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Short Communication

Effectiveness of upper arm and breathing exercises to improve inflammatory markers in severe COVID-19 patients

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Abstract

Studies have suggested associations between inflammatory markers with the severity of coronavirus disease 2019 (COVID-19). Therefore, exercises that could reduce the level of inflammatory markers might be beneficial. The aim of this study was to determine the effect of upper arm and breathing exercises on inflammatory markers such as ferritin, lactate dehydrogenase (LDH), and C-reactive protein (CRP) in severe COVID-19 patients. A quasi-experimental with pre-test and post-test control group design was conducted among severe COVID-19 aged 18–70 years old, with or without comorbidities. Baseline data of inflammatory markers (ferritin, LDH, and CRP) were measured before the exercises and repeated post-exercise. The upper arm and breathing exercises were performed for ten days, twice a day (morning and evening) for ten minutes. A paired Student t-test was used to assess the changes in the inflammatory markers' levels. Our data indicated that levels of ferritin and CRP were not significantly different between pre- and post-exercise. However, the level of LDH decreased significantly from 481.35 U/L to 331.80 U/L (p=0.001). This study highlights that pulmonary rehabilitation exercises might be beneficial to enhance the recovery process in severe COVID-19 patients.

Keywords: COVID-19, pulmonary rehabilitation, upper arm exercise, breathing exercise, C-reactive protein

Introduction

Coronavirus disease 2019 (COVID-10) first emerged in December 2019 when a group of patients with pneumonia of unknown cause appeared in Wuhan, Hubei Province, China [1]. This new type of coronavirus was then isolated from lower respiratory tract samples and was named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [2]. The lungs are the most affected organ of which COVID-19 can cause damage, such as diffuse alveolar damage, microvascular damage, formation of hyaline membranes, the proliferation of alveolar septal connective tissue, and lung consolidation [3].

The current data suggests that three stages represent the entire pathogenic process of COVID-19. When SARS-CoV-2 infects host target cells in the pulmonary phase, angiotensin-converting enzyme 2 (ACE2) insufficiency and the ensuing renin-angiotensin system (RAS)

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Received: August 17, 2023 - Accepted: December 11, 2023 - Published online: January 1, 2024

imbalance results in interstitial pneumonia and acute respiratory distress syndrome (ARDS). Acute lung injury (ALI) and cytokine storm are caused by the overproduction of proinflammatory cytokines by infected target cells and lymphocytes in response to SARS-CoV-2 infection during the pro-inflammatory phase. This leads to systemic inflammation. At the end stage of COVID-19 patients, extensive platelet aggregation and thrombosis in the last prothrombic phase leads to coagulopathy and multi-organ failure (MOF). Serum ferritin, D-dimer, lactate dehydrogenase, and interleukin-6 (IL-6) levels appear to rise throughout disease development, indicating an increased mortality risk [4].

Severe COVID-19 infections induce a hyperinflammatory response that results in a pathological malfunction of the innate host defense systems, potentially leading to MOF and/or cytokine storm [5]. When the body is impacted by inflammation, such as bacterial or viral infection or tissue damage, the liver synthesizes C-reactive protein (CRP), an acute-phase protein that builds up in blood 6–10 hours after any tissue-damaging episode and has a plasma half-life of 19 hours [6]. An iron storage type called ferritin is one of the inflammatory markers. Since iron is released in the endoplasmic reticulum during bacterial or viral infection, ferritin levels rise while liver and spleen damage reduces the protein's transport ability [7]. As an enzyme involved in glycolysis, lactate dehydrogenase (LDH) is found in all tissues and catalyzes the conversion of pyruvate to lactate. The substance is released when a cell's cytoplasmic membrane is damaged, such as by a viral infection [8].

In COVID-19 patients, pulmonary rehabilitation aims to improve dyspnea symptoms, relieve anxiety, reduce complications, minimize disability, maintain function, and enhance quality of life [9]. Pulmonary rehabilitation must also be tailored to the individual patient for optimal results. Previous meta-analyses reported that pulmonary rehabilitation plays a positive role in treating respiratory system diseases and can increase cardiorespiratory endurance [10,11]. Exercises that can reduce inflammatory marker levels are therefore essential. The aim of this study was to determine the effectiveness of pulmonary rehabilitation, particularly upper arm and breathing exercises, on the levels of inflammatory markers in severe COVID-19 patients.

Methods

Study design and setting

This study was quasi-experimental with a pre-test-post-test control group design to assess the changes in inflammatory markers in severe COVID-19 patients who received upper arm and breathing exercises before and after treatment for ten consecutive days. The time frame for this study was January through June of 2021. Baseline data of inflammation markers (the levels of CRP, LDH, and ferritin) were collected in the emergency room before the patients had upper arm and breathing exercises. The exercises were done twice a day in an isolation room for ten consecutive days with guidance from exercise videos using smartphones while supervised by medical personnel (physiotherapists). At the end of the training session, the CRP, LDH, and ferritin levels were rechecked as post-intervention data. Every patient enrolled in this study was diagnosed with severe COVID-19 and treated similarly, following national guidelines for COVID-19 management.

Patients and sampling method

The sample of this study were patients with confirmed severe COVID-19 who were treated in the isolation ward of the H. Adam Malik Hospital, Medan, Indonesia, aged 18–70 years, with oxygen saturation of 95%, and with or without comorbidities. Based on the 4th edition of the Indonesian National Guidelines for COVID-19, patients with severe COVID-19 were classified in this study as those who had one of the following symptoms in addition to clinical indicators of pneumonia (fever, cough, shortness of breath, and rapid breathing): respiratory rate >30x/minute, severe respiratory distress, or SpO_2 <93% in room air. Those who used high flow nasal cannula (HFNC), had musculoskeletal disorders, decreased consciousness, and mental disorders were excluded. This study used a consecutive sampling method, where all samples obtained and met the criteria were included in the study.

Upper arm and breathing exercise

Before starting the exercise, the patients received a short-acting inhaled bronchodilator, salbutamol 2.5 mg. The patients did a light warm-up and muscle stretching for 5–10 minutes to prevent muscle injury. The exercises were done twice a day (morning and evening) for ten days with an intensity of ten minutes. The exercises were temporarily stopped when the patient complained of muscle pain, shortness of breath, or headache before continuing.

The upper arm and breathing exercises had several movements: (1) breathing control and deep breathing movements; (2) the no-way movement (pursed lips breathing movement combined with turning the neck to the left and right); (3) the clucking chicken movement (pursed lips breathing combined with shoulder elevation and rotation movements); (4) the calling movement (elevation movement of the hands up and down); (5) the butterfly movement (both hands straightened forward then arms extended); and (6) the cooling-down movement (upper arm elevation movement combined with pursed lips breathing). Each movement was repeated ten times.

Statistical analysis

Before and after exercise, the percentage changes in LDH, Ferritin and CRP were measured. The significance of the observed changes was tested statistically using a paired Student t-test. The data was processed using SPSS version 22 software (SPSS, IBM Inc, Chicago, USA).

Results

Characteristics of the patients

There was an equal number of male and female subjects in this study - ten individuals each - who were all severe COVID-19 patients. The majority of patients were aged 51–60 years, followed by those aged 61–70 years. When inflammatory markers were evaluated, the largest number of patients had ferritin, LDH, CRP, and procalcitonin values of >400 ng/mL, >150 U/L, ≥0.7 ng/mL, and ≤0.5 ng/mL, respectively (**Table 1**). When comparing the LDH, CRP, and ferritin levels of patients before and after exercise, it was shown that age and gender did not significantly affect the levels of inflammatory markers (**Table 2**).

Table 1. Characteristics of the severe COVID-19 patients included in this study

Characteristics	Frequency	Percentage
Sex		
Male	10	50.0
Female	10	50.0
Age (years)		
30–40	3	15.0
41–50	2	5.0
51–60	7	35.0
61–70	5	25.0
>70	3	15.0
COVID-19 severity		
Mild	0	0.0
Moderate	0	0.0
Severe	20	100.0
Ferritin (ng/mL)		
<300	2	10.0
300–400	1	5.0
>400	17	85.0
Lactate dehydrogenase (LDH) (U/L)		
<50	0	0.0
50–150	0	0.0
>150	20	100.0
C-reactive protein (CRP) (ng/mL)		
<0.7	3	15.0
≥0.7	17	85.0
Procalcitonin (ng/mL)		
<0.5	14	70.0
≥0.5	6	30.0

Table 2. Comparison of inflammatory marker levels based on patient's characteristics before and post upper arm and breathing exercises

Marker	Characteristics	Pre-exercise (mean± SD)	*p*-value	Post-exercise (mean± SD)	*p*-value
Ferritin (ng/mL)					
	Age (years)		0.087		0.180
	30–40	1181.1±926.9		988.6±963.9	
	41–50	1496.0±712.0		1125.5±1064.0	
	51–60	1513.9±564.9		1133.0±709.5	
	61–70	1693.5±438.5		1839.4±918.9	
	>70	465.3±311.9		366.0±133.4	
	Sex		0.100		0.100
	Female	994.5±959.0		729.1±582.1	
	Male	1723.2±446.6		1685.9±872.4	
Lactate dehydrogenase (U/L)	Age (years)		0.355		0.433
	30–40	437.0±103.7		392.3±114.2	
	41–50	367.0±182.4		239.5±57.3	
	51–60	467.8±146.1		310.2±118.9	
	61–70	618.8±262.7		371.0±49.6	
	>70	354.0±231.9		297.6±157.2	
	Sex		0.451		0.710
	Female	445.5±163.8		340.8±105.2	
	Male	517.3±245.4		322.8±107.6	
C-reactive protein (CRP) (ng/mL)	Age (years)		0.792		0.596
	30–40	1.6±1.2		0.9±0.5	
	41–50	0.85±0.8		0.5±0.3	
	51–60	1.3±0.8		0.8±0.3	
	61–70	1.0±0.9		1.2±0.9	
	>70	1.6±1.1		0.8±0.6	
	Sex		0.316		0.636
	Female	1.05±0.7		0.9±0.7	
	Male	1.45±0.9		0.8±0.4	

Changes in inflammatory markers in severe COVID-19 patients

The study found that the mean ferritin value before exercise was 1358.8 ng/mL; after exercise, it changed to 1207 ng/mL with p=0.299. Then, the average value of LDH before exercise was 481.3 U/L; after exercise, it became 331.8 U/L with p=0.001. Next, the mean CRP levels before exercise was 2.83±6.1 ng/mL and after exercise, 0.96±0.5 ng/mL with p=0.134 (**Figure 1** and **Table 3**).

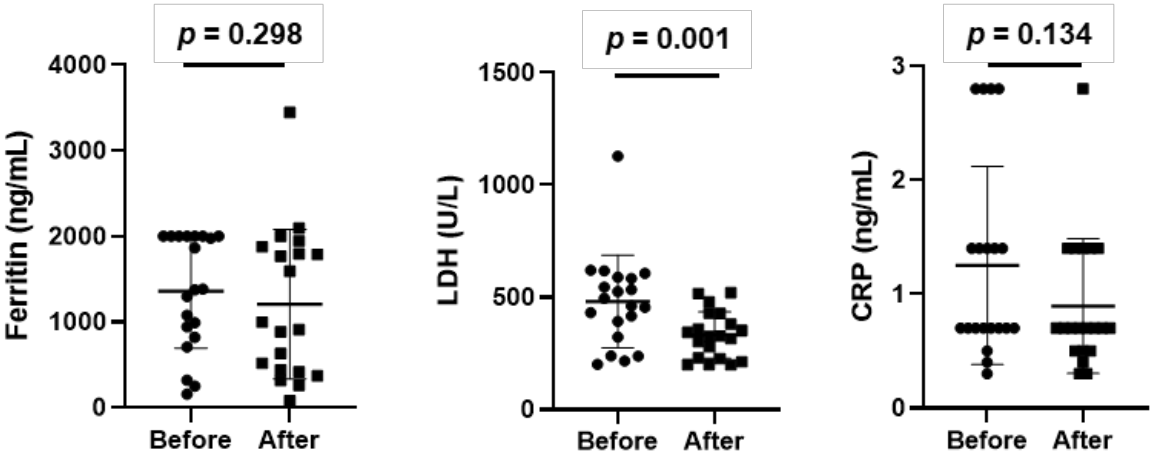

Figure 1. Changes in inflammatory marker values before and after the exercises in severe COVID-19 patients.

Table 3. Level changes in inflammatory markers in severe COVID-19 patients before and after the exercises

Inflammatory marker	Before exercise	After exercise	*p*-value
Ferritin, ng/mL	1358.81±663.3	1207±872.0	0.298
Lactate dehydrogenase (LDH), U/L	481.35±206.4	331.80±103.9	0.001
C-Reactive protein (CRP), ng/mL	2.83±6.1	0.96±0.5	0.134

Discussion

The samples in our study were balanced between males and females, and the age group of 51–60 years was the largest portion, followed by 61–70 years. An increase in ferritin values in severe COVID-19 patients was found in our study with an average value of 1358.81 ng/mL, the normal ferritin value for males is 20 to 500 ng/mL and 20 to 200 ng/mL for females. This is in line with several studies, where hyperferritinemia was found in 38% of all individuals and was most often found in patients with severe or critical COVID-19 [12]. Furthermore, no significant change was observed in the decrease of ferritin values (p=0.299). There are no studies that support this study's findings about the influence of changes in ferritin levels following pulmonary rehabilitation. An inflammatory response can cause hyperferritinemia, but its role in the development of COVID-19 disease is still not fully established. However, hyper-inflammatory conditions associated with altered iron homeostasis play a key role in the pathogenesis [12-14].

The LDH value experienced a significant improvement (p=0.001), with the average value after exercise being 331.80 U/L (**Table 3**). However, a study reported no improvements in LDH values in patients who were given pulmonary rehabilitation, where the mean value for LDH levels of 30 patients with acute severe post-COVID-19 before pulmonary rehabilitation was 202.2±51.0 U/L and after pulmonary rehabilitation was 198.1±36.5 U/L with p=0.335. However, we have not found supporting literature that this is in line with the result of our study because there was a limited amount of study on pulmonary rehabilitation in COVID-19 patients with the aspect of inflammatory markers. The LDH is a biomarker for various inflammatory conditions, such as infection, malignancy, myocardial infarction, sepsis, or heart-lung disorders [15]. Exercise can contribute to limiting the inflammatory response to COVID-19 infection [14].

Several studies found that exercise has an impact on CRP levels in COVID-19, high and moderate physical activity levels were associated with better outcomes in COVID-19 patients [16]. However, the CRP levels in this study did not change significantly (p=0.134). This is in line with the previous study that revealed no significant changes in the CRP levels of 50 COVID-19 patients who were divided into two groups, the mild-moderate grade group and the severe-critical grade group (p=0.95), with a median value of 2.6 before pulmonary rehabilitation and 2.0 after pulmonary rehabilitation [17]. There was an increase in CRP levels in this study, although it was not significant. This is likely because the samples in this study were severe COVID-19 patients.

This study showed a decrease in inflammatory markers values after the breathing and upper arm exercises, but a significant change was found only in the decrease of the LDH values with p=0.001. A study reported that the decrease in the value of these inflammatory markers was influenced by muscle fibers producing anti-inflammatory cytokines, which could inhibit the production of inflammatory cytokines due to the effects of exercise [18,19].

Exercise has been shown to significantly impact neuroendocrine effects, inflammatory markers and the immune system in individuals with COVID-19. Multiple studies found that moderate exercise reduced symptoms, severity, and recovery time in COVID-19 patients [20-22]. A study reported that two weeks of moderate-intensity aerobic exercise decreased the severity and progression of COVID-19-associated disorders and quality of life. Also, in two weeks of aerobic exercise positively affected immune function by increasing the amounts of leucocytes, lymphocytes, and immunoglobulin-A [23]. A study argues that moderate-intensity exercise is safe for most people during COVID-19 infection, while high-intensity exercise may be risky for some people [24]. High-intensity or prolonged exercise can negatively impact immunity, moderate exercise provides protection against infectious diseases like COVID-19 [25,26]. Muscle fiber activity through exercise may play a role in improving inflammatory markers in COVID-19, including inhibiting inflammatory pathways and stimulating anti-inflammatory responses [27].

The limitation of this study was that there was no control data on the value of inflammatory markers of severe COVID-19 patients who did not perform the breathing and upper arm exercises, and this study only compared the inflammatory marker values before and after the exercises. Thus, we cannot further investigate how significant the effect of this exercise is on patients who do the exercises and those who do not, although the pre- and post-exercise effects were seen.

Exercise during COVID-19 can have benefits if done properly and safely, including improved health, immunity, and quality of life during isolation. Care should be taken to exercise safely and at an appropriate level based on one's condition. However, more research is still needed to determine the impact of exercise on other inflammatory markers like IL-6, D-dimer, and leukocyte count since IL-16 is known as central in COVID-19 pathogenesis [28]. Exercise, especially moderate exercise, should be considered as a potentially valuable tool for COVID-19 management.

Conclusion

Pulmonary rehabilitation programs, particularly breathing and upper arm exercises, could significantly reduce LDH levels in individuals with severe COVID-19. Our study found that the program had no effect on reducing the levels of ferritin and CRP. This study highlights that pulmonary rehabilitation exercises could be beneficial for severe COVID-19 patients.

Ethics approval

The Universitas Sumatera Utara Health Research Ethics Committee approved this study with the approval number 292/KEP/USU/2021

Acknowledgments

We would like to thank H. Adam Malik General Hospital, North Sumatera, Indonesia, for providing the research equipment and place.

Competing interests

All the authors declare that there are no conflicts of interest.

Funding

This research was funded by Research TALENTA Universitas Sumatra Utara, 2021 fiscal year (Research Contract Amendment Number: 323/ UN5.2.3.1/ PPM/SPP USU TALENTA/2021).

Underlying data

Derived data supporting the findings of this study are available from the corresponding author on request.

How to cite

Tarigan AP, Firdaus R, Pandia P, *et al.* Effectiveness of upper arm and breathing exercises to improve inflammatory markers in severe COVID-19 patients. Narra J 2024; 4 (1): e417 - http://doi.org/10.52225/narra.v4i1.417.

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