Acu-tens improves lung function in patients with chronic bronchial asthma: a randomized placebo-controlled trial. *Bull Fac Phys Ther*. 2017;22 (1):1.
23 *Global Initiative for Asthma: Global strategy for asthma management and prevention*; 2017 [cited 2019 December 24]. Available from: https://ginasthma.org/2017-gina-report-global-strategy-for-asthma-management-andprevention/.
24 Culver BH, Graham BL, Coates AL, et al. Recommendations for a standardized pulmonary function report. An official American Thoracic Society technical statement. *Am J Respir Crit Care Med*. 2017;196(11):1463–1472.
25 Abdel Hai R, Taher E, Abdel Fattah M. Assessing validity of the adapted Arabic Paediatric Asthma Quality of Life Questionnaire among Egyptian children with asthma. *East Mediterr Health J*. 2010;16(3):274–280.
26 Braga DKAP, Marizeiro DF, Florêncio ACL, et al. Manual therapy in diaphragm muscle: Effect on respiratory muscle strength and chest mobility. *Man Ther Posturology Rehabil J*. 2016;14:302–308.
27 Nickel C, Kettler C, Muehlbacher M, et al. Effect of progressive muscle relaxation in adolescent female bronchial asthma patients: a randomized, double-blind, controlled study. *J Psychosom Res*. 2005;59(6):393–398.
28 Elnaggar RK, Shendy MA, Elfakharany MS. Effect of eight weeks of incremental aerobic training on inflammatory mediators, cardio-respiratory indices, and functional capacity in obese children with bronchial asthma. *Pediatr Exerc Sci*. 2021 [In press].
29 Ngai SP, Hui-Chan CW, Jones AY. A Short review of acupuncture and bronchial asthma—western and traditional Chinese medicine concepts. *Hong Kong Physiother J*. 2006;24(1):28–38.
30 Ngai SP, Jones AY, Hui-Chan CW, Ko FW, Hui DS. Effect of 4 weeks of Acu-TENS on functional capacity and beta-endorphin level in subjects with chronic obstructive pulmonary disease: a randomized controlled trial. *Respir Physiol Neurobiol*. 2010;173 (1):29–36.
31 Jones AY, Ngai SP, Hui-Chan CW, Yu HP. Acute effects of Acu-TENS on FEV1 and blood B-endorphin level in chronic obstructive pulmonary disease. *Altern Ther Health Med*. 2011;17(5):8–13.
32 Cheung LC-T, Jones AY-M. Effect of Acu-TENS on recovery heart rate after treadmill running exercise in subjects with normal health. *Complement Ther Med*. 2007;15(2): 109–114.
33 Vyas B, Shah S, Tiwari H, Singh A. The effect of Acu-TENS on FEV1, six-minute walk distance and dyspnoea in patients with chronic obstructive pulmonary disease: a randomised trial. *Int J Biomed Adv Res*. 2013;4(7):448.
34 Liu X, Fan T, Lan Y, Dong S, Fu J, Mao B. Effects of transcutaneous electrical acupoint stimulation on patients with stable chronic obstructive pulmonary disease: a prospective, single-blind, randomized, placebo-controlled study. *J Altern Complement Med*. 2015;21(10):610–616.
35 Ngai SP, Jones AY, Hui-Chan CW, Ko FW, Hui DS. Effect of acu-TENS on post-exercise expiratory lung volume in subjects with asthma—a randomized controlled trial. *Respir Physiol Neurobiol*. 2009;167(3):348–353.
36 Cukic V, Lovre V, Dragisic D, Ustamujic A. Asthma and chronic obstructive pulmonary disease (COPD) - differences and similarities. *Mater Sociomed*. 2012;24 (2):100–105.
37 Lau KS, Jones AY. A single session of Acu-TENS increases FEV1 and reduces dyspnoea in patients with chronic obstructive pulmonary disease: a randomised, placebo-controlled trial. *Aust J Physiother*. 2008;54(3):179–184.
38 Chan JC, Wong NN, Wong DW, Yeung WC, Jones AY. Effect of Acu-TENS on post exercise airway resistance in healthy individuals. *Hong Kong Physiother J*. 2012;30(1): 29–35.
39 Guan Z, Zhang J. Effects of acupuncture on immunoglobulins in patients with asthma and rheumatoid arthritis. *J Tradit Chin Med*. 1995;15(2):102–105.
40 Yang Y-Q, Chen H-P, Wang Y, Yin L-M, Xu Y-D, Ran J. Considerations for use of acupuncture as supplemental therapy for patients with allergic asthma. *Clin Rev Allergy Immunol*. 2013;44(3):254–261.
41 Nurwati I, Muthmainah M, Huda KN. Acupuncture for asthma: Its potential significance in clinical practice. *Med Acupunct*. 2020;32(5):272–279.
42 Brinkhaus B, Roll S, Jena S, et al. Acupuncture in patients with allergic asthma: a randomized pragmatic trial. *J Altern Complement Med*. 2017;23(4):268–277.