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Acupoint Transcutaneous Electrical Nerve Stimulation in Hospitalized COPD Patients with Severe Dyspnoea: A Randomized Controlled Trial

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Abstract

Objective: To evaluate the effect of acupuncture transcutaneous electrical nerve stimulation (acuTENS) on the reduction of dyspnoea during acute exacerbation of chronic obstructive pulmonary disease (AECOPD). **Methods:** A multicentric randomized control trial with masked patients and evaluators was carried out. During hospitalization, AECOPD patients received 45 min of acuTENS (experimental group) or sham acuTENS (controls) daily on 5 consecutive days. The trial was conducted at the Hospital del Mar, Barcelona, and Hospital Sant Joan de Déu, Manresa (both in Spain). Dyspnoea and peak expiratory flow were measured daily from the first to fifth days. Length of stay, readmissions at 3 months and adverse events were also analysed. **Results:** Finally, 19 patients with moderately to severely exacerbated COPD were included. Although some tendencies in dyspnoea during day 1 and length of hospital stay were found favouring acupuncture, no significant differences were shown between groups. **Conclusions:** The acuTENS intervention was feasible#well tolerated in AECOPD patients and no important side effects were reported.

Keywords

acuTENS, acupuncture therapy, AECOPD, dyspnoea

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Introduction

Chronic obstructive pulmonary disease (COPD) is a complex disease characterized by persistent and progressive airflow limitation associated with a chronic inflammatory response in the airways and the lung parenchyma to noxious particles or gases.[1] COPD is the fourth leading cause of death worldwide, causing the death of 3.17 million people in 2015,[2] and its prevalence in Spain is around the 10% in the population between 40 and 80 years.[3]

Dyspnoea is one of the main symptoms of COPD; it is usually progressive and one of the most limiting symptoms.[4] COPD patients can suffer from important worsening of their condition, during acute exacerbation of COPD (AECOPD), which may even require hospitalization.[5] Although only 10%–15% of all COPD patients will experience severe exacerbations that require hospital admission, expenditure associated with hospitalization represents more than 70% of all COPD-related medical care costs.[6] Hospitalizations for AECOPD impose a great economic burden, with an average cost of 344.96 euros per person per day in Spain,[7] and are associated with 12% mortality and 35% readmissions up to 3 months after discharge.[8,9]

AcuTENS consists of using transcutaneous electrical nerve stimulation (TENS), instead of needles, to stimulate acupuncture points. This stimulation method is safer than traditional

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acupuncture since there is no risk of infection or internal organ injury.[10] A recent systematic review identified 4 studies using acuTENS to treat dyspnoea in COPD.[11] Of those, three studies which included stable patients have suggest that acuTENS stimulation at Ding Chuan point may produce a fast anti-dyspnoeic effect and increase FEV1.[12–14] However, in the only trial including exacerbated participants improvements on dispones were not seen after 20 sessions.[15] We hypothesis that this could be because acuTENS may have fast but short-term effects as some of the positive results of studies including stable patients were seen after a single session.[12,13] If this was true, acuTENS could have a potential role in dyspnoea management during the first days of an AECOPD. The objective of this trial is to assess if acuTENS could be effective for reducing dyspnoea during the first days of hospitalization in AECOPD.

Methods

Design

This was a multicentric, randomized parallel, 1:1 allocation ratio, controlled trial with blinded patients and evaluators. The protocol of this study was previously registered at clinicaltrials.gov (NCT02998957) and published elsewhere.[16]

Settings and Participants

The study was conducted at two hospitals in Spain, the Hospital del Mar in Barcelona, and the Hospital de Sant Joan de Déu in Manresa.

Participants were recruited by the pneumology and emergency services using the following criteria: (1) patients aged between 45 and 75 years, with a diagnosis of COPD according to the GOLD guidelines, (2) with a smoking habit history of 10 pack-years or more, (3) able to correctly understand and answer the modified Borg scale, (4) with a dyspnoea level of at least 5 points in the Borg scale, (5) within the first 48 h after hospitalization and (6) who agreed to participate in the study and sign the informed consent. Participants were excluded if they had any contraindication for using TENS (pregnancy, epilepsy, pacemaker use or skin lesions or irritation in the application area) or any disease that could affect their dyspnoea perception. Participants were all informed about the study characteristics, objectives, and adverse effects before accepting to participate.

Randomization and Allocation

Participant allocated to the intervention and control groups using a computer-generated randomization. A researcher, who was not involved in any other phase of the study created a list by blocks for each centre with a 1:1 allocation ratio. Allocation of the participants was performed by assigning participants a consecutive number and matching it with the randomization list.

Blinding

To minimize possible selection, performance and assessment bias, participant's allocation was blinded for participants, medical providers and assessors. Only the personnel administering the real and sham acuTENS interventions had access to the randomization lists using and electronic key.

Interventions

Interventions were delivered by a physiotherapist, with no acupuncture knowledge, who was trained to deliver both real and sham interventions.

The treatment protocol, including the selection of the acupuncture point, the stimulation method and the duration of each treatment, was based on previous trials which used this intervention to treat dyspnoea in stable COPD participants.[12,13,17]

Both real and sham interventions were delivered at the Dingcuan point. This point is located between C7 and T1 spinous processes at 0.5 cun from the posterior middle line. Electrodes were placed using tape and a plastic sheet with a small hole was used to specifically stimulate the acupuncture point.

AcuTENS Group. The acuTENS group received a stimulation using a 2 Hz stimulation with a pulse width of 200 mS. Stimulation intensity was set to the highest each patient could tolerate without being painful.

Sham acuTENS Group. In the sham acuTENS group we used the same TENS devices but wires were modified to avoid any electrical outlet. However, the device screen was on and showed the same data as the real intervention. Patients were told that, due to the nature of the electric wave they might not perceive the stimulation.

Stimulation time for both groups was 45 min and took place for a maximum of 5 consecutive days or until the patient was discharged.

During the study all participants continued with the standard treatment for AECOPD (bronchodilators, steroids, etc).

Outcomes and Measurements

Data collection was done by masked using a standard form. Dyspnoea was the dyspnoea assessed with the modified Borg scale. Assessors used a printed version of the scale to explain how it worked before asking the patients to rate their dyspnoea. Assessments were performed before the first sessions and after (day 1 to day 5). The modified Borg scale is a valid and reliable assessment tool for dyspnoea in patients with an AECOPD.[16] Secondary outcomes included the hospitalization days, the peak expiratory flow (PEF) on each day (day 1 to day 5), readmissions 3 months after discharge. Any adverse reaction during the 5-day treatment was also recorded.

Sample Size

Sample size was calculated considering a minimal detectable difference in dyspnoea of 2 points in the modified Borg scale,[17] and a standard deviation of 2.6. Using an α error of 0.05, a β error of 0.2 and estimating a 10% of losses, we estimated a sample of 30 patients for each group.

Statistical Methods

For the descriptive analysis of the demographic data, we used means and standard deviations (SD) for continuous variables if normal distribution was found, and median and 25 and 75 percentiles otherwise. Absolute values and percentages were used to describe qualitative outcomes. For the comparative analysis, mean differences and 95% confidence intervals were calculated using a t-test or Mann–Whitney U test depending on the distribution.

Results

Recruitment started in February 2017 and finished in February 2020 due to the impossibility of continuing as a result of the

COVID-19 pandemic. During that period, recruitment was much slower than expected and only 19 participants of the 60 needed for the trial were recruited. All participants, 11 male and 8 female, completed the study; however, we had some missing data due to patients being discharged (3 participants), and being home-hospitalized (1 participant). The flow diagram of participants can be seen in Figure 1. Baseline characteristics in the acuTENS and simulated acuTENS groups are shown in Table 1.

Primary and Secondary Outcomes

Due to the small sample size, we did not have enough statistical power to detect statistical differences. We observed a reduction of dyspnoea in both groups, with a greater reduction in the acuTENS group on day 1 (median (IQR): 6 (5.5-7) versus 7 (6-8.5), $p = 0.39$); however, this difference was not maintained during the following days. Results for dyspnoea changes on days 1 to 5 in both groups are shown in Table 2 and Figure 2.

A reduction in the length of hospital stay was also observed (median (IQR): 8 (6-11) versus 11 (6.5-25), $p = 0.492$) in the acuTENS group compared with the control. Regarding PEF and readmissions, we observed similar values in the treatment and control groups. No adverse events were reported during the 5 intervention days by any of the 19 participants. Secondary outcomes are summarized in Table 3.

Discussion

Although our initial aim was to evaluate the efficacy of the intervention, due to the impossibility of completing the needed sample, this should be considered a pilot trial.

To our knowledge, this is the first trial exploring the effect on acuTENS on dyspnoea during the first days of hospitalization of patients with an AECOPD.

During the period of the study, the recruitment process was much slower than expected, even with two recruiting centres. Moreover, although we anticipated that some participants might be discharged during the trial, we did not expect the rate would be so high (2 of 11 participants in the intervention group and 1 of 8 participants in the control). Therefore, there is a need to find strategies to improve participant recruitment in future trials.

Regarding the interventions, no important implementation issues were found and training of physiotherapists was

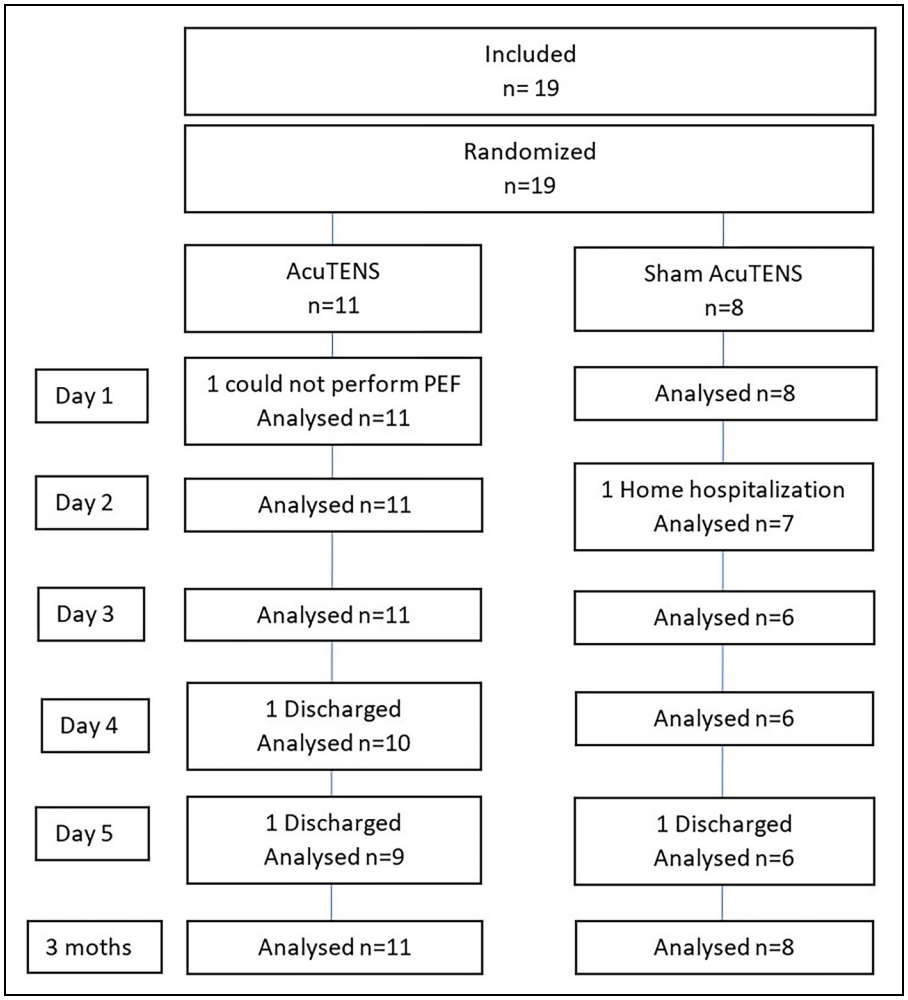

Figure 1. Flow diagram.

Table 1. Participants Baseline Characteristics.

Characteristics	AcuTENS n = 11	Sham AcuTENS n = 8
Age(yr), mean (SD)	62.4 (7.7)	71.3 (3.4)
Missing, n	0	0
Males, n (%)	5 (45.5)	6 (75.0)
Missing, n	0	0
BMI (kg/m^2), mean (SD)	29.78 (13.86)	29.62 (6.95)
Missing, n	2	0
Severity, n (%)		
GOLD 1	1 (9)	0 (0)
GOLD 2	1 (9)	0 (0)
GOLD 3	4 (36)	5 (62.5)
GOLD 4	3 (27)	1 (12.5)
Missing, n	2 (18)	2 (25)
Smoking status, n (%)		
Smoker	9 (81.8)	7 (87.5)
Ex-smoker	2 (18.2)	1 (12.5)
Non-smoker	0 (0)	0 (0)
Missing, n	0	0
Pack-years, mean (SD)	45.75 (21.37)	76.92 (24.17)
Missing, n	1	1
Borg	6.91 (1.57)	7.62 (1.40)
Missing, n	0	0
PEF	126 (51.6)	120 (46.59)
Missing, n	1	0
Blood gas, mean (SD)		
PaO_2	57.40 (14.27)	85.42 (35.38)
Missing, n	3	1
$PaCO_2$	58.58 (19.74)	56.34 (15.51)
Missing, n	3	1
SaO_2	88.48 (10.63)	89.60 (13.94)
Missing, n	4	1
Bic	35.16 (11.80)	30.36 (4.19)
Missing, n	3	2
pH	7.37 (0.06)	7.35 (0.09)
Missing, n	3	1

Yr: years; SD: Standard difference; PaO_2: Arterial oxygen partial pressure; $PaCO_2$: Arterial carbon dioxide partial pressure; SaO_2: Arterial oxygen saturation; Bic: Bicarbonate

successful, even though they did not have any previous experience with acupuncture. This corroborates that acuTENS is a simple and easy intervention that could be implemented elsewhere without professional specialization. Also, interventions were well tolerated by participants, did not interfere with their usual treatment and no adverse events were detected.

We observed some exploratory results that need to be corroborated in future trials.

First, acuTENS might result in an improvement in dyspnoea only during the first days. This might explain why Öncu et al[15] did not find positive results since in their study, the authors compared acuTENS and sham acuTENS after a 20-session treatment. However, Lau et al observed a dyspnoea reduction of 10.7 mm (95% CI −13.9 to −7.6), on a 100 mm visual analogue scale (VAS), after a single 45 min acuTENS session in stable COPD participants.[18] These single-session effects were also seen by Ngai et al who reported a 20% improvement in dyspnoea perception between groups, also using a VAS in stable participants, and an increase of blood β-endorphin levels.[14] These could suggest that the technique may only have short-term anti-dyspnoeic effects and be mediated by δ-opioid receptors.[19]

Table 2. Dyspnoea Changes.

	AcuTENS		Sham AcuTENS		
	n	Median (P25, P75)	n	Median (P25, P75)	*P*-value
Borg					
Day 0	11	7.0 (5.5, 8.0)	8	7.5 (7.0, 9.0)	0.310*
Day 1	11	6.0 (5.5, 7.0)	8	7.0 (6.0, 8.5)	0.392*
Day 2	11	6.0 (5.5, 7.0)	7	6.0 (5.0, 6.5)	0.425*
Day 3	11	5.0 (4.0, 5.5)	7	5.0 (5.0, 6.0)	0.375*
Day 4	10	4.0 (3.0, 5.0)	7	4.0 (3.0, 5.5)	0.887*
Day 5	9	4.0 (3.0, 5.0)	6	4.5 (4, 6.0)	0.864*
Dif Day 1 - Day 5		−2.0 (−4.0, −1.0)		−3.0 (−5.0, −2.0)	0.272*

P25: Percentil 25; P75: Percentil 75. *Independent-Samples Mann-Whitney U Test

Second, we also observed a difference in length of hospital stay. If future trials confirm this preliminary finding, acuTENS could have an important impact on treatment costs, since it is

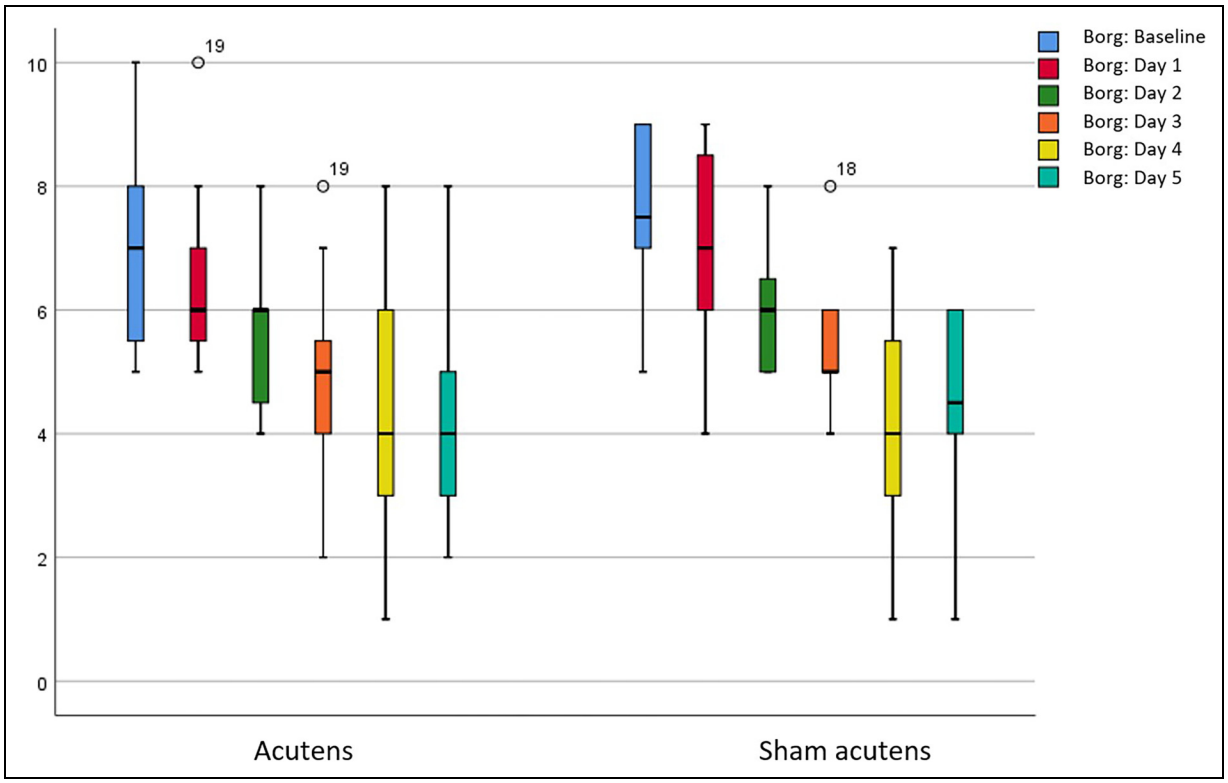

Figure 2. Dyspnoea boxplot.

Table 3. Results of Secondary Outcomes.

	AcuTENS		Sham AcuTENS		
	n	Median (P25, P75)	n	Median (P25, P75)	p-value
Length of stay (days)	11	8 (6, 11)	8	11 (6.5, 25)	0.492*
Readmission	10	0 (0, 0)	8	0.5 (0, 2)	0.46*
PEF (L/min)					
Day 1	10	125 (70, 160)	8	100 (75, 160)	0.799*
Day 2	10	100 (70, 150)	7	120 (100, 160)	0.475*
Day 3	11	130 (75, 150)	7	130 (105, 170)	0.560*
Day 4	10	125 (80, 160)	7	150 (120, 180)	0.363*
Day 5	9	140 (120, 160)	6	140 (130, 160)	0.695*

P25: Percentil 25; P75: Percentil 75. *Independent-Samples Mann-Whitney U Test.

estimated that the hospitalization cost in Spain for acute COPD exacerbations is on average €344.96 per person per day.[7]

Finally, Öncu et al[15] also observed an improvement in the 6 min walking distance that implies improvements in functional capacity that are strongly related to ventilatory capacity. Because of the length of the intervention and the length of stay in our study, this variable could not be measured but should be explored in future trials.

Limitations

Recruitment was more difficult than previously anticipated even though we included two centres in the study. This situation was aggravated when the centres started to receive COVID patients. Due to the impossibility of continuing with the recruitment, the investigation team decided to conclude the study with the participants included until that moment, resulting in insufficient statistical power.

Another limitation was the length of the intervention, 5 days. At that moment, patients are still having acute symptoms and those probably conditioned the results. We observed improvements in the majority of the variables but not large enough to obtain significant differences. Longer interventions that contemplate the length of hospital stay probably should carry better results.

Conclusions

AcuTENS is a feasible and safe intervention that can be applied during AECOPD in hospitalized patients. Although we did not observe any significant difference between groups in the study outcomes, we observed a non-statistical shortening of the hospital stay that needs to be further explored. Recruitment strategies need to be improved in future trials to achieve a larger sample size.

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Authors' Contributions

CF conceived and coordinated the study. JV participated in the study design and data analysis planning. LC performed the data analysis. All authors were involved in writing and approving the final manuscript.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethical Approval

The study was approved by the research ethics committee of each centre (Parc de Salut MAR – Ethic Committee of Research, ID code: 2018/8153/I and Comitè d'Ètica d'Investigació de la FUDACIÓ UNIO CATALANA HOSPITALS, ID code: CEI 17/97).

Informed Consent

All patients were informed about the nature of the study, its objective and the possible adverse effects of the treatments, as well as their voluntary participation. All participants agreed to participate and signed de informed consent.

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