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Review Article

Theoretical and Methodological Foundations Construction and Application of the Model Study of Endothelioprotective Properties of Drugs Used to Treat Coronavirus Infection Covid-19

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Abstract:

So far, with COVID-19 *initiated bythe* SARS-CoV-2 coronavirus, clinical practice has not introduced a method and appropriate treatment practice, either aimed at the cause of the disease or disorder, or the elimination of the main link in the pathogenesis, which would prove its effectiveness and safety. Clinical studies that are currently being conducted around the world mainly include the use of drugs for diseases in COVID-19.

Keyword: Covid-19, Endothelioprotective, Pathogenesis, Drugs.

Introduction:

So far, with COVID-19 *initiated bythe* SARS-CoV-2 coronavirus, clinical practice has not introduced a method and appropriate treatment practice, either aimed at the cause of the disease or disorder, or the elimination of the main link in the pathogenesis, which would prove its effectiveness and safety. Clinical studies that are currently being conducted around the world mainly include the use of drugs for diseases in COVID-19. usually registered for other pathogenetic indications. Against this background, many "scientific" foreign publications have appeared, in which, under the form of "preliminary data", drugs with "positive results" in the treatment of the disease initiated by the SARS-CoV-2 coronavirus are indicated. All these publications clearly benefit commercial companies and bring only harm to clinicians and pharmacologists. [1]

Exhibition:

Over the past two to three years (2020-2022), more and more scientific evidence has been superimposed on the relationship of viral diseases, coronavirus infection (coronavirus SARS-CoV-2) and dysfunction of the endothelial system (DES).

COVID-19 is a disease affecting the lungs and, in addition, the endothelial system. Recent studies show that this can lead to microvailculatory disorders, and as a consequence functional disorder of all internal organs. The combination of endothelial dysfunction with a generalized inflammatory condition and elements of the supplement may together contribute to the overall procoagulant state described in COVID-19 patients. [2]

The novel coronavirus infection COVID-19, caused and generated by the SARS-CoV-2 coronavirus, affects in parallel with the organs of the respiratory system and the organs of the cardiovascular system. The clinical picture in medical practice has clearly shown that: - **Endothelial**

dysfunction is the main link in the pathogenesis of COVID-19 [3].

Over the past 30-35 years, the efforts of researchers have been aimed at creating and applying methodological approaches to the assessment of the function (EF) and dysfunction of the endothelium (ED), which is an important link in the cardiovascular system [4]. In scientific research, they are looking for opportunities and making decisions in the direction of applying universal techniques for Measurements of indicators characterizing endothelial dysfunction (ED) and endothelial function (EF). However, in daily medical practice, the steady **introduction** of **methodologies for the detection of ED and EF as working clinical tools has not yet been adopted**! Clinical guidelines have not yet found a place for mandatory methods for detecting ED in any pathological condition. Targeted approaches for primary or secondary prevention of vascular diseases are not recommended or given. [5] Perhaps the reason for this condition is to hide in the lack of universality in the use of in ***vitro, ex vivo*** and ***in vivo*** models for studying the endothelial properties of drugs and methods for studying the state of the endothelium.

When we adopt strategies for building and applying a model and an appropriate methodology for studying the endothelioprotective properties of drugs used to treat coronavirus infection COVID-19, we should mainly be guided from the principles of clinical drug therapy requirements.

The choice of the appropriate research method is inextricably linked with the choice of successful models of a particular study.

Problematic issues of methodology and research methods in the construction and application *in vitro, ex vivo* and *in vivo* models for the study of endothelioprotective properties of drugs used to treat coronavirus infection COVID-19.

In the guidelines for the treatment of coronavirus infection (COVID-19), the treatment recommendations applicable in clinical practice on a global scale are mainly based on studies of the effectiveness of antiviral drugs used to treat SARS. These studies were conducted during and after the outbreak of genotype IV coronavirus (by about 2003 and then by 2012).

Studies of the effectiveness of medicinal substances were conducted on the following models:

1. ***In vitro*** models - the study used the reproduction of THE SARS virus, tor cell strains 2, Tor7 and Urbani in Vero E-6 cell culture.

2. ***In vivo*** models - the study used a transgenic line of white mice

It should be noted here that back in 2003-2004, the complexity of conducting preclinical and clinical trials of the effectiveness of non-specific medical protective equipment (**NMHS**), against the causative agent of SARS (coronavirus IV genotype), "is associated with the difficulties of developing ***experimental models of*** this infection" [6]

For unexplained reasons, studies aimed at finding effective drugs on ***in vitro*** and ***in vivo*** models against the causative agent of SARS discontinued after a year (2005-6). [6]. Only experimental developments ***of the in vivo*** model of the "transgenic line of white mice" as laboratory forms of SARS infection remained, and the study of vaccines and immunoglobulins continued in the direction of assessing their state of effectiveness as a means of preventing and treating SARS.

As can be seen, for the applicationl pharmacological research approaches in the search for effective drugs in SARS, we have a limited number of models: ***in vitro*** and ***in vivo***. It should also be noted that nowhere in scientific research is it said about the ***ex vivo*** type model**.**

After 17 years (2022), in the absence of adequate ***in vitro, ex vivo*** and ***in vivo*** models for studying the properties of drugs, the problem situation is repeated: again the complexity of conducting pharmacological and subsequent preclinical and clinical trials of the effectiveness of nonspecific and specific medical agents against the causative agent of the coronavirus **SARS-CoV-2** on coronavirus infection COVID-19, associated with the difficulty of developing experimental models of this infection.

In addition, we need to understand that the virus mutates rapidly - in a practically unprotected human body, it creates many mutant forms. For new evidence of the effectiveness of drugs against the virus, adequate fast models for the corresponding mutant forms are needed.

Against this background, only a few pharmacopoeial drugs (the drugis taken "***off label"***), practically accepted according to methodological indications for the treatment of COVID-19, were directly clinically studied in hospitals and hospitals. - Bypassing any pharmacological approaches to the study of medicinal substances!

It turned out, in practice, that only models adopted in research practice ***in vitro, ex vivo*** and ***in vivo*** cannot meet the requirements for studying the endothelioprotective properties of drugs used to treat coronavirus infection COVID-19. There is a need for new or improving old research models.

At the same time, with a number of methods of prevention, diagnosis and treatment of the new coronavirus infection (COVID-19), a methodology for studying effective and safe drugs for the treatment and prevention of the causative agent of the coronavirus **SARS-CoV-2** was proposed. However, until this moment, intensive scientific research has not been conducted with the allocation of adequate amounts of financial and human resources. [1] One of the reasons for this passive behavior we have

already shown is inefficient and unprotected research models.

Likely ways to solve problems.

As part of a study of drugs for the treatment of COVID-19 [1], the following methods were indicated:

The first method is to continue the study of already registered antiviral drugs. Antiviral drugs that have proven clinically effective against RNA viruses, after previous pharmacological clinical trials of varying quality and design:

1. ***Interferon alfa*** (approximately effective in: multiple sclerosis and hepatitis C virus),

2. ***Ribavirin*** (approximately effective for: severe respiratory infections, hepatitis C virus, etc.),

3. ***Lopinavir / ritonavir*** (approximately effective in: acquired immune deficiency syndrome (AIDS)),

4. ***Favipiravir*** (approximately effective in: influenza virus and rhinovirus).

The second method is the sorting of molecules from molecular databases that make up medicinal substances, with mechanisms of action aimed at the **SARS-CoV-2** coronavirus, such as:

1. ***Chloroquine*** and ***Hydroxychloroquine***,

2. ***Remdesivir***.

The third method is based on the targeted development of antiviral drugs (targeted to the coronavirus SARS-CoV-2) by studying biological information and the ability of penetration of various coronaviruses in the body (respectable in a living cell). [7].

However, the proposed methodology does not indicate which models can be continued: 1. the study of already registered antiviral drugs; 2. use of existing molecular databases**;** and 3. targeted development of new antiviral drugs to treat covid-19 coronavirus infection.

For a complete explanation of the problematic issues of theory and practice of methodologies and research methods in the construction and application ***of in vitro, ex vivo*** and ***in vivo*** models the study of the endothelioprotective properties of drugs used to treat coronavirus infection COVID-19 **complement the** methodology with two more **methods** and the proposed direction of construction corresponding **two models**.

This is necessary because it is proven in clinical medical practice that etiotropic and pathogenetic treatment for COVID-19 takes place and needs to be carried out and treatment of coagulopathy and special attention should be paid to the treatment of dysfunction of the endothelial system.

Complement:

The first (new) method is to continue the study of already registered **cardiovascular** drugs that have activity against RNA viruses, the effectiveness of which in terms of the normal functioning of the endothelial system has been proven earlier in clinical studies of various quality and design.

For a pharmacological study of the effectiveness of cardiovascular drugs, ***ex vivo*** and ***in vivo*** models are successfully applicable.

The second (new) method is the **study of a combination** of already registered cardiovascular and antiviral drugs that have activity against RNA viruses, the effectiveness of which in terms of the normal functioning of the endothelial system has been proven earlier in clinical studies of various quality and design.

Successfullyapplicable are ***in vitro***, ***ex vivo*** and ***in vivo*** models for the study of cardiovascular and antiviral drugs.

The adoption of the first (new) and second (new) method, together with the third method, will determine the strategy of targeted development of new antiviral drugs based on a model for the construction and application of the methodology for studying the endothelioprotective properties of drugs used to treat coronavirus infection COVID-19.

With the caveat that we have not yet engaged with a really effective model study of the endothelial proprotective properties of drugs.

Reference:

1. Kolbin A.S. (2020), COVID-19 and Clinical Pharmacology [Text]/A.S. KolbinClinical Pharmacology and Therapy -Volume: 29 - No: 3 pp. 14-24
2. Jung F., Krüger-Genge A., Franke R.P., Hufert F., Küpper J.H. (2020), COVID-19 and the endothelium. [Text] / F. Jung, A. Krüger-Genge, R.P. Franke, F. Hufert, J.H. Küpper //Clin Hemorheol Microcirc.;75(1):7-11. doi: 10.3233/CH-209007. PMID: 32568187; PMCID: PMC7458498.
3. Ivanov M. B., Reinyuk V. L., Shustov E. B., Fomichev A. V., Petlenko S. V., Litvintsev B. S., Sosyukin A. E., Lapina N. Q. (2020), METHODICAL MATERIALS. Possible mechanisms for the formation of the main pathological processes in patients with a new coronavirus infection COVID-19, their prevention, correction, rehabilitation [Text] / Federal State Budgetary Institution of Science "Institute of Toxicology Federal Medical and Biological Agency", St. Petersburg.
4. Flammer A.J., Luscher T.F. (2010), Three decades of endothelium research: from the detection of nitric oxide to the everyday implementation of endothelial function measurements in cardiovascular diseases.

[Text]/ A.J. Flammer, T.F. Luscher // Swiss Med Wklv.140: wl3122.

5. Shabrov A. V., Apresyan A. G., Dobkes A. L., Ermolov S. Yu., Ermolova T. V., Manasyan S. G., Serdyukov S. V., (2016), Modern methods for assessing endothelial dysfunction and the possibilities of their application in practical medicine [Text]/ A. V. Shabrov, A. G. Apresyan, A. L. Dobkes, S. Y. Ermolov, T. V. Ermolova, S. G. Manasyan, S. V. Serdyukov // Rational Pharmacotherapy in Cardiology, 12(6), s733-742
6. Shchukina V.N., Loginova S.Ya., Borisevich S.V., Bondarev V.P. Current state of study of the effectiveness of nonspecific means of medical protection ***in vitro*** and ***in vivo*** against coronavirus IV genotype, which causes severe acute respiratory syndrome. [Text]/ V.N. Shchukina, S.Y. Loginova, S.V. Borisevich, V.P. Bondarev, (2011), // Antibiotics and Chemotherapy. 56(9-10): S. 41-46.
7. Zumla A., Chan J. F., Azhar E. I., Hui D. S., Yuen K. Y. (2016), Coronaviruses - drug discovery and therapeutic options. [Text]/ A. Zumla, J.F. Chan, E.I. Azhar, D.S. Hui, K.Y. Yuen//Nature Reviews Drug Discovery. May;15(5):327-47. doi: 10.1038/nrd.2015.37. Epub 2016 Feb 12. PMID: 26868298; PMCID: PMC7097181.

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