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Review Article on Convalescent Plasma Therapy For COVID-19

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ABSTRACT

In December 2019, China witnessed a novel coronavirus (COVID 19) in Wuhan which eventually became a pandemic on March 11, 2020. No specific drugs, vaccines have been approved yet for its treatment as it is a novel virus, though convalescent plasma is expected to increase the survival rates and also it is easily available. Studies have shown that in every epidemic, medical professionals often use plasma because it is the only available option at that time. This passive antibody therapy has been used since the 1890s to treat emerging infections and diseases like measles, Ebola, H1N1 flu, polio, etc. Researchers at John Hopkins University were specially the first ones to get approval from the FDA for the clinical trials as in some cases of emergency, they tried plasma therapy and got success. After China and the US and several other countries showed relative improvement rates with convalescent plasma therapy, INDIA has therefore also given the go-ahead for framing a protocol to conduct a clinical trial for the same. Plasma collected from recovered COVID patients has neutralizing antibodies which are expected to reduce the duration of infection. According to the scientific data, Convalescent Plasma Therapy in COVID 19 seems effective, safe and reduces death rates. Further development of improved plasma, vaccines and other therapeutic agents depends on the quick generation of data on pathogenesis and immune response of SARS- COV-2

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INTRODUCTION

The novel coronavirus was discovered in December of 2019 in Wuhan, China.

It is characterized by respiratory infection affecting the airways progressing to severe Lung damage. By far there is no evidence of spread of the virus via plasma and plasma-derived products.

Plasma is a clear straw-coloured liquid portion that remains after RBC's, WBC's, platelets and other cellular components are removed. It comprises water, salt, antibodies and other proteins which are essential for the proper functioning of the body; insufficient levels can cause a variety of chronic and life-threatening medical conditions.

Convalescent plasma is plasma collected from patients who have recovered from COVID 19. In addition to the proteins found. In plasma, COVID 19 plasma contains pathogen-specific antibodies. Antibodies are present in people's blood who have recovered from an infection. Antibodies are substances which identify and kill foreign substances such as viruses which are responsible for causing the disease. Recently, all health specialists are considering the chances of using this method to cure people infected with COVID-19 (Cohut, 2020).

Background

As per the data available till now, no transmission of any respiratory virus like influenza SARS, MERS or SARS-COV-2 have been witnessed by transfusion. So, the chances of SARS-CoV-2 transmission by components of blood or blood itself is currently seen as theoretical. Medicinal substances derived from plasma are considered safe as far as SARS-CoV-2 is concerned due to the specific traits of the virus and also the procedure allowing significant and effective removal of virus and its capacity during manufacturing. Considering the sensitive behaviour of the virus, i.e. being big and lipid covered as well as steps allowing inactivation of virus and its removal during the making processes of products derived from plasma, PPTA (Plasma Protein Therapeutics Association) states that the SARS-COV-2 is not a concern as per the points of plasma protein therapies manufactured by PPTA. This is a concrete initiative called The National COVID-19 convalescent plasma project.

Though people are different considering the quantity of antibodies that they produce, few produce huge amounts, few produce tiny amounts, but the best part is that almost all of them

have it, as told by Dr Casadevall ([Duan et al., 2020](#)).

The first medical hospital to transfuse plasma from recovered COVID-19 patients, i.e. Houston Methodist Hospital on March 28 became one of the first medical centres in the U.S. to carry out CPT into two severely affected patients.

Researchers at The University of Texas at Austin developed an antibody test and selected recovered patients with the highest levels of antibody response for donation since no negative side effects were shown due to the transfusion of plasma, the research stated that CPT is a safe treatment method for patients with very severe COVID-19 disease.

Till now, this is one of the largest cohorts organized for the results considering plasma transfusion in COVID-19 patients ([Cheng et al., 2005](#)).

People were first cured according to guidelines of emergency use from the US FDA and then got affirmation on 3rd April to conduct the trial to more patients. This fast affirmation given by the FDA gave permission to CPT for COVID-19 patients. Lots of COVID-19 patients admitted to hospitals all over the globe are being treated with convalescent plasma-like more than 20000 people in the US. Dr Musser and his companions between March and April involved 25 people who were severely infected with COVID-19 in primary research to look into the safety of plasma therapy, out of the 25, 9 of the patients involved gave signs of improvement in their condition almost after a week's time and 19 among

them also improved or been given discharge after 2 weeks' time.

In conclusion to the study, they said that study confirmed safety ([FDA, 2020](#)).

Methods

Prior To Procedure

Prior to CPT, the staff of the health care prepares the recovered patient for the procedure. A staff member puts a needle which is sterile single-usage and it is connected to a tube that is the intravenous line into a vein in one of the arms.

At The Time Of Procedure

As soon as the plasma arrives, the plasma bag which is a sterile bag is attached to a tube and the plasma comes out of the bag into the tube. The whole procedure takes approximately about one to two hours to complete.

After The Procedure

As this therapy hasn't been tested yet, one will have to be closely monitored after the CPT.

The doctor will be recording the response and reaction to the CPT treatment that is the duration of stay of the person and if at all the person needed any assistance with the respiration or any other assistance after the procedure.

The pandemic that the world is currently facing is a great opportunity for testing the benefits provided by plasma therapy ([Zhou et al., 2007](#)).

ICMR on 8th of may got heads up to organize phase-2 randomized controlled trials (RCT) with the help of convalescent plasma on COVID-19 patients with not so severe illness. The three of its studies in almost 20 seriously ill patients have found plasma therapy as a safety measure and also its ability to cure illness or to cure the clinical symptoms.

Since the safety of convalescent plasma collected from recovered people suffering from COVID-19 is not a major concern which is why, the human clinical trial, its first stage has been left.

They will otherwise study the safety of plasma and its efficiency with 452 patients in the phase 2 trial. The patients with not so severe COVID-19 infection will be randomly assigned to get one of them that is either convalescent plasma to 226 people of the study or only standard of care to the control group. The primary outcomes of the RCT in the mentioned 21 hospitals which will be studied incorporate the prevention of progression of the disease from progressing to a severe state and prevention of mortality after 28 days of plasma transfusion from all

causes. The secondary outcomes will include resolution of symptoms, reduction in a hospital stay and respiratory support. Plasma will be collected from donors 28 days after they make a complete recovery from illness or are symptom-free and have more than the required level of antibodies against the novel coronavirus (Zahid, 2020).

New Delhi

One of the first victim, who was administered with CPT on the worthy grounds at Max Hospital in Saket, has now seen full recovery and was accordingly discharged on April 20. The 49-year-old patient was a male who hailed from Delhi and was tested positive with COVID-19 on April 4. The patient was injected with fresh plasma as a treatment method as per the sideline given by the standard protocols and was discharged by the night of April 14. According to the doctors at Max Hospital, a single donor can at most donate up to 400 ml of plasma, which can save up to two lives, as 200 ml quantity is adequate to treat one patient as inferred from the data that they had. Delhi's chief minister announced in the public of setting up a dedicated plasma bank and he also mentioned that the plasma therapy trials were performed on 29 COVID patients and the results were very encouraging.

Also, in Maharashtra, the chief minister launched a convalescent plasma therapy cum trial project titled "PLATINA", calling it the largest initiative of its kind in the world. This will help in saving the life force of some 500 severe Covid-19 patients. All critical patients will receive two doses of 200ml convalescent plasma free of cost.

The convalescent plasma therapy is safe, with 76% of patients improving as the study by country's first peer-reviewed study of therapy, which shows a large part, i.e. 19 out of a total of 25 patients improving with the help of this treatment (Hung *et al.*, 2011).

It is not yet known to us if CPT for COVID-19 will turn out to be an effective treatment for COVID-19. However, what we do know is that this treatment might help in improving one's ability to recover from this disease. In preliminary treatment, most of the patients have benefitted from CPT. Researchers are still continuing to evaluate the results that they got from the people who received this therapy. In addition to its benefits of treatment, studying more about the use of CPT will definitely help health care workers be extra prepared for optimal care of the patients.

Discussion

Positive points of this antibody therapy which is passive in the treatment of COVID-19 are

CPT has been used with changing amounts of success to cure many infections of microbial origin for a lot of years. It can be provided to people with serious covid-19 to improve their capacity to deal with the virus.

It can also help people who are moderately ill from getting more ill and experience COVID-19 complications.

It also helps people who may have an increased risk of comorbidities, like people suffering from chronic, medical problems like cardiovascular diseases or diabetes or those with weakened immune response, it can help these people from getting sicker if they catch COVID-19.

CPT might also be taken into consideration for family members or health professionals who have been accustomed to someone with COVID-19 to help prevent them from getting COVID-19 (Zhao *et al.*, 2020).

The concerns when you give plasma include

1. One could get a transfusion reaction.
2. One can have volume overload which means that we are adding volume in the blood with an increased speed, it can cause overload to the cardio-vascular system which is why scientists looked from the experience of the first 5000 patients. They were relieved that no major complications were witnessed.

According to Dr Casadevall, the plasma therapy when employed by Medical Professionals on patients who are severely ill might not be as effective as it will be when given in the earlier course of the disease. He pointed out this because injection of antibodies against the virus for enhancing the body's immune system might be a lot effective earlier in the course of the disease because till the time a person becomes very ill, the immune system might have gone into an overdose of work resulting in inflammation of lungs and accompanied with an excessive release of immune-related factors causing cytokine storm, but instead of considering all the facts it is still currently being approved only for the cases that are severe (Chan *et al.*, 2013).

Transmission of diseases like hepatitis B, C, HIV, etc. is also a point of concern, but the risk of these disease transmissions is very less, because the blood which is donated is supposed to meet certain criteria delineated by FDA, i.e. the donated blood should be tested for safety before use after which it goes via a process to separate blood corpuscles so that all that is remaining is plasma containing antibodies.

Criteria of Eligibility for convalescent plasma donation or whole blood donation should consider the following points

A valid diagnostic test to confirm a previous infection with COVID-19. After complete recovery, there should be an interval of at least 14 days

Criteria of selection which is standard for plasma donation or whole blood donation like weight, age, etc.

The blood samples should be non-reactive for infections transmitted by the donation like HIV, Hepatitis B, C, syphilis in cases of whole blood donation, whereas in blood components transfusion, nucleic acid tests and other serology and infections which are locally transmitted have to be tested for.

One should preferably use the plasma from male donors in order to safeguard from the risk of Transfusion Related Acute Lung Injury (TRALI) or from female donors who never aborted or never got pregnant. These measures reduce the chances of HLA antibodies or granulocyte antigens being present in the plasma which has the potential of causing transfusion-related acute lung injury. It mostly happens 6 hours following the transfusion of affected plasma ([Hung et al., 2011](#)).

Testing of convalescent plasma donors before screening and donation. The complete Recovery from infection of COVID-19 must be confirmed via

Complete examination (physical) of the donor to state his or her good health which means the absence of COVID-19 symptoms like breathlessness, dry cough (chronic), or fever.

If at all the donor plasma is collected before 28 days following complete recovery from disease, then affirmation that the infection has been resolved must be done via 2 nucleic acid tests (NAT) for COVID-19 which should be non-reactive and which are done at a gap of at a day done by nasopharyngeal swabs.

There should be proper documentation of an approx. Date of contacting the COVID-19 infection, the symptoms, the given treatment and also the date when the symptoms are resolved.

Prior to use whenever possible, the neutralizing and total titers of anti-COVID-19 antibodies must be found out and also the donor plasma or serum or blood samples should be kept frozen at - 80°C for testing it retrospectively and for future investigations.

The criteria through which COVID-19 plasma

should be collected includes

It should be carried out in authorized blood establishments by a properly trained staff.

The collection should be supervised by trained staff.

The plasma volume that must be collected should be at least 200- 600 mL, without anticoagulant.

Units of plasma which are to be used for convalescent plasma should be mentioned clearly.

The treatment of plasma following donation

The pathogen inactivation from plasma through a valid method is very much needed wherever possible to control the risks of transmission of infections and superinfections with SARS-CoV-2.

Till the time of administration, it should be frozen at -20°C or at a cooler temperature. The Convalescent plasma which after collection does not fulfil the criteria for blood donation should be stored separately.

Plasma transfusion recommendations

One should follow the proper hospital procedure for plasma transfusion. It is very important to establish ABO compatibility between donor and recipient. Plasma transfusion from at least two donors may be helpful in achieving more efficient immune protection because of providing diverse antibodies. The samples of the recipient before and after the transfusion must be taken for future investigations ([Myupchar, 2020](#)).

CONCLUSIONS

A protocol is being made by the Indian council of medical research (ICMR) which states that they are in the last steps of creating a protocol for CPT, but this won't be of use in all the patients affected from COVID-19. It will be conducted on a trial basis as it was done in the other countries where it has been shown successfully in some trials. In India, they will perform it only on patients who are on a ventilator or are severe, as said by Dr Manoj Murhekar, Director, ICMR-National Institute of Epidemiology.

Conflict of Interest

The authors declare that they have no conflict of interest for this study.

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