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Mini Review

Promising Treatment of Patients with Coronavirus Infection

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Abstract

The article focuses on the problems of treatment of coronavirus infection. The issues of pathogenesis and disruption of oxygen supply of organs and systems are considered. The causes of hypoxemia and disruption of gas transport function of red blood cells are noted. The history of the development and use of perfluorocarbon emulsions in disorders of gas exchange, hypovolemia and thrombus forming is presenting. Data on the effectiveness of the use of perfluorin to improve the oxygen supply of organs and tissues are considered. The indications of perfluorin use in the symptomatic treatment of various diseases are determined. The appropriateness of using perfluorin to treat coronavirus infection is substantiating. Proposals for research in interest of widespread use of perfluorin in medical practice are formulating.

Keywords: *Perftoran; Use Efficiency; Indications for Use; Coronavirus; Infection; Lung Damage; Acute Respiratory Distress Syndrome*

Introduction

Medical care for the wounded, sick and injured in accidents, incidents, disasters and mass infections should be provided using effective treatments [9]. This fully applies to the treatment of coronavirus, which can affect various organs and tissues of the body and exacerbate the course of their chronic diseases. The epidemic nature of the spread of the disease indicated the need to use the mobilization reserves of states, ministries of health and health facilities and to implement health plans for a large number of patients with coronavirus infection. Already the first studies of pathogenesis and mechanisms of coronary infection have noted the seriousness of disorders of organs and tissues due to insufficient oxygenation of the blood, including due to damage to red blood cells and disruption of their function of delivering oxygen to cells and tissues. At the same time, it turned out that there is no specific treatment and drugs capable of inactivating the pathogenic virus, preventing or reducing its affecting activity. In this regard, the main area of control against coronavirus infection was symptomatic treatment and elimination of emerging cell and tissue lesions in a result of hypoxemia. At the same time, it was found that the most frequent and life-threatening development of coronavirus disease is lung damage.

The function of the lungs to saturate red blood cells with oxygen

In this case, the function of the lungs to saturate red blood cells with oxygen is not realizing, and the needs of tissues and cells, especially organs that have become "targets", are not adequately satisfied. At the same time, the presence of chronic diseases infected with the virus and, above all, lungs, kidneys, heart and a number of other organs and systems of the body, becomes a risk factor and cause of death.

Pathological studies have also shown that in many cases such outcomes in coronavirus infection are the result of damage to the alveoli of the lungs, red blood cells and hemoglobin, vascular wall inflammation, hemolytic micro-thrombovasculitis and generalized intravascular microthrombosis. Coronavirus caused blood flow disorders in micro-sucks and thrombosis in large and medium vessels of the lungs, heart, brain, dermis and kidneys.

The striking effect of coronavirus

The striking effect of coronavirus is also damage to the endothelial, increase blood clotting and disrupt the functioning of the sympathoadrenal system [14]. All this leads to the development of hypoxemia, a decrease in oxygen supply of tissues and cells and the development of inflammatory processes. At the same time, the functionality of the heart and other organs and systems of the body is significantly reducing. Disturbances of their functioning are manifesting by the manifestation of the relevant symptoms and syndromes, including gastric tachycardia and atrial flutter.

The treatment of coronavirus infection

The World Health Organization recommended remdesivir, chloroquine and hydroxychloroquine for the treatment of coronavirus infection, as well as a combination of lopinavir and ritonavir in the complex with interferon beta. It was noted that chloroquine and hydroxychloroquine in doses affecting coronavirus are toxic. Lopinavir suppressed the activity of enzymes that break down protein chains into peptides that form the basis of virus reproduction. The combination of ritonavir and lopinavir under the caletra brand has been used to treat HIV since 2000. Remdesivir was intended to treat Ebola and related viruses by exposure to a key viral enzyme and to suppress virus replication. As a drug capable of coping directly with coronavirus, the possibility of improving alpha-ketoaids, reducing the activity of its protease, which breaks down amino acid chains to form a viral protein, was considered. At the stage of the experimental study are drugs niclosamines and nitazoxanide.

Based on the experience of treating patients with atypical pneumonia in lung coronavirus lesions initially as drugs of choice offered antimalarial therapy, in particular, chloroquine, hydroxychloroquine and mefloquine. The Russian Federal Medical and Biological Agency for the treatment of coronavirus infection has also proposed mefloquine, which prevents the development of inflammatory phenomena caused by the virus at the cellular level. Inhalational form of triazavirin was considered as a drug for the treatment of coronavirus infection. Inhalational form of triazavirin was considered as a drug for the treatment of coronavirus infection. Based on the evaluation of the data on the effectiveness of these drugs, the Russian Ministry of Health has included in the list of drugs for the treatment of coronavirus infection lopinavir in combination with ritonavir used to treat HIV infection, antimalarial chloroquine and hydroxychloroquine, and tocilizumab, umiferovir, remdesivir and favipiravir, as well as drugs interferon. As an antiviral drug recommended arbidol and antipyretic - paracetamol. These drugs of symptomatic treatment have an anti-inflammatory effect or affect the individual pathogenetic mechanisms of tissue damage. However, there is no conclusive evidence of their effectiveness in the treatment of coronavirus infection. They do not have an antiviral effect on infection and are not without side effects. In particular, antimalarial drugs have cardiotoxicity, and parenteral administration of interferon-alpha increases the risk of severe complications with increased anti-inflammatory activity.

The main cause of death of patients with coronavirus infection

According to Russian data, the main cause of death of patients with coronavirus infection is acute respiratory distress syndrome. Stem cells are proposed to treat coronavirus infection in the case of an immune system response manifested by acute respiratory distress syndrome. However, data on the effectiveness of this treatment have not yet been published. In Russia, the drug levilimab, which has a trade name ilsira. The Ministry of Health of the Russian Federation has registered the drug levilimab, which has the trade name ilsira. It is designed to treat severe forms of coronavirus disease. In particular, in the case of hyperreaction on damage to the lung tissue virus. However, it appears that the basis of the tactics of supportive therapy, including in coronavirus infection, should be the prevention, reduction or

elimination of hypoxemia and improved oxygen supply to cells and tissues of the body. The rapid selection of methods, tools and technologies to address this challenge is a critical focus for health authorities and health facilities. It provides timely organization of treatment for seriously ill patients with lung lesions, including coronavirus infection. Artificial ventilation as a means of increasing blood oxygenation, especially with significant lung damage, capillaries, increased blood clots and reduced gas transport function of red blood cells, becomes ineffective. In many cases, ventilators involve the supply of air, including oxygen-enriched, under pressure at the end of inhalation. If alveoli are damaged, this can cause additional damage and secondary infection. In addition, effective blood oxygenation is not provided due to damage to red blood cells and reduced their gas transport capabilities. The ventilators are known to involve decontamination of the elements of the device and periodic replacement of filters if they are used in their design. Sterilization and decontamination of elements of the design of the devices requires several hours and are carried out by special technology.

Meanwhile, there are grounds and opportunities to solve this problem. At one time, search studies were carried out in order to create blood substitutes based on perfluorocarbon emulsions. They were aimed at replacing donor blood with heavy blood loss and ensuring that in the field was able to quickly eliminate hypovolemia with a universal blood substitute without determining the blood group and rhesus factor. Initially, the emphasis was on the rapid removal of the drug from the blood with the use of large-cut emulsion. However, this problem was constrained by an increased risk of blockage of capillaries with emulsion. Studies of this direction were carried out by the staff of the Institute of Biological Physics of the USSR Academy of Sciences under the direction of Professor F.F. Beloyartsev. In 1979, the Institute established a laboratory for medical biophysics to conduct experiments on the cultivation of animal cells on liquid perfluorocarbons and perfusion of the heart and kidneys with perfluorocarbon emulsion. Perfluoroemulcia particles had greater penetrating power and were able to transport oxygen. In addition, they contributed to the expansion of capillaries and better penetration of red blood cells. As a result of research, in 1982 the drug perftoran was created, which has an effective gas transport function. The materials of fundamental and applied research on the use of perfluorocarbons in biology and medicine were presented in the literature [6]. Data from an experimental study of the gas transport function of perfluorocarbon emulsion were published in order to improve myocardial oxygen support [8]. In March 1985, the USSR Pharmaceutical Committee granted permission to conduct clinical trials of perfluorin as a blood substitute with oxygen transfer function.

Transplantation for kidney transplantation perphuzed by perfluorin

Clinical studies were conducted at the Institute of Transplantation for kidney transplantation perphuzed by perfluorin. The Dnipropetrovsk Medical Institute effectively used perftoran in the treatment of traumatic brain injuries, in connected with the blood supply to the brain deteriorates due to the narrowing of capillaries, disruption of cerebrosal fluid outflow and increased intracranial pressure. In Institute of Surgery were noted the positive effect of the use of perfluorin in operations on the "dry" heart. The use of perfluorin in the General Military Medical Hospital was particularly effective. N.N. Burdenko in the provision of medical and surgical assistance to the wounded from the Limited Military Contingent during the fighting in the Republic of Afghanistan. Perftoran has proven to be an effective means of restoring the gas transport function of red blood cells in the fat embolism of blood vessels.

The dissolution of gases in perfluorocarbons

The dissolution of gases in perfluorocarbons and their release during changes in the partial pressure of gases occurred almost instantly, for 14 - 26 msec, while in the system "hemoglobin-oxygemoglobin" it occurs for 200 - 250 msec. Perfluorocarbons were not dissolved in water and blood plasma and were injected into the vein in the form of a fine-dispersed emulsion. Clinical trials of perfluorin were conducted with 234 patients for 19 nosological diseases. However, despite their positive result in 1985 after the tragic death of Professor F.F. Beloyartsev, domestic research in this direction ceased. However, the results showed that perfluorin emulsion improved the oxygen supply of all organs and tissues, including the heart [3]. If the outer shell is disturbed, the perftoran red blood cell protects it from further destruction and performs its function of transporting oxygen, accelerating the supply of organs and tissues of the body several

times, especially in spasms and narrowing of capillaries and the presence of blood clots and fat embolisms. Along with the antihypoxic perftoran had an anti-thrombotic effect. This made it the drug of choice for lung tissue damage, especially in cases of acute respiratory distress syndrome and sepsis.

Perftoran research and production

In 1990, the established "Perftoran" Research and Production Company resumed clinical trials of perfluorin. By order of the Ministry of Health and Medical Industry of the Russian Federation No. 50 of February 13, 1996 perftoran, as a gas transport perfluorocarbon blood substitute, was allowed for use in medical practice and for industrial production. Opportunities for widespread use of perfluorin in medical practice have opened [1]. The effectiveness of its use in clinical medicine has been shown [10]. The reactogeny of the perfluorin emulsion in comparison with perfucol has been studied. Data on the physiological activity of fluoride-containing compounds have been obtained [12]. The physiological activity of perfluorocarbon emulsions and the effectiveness of their use have been assessed [7]. In 1998, participants in the work on the creation of perfluorin were awarded the Russian Government's Prize in Science and Technology in 1998 "for the creation of perfluorocarbon environments for the management of the life of cells, organs and organisms". Developed by the staff of the Institute of Theoretical and Experimental Biophysics of the Russian Academy of Sciences, the polyfunctional plasma substitute perftoran was commissioned by the order of the head of the VVMU No. 341 of June 26, 1998, to be accepted for the medical service of the Armed Forces of the Russian Federation. Its gas transport properties and other characteristics made it possible to use it as a substitute for donated blood in the provision of medical care to victims with massive blood loss in military conflicts, disasters, man-made and natural disasters. It did not need to determine the blood group and rhesus factor and excluded the possibility of transmission of viral and other infections and the development of immunological reactions. In frozen form perftoran did not lose gas transport properties for 3 years. Its use has significantly reduced the need for donated blood. At the same time, special cameras were needed to store the perfluorin in a frozen state to maintain sub-zero temperature. Subsequently, a research laboratory of biological and physical-chemical studies of perfluoroorganic compounds at the Russian Academy of Natural Sciences was established, in which a new modified drug perfluorin with improved physical-chemical and life-biological properties was produced in 1999. He allowed the drug to be defrosted after storage not for 5 - 6 hours, but for a few minutes. His clinical trials in 2000 showed a 2 - 3 reduction in adverse reactions. However, it was not registered in the State Register of Medicines of the Russian Ministry of Health.

The use of perfluorin as a blood substitute

In 2008, a manual was issued for doctors on the use of perfluorin as a blood substitute with a gas transport function [11]. The data on the effectiveness of perfluorin use in medical practice are presented in detail. It is emphasized that perftoran is the only drug of this class in the world, allowed for extensive clinical use. The most effective perftoran carries out gas transport function in the first 6 hours after transfusion when breathing clean oxygen, and in its intolerance - air enriched to 60 - 70% oxygen. However, with the introduction of perfluorin may occur allergic reactions (urticaria, skin itching), heat, chills, suffocation, hyperthermia, tachycardia, blood pressure reduction, chest and headaches, anaphylactic reactions. Perfluoron an effectively performs gas transport function in blood loss, not replacing, but significantly complementing the transport of oxygen, which in perfluorocarbons dissolves 18 - 20 times better than in plasma water. After the introduction of perfluorin, red blood cells are shrouded in a cloud of its particles, increasing the area of gas exchange. Oxygen and carbon dioxide dissolve in perfluorocarbons or leave them depending on their partial pressure around the perfluorin particles. Thus, the body sharply strengthens the processes of gas exchange with oxygen and carbon dioxide and oxidative-restorative metabolism. Fulcia fulcifer incurs not only the membrane membranes of red blood cells, but also endothelial cells of the vessels of the lungs, other organs and tissues. When they come into contact, they form in chains or so-called pearl filamunitions, which transmit oxygen and carbon dioxide in the directions of their lower partial pressure. The particles of perfluorin are 70 times smaller than red blood cells, and this allows them to freely pass through spasmodic capillaries and carry out effective gas exchange in tissues and remove toxic underoxed products and biologically active substances.

The development of hypoxia in the narrowing of capillaries substantiates the use of perfluorin, which freely penetrates into these capillaries, activates microcirculation and the process of detoxification, as well as provides oxygenation of tissues. The ability of the drug to corb lipids explains the effectiveness of its use in injuries associated with the threat of fat embolism and in hyperlipidemia of any genesis. The expressed ability of perfluorin to stimulate diuresis is associated with an improvement in microcirculation and oxygen support of kidney tissues and explains its effective use in swelling of the brain. Perftoran has a high detoxification effect due to its ability to improve the oxygen supply of tissues and the increase in the sorbation surface of the emulsion particles. Its use in infusion-transfusion therapy in cases of massive blood loss, severe diseases and injuries prevents the development or reduces the severity of acute lung injury syndrome and other complications.

In 2010, perfluorin emulsion was used in the comprehensive treatment of critical blood loss by one of the authors of the article at the Moscow Department of Health's City 36th Clinical Hospital. The need to use perfluorin in medicine is not determined only by the above indications for use. It performs the gas transport function of red blood cells at their lack and damage of different etiology, including chemical poisoning and destruction by biological agents, including coronavirus infection. This is confirmed by the high effectiveness of the use of perfluorin in the treatment of acute respiratory distress syndrome and dissected intravascular thrombosis [13]. At the same time, the greatest effect was obtained in the treatment of the initial stages of the development of acute respiratory distress syndrome. It significantly increases the penetration of oxygen from the alveoli into the bloodstream. In addition to intravenous permethrin recognition received inhaling of perfection or with the help of a nebulizer.

Despite years of experience in the use of perfluorin in medical practice, studies on the definition of indications and technologies of its effective use, in particular, in liquid breathing, are still relevant [2]. Research on the development of perfluorin technologies, taking into account the degree and nature of damage to lung tissue in ventilator, remains relevant [5]. Materials of study of pathogenesis of gas-exchange disorders in the lungs in different nosology can become the basis for determining indications and choosing intravenous, inhaled-infusion or inhalation-aerosol method of application of perfluorin. The necessary volumes of inhaled application of perfluorin in various nosological forms need to be determined and refined. Today, perftoran is not produced in the required volumes due to problems with its release in accordance with the "Rules of Medical Products" (international standard GMP). In addition, more research and trials are needed to improve the effectiveness of the clinical use of perfluorin and eliminate side effects. As a result of experimental production, perftoran cannot be delivered to health facilities. Meanwhile, there is a need for research and development to improve its consumer and medical qualities using modern technologies and capabilities, and to conduct a whole range of research and testing on the creation of new perfluorocarbon emulsions derivatives. It seems necessary to conduct comparative studies to determine the possibility of its use in conjunction with other drugs, to assess the effectiveness and to determine the indications for intravenous, inhalation-infusion and inhalation-aerosol methods of its use on the indications.

The authors of the article in the course of official and professional activities were directly involved in the planning of research on the refinement of technologies for the manufacture and storage of perfluorin, its use for infusion therapy in the wounded, sick and injured, the creation of oxygen-breathing equipment and an expert system for diagnosing the diseases of air passengers, as well as the development of liquid breathing technologies to maintain breathing in different environments.

Conclusion

Based on the experience of the authors and the above data, it is possible to formulate the following concluding provisions, conclusions and suggestions. Modern tools, methods and technologies for rapid diagnosis and treatment should be used to provide medical care to the wounded, victims and patients, including with coronavirus infection. The blood supply to organs and tissues and the development of hypoxia of various etiology plays a great role in the pathogenesis of the development of life-threatening conditions and complications. To prevent and eliminate such conditions, means of restoring blood supply to the affected organs and tissues are needed. The effective solu-

tion to this problem is ensured by the use of perfluorocarbon compounds, which have the gas transport ability to saturate the blood with oxygen and supply it to the affected organs and tissues. The practice of using the drug perfluorin confirmed the effectiveness of its use in threatening conditions arising from blood loss, lesion of the pulmonary, renal and other organs and tissues. However, problems remain in determining indications and contraindications of the use of perfluorocarbon compounds in various diseases and lesions of organs and systems, as well as their use of infusion, inhalation-infusion or inhalation-aerosol, liquid breathing and ventilator.

The development of drugs that improve the oxygen supply of organs and tissues in hypoxemia conditions should be considered as an urgent direction of experimental scientific and clinical studies to increase the mobilization readiness of health authorities to epidemics and eliminate biological hotbeds of mass destruction, to treat diseases with lung damage and circulatory system.

The use of perfluorocarbon emulsions in the practice of providing medical care to the wounded, injured and sick should be in the sights of the World Health Organization and receive the necessary support, including for the formation of mobilization stocks and reserves in the event of mass epidemics, infections and injuries. Training of medical personnel for their use in medical practice, including in the system of training and retraining, is a prerequisite for the widespread use of perfluorocarbon emulsions.

Conflict of Interest

The authors state that there is no conflict of interest and express gratitude to E.I. Mayevsky and V.V. Moroz for exhaustive clarifications on the creation and use of perftoran in medical practice.

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