Multidisciplinary rehabilitation in intensive care for COVID-19: randomised controlled trial

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Abstract

Coronavirus disease 2019 (COVID-19) has led to an increasing number of patients in intensive care units (ICUs). The size of this post-ICU cohort will be unprecedented, with many patients vulnerable to post-intensive care syndrome. We analysed the respiratory and functional effects of a multidisciplinary rehabilitation programme on functional performance, in patients hospitalised in the ICU due to COVID-19. We conducted a randomised controlled clinical trial. 96 patients who fulfilled the eligibility criteria were randomised into control or intervention group. The control group received standard of care in the ICU, and the intervention group received a functional and respiratory rehabilitation protocol that included medical, nursing, physiotherapy and occupational therapy interventions.

At discharge, the intervention group showed significantly better muscular strength and respiratory capacity, and significantly fewer days of hospitalisation (12.90±5.8 versus 15.60±6.7 days, p=0.037). At the 4- and 12-week follow-up, we applied our main outcome measure, the 6-min walk test (6MWT). The intervention group had significantly better results than the control group on the 6MWT at the 4-week follow-up (604 ±67 versus 571±57 m, p=0.018) and at the 12-week follow-up (639±53 versus 611±67 m, p=0.025).

These results support the role of a multidisciplinary rehabilitation programme in COVID-19 patients hospitalised in the ICU and adds evidence that the implementation of rehabilitation programmes in ICUs could result in beneficial outcomes for critically ill patients.

Introduction

Coronavirus disease 2019 (COVID-19) is a highly infectious disease, caused by the severe acute respiratory syndrome coronavirus 2, which leads to respiratory, physical and psychological dysfunction in patients [1]. The most common symptoms of COVID-19 are fever and cough [2, 3]. Additional symptoms include weakness, dyspnoea, fatigue, nausea, vomiting, diarrhoea and changes to taste and smell [2, 3]. Approximately 80–90% of cases are mild and self-limited, primarily affecting the upper airway with limited involvement of the lungs [2, 3]. The remaining 10–20% will need medical care, and 5% will require admission to the intensive care unit (ICU) and be exposed to the post-intensive care syndrome (PICS) [2, 3].

PICS refers to the disability that persists in patients who survive critical illness; it is the result of a combination of factors related to the intense care in the ICU [4, 5]. PICS is recognised as a growing public health burden due to the associated neuropsychological and functional disability, and the evidence suggests...
that the prevention of ICU admission is more important and effective than intensive treatment of PICS following ICU discharge [4, 6].

Nowadays, functional and respiratory rehabilitation is increasingly implemented in critically ill patients to prevent or improve pulmonary function [7]. Although there is still no consensus in the literature about the beneficial effects of rehabilitation on PICS, with some studies showing beneficial effects [8–10], and others showing no relevant effects [11, 12], there is a growing body of evidence that respiratory muscular retraining and early mobilisation are a feasible and safe strategy to improve muscular and functional capacities in critically ill patients [7, 13].

Despite the potential of rehabilitation in ICU, it is difficult to test this complex intervention [14]. However, facing the COVID-19 pandemic and estimating the size of the post-ICU cohort associated with this disease, several authors recommended the implementation of a rehabilitation programme to improve these patients’ outcomes, and the study by Stutz et al. [15] highlighted the feasibility of early rehabilitation for critically ill patients with COVID-19 [16–20].

The objective of the study presented herein is to analyse the respiratory and functional effects of a rehabilitation programme on functional performance, in patients affected by COVID-19 hospitalised in the ICU, in comparison with a group subjected to standard of care, at discharge end-point and at 4- and 12-week follow-up.

**Material and methods**

**Study design**

A randomised, controlled, double-arm clinical trial was conducted in the tertiary, interdisciplinary ICU of Centro Hospitalar Entre Douro e Vouga, Portugal. Ethical approval for this study was provided by the ethical committee of Centro Hospitalar de Entre o Douro e Vouga. This trial is registered with the Brazilian Clinical Trials Registry (identifier RBR-7rvhpq9), and was performed in accordance with the Consolidated Standards of Reporting Trials guidelines.

The participants were divided into two groups (standard care (control) and intervention), by means of balanced randomisation at a 1:1 ratio using free software (www.random.org). Physiotherapists, occupational therapists and rehabilitation nurses other than those who provided usual care performed the trial intervention across the trial continuum. The rehabilitation physicians working in the ICU were not blinded, but the outcome assessor was blinded to group allocation. The complete blinding of the patients was not possible, but they were not aware of other treatment modalities.

Both groups received usual medical and nursing care in the ICU, which involved assessment and treatment of the respiratory system, and active bed exercises and mobility were encouraged as soon as possible. The intervention group received a functional and respiratory multidisciplinary rehabilitation programme (which included medical, nursing, physiotherapy and occupational therapy interventions) during their entire hospital stay, starting within the first 24 h from ICU admission, 15–30 min per session, twice per day, 6 days per week. It was individualised to each patient based on their clinical status and consistent with recommendations from the Portuguese Society of Physical and Rehabilitation Medicine [20]. Progression was increased successively, depending on the individual’s tolerance and stability. After discharge from the ICU, the intervention group continued with rehabilitation exercises, prescribed by rehabilitation physicians, which they performed, unattended, whether the patient was discharged home or to an inpatient unit, until 12 weeks after ICU discharge. They reported their execution to the medical team and rehabilitation nurses through teleconsultation. The control group did not receive any further rehabilitation intervention after hospital discharge.

**Study subjects**

Participants were adult patients (aged ≥18 years) with respiratory insufficiency due to COVID-19 hospitalised at the ICU of the Centro Hospitalar Entre Douro e Vouga, who were referred for respiratory and functional rehabilitation by the ICU medical team at this tertiary hospital. Written informed consent was obtained from participants or their authorised representatives.

The inclusion criteria were 1) independent in activities of daily living before the onset of critical illness; 2) fulfil the safety criteria defined by the Portuguese Society of Physical and Rehabilitation Medicine [20], which included a score of ≥2 or higher in the Richmond Agitation–Sedation Scale, designed to assess the level of alertness and agitated behaviour in critically ill patients [21]. Patients were excluded if they did not meet these safety criteria. Other exclusion criteria included 1) prior muscle weakness (such as a
pre-existing neurological or neuromuscular disease); 2) prior pulmonary disease affecting forced expiratory volume in 1 s (FEV₁) and/or Tiffeneau–Pinelli index; 3) acute thrombosis; 4) diagnosis on admission that excludes the possibility of walking at hospital discharge; 5) patients transferred from other hospitals.

**Assessment**

At admission, baseline descriptive data were collected, which included age, sex, body mass, body mass index, smoking status and comorbidities. Other descriptive data, such as the need and length of invasive mechanical ventilation and length of ICU stay (days) were also collected at discharge from the ICU.

Prior to intervention and at discharge participants were evaluated using the following scales: Chelsea Critical Care Physical Assessment tool (CPAx), Medical Research Council sum-score (MRC-SS), handgrip strength test (HST). CPAx is a pictorial composite of 10 numerical evaluations of pertinent functions and impairments used to assess physical and respiratory function impairments and morbidity [22]. MRC-SS evaluates the manual strength of six muscle groups bilaterally [23]. HST uses a handgrip dynamometer to assess muscle strength [23]. At discharge, the Medical Research Council dyspnoea scale (mMRC) was evaluated. mMRC summarises the score of five offered statements about breath possibility during daily activities [24].

The primary outcome measure was functional capacity, evaluated at the 4-week and 12-week marks, using the 6-min walk test (6MWT), which is a practical and simple test that measures the distance a person can quickly walk on a flat, hard surface in 6 min, reflecting the functional exercise level for daily physical activities [25].

The secondary outcome measures included Borg Rating of Perceived Exertion (BRPE), evaluated at the 4-week and 12-week marks, MRC-SS and HST. BRPE is a widely used and reliable indicator to monitor and guide exercise intensity, which allows individuals to subjectively rate their level of exertion during exercise or exercise testing [26]. The option to evaluate 6MWT and BRPE was due to the expected difficulty for patients to perform 6MWT at ICU discharge, as reported by Al Chikhane et al. [27].

**Statistical analysis**

The sample size was estimated using the Winpepi programme with an estimated α risk of 5%, power of 85%, pooled variance of 20%, for which 40 subjects were required in each group. Considering a rate of follow-up losses of 15%, we included 96 patients. We used SSPS (version 27.0; SSPS, Chicago, IL, USA), for all statistical analyses. Categorical variables were expressed as absolute and relative frequencies. Continuous variables were expressed as mean±SD. We used the Chi-squared test or Fisher exact test (as appropriate) to compare categorical variables between the two study groups, including the primary end-point, and the t-test to compare continuous variables. Significant differences between groups or across time were reported at α=0.05. All reported p-values are two-sided.

**Results**

**Characteristics of participants**

96 patients fulfilled the eligibility and inclusion criteria and were enrolled in this study. They were randomly allocated to the intervention group (48 patients) and the standard of care (control) group (48 patients). There were no losses to follow-up (figure 1). Both groups were constituted mainly of females, and the mean age was 68.31 years in the control group and 66.63 years in the intervention group. The demographic and clinical characteristics of participants are presented in table 1.

**Functional status at admission and discharge evaluation**

The values are presented in table 2. There were no statistically significant differences between the two groups in all the scales used. The percentage of patients who needed invasive mechanical ventilation (with sedation) is presented in table 2. The other patients received oxygen support through noninvasive ventilation, such as noninvasive positive pressure ventilation and high-flow nasal cannula oxygen therapy. The intervention group showed shorter length of stay in ICU and those patients who needed mechanical ventilation had a significantly shorter length of use. Additionally, the intervention group showed a statistically significant better functional status in the MRC-SS, HST and mMRC.

**4-week and 12-week follow-up evaluations**

The intervention group showed better functional performance in the 6MWT, BRPE and MRC-SS, on both 4-week and 12-week follow-up evaluations, as shown in table 2. No differences were found between the two groups regarding HST.
**TABLE 1** Demographic and clinical characteristics of the patients

|                      | Control group | Intervention group | p-value |
|----------------------|---------------|--------------------|---------|
| Patients             | 48            | 48                 |         |
| Female               | 27 (56.25)    | 28 (58.33)         | 0.840   |
| Age years            | 68.31±12.47   | 66.63±14.21        | 0.540   |
| Body mass kg         | 76.34±8.76    | 77.49±11.01        | 0.570   |
| BMI kg·m\(^{-2}\)    | 28.04±3.22    | 29.17±4.14         | 0.130   |
| Smokers              |               |                    |         |
| Regular smokers      | 9 (18.75)     | 11 (22.91)         | 0.615   |
| Previous smokers     | 12 (25.00)    | 8 (16.67)          | 0.314   |
| Cormobidities        |               |                    |         |
| Heart failure        | 6 (12.50)     | 3 (6.25)           | 0.293   |
| Hypertension         | 7 (14.58)     | 9 (18.75)          | 0.583   |
| Arrhythmia           | 2 (4.17)      | 4 (8.33)           | 0.399   |
| Myocardial infarction| 3 (6.25)      | 1 (2.08)           | 0.307   |
| Diabetes             | 5 (10.41)     | 3 (6.25)           | 0.460   |
| Dyslipidaemia        | 2 (4.17)      | 3 (6.25)           | 0.645   |
| Stroke               | 2 (4.17)      | 4 (8.33)           | 0.399   |
| Thyroid disease      | 1 (2.08)      | 1 (2.08)           | >0.999  |
| Kidney disease       | 1 (2.08)      | 3 (6.25)           | 0.307   |
| Malignancy           | 8 (16.67)     | 11 (22.91)         | 0.442   |

Data are presented as n, n (%) or mean±sd, unless otherwise stated. BMI: body mass index.
### TABLE 2 Clinical evaluations and group comparisons

|                      | Admission | ICU discharge | 4-week follow-up | 12-week follow-up |
|----------------------|-----------|---------------|------------------|-------------------|
|                      | Control group | Intervention group | Control group | Intervention group | Control group | Intervention group | Control group | Intervention group | Control group | Intervention group |
| CPAx score 0–60      |  33.16±9.77  |  31.33±8.42   |  44.02±4.64     |  41.27±6.07       |  44.02±4.64     |  41.27±6.07       |  0.014       |
| ICU LOS days         |  15.60±6.70  |  12.90±5.8    |  15.60±6.70     |  12.90±5.8        |  15.60±6.70     |  12.90±5.8        |  0.037       |
| Need of IMV during ICU stay |  23 (47.92) |  21 (43.75)  |  23 (47.92)     |  21 (43.75)       |  23 (47.92)     |  21 (43.75)       |  0.682       |
| Length of use of IMV days |  6.1±4.2    |  4.1±3.6      |  6.1±4.2        |  4.1±3.6          |  6.1±4.2        |  4.1±3.6          |  0.037       |
| MRC-SS score 0–60    |  47.2±7.1   |  46.7±6.8     |  52.1±4.1       |  54.4±3.7         |  52.1±4.1       |  54.4±3.7         |  0.005       |
| HST kg               |  14.1±5.6   |  12.7±7.3     |  21.2±4.3       |  23.3±5.1         |  21.2±4.3       |  23.3±5.1         |  0.032       |
| mMRC                 |            |               |                 |                   |                 |                   |  0.031       |
| mMRC ≤1              |  16 (33.3)  |  7 (14.6)     |                 |                   |                 |                   |             |
| mMRC ≥2              |  32 (66.7)  |  41 (85.4)    |                 |                   |                 |                   |             |
| BRPE score 6–20      |  12.5±1.8   |  11.7±2.1     |  11.9±1.1       |  11.3±1.6         |  11.9±1.1       |  11.3±1.6         |  0.035       |
| 6MWT m               |  571±57     |  604±67       |  611±67         |  639±53           |  611±67         |  639±53           |  0.025       |

Data are presented as mean±SD or n (%), unless otherwise stated. ICU: intensive care unit; CPAx: Chelsea Critical Care Physical Assessment; LOS: length of stay; IMV: invasive mechanical ventilation; MRC-SS: Medical Research Council sum-score; HST: handgrip strength test; mMRC: modified Medical Research Council dyspnoea score; BRPE: Borg Rating of Perceived Exertion; 6MWT: 6-min walk test.
Discussion
The results of our study showed that the group of patients who received a multidisciplinary rehabilitation programme had a significant better functional and respiratory performance than the control group. During the COVID-19 pandemic, we observed that ICUs became overwhelmed in many countries, and this fact raised the need to optimise ICU treatment in terms of length and patient outcome [18, 28]. Some studies have already been conducted to study the influence of rehabilitation in COVID-19 patients [15, 19, 27, 29–32], but to our knowledge, this is the first randomised controlled trial to analyse the impact of the implementation of a rehabilitation programme in COVID-19 patients hospitalised in the ICU.

The main outcome of this study, at the 4-week and 12-week assessments, was the 6MWT. The intervention group showed significantly better results than the control group, both on the 4- and 12-week follow-up assessment. These results are in line with the previous data from Liu et al. [17], who reported a significant improvement in 6-min walk distance after 6 weeks of respiratory rehabilitation; those from Schindler et al. [32], who reported an improvement in 6MWT performance after rehabilitation; and those from Al-Chikhahne et al. [27], who reported a significantly better performance on the 6MWT of post-ICU COVID-19 patients who performed a rehabilitation programme, compared to post-ICU non-COVID-19 patients who did not undertake any rehabilitation programme. The difference in 6MWT values in the two groups was >30 m, which, according to the study by Bohannon et al. [33], reflects the minimum clinically important difference value for most diseases. These findings suggest that the rehabilitation programme implemented improves functional and respiratory capacity, supported by the fact that at the 4-week follow-up, the intervention group showed significantly lower levels of perceived exertion in the BRPE scale applied after the 6MWT, and the difference between the groups was clinically important (0.8) [34]. BRPE is a widely used and reliable indicator to monitor and guide exercise intensity, which allows individuals to subjectively rate their level of exertion during exercise or exercise testing [26]. Both groups showed better values at the 12-week evaluation than the 4-week evaluation, which is similar to the results reported by Denehy et al. [11], and suggests that changes in functional capacity tend to improve over time, but the rehabilitation programme seems to enhance the recovery time.

In addition, the groups showed significantly different performances on the other secondary outcome measures. In fact, the intervention group showed larger improvements in different assessments compared to the control group. Similar results were observed in the studies by Hermans et al. [23] and Dantas et al. [35], which showed that early rehabilitation interventions (mobilisation and stimulation of activities) in critically ill intensive care patients could influence or even prevent physical impairments. Moreover, this specific difference in the MRC-SS values was also found in the study Kayambu et al. [36], which analysed the effects of rehabilitation in ICU patients with other medical conditions (not COVID-19). Furthermore, the intervention group had significantly better performances on the mMRC than the control group. The mMRC is moderately correlated with the functional assessments of patients’ cardiopulmonary fitness, including FEV1, being therefore an indirect indicator of respiratory function [24]. Considering the results of the study by Liu et al. [17], who conducted a randomised controlled trial to investigate the effects of 6-week respiratory rehabilitation training in elderly patients with COVID-19, in which the intervention group had a significantly better respiratory function (evaluated using FEV1), and the results from our study, the mMRC might be considered a good indicator of improvement in respiratory function.

There were no significant differences between the two groups in the HST, similar to the results reported by Schweickert et al. [9] and Morris et al. [10]; therefore, this indicator might not be a reliable measure to evaluate the outcomes of rehabilitation programmes in the ICU setting.

Rehabilitation had an impact on the length of ICU stay, as the intervention group had a significantly shorter length of stay in the ICU, which is in line with findings from Iannaccone et al. [37], who implemented specialised COVID-19 rehabilitation units, with decrease of the hospitalisation in acute COVID-19 patients from 15 days to 10 days. Morris et al. [38] also reported shorter stay in the ICU in patients that received early mobility. The percentage of patients who needed invasive mechanical ventilation is in line with that reported by Wang et al. [39]. Both intervention group and control group presented relatively short mean times of invasive mechanical ventilation, that were probably affected by the inclusion and exclusion criteria, namely the exclusion of patients with previous respiratory diseases. The intervention group needed invasive mechanical ventilation for a shorter period than the control group, which may reflect the impact of the rehabilitation programme on respiratory function and is similar to the results found by Schweickert et al. [9], who reported more ventilator-free days in the group that received a rehabilitation intervention.
**Limitations**

This study shows beneficial results regarding the effects of a rehabilitation programme on ICU patients, but these must be interpreted in the light of certain limitations. This clinical trial was performed in one centre only. The application of this protocol to a multicentre population might increase the significance of these results. The blinding of the multidisciplinary treatment team was not possible because they needed the knowledge of the group allocation in order to be able to provide the patient the correct intervention. Nonetheless, the assessors responsible for randomisation and outcome measures were completely blinded to group allocation. It was not possible to achieve complete blinding for patients, but subjects were unaware of other treatment modalities, and they did not know if they belonged to the intervention or standard group. Therefore, we cannot completely rule out placebo effects or experimenter bias in the current study.

**Future directions**

This study strongly indicates that the multidisciplinary rehabilitation programme in the ICU has beneficial outcomes for the patients. Unfortunately, not all ICU units have multidisciplinary professionals, namely rehabilitation physicians, physiotherapists and rehabilitation nurses, available to integrate this kind of programme into the ICU daily routine. However, there is growing evidence that rehabilitation in the ICU can play a major role in patient recovery, thus leading to fewer days of hospitalisation and better outcomes. In this sense, cost-effectiveness studies should be conducted to evaluate the possible benefits associated with the inclusion of these professionals in ICU multidisciplinary teams.

In conclusion, this randomised clinical trial presents beneficial results of a multidisciplinary rehabilitation programme in COVID-19 patients hospitalised in the ICU and adds evidence that the implementation of rehabilitation programmes in the ICU could result in beneficial outcomes for critically ill patients.

This study is registered at https://ensaiosclinicos.gov.br/ with identifier number RBR-7rvhpq9. Individual participant data that underlie the results reported in this article, after deidentification, will be available, beginning 9 months and ending 36 months after article publication, to anyone who wishes to access the data for any purpose. The study protocol will also be available. Proposals should be directed to cristinapbcarvalho@gmail.com.

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