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Research Article

Possibilities of Using Placenta Hydrolysate in Patients with COVID-19

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Abstract

The Relevance of the Problem: At COVID-19, in addition to lung damage, there is a dysfunction of many systems and organs. Blood clotting is disrupted; markers of inflammation increase; liver, kidney, heart and other organs are affected. A number of studies have shown that the use of human placenta hydrolysate leads to positive clinical dynamics and improved laboratory parameters. Therefore, a more detailed study of the effectiveness of this drug in the treatment of COVID-19 seems relevant and practically significant.

The Purpose of the Work: To evaluate the effectiveness of human placenta hydrolysate in the treatment of COVID-19 in patients with moderate to severe disease.

Materials and Methods: 22 patients with COVID-19 were examined, divided into two groups. The first group was 11 people who received placental hydrolysate. The second - 11 people who did not receive the specified drug. The general and biochemical blood tests were examined. Respiratory function of the lungs was assessed by blood oxygenation (SpO2), and computed tomography (CT) of the chest organs. COVID-19 was confirmed by the detection of virus RNA in smears from the nasopharynx and oropharynx and/or biomaterial samples from the lower respiratory tract (in severe cases) in patients with suspected Covid-19 infection. The data is presented in the form of the arithmetic mean and its standard error (M ± m). The differences were considered statistically significant at $p < 0.05$.

Results and Discussion: Along with the clinical symptoms, the examined patients showed changes in the GBT, symptoms of gastrointestinal damage, liver dysfunction, signs of a "cytokine storm", kidney damage, and blood clotting disorders. The introduction of 6 ml of placental hydrolysate daily for 10 days intravenously drip had a positive effect on the general condition of patients and blood biochemical parameters.

Conclusion: Compared with the control, placental hydrolysate (laennec) has a more favorable effect on the dynamics of laboratory parameters, namely: there is a more significant and reliable improvement in the indicators on the drug, a higher percentage of changes in melons, and a shorter period of stay of patients in the hospital.

Keywords: *Patients with COVID-19; Moderate; Severe; Treatment; Human Placenta Hydrolysate*

Abbreviations

APTT: Activated Partial Thromboplastin Time; ALP: Alkaline Phosphatase; ALT: Alanine Aminotransferase; AST: Asparagine aminotransferase; BBT: Biochemical Blood Tests; Spo_2: Blood Oxygenation; BP: Blood Pressure; CI: Color Index; CBC: Complete Blood Count; CT: Computed Tomography; CHD: Coronary Heart Disease; CRP: C Reactive Protein; DM2: Diabetes Mellitus Type 2; DICF: Disseminated Intravascular Coagulation; FRM: Frequency of Respiratory Movements; Eo: Eosinophils; Er: Erythrocytes; ESR: Erythrocyte Sedimentation Rate; GBT: General Blood Test; GD: Gallstone Disease; Ht: Hematocrit; Hb: Hemoglobin; ICU: Intensive Care Unit; INR: International Normalized Ratio; Leu: Leukocytes; L: Lymphocytes; MRI: Magnetic Resonance Tomography; M: Monocytes; PUSD: Peptic Ulcer of the Stomach and Duodenum; Pl: Platelets; PCR: Polymerase Chain Reaction; PTI: Prothrombin Index; RNA: Ribonucleic Acid; ESR: Sedimentation Rate of Erythrocytes

Introduction

In 2019, the world faced a previously unknown, highly contagious respiratory viral infection COVID-19 [10,16]. Unlike other similar diseases, in most patients, COVID-19 can flow asymptomatically or relatively easily. However, in some cases, it leads to dangerous and severe complications [14]. Therefore, the main task of therapy, in this situation, is to prevent a fatal outcome.

COVID-19 is characterized by multiple organ pathology. In addition to lung damage, there is a dysfunction of many systems and organs. Blood clotting is disrupted (sometimes with the development of disseminated intravascular coagulation (DIC); a "cytokine storm" develops - an avalanche like increase in inflammatory markers in the blood (pro-inflammatory interleukins, CRP, TNF-α, ferritin); liver damage appears (increased levels of bilirubin, ALT, AST, and ALP and decreased albumin) [6], kidney damage (increased levels of creatinine and urea in the blood), heart failure and other organs [12].

These multiple organ lesions aggravate the course of COVID-19 and lead to a high risk of death. Their treatment requires the appointment of various medications, which leads to polypragmasia and, to the appearance of iatrogeny. In this situation, the choice of a drug for the treatment of patients with COVID-19 is of fundamental importance for reducing mortality from this disease [17].

In a number of studies [13], it was shown that the use of the drug human placenta hydrolysate (laennec) in patients with COVID-19, it leads to positive clinical dynamics: blood oxygenation increases and the area of lung damage decreases; many laboratory parameters (ALT, AST, CRP, ferritin, etc.) improve, showing a pronounced hepatoprotective, anti-inflammatory and immunomodulatory effect. They also showed that the drug human placenta hydrolysate has a good safety profile and a high degree of pharmaceutical standardization. Previously [33,42] the drug human placenta hydrolysate was studied in patients with alcoholic and non-alcoholic liver damage and demonstrated a good hepatoprotective effect.

Taking into account the above, it seems to us relevant and practically significant to study in more detail the effectiveness of this drug in the treatment of COVID-19.

Objective of the Study

To evaluate the effectiveness of human placenta hydrolysate in the treatment of COVID-19 in patients with moderate to severe disease.

Materials and Methods

We examined 22 patients with COVID-19, with a moderate and severe degree of illness, who were on therapy according to Temporary Methodological Recommendations [23], divided into two groups in the temporary infectious diseases hospital of city clinic No. 12 in Kazan. The first group - 11 people, additionally received placental hydrolysate (laennec) (men-7 people, average age 67.9 ± 1.89 years,

women- 4 people, average age 69.8 ± 2.17 years, p > 0.05). The second (control) group - 11 people who did not receive the specified drug (men - 7 people, average age 69.5 ± 1.40 years, women - 4 people, average age 72.9 ± 2.21 years, p > 0.05). Of the examined patients, 8 suffered from coronary heart disease (CHD), 18 - arterial hypertension (2 stages - 11 people, 3 stages - 7 people), 4 - type 2 diabetes mellitus (DM2), 8 - obesity (5 - 1 degrees, 1 - 2 degrees, 2 - 3 degrees), 2 - breast cancer, 2 - bronchial asthma, 1 - peptic ulcer of the stomach and duodenum (PUSD), 1 - gallstone disease (GD), 1-Bekhterev-Strumpel-Marie disease. The diagnoses of the patients were coded as U07.1-U08.1. Thus, we see polymorbidity in our patients, which aggravates their condition.

The severity of the patients was assessed according to the Temporary Guidelines "Prevention, diagnosis and treatment of new coronavirus infection COVID-19" [24,25]: Moderate-severe form (2 of the 4 following main criteria (hospitalization): 1) Body temperature ≥ 38.0°C; 2) SpO_2 < 95%; 3) Frequency of respiratory movements (FRM) > 22/min; 4). Serum CRP > 10 mg/l. Additionally: CT 1 or 2: less than 25 to 50%. Explanation: changes on CT 1 or 2, typical for a viral lesion (minimal or medium lesion volume: frosted glass ± consolidation). Severe form (emergency hospitalization in the intensive care unit (ICU): 2 of the following 3 main criteria): 1) Body temperature ≥ 39°C; 2) FRM ≥ 30/min; 3) SpO_2 ≤ 93%. Additional criteria: PaO_2/FiO_2 < 300 mmHg; decreased level of consciousness, agitation; unstable hemodynamics (BP) < 90 mmHg or AD diast. < 60 mm Hg; diuresis < 20 ml/hour); changes in the lungs during CT (radiography, typical of a viral lesion: the volume of the lesion is significant or subtotal; CT 3 (50 - 75%), CT 4 > 75%; blood lactate.

According to these criteria, there were 18 patients with moderate-severe form and 4 patients with severe form.

Since the patients were representative by age and gender and had no significant differences in laboratory parameters, they were grouped by gender and age (Table 1).

Groups	Men	Women	Total	P
Quantity	14	8	22	
Group 1 (laennec)	67,9 ± 1,89 (n = 7)	69,8 ± 2,17 (n = 4)	68,5 ± 1,40 (n = 11)	> 0,05
Group 2 (control)	74,4 ± 3,12 (n = 7)	73,2 ± 3,60 (n = 4)	72,9 ± 3,21 (n = 11)	> 0,05
P	> 0,05	> 0,05	> 0,05	

Table 1: *Examined patients.*

The protocol of the study included the traditional provisions: obtaining informed consent to participate in the study; collecting complaints, anamnesis of the disease and life, objective examination using physical examination methods; studying medical documentation data; using laboratory and instrumental methods with entering the information obtained into the developed individual cards; prescribing pathogenetic therapy. Basic therapy was carried out according to the Temporary Guidelines for the Treatment of COVID-19 of the Ministry of Health of the Russian Federation (version 7 of 03.06.2020 [23]).

Criteria for including patients in the study [23]: the participant wants and agrees to sign an informed consent and is ready to be monitored by doctors for a long time; verified diagnosis of COVID-19; age 18-90 years; moderate severity and severe course of COVID infection (high rates of inflammatory reaction, the presence of concomitant pathology). Criteria for excluding patients from the study [23]: the participant does not want and does not agree to sign an informed consent and is not ready to be monitored by doctors for a long time; a dubious diagnosis of COVID-19; a mild course of COVID infection that does not require inpatient treatment.

General blood test (GBT), blood clotting indicators and biochemical blood tests (BBT) were performed using standard methods. The GBT included the calculation of red blood cells, hemoglobin, color index, platelets and leukocytes with a leukocyte formula. Blood clotting was evaluated by the prothrombin index (PTI), activated partial thrombin time (APTT), international normalized ratio (INR), fibrinogen and D-dimers. The inflammatory response of the body was evaluated by C-reactive protein (CRP), erythrocyte sedimentation rate (ESR)

and ferritin. Alanine aminotransferase (ALT), asparagine aminotransferase (AST), the level of total bilirubin and its fractions, alkaline phosphatase (ALP), cholesterol, glucose, total protein, creatinine and urea were determined in the tank.

Respiratory function of the lungs was assessed by pulse oximetry (SpO2) and computed tomography (CT) of the chest organs.

SpO_2 was determined by a pulse oximeter (MD-300 C3 (China)) (the norm is more than 95%). The assessment of lung damage was performed by CT (Siemens Somatom Emotion 16 (Germany)). The manifestations of COVID-19 on CT were characterized by compaction of the lung tissue by the type of frosted glass; the presence of areas of frosted glass with reticular changes; areas of consolidation of lung tissue; "reverse halo" syndrome; an increase in the diameter of vessels in the compacted lung tissue; traction bronchiectasis. According to CT data, the total area of damage (0 - 100%) and the degree of damage (0 - 5 points) were estimated. The degree of damage was calculated as the average for each of the 5 lobes of the lungs (1 point - < 5% of the tissue is involved, 2 - 5-25%; 3 - 26-49%; 4 - 50-75%; 5 - > 75%) [14].

COVID-19 was confirmed by the detection of coronavirus ribonucleic acid (RNA) by polymerase chain reaction (PCR) in the study of a smear from the nasopharynx and oropharynx and/or samples of biomaterial from the lower respiratory tract (in severe cases) in patients with suspected COVID-19 infection.

Antibodies to the SARS-CoV-2 coronavirus: IgM, IgG (anti-SARS-CoV-2, IgM, IgG), were determined if necessary.

All patients were hospitalized on the 5 - 10^{th} day from the onset of the disease, which corresponds to the stage of progression (5 - 8 days of the disease) and the peak stage of COVID-19 (10 - 13 days of the disease). According to CT data, the stage of progression was characterized by an increase in the prevalence of the "frosted glass" symptom, local reticular changes and the appearance of foci of consolidation. At the peak of the disease, the formation of perilobular seals was noted on CT.

The study was conducted on the basis of the approval of the Ethics Committee of the KSMAA-a branch of the FSBEI DPO RMANPO of the Ministry of Health of the Russian Federation (Protocol No. 2/06 of 25.06.2020) in the temporary infectious diseases hospital (VIG) of JSC "City Clinical Hospital No. 12" (Kazan). The drug is presented by Placenta Pharm LLC (Russia).

Laennec is an injectable drug for intravenous and intramuscular administration, based on human placenta hydrolysate, produced by the Japanese pharmaceutical concern JapanBioProductsCo.Ltd. (JBP Co.Ltd.), registered in the territory of the Russian Federation as a hepatoprotector and immunomodulator. ATC code: L03, A05BA (registration certificate of the Ministry of Health of the Russian Federation P No. 013851/01 [8]. 2 ml of the drug contains 112 mg of human placenta hydrolysate. The drug was administered daily for 10 days intravenously drip into the ulnar vein for 1.5 hours (6 ml (336 mg of placenta hydrolysate) of the drug (3 ampoules) was dissolved in 200 ml of saline solution).

Static processing of the results was carried out using the package of applied statistical programs STATISTICA v. 7, Microsoft Excel v. 2000. The normality of the data distribution was confirmed by the Kolmogorov-Smirnov and Shapiro-Wilcoxon test. The results are presented in the form of the arithmetic mean and its standard error (M ± m). The Mann-Whitney test was performed with a nonparametric distribution of data. The reliability of the differences in the mean values in the two groups was evaluated by the Student's t-test for independent samples and the Student's paired t-test for independent samples, with reliable confirmation of the normal distribution in the compared samples. The presence of correlations was determined by the Spearman rank correlation coefficient. The differences were considered statistically significant at $p < 0.05$.

Results and Discussion

All patients complained of weakness, decreased or lack of appetite, some - 8 people (36.4%) - of muscle pain. 14 people (63.3%) lost their sense of smell, 6 (27.3%) had signs of conjunctivitis. All patients had an elevated body temperature (from 37^0C to 39^0C) and pale skin.

Upon admission, the frequency of respiratory movements (FRM) in the examined patients ranged from 20 to 30 per minute, pulse oximetry was 92-95%. All patients received high-flow nasal oxygen therapy.

On the part of the cardiovascular system, a decrease in systolic blood pressure < 100 mm Hg was noted in 73% of patients.

The examined patients have changes in the general (GBT) and biochemical (BBT) blood tests (hereinafter, the reference values of the GBT and BBT used in our clinic are indicated in parentheses, which coincide with the data presented in the reference books of S.S. Vyalov., *et al.* (2008) [3] and V.M., Lifshits, V.I. Sidelnikova (2006) [9]. Liver dysfunction, signs of a "cytokine storm" were also revealed: CRP of more than 5 mg/l, a decrease in the relative content of lymphocytes (N 20 - 37%), an increase in the level of ferritin (N in men 20 - 250 mcg/l, in women 10 - 120 mcg/l, respectively), kidney damage (an increase in the level of creatinine (N 59 - 104 mmol/l) and urea (N 2.8 - 7.2 mmol/l) in the blood), and blood clotting disorders. The data of the GBT and the BBT are presented in table 2 and 3 respectively.

Due to the fact that the indicators of the general blood test in men and women had the same orientation, we combined them into one group (Table 2). At hospitalization, 50% of patients were diagnosed with anemia of the first degree: in 5 men, hemoglobin was 117.4 ± 0.68 g/l (130 - 150 g/l) and in 6 women - 114.5 ± 4.5 g/l (N 120 - 140 g/l). During the stay in the hospital, there was a tendency to develop normochromic anemia, reaching the first degree of severity.

Some authors [14] also note anemia in patients with COVID-19, explaining its mass death of red blood cells. However, in our patients, we did not see signs of hemolysis of red blood cells (there is no reticulocytosis and an increase in the level of indirect bilirubin in the blood, there is no increase in urobilin in the urine). Zheying Tao., *et al.* [48] indicate that anemia is associated with the severity of coronavirus disease. According to their data, in patients with a severe form of COVID-19, the hemoglobin level, at admission, was significantly lower, compared with patients with a milder form (111.5 g/l versus 128 g/l, P = 0.002, respectively). Of course, anemia and low hemoglobin levels reduce the delivery of oxygen to organs and tissues, impairing lung function and tissue oxygenation, because of this, patients with COVID-19 have a more severe course of the disease [41]. According to our data, before discharge, anemia of the 1st degree was detected in 63.6% of patients (9 men had hemoglobin of 113.4 ± 3.0 g/l (N 130 - 150 g/l) and 5 women had hemoglobin of 107.2 ± 4.13 g/l (N 120 - 140 g/l)). But the association of anemia with the severity of COVID-19 was not revealed.

Any pronounced inflammatory disease causes anemia (the so-called anemia of chronic diseases [25]). Therefore, it is difficult to say whether anemia is a cause or a consequence. It is possible that the SARS-CoV-2 virus itself has a toxic effect on the bone marrow. To clarify the reasons, it is necessary to study the level of serum iron, B_{12} and folic acid. All this may shed light on this phenomenon under discussion. For example, Thomas Sonnweber., *et al*. iron homeostasis in patients with COVID-19 is considered only from the position of ferritin metabolism [40].

From the moment of admission to treatment until discharge, in the patients we observed with COVID-19, a slight increase in the content of white blood cells (N 4-9 x 10^9/l) was detected: group 1, 8.8 ± 1.28 and 11.0 ± 0.59 ($p > 0.05$), group 2: 7.1 ± 1.59 and 9.2 ± 0.84 ($p > 0.05$), respectively (Table 2). We believe that moderate leukocytosis is caused by the use of glucocorticosteroids. As can be seen from table 2, during the same period, there is a decrease in the content of lymphocytes. So, in group 1, it was: 16.8 ± 3.57 and 8.4 ± 2.09 ($p > 0.05$), in group 2: 14.0 ± 3.32 and 9.4 ± 2.20 ($p > 0.05$), respectively. The data are not statistically reliable, but it should be noted that patients are already admitted with a lymphocyte level below normal values (N 20 - 37%). We analyzed the dynamics of lymphocytes from the moment of admission to the hospital and their minimum content during treatment. So, in group 1, it was 16.8 ± 3.57 and 6.0 ± 1.91 ($p < 0.05$), in group 2, 14.0 ± 3.32 and 4.0 ± 0.65 ($p < 0.01$), respectively. From these data, we see a significant decrease in the level of lymphocytes during the course of COVID-19. By the time of discharge, their level increases, but does not return to normal (Table 2). A decrease in the content of lymphocytes in the GBT is detected with COVID-19 [27]. Some authors attribute the decrease in their number to immunosuppression [37]. Tsinzerling V.A. and Vashukova M.A. revealed changes in the lymph nodes of patients with COVID-19, linking this with the generalization of coronavirus infection [21].

Indicators	Group 1 (Laennec)		P	Dynamics of indicators (%)	Group 2 (control)		P	Dynamics of indicators (%)
	М+ж (1)	М+ж (2)			М+ж (1)	М+ж (2)		
	A	B			A	B		
Red blood cells (x10^{12}/l)	4,4 ± 0,18	4,1 ± 0,12	< 0,05	-6.8	4,6 ± 0,1	4,3 ± 0,1	< 0,05	-6.5
Hemoglobin (Нв) (g/l)	126,6 ± 3,93	115,2 ± 2,37	< 0,05	-9.1	123,9 ± 4,33	115,1 ± 2,80	> 0,05	-7.1
Color indicator (Ci)	0,86 ± 0,02	0,83 ± 0,01	> 0,05	-3.5	0,8 ± 0,03	0,8 ± 0,02	> 0,05	0.0
Platelets (x10^{9}/l)	231,0 ± 25,78	367,9 ± 40,0	> 0,05	+59.3	218,6 ± 17.59	298,3 ± 36,49	> 0,05	+36.4
Hematocrit (Ht) (%)	36,7 ± 1,12	33,0 ± 0,68	< 0,05	-10.1	36,3 ± 1,26	33,7 ± 0,76	> 0,05	-7.2
White blood cells (x10^{9}/l)	8,8 ± 1,28	11,0 ± 0,59	> 0,05	+25	7,1 ± 1,59	9,2 ± 0,84	> 0,05	+29.6
Stick/nuclear s/n (%)	1,9 ± 0,28	2,4 ± 0,34	> 0,05	+26.3	1,4 ± 0,18	2,4 ± 0,38	> 0,05	+71.4
Segment/nuclear s/n (%)	73,7 ± 5,69	84,8 ± 2,26	> 0,05	+15.1	74,8 ± 5,74	81,9 ± 3,34	> 0,05	+9.5
Lymphocytes (%)	16,8 ± 3,57	8,4 ± 2,09	> 0,05	-48.5	14,0 ± 3,32	9,4 ± 2,20	> 0,05	-40.1
Monocytes (%)	6,3 ± 1,33	4,6 ± 0,87	> 0,05	-27.0	7,9 ± 2,01	6,2 ± 1,44	> 0,05	-21.5
Rate erythrocyte sedimentation (RES) (mm/hour)	32,8 ± 4,16	20,7 ± 5,42	< 0,05	-36.9	28,7 ± 4,29	23,2 ± 1,75	> 0,05	-19.2
Days of hospitalization		12,1 ± 0,10				13,4 ± 0,34	< 0,05	-10,7

Table 2: *Indicators of the general blood test in the examined patients (M ± m) and the dynamics of indicators (%).*

We analyzed the platelet count (N 180-320 x 10^{9}/l) in the patients we examined. As can be seen from table 2, in both groups their content did not differ from the reference values. However, upon admission to the hospital, a decrease in their level was detected in 6 men (22.2%) and 2 women (9.9%). Before discharge, their number increased to normal values in 20 people, decreased in 2 people (in men and women) (9.9%). It should be noted that there is a correlation between the platelet count and the level of D-dimers (r = -0.57). That is, the more thrombosis, the fewer platelets. Thrombocytopenia was previously described in other viral infections [30]. Several mechanisms of its development are proposed for COVID-19: reduced platelet production in the bone marrow, destruction in blood vessels and organs, consumption in intravascular clots (consumption thrombocytopenia), the development of an autoimmune process [10,36]. According to our data, we can conclude that the decrease in the number of platelets is more likely due to their consumption in thrombosis.

As can be seen from the table 3 liver dysfunction is noted, accompanied by an increase in the levels of total bilirubin (N 5-21 mkmol/L) and its fractions, ALT (N (⩽40 u/l) and AST (N (⩽40 u/l).

Initially, total bilirubin was normal in 12 people (59%), and it did not change during treatment: 11.8 ± 1.01 and 10.3 ± 1.09 ($p > 0.05$), respectively. In 10 people (41%), the total bilirubin was already increased at admission, and during treatment it significantly decreased, but did not reach normal values: 68.7 ± 2.30 and 56.1 ± 1.88 ($p < 0.01$).

In our patients, when ALT and AST were received, the norms were increased by 1.5-2.0 in 8 people (36%) and 11 people (49%), respectively. During their stay in the hospital, their content fluctuated, but did not exceed 2 norms. Other authors also point to the rise in the level of transaminases [2,20,34,46]. However, there is still no unanimous agreement on understanding the cause of liver damage [15,18]. Some believe that this is due to a change in the liver before the disease COVID-19 [26], others - polypragmasia in the treatment of COVID-19 [28,31,35], still others - the influence of the SARS-CoV-2 virus itself on the liver [22,29,33,43,45]. Some colleagues believe that the abnormalities in the functional state of the liver detected in COVID-19 are due to the progression and severity of the infectious process [29,46]. We also noticed a similar trend. A number of authors are inclined to believe that in COVID-19, changes in the liver are determined primarily by damage to cholangiocytes [7,47]. However, in our patients, we did not detect a significant increase in the marker of damage to the biliary tract, namely, alkaline phosphatase.

The patients examined by us have a high level of ferritin and CRP, which is characteristic of the "cytokine storm" in COVID-19 [6,7,12]. According to our data, there is a significant correlation between these indicators ($r = + 0.47$, $p < 0.05$). Some authors explain hyperferritinemia by cytolysis of red blood cells [5,14]. However, ferritin is not contained in red blood cells [1]. Therefore, some other explanation of this phenomenon is required. Apparently, ferritin in COVID-19 under the influence of the SARS-CoV-2 virus is released from organs (liver, spleen) and activates inflammation ("cytokine storm"), participating in redox processes with its iron atoms. Some authors [21] generally deny the significant role of iron metabolism disorders in the pathogenesis of COVID-19.

From table 3, we also see pronounced violations of the blood coagulation profile (increased fibrinogen, D-dimer, APTT, decreased PTI associated with a high risk of mortality. Similar data were obtained by other authors [10,39]. Of course, APTT is more likely to increase due to the use of anticoagulants in the treatment of these patients.

Indicators	Group 1 (Laennec)		P	Dynamics of indicators (%)	Group 2 (Control)		P	Dynamics of indicators (%)
	men+women (1)	men+women (2)			men+women (1)	men+women (2)		
	A	B			A	B		
Glucose (mmol/L)	6,9 ± 0,42	8,7 ± 0,88	< 0,05	+26,1	8,5 ± 0,78	9,3 ± 1,12	> 0,05	+9,4
Total bil. (mcmol/l)	63,5 ± 5,55	37,6 ± 2,80	< 0,05	-40.8	56,9 ± 1,34	38,5 ± 1,26	< 0,05	-32.4
ALT (units/l)	61,8 ± 8,11	34,7 ± 4,62	< 0,05	-43,9	32,6 ± 7,90	47,7 ± 8,63	> 0,05	+46.3
AST (units/l)	64,2 ± 10,44	38,1 ± 6,48	< 0,05	-40,7	54,3 ± 3,06	41,6 ± 2,36	< 0,05	-23.4
CRP (mg/l)	108,0 ± 21,22	21,2 ± 11,54	< 0,05	-80.4	107,8 ± 27,94	35,4 ± 8,63	> 0,05	-67.2
D-dimers (mg/L)	1,9 ± 0,39	1,1 ± 0,39	< 0,05	-42.1	1,15 ± 0,30	1,82 ± 0,49	> 0,05	+58.3
Ferritin (mcg/l)	314,6 ± 61,01	187,4 ± 43,82	< 0,05	-40.4	485,5 ± 83,93	346,5 ± 81,52	> 0,05	-28.6
Protrombin (%)	85,5 ± 5,92	92,4 ± 7,61	> 0,05	+8,1	98,9 ± 5,46	95,2 ± 6,84	> 0,05	-3,7
APTT activated partial thromboplastin time	41,3 ± 4,29	75,1 ± 15,04	< 0,05	+81.8	41,6 ± 3,13	49,5 ± 12,09	> 0,05	+19.0
Fibrinogen (g / l)	3,7 ± 0,33	2,9 ± 0,36	< 0,05	-21,6	4,5 ± 0,50	3,8 ± 0,21	> 0,05	-15,6
Urea (mmol/L)	7,4 ± 0,79	8,1 ± 0,86	> 0,05	+9.5	8,5 ± 1,07	8,9 ± 1,16	> 0,05	+4,7
Creatinine (mmol/L)	109,4 ± 7,08	61,4 ± 4,94	< 0,05	-43.9	121,7 ± 18,55	86,9 ± 8,08	> 0,05	-28.6

Table 3: *Indicators of biochemical blood analysis (M ±) in the examined patients and the dynamics of indicators (%).*

As can be seen from table 3, the patients examined by us have impaired renal function (increased levels of creatinine and urea in the blood). At the time of hospitalization, the normal level of urea was in 11 (50%), and creatinine was in 15 (68%). In the course of treatment, regardless of the initial value, they increased the higher, the more severe the course of the disease was. 8 patients were discharged with normal urea levels, 16 with creatinine. In no case did the picture of acute renal failure (acute renal failure) develop. Kidney damage in COVID-19 is described in the works [13,16,17,29]. Although our data and the work of other authors demonstrate that COVID-19 infection affects the renal system, the pathophysiology of this phenomenon is insufficiently studied due to the lack of kidney biopsies. In one of the works [38], after conducting several post-mortem studies, it was postulated that kidney damage is caused by a virus that causes endotheliitis. The authors of this work suggest the possibility of cross-interaction between the lungs and the kidneys with initial lung damage, followed a few days later by renal failure mediated by inflammatory particles, such as cytokines or extracellular vesicles.

It should be remembered that nonsteroidal anti-inflammatory drugs (as antipyretics) should be prescribed with caution in case of COVID-19 infection, since they can cause kidney damage [44]. As can be seen from our data, more than 50% of patients were admitted with normal kidney function. While in the course of treatment, their function worsened the more pronounced, the more severe the course of the disease was.

As we can see, COVID-19 infection includes combined disorders of the function of parenchymal organs, accompanied by a violation of the rheological properties of blood with an increased risk of intravascular coagulation, as well as the risk of developing a "cytokine storm", leading to overload of all organs and systems and increasing the risk of death [13].

Therefore, the above complications require immediate correction, usually accompanied by the simultaneous administration of various drugs, the pharmacodynamics and interaction of which is difficult to predict in an infected SARS-CoV-2 organism. Moreover, the simultaneous administration of drugs against the background of the risk of developing a "cytokine storm" significantly increases the toxic load on the liver.

In the experiment [5] and in the clinic [4], it was shown that placenta hydrolysate (laennec) eliminates chronic iron overload, reduces damage to hepatocytes and prevents the formation of hemosiderosis in the liver, brain and other organs. The use of the drug helps to reduce hyperferritinemia in patients with moderate and severe COVID-19 [13]. Also in the work of Eun-Ha Kim et al. the direct antiviral effect of this drug against SARS-CoV-2 has been shown [34].

According to our data (See table 2 and 3), the administration of the human placenta hydrolysate drug has a favorable effect on many biochemical parameters of the blood and the general condition of patients. Firstly, in the first group of patients, compared with the control, the dynamics of laboratory parameters on laennek was more reliable. Secondly, the percentage of improvement of indicators in the first group, compared with the control, is more significant. For example, (See table 2) the number of platelets after 10 days of taking the drug increased by 59.3%, while in the control - by 36.4%; ESR decreased by 36.9% and 19.2%, respectively. A similar trend can be traced in biochemical indicators. For example, AST fell by 40.7% and 23.4%, respectively; ferritin-by 40.4% and 28.6%, respectively, etc. This favorable effect of placenta hydrolysate also affected the duration of patients stay in the clinic. Patients of the first group were discharged from the hospital earlier, compared with the control (from 13.4 ± 0.34 to 12.1 ± 0.10; $P < 0.05$).

Conclusion

1. Mild anemia, unrelated to the severity of COVID-19, develops in 63.6% of patients.

2. During the course of COVID-19, the level of lymphocytes significantly decreases significantly. By the time of discharge, their level increases, but does not reach the norm.

3. A decrease in the number of platelets is more likely due to their consumption in thrombosis.
4. COVID-19 occurs with liver dysfunction and impaired kidney function.
5. The examined patients have a high level of ferritin and CRP, which is characteristic of a "cytokine storm".
6. Compared with the control, human placenta hydrolysate (laennec) has a more favorable effect on the dynamics of laboratory parameters, namely:
    a. The improvement of indicators on the drug is more significant and reliable,
    b. The percentage of changes in indicators is higher.
7. The appointment of human placenta hydrolysate (laennec) reduces the period of stay of patients in the hospital by 1.3 days.

Conflict of Interest

There is no financial interest or conflict of interest.

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