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A Personalized approach to Comprehensive Rehabilitation after Coronavirus pneumonia using hypoxic-hyperoxic Therapy: Randomized trials

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Abstract

Introduction: After the end of the pandemic, there is still a need for medical rehabilitation for patients with long-term covid and post-covid syndrome. Given the complex pathogenesis of coronavirus infection, complex rehabilitation methods with a personalized approach are of the greatest interest.

Goal: To determine the effectiveness of medical rehabilitation using personalized normobaric interval hypoxic-hyperoxic therapy (NBIHHT) in patients after coronavirus pneumonia in a day hospital.

Materials and Methods: 120 patients with moderate-severity coronavirus pneumonia, randomized into two homogeneous groups, were examined in a day hospital. 60 patients of the comparison group underwent the procedures of the basic rehabilitation program: physical therapy, hydrokinesiotherapy, selective chromotherapy, halotherapy, sessions of psychoemotional relaxation. In addition to the basic program, 60 patients in the main group underwent personalized NBIHHT procedures. In patients of both groups, the intensity and severity of dyspnea (mMRC, BDI/TDI scales), hypoxia tolerance (Stange and Genchi tests), cardiovascular system condition (Martine test), exercise tolerance (six-minute walk test), microcirculation (laser Doppler flowmetry), anxiety and depression severity (HADS scale), and quality of life (SF-36 before, after rehabilitation and in the follow-up after 3 and 6 months) were assessed before and after rehabilitation.

Results: After rehabilitation, statistically significant positive dynamics were determined at a significance level of $p < 0.05$ in patients of both groups, however, in patients of the main group, the positive result was statistically more significant, which was manifested by a decrease in the intensity and severity of dyspnea, an increase in hypoxia tolerance, an improvement in the functional state of the cardiovascular system, an increase in tolerance to physical activity, an increase in the activation of microcirculation, a decrease in the level of anxiety and depression, an improvement in the quality of life after rehabilitation and during 3 months of observation and stabilization in the follow-up after 6 months.

Conclusion: The inclusion of personalized NBIHHT procedures in the rehabilitation complex of patients with coronavirus pneumonia makes it possible to significantly improve the immediate and long-term results of the rehabilitation program in a day hospital.

Keywords: Medical rehabilitation, COVID-19, coronavirus pneumonia, quality of life, personalized normobaric interval hypoxic-hyperoxic therapy.

Introduction

The outbreak of an infectious disease caused by the severe acute respiratory distress syndrome 2 virus (SARS-CoV-2) was a pandemic of the coronavirus disease, announced by WHO on March 11, 2020. The pandemic lasted for more than 3 years, and on May 5, 2023, WHO announced its end. Nevertheless, despite the end of the pandemic, there remains a high need for medical care for patients with long-term covid and post-covid syndrome [1]. Currently, more than a year after the pandemic, the registration of appeals to the primary health care of patients with respiratory diseases who have been diagnosed with SARS-CoV-2 remains, which indicates that the infection has not disappeared.

The most common clinical manifestation of moderate to severe coronavirus disease is bilateral pneumonia with respiratory failure, as well as damage to the nervous system and thrombotic complications. Up to 15% of patients with moderate to severe pneumonia and acute respiratory distress syndrome require medical rehabilitation [2]. Given the complex pathogenesis of coronavirus infection, multiorgan damage leading to functional insufficiency and intoxication, complex rehabilitation methods that affect several main pathogenetic mechanisms of the disease, taking into account its stage, are of the greatest interest. When choosing a rehabilitation program, it is important to take a personalized approach to the patient, which is based on the initial state of health, a combination of concomitant nosologies, existing risk factors, as well as the severity of the disease and the complications that have arisen [3].

It is known that the use of controlled hypoxic effects in patients after coronavirus infection increases the tolerance of physical activity due to the activation of microcirculation and optimization of oxygen consumption by tissues [4]. It has also been proven that the most effective adaptive effect is provided by the repeated alternation of several episodes of moderate hypoxia with periods of hyperoxia in an individual regime [5]. It was determined that short–term breathing of a gas mixture with an oxygen concentration of 11-12% in it does not lead to negative consequences in the human body, while saturation reaches the level required for the development of adaptive reactions below 90% and above the critical level of 77-80%. This interval of tissue hypoxia is optimal for activating the chain of adaptation reactions and does not trigger negative damaging mechanisms [5-6].

A number of authors have reflected the effect of the degree of intensity and duration of hypoxia on the activation and suppression of various physiological mechanisms at different times, which can cause either a lack of adaptive effect with low intensity of exposure, or a cascade of negative reactions with excessive hypoxia. Only a properly selected intensity and severity of hypoxic effects forms the necessary physiological response to the procedure of personalized normobaric hypoxic-hyperoxic therapy (NBIGT) [7]. Modern publications have noted that different patients with the same intensity and duration of hypoxic exposure have different levels of SpO2 and heart rate, depending on their current physiological condition and personal sensitivity to oxygen deficiency, which is influenced by genotype, age, concomitant pathology, drug load, patient fitness, and other factors [8].

Based on the fact that patients are weakened after suffering from coronavirus pneumonia, and also have a number of functional changes due to concomitant pathology, individual dosing of hypoxia is necessary during rehabilitation measures, taking into account changes in physiological parameters, as well as regular monitoring of SpO2 and heart rate parameters through biofeedback and the possibility of automatic changes in the duration of hypoxic and hyperoxic intervals and oxygen concentration in the breathing gas mixture in real time. Accordingly, it is important to determine the degree of hypoxia exposure in a personalized manner, in accordance with the functional capabilities of each patient during the procedure [6].

The purpose of the study

To determine the effectiveness of medical rehabilitation using personalized HRT in patients after coronavirus pneumonia in a day hospital.

Materials and Methods

We examined 120 people who had suffered from bilateral coronavirus pneumonia, the severity of which was defined as average, the age of the examined was from 35 to 75 years (average age 62.42 ± 6.76 years), of which 25% (30) were men, 75% (90) were women. Each patient underwent a rehabilitation program daily for 10 days in the day hospital of LLC Clinical Treatment and Rehabilitation Center "Territory of Health" in Barnaul. The patients were divided into two groups with homogeneous characteristics, 60 people each using the envelope method. Patients in both observation groups received a basic course of medical rehabilitation, which consisted of physical therapy with the addition of breathing exercises, hydrokinesiotherapy in the pool, halotherapy, selective yellow light color therapy on the surface of the chest and sessions of psycho-emotional relaxation. In addition to the basic course, patients in the main group were prescribed daily procedures for personalized HRT on a device that generates hypoxic respiratory mixtures with an oxygen concentration of 10-15% and hyperoxic respiratory mixtures with an oxygen content of up to 40%. In this research work, a ReOxy device with a registration certificate dated 30.04.2019 was used for preliminary hypoxic testing and implementation of personalized NBIGT procedures. No. RZN 2014/1486. This device meets all safety and efficiency requirements. The patients took all the procedures daily for 10 days. The basis of the personalized NBIGTT method is the controlled alternating use of hypoxic and hyperoxic gas mixtures at normal atmospheric pressure in an interval mode with the possibility of individual dosing of hypoxia due to the BOS mechanism, which allows real-time monitoring of oxygen saturation in the bloodstream and heart rate using pulse oximetry. Due to the possibility of preliminary testing of sensitivity to hypoxia before the first procedure and the presence of BOS, the device's software develops an individual treatment regimen for each patient, therefore, the use of this rehabilitation technique is as safe and effective as possible.

In order to determine the individual concentration of the hypoxic mixture and the optimal duration of hypoxic and hyperoxic intervals necessary for the formation of an optimal adaptive response, all patients in the main group underwent a hypoxic test under the control of SpO2 and heart rate before undergoing rehabilitation, after which the device software created an individual training program for daily use for 10 days, based on which further procedures of personalized NBIGT were carried out.

Patients of both groups were examined according to the criteria of effectiveness before and after rehabilitation. The severity of dyspnea was assessed using a modified mMRC dyspnea scale. Initial indicators of the severity of dyspnea were determined using the Baseline Dyspnea Index (BDI), dynamic indicators were determined using the Transition Dyspnea Index (TDI). Resistance to hypoxia was assessed by determining the time of respiratory retention on inspiration (Stange test) and exhalation (Genchi test), the functional state of the cardiovascular system was determined by calculating heart rate at rest and after exercise (modified Martinet test). Physical activity tolerance was determined by a six-minute walking test (TSX). Determination of microcirculation status and measurement of blood perfusion in chest tissues were performed using laser Doppler flowmetry (LDF) on a laser portable blood microcirculation analyzer "LAZMA PF", Registration certificate of Roszdravnadzor No. RZN 2018/7853 dated 11/26/2018. The level of anxiety-depressive disorders was determined using the HADS scale. The quality of life was assessed using the Short-Form Health Survey (SF-36) questionnaire.

Results / Discussion

An analysis of the initial parameters of the severity of dyspnea on the mMRC scale and the severity of the BDI index showed that in patients of both groups, dyspnea was initially defined as moderate, bothered with moderate exertion, the initial values in both groups did not significantly differ (Table 1).

Scale	Stages of observation	Main group (n = 60)		Comparison group (n = 60)		p_1	Difference of averages, Δ%
		M	±SD	M	±SD		
mMRC	Before rehabilitation	2,77	0,51	2,73	0,48	0,961	1,5%
	After rehabilitation	0,96	0,52	1,24	0,56	0,017	-22,6%
	p_2	<0,001		<0,001		-	
	Difference of averages, Δ%	-65,3%		-54,6%		-	
BDI/TDI	Before rehabilitation	5,17	0,96	5,21	0,95	0,994	-0,8%
	After rehabilitation	10,64	1,46	9,35	1,12	<0,001	13,8%
	p_2	<0,001		<0,001		-	
	Difference of averages, Δ%	105,8%		79,5%		-	

Table 1: Intensity (mMRC) and severity (BDI/TDI) of dyspnea in patients after coronavirus pneumonia in the study groups before and after the course of rehabilitation (M ± SD).

Notes: p1 - is the reliability of the differences in parameters within the groups; p2 - is the reliability of the differences in parameters between the groups upon completion of rehabilitation

The analysis of Table 1 revealed a significant decrease in the initial parameters of the intensity and severity of dyspnea on the mMRC and BDI/TDI scales after undergoing rehabilitation in both groups, however, the introduction of personalized HRT procedures in patients of the main group demonstrates a more significant improvement in lung ventilation (p<0.001), which is reflected in modern publications [9].

The baseline values of the Stange and Gencha samples, which characterize resistance to hypoxia, did not differ significantly in both observation groups and were significantly below the norm (Table 2). The norm for the Stange sample is at least 40 seconds, for the Gencha sample at least 20 seconds [10].

Samples	Stages of observation	Main group (n = 60)		Comparison group (n = 60)		p_1	Difference of averages, Δ%
		M	±SD	M	±SD		
Stange	Before rehabilitation	19,63	8,63	20,30	8,90	0,998	-3,20%
	After rehabilitation	29,67	8,03	25,20	8,89	0,043	15,07%
	p_2	0,000		0,006		-	
	difference of averages, Δ%	51,15%		24,14%		-	
Genchi	Before rehabilitation	18,91	6,82	18,69	5,13	0,998	1,18%
	After rehabilitation	26,12	5,75	20,12	4,96	0,000	29,82%
	p_2	<0,001		0,011		-	
	Difference of averages, Δ%	38,13%		7,65%		-	

Table 2: Stange and Genchi test indicators in patients after coronavirus pneumonia in the study groups before and after the rehabilitation course (M ± SD).

Notes: p_1 - is the reliability of the differences in parameters within the groups; p_2 - is the reliability of the differences in parameters between the groups upon completion of rehabilitation.

The indicators shown in Table 2 confirm an improvement in the tolerance of hypoxia in patients of both groups, which is statistically significant. Thus, the data obtained confirm the effectiveness of personalized NBIGT in increasing the tolerance of hypoxia, which is explained by optimizing oxygen homeostasis, improving microcirculation in organs and tissues, and is confirmed by the work of other authors [11].

The dynamics of the state of the cardiovascular system was assessed based on the results of the Martinet test with the calculation of heart rate before exercise (Martin 1) and after exercise (Martin 2) before and after the course of medical rehabilitation. Exercise tolerance was determined before and after rehabilitation using a six-minute walking test (Table 3).

Samples	Stages of observation	Main group (n = 60)		Comparison group (n = 60)		p_1	Difference of averages, Δ %
		M	±SD	M	±SD		
Martine 1	Before rehabilitation	72,82	5,83	72,16	6,22	0,911	0,91%
	After rehabilitation	63,14	6,84	66,92	5,84	0,005	-5,99%
	p_2	0,000		0,000		-	
	Difference of averages, Δ%	13,29		7,26		-	
Martine 2	Before rehabilitation	138,91	11,39	139,12	9,89	1,000	-0,15%
	After rehabilitation	104,82	6,41	117,16	7,38	0,000	-11,77%
	p_2	0,000		0,000		-	
	Difference of averages, Δ%	24,54		15,78		-	
Six-minute walking test	Before rehabilitation	374,82	64,87	376,48	69,44	0,999	-0,44%
	After rehabilitation	449,30	59,90	421,70	64,10	0,051	6,54%
	p_2	0,000		0,001		-	
	Difference of averages, Δ%	19,87		12,01		-	

Table 3: Martine test indices in patients after coronavirus pneumonia in the study groups before and after the rehabilitation course (M ± SD).

Notes: p_1 - is the reliability of the differences in parameters within the groups; p_2 - is the reliability of the differences in parameters between the groups upon completion of rehabilitation.

An analysis of the data in table 3 showed in both groups a decrease in the initial parameters of the functioning of the cardiovascular system according to the results of Martinet's tests (normally, the pulse rate after exercise is less than 75% of the initial value) and physical activity tolerance according to TCX (the norm is a distance of more than 551 meters traveled in 6 minutes). The provided results of the Martinet and TSH tests confirm that the rehabilitation program optimized by the NBIGT procedures statistically significantly improves the functioning of the cardiovascular system and increases exercise tolerance. This can be explained by optimizing oxygen consumption and improving perfusion of organs and tissues, including the myocardium, which is consistent with previously published studies [6-7, 11].

There is an increasing amount of evidence in the modern literature confirming microcirculation disorders in COVID-19, which are widespread [12-16]. The research results presented in a number of modern articles indicate disorders in the vascular bed, manifested in endothelial dysfunction during activation of inflammatory processes, which leads to impaired hemostasis and negative consequences in patients with COVID-19 [17]. Various researchers have identified profound endothelial dysfunction [18-19], dysregulation of vascular tone with a predominance of the vasoconstrictor component [20-22].

Our work confirms the above scientific data. Thus, before the rehabilitation course, patients in both groups showed a deterioration in the functioning of the microcirculatory system (Table 4).

Indicator	Stages of observation	Main group (n = 60)		Comparison group (n = 60)		p_1	Difference of averages, Δ%
		M	±SD	M	±SD		
M, п.е.	Before rehabilitation	6,04	1,12	6,42	1,08	0,178	-5,9%
	After rehabilitation	13,17	2,17	10,32	1,94	<0,001	27,6%
	p_2	<0,001		<0,001		-	
	Difference of averages, Δ%	118,0%		60,7%		-	
σ, п.е.	Before rehabilitation	0,39	0,07	0,42	0,1	0,173	-7,1%
	After rehabilitation	1,71	0,43	1,13	0,35	<0,001	51,3%
	p_2	<0,001		<0,001		-	
	Difference of averages, δ%	338,5%		169,0%		-	
Kv, %	Before rehabilitation	6,57	1,18	6,76	1,08	0,742	-2,8%
	After rehabilitation	12,96	1,94	10,44	1,82	<0,001	24,1%
	p_2	<0,001		<0,001		-	
	Difference of averages, Δ%	97,3%		54,4%		-	

Table 4: Indicators of the state of microcirculation in patients after coronavirus pneumonia in the study groups before the course and upon completion of the rehabilitation course (M ± SD).

Notes: p1 - is the reliability of the differences in parameters within the groups; p2 - is the reliability of the differences in parameters between the groups upon completion of rehabilitation.

Table 4 confirms the optimization of microcirculation after a course of rehabilitation in patients in both groups. At the same time, in the main group, microcirculation indicators after the rehabilitation course corresponded to the reference, which indicates a statistically significant improvement in microcirculation in patients who suffered from coronavirus pneumonia after the inclusion of personalized HRT procedures in the basic course of medical rehabilitation. Indicators of the microcirculation status in patients of the comparison group also increased at the end of the rehabilitation course and reached reference values.

Scientific publications provide data on the increasing levels of anxiety and depression in patients after coronavirus pneumonia, which have a negative impact on the course of the disease and further recovery [23]. Thus, a relationship has been described between disorders in the microcirculatory system of the brain during the development of respiratory failure [24], as well as in patients with COVID-19 who are in serious condition [25]. The situation is further aggravated by the fact that anxiety-depressive disorders are detected for many months after the resolution of the acute phase of the disease [26].

The results of our study confirmed that initially, according to the HADS scale, the indicators of anxiety HADS (A) and depression HADS (D) were close to subclinical values. Upon completion of the rehabilitation course, anxiety and depression levels decreased by 63.8% ($p < 0.001$) and 61.0% ($p < 0.001$), respectively, in patients of the main group who underwent a rehabilitation program optimized by NBIGT procedures. The patients in the comparison group who underwent the procedures of the basic rehabilitation program had a decrease in anxiety levels by 52.0% ($p < 0.001$) and depression levels by 42.5% ($p < 0.001$). A statistically more significant decrease in anxiety and depression levels when optimizing the basic rehabilitation program with personalized HRT procedures can be explained by a decrease in mitochondrial dysfunction, improved microcirculation and optimization of oxygen consumption by nervous system tissues, increased cellular protection against oxidative stress and inflammation [27].

The decrease in the quality of life of patients after coronavirus pneumonia is reflected in the work of many researchers [28-29]. The presented results of our work also demonstrate a decrease in the parameters of physical and mental health according to the SF-36 questionnaire in patients in both groups, which indicates a marked restriction of daily activities before the start of rehabilitation measures (Fig. 1).

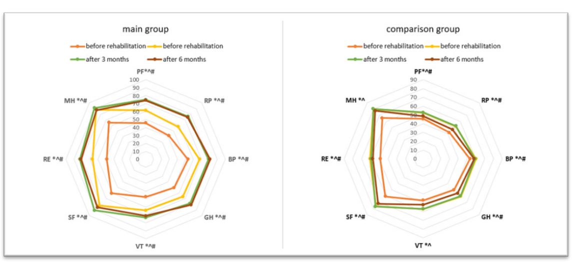

Figure 1: Quality of life indicators according to the SF-36 questionnaire in patients after coronavirus pneumonia in the study groups before the course, immediately after the course, 3 and 6 months after completion of the rehabilitation course.

Note: * – statistically significant differences in the groups immediately after rehabilitation (p 0.05); ^ – statistically significant differences between the groups 3 months after rehabilitation ($p < 0.05$), #– statistically significant differences between the groups 6 months after rehabilitation ($p < 0.05$), PF – Physical Functioning, physical functioning; RP – Role-Physical Functioning, role functioning; BP – Bodily pain, pain intensity; GH – General Health, general health; VT – Vitality, vital activity; SF – Social Functioning, social functioning; RE – Role Emotional, role functioning; MN – Mental Health, mental health.

The indicators of the psychoemotional component of health in patients of the main group shown in Figure 1 reflect an increase in the value immediately after rehabilitation of the scale "PF" – "physical functioning" by 34.3% (p. 0.001), "RP" – "role functioning" by 38.9% (p. 0.001), "BP" – "pain intensity" by 27.5% (p. 0.001), "GH" – "general health" by 30.8% (p. 0.001), "VT" – "vital activity" by 35.6% (p. 0.001), "SF" – "social functioning" by 36.0% (p. 0.001), "RE" – "role functioning" by 36.7% (p 0.001), and "MH" – "mental health" increased by 34.8% (p 0.001). There was also a positive trend in the comparison group, but it was less statistically significant.

In the catamnesis, after three months in the main group, there was a statistically significant improvement in all parameters of the quality of life on the SF-36 scale, possibly due to the activation of oxygen delivery and consumption by tissues, an increase in overall endurance and the ability to withstand physical exertion. Our results are consistent with the results of other scientific observations [30]. In the patients of the comparison group, the preservation of the level of physical and psychological parameters of quality of life was noted.

During the 6 months of follow–up, stabilization of the studied indicators was noted in the main group, while in the comparison group there was a downward trend, in particular, in terms of "PF" – "physical functioning" by 7.7% (p 0.001), "RP" - "role functioning" by 9.8%, "GH" – "general health" by 8.7% (p. 0.001), "VT" – "vital activity" by 8.6% (p. 0.001).

Conclusions

Thus, comprehensive rehabilitation of patients after coronavirus pneumonia with the inclusion of personalized normobaric interval hypoxic-hyperoxic therapy significantly improves its effectiveness, which is manifested by a decrease in the intensity and severity of shortness of breath, increased resistance to hypoxia, increased cardiovascular functioning and improved exercise tolerance, optimization of microcirculatory parameters, reduction of anxiety and depression., positive dynamics of physical and psychological parameters of the quality of life. In the catamnesis, after 3 months, the improvement in the quality of life in the main group remains, and after 6 months their stabilization.

The comparison group also noted the effectiveness of comprehensive rehabilitation of patients after coronavirus pneumonia, but the severity of changes in most examination parameters is statistically less significant. However, in the catamnesis, after 3 months, the stabilization of the values of the quality of life scales was determined in the patients in the comparison group, and after 6 months, a tendency to decrease was revealed. Thus, the data presented in this work indicate a statistically reliable effectiveness of including personalized normobaric interval hypoxic-hyperoxic therapy procedures in rehabilitation programs for patients after coronavirus pneumonia.

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