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The use of an Inhaled Surfactant in Patients With Severe and Extremely Severe new Coronavirus Infection COVID-19 With Concomitant Cardiovascular Pathology

Aim	To study the effectiveness of nebulized surfactant therapy as a part of a multimodality treatment of severe and extremely severe COVID-19 viral pneumonia with concomitant cardiovascular diseases (CVDs).
Material and Methods	This retrospective controlled study analyzed a multimodality treatment of 38 patients with severe and extremely severe COVID-19 viral pneumonia and concomitant CVDs who were administered nebulized surfactant for correction of acute respiratory distress syndrome (ARDS). The control group consisted of 105 patients with severe and extremely severe novel coronavirus infection with concomitant CVDs who were not administered surfactant as a part of the multimodality therapy.
Results	Administration of nebulized surfactant as a part of the multimodality treatment in patients with COVID-19 allowed alleviating the severity of respiratory insufficiency ($p<0.001$), which decreased the death rate of patients with severe and extremely severe COVID-19 and undoubtedly demonstrated the effectiveness of this medicine. The timely multimodality therapy, including nebulized surfactant, improves the course of the disease. Thus, the absence of a possibility for administering nebulized surfactant for more than 4 days was associated with fatal outcomes ($p=0.045$).
Conclusion	Administration of nebulized surfactant as a part of the multimodality treatment of severe and extremely severe COVID-19 and concomitant CVDs increases the survival ($p<0.001$) and reduces the mortality by 46%. The risk factors of an unfavorable outcome of this disease include an age older than 65 ($p=0.020$), a positive polymerase chain reaction test ($p=0.037$), a ferritin concentration at baseline >600 mg/ml ($p<0.001$), and a surfactant treatment duration<4 days ($p=0.045$). Further study of the efficacy of nebulized surfactants as a part of the multimodality therapy is required and should include randomized clinical trials with a large number of patients and the development of distinct criteria for the treatment of ARDS.

Keywords	COVID-19; surfactant; acute respiratory distress syndrome; cardiovascular diseases
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The pandemic of COVID-19 caused by the SARS-CoV-2 virus has affected every corner of the world and continues spreading at a high rate, taking the lives of tens of thousands of people every day. There is no perfectly effective treatment for this virus disease; targeted antiviral medicines do not completely block the virus; herd immunity requires mass vaccination, which is carried out not fast enough and not in all countries of the world. Moreover, various new strains of coronavirus offset the efficacy of existing treatment regimens and necessitate the development of new medicines and therapeutic algorithms.

The pathogenesis of the severe course of COVID-19 is determined by three main aspects: massive lung tissue damage, vascular glycocalyx damage with the development of generalized endotheliitis, and the body's hyperimmune response to the infection [1]. Hormonal therapy, interleukin inhibitors significantly reduce the manifestations of cytokine storm, and the anticoagulant therapy with low-molecular or unfractionated heparin allows controlling to some extent the development of thromboembolic events. The leading mechanism that determines the severity of the disease remains massive lung damage with severe pneumonia and progressive acute respiratory failure called acute respiratory distress syndrome (ARDS).

ARDS was first described in 1967 by Ashbaugh et al. [2] as a lung lesion with acute onset, a severe decrease in blood oxygen saturation (SpO_2), impaired tissue compliance with lung infiltration, without signs of left ventricular failure. In modern literature, ARDS is commonly referred to as non-cardiogenic pulmonary edema, shock or wet lung [3, 4]. In 2012, new ARDS criteria were developed by an international consensus expert panel in Berlin (The Berlin definition of ARDS). According to these criteria, ARDS is a form of acute diffuse lung damage characterized by inflammation with increased vascular permeability and poorly aerated pulmonary parenchyma. The diagnostic criteria of the syndrome include the timing of its development and the obligatory consideration of the positive end-expiratory pressure (PEEP); the determination of pulmonary capillary wedge pressure (PCWP) was eliminated [5]. The Berlin criteria for ARDS include the following:

1) Presence of a time interval: not more than 1 week from the action of a known causative factor to the onset of ARDS symptoms;
2) Consideration of chest imaging data (presence of bilateral opacities, which cannot be explained by effusion, atelectasis, or nodes);
3) respiratory failure (RF), which cannot be explained by heart failure or fluid overload;
4) Presence of oxygenation disorders that determine the severity of ARDS (mild – PaO_2/FiO_2 >200 mm Hg but<300 mm Hg in PEEP or continuous positive airway pressure (CPAP) mode ≥5 cm H2O; moderate – PaO_2/FiO_2 > 100 mm Hg but<200 mm Hg in PEEP or CPAP ≥5 cm H2O, and severe – PaO_2/FiO_2<100 mm Hg in PEEP or CPAP ≥5 cm H2O) [5–9].

The analysis of treatment of 4,457 patients with ARDS showed that mortality in mild, moderate, and severe ARDS was 27%, 32%, and 45%, respectively (p<0.001).

According to several authors, mortality in COVID-19-associated ARDS reaches 45–56% and increases to 61–78% in severe ARDS [6–8].

The effect of the novel coronavirus infection on the lungs is characterized by injuries in type II alveolar cells, which leads to a decrease in the secretion of pulmonary surfactant. The lack of surfactant is the main reason for the severe impairment of ventilation-perfusion function of the lungs due to alveolar collapse with microatelectases [9].

The use of surfactants in the treatment of ARDS has a 30 year clinical history. In Russia, the works by Bautina et al. [10, 11] play the leading role in the development of this treatment strategy. They studied the administration of surfactant-BL in cardiopulmonary bypass surgeries, and actively work with patients with SARS-CoV-2-associated ARDS over the past year.

The positive experience of using surfactants in the combination therapy of severe A/H1N1 influenza in 2009–2010 contributed to the inclusion of this medicine in the National Clinical Guidelines for the Treatment of A/H1N1-Associated Pneumonia [12].

The existing experience of using surfactants, the established pathophysiological mechanism of ARDS in patients with COVID-19, experimental and clinical studies confirming the efficacy of surfactants in viral pneumonia contributed to the prescription of this medicine in the comprehensive therapy of COVID-19 patients.

Objective

Analysis of the efficacy of inhaled surfactant in a combination therapy for patients with severe and extremely severe COVID-19-associated pneumonia and concomitant cardiovascular diseases (CVDs).

Material and methods

This retrospective controlled study included the analysis of the use of an inhaled surfactant as part of combination therapy for patients with severe and extremely severe COVID-19-associated pneumonia and concomitant CVDs. The patients were treated in the departments converted to treat COVID-19 in patients with CVDs.

Inclusion criteria:

1) Presence of pneumonia associated with COVID-19 confirmed by polymerase chain reaction (PCR) test or a specific lung damage picture on computed tomography (CT);
2) Bilateral polysegmental viral lung damage (CT grade 2 or more);
3) Severe and extremely severe disease in accordance with the Russian Temporary Guidelines for the Prevention, Diagnosis, and Treatment of the Novel Coronavirus Disease (COVID-19), version 11;
4) Administration an inhaled surfactant-BL as part of the combination therapy.

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Exclusion criteria:

1) Administration of the inhaled surfactant-BL with violations of the prescribing information;
2) Cardiogenic shock at admission accompanied by emergency intubation before or at admission to the hospital;
3) Presence of concomitant surgical pathology, which was the main cause of death.

Inhaled surfactant-BL was used in accordance with the prescribing information to treat ARDS.

The treatment group included 38 patients with severe COVID-19-associated pneumonia (respiratory rate >30 breaths per minute; $SpO_2 \leq 93\%$; $PaO_2/FiO_2 \leq 300$ mm Hg; decreased consciousness, agitation; unstable circulatory dynamics (systolic blood pressure (BP)<90 mm Hg or diastolic BP<60 mm Hg, diuresis<20 mL/h); CT or X-ray changes in the lungs typical of viral damage (significant or subtotal volume of the damage equal to CT 3–4); arterial lactate >2 mmol/L; qSOFA >2)) and extremely severe COVID-19-associated pneumonia (persistent low-grade fever; ARDS; acute RF requiring mechanical ventilation; septic shock; multi-organ failure; CT or X-ray changes in the lungs typical of critical viral damage of CT 4 grade, or the picture of ARDS) with concomitant CVDs, who received the inhaled surfactant to manage ARDS. The mean age of patients was 67.5±11.3 years; there were 17 (44.7%) female patients and 21 (55.3%) male patients. Clinically significant cardiovascular pathologies included acute myocardial infarction (MI) in 16 (42%) patients; exertional angina functional class (FC) III in 8 (21%) patients, unstable angina in 4 (10.5%) patients, hemodynamically significant valvular heart disease in 3 (8%) patients, and atrial fibrillation (AF) in 10 (26.3%) patients.

The control group consisted of 105 patients with severe and extremely severe COVID-19 and concomitant CVDs who did not receive inhaled surfactant as a part of combination therapy. The mean age of control patients was 74.5±11.2 years; there were 51 (48.6%) female patients and 54 (51.4%) male patients. Cardiovascular pathologies were presented mainly by acute MI in 47 (44.8%) patients; exertional angina FC III in 13 (12.4%) patients, unstable angina in 7 (6.7%) patients, hemodynamically significant valvular heart disease in 7 (6.7%) patients, and AF in 23 (22%) patients.

Combination medical therapy included antiviral agents (favipiravir, umifenovir), anticoagulants; hyperimmune response was managed using inhibitors of interleukin-6 (tocilizumab, olokizumab, levilimab), interleukin-17 (netakimab), JAK inhibitors (tofacitinib); hormonal and antibacterial therapy according to the indications. CVD treatment strategy agreed with the standards of care for cardiovascular patients and did not differ in the groups.

Humidified oxygen inhalation was used at 5–10 L/min through a nasal or face mask to manage RF. If low oxygen blood saturation persisted, patients were transferred to non-invasive oxygen delivery methods: high-flow oxygenation with the AIRVO-2 system or non-invasive mechanical ventilation of the lungs with the Drager ventilation system (Germany). All patients were kept in prone position for as long as possible.

Inhalation therapy with surfactant-BL was carried out in accordance with prescription information at a dose of 1 mg/kg 2–3 times a day for up to 10 days using the Omron nebulizer (Japan). The ready-for-use solution contained 5 mg of surfactant-BL and 1 mL of 0.9% sodium chloride solution. If SpO_2increased and RF manifestations reduced persistently during the use of mechanical ventilation or non-invasive oxygen delivery, patients were switched to mask oxygenation and surfactant inhalation was canceled.

The data obtained were analyzed with StatPlus and Statistica 7.0. Qualitative data are presented as the absolute and relative rates (n (%)); the comparison was performed using the chi-squared test. Normally distributed quantitative data are expressed as the means and standard deviations (M±ó) or the means and standard errors of mean (M±m); the data were compared using the Student's t-test. Abnormally distributed quantitative data were presented as the medians and interquartile ranges (Me [Q1; Q3]); the data were compared using the Mann-Whitney test. Relative risk (RR) calculated using a four-fold conjugation table was used to compare the probability of outcomes depending on the presence of a risk factor. The results were considered statistically significant with $p<0.05$.

Results and discussion

Patients of the study and control groups did not differ in the main clinical characteristics (Table 1) and baseline grade of RF.

Combination treatment regimen complied with the Russian Temporary Guidelines for the Prevention, Diagnosis, and Treatment of the Novel Coronavirus Disease (COVID-19), version 11 (Table 2).

The use of the inhaled surfactant as part of the combination treatment of patients with COVID-19 allowed reducing the manifestations of RF ($p<0.001$), which reduced mortality in the group of patients with severe and extremely severe COVID-19 and undoubtedly shows the efficacy of this medicine (Figure 1).

The use of the inhaled surfactant in the combination therapy was a turning point in the treatment of severe and extremely severe patients with COVID-19 and CVDs.

At the same time, the data presented in Figure 1 could not be attributed to just the surfactant effect. Both groups were formed by continuous selection of patients, but the

control group includes patients admitted in the first days after the hospital conversion, which could reduce the efficacy of treatment given the learning curve, restrictions of treatment, and technical reasons.

However, the pathogenetic justification for the positive effect of inhaled surfactants, i.e., prevention of alveolar cell collapse with the formation of microatelectases, and the data of some clinical and experimental studies, the positive effect of administering this medicine in A/H1N1 influenza pneumonia, allow us to conclude that surfactant-BL is beneficial in the treatment of patients with COVID-19.

Analysis of mortality rate in the treatment group allowed us to identify patients at the highest risk of death, even during the combination medical therapy. First, this is

Table 1. Baseline clinical characteristics of patients (n = 143)

Parameter		Study group (n = 38)	Control group (n = 105)	p
Age, years		67.5±11.3	74.5±11.2	0.093
Sex	Male	21 (55.3%)	51 (48.6%)	0.736
	Female	17 (44.7%)	54 (51.4%)	0.853
Positive PCR for COVID-19		25 (65.6%)	66 (62.8%)	0.912
Degree of lung damage on CT		2.37±0.93	2.51±0.31	0.745
CHF FC (NYHA)		3 [3; 4]	3 [3; 4]	0.675
RF grade		2 [2; 3]	2 [2; 3]	0.812
SpO_2 at admission, %		88.2±1.42	86.4±2.35	0.323
Respiratory support	Nasal mask	18 (47.4%)	60 (57.2%)	0.577
	HFO_2	18 (47.4%)	41 (39%)	
	MV	2 (5.3%)	4 (3.8%)	
Comorbidities	AMI	16 (42%)	47 (44.8%)	0.892
	Chronic form of CAD	8 (21%)	13 (12.4%)	0.625
	Unstable angina	4 (10.5%)	7 (6.7%)	0.824
	Arterial thrombosis	4 (10.5%)	13 (12.4%)	0.723
	Phlebothrombosis	3 (8%)	11 (10.5%)	0.698
	Structural heart defects	3 (8%)	14 (13.3%)	0.822
	Atrial fibrillation	10 (26%)	39 (35.7%)	0.412
	DM	10 (26.3%)	37 (35.2%)	0.523
	HHD	29 (76.3%)	88 (83.8%)	0.245
	History of CVA	4 (10.5%)	17 (16.2%)	0.534
	VV, PTS	19 (50%)	43 (40.9%)	0.401
	Obesity grade II-IV	18 (47.4%)	59 (56.2%)	0.348

PCR, polymerase chain reaction; CT, computed tomography; FC, functional class;
CHF, chronic heart failure; NYHA, New-York Heart Association; RF, respiratory failure; SpO_2, oxygen blood saturation;
HFO_2, high-flow oxygen; MV, mechanical ventilation; CVA, cerebrovascular accident; VV, varicose veins; PTS, post-thrombotic syndrome.

Table 2. Drug treatment of the subjects (n = 143)

Parameter		Study group (n = 38)	Control group (n = 105)	p
SpO_2 before treatment, %		88.2±1.42	86.4±2.35	0.323
SpO_2 after treatment, %		94.2±2.32	91±3.11	0.213
Duration of surfactant therapy, days		3.6±2.1	–	–
Preemptive treatment	IL-6 inhibitors	31 (81.6%)	93 (88.6%)	0.756
	IL-17 inhibitors	4 (10.5%)	16 (15.2%)	0.624
	JAK inhibitors	7 (18.4%)	28 (26.7)	0.597
Hormone therapy		38 (100%)	105 (100%)	–
Antibacterial therapy		38 (100%)	105 (100%)	–
Anticoagulant therapy		38 (100%)	105 (100%)	–
Respiratory support	Nasal mask	21 (55.3%)	10 (9.5%)	<0.001*
	HFO_2	8 (21%)	32 (30.5%)	
	MV	9 (23.7)	63 (60%)	

SpO_2, oxygen blood saturation; HFO_2, high-flow oxygen; MV, mechanical ventilation;
* – significant value..

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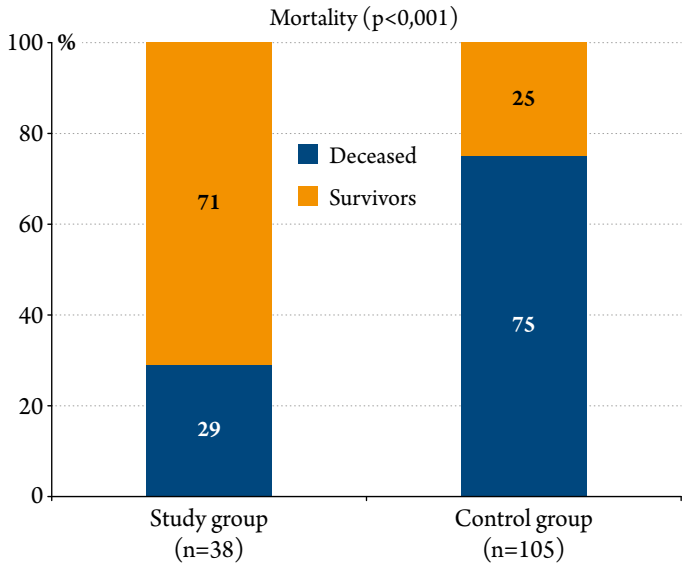
Figure 1. Patient mortality in the inhaled surfactant group and the reference treatment (control) group



age: patients older than 65 years were more likely to die in our study than younger patients (relative risk (RR) 0.16; p=0.020). Surely, it is not only COVID-19 that contributes to the fatal outcome. Accompanying CVDs are more severe in elderly patients due to the longer duration and the development of more severe heart failure.

PCR diagnosis is obligatory for patients with suspected SARS-CoV-2 pneumonia, both at the outpatient stage and at admission to the hospital. A positive PCR test indicates the presence of viruses on the nasal and oropharyngeal mucosa and continuing virus shedding. However, the diagnosis of COVID-19 consists in some cases in the interpretation of a CT picture of the lung damage based on a physical examination and patient's complaints. Analysis of fatal outcomes showed that a positive PCR test was a predictor of death in the treatment group (p=0.037), which emphasizes the importance of this test in the diagnosis and treatment of this category of patients (see Table 1).

The evaluation of the blood levels of ferritin, a marker of inflammation and a precursor of the cytokine storm, is also included in the standard of care for patients with COVID-19. It was found during the study that ferritin >600 μg/mL (p<0.001) is a predictor of severe ARDS and death.

Adequate and timely treatment is a key to the beneficial outcome of any disease, and COVID-19 is no exception. During the study, patients received inhaled surfactant for at least 2 days due to late admission to the hospital. Timely combination therapy including an inhaled surfactant promotes a favorable course of the disease. For example, the inability to administer the inhaled surfactant for more than 4 days was associated in the treatment group with a fatal outcome (p=0.045).

This study is the first experience of using an inhaled surfactant in the combination treatment of cardiac patients with severe and extremely severe COVID-19. Preliminary findings show positive effects of the surfactant, such as reduced manifestations of RF and, thus, increased survival of patients.

Conclusions

1. The use of an inhaled surfactant as part of the combination therapy of severe and extremely severe COVID-19 in patients with concomitant cardiovascular diseases allows increasing the survival of this category of patients (p<0.001) and decreasing mortality by 46%.
2. Age over 65 years (p=0.020), positive polymerase chain reaction test (p=0.037), baseline ferritin levels more than 600 μg/mL (p<0.001), and the administration of inhaled surfactant for less than 4 days (p=0.045) should be regarded as the risk factors for unfavorable outcome in the studied patients.
3. Further research is required to assess the efficacy of inhaled surfactants as part of the combination therapy, and specifically, randomized clinical trials including more patients and the development of strictly defined criteria for the treatment of acute respiratory distress syndrome.

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