https://doi.org/10.18093/0869-0189-2020-30-5-569-576

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Randomized controlled study on pulmonary rehabilitation in COVID-19 patients with pneumonia

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Abstract

Pulmonary rehabilitation in COVID-19 patients with pneumonia is associated with better treatment outcomes. However, existing protocols have never been evaluated in randomized control studies. **The aim.** To evaluate the effectiveness of newly-developed pulmonary rehabilitation protocol compared to basic Russian COVID-19 guidelines for patients with oxygenation index (OI) between 200 and 400 points without IMV. **Methods.** Based on literature reviews and own clinical experience, standard rehabilitation protocol was designed and tailored for specific needs of low-OI patients. Two clinical centers participated in the study and included total 73 patients in main group. Control group included 73 retrospective patients based in propensity score; this patients received standard protocol of early pneumonia activation from official COVID-19 guidelines. Ten-days clinical outcomes were assessed based on parameter distribution type. **Results.** Evidence show significant difference in required time of continuous oxygen support in (5.1 ± 3.3 *vs* 8.0 ± 4.6 days for main and control group respectively. Main group also had mildly better functional. We've observed less mortality in main group, but attribute it not to the program, but for growing experience of health professionals and decreased loads on health system. Malignancy as comorbidity was considered a significant cofactor also. **Conclusion.** New pulmonary rehabilitation protocol improves clinical outcomes in critical COVID-19 patients by decreasing the demand fox oxygen support.

Key words: rehabilitation, COVID-19, breathing exercises, oncology, survival rate.

Conflict of interests. The authors declare the absence of conflict of interests.

For citation: Lyadov K.V., Koneva E.S., Polushkin V.G., Sultanov E.Yu., Lukashin M.A. Randomized controlled study on pulmonary rehabilitation in COVID-19 patients with pneumonia. *Pul'monologiya*. 2020; 30 (5): 569–576 (in Russian). DOI: 10.18093/0869-0189-2020-30-5-569-576

Дыхательная реабилитация у больных вирусной пневмонией на фоне новой коронавирусной инфекции

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Резюме

При использовании дыхательной реабилитации при пневмонии, ассоциированной с новой коронавирусной инфекцией (НКИ), отмечено улучшение результатов лечения. Однако типовые протоколы дыхательной реабилитации для тяжелых форм коронавирусной пневмонии по данным рандомизированных исследований до настоящего момента не оценивались. **Целью** рандомизированного клинического исследования, проведенного в 2 клинических центрах, явилось определение эффективности протокола дыхательной реабилитации у больных с индексом оксигенации < 400 и > 200 при самостоятельном дыхании или кислородной поддержке по сравнению с пациентами, у которых реабилитация не проводилась. **Материалы и методы.** В исследовании приняли участие пациенты (n = 146) с ДН, отобранные методом ретроспективной псевдорандомизации среди больных, проходивших лечение ранее. Разработан протокол из 5 последовательных упражнений дыхательной гимнастики. Пациентам основной группы (n = 73) к лечению в течение 10 дней добавлена исследуемая реабилитационная программа, затем оценивались результаты. **Результаты.** Получено достоверное различие продолжительности непрерывной кислородной поддержки между группами (5,1 ± 3,3 дня *vs* 8,0 ± 4,6 дня). При анализе в подгруппах важной самостоятельной ковариатой исхода оказалось наличие онкологического заболевания. **Заключение.** При

использовании комплекса лечебной физической культуры в остром периоде течения НКИ повышается эффективность лечения за счет раннего снижения потребности в кислородной поддержке, ускоренной нормализации индекса оксигенации, повышения толерантности к физической нагрузке.

Ключевые слова: реабилитация, новая коронавирусная инфекция, дыхательная гимнастика, онкология, выживаемость.

Конфликт интересов. Авторы заявляют об отсутствии конфликта интересов.

Для цитирования: Лядов К.В., Конева Е.С., Полушкин В.Г., Султанов Э.Ю., Лукашин М.А. Дыхательная реабилитация у больных вирусной пневмонией на фоне новой коронавирусной инфекции. *Пульмонология*. 2020; 30 (5): 569–576. DOI: 10.18093/0869-0189-2020-30-5-569-576

The new COVID-19 infection (NCI) created an unprecedented challenge to healthcare systems around the world. The combination of high virulence with a severe course of the disease, in the clinical picture of which viral pneumonia phenomena dominate, resulted in a situation where in-patient departments quickly filled with patients who have confirmed COVID-19 infection or suspected of it [1].

Early activation improves the prognosis for the life of patients with severe pneumonia in an evidence-based manner [2]. However, clinical practice showed that for COVID-19 infection, it is relevant to develop specific restorative complexes with respect to the extremely high risk of breathing with resistance and severe asthenization of patients. In addition, in the context of the NCI pandemic, the problem of attracting professional exercise therapeutists and instructors for these tasks, the deficiency of which was observed earlier, becomes especially acute. This makes it desirable to use techniques that are available to all personnel involved in the treatment of patients, as well as suitable for their implementation by patients themselves. Finally, while the researchers proposed several options for rehabilitation protocols for the new COVID-19 infection, there were no comparative studies between them – this does not allow making a definitive conclusion about the reasonability of their inclusion in the treatment program [3].

This paper describes a clinical study comparing the effectiveness of the respiratory rehabilitation protocol developed by us with the standard treatment of patients with the NCI complicated by respiratory failure.

The purpose of the study was to evaluate the effectiveness of the respiratory rehabilitation protocol in patients with the oxygenation index between 200 and 400 on spontaneous breathing or with oxygen support in comparison with patients without rehabilitation support.

Objectives:

- To create the protocol for the first stage rehabilitation of patients with the COVID-19 infection under the conditions of respiratory failure based on literature data and clinical experience.
- To select the treatment group from among patients who meet the inclusion and exclusion criteria and received an appropriate early rehabilitation according to the protocol.
- To form the comparison group using the pseudo-randomization method from the number of patients who meet the inclusion and exclusion criteria, but have not received an appropriate early rehabilitation according to the protocol.
- To compare clinical results in the two groups.

Materials and methods

Study design

Primary endpoint was the period from the start of treatment to the refusal of oxygen support

Secondary endpoints:

- Frequency of transferring patients to artificial lung ventilation (ALV)
- Dynamics of the oxygenation index measurement.
- Evaluation of subjective general state according to SF-36 on the 1st and 10th days.
- Break-in exercise therapy for 2 or more days.
- Patient survival rate in 10 days from starting exercise therapy.

In our opinion, the duration of the period from starting the treatment to normalizing oxygenation sufficiently to terminate the oxygen support is the most adequate indicator of the effectiveness of treatment for assessing the significance of the proposed protocol.

Endpoints 3 and 4 were ultimately excluded from the study because of the impossibility of collecting relevant data in the control group due to the lack of this information in the source medical records. To ensure data collection, endpoint 3 was replaced with data from medical records for self-care of patients, who, according to the literature, can make an adequate contribution to the assessment of the program [4]. To assess the indicator, a binary model was used, in which “1” corresponded to patients who were able to get out of the bed on their own, dress themselves to a limited extent and move around the ward at the end of 10 days, and “0” corresponded to those who could not perform any of these actions.

After releasing several updates to the temporary protocol of the Ministry of Health of Russia on the treatment of the new COVID-19 infection in the course of the study, as well as an obvious increase in clinical experience, we decided to put aside the assessment of the survival rate as an endpoint. In our opinion, a sufficient number of fundamental changes were added to the treatment protocol that directly affects the survival rate. However, we included the survival rate in the study summary for the interpretation of the ANOVA data.

Inclusion criteria:

- Age over 18 years old;
- Patients with the IO < 400 in the ICU.

Exclusion criteria:

- Patients on ALV;
- Patients with the IO < 200;
- Patients inaccessible to the productive contact;

- Patients with the following contraindications (extensive contractures of the extremities; severe pain syndrome; ostomy patients; patients with severe decompensation of a concomitant disease);
- Patients who cannot leave the pron position without a prolonged (over 2 minutes) cough or a steady decrease in oxygen saturation by more than 3%;
- Patients who did not comply with the protocol during the study.

Comparison groups. The treatment group consisted of the patients who met the inclusion criteria, had no exclusion criteria, and underwent the selected rehabilitation program.

The control group consisted of the patients who underwent pseudo-randomization according to archival data. The control group was formed by the pseudo-randomization method after assessing the nature of the parameter distribution using the Kolmogorov–Smirnov method; parametric distribution was carried out by Student's t-test, binary distribution was carried out by McNamar's χ^2 test, and non-parametric distribution was carried out by Mann–Whitney's U-test. Pseudo-randomization in the retrospective group was performed based on the concordance of the sample by the following parameters:

- Gender;
- Age;
- Oxygenation index at the date of starting the treatment;
- Therapy with tocilizumab;
- CIRS (Cumulative Illness Rating Scale) [5].

Analyses in subgroups:

- By gender and age groups;
- By the number of accompanying complications;
- By the APACHE/SOFA index;
- By the frequency and multiplicity factor of the exercises performed;
- By routing the start of the exercise therapy (initial admission to the ICU in compliance with the inclusion criteria; transferring to the ICU for deterioration and in compliance with the criteria; transition to exercise therapy after ALV).

Estimated number of patients

100 people in each of the main and control groups or reaching the first endpoint.

Patient selection principle

Patients were included in the study on the first day of admission to the ICU if they met the inclusion criteria and had voluntary informed consent for participation in the study. The distribution into groups was carried out randomly. Rehabilitation assistance was provided according to the protocol specifying the actual number of exercises performed. The endpoints were assessed for 10 days.

Data analysis

The database was formed based on source medical records in SPSS Statistics (IBM, USA). The odds ratio (with a significant difference of 3% and 95% CI) was calculated for the primary endpoint. The ANOVA analysis by subgroups was carried out for the primary and secondary endpoints.

Group recruitment and treatment

The recruitment of groups was carried out on a multi-center principle with the participation of two clinical centers: City Clinical Hospital No.40 of the Moscow City Department of Health and Mytishchi City Clinical Hospital, State Budgetary Institution of Health Care of the Moscow Region. The selection and rehabilitation process at the clinical center ware managed by a full-time exercise physician or the Head of the ICU, and the actual implementation of patient education was carried out by doctors, nurses and/or volunteers of the clinical base, whose competence included control of the frequency and accuracy of exercises by patients.

Treatment protocol

Protocol development

The protocol was developed based on the analysis of literature data and our own clinical experience. The work of Chinese specialists, from which we made three main conclusions about the factors that directly affect the effectiveness of the early rehabilitation process, formed a methodological backbone of the protocol:

- Rehabilitation should begin as early as possible, as soon as the patient's condition allows, to prevent the vicious circle of asthenization, weakening of the respiratory muscles, and worsening respiratory failure.
- There is a high risk of further damage to the lung tissue with techniques that significantly increase resistance to expiration or force expiration.
- Rehabilitation techniques in the format of respiratory exercises, which mainly stimulate the auxiliary respiratory muscles, improve the indicators of external respiration function in an evidence-based manner [6–11].

In the Chinese research protocols, traditional Chinese exercises were mainly used; however, due to the lack of prior experience working with it, the Chinese exercises were replaced with traditional ones in Russian exercise therapy, with respect to the recommendations for the muscle groups involved.

In the period from March to April 2020, the protocol was tested within the separate exercises, performed first by patients with mild respiratory failure (with the IO over 400 and breathlessness), and then by individual patients in the ICUs. During approbation, the initial list of exercises for ICU patients was reduced to 5, which was close to the maximum tolerable one-time physical activity on the one hand and made it possible to quickly train patients and staff on the other hand.

To ensure the greatest availability of data, the reference performance of the exercises with comments was recorded in a video lesson format, which was then posted on a public website on the Internet. Given the absence of any data on how long a patient should do respiratory exercises, we recommended all patients to continue the exercises until the health authorities form a procedure for screening and rehabilitating such patients, and for this purpose, we also recorded specific videos with the entire complex of exercises and instructions on their own implementation tested by us.

Formalized protocol

- For the first time, the exercises shall be performed jointly by the patient and medical staff; then the medical staff shall control the patient's doing exercises himself/herself.
- The exercises shall be performed only in the presence of productive contact with a patient, with a properly operating oxygen saturation sensor put on.
- The supine position shall be a starting position.
- The exercises shall be repeated 3 to 10 times, in a given order (Table 1). The frequency of approaches is 4 – 6 per day at a patient's request, while the range and number of repetitions performed within one approach shall not be regulated. If less than four approaches were performed per day, the mark "no exercises were performed" was recorded in the research protocol for such a patient.
- The exercises shall be terminated under the following conditions:
  - If initial SaO_2 > 92: with a decrease in SaO_2 below 88. If the indicator is restored within 30 seconds or less, it is possible to continue the exercise.
  - If initial SaO_2 was within the range of 87 – 92: with a decrease in SaO_2 below 80. If the indicator is restored within 30 seconds or less, it is possible to continue the exercise.
  - If initial SaO_2 < 80 (a sensor malfunction is suspected; the current acid-base balance should be clarified): the exercises shall be performed only in the presence of the attending physician.
  - In the case of the patient's complaints of severe fatigue, weakness, dizziness, or nausea, the exercises shall be terminated at any time.

The exercises were performed in the order shown in Table 1.

Compliance with Ethical standards

The study protocol and the patient's brochure were approved by the Protocol No.2 of the Ethics Committee of the City Clinical Hospital No.40 of the Moscow City Department of Health, State Budgetary Institution of Health Care of the City of Moscow, dated May 11, 2020. All study participants signed informed voluntary consent in accordance with the Declaration of Helsinki. Patients who refused to participate in the study received standard treatment in accordance with the current edition of the Interim Methodological Guidelines for the Prevention, Diagnostics, and Treatment of the New COVID-19 Infection and (since 21.05.20) in accordance with the Interim Methodological Guidelines for Medical Rehabilitation in the New COVID-19 infection.

In total, 146 patients were included in the study: 73 patients each in the treatment and control groups. The gender and age structure of the patients studied and the indicators selected for calculating the Propensity score are presented in Table 2.

Results and Discussion

During the study, the primary endpoint was reached with a significantly lower need for oxygen support in the treatment group. The results were systematized in Table 3.

Table 1
Order and description of program's excercises
Таблица 1
Порядок и описание упражнений программы

No.	Description
1	In the starting position, the patient shall make breathing-in. Then sliding the heel along the bed, the patient shall bend his/her leg in the knee and make breathing-out to painless level
2	Hands to the shoulders, spread the elbows to the sides – the patient shall make breathing-in. Then lower the elbows, press them against each other to the chest and bend in the stomach (if possible) – the patient shall make breathing-out
3	Support on the elbows, raise the chest – the patient shall make breathing-in. Then straighten the arm diagonally and make a reach for the arm by tearing off the shoulder blade – the patient shall make breathing-out ("Boxing" exercise)
4	One hand is behind the head. Twist the body in the opposite direction (with the pelvis staying the same place) and with the other hand clapping himself/herself on the side on the ribs – the patient shall make breathing-in. Then take the starting position with the hand put behind – the patient shall make breathing-out
5	Being supported by the elbows, raise the chest so that the shoulder blades go towards each other – the patient shall make breathing-in. Then relax – the patient shall make breathing-out

Table 2
Pseudo-randomization parameters structure
Таблица 2
Характеристика пациентов исследуемых групп по параметрам псевдорандомизации

Parameter	Treatment group	Control group	Significance of differences
Group size	73	73	< 0.05
Males, %	57.5	53.4	< 0.05
Average age	59.2 ± 14.4	60.3 ± 15.3	< 0.05
BMI	27.2 ± 4.1	29.2 ± 3.9	> 0.1
Average oxygenation index at the date of starting the treatment	330 ± 36	332 ± 54	< 0.05
Patients receiving tocilizumab, %	5.4	6.8	< 0.05
Cumulative Illness Rating Scale-Geriatric (CIRS-G), the average score	3.4 ± 2.3	3.3 ± 2.8	< 0.05

Note: BMI, body mass index.

Table 3
Study results
Таблица 3
Результаты исследования

Endpoint	Treatment group	Control group	Difference
The period from the start of treatment to the refusal of oxygen support	5.1 ± 3.3	8.0 ± 4.6	Significant ($p < 0.05$)
Daily average dynamics of changes in the oxygenation index	± 28.3 ± 39.0	± 14.3 ± 32.3	Significant ($p < 0.05$)
Self-service status assessment	0.6 ± 0.3	0.3 ± 0.5	Non-significant ($p = 0.12$)
Fatal outcomes, *n* (%)	1 (1.4)	4 (5.5)	Significant ($p < 0.05$)*
Transfer to ALV after treatment, *n* (%)	2 (2.7)	6 (5.5)	Non-significant ($p = 0.17$)

Note: ALV, artificial lung ventilation; *, They were excluded from the study analysis.

As the data in the table show, the study reached the primary endpoint – there is a significant difference in mortality rates between the groups. At the same time, the interpretation of the result requires several clarifications presented below and related to the peculiarities of patient selection in studies without the existing standard comparator intervention.

When analyzing the subgroups, no significant differences were revealed in age and sex. Among concomitant diseases, the difference in mortality rates in the presence of an oncological disease detected in 8 patients and accompanied by 3 (37.8%) fatal outcomes turned out to be significant. Moreover, cancer turned out to be a significant covariate of another indicator – exercise tolerance in those patients in whom it was managed to reliably measure it. At the same time, the ANOVA analysis did not reveal significant outcome covariates among the parameters entered.

When evaluating data on the mortality rate, it is necessary to take into consideration a combination of organizational and methodological factors, which, in our opinion, do not allow us to say about the presence of a causal relationship between this indicator and the treatment performed. First of all, most of the patients of the treatment group entered it in the period from May to June 2020, when the treatment protocols for patients with the new COVID-19 infection were well developed, and doctors gained experience in working with this category of patients. In contrast, the majority of the patients in the control group entered it in the period from March to April 2020 when many treatment principles were still being developed. It is necessary to say that during May, hospital occupancy also began to decrease, which led to the fact that the medical staff burden became lower, and they were able to more efficiently allocate time between patients.

In addition, attention should be drawn to the fact that in the existing method of patient selection, the treatment group definitly consisted of the patient contingent motivated for active prevention, while the control group, among other things, could have a high proportion of low-active patients with the severe depressive syndrome, high subjective asthenization, and low culture of physical activity in general. This is partly supported by a significantly higher BMI of the patients in the control group.

With regards the analysis in subgroups, the result is probably self-evident – the patient group was quite homogeneous in terms of age and sex composition, while patients with oncological diseases, especially those who underwent the course of anticancer therapy, dramatically stand out against it by the severity of their condition [12, 13].

The lack of ANOVA analysis results can be explained by two main classes of reasons having the opposite direction to a certain extent. First of all, probably, there were too many parameters for the relatively small sample, even for the minimal list of partition that was used in the study. And secondly, a large number of factors that could turn out to be significant covariates were not taken into consideration: for example, the study did not involve using the depression scale, recovery motivation scale, assessment of haemocoagulative parameters, interpretation of signs of a systemic inflammatory response in individual indicators (levels of interleukins, TNF-α, etc.). Moreover, we used the integral comorbidity parameter, while the literature data highlight very specific and diverse predictors of fatal outcomes depending on the number and nature of the concomitant disease [14–21].

Providing insight into the prospects for further studying the topic, we consider it reasonable to develop a comparator program with conducting a further study on their comparative assessment in conditions of COVID-19 infection. However, the primary objective is to form the evidence base for the first stage of rehabilitation in uncomplicated patients, as well as the second and third stages of rehabilitation. From our point of view, these objectives are largely related, since only the specification of the long-term medical and social effects of the new COVID-19 infection can give a clue to promising rehabilitation methods.

The use of larger samples allowing to better estimate the outcome covariates, in our understanding, is not reasonable, since the presented technique is only an auxiliary tool of the treatment protocol. And in contrast, comparing different early rehabilitation protocols as covariates in large population studies devoted to different complex treatment protocols can come useful.

In such a way, currently, we can say for sure that the proposed algorithm of respiratory exercises significantly accelerates the recovery of patients with severe respiratory failure against the background of the new COVID-19 infection, and it is associated with a better life prognosis for them. It is currently impossible to conclude the long-term effects of rehabilitation, but this assessment is included in our research strategy.

Conclusion

Using the complex of exercise therapy in the acute period of the new COVID-19 infection reduces the need for oxygen support in patients with respiratory failure and the oxygenation index of more than 200 and less than 400 against the background of the new COVID-19 infection. This results in a decrease in the inpatient unit burden under the epidemic conditions, and it was associated with an accelerated recovery rate of patients and reduced rates of transferring to ALV and mortality rates, for which, however, there were probably more significant success cofactors.

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Received: July 03, 2020

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Поступила 03.07.20

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