СОХРАНЕНИЕ ИММУНОМОДУЛИРУЮЩЕГО ДЕЙСТВИЯ ИНТЕРВАЛЬНОЙ ГИПОКСИТЕРАПИИ ПОСЛЕ КОРОНАВИРУСНОЙ ИНФЕКЦИИ В ОТДАЛЕННОМ ПЕРИОДЕ

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Резюме. Новая коронавирусная инфекция COVID-19 ввиду сложного патогенеза заболевания, системного воздействия на органы, развития осложнений и стойких нарушений после перенесенной инфекции остается важной проблемой медицины. С каждым годом увеличивается число пациентов с постковидным синдромом, нуждающихся в своевременной и полноценной реабилитации. Недавно стали появляться единичные работы по применению интервальной гипокситерапии для лечения пациентов с коронавирусной инфекцией. Целью нашего исследования было выявление отдаленных результатов влияния интервальной гипокситерапии на иммунологический и коагуляционный статус пациентов после перенесенной коронавирусной инфекции COVID-19. Обследовано 170 пациентов в возрасте от 45 до 59 лет после перенесенной коронавирусной инфекции средней степени тяжести до, после и через три месяца после интервальной гипокситерапии. Определялось количество лимфоцитов, иммуноглобулинов A, M, G, E и цитокинов (IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, TNFα) в крови, D-димера крови, протромбинового времени, фибриногена в крови, антитромбина III, С-реактивного белка и ферритина в крови. Проведенные исследования выявили изменения иммунологической реактивности после перенесенной коронавирусной инфекции COVID-19, требующие коррекции. Интервальная гипокситерапия оказала иммуномодулирующее действие и привела к нормализации основных иммунологических показателей, которые сохранились через три месяца после гипокситерапии: отмечалось достоверное ($p < 0,05$) повышению количества Т-лимфоцитов $CD3^+$, Т-лимфоцитов $CD4^+$, Т-лимфоциты $CD8^+$. Об улучшении иммунного статуса также свидетельствовали нормализация иммунорегуляторного индекса, повышение уровня иммуноглобулинов A и G. Снижение иммуноглобулинов E в крови являлось показателем уменьшения выраженности сенсибилизации организма. Курс гипокситерапии привел к снижению содержания провоспалительных цитокинов: IL-1β, IL-2, IL-6, IL-8, TNFα и повышению противовоспалительных цитокинов: IL-4

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*И.Х. Борукаева, З.Х. Абазова, А.Б. Иванов, И.А. Мисирова, К.Ю. Шхагумов, Ф.В. Шаваева, А.А. Молов, Т.Б. Кипкеева, А.Г. Шокуева «Сохранение иммуномодулирующего действия интервальной гипокситерапии после коронавирусной инфекции в отдаленном периоде» // Медицинская иммунология, 2023. Т. 25, № 4. С. 809-814.
doi: 10.15789/1563-0625-POT-2767*

For citation:

*I.Kh. Borukaeva, Z.Kh. Abazova, A.B. Ivanov, I.A. Misirova, K.Yu. Shkhagumov, F.V. Shavaeva, A.A. Molov, T.B. Kipkeeva, A.G. Shokueva "Preservation of the immunomodulatory effect of interval hypoxytherapy after coronavirus infection in the long-term period", Medical Immunology (Russia)/ Meditsinskaya Immunologiya, 2023, Vol. 25, no. 4, pp. 809-814.
doi: 10.15789/1563-0625-POT-2767*

DOI: 10.15789/1563-0625-POT-2767

и IL-10 в крови, что свидетельствовало о затухании воспалительного процесса в легочной ткани и в организме в целом. Отмечалось снижение содержания ферритина в крови через 3 месяца после курса гипокситерапии. Как показали проведенные исследования, эффект от гипокситерапии сохраняется в течение трех месяцев после курса лечения. Таким образом, интервальная гипокситерапия может быть рекомендована для реабилитации больных после перенесенной коронавирусной инфекции средней степени тяжести. Повторный курс гипокситерапии может быть проведен через три месяца после первого курса гипокситерапии.

Ключевые слова: коронавирусная инфекция, интервальная гипокситерапия, иммунологический статус, коагуляционный статус, реабилитация, постковидный синдром

PRESERVATION OF THE IMMUNOMODULATORY EFFECT OF INTERVAL HYPOXYTHERAPY AFTER CORONAVIRUS INFECTION IN THE LONG-TERM PERIOD

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Abstract. The new coronavirus infection COVID-19, due to the complex pathogenesis of the disease, systemic impact on organs, the development of complications and persistent disorders after the infection, remains an important medical problem. Every year the number of patients with postcovid syndrome in need of timely and full rehabilitation is increasing. Recently, isolated work began to appear on the use of interval hypoxytherapy for the treatment of patients with coronavirus infection. The purpose of our study was to identify the long-term results of the effect of interval hypoxytherapy on the immunological and coagulation status of patients after suffering coronavirus infection COVID-19. 170 patients aged 45 to 59 years were examined after a moderate coronavirus infection before, after and three months after interval hypoxytherapy. The number of lymphocytes, immunoglobulins A, M, G, E and cytokines (IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, TNFα) in blood, blood D-dimer, prothrombin time, fibrinogen in blood, antithrombin III, C-reactive was determined protein and ferritin in the blood. The conducted studies revealed changes in immunological reactivity after the coronavirus infection COVID-19, requiring correction. Interval hypoxytherapy had an immunomodulatory effect and led to the normalization of the main immunological parameters, which remained three months after hypoxytherapy: there was a significant ($p < 0.05$) increase in the number of $CD3^+$T lymphocytes, $CD4^+$T lymphocytes, $CD8^+$T lymphocytes. The improvement in immune status was also evidenced by the normalization of the immunoregulatory index, an increase in the level of immunoglobulins A and G. The decrease in immunoglobulins E in the blood was an indicator of a decrease in the severity of sensitization of the body. The course of hypoxytherapy led to a decrease in the content of pro-inflammatory cytokines: IL-1β, IL-2, IL-6, IL-8, TNFα and an increase in anti-inflammatory cytokines: IL-4 and IL-10 in the blood, which indicated an attenuation of the inflammatory process in the lung tissue and in the body as a whole. Blood ferritin decreased 3 months after hypoxytherapy. As studies have shown, the effect of hypoxytherapy persists for three months after the course of treatment. Thus, interval hypoxytherapy can be recommended for the rehabilitation of patients after a moderate coronavirus infection. A repeated course of hypoxytherapy may be performed three months after the first course of hypoxytherapy.

Keywords: coronavirus infection, interval hypoxic therapy, immunological status, coagulation status, rehabilitation, postcoronavirus syndrome

Introduction

The new coronavirus infection COVID-19, which caused a pandemic in 2020, and currently remains a serious health problem due to the complex pathogenesis of the disease, systemic effects on organs, the development of complications and persistent disorders after infection [1, 14].

Every year, the number of patients with postcovid syndrome after a coronavirus infection who need timely and full-fledged rehabilitation increases [11]. The treatment of such patients is a difficult task, since the therapy of a new coronavirus infection and its complications often causes the development of various side effects that make it difficult to help

patients. The first target of coronavirus infection is the lung tissue and complications primarily affected the bronchopulmonary system with the development of pneumosclerosis and bronchial obstruction. Postcovid complications from the cardiovascular system include specific virus-associated myocardial damage, accompanied by the development of arrhythmias, coronary and heart failure. There are pronounced vascular changes with prolonged thrombotic microangiopathy and persistent hypercoagulation syndrome, as a result, thrombotic complications develop, which increases the risk of pulmonary embolism, stroke, heart attack, deep vein thrombosis. The coronavirus infection caused cognitive and psychological disorders [1, 6]. All this has led to the need to search for new, non-drug methods of treatment and rehabilitation of patients after a coronavirus infection.

Normobaric interval hypoxytherapy has found wide application in the treatment and recovery of many chronic diseases, since properly performed hypoxytherapy does not cause side effects and complications [5]. Recent studies have shown that adaptation to hypoxia during interval hypoxytherapy has a pronounced effect on the cardiovascular system: the efficiency and effectiveness of its work increases due to an increase in the systolic volume of the heart [10]. On the part of the respiratory system, an increase in respiratory and minute breathing volumes provides an improvement in alveolar ventilation and gas exchange processes in the lung tissue. Adaptation to hypoxia has a pronounced stimulating effect on hematopoiesis due to the production of HIF factor (hypoxia–induced factor), which leads to an increase in the content of erythrocytes and hemoglobin in the blood [12]. W.G. Kaelin, G.L. Semenza, P.J. Ratcliffe for the discovery of HIF factor were awarded the Nobel Prize in Physiology and Medicine in 2019. The formation of long-term adaptation to insufficient oxygen supply to cells is genetically determined and associated with the expression of a specific protein factor HIF, which functions as a transcription activator and a key regulator of various cellular and systemic responses to hypoxia [8].

Hypoxytherapy has an effect on morphofunctional changes of the myocardium, manifested by an increase in the capillary reserve of the myocardium, an improvement in blood supply and oxygen supply of the myocardium and an increase in the reserve potential of the heart muscle [3]. In recent years, there has been information about the specific effect of HIF factor on the expression of genes of various types of immune cells and their effector function. HIF-factor increases the life expectancy of neutrophils, enhances the synthesis of various antimicrobial substances and apoptosis [7]. Titova O.N., Kuzubova N.A., Lebedeva E.S. in their works, they proved that hypoxia, due to the action of HIF factor, can actively affect inflammatory processes by regulating oxygen-sensitive signaling pathways in multiple subtypes of immune cells [13]. All of the above adaptive mechanisms caused by hypoxia lead to an improvement in the clinical course of diseases and emergency rehabilitation.

Interval hypoxytherapy cautiously entered the rehabilitation of patients after coronavirus infection, as it caused a lot of controversy about the possibility of using hypoxytherapy after a coronavirus infection. Isolated works on the use of hypoxytherapy for the treatment of patients with coronavirus infection began to appear, in which the effectiveness of the use of normobaric interval hypoxytherapy in the rehabilitation of patients after a coronavirus infection COVID-19 has been proven [15]. Articles on the state of the immune system in patients with a new coronavirus infection began to appear, however, articles on identifying the long-term results of the effect of interval hypoxytherapy on the immunological status of patients after the COVID-19 coronavirus infection was not encountered. There is also no information in the available literature on the persistence of changes in the coagulation status of patients 3 months after interval hypoxytherapy.

The aim of the study was to identify the long-term results (3 months after the course of hypoxytherapy) of the effect of interval hypoxytherapy on the immunological and coagulation status of patients after COVID-19 coronavirus infection.

Materials and methods

The main group consisted of 170 patients aged 45-59 years after a moderate coronavirus infection. The control group was represented by 60 patients after suffering from COVID-19 coronavirus infection, who underwent standard rehabilitation without interval hypoxytherapy. Interval hypoxytherapy and laboratory studies were carried out on the basis of the University Clinic of the Kabardino-Balkarian State University named after H.M. Berbekov. Patients underwent normobaric interval hypoxytherapy in the mode of alternating hypoxic intervals with normoxic ones. The hypoxic effect was carried out using the hypoxytherapy unit "Hypo-Oxy" of the company "Oxyterra" (Russia), which generated a hypoxic mixture with different oxygen content. Hypoxytherapy was performed in the hypoxia-normoxia mode, including alternating 5-minute hypoxic effects with 5-minute hyperoxic (20.9% O_2). To determine individual sensitivity to hypoxia and tolerance of hypoxic mixtures, a hypoxic test was performed for all patients, after which the optimal oxygen content in the hypoxic mixture was selected, the duration of hypoxic effects and the number of procedures were determined. Usually the course of hypoxytherapy was 15 days. As a result, there was a gradual adaptation to hypoxia.

All patients before, after and 3 months after hypoxytherapy underwent a study of D-dimer by immunoturbidimetry (ACL TOP 750, Instrumentation Laboratory, USA), prothrombin (thromboplastin) time – according to the time of plasma recalcification

with the addition of tissue thromboplastin. INR was calculated using the formula: INR (INR) = BY mich(isi), where BY = patient's prothrombin time / normal mean prothrombin time. Determination of activated partial thromboplastin time (APTT) by the clotting time of decalcified plasma after adding kaolin-kefalin-calcium mixture to it. To determine fibrinogen in the blood, the method of detecting lateral light scattering, determining the percentage at the endpoint, was used. Determination of antithrombin III was carried out by colorimetric method (%). All studies were carried out on the device coagulometer analyzer automatic CS-5100 Sysmex (Japan). Determination of C-reactive protein and ferritin in the blood was carried out by immunoturbidimetry on a biochemical analyzer Cobas 6000 (Roche Diagnostics, Switzerland).

The determination of the number of lymphocytes was carried out by flow cytofluorimetry on the XN-9000, Sysmex (Japan), immunoglobulins A, M, G by immunoturbidimetry on the Cobas 6000, Roche Diagnostics (Switzerland); the content of immunoglobulins E and cytokines (IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, TNFα) in the blood was determined by electrochemiluminescent immunoassay on the Cobas 6000 apparatus, Roche Diagnostics (Switzerland). Studies were conducted only after obtaining the personal consent of patients in accordance with ethical principles.

Statistical processing of the results was carried out in accordance with the rules of mathematical statistics using the program "Microsoft Excel" and "Statistica 6.0" for "Windows". During the parametric analysis, the paired and unpaired Student's t-test was used. The nonparametric Mann–Whitney criterion was used to assess the reliability of intergroup differences. All numerical data in the form of the arithmetic mean and the standard error of the mean M±m, and with the nonparametric nature of the distribution of quantities – in the form of a median indicating the 25^{th} and 75^{th} quartiles: Me ($Q_{0.25}$-$Q_{0.75}$). The differences were considered statistically significant at $p < 0.05$.

Results and discussion

Coronavirus infection had a significant impact on the coagulation system of patients, which is consistent with the data of many authors [2, 4]. In patients, there was a moderate decrease in the platelet content in the blood (165.41±10.22 × 10^9/L), which, apparently, was associated with increased consumption due to damage to the vascular wall and the action of the virus [9]. On the part of coagulation hemostasis, there was a statistically significant ($p < 0.05$) decrease in APTT, INR, antithrombin III, an increase in the Quick prothrombin index, fibrinogen, D-dimer, which indicated an increased tendency to thrombosis in patients.

After the course of hypoxytherapy, the coagulogram indicators normalized and approached the indicators of the control group. Three months after the course of hypoxytherapy, the preservation of changes in the hemostasis system was noted: the platelet count increased statistically significantly ($p < 0.05$) to 223.63±11.42 × 10^9/L and remained at the level of 237.54±13.36 × 10^9/L three months after hypoxytherapy. Activated partial thromboplastin time significantly ($p < 0.05$) increased to 25.89±1.46 sec after hypoxytherapy and remained at the level of 26.15±1.12 sec 3 months after hypoxytherapy. INR significantly ($p < 0.05$) increased to 0.82±0.04 after hypoxytherapy and remained at the achieved level after 3 months.

There was a statistically significant ($p < 0.05$) increase in the content of antithrombin III in the blood 3 months after hypoxytherapy (87.57±3.15%). The prothrombin index for Quick decreased to 125.61±3.15% after hypoxytherapy and remained at 124.84±3.57% 3 months after hypoxytherapy. The reduced fibrinogen content in the blood was noted 3 months after hypoxytherapy and amounted to 9.52±1.03 g/L. An important result of hypoxytherapy was a decrease in the content of D-dimer in the blood serum after hypoxytherapy and 3 months after its implementation at the level of 1.52±0.03 mg/L. The revealed changes testified to the normalization of coagulation hemostasis after the course of hypoxytherapy and the preservation of these changes 3 months after hypoxytherapy. A statistically significant ($p < 0.05$) persistent decrease in C-reactive protein in the blood indicated the suppression of the inflammatory process and the preservation of the effect of hypoxytherapy in the long term.

The conducted studies of immunological reactivity after coronavirus infection revealed changes in cellular immunity, manifested in a decrease in the number of $CD3^+$T lymphocytes to 48.6 (37.3-57.5) %, the level of $CD4^+$T helper cells to 28.4 (20.8-40.8) %, which led to a violation of humoral and cellular immunity. There was also a significant ($p < 0.05$) decrease in $CD8^+$T lymphocytes to 14.5 (10.3-19.8) %. The number of B-lymphocytes was not significantly changed and was 19.6 (12.7-24.2) %.

There was a significant ($p < 0.05$) decrease in the level of immunoglobulins A and M. Reduction of immunoglobulin A levels to 0.88 (0.67-0.98) g/L resulted in decreased resistance to various infections against the background of developing lymphopenia after a coronavirus infection COVID-19. The results of our studies revealed a significant ($p < 0,01$) increase in the content of immunoglobulins E to 97.43 (78.7-121.5) IU/L, which indicated increased sensitization of patients. There was a statistically significant ($p < 0.05$) increase in the content of circulating immune complexes to 96.57 (86.4-99.5) standard units and the immuno-regulatory index up to 2.08 (2.05-2.20) standard units as a result of increased immunological reactivity. A decrease in the content of $CD3^+$T lymphocytes, $CD4^+$T helper cells, the level of immunoglobulins A and an increase in the content of immunoglobulins E and circulating immune

complexes led to a change in the immunological status of patients after a coronavirus infection and the maintenance of the inflammatory process in the bronchopulmonary system even during recovery.

Interval hypoxytherapy had an immunomodulating effect and led to the normalization of the main immunological parameters. There was a significant ($p < 0.05$) increase in the number of $CD3^+$T lymphocytes to 59.3 (37.5-67.1) % after hypoxytherapy and to 60.1 (45.3-68.4) % 3 months after hypoxytherapy. The increase in $CD4^+$T lymphocytes after hypoxytherapy persisted 3 months after hypoxytherapy at the level of 41.7 (29.6-49.6) %. Normalization of cellular immunity was also observed in the long-term periods after hypoxytherapy; the number of $CD8^+$T lymphocytes was 24.4 (13.7-28.5) % 3 months after hypoxytherapy.

The improvement of the immune status was evidenced by the normalization of the immune regulatory index to 1.77 (1.83-1.91) units, an increase in the level of immunoglobulins A to 1.37 (1.11-1.55) g/L and immunoglobulins G to 9.64 (6.32-12.68) g/L, which increased the body's resistance to re-infection. The retention of a statistically significant ($p < 0.05$) decrease in immunoglobulin E to 289.45 (272.4-374.3) IU/L in the blood indicated a decrease in the sensitization of the body. These changes persisted 3 months after the course of hypoxytherapy.

The study of the cytokine status of the blood revealed changes even during the period of convalescence. The increased content of pro-inflammatory and decreased anti-inflammatory cytokines remained, which indicated the depletion of sanogenetic mechanisms and contributed to the maintenance of the inflammatory process in the bronchopulmonary system and in the body. Hypoxytherapy had a positive effect on the cytokine profile of the blood: in the long-term periods (after 3 months), there was a significant ($p < 0.05$) decrease in the content of proinflammatory cytokines: IL-1β to 3.46±0.84 pg/mL, IL-2 to 3.32±0.04 pg/mL, IL-6 to 3.72±0.11, IL-8 to 4.33±0.13 pg/mL, TNFα to 9.51±0.15 pg/mL and an increase in anti-inflammatory cytokines: IL-4 to 5.83±1.23 pg/mL, IL-10 to 8.63±0.11 pg/mL in the blood, which indicated the activation of sanogenetic mechanisms.

Conclusion

An important result of hypoxytherapy was the preservation of the ferritin content in the blood 3 months after the course of hypoxytherapy at the level of 86.25±5.07 mcg/L, which, along with a decrease in the content of pro-inflammatory interleukins and an increase in anti-inflammatory interleukins, indicated the attenuation of the inflammatory process in the lung tissue and in the body as a whole. Studies have shown that the effect of hypoxytherapy persists for 3 months after the course of hypoxytherapy, which is consistent with the literature data on the effectiveness of hypoxytherapy. Thus, interval hypoxytherapy can be recommended for the rehabilitation of patients after a moderate coronavirus infection. A second course of hypoxytherapy can be carried out 3 months after the first course of hypoxytherapy.

Acknowledgements

We express our gratitude and deep appreciation to Miziev Ismail Alimovich, Professor, the Dean of medical faculty of the Kabardino-Balkarian State University named after H.M. Berbekov for the valuable advice and comments on the article.

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Поступила 14.04.2023
Отправлена на доработку 17.04.2023
Принята к печати 21.04.2023

Received 14.04.2023
Revision received 17.04.2023
Accepted 21.04.2023