REVIEW ARTICLE

Convalescent plasma therapy and donor selection for COVID-19 outbreak: A help from survivors to patients

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ABSTRACT

The Coronavirus pandemic, which began in Wuhan-China in December 2019, was evaluated with WHO data. The effectiveness of convalescent plasma therapy in the pandemic was discussed in the present review. The importance of donor selection for this treatment method was emphasized. We offer the world that convalescent plasma therapy should be developed to combat the pandemic. But not all cases have closed, and new cases continue to be diagnosed around the world. The pandemic is very aggressive, and the world is under serious threat. No vaccine or antiviral agent effective on Coronavirus has yet been produced. Each country can combine survivor-induced convalescent plasma treatment into existing treatments until the Coronavirus vaccine and antiviral agent are produced. This method can offer a time-saving treatment option for every country with its advantages such as easy applicability, low cost and limited medical equipment requirements, but vaccine-drug researches should be accelerated internationally. We believe that target donor selection will determine success in convalescent plasma treatment. Multicenter international clinical trials are needed to combat the COVID-19 pandemic and to develop convalescent plasma therapy.
Keywords: convalescent plasma therapy; coronavirus; COVID-19; outbreak; pandemic

INTRODUCTION

In December 2019, in Wuhan, China, an upper respiratory infection that started with complaints of high fever, cough, and shortness of breath in patients turned into pneumonia. The infection soon spread primarily to other far eastern countries. The aviation sector, which is growing today, has helped spread the infection to Europe and the whole world in a short time. In about seven months, the disease was reported in 216 countries and on 2 international cruise ships. However, not all cases have been closed and new cases continue to be diagnosed worldwide. The disease was named Coronavirus Disease-19 (COVID-19). The cause of the outbreak was described as Novel Coronavirus SARS-CoV-2.[1] SARS-CoV-2 or Novel Coronavirus, the virus responsible for the 2019–20 Coronavirus pandemic, is a member of the family Coronaviridae. Coronaviridae is a family of enveloped, positive-sense, single-stranded RNA viruses. The viral genome is 26–32 kilobases in length. The particles are typically decorated with large (~20 nm), club- or petal-shaped surface projections (the "peplomers" or "spikes"), which in electron micrographs of spherical particles create an image reminiscent of the solar corona.[2,3] The infection was soon declared a pandemic by the World Health Organization, and many countries had to take measures restricting normal life or even implement quarantine procedures. In order to prevent viral contamination all over the world, flights and crossings between countries were restricted and a serious chaos began to take place in the world. Especially when the new COVID-19 studies in China were examined, it was seen that the existing antibiotics used, antiviral agents did not respond adequately to treatment and did not provide viral eradication.[4,5,6] COVID-19 associated deaths could not be prevented worldwide because therapeutic breakthroughs such as vaccine production, antiviral agent development could not be made or succeeded in the short term.

In the present review, we aimed to evaluate the COVID-19 pandemic using WHO data and to discuss the effectiveness of convalescent plasma therapy for the pandemic, whether it could be an alternative treatment option.

The latest situation of the pandemic by WHO data: Case-death rates were highest in developed regions and countries such as the USA, Europe.[7] The WHO explained that there were no fatal cases in the 0-9 age range, but the mortality rates were 0.2% in the 10-39 age range, 0.4% in the 40-49 age range, 1.3% in the 50-59 age range, 3.6% in the 60-69 age range, 8.0% in the 70-79 age range, 14.8% in the 80 and over age range.[8] COVID-19 fatality rate by age from WHO data is presented in Table 1.

Table 1. COVID-19 fatality rate by age from WHO data

Age groups	Death Rate
0-9 years old	No fatalities
10-19 years old	0.2%
20-29 years old	0.2%
30-39 years old	0.2%
40-49 years old	0.4%
50-59 years old	1.3%
60-69 years old	3.6%
70-79 years old	8.0%
80+ years old	14.8%

Table 2. COVID-19 fatality rate by comorbidity from WHO data

Pre-existing condition (Comorbidity)	Death Rate (all cases)
Cardiovascular disease	10.5%
Diabetes	7.3%
Chronic respiratory disease	6.3%
Hypertension	6.0%
Cancer	5.6%

The presence of comorbidities such as cardiovascular disease, diabetes, chronic respiratory diseases,

hypertension and cancer in cases of death was indicated by the WHO.[8] COVID-19 fatality rate by comorbidity from WHO data is presented in Table 2.

As of November 11, 2020, there were 52.278.001 cases, 1.286.877 deaths, 36.600.617 recovered in 216 countries and 2 cruise ships worldwide. The average worldwide death rate was 2.46%.

Treatment Suggest for COVID-19 Outbreak: The pandemic included many difficult conditions such as international transportation restrictions, lack of vaccine-medicine, lack of food, lack of medical supplies, and lack of protective equipment, and the situation was no different even in the most developed countries. In particular, given that international air travel is prohibited, it is clear that each country must fight the pandemic by using a successful treatment method on its own, but effective treatment method, drug-vaccine, is not available. The WHO and other humanitarian organizations have a hard time reaching every country in the pandemic. Because vaccine and drug production cannot be done in a very short time, we recommend antibody-laden blood transfusion treatment, which is a historical method of treatment. This method is also called convalescent plasma therapy. We offer convalescent treatment method as a workaround, but we do not claim that this method will prevent all COVID-19-related deaths, we believe that international vaccine and drug investigations should be accelerated. Since the pandemic occurs in all undeveloped, underdeveloped, developing and developed countries, we think that each country can use this treatment method with its own means and that this treatment method can reduce the COVID-19 associated mortality rate. We recommend three different methods for this treatment according to the state of development of countries. These are whole blood transfusions, fresh frozen plasma, separated antibody (Anti-COVID-19 Ig G) transfusions.

Convalescent Plasma Therapy: The method was first used in the Spanish flu (H1N1) pandemic in 1918.[9,10] and was also used successfully in the latest Severe Acute Respiratory Syndrome (SARS) epidemic.[11] The basis of convalescent plasma therapy method can be summarized as transfusions of the blood of suitable patients who have had the infection and have recovered to new patients after a certain period of time. The method can also be described as transporting the survivor's ready antibody to new patients. For the success of this method in the fight against the pandemic, it is very important to have enough suitable volunteer donors. When we examine the age distribution and mortality rates in COVID-19 cases, it is clear in the WHO data that the mortality rate of the young population is low and the remission rate is high, so it is not difficult to find enough survivors. The advantages and disadvantages of the method can be discussed in general conditions, but in pandemic conditions -with the absence of vaccines and antiviral agents- this method can be seen as an important option for all countries.

The clinical studies using of Convalescent plasma therapy on SARS-CoV-2: When we ran a scan on 'convalescent plasma' on the Pubmed search engine for the years 1930-2020, we found it had published totaly 1309 article. Published 460 articles on convalescent plasma in only 2020 alone, researchers have expressed considerable interest in this topic. But the sad thing is that only 6 clinical trials and randomized controlled trials and 28 case report have been identified on this issue. Further clinical trials showing the effect of convalescent plasma on COVID-19 disease, pilot studies, case-report studies, randomized case-control are needed. In the begining of the pandemic, convalescent plasma therapy was not mentioned on the treatment of COVID-19 patients but in 2020 some clinical trials and case reports were presented in the scientific medical journal. Shen et al. administered 200 ml*2 in a day convalescent plasma to 5 critical patients diagnosed with SARS-CoV-2 by RT-PCR. After 3 days, the body temperature of 4/5 patients returned to the normal ranges. Within 12 days the SOFA score of the patients decreased. The PAO_2/FIO_2 ratio increased, and ARDS was resolved in 4 patients.[12] Duan et al. administered 200 ml convalescent plasma on 10 critically COVID-19 patients and observed that oxygen saturations of the patients improved, inflammation and viral load decreased.[13] Zhang et al. administered convalescent plasma therapy to 4 COVID-19 patients and all 4 patients recovered.[14] Salazar et al applied convalescent plasma therapy to 25 patients diagnosed with COVID-19 in their clinical study. A six-point ordinal scale and laboratory criteria have been analysed based on the clinical improvement of the amended World Health Organisation. On the donor and recipient strains, viral genome sequencing was performed. Nine patients experienced at least one-point change on clinical level on day 7 after transfusion with convalescent plasma and seven of those were discharged. At least one-point clinical progress was achieved in 19 (76%) patients on Day 14 after transfusion, 11 of them were released. There have been no adverse effects caused by plasma transfusion. Whole genome sequencing data did not detect a severity association between strain genotype and disease. They claim that treatment for people with serious COVID-19 disease is a safe treatment option15.

Selection of Target donors:

Donors must have the following criteria stated below:

- Volunteer survivors aged 18-39 who were diagnosed with COVID-19 RNA (+) by PCR method and confirmed with COVID-19 RNA (-) by PCR method after treatment.
- If possible, survivors living in the same area as the patient should be preferred as donors. A possible mutation of SARS-CoV-2 can cause different types of antibodies to be produced. This can reduce the success of the treatment we are looking for.
- Patients who follow the general principles of blood transfusions (without infectious diseases such as hepatitis, HIV, no sexually transmitted diseases, no anemia, no thrombocytopenia, no coagulation disorders, etc.)
- Blood must be taken 14 days after the COVID-19 RNA (-) PCR test result from survivor donor.

DISCUSSION

A different terminology, such as passive immunion or plasma convalescent therapy, defines the treatment approach we are proposing in our papers16,17 This method has been employed in the treatment of several

diseases mediated by pathogenes and toxin before the development of "modern" medicines in the 1950ies18,19. In the Spanish influenza pandemic, researchers recorded that convalescent blood products were highly successful in dealing with influenza pneumonia and now called acute breathing distress syndrome20,21 Studies published in the Spanish H1N1 flu pandemic have reported a drop in human blood transfusion (whole blood, plasma, or serum) A recent meta-analysis of these studies found that patients who have received influenza-convalectible human blood products with Spanish influenza pneumonia may have seen a clinically significant reduction in their deaths.22 During the Democratic Republic of Congo 1999 Ebola outbreak, Mupapa etal. They confirmed that Ebola IgG has been found in donor blood and that the Ebola antigen was not present. It was found that only one of the transfused patients died. The experiment found that the rate of mortality was substantially lower than in the Congo outbreak.23 Human recoverants serum is used in treating and preventing measles, mumps, polio, Spanish flu, vaccines and varicella. A 1943 study of the use of convalescent sera showed that measles and mump convalescent sera are effective in preventing illness in exposed people at risk for disease. 24 At an outbreak in Baltimore during the winter of 1942, convalescent serum had been separated into anticorpal enrichment fractions, which were used with high effectiveness for disease prevention.25 The only infectious disease in which, to our knowledge, convalescent plasma is the standard of treatment is hemorrhagic fever — the Junin virus. Enria et al. published a summary detailing Argentina's national programme for the treatment of Argentine hemorrhagic fever history, preclinical development, clinical trials and the current situation. This programme was developed following definitive findings of a double-blind, placebo-controlled trial showing patients with 500 mL of intravenous convalescent plasma within 8 days of the onset of symptoms had a case-by-case fatality of 1.1% as opposed to 16.5% for non-convalescent plasma. Plasma was collected from a person 16 months previously recovered from H5N1. Three 200 mL plasma convalescent transfusions over 24 hours were administered. After the first transfusion, the viral load of a patient was decreased within the first 8 hours and undetectable within 32 hours by a factor of about 12 (from 1:68 to 105 copies/ml), or by 104 copies/ml. In addition, the patient obtained oseltamivir as normal treatment with plasma administration. In2005 convalescent therapy was also given for SARS-coronavirus patients in Hong Kong.28 Researchers reported good outcomes through the application of co-validation therapy to MERS-CoV infectant patients in Saudi Arabia in2016. In addition, the patient recovered fully and was discharged27. However, various techniques for the adequacy of antibody titers obtained from donor have been developed29. Prior research has shown that convalescent plasma therapy can, however, be used in viral diseases, Donor selection is highly effective in successfully conducting the treatment and immunoglobulin levels determine the treatment's success. The data of the WHO on the pandemic at COVID-19 indicate that the mortality rate in 18 to 39 years of age for other age groups is relatively low, so we believe it can be a high therapeutic achievement for survivors in this age group to be donors. In the development of immunoglobulin B-type survivor lymphocytes may be more productive in this age group than in other age groups. The required selection of donors can be efficient and targeted by means of cytometric analysis of the flow. Because vaccinations with effective antivirals in 213 countries around the world have not yet been developed to treat the pandemic, plasma convalescence and other recommended strategies for blood transfusion will save humanity time. This treatment method can be implemented in three ways depending on the country's medical facility until effective vaccine and effective antiviral agent are made. The treatment protocols can take the form of whole blood transfusion, freshly frozen transfusion of plasma and separate transfusion of immunoglobulin. It is proposed that survivors are selected to minimise modification and recovery progress by those who live in the same region as patients due to potential genetic diversity. Good findings started in 2020 when COVID-19 patients were tried with convalescent plasma therapy, and several trials did not show any side effects. Continuing with pandemics the use of tocizumab, favipiravir, tocilizumab and azithromycin for COVID-19 can be augmented with the addition of medicines such as fluid-electrolyte help, hydroxychloroquine (HE), and oseltamivir.

Highlights: The advantage of this treatment is that it can be applied in all countries of the world regardless of the level of development. Expensive and hard-to-reach devices and medical supplies advanced medical technological equipment is not required. A method that can be tried until a drug-vaccine is developed to combat the COVID-19 pandemic globally. The side effect of the method has not yet been shown.

Limitations: In this review, plasma separation methods were not mentioned and technical information about these methods was not given. This review did not recommend any dose amount for convalescent plasma therapy. Each country should regulate the algorithm for this treatment according to its own medical facilities.

CONCLUSION

The whole world is struggling with the COVID-19 outbreak, which started in Wuhan and soon became a pandemic. However, the pandemic continues to spread, threatening more human lives, and the number of cases and deaths continues to rise. We suggest convalescent plasma therapy that has a place in history of medicine, which we think will save humanity time until the effective antiviral agent and vaccine are produced. We suggest blood-plasma donations from survivors who recovered from COVID-19 between the ages of 18 and 39, and transfusions of this blood to the patients. This method may be an alternative or option to vaccine and drug treatments, but it is necessary to speed up vaccine and drug studies. Convalescent plasma treatment procedure can be enriched with common studies with multidisciplinary approach of different medical fields such as Immunology, Hematology, Clinical Microbiology and Infectious Diseases. That is unknown to what extent convalescent plasma therapy might blunt the development of a natural immune response, especially when administered for prophylaxis. Target donor selection can determine the treatment success on the COVID-19

patients. Possible side effects of treatment, the body's reaction to the given plasma, possible allergic effects should be considered. In addition, the effect-side effect of convalescent therapy in COVID-19 patients with autoimmune disease is a topic worth investigating. We recognize that a definitive conclusion cannot be drawn on optimal doses and treatment time point for the convalescent plasma therapy to COVID-19 disease, large multicenter clinical trials are urgently needed to tackle this pandemic.

Conflict of Interest: All the authors declare no conflict of interest.

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