Rational nutrition during coronavirus infection

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ABSTRACT

The COVID -19 pandemic is creating completely new and unexplored challenges for patients and healthcare around the world. The severe course of the disease, including lung damage, requires various types of respiratory support both in the intensive care unit and in the clinical infectious diseases departments [1, 2].

The main risk group, in which there is a high incidence of adverse outcomes and a higher mortality rate, are the elderly, persons with severe concomitant comorbidities, as well as patients with protein - energy malnutrition. Dependence on respiratory support, a pronounced immune response of the body, comorbidities, advanced age are usually associated with a high risk of developing malnutrition, which in itself is a risk factor for the development of additional infectious and inflammatory complications, an increase in the time spent on respiratory support, in the intensive care unit and intensive care unit. therapy in the hospital.

Recommendations for nutritional support for patients with coronavirus infection from the European Association for Clinical Nutrition and Metabolism (European Society for Clinical Nutrition and Metabolism , ESPEN) suggest using additional nutritional support in the form of sips where possible [3].

This is especially true for patients recovering from severe illness and being on respiratory support, as they are most susceptible to catabolism and muscle loss.

Malnutrition and a decrease in muscle mass in this category of patients cause longer respiratory support, an increase in the time spent in the intensive care unit and intensive care unit and in the hospital, as well as a decrease in muscle strength and, accordingly, the quality of life, an increase in the duration of asthenia in patients in the recovery period after a viral infection. pneumonia caused by the coronavirus .

Thus, the use of additional nutritional support for patients with respiratory therapy at the stage of their transfer to independent nutrition can accelerate recovery, improve the quality of life of patients who have had a viral pneumonia caused by a new coronavirus infection COVID-19.

The aim of the study is to investigate the impact of additional nutritional support on the recovery of physical health of patients with COVID-19.

Keywords: nutritional support, coronavirus infection, oral nutritional support, recovery, wrist force

Material and methods. Study design

A prospective , open-label , multicentre , two-arm , comparative, observational study initiated by an investigator to evaluate the effects of Nutridrink ® 200ml Specialized Nutritional Blend (ONS) on the ability of COVID-19 patients to recover.

Investigating physicians screen patients according to inclusion/exclusion criteria, inform patients about the aims and methods of the study, obtain informed consent from patients, and enroll patients in the study. Patients are randomized into the study and control groups according to an end-to-end algorithm using a Mersenne vortex random number generator . Regardless of the center and the investigator, the next registered patient is automatically assigned to one or another group after the investigator decides to include the patient. Information about the distribution of the patient becomes known to the doctor and the patient. If a patient is excluded from the study, their randomization number is returned to the general pool of numbers.

Eligibility Criteria

Inclusion Criteria. Patients who simultaneously meet all of the following inclusion criteria are included in the study:

age 18–69;

the presence of a confirmed novel coronavirus infection COVID-19 (based on laboratory diagnostics and/or computed tomography data);

the need for respiratory support (oxygen insufflation, non-invasive ventilation of the lungs, artificial ventilation of the lungs (provided that the possibility of independent food intake is preserved, including in the prone position);

the ability to spontaneously take food in an amount of 60% or more of the need for energy and protein (the possibility of spontaneous eating is determined by the three- sip test; food consumed is controlled by the "quarter plate" method);

availability of informed consent signed by the patient for inclusion in the study and processing of personal data.

Criteria for non-inclusion. If a patient meets at least one of the exclusion criteria below, they will not be included in the study:

diabetes;

kidney failure;

liver failure;

systemic disease;

oncological disease in the active phase;

poor survival prognosis.

exclusion criteria. If during the course of the study, the patient meets at least one of the following exclusion criteria, then he is excluded from the study:

deterioration of the patient's condition, requiring his transfer to enteral tube and / or parenteral nutrition;

the occurrence of complications requiring surgical interventions;

transfer of a patient for treatment to another hospital;

complications of using the drug for additional nutritional support (diarrhea, nausea, vomiting);

withdrawal by the patient of informed consent for inclusion in the study and processing of personal data.

Terms and Conditions

The study included 2 centers

“City Infectious Diseases Hospital Hospital No. 1;

City Infectious Diseases Hospital Hospital No. 2

Study duration

In total, the study included screening and 4 visits: B0 (screening) and B1–B4 (observation).

The screening visit was carried out on the day the patient was admitted to the intensive care unit or when the patient was prescribed respiratory oxygen support in the infectious diseases unit.

Visit 1 took place on the same day as the screening visit.

Visit 2 was conducted on the day of transfer of the patient from the intensive care unit to the infectious diseases unit or on the day of termination of respiratory support (days 7–14 from the date of the first visit).

Visit 3 was held on the day of the patient's discharge from the medical organization for follow-up care or outpatient follow-up (approximately 14–21 days from the date of the first visit).

Visit 4 took place 28 days after Visit 1.

Outcome Registration Methods

Research physicians used electronic forms of individual registration cards (CRFs) and electronic reports of adverse events that were automatically generated in the general electronic CRF for data collection. Doctors also filled out electronic questionnaires on the quality of life by the number of the visit according to the patients' words.

The following parameters of intervention effectiveness were used in the study.

Quality of life indicators based on the SF-36 quality of life questionnaire [4].

The SF-36 CRF questionnaires were filled in by the research physician based on the words of the patients during personal (visits 1–3) and remote (visit 4) contact:

overall score of the quality of life indicator (score);

quality of life indicator "physical component of health" (score);

quality of life indicator "mental component of health" (score).

Change in hand force.

The absolute values of the patient's arm strength were measured by the research physician using a DK-50 dynamometer (China) at visits 1–3. Next, to assess the changes, a composite indicator was calculated representing the difference in the grip strength of the patient's hand at visit 3 and at visit 1.

Duration of respiratory support.

The indicator was measured by the research physician as the period of time (days) between the date the patient was prescribed respiratory oxygen support (Visit 1) and the date it was discontinued (Visit 2).

Length of stay in the hospital.

The indicator was measured by the research physician as the period of time (in days) between the date of hospitalization of the patient (according to the medical history) and the date of discharge from the hospital (visit 3).

Changes in the severity of the patient's condition on a scale of functional status after COVID-19 (Post-COVID-19 Functional Status , PCFS) [5].

Severity assessment on a standardized scale from 0 to 4 was carried out by the research physician based on the words of patients during personal (visits 1–3) and remote (visit 4) contact.

Alterations in the Nutritional Effects Symptom Scale (Nutritional Impact Symptom NIS).

The checklist includes 12 symptoms and a scale of the severity of each symptom from 1 to 4. Thus, the minimum total checklist score is 12 (in the absence of symptoms), the maximum is 48. To assess changes for each patient at each visit (visits 1– 4) the sum of the symptom scores was calculated as the difference between the actual and the minimum score. Additionally, for each visit, the variance of the value scale >1 was calculated.

The study assessed primary and secondary endpoints.

Description of medical intervention

The study group received additional oral nutritional support by sipping Nutridrink ONS 200 ml, 2 vials (400 ml) daily for 28 days from the inclusion date. In the hospital setting, additional oral nutritional support was added to the patient's standard therapeutic diet. After discharge from the hospital, the patient received at his disposal the required amount of Nutridrink ONS 200 ml at the rate of 400 ml/ day and took it in addition to his usual and habitual diet. Nutridrink ONS 200 ml was recommended to be taken between main meals.

In the other group, patients received a standard hospital diet and, upon discharge from the hospital, a normal habitual diet.

Study Outcomes

The main outcome of the study:

assessment of the quality of life "Component of physical health" according to the SF-36 questionnaire;

assessment of the quality of life "Component of mental health" according to the SF-36 questionnaire;

assessment of the quality of life "General quality of life" according to the SF-36 questionnaire;

change in hand force (decanewton) between visits 3 and 1.

Additional research outcomes:

the length (days) of the patient's stay on respiratory support or in the intensive care unit between visit 2 and visit 1;

total duration (days) of patient hospitalization up to visit 3;

the severity of the patient's condition on the post-COVID-19 functional status scale (PCFS) at each visit;

Nutritional Influence Symptom Scale (NIS) score at each visit.

The "All-cause mortality" endpoint could not be analyzed during the study because patients who were deteriorating and requiring mechanical ventilation with an inability to feed themselves were not included or were excluded from the study. According to the information received from the investigators, since the beginning of the observation, 6 patients died for various reasons, who had previously given their informed consent to participate in the study, but were excluded due to a deterioration in their condition: 3 patients from the study group and 3 patients from the control group. groups. Additionally, according to the results of the study, the frequency of adverse events and adverse reactions was analyzed.

Subgroup Analysis

For each efficacy parameter, analyzes were performed for the entire population, male/female, and younger than 55/55 and older subgroups.

Ethical review

The study was approved by the decision of the Independent Interdisciplinary Committee on Ethical Review of Clinical Research (Extract from the minutes of the meeting No. 11 of June 19, 2020).

A patient information sheet and informed consent were automatically created when a new patient was enrolled. The document contains the initial data, including the indication of the date, time and IP from which the signing took place. The document was signed either with a simple electronic signature with two-factor authentication on the screen of a mobile device, or on paper, followed by scanning or photographing the signed document.

Statistical analysis

The sample size was not previously calculated. Statistical analysis was carried out under the supervision of a responsible biostatistician in accordance with applicable requirements using suitable statistical analysis software.

Statistical analysis included data from all patients for whom there is an assessment of the effects of the intervention for at least one visit. The missing data were filled by the method of separate substitutions using the LOCF approach (last observation carried forward) on the assumption that positive dynamics of changes is expected for indicators.

The null hypothesis reflected the absence of differences between the groups, the alternative one reflected the presence of differences in the indicator between the intervention and control groups.

To analyze data on the SF-36 quality of life questionnaire and its components, a two-way analysis of variance was performed. In addition, pairwise comparisons were additionally made across group visits using the appropriate variant of Student's t-test.

For the remaining variables, the data of which were not considered as continuous, the use of non-parametric tests was envisaged (the Wilcoxon test for comparing the dynamics of changes within groups and the Mann-Whitney test for analyzing values between groups at visits). In addition, a Mann-Whitney test for differences between Visits 1 and 4 was performed to evaluate the change in patient severity on the Functional Status Scale after

COVID-19 infection and the change in the Nutritional Exposure Symptom Index for malnourished patients.

For each variable, subgroup analyzes were performed by sex and age (<55 and ≥55 years). The analysis in subgroups was carried out using the same method as in the main population.

The study used a two-sided significance level of 0.05.

results

Objects (participants) of the study

The study included 102 people infected with COVID -19 who were hospitalized in intensive care units or receiving respiratory oxygen support in the infection wards of research centers according to the inclusion/exclusion criteria. For reasons related to COVID-19 and concomitant diseases, 6 deaths were recorded among patients who had previously given their informed consent to participate in the study, but were excluded before the start of observations due to the deterioration of their health status: 3 patients from the study group and 3 patients from the control group.

After assessing the quality of filling in the CRF, 105 people remained under observation.

The change in muscle strength, measured by carpal dynamometry, was statistically significantly different in the control (Δ4.01±1.15 daN) and research (Δ6.1±2.06 daN) groups (p<0.0001).

Analysis of additional disease outcomes also revealed statistically significant differences between the groups. Thus, the timing of respiratory support was significantly lower in the study group — 6.7±1.30 versus 8.14±1.52 days in the control group (p<0.0001). In the group with additional nutritional support, the duration of hospitalization was also statistically significantly reduced. In the control group, hospitalization lasted an average of 16.47±2.93 days, while in the research group it was 13.16±2.69 (p<0.0001).

Additional research results

When analyzing the main outcomes of the study in subgroups separated by gender, statistically significant differences were obtained between the control and study groups at visits 3 and 4 in the subgroup of men in the physical component of the SF-36 quality of life scale. At visit 3 in the control group, participants scored 42.8±2.96 points, in the research group — 44.20±3.62 points (p=0.037), and at visit 4 — 45.39±3.38 and 47, 80±5.14 points, respectively (p=0.007).

When analyzing the total score on the SF-36 quality of life scale and its psychological component, no statistically significant difference was obtained between the groups in the subgroups of men and women.

The change in hand force also differed statistically significantly between the two groups in the male and female subgroups. Muscle strength measured by carpal dynamometry in the subgroup of men in the control group was Δ4.06±1.19 daN , while in the study group it was Δ5.98±1.95 daN (p<0.0001). In the subgroup of women, the index of hand force in the control group was Δ3.94±1.11 daN versus Δ6.27±2.23 daN in the study group (p<0.0001).

In the analysis of additional outcomes of the study in the subgroups of men and women, a statistically significant reduction in the duration of respiratory support and the duration of hospitalization was obtained in the group receiving additional nutritional support. Thus, in the subgroup of men, the terms of respiratory support in the control group were 8.12±1.66 days, in the research group — 6.68±1.42 (p<0.0001), and the terms of hospitalization in the control and research groups were 16 .58±3.05 and 13.11±2.70 days, respectively (p<0.0001). In the subgroup of women, the duration of respiratory support in the control group was 8.17±1.34 days, in the research group - 6.72±1.13 (p<0.0001), and the duration of hospitalization was 16.31±2.79 and 13 .22±2.71 days, respectively (p<0.0001).

Assessment of the physical component of the SF-36 quality of life scale showed a statistically significant difference between the control and study groups at visits 3 and 4 in the subgroup of people younger than 55 years. At visit 3 in the control group, this indicator was 42.39±2.98 points, and in the research group it was 44.34±3.59 (p=0.010). At visit 4, these indicators in the control and study groups were 45.05±3.51 and 48.08±5.10 points, respectively (p=0.003).

For other indicators of the SF-36 quality of life scale in subgroups of people older than and younger than 55 years, no statistically significant differences were obtained between the control and study groups (Table 4).

The change in muscle strength, measured by the method of carpal dynamometry, significantly differed between the control and study groups in subgroups of people older than and younger than 55 years. Thus, in the subgroup of persons younger than 55 years, the change in hand force in the control group averaged Δ3.88 ± 0.95 daN , while this indicator was statistically significantly higher in the study group - an average of Δ6.04 ± 2.13 daN ($p < 0.0001$). In the subgroup of people ≥55 years old, the rate of change in muscle strength in the control and study groups was Δ4.13±1.30 and Δ6.16±2.01 daN , respectively ($p<0.0001$).

When evaluating additional outcomes in subgroups of people older than and younger than 55 years, statistically significant differences were obtained between the two groups. Thus, in the subgroup of people under 55 years of age, the terms of respiratory support in the control group were 7.93±1.26 days, and in the study group — 6.78±1.36 days ($p=0.0001769$), hospitalization terms — 16, 8±3.01 and 13.33±2.72 days, respectively ($p<0.0001$). In the subgroup of persons ≥55 years of age, the duration of respiratory support in the control group was 8.33 ± 1.71 days, and in the study group - 6.6 ± 1.25 days ($p < 0.0001$), and the duration of hospitalization was 16.17 ±2.86 and 12.98±2.68 days, respectively ($p<0.0001$).

Adverse events

Patients in both groups experienced loss of taste or smell, nausea, diarrhea, pain, shortness of breath, and weakness, which did not differ between groups. Thus, during the study, no serious side effects were observed that could be attributed specifically to the study product.

According to information received from the investigators, since the start of observation for reasons related to COVID-19 and comorbidities, there have been 6 deaths among patients who had previously given their informed consent to participate in the study, but were excluded before the start of observation due to deterioration health: 3 patients from the study group and 3 patients from the control group. None of the deaths were related to the study product.

The study product was expected to be safe when used in patients infected with COVID-19, at a level that is fully consistent with a dietary supplement.

Discussion

Summary of the main result of the study

This study has shown the efficacy of supplemental oral nutritional support in relation to the impact on health recovery in patients with novel coronavirus infection. The results of the study indicate an increase in the rehabilitation potential, a decrease in dependence on oxygen support and a decrease in the time the patient stays in the hospital.

Discussion of the main result of the study

Coronavirus infection caused by SARS-CoV-2 can lead to the development of interstitial viral pneumonia (viral diffuse alveolar damage with microangiopathy), in 3–4% of patients the development of acute respiratory distress syndrome has been reported. Some patients develop hypercoagulable syndrome with thrombosis and thromboembolism, other organs and systems are also affected (central nervous system, myocardium, kidneys, liver, gastrointestinal tract, endocrine and immune systems), sepsis and septic shock may develop, which as a result may result in the development of multiple organ failure and death [1, 2, 6].

Damage to the lungs often leads to the development of a temporary dependence on oxygen support to ensure normal blood saturation. Oxygen support is more required for patients with a more severe course of coronavirus infection. The immobilization that accompanies patients on oxygen support, in turn, can lead to a decrease in muscle function and sarcopenia [7]. A normal body mass index does not always reflect muscle loss. Lean body weight and muscle functionality are an important condition for a good rehabilitation and recovery of the patient, including after a new coronavirus infection.

For such patients, adequate nutritional support is essential to avoid the development of protein - energy malnutrition, which will lead to an even more pronounced decrease in muscle mass and worse outcomes. It is known that the more severe the degree of malnutrition, the worse the prognosis in a patient with a new coronavirus infection [6].

The ESPEN guidelines for providing nutritional support to patients with SARS-CoV-2 dictate that oral nutritional support should be used whenever possible when the patient's needs cannot be met by adjusting the normal diet. At the same time, it should provide at least 400 kcal and at least 30 g of protein, and the effect should be evaluated no earlier than after 1 month. According to these recommendations, protein-energy malnutrition should be prevented or treated with oral nutritional support, which is absolutely applicable to patients with a new coronavirus infection COVID-19.

Nutritional therapy should be started as early as possible after hospitalization, within 24–48 hours, on an individualized basis. It should also be remembered that increasing the amount of energy and protein should be gradual, especially in polymorbid and elderly patients, in order to prevent refeeding syndrome. Oral nutritional support should be used as an alternative to regular meals or as a supplement to regular meals to achieve coverage of the patient's essential energy, protein, vitamins and micronutrient needs. If the patient's adherence to food intake is reduced, then constant monitoring of its intake (for example, once a week) should be carried out to correct the diet and include oral nutritional support in therapy. It is necessary to continue nutritional therapy after discharge from the hospital according to an individualized plan using oral nutritional support. This is especially important because patients have additional risk factors for malnutrition due to the severity of the disease requiring hospital treatment. These risk factors may worsen the manifestation of protein - energy malnutrition even after discharge from the hospital [3].

In designing our study, we identified the need for supplemental nutritional support in all patients who are dependent on oxygen support and without a reduction in their usual diet. Control over the intake of a sufficient amount of ordinary food was carried out by the "quarter plate" method. The study included only those patients who took at least 60% of their usual diet. At the same time, we regarded all patients with respiratory support as patients at high risk of malnutrition according to the NRS-2002 scale (>2 points) [8].

A prerequisite for successful rehabilitation is a sufficient amount of muscle mass and its functionality, even during respiratory rehabilitation [9]. As a result of the study, a statistically significant improvement in the physical component of health on the SF-36 scale was obtained, while statistically significant differences were obtained in the subgroups of men and younger patients. Despite this, in all subgroups of patients, a statistically significant increase in muscle strength, measured by carpal dynamometry, was obtained. The SF-36 quality of life score, although validated , has a number of disadvantages, such as difficulty in application and processing, and may not take into account important clinical changes. It is possible that there were no significant differences in other indicators of psychological status and the overall score on the SF-36 quality of life scale, which may also be due to the sample size and the inevitable inaccuracy in interpreting one's own state.

It is also possible that in older patients, in order to experience subjective improvements associated with nutritional intervention, additional oral nutritional support should be given longer than in younger patients. The subjective effect measured by the SF-36 scale for other indicators could manifest itself with an increase in the duration of nutritional support.

The strength of the muscles of the hand is a more adequate marker of muscle function, which is also associated with the provision of proper nutritional support [10], than the subjective scale of quality of life SF-36. In all subgroups, there was an increase in muscle strength measured by carpal dynamometry in the oral nutritional support group.

As a result of improving the nutritional status and maintaining sufficient muscle volume and functionality in patients who received

nutritional support with Nutridrink 200 ml, a statistically significant decrease in the time of oxygen support and the time of the patient's stay in the hospital was obtained.

Literature has shown that malnutrition delays wound healing and increases hospitalization time [11].

When analyzing adverse and side effects between groups, no statistically significant differences were obtained.

Study Limitations

The study had a number of limitations that may have altered the results. The sample used in the study was taken randomly, without statistical calculation. At the same time, it should be noted that by the time of planning the study, we had not found the results of studies on this cohort of patients. This could also lead to the fact that no significant differences were obtained on the SF-36 quality of life scale.

The study did not include any patients on mechanical ventilation, both invasive and non-invasive, but only patients on oxygen support and high-flow oxygen therapy. No analysis was conducted in these subgroups.

Patients did not perform comparisons of laboratory parameters at admission and at discharge. An accurate personalized calculation of energy and protein for each patient was not carried out, but only the method of estimating the amount of standard hospital food eaten was used.

All patients included in the study were regarded as patients with a high risk of developing malnutrition on the NRS-2002 scale of more than 2 points.

Patients older than 69 years were excluded from the study, although this category of patients has an increased sensitivity to adequate nutritional support [12].

Conclusion

Supplemental oral nutritional support given to patients with COVID-19 requiring oxygen support improves rehabilitation potential, including by maintaining muscle mass and muscle function, indirectly confirmed by the study of hand grip strength; reduces the need for oxygen support and hospitalization time. Patients with COVID-19 with additional nutritional support have a faster recovery process.

It is necessary to conduct additional studies with an increase in the sample and the inclusion of elderly patients in the study.

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