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Effects of neuromuscular electrical stimulation therapy on physical function in patients with COVID-19 associated pneumonia: Study protocol of a randomized controlled trial

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ABSTRACT

Purpose: Neuromuscular electrical stimulation (NMES) has been considered as a promising approach for the early rehabilitation of patients during and/or after intensive care unit (ICU) stay. The overall objective of this study is to evaluate the NMES effectiveness to counteract the post-ICU impairment in physical function of COVID-19 patients. The specific aim of this manuscript is to describe the study design, protocol, content of interventions, primary and secondary outcomes and to discuss the clinical rehabilitation impact of the expected experimental results.

Methods: This prospective, randomized, controlled, parallel-group, single-blind trial will include 80 patients who had undergone mechanical or non-invasive ventilation following pneumonia-induced respiratory failure. Patients are randomized to a control group (routine physical therapy for 3 weeks) or a NMES group (routine physical therapy plus NMES of quadriceps and gastrocnemius muscles for 3 weeks). The primary outcome is physical performance assessed through the Short Physical Performance Battery (SPPB). Secondary outcomes include independence level, perceived fatigue, muscle strength, rectus femoris thickness, and walking performance. The SPBB and walking performance are assessed once (after the intervention), while all other outcomes are assessed twice (before and after the intervention).

Conclusion: NMES is a simple and non-invasive technique for muscle strengthening that is usually well tolerated, does not produce adverse effects, requires no or little cooperation from patients and is quite inexpensive. Therefore, proving the effectiveness of NMES therapy for physical and muscle function in COVID-19 patients could support its systematic incorporation in post-ICU rehabilitation protocols of patients presenting with post-intensive care syndrome.

1. Introduction

All healthcare sectors are currently involved in the management of the COVID-19 epidemic, including the area of post-acute care and rehabilitation [1]. Similar to other survivors of critical illness such as brain injury patients [2] and septic patients [3], COVID-19 patients show a post-intensive care syndrome that includes the impairment in mobility and physical function [4]. It may be hypothesized that such alteration can result from the development of inactivity-related muscle wasting and/or critical illness neuromyopathy occurring during sedation/paralysis and mechanical ventilation [5–7]. Consistently, it has been previously shown that a combination of disuse atrophy, myopathy, and polyneuropathy could underlie the so-called intensive care unit (ICU)-acquired muscle weakness [5–7]. Therefore, it has been proposed that early rehabilitation in (or immediately after) ICU could be useful for prevention and treatment of muscle weakness [8]. Among the treatments available for the early rehabilitation of patients in and/or after ICU stay, neuromuscular electrical stimulation (NMES) has been considered as a promising approach [9–11]. This physical therapy modality consists in the application of intermittent electrical stimuli to the skin

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above the skeletal muscles, with the main objective to generate involuntary muscle contractions (through the excitation of motor nerves and their terminal axonal branches), most often in isometric tetanic conditions [12,13]. Previous systematic reviews showed that NMES added to usual care proved to be more effective than standard care alone for prevention of ICU-acquired weakness [9,10]. Recent randomized controlled trials also showed that adding a NMES program to standard rehabilitation improved physical function in elderly patients hospitalized due to bacterial pneumonia [14] and in patients with chronic obstructive pulmonary disease [15]. We hypothesized that NMES can also be effective to counteract the post-ICU impairment of physical function in COVID-19 patients. No recommendations have been provided yet for a disease-specific rehabilitation of physical function in these patients and, to the best of our knowledge, no previous study investigated the NMES effectiveness for post-ICU rehabilitation of COVID-19 patients. Therefore, the overall objective of this study is to evaluate NMES effect on physical function of COVID-19 patients. The specific aim of this manuscript is to describe the study design, protocol, content of interventions, primary and secondary outcomes and to discuss the clinical rehabilitation impact of the expected experimental results.

2. Methods

2.1. Study design and randomization

The study is a prospective, randomized, controlled, parallel-group, single-blind trial that is be conducted according to the SPIRIT recommendations [16]. Following informed consent from the patient or the substitute decision maker, patients are randomized (with a 1:1 allocation ratio) to a control group or a NMES group. Computer-generated randomization lists are used (using the website www.random.org) to sequentially distribute the patients into one of the two groups.

Generation of the allocation sequence is performed by one of the authors (CB), enrolment of participants and assignment of participants to interventions are performed by another author (FG).

The study conforms to the guidelines of the Declaration of Helsinki, was approved by the local ethics committee ("Comitato Etico Interaziendale San Luigi Gonzaga": protocol n. 52/2020), and registered at the ClinicalTrial.gov website (identifier NCT04382729).

2.2. Study setting and patients

The study setting is an academic hospital where patients of both genders who had undergone mechanical or non-invasive ventilation following pneumonia-induced respiratory failure are recruited. Inclusion criteria are: i) age above 18 years, ii) respiratory (PaO2/FiO2 ratio > 180 mmHg) and hemodynamic stability for at least two days after withdrawal of controlled mechanical ventilation and neuromuscular blocking agents, iii) normal level of alertness, orientation, and responsiveness to verbal stimulus. Exclusion criteria are: i) pregnancy, ii) known or suspected malignancy in the lower limbs, iii) body mass index equal or greater than 35 kg/m^2 (patients with severe and morbid obesity were not included because of previous studies showing that current tolerance to motor stimulation is reduced in obese individuals) [17,18], iv) conditions preventing NMES treatment (e.g., deep vein thrombosis, skin lesions, rhabdomyolysis), v) conditions preventing outcome assessment (e.g., amputation or inability to transfer independently from bed to chair before hospital admission), vi) presence of an implanted cardiac pacemaker or defibrillator.

2.3. Interventions

Patients in both groups receive normal daily care, as directed by the medical staff, including drug treatments, oxygen delivery, and physical therapy exercises according to the protocol (level IV) proposed by Morris et al. [19]. Briefly, the protocol is applied once a day for 30 min (5 days per week for 3 weeks) by the staff physical therapists. It starts with global passive range of motion exercises, followed by active and resistive exercises (including controlled breathing exercises and respiratory muscle training), transfer to the edge of the bed or to a chair, standing and walking.

The intervention group, in addition to the daily routine physical therapy, receives NMES for 15 days (5 days per week for 3 weeks). NMES is applied bilaterally using an electrical stimulator (T-One Rehab, I-Tech Medical Division - IACER, Martellago, Italy) with pairs of electrodes (10 × 5 cm) placed transversally on the quadriceps muscle (5 cm below the inguinal crease and 5 cm above the patella) and on the gastrocnemius muscles (3 cm below the popliteal crease and over the distal third of the muscles) [20]. The stimulation protocol consists in the application of symmetrical biphasic rectangular pulses with a frequency of 30 Hz (pulse duration: 400 μs). The total duration of the NMES session is 30 min for the first week and 45 min for the second and third week. Stimulation (on) time is 5 s and relaxation (off) time is 15 s, thus eliciting a total of 90 evoked contractions per day during the first week and 135 contractions per day during the second and third week. Both lower limbs and muscle groups are stimulated synchronously. Stimulation intensity is adjusted daily by the physical therapist to elicit a visible twitch in each muscle, as previously described [20]. The maximal stimulation intensity is recorded for each session and considered as a surrogate marker of NMES dose [12].

Criteria for discontinuing interventions include participant request (for patients of both groups) and intolerance to NMES (for patients of the NMES group).

2.4. Blinding and outcomes

A blinded physician (SDF) completes all functional assessments and gathers all clinical data on the electronic medical record of each patient.

The following clinical data are acquired from electronic patient files, interviews, and clinical assessments: gender, age, body mass index, length of ICU and hospital stay, length of mechanical or non-invasive ventilation, length of neuromuscular blocking agent administration, pulmonary function (PaO2/FiO2 ratio), and comorbidities (assessed through the Cumulative Illness Rating Scale) [21].

The primary outcome is physical performance assessed through the Short Physical Performance Battery (SPPB) [22]. The SPPB score is a composite measure assessing standing balance (ability to stand for up to 10 s with feet positioned in three ways: together side-by-side, semi-tandem and tandem), walking speed (time to complete a 4-m walk), and sit-to-stand performance (time to rise from a chair five times). Each task is scored out of 4 points, with the scores from the three tests summed up to give a total, with a maximum of 12 points and a minimum of 0.

Previous studies showed this battery of physical assessment tests can discriminate between physically fit subjects (presenting SPPB score > 8) and frail/sarcopenic patients (score ≤8) [23,24] and is responsive to clinical changes in different populations of patients, with the inclusion of ICU survivors [25].

Secondary outcomes include: i) independence level (assessed through the Functional Independence Measure – FIM – scale) [26]; ii) perceived fatigue (assessed through the Fatigue severity scale) [27]; iii) muscle strength (see below); iv) two-step test performance (assessed through the maximal length of two steps taken by the subject) [28]; v) 6-min walking test performance; vi) thickness of the rectus femoris muscle (see below).

Patients perform the SPPB, two-step test, and 6-min walking test once (after the 3-week intervention period), while all other outcomes are assessed twice (before and after the intervention).

2.5. Assessment of muscle strength

Handgrip strength is assessed for both sides using a handheld device (Jamar Plus Digital Dynamometer, Patterson Medical, Warrenville, IL, USA). Patients are instructed to perform a maximal voluntary isometric contraction by contracting their muscles as forcefully as possible for 4–5 s. The test is repeated three times for each side and the highest value is retained.

Lower limb strength is assessed as the sum of knee extension and plantar flexion strength of both sides. Muscle strength is rated using the Medical Research Council (MRC) scale that ranges from 0 (no muscle contraction) to 5 (normal resistance) [29], for a maximum score of 20 points.

2.6. Assessment of muscle thickness

The same experienced sonographer (SDF), blinded as to the allocation group, performs all the ultrasound assessments and acquires all the images using a MyLab™ X6 ultrasound device (Esaote, Genoa, Italy) equipped by a linear-array transducer with variable frequency band (3–13 MHz). Gain is set at 50% of the range, dynamic image compression is turned off, and time-gain compensation is maintained in the same (neutral) position for all depths. All system-setting parameters are kept constant throughout the study and for each subject, except depth (initially set at 40 mm) that can be modified during the examination to visualize the entire muscle thickness. Three consecutive static scans of the rectus femoris of both thighs are acquired in the transverse plane. The rectus femoris is assessed half-way along the line from the anterior-superior iliac spine to the superior border of the patella, according to previous studies [30,31]. All three images acquired for each side are analysed and the mean of six measurements (three measurements per side) is considered. Muscle thickness is measured as the distance between the superficial and deep aponeuroses of the rectus femoris muscle, which originate hyperechoic interfaces, as previously described [30,31].

2.7. Sample size estimation and statistical analyses

To elucidate a difference in physical performance between the NMES group and the control group, we used the following data from previous studies to determine the required sample size: standard deviation of the SPPB score in older adults of 2.7 points [32] and minimal detectable change of 1.6 points [33]. Thirty-six participants per group will provide adequate power to detect a statistically significant difference in SPPB score between the two groups [statistical power: 80%; alpha level (1-sided): 0.05], but 80 patients will be recruited in total anticipating a drop-out rate of 10%.

The Shapiro–Wilk test will be adopted to check the normality of data distribution. Normally-distributed data will be analysed with paired sample *t*-test (within-group comparisons: before vs after intervention) and unpaired two-sample *t*-test (between-group comparisons: NMES group vs control group), while non-normally distributed data will be analysed with the Wilcoxon signed-rank test (within-group comparisons) and the Mann–Whitney *U* test (between-group comparisons), as appropriate.

Data will be expressed as mean ± SD (normally distributed data) or median and interquartile range (non-normally distributed data). The threshold for statistical significance will be set to $P = 0.05$. All statistical tests will be performed with SPSS 20.0 (SPSS Inc., Chicago, IL, USA) software package.

2.8. Trial status

The first study participants were recruited into the trial in April 2020. Patient recruitment and data collection are ongoing and will continue until the required number of study participants will be included.

3. Discussion

This study aims to assess the effect of a NMES-based intervention specifically targeting the physical function impairment that may occur in COVID-19 patients presenting with a post-intensive care syndrome.

Anterior thigh (quadriceps femoris) and posterior leg (gastrocnemii) muscles were specifically selected for the application of NMES because ICU-acquired muscle weakness and sarcopenia (that could represent a pre-existing condition in COVID patients given their demographic characteristics) have a regional distribution, preferentially affecting lower limb muscles [6,7,34,35]. The randomized controlled design, blinding of the physician performing the outcome assessments, and use of valid tools for the assessment of physical performance and muscle size (SPPB score and ultrasound-derived muscle thickness, respectively) are notable strengths of the study.

Limitations of the study include the absence of specific investigations (e.g., electromyography, electroneurography, muscle biopsy) providing possible insights into the neural and muscular mechanisms underlying the effects of NMES in responder patients (or explaining the non-responder phenotype) and the use of the MRC scale for the assessment of lower limb strength. Although this scale is widely used in routine clinical examinations, it is characterized by well-known limitations such as poor validity and inaccuracy of subjective ratings [36]. Other study limitations are represented by the short intervention duration, the lack of a direct assessment of NMES dose (through the quantification of the electrically-evoked force level) [12], and the lack of a post-intervention follow-up that could help determine whether the possible improvements in physical function induced by NMES may produce long-lasting benefits in physical performance and health.

Notwithstanding these limitations, demonstrating the effectiveness of NMES therapy to counteract the post-ICU impairment in physical function and/or muscle size could have relevant implications for the post-acute rehabilitation of COVID-19 patients. In fact, NMES is a simple and non-invasive technique for muscle strengthening that is usually well tolerated (only few patients with chronic disease and able-bodied elderly adults do not tolerate NMES) [13], does not produce adverse effects, requires no or little cooperation from patients and is quite inexpensive. Therefore, proving the effectiveness of NMES therapy for physical and muscle function could support its systematic incorporation in neuromuscular rehabilitation protocols for COVID-19 patients, without interference to their routine care (devices are easily portable and training sessions can be performed as bedside treatments) and without relevant increase to the staff work load.

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Authors' contribution

All authors took part in the design of the study. FG, PA, SDF are responsible for the daily operational aspects of the study including data collection. CB and MAM wrote the first drafts of the study protocol. All

authors participated in the preparation of the manuscript and all authors read and approved its final version.

Declaration of competing interest

The authors declare that they have no competing interests.

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