Convalescent plasma therapy for COVID-19

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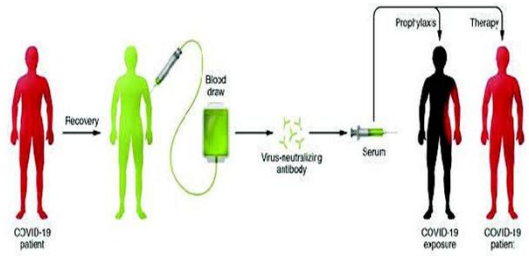
***Abstract*- The discovery of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the outbreak of coronavirus disease 2019 (COVID-19) are causing public health emergency. A handful of literatures have summarized its clinical and radiologic features, whereas therapies for COVID-19 are rather limited. In order to evaluate the efficacy of convalescent plasma therapy in COVID-19 patients, we did this timely descriptive study. 6 laboratory confirmed COVID-19 patients were enrolled and received the transfusion of ABO-compatible convalescent plasma. The efficacy of this intervention was determined by the alleviation of symptoms, changes in radiologic abnormalities and laboratory tests. No obvious adverse effect observed during the treatment. Transfusion of convalescent plasma led to a resolution of ground glass opacities (GGOs) and consolidation in patient #1, #2, #3, #4 and #6. In patient #1 and #5 who presented with SARS-CoV-2 in throat swab, convalescent plasma therapy elicited an elimination of virus. Serologic analysis indicated an immediate increase in anti-SARS-CoV-2 antibody titers in patient #2 and #3, but not in patient #1. This study indicates that convalescent plasma therapy is effective and specific for COVID-19. This intervention has a special significance for eliminating SARS-CoV-2 and is believed to be a promising state-of-art therapy during COVID-19 pandemic crisis.**

***Index terms*- SARS-CoV-2; COVID-19; convalescent plasma therapy**

INTRODUCTION

The global outbreak of a novel human coronavirus, newly named as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by the international committee on taxonomy of viruses, has attracted increasing attentions and public emergency 1, 2. This virus was initially detected in Wuhan, China, in December 2019. A cluster of pneumonia patients manifesting as fever, cough, and dyspnea with unknown etiology emerged at that time 3-5. The virus was presumed to be zoonotic because preliminary investigation demonstrated that the first generation patients in Wuhan geographically linked to Huanan seafood whole sale market where live animals were sold. While patients outside of Wuhan usually had traveled to the city, or had contact with city residents 6. These epidemiologic findings strongly suggest that SARS-CoV-2 transmits from human-to-human, and causes the disease now named coronavirus disease 2019 (COVID-19) 7. By the end of March, 2020, COVID-19 has spread up to 199 countries and causing more than 27000 deaths 8 SARS-CoV-2 belongs to the β-coronavirus family. Its genome is a single-stranded RNA composed of about 30 kb nucleotides, which encodes four major structural proteins: spike protein (S), membrane protein (M), envelope protein (E), and nucleocapsid protein (N). Among these proteins, the S protein is of special interest because this club-shaped glycoprotein spikes give the virus a crown-like appearance 9. Translational studies have demonstrated that the

interaction between the receptor binding motif of S protein and the angiotensin-converting enzyme 2 (ACE2) mediates the recognition and entry of SARS-CoV-2 into the host cells, and ACE2 is defined as a putative receptor for SARS-CoV-2 10,11. The homogeneity in the receptor binding domain between SARS-CoV-2 and SARS-CoV underlies their overlapping pathogenicity and biological properties. Indeed, the clinical manifestations and radiologic features of COVID-19 and those of SARS are quite similar 12,13. For example, both diseases are highly infectious, and the incubation period ranges from several days to two weeks. Common symptoms at the onset of disease include fever, cough, myalgia and shortness of breath. Laboratory test may indicate white blood cell count below normal range, lymphopenia, hypoxemia, deranged liver and renal function 3, 5. The typical radiologic abnormalities include multifocal ground glass opacities (GGOs) and sub segmental areas of consolidation 14-16. The moment, therapeutic strategy for COVID-19 is largely supportive 17. Several off-label anti-viral and anti-HIV agents seem to be clinical beneficial, but their efficacy is far from satisfactory 18. To this end, there are urgent needs to develop COVID-19-specific treatment to alleviate the symptoms and reduce the mortality. Previous experience with SARS suggested that convalescent plasma exhibit a neutralizing antibody response directed against the viral S protein. This antibody blocks SARS-CoV-ACE2 entry and can be detected even 24 months after infection 19. A retrospective study by So and colleagues compared the clinical outcome of convalescent plasma therapy verses high-dose steroids pulse therapy in SARS patients with deteriorated disease. They found that patients in the plasma group had a shorter hospital stay and lower mortality than the comparator group, and no immediate adverse effect noted after plasma infusion 20. A systemic meta-analysis involving 1703 influenza pneumonia patients who received influenza-convalescent human blood products, showed reduced virus load and pooled absolute reduction of 21% in mortality 21. Since the number of COVID-19 cases and disease-related death is increasing at an incredible speed, an urgent question that needs to be addressed promptly is whether it is also effective to use convalescent plasma therapy in the COVID-19 setting. One going clinical trial is recruiting patient for anti-SARS-CoV-2 convalescent plasma therapy in Shanghai, China, but no relevant data has been announced yet (NCT04292340). The outcomes of this trial are definitely essential for formulating the principles of therapeutic strategy. In this study, we provided preliminary data showing the efficacy of convalescent plasma therapy in COVID-19 patients. We found this intervention was effective in improving patient's symptoms and ameliorating radiologic abnormalities. More timely multi-center randomized clinical trials are warranted to determine the safety and efficacy of convalescent plasma therapy for COVID-19.



CONVALESCENT PLASMA THERAPY

The convalescent plasma therapy aims at using antibodies from the blood of a recovered Covid-19 patient to treat those critically affected by the virus. The therapy can also use to immunise those at a high risk of contracting the virus -- such as health workers, families of patients and other high-risk contacts. This therapy's concept is simple and is based on the premise that the blood of a patient who has recovered from Covid-19 contains antibodies with the specific ability of fighting novel coronavirus. The theory is that the recovered patient's antibodies, once ingested into somebody under treatment, will begin targeting and fighting the novel coronavirus in the second patient. The convalescent plasma therapy is akin to passive immunisation as, according to researchers, it is a preventive measure and not a treatment for the Covid-19 disease.

CONVALESCENT PLASMA THERAPY WORKS

The convalescent plasma therapy uses antibodies developed within an infected person while he/she is infected with the novel coronavirus. These antibodies are developed in a patient as part of the body's natural immune response to a foreign pathogen or in this case, the novel coronavirus. These antibodies are

highly specific to the invading pathogen and so, work to eliminate the novel coronavirus from the patient's body. Once the patient has recovered, they donate their blood so that their antibodies can be used to treat other patients. The donated blood is then checked for the presence of any other disease-causing agents such as Hepatitis B, Hepatitis C, HIV etc.

If deemed safe, the blood is then taken through a process to extract 'plasma', the liquid part of the blood that contains antibodies. The antibody-rich plasma, once extracted, is then ingested into the body of a patient under treatment. Speaking about the process the plasma therapy involves, John Hopkins University immunologist Arturo Casadevall, who is spearheading a project to use the therapy, has said, "The concept is simple. Patients who recover from an infectious disease often produce antibodies that can protect against later infections with the same microbe. This immunity can be transferred by giving serum to those at risk of infection."

In a study co-authored by Casadevall and immunologist Liise-anne Pirofski, the authors write that for effective therapy "a sufficient amount of antibody must be administered. When given to a susceptible person, this antibody will circulate in the blood, reach tissues, and provide protection against infection. Depending on the antibody amount and composition, the protection conferred by the transferred immunoglobulin [antibodies] can last from weeks to months."

RISKS INVOLVED

Besides speaking about the success of the convalescent plasma therapy, the study by John Hopkins immunologists stated some of the risks associated with it:

1. Transfer of blood substances: As the blood transfusion takes place, there are risks that an inadvertent infection might get transferred to the patient.
2. Enhancement of infection: The therapy might fail for some patients and can result in an enhanced form of the infection.
3. Effect on immune system: The antibody administration may end up suppressing the body's natural immune response, leaving a Covid-19 patient vulnerable to subsequent re-infection.

NOT THE FIRST TIME

This is not the first time convalescent plasma therapy is being considered as a treatment for viral infections.

1. In 2014, the World Health Organisation (WHO) had recommended the use of convalescent plasma therapy to treat patients with the antibody-rich plasma of those who had recovered from the Ebola virus disease.
2. For the treatment of people infected with Middle East respiratory syndrome (MERS), which is also caused by a coronavirus, a protocol for use of convalescent plasma was established in 2015.
3. During the 1918 H1N1 influenza virus (Spanish flu) pandemic, the therapy was used experimentally.
4. The plasma therapy was used as a treatment during the H1N1 infection of 2009

Others serious outbreaks that have seen the use of this therapy are the SARS outbreak, Measles, HIV, polio and mumps.

PLASMA THERAPY AND COVID-19

Plasma therapy's potential as treatment for Covid-19 has already been explored in limited trial in China, where the outbreak first emerged. In one trial, 10 critically-ill Covid-19 patients were subject to convalescent plasma therapy. The trial showed some improvement in patients' condition.

"No severe adverse effects were observed. This study showed CP [convalescent plasma] therapy was well tolerated and could potentially improve the clinical outcomes through neutralizing viremia [the presence of viruses in the blood] in severe Covid-19 cases," the researchers who conducted the trial said. Another trial conducted by researchers in Shenzhen, China treated five critically-ill Covid-19 patients with the plasma therapy and found "improvement in [their] clinical status".

RAY OF HOPE

These studies have sparked a ray of hope. However, researchers caution that it's too early to think of plasma therapy as an effective treatment. For example, the sample sizes in the Covid-19 plasma therapy trials are too small to arrive at definite conclusions.

According to a report published in Mayo Clinic's Research Magazine, the researchers across the world have also raised the point that there are too many unknowns right now. For instance, what is the optimal dose of antibodies? At what point during a patient's illness should treatment be given? Which patients will benefit? These are some that need to be addressed before reaching concrete conclusions. The researchers also noted that "some participants had also received other experimental drugs, such as antivirals, making it hard to tease out the precise effect of convalescent plasma".

So while plasma therapy remains a ray of hope, we will only know the treatment's efficacy once more studies and trials are conducted.

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