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N-acetylcysteine as a part of complex treatment of moderate COVID-associated pneumonia

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Резюме

The need for safe and effective treatment is becoming increasingly urgent due to the high COVID-19 mortality rates observed worldwide. The choice of drug products for COVID-19 treatment regimens is based on the efficacy and safety data, the mechanism of action, and potential interactions. N-acetylcysteine's (NAC) pharmacological activity and its potential to suppress the progression of COVID-19 make it a promising therapeutic agent for COVID-19. **Aim** of the study was to evaluate the efficacy of NAC in the complex treatment of moderate COVID-associated pneumonia. **Methods.** The study included adult patients (n = 46) with moderate COVID-associated (the 2nd – 3rd degree on CT) pneumonia (age 57 (51; 71) years, body mass index – 30 (27.1; 32.3) kg/m^2, duration of the disease before hospitalization – 7 (6; 8) days, body temperature at the admission – 37.5 (37.1; 37.8) °C). The patients were randomized into two study groups. The 1st group (n = 22) received standard COVID-19 treatment [1]. The 2nd group (n = 24) additionally received NAC 1,200 – 1,500 mg/day intravenously. Treatment with NAC was started together with the standard therapy. **Results.** Our study showed that the inclusion of NAC in the complex treatment of moderate COVID-associated pneumonia led to a statistically significant increase in blood oxygen saturation, oxygenation index, the difference in delta increase in oxygenation index, a quicker reduction in the volume of lung damage, and the difference between the groups in delta reduction of this index. Also, the rate of reduction of C-reactive protein and reduction of the duration of hospitalization in the group of patients who received NAC was statistically significantly more profound than in the standard treatment group.
Conclusion. The study confirmed the effectiveness of NAC as a part of the complex treatment of moderate COVID-associated pneumonia.
Key words: COVID-associated pneumonia, treatment, N-acetylcysteine.
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Опыт применения N-ацетилцистеина в комплексном лечении среднетяжелой COVID-ассоциированной пневмонии

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Abstract

Потребность в безопасном и эффективном лечении COVID-19 становится все более актуальной из-за высоких показателей смертности в мире. Выбор лекарственных средств (ЛС), входящих в схемы лечения COVID-19, основан на данных об их эффективности и безопасности, механизме их действия и потенциальных взаимодействий. Фармакологическая активность N-ацетилцистеина (NAC) и потенциально возможное действие в подавлении прогрессирования COVID-19 делают его многообещающим терапевтическим средством при COVID-19. **Целью** исследования явилась оценка эффективности NAC в комплексном лечении среднетяжелой COVID-ассоциированной пневмонии. **Материалы и методы.** В исследование включены взрослые пациенты (n = 46; возраст – 57 (51; 71) лет, индекс массы тела – 30 (27,1; 32,3) кг / м^2, продолжительность заболевания до госпитализации – 7 (6; 8) дней, температура тела на момент госпитализации – 37,5 (37,1; 37,8) °C) со среднетяжелой (II–III степенью по данным компьютерной томографии) COVID-ассоциированной пневмонией. Случайным образом сформированы 2 группы: пациенты 1-й группы (n = 22) получали стандартное лечение COVID-19; больные 2-й (n = 24) группы

дополнительно получали NAC 1 200–1 500 мг в сутки внутривенно капельно. NAC назначался одновременно с началом стандартной терапии. **Результаты.** По данным исследования показано, что при включении в комплексное лечение среднетяжелой COVID-ассоциированной пневмонии NAC статистически значимо повысились уровень насыщения крови кислородом, индекс оксигенации, различия разности дельта (Δ), индекс оксигенации, скорость снижения объема поражения легких и межгрупповое различие Δ уменьшения данного показателя. Также отмечены статистически значимо более интенсивная, чем в группе стандартного лечения, скорость снижения уровня С-реактивного белка и сокращение продолжительности госпитализации в группе пациентов, получавших NAC. **Заключение.** Результаты проведенного исследования свидетельствуют об эффективности включения NAC в комплексное лечение среднетяжелой COVID-ассоциированной пневмонии.

Ключевые слова: COVID-ассоциированная пневмония, лечение, N-ацетилцистеин.

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The main clinical manifestations of the novel COVID-19 coronavirus infection are viral lung damage (viral pneumonia) and acute respiratory distress syndrome (ARDS) leading to acute respiratory failure (RF) [1]. Viral pneumonia and ARDS usually develop during the later stages of the infection, between the 5th and the 10th day after the onset of the symptoms [2].

COVID-19 lung damage is related to the immune system activating uncontrollably, similarly to the activation that can be observed in the case of hemophagocytic lymphohistiocytosis [3] or sepsis cytokine release syndrome [4]. In severe COVID-19 cases, a "cytokine storm" [5] results from T-cell depletion, rising (IL)-6, -10, interleukin levels, and tumor necrosis factor-a (TNF-a), and causes significant damage to the lung tissue [6]. Cytokines such as IL-1β, IL-8, IL-12, interferon-γ-inducible protein (IP10), macrophage inflammatory protein 1A (MIP1A) and monocyte chemoattractant protein-1 (MCP1) are also involved in the pathogenic cascade of the disease.

It has been established that binding the SARS-CoV-2 virus with toll-like receptors induces the release of pro-IL-1β, which breaks down into the active mature IL-1β that mediates lung inflammation before fibrosis [7, 8].

Increased IL-6 – the main cytokine causing inflammation in the case of COVID-19–contents enable the development of mitochondrial oxidative stress as well as an imbalance in the "oxidants/antioxidants" system. The reduction-oxidation imbalance in the alveolar epithelium cells, their apoptosis, the increased inflammation and, consequently, gaseous exchange disruption also cause locally increased levels of angiotensin-2 after deactivation of the angiotensin-converting enzyme 2 (ACE-2) by the SARS-CoV-2 virus [9, 10].

Oxidants activate transcription factors and cell signal transduction. They initiate the expression of proinflammatory genes, which leads to a severe lung tissue inflammation and systemic inflammation [11, 12]. The endogenous failure of the main intracellular antioxidant – glutathione – and increased glutathione reductase may be the bases for serious forms of and death from COVID-19 [9, 10]. According to literature, reducing oxidative stress may lead to lesser lung damage [13].

Safe and effective treatment is needed increasingly urgently given the high COVID-19 mortality rates observed around the world. The medical therapy choice for COVID-19 treatment regimens is based on their effectiveness and safety data, mechanism of action and potential interactions. Not only is the medical therapy capacity to strengthen the human body's physiological response to inflammation considered (their potential contributes to the homeostasis of clinical markers of inflammation), but also their ability to act in the early stages of the disease. The pharmacological activity of N-Acetyl-cysteine (NAC) and its possible action suppressing the progression of COVID-19 make it a very promising therapy against COVID-19 [14].

NAC suppresses oxidative stress, acting as a cell-permeable aminoacid antecedent for glutathione and breaking disulfide bonds within ACE-2 – a cellular receptor for SARS-CoV-2 [12]. In addition, NAC suppresses the formation of proinflammatory cytokines such as IL-8 and TNF-α [15]. According to numerous studies, NAC can be used successfully in various lung diseases [16, 17]. The protective effects of NAC in ARDS have been established by several experimental and clinical studies [18–21].

Thanks to its mechanism of action which increases glutathione, improves T-lymphocyte response and modulates the inflammation, NAC may be considered a potential MD to cure COVID-19 [6, 22]. Taking systemic inflammation into account, NAC may be used as a protection against endothelial damage caused by oxidative stress, which activates a high thrombotic subtype of disseminated intravascular coagulation syndrome observed with COVID-19 [23].

The goal of the present study was to assess the effectiveness of NAC as part of the complex treatment of moderate COVID-associated pneumonia.

Materials and techniques

The study included adult patients (n = 46; median age: 57 [51; 71] years; body mass index [BMI]: 30 [27.1; 32.3] kg/m^2; duration of disease before hospitalization: 7 [6; 8] days) with moderate COVID-associated pneumonia (2nd – 3rd degree according to computerized tomography – CT-data). The patients were being treated in a COVID-hospital within the University clinical hospital No.4 of the Federal State autonomous higher education facility I.M.Sechenov First Moscow State Medical University Healthcare Ministry of Russia (Sechenov University). The patients' body temperature upon admission was 37.5 (37.1; 37.8) °C.

The patients were randomized into 2 study groups: the patients in the 1st group ($n = 22$; control) were given standard treatment [1], i.e. hydroxychloroquine 200 mg (800 mg/day for 1 day); 400 mg/day from the 2nd to the 7th day; azithromycin 500 mg/day for 5 days; enoxaparin 0,4 mg/day subcutaneously; dexamethasone 8–12 mg/day; and with C-reactive protein (CRP) levels ⩾ 60 mg/L, tocilizumab 400 mg/day. The patients in the 2nd group ($n = 24$) were given, in addition, NAC (Fluimucil) (*Zambon Switzerland Ltd*, Switzerland) 1,200–1,500 mg/day intravenously with 8 – 10 drops. The NAC treatment started at the same time as the standard treatment.

The presence of COVID-19 was confirmed based on the results of lab studies (SARS-CoV-2 virus RNA smear from the upper respiratory tract by polymerase chain reaction) and/or clinical and radiological study (presence of characteristic clinical picture and characteristic signs of COVID-19 polysegmental viral pneumonia). To establish the diagnosis and determine the treatment for COVID-associated pneumonia, the 9th version of the Temporary Recommendations for Prevention, Diagnosis and Treatment of COVID-19 of the Ministry of Health of the Russian Federation was followed.

Criteria for inclusion in the study:

- Body temperature > 38 °C;
- Respiratory rate (RR) > 22/minute;
- Dyspnea during physical exertion;
- Typical CT changes for a viral lesion (average lesion volume [25–75%], i.e. 2nd – 3rd degree according to CT data);
- Blood oxygen saturation (SpO_2) < 95%;
- CRP contents in blood serum > 10 mg/L.

Criteria for exclusion from the study:

- Non-conformity with inclusion criteria;
- Patient failure to comply with the protocol;
- Patient refusal to participate in the study.

The following demographic indicators were assessed in all patients: BMI; alternative oxygen saturation index (SpO_2/FiO_2); disease symptoms; objective, laboratory (complete blood count, CRP, coagulogram) and instrumental (rib cage CT) data research, comorbidities. The blood oxygen saturation was measured with pulse oximetry to identify RF and assess the severity of hypoxemia.

RF was determined according to a severity classification based on pulse oximetry indicators (SpO_2). BMI was used to assess the patients' nutritional status, calculated with the generally accepted formula:

$$BMI = \text{body mass (kg)}/\text{height (m)}^2.$$

Oxygen saturation SpO_2/FiO_2 (the ratio of blood oxygen saturation to the fraction of inhaled oxygen) was calculated according to the formula:

$$SpO_2 / 21 + 3 \times \text{oxygen flow rate [24]}.$$

Pulse oximetry was measured with a MD300C series pulse oximeter.

Lung CT were carried out on a spiral computed tomography Aquillion TSX-101A (Toshiba Medical Medical Systems, slice thickness: 1 mm, pitch: 1.5) upon admission and 10 days after the treatment started.

The quantity of CRP in the blood serum was calculated using the latex immunoturbidimetric method (Beckman Coulter series AU analyzer using CRP Latex reagents, Russia) on the 1st, 3rd, and 10th days of observation.

The levels of fibrinogen was determined in blood plasma ("Astra" analyzer ACK 2-01 using the NGO Renam sets), the levels of D-dimers by micro-latex agglutination with photometric registration of the reaction (immunoturbidimetry) using sets of the ReDimer-latex test (Renam NGO).

Statistical data was processed with the IBM SPSS Statistics Version 22 package of applied programs (license 20160413-1). Descriptive statistics of the original quantitative traits are presented by median and interquartile range. In addition to the original traits, the delta (D) changes (before and after treatment difference) of each indicator were analyzed as well as the intensity of the indicator change rate (D changes relative to baseline, %). Descriptive statistics of delta and change rate are represented by mean and standard deviation. The comparison of 2 independent samples (experimental and control groups) in quantitative terms was carried out with the Mann–Whitney test (U), depending on (before/after treatment) the Wilcoxon criteria for related samples (W). The comparison of 3 independent samples in quantitative terms (at different times during the study) was carried out using the Friedman test, and the Nemenyi post-hoc test for retrospective comparison. The differences in patient hospitalization lengths (number of bed-days in the hospital) of the 2 groups were assessed with the Kaplan–Meier technique and Taron–Wehr test.

Results

The studied groups were comparable for all indicators under consideration, i.e. RR ($p = 0,11$) 24 (24; 24) and 24 (22; 25) per minute respectively, heart rate (HR) ($p = 0.11$) 89 (85; 100) and 88 (82; 100) per minute, SpO_2 level ($p = 0.42$) 92,5 (92; 93) and 93 (92; 95) %, SpO_2/FiO_2 ($p = 0.39$) 251 (247; 266) and 251 (248; 272), CRP concentration ($p = 0.08$) 80.5 (57; 96) and 54 (28; 91.5) mg/L and fibrinogen level 5.6 (4.8; 6.1) and 5.1 (4.4; 5.7) g/L respectively. According to the rib cage CT, the volumes of lung damage were 45.5 (44.5; 50) and 39 (35; 52) % respectively ($p = 0.06$); table 1.

Statistically significant changes were established for all indicators under consideration as a result of treatment in both groups, with the exception of the leukocyte level.

However, it should be noted that during the analysis, different values were observed between the groups for a series of indicators (table 2).

The SpO_2 level of every patient in the standard treatment group increased on average by 3.0 ±1.5% from the baseline, from 93 (92; 95) to 96 (96; 97) % (statistically significant change: $p < 0,001$), at the same time, the same indicator in the NAC group grew on average by 4.6 ± 1.1% – from 92.5 (92; 93) to 97 (96; 98) % ($p < 0,001$). The difference between the increase rates was statistically significant ($p = 0,001$). As a result, the SpO_2 indicator became statistically significantly higher after treatment in

Table 1
Initial clinical characteristics of the study subjects
Таблица 1
Исходная клиническая характеристика обследуемых пациентов

Indicators	Whole sample		1st group (standard treatment)		2nd group (standard treatment + NAC)		*p****
	n = 46		*n* = 22		*n* = 24		
	M ± *SD**	*Me* (Q1; Q3)**	*M* ± *SD*	*Me* (Q1; Q3)	*M* ± *SD*	*Me* (Q1; Q3)	
Age, years	57.90 ± 12.73	57 (51; 71)	54.5 ± 12.1	57 (46; 58)	61 ± 12,8	66 (52; 71)	0.08
BMI, kg/m^2	29.50 ± 3.01	30 (27.1; 32.3)	28.60 ± 3.62	28.8 (26.4; 31.2)	30.4 ± 2	31.2 (28.5; 32.3)	0.07
Duration of disease before hospitalization, days	7.30 ± 1.64	7 (6; 8)	7.00 ± 1.51	7 (6; 8)	7.5 ± 1.7	7.5 (6; 9)	0.37
Duration of fever, days	9.30 ± 1.87	9 (7; 10)	9.20 ± 2.38	9 (7; 10)	9.3 ± 1.3	9.5 (9; 10)	0.28
Body temperature, C	37.50 ± 0.43	37.5 (37.1; 37.8)	37.40 ± 0.37	37.4 (37.3; 37.5)	37.6 ± 0.5	37.7 (37.1; 38)	0.08
Respiratory rate per minute	23.70 ± 1.25	24 (23; 24)	23.20 ± 1.62	24 (22; 25)	24.1 ± 0.5	24 (24; 24)	0.11
Heart rate per minute	89.80 ± 7.94	88 (82; 100)	88.70 ± 8.63	88 (82; 100)	90.8 ± 7.3	89 (85; 100)	0.48
SpO_2, %	92.80 ± 1.01	92.5 (92; 93)	93.10 ± 1.32	93 (92; 95)	92.6 ± 0.5	92.5 (92; 93)	0.42
SpO_2/FiO_2	253.0 ± 19.4	251 (248; 272)	254.0 ± 20.5	251 (248; 272)	254.0 ± 18.8	251 (247; 266)	0.93
Leukocytes, x 10^9/L	6,5 ± 2,8	6.0 (4.3; 7.5)	6.5 ± 2.1	6.3 (5.1; 8.3)	6.5 ± 3.4	5.9 (3.6; 7.5)	0.54
Thrombocytes, x 10^9/L	213.90 ± 78.39	189 (150; 270)	197.80 ± 40.54	189 (177; 242)	228.7 ± 100.2	220.5 (127; 280)	0.72
Lymphocytes, x 10^9/L	0.90 ± 0.37	0.8 (0.7; 0.9)	0.80 ± 0.11	0.8 (0.7; 0.9)	1.0 ± 0.5	0.8 (0.7; 0.8)	0.66
Lymphocytes, %	15.3 ± 6.1	15.6 (11.9; 21.8)	16.20 ± 4.18	16.4 (12; 20.3)	14.4 ± 7.4	13.1 (11; 23.1)	0.43
CRP, mg/L	66.70 ± 27.85	74 (42; 96)	59.30 ± 27.85	54 (28; 91.5)	73.50 ± 24.25	80.5 (57; 96)	0.08
Fibrinogen, g/L	5.4 ± 1.37	5.4 (4.4; 5.7)	5.20 ± 1.41	5.1 (4.4; 5.7)	5.6 ± 1.4	5.6 (4.8; 6.1)	0.07
D-dimers	0.6 ± 0.33	0.6 (0.4; 0.9)	0.50 ± 0.32	0.6 (0.2; 0.7)	0.7 ± 0.3	0.8 (0.6; 0.9)	0.07
CT, % lung damage	44 ± 6.46	45 (39; 50)	41.90 ± 8.23	39 (35; 52)	46.0 ± 3.4	45.5 (44.5; 50)	0.06

Note: *, mean and standard deviation; **, median and interquartile range; ***, the statistical significance of the differences between the experimental and control groups. The Mann–Whitney test was applied.

Примечание: NAC – N-ацетилцистеин; ИМТ – индекс массы тела; SpO_2 – насыщение крови кислородом; ЧДД – частота дыхательных движений; ЧСС – частота сердечных сокращений; SpO_2 – насыщение крови кислородом; FiO_2 – фракция кислорода, поступающего в организм при вдохе; СРБ – С-реактивный белок; КТ – компьютерная томография; * – среднее и стандартное отклонение; ** – медиана и интерквартильный размах; *** – статистическая значимость различий между экспериментальной и контрольной группой. Применялся критерий Манна–Уитни.

Table 2
Values of the analyzed indicators after treatment
Таблица 2
Значения анализируемых показателей после лечения

Indicators	1st group (standard treatment)		2nd group (standard treatment + NAC)		*p****
	n = 22		*n* = 24		
	M ± *SD**	*Me* (Q1; Q3)**	*M* ± *SD*	*Me* (Q1; Q3)	
Body temperature, °C	36.60 ± 0.15	36.6 (36.4; 36.7)	36.5 ± 0.1	36.5 (36.4; 36.5)	0.07
Respiratory rate per minute	18.40 ± 0.73	18 (18; 18)	18.8 ± 0.9	18.5 (18; 20)	0.06
Heart rate per minute	76.70 ± 8.14	76 (74; 78)	80.2 ± 6	80 (75; 84)	0.08
SpO_2, %	96.10 ± 1.11	96 (96; 97)	97.0 ± 0.9	97 (96; 98)	0.02
SpO_2/FiO_2	398.0 ± 57.8	401 (331; 451)	429.0 ± 58.0	459 (399; 476)	0.03
Leukocytes, x 10^9/L	7.60 ± 2.32	6.7 (6.1; 9.9)	8.4 ± 3.0	8.4 (5.2; 9.5)	0.72
Thrombocytes, x 10^9/L	283.50 ± 105.64	264 (191; 375)	308.5 ± 70.7	310.5 (239; 353)	0.16
Lymphocytes, x 10^9/L	1.60 ± 0.52	1.5 (1.1; 1.8)	1.5 ± 0.3	1.4 (1.4; 1.8)	0.86
Lymphocytes, %	20.20 ± 4.52	21.2 (16.5; 23.3)	22.6 ± 14.2	16.8 (14.6; 19.6)	0.06
CT, % lung damage	35.00 ± 7.42	35 (30; 45)	31.7 ± 4.3	35 (27.5; 35)	0.17

Note: *, mean and standard deviation; **, median and interquantile range; ***, the statistical significance of the differences between the experimental and control groups. The Mann–Whitney test was applied.

Примечание: * – среднее и стандартное отклонение; ** – медиана и интерквартильный размах; *** – статистическая значимость различий между экспериментальной и контрольной группой. Применялся критерий Манна–Уитни.

patients of the NAC group than the control group – 97 (96; 98) % vs 96 (96; 97) % ($p = 0.02$).

The oxygenation index of the NAC group patients increased on average by 88 ±16.6% from the baseline, from 251 (247; 266) to 459 (399; 476) % ($p < 0.001$), and by 70 ± 28.9% in the group with standard treatment, from 251 (248; 272) to 401 (331; 451) % ($p < 0.001$), the difference between the increase rates was statistically significant ($p = 0.04$). After treatment, the oxygenation index of patients in the NAC group was statistically significantly higher than the control group: 59 (399; 476) *vs* 401 (331; 451) ($p = 0.03$); figure 1.

The delta of the oxygenation index growth for patients in the NAC group was statistically significantly higher than that of patients given standard treatment: 175 ± 54.3 *vs* 144 ± 54.4 (p = 0.02); figure 2.

According to CT data, the volume of lung damage before treatment was 45.5 (44.5; 50) % for patients in the NAC group and 39 (35; 52) % for patients of the standard treatment group. As a result of treatment, this indicator reached 35 (27.5; 36) % in the 1st group (statistically significant reduction compared to the pre-treatment level $p < 0.001$) and 35 (30; 45) % – in the 2nd group ($p < 0.001$) (figure 3). The average change rate for this indicator (difference before and after treatment for this indicator [% of the values of the indicator before treatment]) for the patients of the groups under consideration were 31.0 ± 8.3 and 17.0 ± 6.2% respectively; the differences are statistically significant ($p < 0.001$); figure 3.

The statistically significant difference of the indicator Δ lung damage volume reduction according to CT is note-

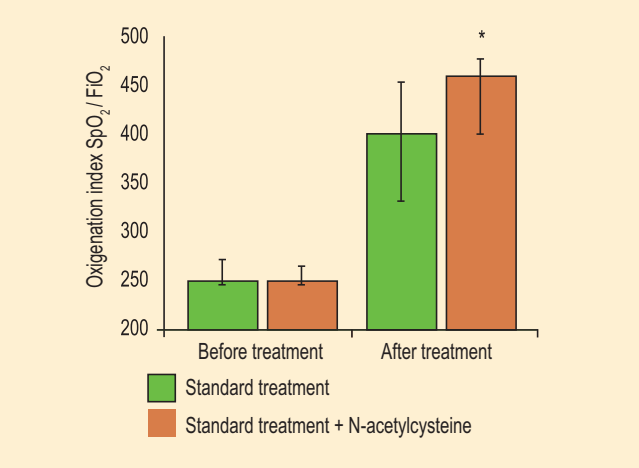

Figure 1. SpO_2/FiO_2 oxygenation index before and after treatment in the study groups, MD (IQR)
Note: *, the difference versus the standard treatment group was statistically significant ($p \leq 0.05$).
Рис. 1. Индекс оксигенации SpO_2 / FiO_2 до и после лечения в группах исследования; MD (IQR)
Примечание: SpO_2 – насыщение крови кислородом; FiO_2 – фракция кислорода, поступающего в организм при вдохе; IQR (InterQuartile range) – интерквартильный интервал; * – статистически значимые различия с группой стандартного лечения на уровне p ⩽ 0,05.

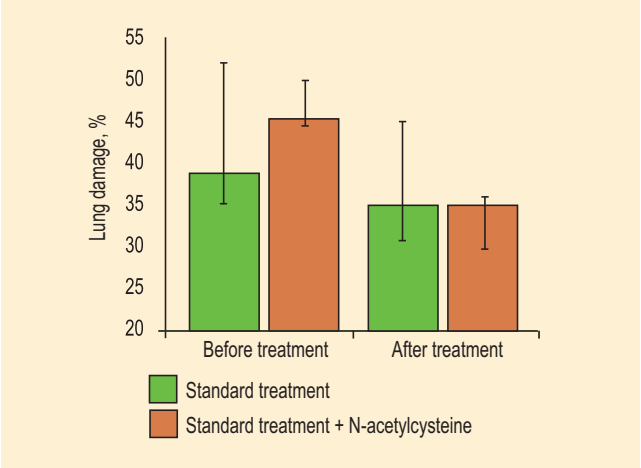

Figure 3. Percentage of lung damage (showed by computed tomography) before and after treatment in the study groups; MD (IQR)
Note: IQR, InterQuartile range.
Рис. 3. Процент поражения легких (по данным компьютерной томографии) до и после лечения в группах исследования; MD (IQR)
Примечание: IQR (InterQuartile range) – интерквартильный интервал.

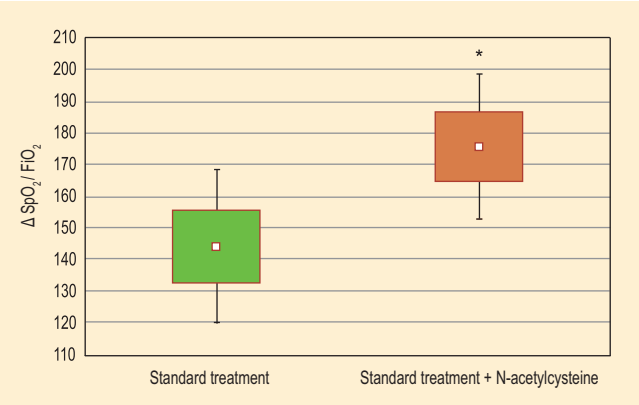

Figure 2. Delta of SpO_2/FiO_2 ratio before and after treatment in the study groups; M (SE); 95% CI
Note: IQR, InterQuartile range; *, the difference versus the standard treatment group was statistically significant ($p \leq 0.05$).
Рис. 2. Дельта SpO_2 / FiO_2 до и после лечения в группах исследования; M (SE); 95%-ный доверительный интервал
Примечание: SpO_2 – насыщение крови кислородом; FiO_2 – фракция кислорода, поступающего в организм при вдохе; * – статистически значимые различия с группой стандартного лечения на уровне $p \leqslant 0,05$.

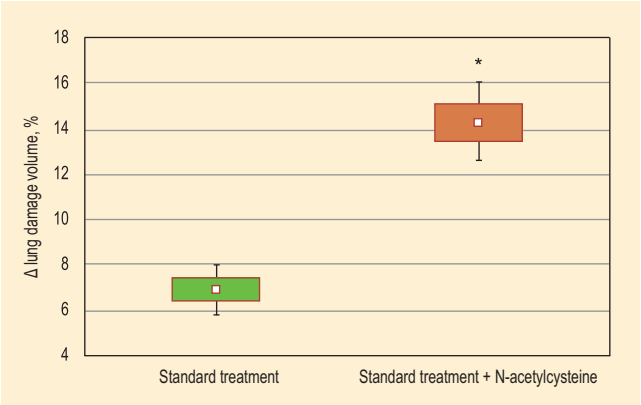

Figure 4. Delta of the lung damage volume (showed by computed tomography) before and after treatment in the study groups; *M* (*SE*); 95% CI
Note: *, the difference against the standard treatment group was statistically significant ($p \leq 0.05$).
Рис. 4. Дельта объема поражения легких (по данным компьютерной томографии) до и после лечения в группах исследования; *M* (*SE*); 95%-ный доверительный интервал
Примечание: * – статистически значимые различия с группой стандартного лечения на уровне $p \leqslant 0,05$.

worthy. The Δ indicator was 14.00 ± 3.94 for patients in the NAC group, at the same time, 6.90 ± 2.56 ($p < 0.001$) for patients who were given standard (figure 4).

The analysis was carried out during the inflammation process based on concentration. On the 3rd day of treatment, only the experimental group showed statistically significant ($p = 0{,}002$) CRP level reductions, which was initially comparable in both groups, from 81 (57; 96) to 44 (40; 57) mg/L. On the 10th day of treatment, a statistically significant CRP level reduction was observed in both study groups: 6 (4; 13) mg/L in the control group (statistically significant reduction compared with the 1st [*vs* < 0.001] and 3rd days [$p < 0.001$]) and 5 (2; 6) mg/L in the experimental group (statistically significant reduction compared to the 1st [*vs* < 0.001] and 3rd [*vs* = 0.002] days). No statistically significant differences in CRP level were noted between the groups in any of the studied time periods, but a statistically significant reduction of CRP level, stronger than in the control group, was observed in the experimental group on the 10th day, compared to the 1st day 90.0 ±10.2% *vs* 82.0 ±13.9% ($p = 0.03$).

The results of the hospitalization duration analysis (number of bed days) showed that adding NAC to the standard treatment led to a statistically significant decrease of the hospitalization duration (*vs* < 0.001). In the group of patients only given standard treatment, the median hospitalization duration was 13 (11; 16) bed-days, versus 11 (10; 12) bed days in the experimental group (figure 5).

Discussion

During treatment, a statistically significant change for all indicators under consideration was observed in both groups, with the exception of the level of leukocytes. However, it should be noted that the analysis results data show differences within the groups in terms of change intensity for a slew of indicators.

In particular, blood oxygen saturation after treatment was statistically significantly higher for patients of the NAC group than for patients of the control group.

Accordingly, after treatment, the oxygenation index of the NAC group patients also became statistically significantly higher than that of the patients given standard treatment, the growth delta of that indicator was statistically significant.

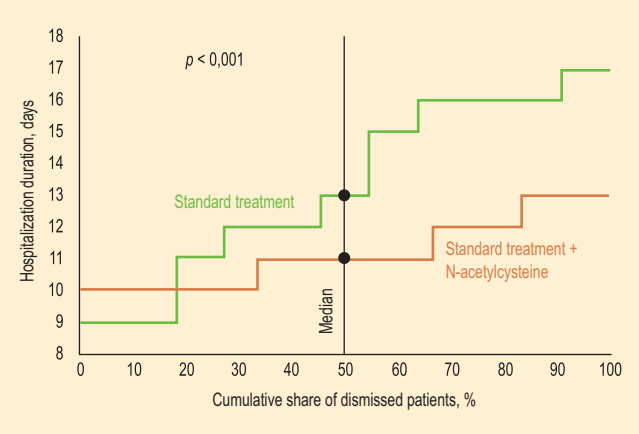

Figure 5. Kaplan–Meier curves of hospitalization duration in the study groups
Рис. 5. Кривые Каплана–Мейера продолжительности госпитализации в группах исследования

A fact that stands out is the nature of the change of volume of lung damage after treatment according to CT data. It was established that the average lung damage volume reduction rate was statistically significantly higher in the group of patients who were also given NAC. In this group, the decrease delta of that indicator was also statistically significant.

No statistically significant difference was observed between the two study groups for CRP levels in any of the time periods under consideration, but the CRP level reduction rate was statistically significantly higher in the NAC group than in the control group.

Analyzing the patient hospitalization times (number of bed-days) showed that adding NAC to standard treatment led to a statistically significant reduction of hospitalization time.

According to the study data, NAC is considered effective in various potential target therapies for the pathophysiology of the SARS-CoV-2 infection. SARS-CoV-2 pathogen factors that may be mediated by NAC are T-lymphocyte depletion, which manifests in the reduction of the quantity of cells and of functional capacities of $CD4^+$- and $CD8^+$-cells; proinflammatory conditions via a higher level of TNF-α, IL-1, IL-18; and the modulation of viral activity as a consequence of the higher glutathione level [20].

According to the results of the randomized controlled study, NAC bonds with glutamine and glycine to form a powerful antioxidant known as glutathione, which counteracts the inflammatory reaction in the case of community-acquired pneumonia [22, 23]. When adding NAC to standard treatment for patients with community-acquired pneumonia, the following were observed: reduction of the concentration of malondialdehyde, superoxide dismutase, TNF-α; increase of general antioxidant activity. The conclusion is that treating pneumonia patients with NAC may reduce oxidative and inflammatory lesions [22]. It was noted that adding NAC led to a lower level of IL-6-dependent CRP in the case of pneumonia caused by the A/H1N1 influenza [25].

The use of NAC enables to decrease the inflammation in the lung tissue. During NAC treatment, peripheral blood contains more neutrophils, which are less present in the respiratory tract tissue, and there is a lower NF-ϰB transcription activity in the respiratory tract cells and a lower concentration of eosinophil cationic protein in the sputum [26, 27].

It is known that NAC prevents the action of the transforming growth factor (TGF)-β1, which enables epithelial-mesenchymal transdifferentiating and induces fibrosis, reduces the activity of TGF-β1-induced production of fibronectin, vascular endothelial granulocytic factor and collagen. NAC also suppresses the phosphorylation of Smad 2/3, prevents the dimerization of TGF-β1 monomers, and inhibits the functioning of TGF-β1-induced reporter gene [28].

In the study carried out by *H.Ibrahim et al.* (2020), NAC was administered to 9 patients with a severe form of COVID-19 and RF. During NAC treatment, clini-

cal improvements were observed: a notable reduction of CRP levels for all patients and of ferritin levels in 9 out of 10 patients. It is anticipated that the NAC action mechanism may contain a blocker to the viral infection and consequent "cytokine storm;" however, further studies in controlled clinical experiments are necessary to confirm this [12].

At the same time, the double-blind randomized placebo-controlled single-center study carried out in Brazil, studied the influence of high doses of NAC on the need for and duration of artificial lung ventilation, cure and duration in intensive care treatment, and mortality. The study showed that administering high doses of NAC did not influence the severity of COVID-19 [29].

Therefore, further studies are necessary to assess the effectiveness of NAC against COVID-19.

Conclusion

It was shown that including NAC in a complex treatment for moderate COVID-associated pneumonia led to a statistically significant increase of the level of SpO_2, of the oxygenation index, of various differences (D) of the increased oxygenation index, the lung damage volume reduction rate, and inter-group difference (D) of the reduction of the given indicator. Statistically significantly stronger CRP reduction rates and reduction of hospitalization duration were also noted in the group of patients also given NAC compared to the control group. The results of the study support the effectiveness of adding NAC to a complex treatment for moderate COVID-associated pneumonia.

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