Plasmapheresis methods for COVID-19

Prospects of plasmapheresis for patients with severe COVID-19
Ilmira R. Gilmutdinova, Maksim Yu. Yakovlev, Petr S. Eremin, Anatoliy D. Fesun
Federal State Budgetary Institution “National Medical Research Centre for Rehabilitation and Balneology” of the Ministry of Health of Russia, Moscow, Russia

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Abstract
On February 11, 2020, the World Health Organization officially named the infection caused by the new coronavirus “Coronavirus disease 2019” (COVID-19). On February 11, 2020, the International Committee on Taxonomy of Viruses (ICTV) officially named the infectious matter “severe acute respiratory syndrome coronavirus 2” (SARS-CoV-2). Emergence of severe complications with new coronavirus disease is due to the development of hypercytokinaemia, also known as “cytokine storm”. These complications comprise acute respiratory distress syndrome (ARDS), respiratory failure and death. Emerging data point to the logic of using extracorporeal haemocorrection to normalise cytokine levels and reduce the severity of organ disorders. The analysis of the literature indicates that to date, a certain positive experience has been accumulated in the world in the application of extracorporeal methods in clinical practice in patients with COVID-19.

Key Words: plasmapheresis, extracorporeal haemocorrection, COVID-19, coronavirus.

On February 11, 2020, the World Health Organization officially named the infection caused by a new coronavirus “Coronavirus disease 2019” (COVID-19) and the International Committee on Taxonomy of Viruses (ICTV) officially named the infectious matter “severe acute respiratory syndrome coronavirus 2” (SARS-CoV-2). Throughout the ongoing COVID-19 pandemic, over 13.8% of cases are severe and over 6.1% are critical. The severity of the condition in patients of these subgroups is caused, interalia, by the development of hypercytokinaemia, also known as “cytokine storm”.2,3

Hypercytokinaemia
Cytokine Storm Syndrome (hypercytokinaemia) is a severe uncontrolled immune response, when cells of the immune system release excessive amounts of cytokines (interferons, interleukins, chemokines, colony stimulating factors, tumour necrosis factors, etc.) into the blood.4 For instance, a study published in Lancet Journal by Chinese scientists showed an increase in inflammatory cytokines/chemokines (IL-2, IL-7, IL-10, GCSF, IP-10, MCP-1, MIP1A and TNF-α) in patients with severe and critical COVID-19 infection.5–8 It has been proven that the severity of COVID-19 disease is directly related to the cytokine storm and the amount of pro-inflammatory agents.7 Under normal conditions, levels of inflammatory and anti-inflammatory cytokines in the organism are balanced. However, when the virus implants into the body, the general immune response is triggered by activation of neutrophils, dendritic cells, macrophages, lymphocytes and natural killer cells, along with initiation of the local immune response. Activated cells release a large number of cytokines, especially of inflammatory type, triggering immune cells, which, in turn, release new cytokines. This positive feedback effect causes hyperexpression of cytokines in response to the etiological stimulus and the development of “cytokine storm”.2,4 This phenomenon is most often observed in patients with chronic diseases, compromised immunity and deep hypoxia. Such patients are more likely to develop acute respiratory distress syndrome (ARDS) and multiple organ dysfunction syndrome (MODS). In addition, they demonstrate high levels of C-reactive protein (CRP) and IL-6, a decrease in the number of lymphocytes, as well as abnormal hemostasis indicators.8 Thus, the world medical community is challenged to select therapeutic methods that allow to decrease the amount of inflammatory cytokines/chemokines and, consequently, to abate the cytokine storm, which aggravates the course of COVID-19 disease.6 Emerging data point to the logic of using extracorporeal haemocorrection to normalise cytokine levels and reduce the severity of organ disorders primarily in severe and critical ill patients.1,6,8–10 However, the use of
extracorporeal haemocorrection methods in less severe patients is also possible. So, in scientific publications there are already positive results of the use of simple plasmapheresis, plasma exchange with of convalescent plasma and plasmapheresis with immunoglobulin therapy.\textsuperscript{11}

**Plasmapheresis**

Plasmapheresis is the procedure of removal, treatment, and return of blood plasma or components thereof from and to the blood circulation. Plasmapheresis can be either therapeutic (extracorporeal methods of blood treatment by removing some plasma components) or donated (donated plasma is obtained from stored whole donor blood with subsequent return of cell blood elements).\textsuperscript{12-14} Plasmapheresis has been used for treatment of various diseases for many years. Apheresis Applications Committee of the American Society for Apheresis (ASFA) identified 4 groups of diseases, for treatment of which plasmapheresis can be used. The 1\textsuperscript{st} group includes diseases that reveal maximum efficiency of treatment with plasmapheresis. The 4\textsuperscript{th} group is for diseases, plasmapheresis treatment of which is inefficient. For instance, plasmapheresis proved best as part of a comprehensive treatment program for kidney diseases (glomerulonephritis, Goodpasture syndrome, focal segmental glomerulosclerosis, kidney transplantation etc.), in liver transplantation (desensitization), for treatment of myasthenia, thrombotic microangiopathy, thrombocytopenic purpura, Wilson disease, antiphospholipid syndrome, drug overdose, intoxications, systemic lupus erythematosus and various other diseases.\textsuperscript{15-19}

In accordance with the classification of methods of extracorporeal haemocorrection (Sokolov AA, 2017)\textsuperscript{20} the following methods relate to the effect on blood plasma:

- membrane technology (plasma filtration, selective plasma filtration or selective plasma exchange, cascade plasma filtration, plasma diafiltration)
- centrifuge technology (plasmapheresis)
- sorption technology (plasmosorption) and others.\textsuperscript{20}

In terms of efficiency and safety in regard to severe and critical patients, the procedure of selective and cascade plasma filtration has proved to be the most effective and safe of all. This technique is a method of extracorporeal haemocorrection based on the principle of filtration and convection plasma mass transfer through a semipermeable membrane due to the pressure gradient, which contributes to the effective removal of high-molecular large-globular blood plasma components exceeding the size of the albumin molecule. The plasma itself is obtained from whole blood through centrifugal or membrane plasmapheresis.\textsuperscript{17,20,21} Ig M, circulating immune complexes, cryoglobulins, some viruses and other large molecules and supramolecular complexes are effectively removed.\textsuperscript{13,20,22} Selective plasma filtration may be accompanied by a plasma exchange procedure in which the effused volume is replaced by donor plasma. In this case, donor convalescent plasma containing antibodies against SARS-CoV-2 is used.\textsuperscript{23-25} The use of anti-COV-2 immunoglobulins, which are contained in the COVID-19 convalescent plasma, is a highly logical therapeutic approach aimed at forming a passive immunity. It should be noted that the safety and effectiveness of this COVID-19 treatment method has not yet been fully confirmed. An international survey was done to question centers that studied the use of convalescent plasma in treatment of COVID-19 patients. The survey identified 64 research studies in 22 countries. However, only 20 centers from 12 countries revealed information on their studies. Out of all studies, only 4 are set to comprise 400 or more patients. The authors of this research express a hope that blind studies, randomization and larger sampling would allow these studies to provide objective results of high level of evidence.\textsuperscript{26} Clinical studies on this matter are being conducted in China, USA, Russia, France, and some other countries. However, some scientists have already published intermediate data indicating the positive effects of convalescent plasma in the treatment of COVID-19.\textsuperscript{23,27} The procedure of donor plasmapheresis is not only safe for donors themselves, but also useful in terms of improving blood rheology and correcting hypercoagulation. This effect is achieved through the use of anticoagulants based on citrate and removal of high-molecular blood components that increase blood viscosity.\textsuperscript{28} It is widely known that the majority of patients with COVID-19 have a hypercoagulation condition characterised by an increase in prothrombin time, D-dimer and fibrinogen levels at practically normal values of activated partial thromboplastin time.\textsuperscript{29,30}

**Operating principles of plasmapheresis methods**

Figure 1 shows the basic operating principles of plasmapheresis methods in patients with severe form of COVID-19, that mainly include the following:\textsuperscript{8,31,32}

- removing pathogenic circulating molecules, inflammatory cytokines;
- removing metabolic products such as creatinine, urea nitrogen;
- maintaining hemodynamic stability in the organism;
- correction of blood rheological disorders;
- correction of electrolyte and acid-alkaline balance disorders to maintain stability of internal environment

**Case reports and recommendations**

Chinese scientists presented the results of treatment of three patients in severe condition with bilateral pneumonia and confirmed COVID-19 in Wuhan, China in the paper published in early April 2020.\textsuperscript{1} One of the patients underwent 3 plasma exchange sessions and two patients underwent plasma filtration using oXiris®...
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**Fig 1. Operating principles of plasmapheresis methods**

Indications for an urgent start of treatment:
- clinical signs of progressive respiratory failure;
- signs of severe coronavirus infection (respiration rate ≥ 30/min and/or blood oxygen saturation ≥ 93% and/or PO2/FiO2 index ≥ 200 mm Hg);
- progression of lung damage at the rate of ≥10% per day, identified using one of the imaging methods;
- progressive increase of inflammatory marker levels

**Fig 2. The choice of methods depends primarily on the capabilities of the medical staff**

According to the manufacturers’ statement, the adsorption cartridge D2000 is effective in reducing the level of IL-3, IFN-gamma, IL-10, IL-1B, IL-6, IL-8, MCP-1 and TNF-alpha.33 The use of FDA-approved technology is allowed for patients over 18 years of age who have any of the following symptoms: i) early acute lung injury/early acute respiratory distress syndrome; or ii) severe health condition characterized by respiratory embarrassment; respiratory rate ≥ 30/min; SpO2 level ≤ 93%; oxygenation (respiratory) index <300, and/or increase in lung infiltrates >50% within 24–48 hours; iii) critical health condition, determined by respiratory failure; toxic shock syndrome and/or multiple organ dysfunction.

The issue of using plasmapheresis technologies was also addressed in the Russian Federation. Thus, the Scientific Society of Experts of Extracorporeal Blood Treatment in Intensive Care presented interim recommendations “on the use of methods of extracorporeal haemocorrection in the complex treatment of patients with new coronavirus disease COVID-19”. According to these recommendations, a key point of reaching the maximum efficiency of the extracorporeal haemocorrection technique is its early application, namely, during the early stages of clinical and laboratory manifestation of cytokine storm syndrome and multiple organ dysfunction.

Below are indications for an urgent start of extracorporeal treatment (Figure 2):
- clinical signs of progressive respiratory failure;
- signs of severe coronavirus infection (respiration rate ≥ 30/min and/or blood oxygen saturation ≤ 93% and/or PO2/FiO2 index ≤ 200 mm Hg);
- progression of lung damage at the rate of ≥10% per day, identified using one of the imaging methods;
- progressive increase in inflammatory marker levels (CRB, IL-6 etc.)

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Following these recommendations, the choice of extracorporeal haemocorrection method depends primarily on the capabilities of the medical staff as well as on the clinical situation presented. In conclusion, there is a need for more statistical data and, consequently, for carefully planned clinical tests to further evaluate effectiveness and safety of plasmapheresis treatment and of the combined techniques described in this narrative review.

List of acronyms

ARDS - acute respiratory distress syndrome
COVID-19 - Coronavirus disease 2019
CRP - C-reactive protein
ICTV - International Committee on Taxonomy of Viruses
MODS - multiple organ dysfunction syndrome
SARS-CoV-2 - Severe acute respiratory syndrome coronavirus 2

Authors contributions

Ilmira R. Gilmudtinova, Yu M. Yakovlev, Petr S. Eremin and Anatoliy D. Fesun have contributed equally to this work.

Acknowledgments

The Authors thank the A&C M-C Foundation for Translational Myology, Padova, Italy and the Federal State Budgetary Institution “National Medical Research Centre for Rehabilitation and Balneology” of the Ministry of Health of Russia, Moscow, Russia for supporting this publication.

Funding

None

Conflict of Interest

The authors declare they have no financial, personal, or other conflicts of interest.

Ethical Publication Statement

We confirm that we have read the Journal’s position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Corresponding Author

Gilmudtinova Ilmira R., Federal State Budgetary Institution “National Medical Research Centre for Rehabilitation and Balneology” of the Ministry of Health of Russia, Moscow, Russia.
ORCID iD: 0000-0001-6743-2615
Email: gilm.ilmira@mail.ru

Emails and ORCID iD of Coauthors

Maksim Yu. Yakovlev: masdat@mail.ru
ORCID iD: 0000-0002-5260-8304

Petr S Eremin: eremipss@gmail.com
ORCID iD: 0000-0001-8832-8470

Anatoliy D Fesun: nmicrk@nmicrk.ru
ORCID iD: 0000-0003-3097-8889

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Submission: June 5, 2020
Revision received: September 2, 2020
Accepted for publication: September 2, 2020