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## ROLE OF EXTRACORPOREAL THERAPIES IN CRITICALLY ILL PATIENTS WITH SARS-COV-2

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## РОЛЬ ЕКСТРАКОРПОРАЛЬНИХ МЕТОДІВ ТЕРАПІЇ У ПАЦІЄНТІВ З SARS-COV-2 В КРИТИЧНИХ СТАНАХ

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*Мета.* Проаналізувати досвід застосування екстракорпоральних методів лікування пацієнтів з SARS-CoV-2. *Методи.* Проведено 48 екстракорпоральних процедур 27 пацієнтам з лабораторно підтвердженим SARS-CoV-2, двобічною пневмонією та різними супутніми хронічними захворюваннями. Всі пацієнти мали середній бал за шкалою SOFA  $8,1 \pm 3,1$  [мінімум 3, максимум 16] під час надходження до відділення інтенсивної терапії. 19 пацієнтів (70,4%) мали тяжке ушкодження легенів більше 75% за даними комп'ютерної томографії грудної клітини. Показання до початка екстракорпоральної терапії включали цитокіневий шторм, пов'язаний з гострим респіраторним дистрес-синдромом (ГРДС) і септичним шоком. *Отримані результати.* В цілому кожен пацієнт пройшов як мінімум одну процедуру екстракорпоральної терапії. 11 пацієнтів пройшли від 2 до 6 сеансів. Ізольоване відділення плазми і гемоперфузія дозволили знизити вазопресорну/кардіотонічну підтримку, дещо поліпшити параметри вентиляції, зі значною виразністю, але не тривалим зниженням рівня маркерів запалення. Найбільш раціональним виявилось поєднання методів, що забезпечують швидке видалення агентів, тривалу корекцію гомеостазу і детоксикацію, контрольовану температурну реакцію і гідратацію. Екстракорпоральна терапія не вплинула на обсяг і виразність ушкодження паренхіми легені. 19 (70,4%) пацієнтів, які отримували екстракорпоральну терапію, були переведені з ШВЛ на самостійне дихання, тоді як 8 (29,6%) пацієнтів мали важкі ураження легень понад 75% за даними повторної комп'ютерної томографії грудної клітини. Середня тривалість пере-

бування у відділенні інтенсивної терапії серед тих, що вижили, склала  $9 \pm 3,5$  [хв. 4 макс. 22]. 28-денна летальність і госпітальна летальність склали 25,9% (7). *Висновок.* Тривала екстракорпоральна терапія у пацієнтів з SARS-CoV-2 продемонструвала ефективність в корекції дисфункцій органів і шоківих станів, але не призвела до значного поліпшення виразності тяжкості пошкодженої паренхіми легені.

**Ключові слова:** екстракорпоральна терапія, COVID-19, гемоперфузія, поділ плазми, гемодіалізації, МСКТ грудної клітки, ущільнення, затемнення по типу матового скла

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## **ROLE OF EXTRACORPOREAL THERAPIES IN CRITICALLY ILL PATIENTS WITH SARS-COV-2**

**A.V. Geyze, A.A. Kleuzovich, G.P. Plotnikov, M.S. Rubtsov**

*Aim.* To analyze the experience of using extracorporeal therapies to treat patients with SARS-CoV-2. *Methods.* 48 extracorporeal procedures were performed in 27 patients with a laboratory confirmed SARS-CoV-2, bilateral pneumonia, and various concomitant chronic diseases. All patients had the mean SOFA score of  $8.1 \pm 3.1$  [min 3, max 16] at admission in the ICU. 19 patients (70.4%) had severe lung injury over 75% according to the chest CT scans. Indications for extracorporeal therapies initiation included cytokine storm associated with acute respiratory distress syndrome (ARDS) and septic shock. *Results.* Overall, each patient received at least one extracorporeal therapy. 11 patients underwent 2 to 6 sessions. Isolated plasma separation and hemoperfusion allowed reducing vasopressor / cardiotoxic support, slightly improved ventilation parameters, with a significant, but not prolonged decrease in the levels of inflammation markers. The combination of methods that provide rapid elimination of agents, with prolonged correction of homeostasis and detoxification, with controlled temperature response and hydration, appeared to be the most rational. Extracorporeal therapy did not improve the volume and severity of damaged lung parenchyma. 19 (70.4%) patients who received extracorporeal therapy were transferred from mechanical ventilation to spontaneous breathing, whereas 8 (29.6%) patients had severe lung lesions over 75% according to the repeated chest CT scans. The mean length of stay in the ICU among survivors was  $9 \pm 3.5$  [min 4 max 22]. The 28-day mortality and in-hospital mortality rate was 25.9% (7). *Conclusion.* Prolonged extracorporeal therapy in patients with SARS-CoV-2 have demonstrated efficacy in relieving organ dysfunctions and shock states, but did not significantly improve the severity of damaged lung parenchyma.

**Keywords:** extracorporeal therapy, COVID-19, hemoperfusion, plasma separation, hemodiafiltration, chest MSCT, consolidation, ground-glass opacities

**Background.** Over 13.8% of patients infected with SARS-CoV-2 are severe and 6.1% are critical during the ongoing COVID-19 pandemic [1]. Patients of these subgroups may develop hypercytokinemia or so-called cytokine storm [2] with the systemic capillary leak syndrome and dysfunction of the lungs, heart, and kidneys. The production of interleukin-6 increases along with ferritin and C-reactive protein. Elevated biomarkers are considered as a risk factor for developing acute respiratory distress syndrome (ARDS) [3]. The available medical data suggest the beneficial potential of extracorporeal therapy to purify the blood from pro-inflammatory agents and fight the cytokine

storm [4]. Despite WHO has suggested the favorable effects of extracorporeal therapy for treating MERS, its effectiveness for SARS-CoV-2 remains debatable [5]. The guidelines released by the Association of Anesthesiologists and Intensivists of the Russian Federation defines three scenarios of extracorporeal therapy for treating patients infected with coronavirus [6], that are partially included in the Temporary Guidelines of the Ministry of Healthcare of the Russian Federation for Treating SARS-CoV-2, version 7 [7]. We present our experience of using various extracorporeal therapies to treat critically ill patients on mechanical ventilation in the intensive care unit.

**Aim.** To analyze the accumulated experience of using extracorporeal therapy in patients with SARS-CoV-2.

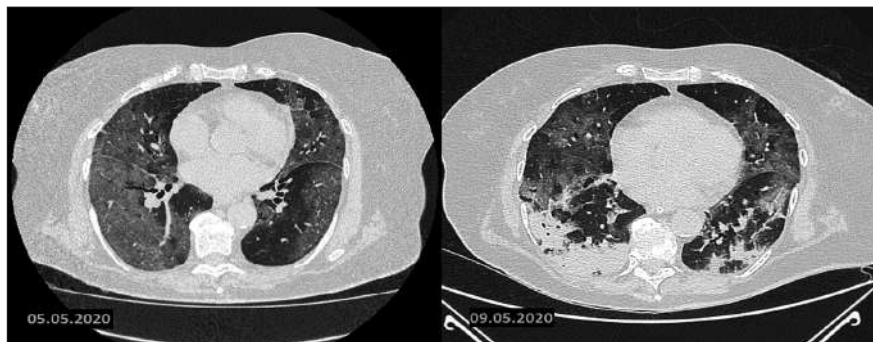
**Methods.** 27 critically ill patients underwent 48 extracorporeal procedures in the Infectious Disease Hospital for SARS-CoV-2 at the Center of Surgery. All patients had confirmed SARS-CoV-2 infection, bilateral pneumonia, and several concomitant chronic diseases. 17 patients (62.9%) suffered from diabetes mellitus, 19 patients (70.4%) from hypertension, 8 patients (29.6%) from chronic obstructive pulmonary disease, 6 patients (22.2%) from chronic kidney disease, and 4 patients (14.8%) from chronic heart failure. Two patients (7.4%) had a prior stroke. At admission to the ICU, all patients had the SOFA score of  $8.1 \pm 3.1$  [min 3, max 16]. 19 patients (70.4%) had severe lung injury of >75%. 24 (88.9%) patients undergoing extracorporeal therapy required prolonged mechanical ventilation. Three (11.1%) patients underwent non-invasive ventilation before extracorporeal therapy was initiated. All patients received standard medical therapy recommended by the Temporary Guidelines of the Ministry of Healthcare of the Russian Federation for Treating SARS-CoV-2, versions 5 and 6 [7]. Upon admission to the hospital, all patients underwent the SARS-CoV-2 RT-PCR test. ECG was recorded in all patients. Clinical and biochemical studies were performed according to the adopted protocols. Chest MDCT was performed according to the standard protocol on a Philips Ingenuity CT 64 multidetector computed tomography. Imaging postprocessing was performed using Philips IntelliSpace Portal software (Philips Medical Systems, Cleveland). Extracorporeal procedures were performed using Multifiltrate (Fresenius Medical Care, Germany) and Aquarius (Nikkiso Aquarius RCA, Great Britain) hemofiltration machines. The statistical analysis was not performed because of the absence of the control group. The effectiveness of the selected treatment was considered based on the clinical and laboratory data.

**Results and Discussion.** The overall duration of extracorporeal therapy was  $4.9 \pm 1.9$  [min 1 max 6] days, including  $56.6 \pm 14.2$  [min 2 max 144] hours from admission to the ICU. Indications for extracorporeal therapy in (77.8% of cases included the cytokine storm with acute respiratory distress syndrome (ARDS) and septic shock. Patients with COVID-19 pneumonia have a high risk of thrombotic complications, and a critical increase in D-dimer and fibrinogen degradation products (FDP) are predictors of death [8,9]. Since FDPs cannot be removed by filtration due to their molecular weight of >240 kDa, plasma exchange or plasma separation is the method of choice [10]. Several researchers have shown lower mortality in patients with high levels of markers for hypercoagulation at baseline undergoing plasmapheresis than those who did not receive it (45.7% vs. 58.3%) [11]. Other research groups have noted that mortality in patients present with COVID-19 pneumonia who received plasma exchange as an additional method of treatment was 47.8% versus 81.3% in the standard therapy group

( $p < 0.05$ ). Therefore, they recommend it to use at earlier stages not limiting only to anti-shock therapy [12].

*Selective plasma filtration* was used in 3 (11.1%) patients with the cytokine storm on an Evaclio, EC-3C20 filter (Kawasumi Laboratories, Inc., Japan) in a volume of  $3700 \pm 900$  mL with 20% albumin replacement and donor anticoid plasma. In all cases, we were able to relatively stabilize the hemodynamic parameters with a decrease in the dosages of vasopressor or cardiotoxic support and to improve or soften the ventilation parameters. A decrease in the levels of inflammatory markers was significant, but not prolonged. D-dimer and ferritin decreased to the upper limit of the reference values and remained the same after. Two patients were switched to spontaneous breathing on days 4 and 6 after the procedure. They were discharged from the ICU on days 9 and 19. Both patients were subsequently discharged upon recovery. One patient with pre-existing POCD (33.3%) died because of the progression of respiratory failure and decompensated CHF. After two procedures, the percentage of lung injury decreased from 72% to 60% and from 80% to 76%, respectively. After one procedure, no positive changes were found during the control study. In all cases, ground-glass opacities changing to consolidations were found in these patients suggesting a positive trend.

The strategy of cytokine sorption on various hemoperfusion sets has been used worldwide in 58 countries with a positive result of reducing organ dysfunction in COVID-19 [13]. We performed isolated hemoperfusion on a Jafron HA330 hemofilter (China) in two critically ill patients who were admitted to the intensive care unit. The procedure lasted for 6 hours with the replacement of the hemoperfusion cartridge. The blood flow rate was 150 mL/min. One patient demonstrated a decrease in the severity of organ dysfunction and improved hemodynamic parameters after the procedure. The dosage of vasopressors was decreased. Ventilation parameters improved along with the levels of inflammatory markers and hemostasis parameters. After 5 days, the patient was switched to spontaneous breathing and transferred to the department ward. The second patient was admitted with viral/bacterial pneumonia, hemodynamic instability, and persistent hypoxemia, followed by the onset of sepsis, septic shock. The patient required long-term intensive therapy and mechanical ventilation through the tracheostomy tract. The patient was transferred to another hospital when the SARS-CoV-2 hospital was closed. The patient had more consolidations than ground-glass opacities according to the CT scan findings. These findings suggested a tendency towards recovery with a decrease in the zones of lung tissue damage (Fig. 1).



**Figure 1.** Chest MSCT scan of the patient with selective hemoperfusion

Hemodiafiltration (HDF) was the main method of extracorporeal therapy, including its combination with hemoperfusion. We noted the effect of tissue release in those patients who underwent isolated hemoperfusion or plasma separation. After a short period (4-6 hrs), an increase in the levels of inflammatory markers and fibrinogen degradation products was reported. Therefore, a combination of methods providing rapid elimination of agents, with prolonged correction of homeostasis and detoxification, controlled temperature response, and hydration seemed to be rational. 20 cases of combined techniques (hemoperfusion + hemofiltration or hemodiafiltration) – 20 (Jafron HA-330-I + “Toray” Filtryzer BK U-2.1) were used in 17 patients with the cytokine storm and bilateral viral/ bacterial pneumonia with subsequent sepsis and multiple organ dysfunction syndrome. The mean time of dialysis and filtration procedures was 12±9.3 [min 6 max 36] hours, effluent 35-40 mL/kg/h [min 25 max 150]. The procedures were initiated at admission to the ICU. The venovenous access was used in all cases. Anti-coagulation with heparin 500 U/h was performed in 95.8% of cases. Two procedures were completed without heparinization. Taking into account the presence of initial cytotoxicity in patients receiving three-component antiviral therapy, we did not use citrate anticoagulation. Citrate is known to metabolize mainly in the liver and skeletal muscles in the systemic circulation [14], proceeds anaerobically and can be limited in respiratory and heart failure with low cardiac output [15]. A single replacement of sets was required during HDF without anticoagulation due to a critical increase in transmembrane pressure. Changes in laboratory parameters during combined methods are presented in Table 1.

**Table 1**

*Changes in the laboratory data using the combined extracorporeal therapies*

n=20	SOFA scores	PaO <sub>2</sub> / FiO <sub>2</sub>	WBC, x10 <sup>9</sup>	PCT ng/mL	PLT, x10 <sup>12</sup>	D-dimer, µg/L	CPR, mg/L	Lactate, mmol/L	Ferritin, ng/mL
Before	9,9 [7;11]	81,3 [72; 104]	12,9 [10,7;18,9]	4,11 [3,45;5,2]	330 [297; 385]	5760 [4055;6183]	173,7 [151;181]	8,9 [4,9;5,95]	672,5 [474;756]
After	6,9 [5,3; 9,1]	138 [100;145]	14,7 [9,9;18,2]	2,7 [1,9;3,6]	226 [185; 290]	2178 [1660;2300]	152 [137;166]	2,3 [1,75;3,3]	372 [217;415]

SOFA – Sequential Organ Failure Assessment; PaO<sub>2</sub>/ FiO<sub>2</sub> – oxygenation index; WBC – white blood cells; PCT – procalcitonin; PLT – platelets. CRP – C-reactive protein.

The use of prolonged combined procedures allowed achieving positive results in patients with ARDS and shock, including a significant improvement in the oxygenation index and improved pulmonary injury according to the CT scan. Obtained data are consistent with the results previously reported by other research groups [16]. However, we assume that the main mechanism underlying the lung injury in SARS-CoV-2 is the direct damage of the vessels and endothelium, causing the formation of microvascular clots and angiopathy [17]. We suppose that the demonstrated effectiveness of extracorporeal therapy in relieving shock states does not have a significant influence on the improvement of the lung injury. Positive CT changes may be explained by the natural course of the process during regression of lesions and complications.

**Conclusion.** Our experience has not shown positive effects of using extracorporeal therapy on the severity and volume of damage to the lung tissue in patients with SARS-CoV-2. Prolonged extracorporeal therapy for treating patients with SARS-CoV-2 is effective in relieving organ dysfunctions and shock.

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