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Multidisciplinary rehabilitation in intensive care for COVID-19 - randomized controlled trial

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In this study, we analysed the respiratory and functional effects of a multidisciplinary rehabilitation program in COVID-19' intensive care patients and obtained encouraging results of its beneficial outcomes and future implementation.

Abstract

The coronavirus disease 2019 (COVID-19) has led to an increasing number of patients in the intensive care units (ICU). 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 program on functional performance, in patients hospitalized in ICU due to COVID-19.

We conducted a randomized controlled clinical trial. Ninety-six patients, who fulfilled the eligible criteria, were randomized 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 less days of hospitalization (12.90±5.8 vs 15.60±6.7 days, P=0.037). At the 4- and 12-week follow-up we applied our main outcome measure – 6-minute walking test. The intervention group had significantly better results than the control group on the 6-minute walking test at the 4-week follow-up (604±67 vs 571±57 m, P=0.018) and at the 12-week follow-up (639±53 37 vs 611±67, P=0.025).

These results support the role of a multidisciplinary rehabilitation program in COVID-19 patients hospitalized in ICU and adds evidence that the implementation of rehabilitation programs in ICU could result in beneficial outcomes for the critical ill patients.

Keywords: COVID-19, functional rehabilitation, intensive care, post-intensive care syndrome, respiratory rehabilitation

Introduction

The coronavirus disease 2019 (COVID-19) is a highly infectious disease, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), that 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, dyspnea, fatigue, nausea, vomiting, diarrhea, 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 20-10% will need medical care, and 5% of them will require admission to the intensive care unit (ICU) and be exposed to the post-intensive care syndrome (PICS) [2, 3].

PCIS refers to the disability that persists in the patients who survives critical illness, and it is the result of a combination of factors related with the intense care in the ICU [4, 5]. PICS is recognized as a growing public health burden due to the associated neuropsychological and functional disability, and the evidence suggests that the prevention from ICU admission is more important and effective than intensive treatment of PCIS 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 or 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 mobilization are a

feasible and safe strategy to improve muscular and functional capacities in critical 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 program to improve these patients' outcomes, and the study by Stutz et al. highlighted the feasibility of early rehabilitation for critically ill patients with COVID-19. [15-20]

The objective of the presented study is to analyze the respiratory and functional effects of a rehabilitation program on functional performance, in patients affected by the COVID-19 hospitalized in ICU, in comparison with the group subjected to standard of care, at discharge endpoint and at 4- and 12-week follow-up.

Material and Methods

Study design

A randomized, 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 Brazilian Clinical Trials Registry, number RBR-7rvhpq9, and was performed in accordance with the CONSORT guidelines.

The participants were divided into two groups, standard care (control group – CG) and intervention group (IG), by means of balanced randomization at a 1:1 ratio using a free software [21]. 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 to achieve, 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 IG received a functional and respiratory multidisciplinary rehabilitation program (that included medical, nursing, physiotherapy and occupational therapy interventions) during their entire hospital stay, starting within the first 24 hours from ICU admission, six days per week, 15-30 minutes per session, twice per day. It was individualized to each patient based on the clinical status and consistent with recommendations from the Portuguese Society of Physical Rehabilitation Medicine [20]. Progression was increased successively, depending on the individual's tolerance and stability. After discharge from the ICU, the IG 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 CG did not receive any further rehabilitation intervention after hospital discharge.

Study subjects

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

The inclusion criteria were: (1) independent in their activities of daily living before the onset of critical illness; (2) fulfil the safety criteria defined by the Portuguese Society of Physical Rehabilitation Medicine [20], which included a score of -2 or higher in the Richmond Agitation Sedation Scale, that was designed to assess the level of alertness and agitated behavior in critically ill patients [22]. Patients were excluded if they did not meet these safety criteria. Other exclusion criteria: (1) prior muscle weakness (such as a preexisting neurological or neuromuscular disease), (2) prior pulmonary diseases that condition forced expiratory volume on 1 second (FEV1) and/or Tiffeneau-Pinelli index, (3) acute thrombosis, (4) patients with a diagnosis on admission that excludes the possibility of walking at hospital discharge, (5) patients transferred from other hospitals.

Assessment

At admission, baseline descriptive data was collected, which included age, sex, body mass, body mass index (BMI), smoking status, comorbidities. Other descriptive data, such as the

need and length of invasive mechanical ventilation, length of ICU stay (days) was also collected at discharge from ICU.

Prior to intervention and at discharge participants were evaluated using the following scales: Chelsea Critical Care Physical Assessment (CPAx), Medical Research Council sumscore (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 [23]. MRC-SS evaluates manual strength of six muscle groups bilaterally [24]. HST uses a handgrip dynamometer to assess muscle strength [24]. At discharge, Medical Research Council dyspnea scale (mMRC) was evaluated. mMRC summarizes the score of five offered statements about breath possibility during the daily activities [25].

The primary outcome measure was functional capacity, evaluated at 4-week and 12-week mark, using the 6-Minute 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 minutes, reflecting the functional exercise level for daily physical activities [26].

The secondary outcome measures included Borg Rating of Perceived Exertion (BRPE), evaluated at 4-week and 12-week mark, MRC-SS and HST. BRPE is a widely used and reliable indicator to monitor and guide exercise intensity, that allows individuals to subjectively rate their level of exertion during exercise or exercise testing [27]. The option to evaluate 6MWT and BRPE was due to the expected difficulty of patients to perform 6MWT at ICU discharge, as reported by Al Chikhaine et al. [28].

Statistical Analysis

The sample size was estimated using the Winpepi® program with an estimated alfa risk of 5%, a power of 85%, a pooled variance of 20% and detect differences of 30%, for which 40 subjects are required in each group. Considering a rate of follow-up losses of 15%, we included 96 patients. We used SSPS®, version 27.0 (SSPS Inc., Chicago, IL, USA), for all statistical analysis. Categorical variables were expressed as absolute and relative frequencies. Continuous variables were expressed as mean and standard deviation. We used the chi-square test or Fisher Exact test (as appropriate) to compare categorical variables between the two study groups, including the primary endpoint, and t-test to compare continuous variables. Significant differences between groups or across time were reported at the alpha level of 0.05. All reported p-values are two-sided.

Results

Characteristics of participants

Ninety-six patients fulfilled the eligibility and inclusion criteria and enrolled in this study. They were randomly allocated in the intervention group (48 patients) and in the standard of care group (48 patients). There were no losses in follow-up (figure 1). Both groups were constituted mainly by females, and the mean age was 68,31 years old in the CG and 66,63 years old in the IG. The demographic and clinical characteristics of participants are represented in table 1.

Functional status at admission and discharge evaluation

The values are represented at table 2. There were no statistically significant differences between the two groups in all the scales used. The percentage of patients that 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 IG showed shorter length of stay in ICU and those patients who needed mechanical ventilation had a significantly shorter length of use. Additionally, the IG showed a statistically significantly better functional status in the MRC-SS, HST and mMRC.

4-week and 12 -week follow-up evaluation

The IG 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.

Discussion

The results of our study showed that the group of patients that received a multidisciplinary rehabilitation program had a significant better functional and respiratory performance than the control group. During the COVID-19' pandemic, we have observed that ICUs became overwhelmed in many countries, and this fact raised the need to optimize ICU treatment in terms of length and patient outcome [17, 29]. Some studies have already been conducted to study the influence of rehabilitation in COVID-19' patients [18, 19, 28, 30-33], but to the authors' knowledge, this is the first randomized controlled trial to analyse the impact of the implementation of a rehabilitation programme in COVID19 patients' hospitalized in the ICU.

The main outcome in this study, namely in the 4-week as 12-week mark assessment, was the 6MWT. The IG showed significantly better results than the CG, both on the 4 and 12-week follow up. These results are in line to the previous showed by Liu et al. [16], that reported a significant improvement in 6MWD after 6 weeks of respiratory rehabilitation, those by Schindler et al. [33] that reported an improvement in 6MWT performance after rehabilitation, and those showed by Al Chikhaine et al.[28], that reported a significantly better performance on the 6MWT of post-ICU COVID-19 patients, who performed a rehabilitation program, compared to post-ICU non-COVID-19 patients who did not perform any rehabilitation program. The difference in 6MWT values in the two groups was greater than 30 meters, which according to the study by Bohannon et al. [34] reflects the minimum clinically important difference value for most diseases. These findings suggest that the rehabilitation program implemented improves functional and respiratory capacity, supported by the fact that, at the 4-week follow-up, the IG showed significantly lower lever of perceived exertion in the BRPE scale applied after the 6MWT, and the difference between the groups was clinically important (0.8) [35]. BRPE is a widely used and reliable indicator to monitor and guide

exercise intensity, that allows individuals to subjectively rate their level of exertion during exercise or exercise testing [27]. Both groups showed better values on the 12-week evaluation than on 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 program seems to enhance the recovery time.

The groups also showed significantly different performances on the other secondary outcome measures. In fact, the IG showed larger improvement in different assessments compared to the CG. Similar results were observed in the studies by Hermans et al. [24] and Dantas et al. [36], that showed that early rehabilitation interventions (mobilization 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. [37], that analysed the effects of rehabilitation in ICU' patients with other medical conditions that not COVID-19. Additionally, the IG had significantly better performances on the mMRC than the CG. The mMRC is moderately correlated with the functional assessments of patients' cardiopulmonary fitness, including FEV1, being therefore an indirect indicator of the respiratory function [25]. Considering the results of the study by Liu et al. [16], that conducted a randomized 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 the improvement in the respiratory function.

There were no significant differences between the two groups in the HST, which similar to the results reported by Schweickert et al. [9] and Morris et al. [10], and therefore this

indicator might not be a reliable measure to evaluate the outcomes of rehabilitation programs in ICU setting.

Rehabilitation had an impact on the length of ICU stay, as the IG had a significantly shorter length of stay in the ICU, which is in line with findings from Iannaccone et al. [38], that implemented specialized COVID-19 rehabilitation units, with decrease of the hospitalization in acute COVID-19 patients from 15 days to 10 days. Morris et al. [39] also reported shorter stay in the ICU in patients that received early mobility. The percentage of patients that needed invasive mechanical is in line with that reported by Wang et al. [40] . Both IG and CG 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 IG needed invasive mechanical ventilation for a shorter period than the CG, which may reflect the impact of the rehabilitation program on the 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 program on ICU' patients, but these must be interpreted in the light of certain limitations. This clinical trial was performed only in one center. The application of this protocol on a multi-center population might increase the significance of these results. On the other hand, the blinding of the multidisciplinary treatment team was impossible because, in order to be able to provide the patient the correct intervention, they needed the knowledge of the group allocation. Nonetheless, the assessors responsible for randomization and outcome measures were completely blinded to group allocation. Blinding for patients was not possible to achieve

completely, but subjects were unaware of other treatment modalities, and they did not know if they belong 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 program in 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 on the ICU daily routine. However, there is growing evidence that the rehabilitation on the ICU can play a major role on the patient recovery, thus leading to less days of hospitalization and better outcomes. In this sense, cost-effectiveness studies should be conducted to evaluate the possible benefits associated with the inclusion of these professional in the ICU multidisciplinary teams.

In conclusion, this randomized clinical trial presents beneficial results of a multidisciplinary rehabilitation program in COVID-19 patients hospitalized in ICU and adds evidence that the implementation of rehabilitation programs in ICU could result in beneficial outcomes for the critical ill patients.

Tables

Table 1 – Demographic and clinical characteristics of the patients.

	CG (N=48)	IG (N=48)	P-value
Female Sex, N (%)	27 (56.25)	28 (58.33)	0.840
Age in years, mean (SD)	68.31 (12.47)	66.63 (14.21)	0.540
Body mass in kg, mean (SD)	76.34 (8.76)	77.49 (11.01)	0.570
BMI in kg/m^2, mean (SD)	28.04 (3.22)	29.17 (4.14)	0.130
Smokers, N (%)			
Regular Smokers	9 (18.75)	11 (22.91)	0.615
Previous Smokers	12 (25.00)	8 (16.67)	0.314
Cormobidities, N (%)			
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
Dyslipidemia	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

CG, control group; IG, intervention group; BMI, body mass index

Table 2 – Clinical evaluations and group comparisons.

	Measurement time point											
	Admission			ICU discharge			4-week follow up			12-week follow up		
	CG	IG	p-value	CG	IG	p-value	CG	IG	p-value	CG	IG	p-value
CPAx, score 0-60 (SD)	33.16 (9.77)	31.33 (8.42)	0.330	44.02 (4.64)	41.27 (6.07)	0.014						
LOS in days (SD)				15.60 (6.70)	12.90 (5.8)	0.037						
Need of IMV during ICU stay, N (%)				23 (47.92)	21 (43.75)	0.682						
Length of use of IMV in days, N (%)				6.1 (4.2)	4.1 (3.6)	0.037						
MRC-SS, score 0-60 (SD)	47.2 (7.1)	46.7 (6.8)	0.730	52.1 (4.1)	54.4 (3.7)	0.005	57.9 (2.3)	58.9 (1.1)	0.008	59.4 (0.7)	59.6 (0.3)	0.007
HST in kg, mean (SD)	14.1 (5.6)	12.7 (7.3)	0.290	21.2 (4.3)	23.3 (5.1)	0.032	25.9 (5.1)	27.1 (4.4)	0.220	26.6 (4.9)	27.4 (4.2)	0.393
mMRC						0.031						
mMRC ≤ 1, N (%)				16 (33.3	7 (14.6)							
mMRC ≥ 2, N (%)				32 (66.7)	41 (85.4)							
BRPE, score 6-20 (SD)							12.5 (1.8)	11.7 (2.1)	0.048	11.9 (1.1)	11.3 (1.6)	0.035
6MWT in meters, mean (SD)							571 (57)	604 (67)	0.018	611 (67)	639 (53)	0.025

CPAx, Chelsea Critical Care Physical Assessment; LOS, Length of stay in ICU; IMV, Invasive mechanical ventilation; MRC-SS, Medical Research Council sum-score; HST, handgrip strength test; BRPE, Borg Rating of Perceived Exertion; 6MWT, 6-Minute Walk Test;

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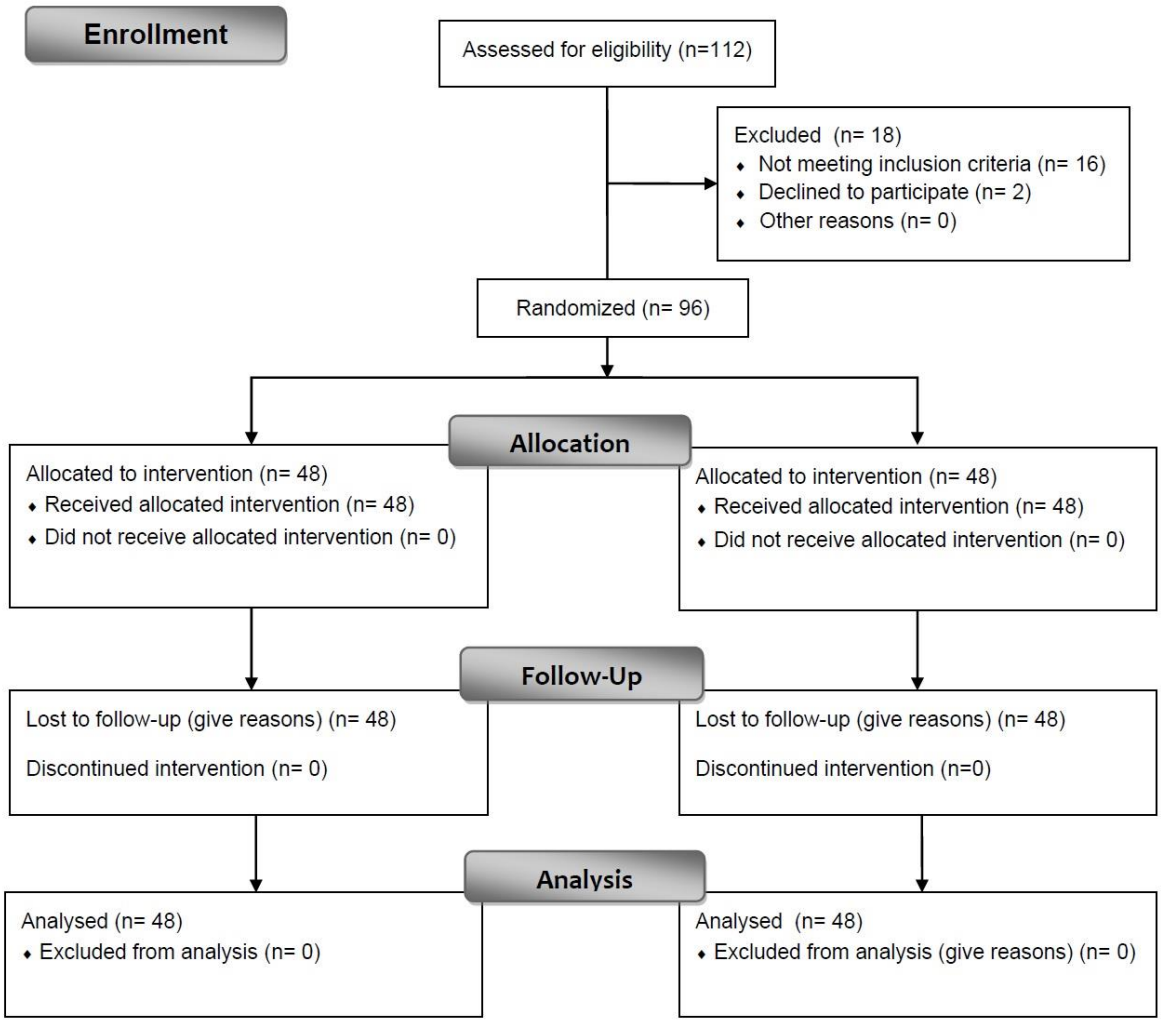

Figure 1 – Participant flow through the trial. 458