CONVALESCENT PLASMA THERAPY : A RAY OF HOPE FOR COVID-19 TREATMENT

Medicine

Dr. Nitin Tyagi*

Senior Resident, Department of Biochemistry, Vardhman Mahavir Medical College & Safdarjung Hospital, New Delhi-110029. *Corresponding Author

Dr. Charanjeet Kaur

Director-Professor and Head, Department of Biochemistry, Vardhman Mahavir Medical College & Safdarjung Hospital, New Delhi-110029.

ABSTRACT

For COVID-19, no exact cure has been discovered yet. According to the Food and Drug Administration (FDA), the Convalescent Plasma Therapy has already been used earlier with patients in many outbreaks like SARS-CoV, H1N1, and MERS-CoV. As COVID-19 is similar to SARS-CoV, might be convalescent plasma therapy prove to be effective and safe. Further FDA stated that more clinical trials are required for the same to prove.

KEYWORDS

COVID-19, Convalescent Plasma Therapy

INTRODUCTION

COVID-19 is a highly infectious respiratory illness caused by a novel coronavirus, which has affected more than 35,85,051 patients worldwide and caused more than 2,48,655 deaths. In the absence of effective established therapy, treatment of coronavirus to date has mainly been empirical and experimental. In Hong Kong, ribavirin and steroids have been used, and 74% of patients have recovered without requiring admission to the intensive care unit. However, no control study has yet been conducted comparing ribavirin/steroid treatment with a placebo, and the potential efficacy of ribavirin against the SARS-coronavirus has been controversial. Many experts are also concerned about the side-effects of high-dose steroids.¹

Convalescent plasma therapy has been used to treat patients with Machupo virus (Bolivian hemorrhagic fever), Junin virus (Argentinian hemorrhagic fever), Lassa fever and Ebola virus. The use of pooled plasma or immunoglobulin from patients who recovered from West Nile encephalitis has demonstrated protective effects in infected mice and clinical benefits in patients. Despite some limitations in the methodologies described in these previous reports, the data has suggested there is a clinical benefit to convalescent plasma therapy.²

What Is Plasma?

Plasma is the often forgotten part of blood. White blood cells, red blood cells, and platelets are important to body function. But plasma also plays a key role. This fluid carries the blood components throughout the body.

What are antibodies?

Antibodies produced in the body, are a type of proteins that defend from the infection caused due to pathogen and antigen. After this, some blood cells start functioning as memory cells so that they can identify and defeat the same enemy if and when it again invades by quickly producing the same antibodies.

How does plasma keep you healthy?

Plasma is a critical part of the treatment for many serious health problems. This is why there are blood drives asking people to donate blood plasma.

Along with water, salt, and enzymes, plasma also contains important components. These include antibodies, clotting factors, and the proteins albumin and fibrinogen. When you donate blood, healthcare providers can separate these vital parts from your plasma. These parts can then be concentrated into various products. These products are then used as treatments that can help save the lives of people suffering from burns, shock, trauma, and other medical emergencies.

The proteins and antibodies in plasma are also used in therapies for rare chronic conditions. These include autoimmune disorders and hemophilia. People with these conditions can live long and productive lives because of the treatments. In fact, some health organizations call plasma "the gift of life."³

CONVALESCENT PLASMA THERAPY⁴

It is an experimental procedure for COVID-19 patients. In this treatment, plasma from a COVID-19 patient who has recovered from the disease, is transfused into a coronavirus patient who is in critical condition.

Or in other words, when pathogens attack our body, our immune system starts working and releases proteins to fight with an infection. These proteins are known as antibodies. If the infected person produces a sufficient amount of protein then he or she will be recovered by antibodies itself.

HISTORY OF CONVALESCENT PLASMA THERAPY⁵

The concept dates back more than a century that is in 1890 when a German physiologist Emil von Behring discovered that when he took the serum from an infected rabbit with diphtheria, it was effective in preventing the infection caused due to diphtheria. In the past, same types of treatments are used during several outbreaks, including Spanish flu pandemic 1918, the diphtheria outbreak 1920, etc. That time convalescent therapy was less effective and had substantial side effects.

The therapy was recently tried for Ebola virus and other coronavirus diseases like SARS in 2003 and MERS in 2012. The method was used with improved extraction and screening techniques and appears to be more safe and effective than ever before.

GUIDELINES BY FOOD AND DRUG ADMINISTRATION UNITED STATES (U.S.)^{3,6}

The Food and Drug Administration (FDA or Agency) plays a critical role in protecting the United States (U.S.) from threats including emerging infectious diseases, such as the Coronavirus Disease 2019 (COVID-19) pandemic. FDA is committed to providing timely guidance to support response efforts to this pandemic.

One investigational treatment being explored for COVID-19 is the use of convalescent plasma collected from individuals who have recovered from COVID-19. Convalescent plasma that contains antibodies to severe acute respiratory syndrome coronavirus 2 or SARS-CoV-2 (the virus that causes COVID-19) is being studied for administration to patients with COVID-19. Use of convalescent plasma has been studied in outbreaks of other respiratory infections, including the 2003 SARS-CoV-1 epidemic, the 2009-2010 H1N1

influenza virus pandemic, and the 2012 MERS-CoV epidemic.

Although promising, convalescent plasma has not yet been shown to be safe and effective as a treatment for COVID-19. Therefore, it is important to study the safety and efficacy of COVID-19 convalescent plasma in clinical trials.

Patient Eligibility

To facilitate requests for eINDs for use of COVID-19 convalescent plasma to treat patients, health care providers seeking an emergency IND may want to consider the eligibility criteria used for the National Expanded Access Treatment Protocol External Link Disclaimer. These criteria include:

- Laboratory confirmed COVID-19
- Severe or immediately life-threatening COVID-19, for example,

Severe disease is defined as one or more of the following:

- shortness of breath (dyspnea),
- respiratory frequency $\geq 30/\text{min}$,
- blood oxygen saturation $\leq 93\%$,
- partial pressure of arterial oxygen to fraction of inspired oxygen ratio < 300 ,
- lung infiltrates $> 50\%$ within 24 to 48 hours

Life-threatening disease is defined as one or more of the following:

- respiratory failure,
- septic shock,
- multiple organ dysfunction or failure

Informed consent provided by the patient or healthcare proxy.

COLLECTION OF COVID-19 CONVALESCENT PLASMA

Health care providers or acute care facilities seeking to use COVID-19 convalescent plasma should include information in the IND submission that the COVID-19 convalescent plasma will be obtained from an FDA-registered blood establishment that follows the donor eligibility criteria and donor qualifications described below in collecting plasma from donors.

Donor Eligibility

a. COVID-19 convalescent plasma must only be collected from individuals who meet all donor eligibility requirements (21 CFR 630.10, 21 CFR 630.15). Note the additional donor eligibility requirements for the collection of plasma by plasmapheresis in 21 CFR 630.15 (b). Donation testing for relevant transfusion-transmitted infections must be performed (21 CFR 610.40) and the donation must be found suitable (21 CFR 630.30).

b. COVID-19 convalescent plasma is collected from individuals who meet the following qualifications:

1. Evidence of COVID-19 documented by a laboratory test **either** by:

- i. A diagnostic test (e.g., nasopharyngeal swab) at the time of illness **or**
- ii. a positive serological test for SARS-CoV-2 antibodies after recovery, if prior diagnostic testing was not performed at the time COVID-19 was suspected.

2. Complete resolution of symptoms at least 14 days before the donation. A negative result for COVID-19 by a diagnostic test is not necessary to qualify the donor.

3. Male donors, or female donors who have not been pregnant, or female donors who have been tested since their most recent pregnancy and results interpreted as negative for HLA antibodies.

a. SARS-CoV-2 neutralizing antibody titers, if available

i. When measurement of neutralizing antibody titers is available, we recommend neutralizing antibody titers of at least 1:160. A titer of 1:80 may be considered acceptable if an alternative matched unit is not available.

ii. When measurement of neutralizing antibody titers is not available, consider storing a retention sample from the convalescent plasma donation for determining antibody titers at a later date. Although optional for all IND pathways, storing samples for single patient eINDs is not recommended.

Registered and licensed blood establishments that collect plasma intended for transfusion do not need to request a supplement to their

license or obtain their own IND to collect and manufacture COVID-19 convalescent plasma for investigational use provided they 1) follow their standard operating procedures for plasma collection and all applicable regulations, and 2) collect plasma from individuals that meet the donor qualifications specified above, which would be included in the applicable IND(s) held by a health care provider or other sponsor.

Once manufactured, the COVID-19 convalescent plasma may be distributed for investigational use.

Blood establishments do not need to request an alternative procedure or exception under 21 CFR 640.120(a) to collect COVID-19 convalescent plasma.

Labeling

a. The container label of COVID-19 convalescent plasma units must include the following statement, "Caution: New Drug--Limited by Federal (or United States) law to investigational use." (21 CFR 312.6(a)).

In addition, the requirements in 21 CFR 606.121 for the container label apply, including the requirement to include a reference to the circular of information.

i. FDA recognizes that the current circular of information does not contain specific information about COVID-19 convalescent plasma regarding indications for use, dosage information, contraindications or cautions, but it provides information on the use of plasma.

b. We recommend the use of a uniform container label for COVID-19 convalescent plasma. In particular, we recommend the use of the International Society of Blood Transfusion (ISBT) format specified in the United States Industry Consensus Standard for the Uniform Labeling of Blood and Blood Components Using ISBT 128.

c. The manufacturing process used and the expiration date on the label for COVID-19 convalescent plasma should be the same as for other plasma products that are of the same type. For example, COVID-19 Convalescent Plasma, Fresh Frozen, should be frozen within 8 hours after collection, stored at -18°C or colder and have an expiration date one year from the date of collection.

How does Convalescent Therapy work?

In this technique, the blood is ejected from the recovered patient from COVID-19. Then the serum is separated and screened for virus-neutralising antibodies. The antibodies rich serum is then administered to a COVID-19 patient showing severe symptoms.

According to Houston Methodologist, the process takes around one hour for donating plasma just like to donating blood. It is said that the donors of the Plasma are hooked up to a small device that removes plasma while simultaneously returning red blood cells to their bodies. In regular blood donation, donors have to wait for red blood cells to replenish between donations but in the case of plasma, it can be donated frequently, that is twice a week.

The plasma rich with antibodies is taken from the recovered patients of COVID-19 and then is infused into the bloodstream of other infected coronavirus patients. When the body gets into contact with external pathogens like bacteria or germs, it automatically starts a defence mechanism and started releasing antibodies.

According to the researchers, the therapy is not as simple as to obtain a significant amount of plasma from survivors is difficult. In the case of covid-19, a new disease, where most patients are aged and already suffering from other diseases like hypertension, diabetes, etc. Therefore, effectiveness remains questionable.

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**.

Various trials and study related to Convalescent Plasma Therapy^{9,10}

In China, a study found the therapy as effective, on small sample size, in treating COVID-19 patients. In the study, it was given that a trial was conducted in which 200 ml dose of convalescent plasma was administered to 10 adult COVID-19 patients with severe symptoms. The patients showed significant improvement and in seven patients virus disappeared without any severe adverse side effects. In this therapy, the sick acquires only temporary passive immunisation. It last mainly less than a week that is till the time the injected antibodies remain in the bloodstream.

In Houston also, the same trial was conducted and it is said that three critical ill COVID-19 patients are also showing signs of recovery from the convalescent plasma therapy.

According to the US Food and Drug Administration (FDA), prior experience with respiratory viruses and the data that have emerged from China shows that the therapy has the potential to lessen the severity or shorten the length of illness caused by COVID-19.

In India, the Indian Council of Medical Research (ICMR) has given the nod to Kerala to conduct convalescent plasma therapy. Kerala is the first state in the country. ICMR has not yet recommended it as a treatment option outside of clinical trials.

Several countries including China, South Korea, US and UK have also tried this therapy treatment. Some leading medical journals say that initial small trials are encouraging. Trials and researches are going for COVID-19 treatment. Therefore, it is necessary to take precautions as per the advisory of the government. Stay home and be safe!

REFERENCES:

1. Holshue ML, DeBolt C, Lindquist S, et al. First case of 2019 novel coronavirus in the United States. *N Engl J Med* 2020; published online Jan 31. <https://doi.org/10.1056/NEJMoa2001191>.
2. Lai ST. Treatment of severe acute respiratory syndrome. *Eur J Clin Microbiol Infect Dis* 2005; 24: 583–91.
3. Soo YO, Cheng Y, Wong R, et al. Retrospective comparison of convalescent plasma with continuing high-dose methylprednisolone treatment in SARS patients. *Clin Microbiol Infect* 2004; 10: 676–78.
4. Cheng Y, Wong R, Soo YO, et al. Use of convalescent plasma therapy in SARS patients in Hong Kong. *Eur J Clin Microbiol Infect Dis* 2005; 24: 44–46.
5. WHO. Use of convalescent whole blood or plasma collected from patients recovered from Ebola virus disease for transfusion, as an empirical treatment during outbreaks. 2014. <http://apps.who.int/iris/rest/bitstreams/604045/retrieve> (accessed Feb 20, 2020).
6. Arabi Y, Balkhy H, Hajer AH. Feasibility, safety, clinical, and laboratory effects of convalescent plasma therapy for patients with Middle East respiratory syndrome coronavirus infection: a study protocol. *Springerplus* 2015; 4: 709.
7. Hung IF, To KK, Lee CK, et al. Convalescent plasma treatment reduced mortality in patients with severe pandemic influenza A (H1N1) 2009 virus infection. *Clin Infect Dis* 2011; 52: 447–56.
8. Hung IFN, To KKW, Lee CK, et al. Hyperimmune IV immunoglobulin treatment: a multicenter double-blind randomized controlled trial for patients with severe 2009 influenza A(H1N1) infection. *Chest* 2013; 144: 464–73.
9. Mair-Jenkins J, Saavedra-Campos M, Baillie JK, et al. The effectiveness of convalescent plasma and hyperimmune immunoglobulin for the treatment of severe acute respiratory infections of viral etiology: a systematic review and exploratory meta-analysis. *J Infect Dis* 2015; 211: 80–90.
10. Luke TC, Kilbane EM, Jackson JL, Hoffman SL. Meta-analysis: convalescent blood products for Spanish influenza pneumonia: a future H5N1 treatment? *Ann Intern Med* 2006; 145: 599–609.