Synthetic Analogue of Leu-Enkephalin in COVID-19 (a Prospective Clinical Study)

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Синтетический аналог лей-энкефалина при COVID-19 (проспективное клиническое исследование)

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Summary

One of the main problems facing intensivists when treating patients with COVID-19 is severe and critical acute respiratory distress syndrome (ARDS) with the underlying viral pneumonia. The current guidelines of the Russian Ministry of Health (Version 15 of 22.02.22) do not include drugs with a lung protective effect. This issue could be solved by administration of a synthetic analogue of leu-enkephalin.

Aim. Study the efficacy of a synthetic analogue of leu-enkephalin in ARDS in patients with COVID-19.

Materials and methods. The study included 35 patients divided into 2 groups. Group 1 (main) patients (*n*=15) in addition to standard therapy received a continuous infusion of synthetic analogue of leu-enkephalin at a rate of 5 **μ**g/kg/hour for 5 days. Patients from group 2 (control, *n*=20) were treated according to the Temporary Guidelines of the Ministry of Health (V.15), but without the synthetic analogue of leu-enkephalin. The radiological data, frequency, severity and evolution of respiratory complications, changes in P/F (PaO_2/FiO_2) ratio, as well as changes in the scores of prognostic APACHE II, SOFA, and NEWS scales were evaluated.

Results. In patients taking the studied drug, the percentage of lung damage did not change with the median (IQR) of 0 [–8; 0], while in the control group it increased by approximately 10% with the median (IQR) of +10,0 [+2; +20] (*P*=0.001). The proportion of patients in group 1 with positive disease evolution within 5–9 days after treatment initiation was significantly higher and reached 46.7 [24.8; 69.9]%, whereas in group 2 it was 15.0 [5.2; 36.0]% (*P*=0.04). Also, in group 1, starting from day 4, the median P/F ratio was significantly higher

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than in group 2 reaching 220 [185;245] versus 127 [111;158], respectively (P=0.014). The need for non-invasive lung ventilation in group 1 on day 7 averaged 6.7%, while in group 2 it was as high as 45.0%, which was significantly higher than in the main group (P=0.013).

Conclusions. The use of synthetic analogue of leu-enkephalin according to the specified regimen had a significant impact on the main parameters of the viral pneumonia severity. The results serve as a rationale for the development of a novel effective treatment strategy to supplement the current standard COVID-19 management.

Keywords: COVID-19; pneumonia; ARDS; dalargin; lung protection; intensive care

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Introduction

The coronavirus disease 2019 (COVID-19) is a respiratory infection caused by the SARS-CoV-2 virus. It is generally recognized that the SARS-CoV-2-induced increase in cytokines, often manifested as a «cytokine storm» is associated with worsening of COVID-19 patients [1]. The course of COVID-19 can rapidly deteriorate if complicated by life-threatening pneumonia and acute respiratory distress syndrome (ARDS) [2].

More than 30 years ago, the clinical use of dalargin, a synthetic analogue of leu-enkephalin with delta-opioid activity, began. Early studies revealed the cardioprotective properties in patients operated under cardiopulmonary bypass [3]. Further studies demonstrated lung-protective effects of the drug [4]. Besides, several studies demonstrated reduced frequency of infectious complications [5,6]. However, the mechanism of organoprotective properties of dalargin remained unclear until recently. In 2018, an experimental study demonstrated the protective effect of dalargin in endothelium exposed to the septic shock serum [7], while a recent *in vitro* study revealed a dose-dependent anti-inflammatory effect of a synthetic analogue of leu-enkephalin due to its action on neutrophils activated by bacterial components (lipopolysaccharide and formyl peptide) [8].

Recent *in vivo* studies, in which a synthetic analogue of leu-enkephalin possessed anti-inflammatory effects and reduced mortality in an acute respiratory distress syndrome model in mice, proved particularly interesting [9,10].

Our clinical research was based on the following hypothesis: dalargin efficacy with respect to the rate of clinical symptom resolution in moderate to severe acute respiratory distress syndrome resulting from the novel coronavirus infection SARS-CoV-2 is superior to those of standard treatment recommended by the current Temporary Guidelines of Russian Ministry of Health (Version 15 dated February 22, 2022).

The aim of the study was to examine the efficacy of a synthetic analogue of leu-enkephalin in patients with COVID-19 and ARDS.

Material and Methods

Before a patient was included in the study, the researcher offered to fill out an informed consent form with a detailed explanation of the study goals, objectives, and design, as well as clearly explained all aspects related to dalargin, a synthetic analogue of leu-enkephalin, which was the drug under study.

According to the current instructions for use, dalargin is classified into the «antiulcer drug with antisecretory activity» pharmacological group. The critically ill patients have an extremely high risk of peptic ulcer in general [11, 12] which is even higher if they receive steroids [13], so prolonged infusion of dalargin was administered for gastroprotection by medical team based on indications (history of peptic and duodenal ulcer). The comparison group included patients with similar disease severity and medical history. The study of the organoprotective effects of dalargin was approved by the local ethical committee of the Federal Research and Clinical Center of Intensive Care Medicine and Rehabilitology, Protocol 5/21/7 of 23/12/2021.

This prospective study was done in 2 centers:

- Temporary Branch of Clinical Hospital No. 24 of the Moscow City Health Department;
- Dedicated COVID hospital in Sokolniki of the F. I. Inozemtsev Clinical Hospital of the Moscow City Health Department.

The main criterion for primary admission or transfer of patients to the intensive care unit was inadequate gas exchange despite the low-flow oxygen therapy (up to 10 L/min). Additional criteria for transfer included significant worsening on CT scans, deterioration according to the patient's own assessment, unstable hemodynamic parameters and rapidly progressive respiratory failure. All patients were treated in accordance with current Temporary Guidelines for the Treatment of Coronavirus Infection of Russian Ministry of Health (version 15 dated February 22, 2002). The patients were divided into two groups (Table 1). In group 1 (main, n=15), the patients received dalargin intravenously at the rate of 5 μg/kg/hour over 5 days for gastroprotection. In group 2 (control, n=20), only standard treatment was given.

Inclusion criteria were

- Written patient consent for study participation
- Age 18–85 years
- Confirmed diagnosis of severe or critical COVID-19 according to the Guidelines of the Russian Ministry of Health (Version 15 from 22.02.2022).

• Moderate or severe ARDS (according to the Berlin definition)

• Radiological evidence of ARDS (CT grades 2, 3, 4)

The non-inclusion criteria (at least one was required) were:

• History of hypersensitivity to dalargin or any of its components

• Severe, decompensated or unstable conditions (liver cirrhosis, HIV infection, syphilis, hepatitis B and C, decompensated diabetes, uncontrolled hypertension, pheochromocytoma, myocardial infarction or stroke within 6 months before study inclusion, unstable angina, rhythm and conduction disturbances with poor prognosis; severe chronic lung disease (FEV_1 less than 20 ml/kg of ideal body weight), chronic interstitial lung disease with persistent interstitial infiltration on chest x-ray or CT scan, documented chronic CO_2 retention ($PaCO_2 > 50$ mmHg) or chronic hypoxemia ($PaO_2 < 55$ with $FiO_2 = 0.21$) and any other disease or condition hampering the interpretation of treatment results in investigator's opinion.

• Underlying disease with an expected 6-month mortality of 50% and higher.

• Neurological diseases with risk of intracranial hypertension (where hypercapnia should be avoided).

• Neuromuscular diseases that may have required prolonged mechanical ventilation.

• Severe hypotension

• History of allergic reactions

• Acute psychiatric manifestations (psychosis, delirium, hallucinations)

• Current neoplasm or carcinoid syndrome

• Existing tuberculosis

• Liver failure (ALT or AST > 5 times upper limit of normal [ULN] or total bilirubin or alkaline phosphatase > 3 ULN)

• Documented renal dysfunction or severe decompensated renal failure requiring hemodialysis or peritoneal dialysis.

• Alcoholism

• Drug addiction

Exclusion criteria were

• Patient's refusal to continue participation in the study.

• Adverse events preventing further therapy.

• Development of life-threatening conditions.

• Liver function abnormality (i. e., a 3-fold increase in AST, ALT, or AP above the upper limit of normal, or a 2-fold increase in total bilirubin above the upper limit of normal, or development of jaundice).

• Clinically evident kidney dysfunction

• Occurrence of comorbid conditions/manifestations or exacerbation of chronic diseases not related to drug administration (in physician's opinion).

• Other reasons preventing the patient from continuing the study participation (in the opinion of the research physician).

Criteria of efficacy assessment were as follows.

Primary endpoint:

• Percentage of patients with improvement on chest CT (decreased severity and/or area of lung involvement and/or lesions) in the study groups

Secondary endpoints:

• Changes in P/F ratio on days 1–7 in the study groups

• Percentage of patients (%) with clinical improvement by the APACHE II, SOFA and NEWS scales on days 5–7 in the study groups

• Percentage of patients requiring non-invasive ventilation (NILV) in the study groups

• Percentage of patients requiring mechanical ventilation in the study groups

• Percentage of patients (%) who required vasopressor/inotropic support (VIS).

• 28-day mortality in the study groups.

Statistical analysis of the data. Quantitative variables (intergroup comparison and changes within the groups) were analyzed with the aid of AtteStat, STATISTICA, XLSTAT software using the nonparametric statistical methods (Mann–Whitney *U*-test, Wilcoxon test for related samples, Friedman nonparametric analysis of variance, Pearson Chi-square test, Fisher exact test, Freeman–Holton test). The significance level for bilateral tests was α=0.05. The 95-percent two-sided confidence intervals for differences were calculated to prove the superiority of the treatment.

Due to the nature of the study design, «blinding» was performed only at the stage of interpretation of CT images by the radiologist.

Results

The study groups were comparable in demographic and anthropometric characteristics (Table 1).

The groups were also comparable in most clinical characteristics at the beginning of treatment (Table 2), except for the percentage of lung tissue and structural damage, which was higher in the main group than in the control (differences were significant at P=0.048 according to Mann–Whitney *U*-criterion).

On days 5–9 of the treatment, the change in the lung tissue involvement according to CT data in the main group was on average M=+5.8% (SD=11.1%), while in the control group it was +10.1% (16.9%), i. e., 1.7 times less. The median value of this parameter did not change in the main group and increased by 10% in the control group. The upper limit of the 95% confidence interval (CI) of the median difference between the groups was

Table 1. Demographic and anthropometric characteristics of patients.

Parameter	Units	Values in groups		*P*-value
		Main group (*n*=15)	Control group (*n*=20)	
Sex:				
Male	*n* (%)	6 (40%)	13 (65%)	0.142#
Female	*n* (%)	9 (60%)	7 (35%)	
Age (full years)	Median [IQR]	70 [65; 74]	68.5 [61; 74]	0.442*
	min–max	60–86	50–84	
Body weight (kg)	Median [IQR]	82 [78; 98]	85 [72; 93]	0.640*
	min–max	50–138	50–108	
Height (cm)	Median [IQR]	165 [164; 173]	166 [166; 175]	0.471*
	min–max	155–181	155–187	
BMI (kg/m^2)	Median [IQR]	31.6 [26; 35]	28.7 [26; 31]	0.309*
	min–max	20.8–48.9	19.5–45	
Comorbidities				
Diabetes mellitus, %		5 (33.3%)	4 (20%)	0.174#
Hypertension, chronic heart failure		7 (46.6 %)	10 (50%)	0.241#
Bronchial asthma, chronic obstructive pulmonary disease		3 (20%)	5 (25%)	0.221#
Genitourinary diseases		1 (6.6%)	2 (10%)	0.116#
Mental conditions		0 (0%)	1 (5%)	0.165#

Note. For tables 1–4: IQR — interquartile range (first-third), min–max — range. *P*-value calculated using the χ^2 test (#) or Mann–Whitney *U*-test (*).

Table 2. Comparison of groups by clinical aspects of the underlying disease.

Clinical aspect	Statistical units	Groups		*P*-value
		Main (*n*=15)	Control (*n*=20)	
Instrumental investigation results				
Lung tissue involvement:				
CT grade 1	*n* (%)	0 (0%)	1 (5%)	0.545##
CT grade 2		2 (13%)	4 (20%)	
CT grade 3		7 (47%)	11 (55%)	
CT grade 4		6 (40%)	4 (20%)	
Percentage (%) of lung involvement based on CT scan	Median [IQR]	62.5% [55%; 78.1%]	54.4% [45%; 67.8%]	0.048*
	min–max	27.5–85.0%	10.0–80.0%	
SpO_2, %	Median [IQR]	88.0% [85%; 91%]	86.5% [83%; 87%]	0.192*
	min–max	76–94%	60–92%	
Oxygenation index (PaO_2/FiO_2)	Median [IQR]	196.0 [177; 237]	194.5 [166.25; 227]	0.828*
	min–max	150–262	105–290	
Respiratory rate (per min.)	Median [IQR]	24 [22.5; 24]	23 [21; 24]	0.400*
	min–max	21–26	18–29	
Clinical assessment of severity based on scales				
WHO scale:				
4 points	*n* (%)	0 (0%)	3 (15%)	
5 points		15 (100%)	17 (85%)	0.244**
APACHE II (points)	Median [IQR]	15 [13; 19]	16 [15; 24]	0.133*
	min–max	9–20	3–38	
SOFA (points)	Median [IQR]	4 [3; 4.5]	6 [4; 6]	0.066*
	min–max	2–7	2–10	
NEWS (points)	Median [IQR]	6 [4.75; 7]	7 [5; 8.25]	0.351*
	min–max	2–9	3–14	
Comorbidities				
Obesity (BMI⩾35 kg/m^2):				
yes	*n* (%)	5 (33%)	2 (10%)	0.088#
no		10 (67%)	18 (90%)	
Age ⩾60 years				
yes	*n* (%)	15 (100%)	16 (80%)	0.119**
no		0 (0%)	4 (20%)	

Note. For tables 2–7: *P*-value calculated using the Fisher exact test (**); Freeman-Halton test (##); Pearson χ^2 test (#); or Mann–Whitney *U*-test (*).

7.5%, which proved the positive effect of dalargin (Table 3).

The reduction in lung lesion percentage based on CT scan on day 5-9 was considered as «improvement». Among the patients in the main group, CT improvement was observed 3.2 times more frequently than in the control group, the lower limit of the 95% CI of the difference in percentage between the groups being +1.3% (Table 3).

When comparing the changes in lung involvement severity (CT grades 1, 2, 3, and 4 according to a semiquantitative visual scale used in Russia), no sig-

Table 3. The studied parameters on days 5–9 from the beginning of treatment.

Parameter	Values in groups		Difference between the groups, % [95% CI]	*P*-value
	Main (*n*=15)	Control (*n*=20)		
% lung tissue involvement, median [IQR], min–max	0 [–8;0] –28.8; +6.3	+10.0 [+2; +20] –35.0; +37.5	–15.0 [–27.5; –7.5]	0.001*
Percentage of patients with CT improvement, % [95% CI]	46.7 [24.8; 69.9]	15.0 [5.2; 36.0]	+31.7 [+1.3; +56.9]	0.040#
Severity of lung tissue and structural damage, % [95% CI]	20.0 [7.0; 45.2]	5.0 [0.9; 23.6]	+15.0 [–7.7; 40.5]	0.292**

nificant differences between the groups were found at *P*=0.292 using the Fisher exact test (Table 3).

In both groups, significant changes in the P/F ratio were seen with its drop on day 2 and gradual increase in the following days (Fig.). Significance of the changes in both groups was confirmed by Friedman's analysis of variance at *P*=0.001 in the main group and at *P*=0.013 in the control group.

There were no differences in oxygenation index values between the groups from day 1 to day 4 of treatment but starting from day 5, the lower limit of 95% CI of the median difference was significantly higher in the main group than in the control one (Table 4). On day 7 of treatment the mean value of P/F ratio was 211.9 (SD=80.5) in the main group, and 147.2 (54.9) in the control group, i. e., was 1.4 times higher.

There were no significant differences between the main and control groups in the percentage of patients with clinical improvement on days 3 and 7 as assessed by both the APACHE II and the SOFA and NEWS scales (*P*>0.05) (Table 5).

The main and control groups were comparable in terms of the need for mechanical ventilation (no significant differences at *P*>0.05, Table 6).

The main and control groups did not differ significantly at *P*>0.05 in the percentage of patients who required NILV from day 2 to day 5 of treatment

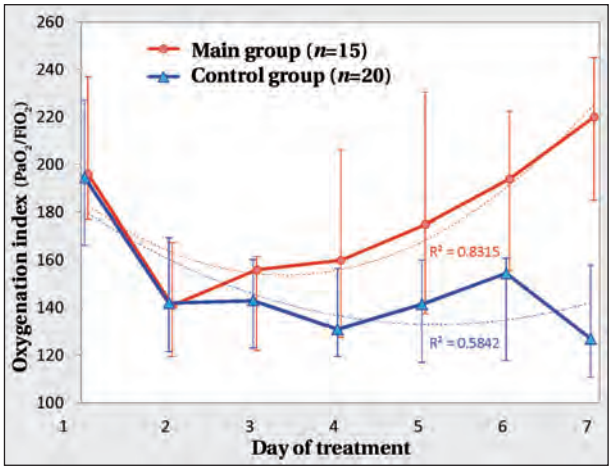

Fig. Changes in the P/F ratio (median ± quartiles, R² — coefficient of determination).

(Table 6). On days 6 and 7 of treatment, the difference between the groups became significant at *P*<0.05 according to Pearson χ^2 test. On days 6–7 of treatment, the rate of NILV use was 4.9–6.7 times lower in the main group than in the control one.

The main and control groups did not differ significantly in the percentage of patients who required VIS (*P*>0.05) (Table 6).

The 28-day mortality rate in the main group was 1.9 times lower than in the control one. However,

Table 4. Changes in the P/F (PaO_2/FiO_2) ratio depending on the day of treatment.

Day of treatment	P/F ratio in groups, Median [IQR], min–max		Difference between the groups, % [95% CI]	*P*-value*[1]
	Main (*n*=15)	Control (*n*=20)		
1	196 [177; 237] 150–262	194.5 [166; 227] 105–290	+4.5 [–24; +41]	0.828
2	141 [120; 168] 108–256	142 [122; 170] 111–277	–1.5 [–26; +21]	0.920
3	156 [122; 162] 92–258	143 [120; 157] 102–240	+2 [–26; +22]	0.777
4	160 [128; 207] 105–330	131 [117; 160] 89–194	+33 [0; +65]	0.040
5	175 [138; 231] 105–323	141.5 [117; 160] 95–213	+41 [+8; +82]	0.020
6	194 [156; 245] 95–310	154.5 [118; 161] 94–190	+55.5 [+24; +95]	0.004
7	220 [185; 245] 150–355	127 [111; 158] 98–320	+64.5 [+15; +114]	0.014
P-value[2]	0.001	0.013		

Note. [1] — intergroup comparison; [2] — *P*-value calculated using the Friedman analysis of variance.

Table 5. Percentage of patients with clinical improvement on assessment scales.

Day of treatment	Scale	Percentage of patients with clinical improvement in groups, % [95% CI]		Difference between the groups, % [95% CI]	*P*-value
		Main (*n*=15)	Control (*n*=20)		
3	APACHE II	6.7 [1.2; 29.8]	10.0 [2.8; 30.1]	–3.3 [–24.2; +20.9]	>0.999**
	SOFA	20.0 [7.0; 45.2]	5.0 [0.9; 23.6]	+15.0 [–7.7; +40.5]	0.292**
	NEWS	26.7 [10.9; 52.0]	10.0 [2.8; 30.1]	+16.7 [–8.9; +43.0]	0.195*
7	APACHE II	33.3 [15.2; 58.3]	10.0 [2.8; 30.1]	+23.3 [–3.8; +49.3]	0.088*
	SOFA	33.3 [15.2; 58.3]	15.0 [5.2; 36.0]	+18.3 [–9.5; +45.1]	0.201*
	NEWS	20.0 [7.0; 45.2]	5.0 [0.9; 23.6]	+15.0 [–7.7; +40.5]	0.292**

Table 6. Percentage of patients requiring MV, NILV, VIS.

Day of treatment	Parameter	Percentage of patients in groups, % [95% CI]		Difference between the groups, % [95% CI]	*P*-value
		Main (*n*=15)	Control (*n*=20)		
2	MV	6.7 [1.2; 29.8]	5.0 [0.9; 23.6]	+1.7 [–17.7; +25.2]	>0.999**
	NILV	20.0 [7.0; 45.2]	50.0 [29.9; 70.1]	–30 [–53.9; +2.2]	0.069*
	VIS	6.7 [1.2; 29.8]	0.0 [0.0; 16.1]	+6.7 [–10.4; +29.8]	0.429**
3	MV	13.3 [3.7; 37.9]	5.0 [0.9; 23.6]	+8.3 [–12.6; +33.2]	0.565**
	NILV	20.0 [7.0; 45.2]	50.0 [29.9; 70.1]	–30 [–53.9; +2.2]	0.069*
	VIS	0.0 [0.0; 20.4]	0.0 [0.0; 16.1]	0 [–16.1; +20.4]	>0.999**
4	MV	—	—	—	—
	NILV	—	—	—	—
	VIS	0.0 [0.0; 20.4]	0.0 [0.0; 16.1]	0 [–16.1; +20.4]	>0.999**
5	MV	13.3 [3.7; 37.9]	10.0 [2.8; 30.1]	+3.3 [–18.9; +28.9]	>0.999**
	NILV	20.0 [7.0; 45.2]	50.0 [29.9; 70.1]	–30 [–53.9; +2.2]	0.069*
	VIS	6.7 [1.2; 29.8]	5.0 [0.9; 23.6]	+1.7 [–17.7; +25.2]	>0.999**
6	MV	—	—	—	—
	NILV	13.3 [3.7; 37.9]	65.0 [43.3; 81.9]	–52 [–71.1; –18.9]	0.002*
	VIS	20.0 [7.0; 45.2]	10.0 [2.8; 30.1]	+10.0 [–13.9; +36.2]	0.403*
7	MV	0.0 [0.0; 20.4]	30.0 [14.5; 51.9]	–30 [–51.9; –4.4]	0.060*
	NILV	6.7 [1.2; 29.8]	45.0 [25.8; 65.8]	–38 [–59.8; –8.3]	0.013*
	VIS	0.0 [0.0; 20.4]	20.0 [8.1; 41.6]	–20.0 [–41.6; +3.6]	0.119**

Table 7. Mortality on day 28.

Frequency of lethal outcome in groups % [95% CI]		Difference between groups, % [95% CI]	*P*-value*
Main (*n*=15)	Control (*n*=20)		
26.7 [10.9; 52.0]	50.0 [29.9; 70.1]	–23.3 [–48.9; +8.9]	0.163

Table 8. The Berlin definition of acute respiratory distress syndrome.

Timing	Within 1 week of a known clinical insult or new/worsening respiratory symptoms
Chest imaging	Bilateral opacities — not fully explained by effusions, lobar, lung collapse, or nodules
Origin of edema	Respiratory failure not fully explained by cardiac failure or fluid overload; need of objective assessment (e.g., echocardiography) to exclude hydrostatic edema if no risk factor present
	Oxygenation impairment
Mild	$200 < PaO_2/FiO_2 \leqslant 300$ with PEEP or CPAP $\geqslant 5$ cmH_2O
Moderate	$100 < PaO_2/FiO_2 \leqslant 200$ with PEEP $\geqslant 5$ cmH_2O
Severe	$PaO_2/FiO_2 \leqslant 100$ with PEEP $\geqslant 5$ cmH_2O

no significant differences of this parameter values between the groups at P=0.163 (Pearson χ^2 test) were found (Table 7) presumably due to a relatively small sample size.

Discussion

The epidemic of the novel coronavirus infection SARS-CoV-19 has drawn the attention of clinicians and researchers around the world to the phenomenon of rapidly developing lung damage, which requires timely and reasonable intervention. To develop and implement new management principles, the understanding the pathophysiological mechanisms of ARDS underlying the lung tissue damage in this category of patients is required.

In 1988, one of the first classifications of ARDS was proposed and introduced into routine practice, which was based on clinical and laboratory data and identified 4 stages of the condition [14]. Later, in 2007, a new classification was proposed, which was based both on clinical and experimental diagnostic findings and morphological examination of lung tissue as well as its correlation with clinical manifestations [15]. This classification was directly related to morphological classification of ARDS which also included the exudation, connective tissue proliferation, and pulmonary fibrosis stages [16, 17]. Nowadays, the Berlin definition (Table 14) adopted in 2012 and used to for severity assessment in ARDS, including that developing in COVID-19-associated pneumonia, is considered most relevant [18].

The current guidelines on the treatment of COVID-19 were driven by the necessity to control the key links in the development of ARDS.

However, according to the current guidelines. the treatment of pneumonia caused by the novel coronavirus infection does not include drugs with lung-protective effects [19]. Opiates are worth mentioning when considering the drugs that could be efficient in this aspect being a part of comprehensive therapy. They are a fairly extensive group of drugs intended for cytoprotection in critical conditions [20, 21]. Among the entire range of opiates used in clinical practice, dalargin stands out because of its unique delta-opioid blocking effect. The latter is suggested to underlie the opioid-induced organoprotection [22]. The use of dalargin in a series of experimental studies was clearly associated with cytoprection when exposed to a wide range of unfavorable factors.

Besides, the presence of delta-opioid receptors practically in all organs and tissues favores a certain versatility of its effects [7, 23, 24].

Earlier patent-pending experimental data [25, 26], as well as the vast clinical experience with the drug provided a rationale for a prospective pilot study of its lung-protective potential in patients with severe COVID-19 associated pneumonia. Impaired air-blood barrier underlies ARDS pathophysiology, while the targeted action of dalargin on key elements of this process could reduce the severity of lung tissue damage.

The most significant effect of dalargin administration was the reduction of lung tissue involvement area, which probably resulted in clinical improvement. The increase in the oxygenation index on days 4–7 after the start of dalargin suggests that further research with the drug will help clarify the timing and scheme of its administration. In addition, a decrease in the frequency and duration of NILV associated with dalargin suggests that the patients with «borderline» severe acute respiratory distress will benefit most from its use.

Conclusion

Improvement on chest CT scans was observed 3.2 times more frequently in patients who received dalargin (the main group) than in the control subjects (P=0.040).

In patients on dalargin, starting from the day 5 of treatment, the P/F ratio was significantly better compared with the control group, which indicates an improved pulmonary oxygenation.

The NILV was used 4.9 times less frequently on day 6 (P=0.020) and 6.7 times less frequently on day 7 (P=0.013) than in the control group.

The results of the pilot study of dalargin use in patients with moderate to severe acute respiratory distress syndrome with the underlying severe and critical novel coronavirus infection SARS-CoV-2 have been promising. This appears to warrant the initiation of a phase III clinical trial of dalargin for new indications. We hope that adding dalargin to the current therapy will significantly improve the prognosis in patients with severe and critical SARS-CoV-2.

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