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REVIEW ARTICLE **OPEN ACCESS**

Convalescent Plasma Therapy Effective Against COVID-19 – An Review on Updated Guideline and Procedure to use

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ABSTRACT
The primary objective of this review is to assess the safety and efficacy of Convalescent Plasma therapy (CPT) in treating COVID-19 patients. Globally, approximately 20 lakh people have been now infected by COVID-19. To date, no specific treatment has been proven to be effective for SARS-CoV-2 infection. In the absence of a vaccine, doctors and scientists are looking at convalescent plasma because they consider it low risk. Plasma from a cured patient is assumed to have antibodies against the virus and this can then be used to cure another patient. Researchers are testing the use of donated blood as a treatment for people with severe coronavirus disease 2019 (COVID-19).The treatment method has reportedly shown promising results in China - the epicenter of novel coronavirus. The U.S. Food and Drug Administration has approved the use of convalescent plasma therapy as an experimental treatment in clinical trials and for critically ill COVID-19 patients without other treatment options.
Key Words: Convalescent Plasma therapy (CPT), COVID-19, Antibodies, Guideline

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INTRODUCTION

A new virus called the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was identified as the cause of a disease outbreak that began in China in 2019. The disease is called coronavirus disease 2019 (COVID-19).[1]It spreads from person to person among those in close contact (within about 6 feet, or 2 meters). The virus spreads by respiratory droplets released when someone infected with the virus coughs, sneezes or talks. COVID-19 symptoms can be very mild to severe. Some people have no symptoms.[2] Mild symptoms may include fever, fatigue, cough, sore throat, headache, and decreased sense of smell or taste. More severe symptoms may include shortness of breath, chest pain, severe vomiting and diarrhea. Symptoms may appear two to 14 days after exposure.[3]Globally, the novel coronavirus has killed 1.5 million people and nearly 65 million *people globally have* been *infected* in last week of November 2020.The US has the highest number of infection at 14.2 millionin first week of December 2020.[4]In March 2020, the World Health Organization (WHO) declared COVID-19 a pandemic. Public health groups, including the U.S. Centers for Disease Control and Prevention (CDC) and WHO also issued recommendations for preventing and treating the illness.[5]

THE CDC RECOMMENDS FOLLOWING THESE PRECAUTIONS FOR AVOIDING COVID-19:

- Avoid large events and mass gatherings
- Wear a cloth face mask in public areas
- Avoid close contact (within about 6 feet, or 2 meters) with people outside of your home
- Wash your hands often with soap and water for at least 20 seconds, or use an alcohol-based hand sanitizer that contains at least 60% alcohol
- Cover your mouth and nose with your elbow or a tissue when you cough or sneeze. Throw away the used tissue
- Avoid touching your eyes, nose and mouth
- Clean and disinfect surfaces you often touch on a daily basis

If you have a chronic medical condition and may have a higher risk of serious illness.Take the following precautions to avoid spreading the illness:

- Stay home from work, school and public areas, except to get medical care.
- Avoid taking public transportation if possible
- Wear a mask around other people
- Isolate yourself as much as possible from others in your home
- Use a separate bedroom and bathroom if possible
- Avoid sharing dishes, glasses, bedding and other household items

WORLD HEALTH ORGANIZATION ADVICE FOR AVOIDING SPREAD OF CORONAVIRUS DISEASE (COVID-19)

Hygiene advice[6-7]

- Clean hands frequently with soap and water, or alcohol-based hand rub.
- Wash hands after coughing or sneezing; when caring for the sick; before, during and after food preparation; before eating; after using the toilet; when hands are visibly dirty; and after handling animals or waste.
- Maintain at least 1 meter (3 feet) distance from anyone who is coughing or sneezing.
- Avoid touching your hands, nose and mouth. Do not spit in public.
- Cover your mouth and nose with a tissue or bent elbow when coughing or sneezing. Discard the tissue immediately and clean your hands.

Medical advice

- If you feel unwell (fever, cough, difficulty breathing) seek medical care early and call local health authorities in advance.
- Stay up to date on COVID-19 developments issued by health authorities and follow their guidance.

Mask usage

- Healthy individuals only need to wear a mask if taking care of a sick person.
- Wear a mask if you are coughing or sneezing.
- Masks are effective when used in combination with frequent hand cleaning.
- Do not touch the mask while wearing it. Clean hands if you touch the mask.
- Learn how to properly put on, remove and dispose of masks. Clean hands after disposing of mask.
- Do not reuse single-use masks.

According to WHO, management of COVID-19 has mainly focused on infection prevention, case detection and monitoring, and supportive care, however, no specific anti-SARS-CoV-2 treatment is recommended because of the absence of evidence. No antiviral medication is recommended to treat COVID-19. Treatment is directed at relieving symptoms. Most importantly, the current guidelines emphasize that systematic corticosteroids should not be given routinely for the treatment of COVID-19. With the FDA's blessing, doctors have also been trying to treat COVID-19 patients with hydroxychloroquine, a drug typically used to treat malaria and lupus that has shown in limited research potential to speed recovery.Butit comes with risks if administered in high doses, the drug can cause heart arrhythmia and cardiac arrest. Vaccine for broad use would take about 12-18 months, and we don't have time to wait. In the absence of a vaccine, doctors and scientists are looking to convalescent plasma therapy because they consider it low risk.[7-8]

CPT EFFECTIVENESS DURING PAST EPIDEMICS

The use of convalescent plasma is not a new concept. It has been used since the 1800s. The treatment was first used in the 1890s,when Emil von Behring, a German physiologist, discovered that the serum obtained from a rabbit infected with diphtheria was effective in preventing the diphtheria infection. Behring was awarded the first-ever Nobel prize for medicine in 1901.Initially blood serum was used for convalescent therapy but soon whole blood or plasma recovered from donors with specific humoral immunity were identified as a possible source of specific antibodies of human origin. During the Spanish influenza pandemic of 1918 convalescent plasma was used as a potential therapy with mixed results. In the 1920s, it was used to treat scarlet fever and also outbreak in the 1930s, for a flesh-eating bacteria epidemic. Horse serum was used to treat tetanus until the 1970s as well. This technique was also used to treat hemorrhagic fever in 1979.[9-12]

In the early 20th century, convalescent plasma treatment was used during outbreaks of diseases such as measles, mumps and influenza. More recently, it was used during the H1N1 influenza pandemic andother coronavirus diseases like SARS in 2003 and MERS in 2012, with varied efficacy. In 2013 convalescent serum was used to treat Ebola virus (Ebola outbreak) in West Africa. Following the Ebola outbreak, the

World Health Organization issued guidance for its use in treating the disease, saying the small group it was used on showed "promising results". Moreover, with improved extraction and screening techniques, the method appears much more safe and effective now than ever before. Several studies showed a shorter hospital stay and lower mortality in patients treated with convalescent plasma than those who were not treated with convalescent plasma. Such a treatment would be a boon for people at high risk such as with underlying medical conditions, as well as family members and health care workers who have been exposed. In addition, learning more about the use of convalescent plasma now will help health care workers be better prepared if a second wave of disease occurs, as has happened with past viral outbreaks. It has been used in a variety of viral infections, although studies have been small and inconclusive. So Convalescent plasma therapy definitely is one of those things we can actually pursue with severe COVID-19 to boost patients ability to fight the virus and improve the survival rate of patients with SARS.[13-17]

CONVALESCENT PLASMA THERAPY (CPT)

Convalescent plasma refers to the liquid part of the blood. The idea behind convalescent plasma therapy is that such immunity can be transferred from a healthy person to a sick using blood plasma. When pathogens (Virus / Bacteria) entered in the body system, our immune systems produce proteins called antibodies. These antibodies are proteins in blood that fight specific bacteria and viruses. The infected person can produce sufficient antibodies to recover from the disease caused by that pathogen.[18]

PROCEDURE OF CONVALESCENT PLASMA THERAPYFOR COVID-19

In this procedure, the blood is drawn from a person who has recovered from COVID-19 infection (who have developed antibodies to particular coronavirus).The serum is separated and screened for virus-neutralizing antibodies. The serum, which is rich in antibodies are infused into another critically ill COVID-19 patient so that these specific antibodies give a massive boost to their adaptive immune system, which confers passive immunity can help fight the COVID-19 infection.

The process for donating plasma is similar to donating blood and takes about an hour, according to Houston Methodist, which became the first academic medical centre in the US to transfuse donated plasma from a recovered COVID-19 patient into a critically ill patient.Plasma donors are hooked up to a small device that removes plasma while simultaneously returning red blood cells to their bodies. Unlike regular blood donation in which donors have to wait for red blood cells to replenish between donations, plasma can be donated more frequently, as often as twice a week.This therapy is not simple to harness, primarily due to the difficulty of obtaining significant amounts of plasma from survivors. In diseases like COVID-19, where most of the patients with severe symptoms are aged, and often suffer from other medical conditions such as hypertension, diabetes, and so on.[19-20]

PROTOCOL FOR USE OF CONVALESCENT PLASMA THERAPY-

The U.S. Food and Drug Administration has outlined the requirements that individuals must meet to donate blood for this treatment. Before donated blood can be used, it must be tested for safety. It then goes through a process to separate out blood cells so that all that's left is plasma with antibodies. Donors for convalescent plasma must have received a lab-confirmed positive test for the coronavirus or test positive for COVID-19 antibodies after recovery and be symptom-free for at least 28 days before donating, adding that many potential donors have been unable to get tested for the coronavirus because their symptoms were not severe enough to qualify for one. The FDA has issued guidelines about the treatments with plasma.[21-22]

The FDA states that, convalescent plasma can only be collected from recovered individuals who have had initially tests positive and then has a second test for the coronavirus that comes back negative to COVID-19 either by nasopharyngeal swabs or by molecular diagnostic tests from the blood. It can donate after being symptom-free for at least 14 days before donation days. COVID-19 survivors appear to start increasing the titer of antibody around day 28; therefore, suitable donors will not be selected unless they have had a documented infection that began 28 days before they can donate plasma. Plasma recipients must be of the same blood type group as the donor.Potential donors are going to be screened like all blood donors are screened. Female donors must be negative for HLA antibodies. The FDA also advises that donors have defined SARS COV-2 neutralizing antibody titers with a titer greater than 1/320.

Eligible patients must have severe or immediately life-threatening infections with laboratory-confirmed COVID 19. The agency defines a life-threatening disease as one that causes acute respiratory distress with increased respiratory rate and decreased blood oxygenation. One of the ways to avoid complications associated with transfusion of plasma would be to use only purified antibodies derived from the serum of patients who have recovered from COVID 19. [22-23]

GUIDELINE FOR DONOR INFORMATION, CONSENT AND SELECTION

When a COVID-19 recovered patient has been identified as a potential donor, the need for collecting his/her whole blood or plasma donation should be explained, emphasizing that this could be useful as an empirical treatment for other COVID-19 patients. Potential donors should be informed that there will be no payment to them for their blood or plasma donation. In the event that the potential donor agrees to be considered for CWB/CP donation, he/she should be assessed for suitability to donate blood or plasma through a donor selection process, including general health criteria such as weight, medical and social (i.e. behavioural risk factors) history, basic physical examination and haemoglobin estimation.

Potential donors who meet the WHO criteria of recovery from COVID-19 and who also meet the donor selection criteria identified above and have given informed consent should then be subjected to pre-donation testing to assess final suitability for donation, according to the national policy and routine procedures.

Pre-donation testing should include: • ABO and RhD grouping • Blood screening tests for HIV, HBV, HCV, syphilis and other locally transmitted infections, as applicable • Haemoglobin estimation (unless performed as part of the initial donor selection process • Where possible, titration of total COVID-19 antibodies and coronavirus neutralizing antibodies could also help in the qualification of the donor, particularly if the donor is willing to continue serving as CWB/CP source.[24-26]

Blood collection and donor care

Potential donors who test negative for all TTI tests and meet all other criteria of donor suitability should be selected for CWD/CP donations. In the event that the time between the pre-donation testing and the donation exceeds 48 hours then the routine TTI testing should be repeated at the time of donation. Whole blood donation should be collected in a single blood collection bag or if feasible, in a double blood collection bag for the separation of plasma from the red cells by sedimentation or centrifugation. Where possible CP could also be collected by apheresis procedure from suitable donors. Plasmapheresis will enable collection and storage of large volumes of CP that may be used for more than one patient. The donor should be provided with good care before, during and after the whole blood or plasma donation procedure. Any adverse donor reactions should be adequately and promptly managed and recorded. The WHO Guidelines on drawing blood: Best practices in phlebotomy may provide a useful source of information.[24-26]

GUIDANCE ON TRANSFUSION OF CONVALESCENT WHOLE BLOOD OR PLASMA

Informed consent if feasible, informed consent for transfusion of CWB/CP should be obtained from the COVID-19 patient or the family members. Collection of patient's blood samples for laboratory testing.The patient should be correctly identified. Two venous blood samples of 5 mL each should be collected from the patient prior to transfusion; one in EDTA for a plasma sample and the other one in a plain tube (without anticoagulant) for a serum sample.These samples are for (a) ABO and RhD blood grouping and cross-matching and (b) for baseline viral load assay. One 5mL sample should be taken in a plain tube (without anticoagulant) for a serum sample on the day after transfusion to measure viral load and for any other tests, as required.

Prior to discharge of patients that recover, two additional 5 mL samples (each in a plain tube without anticoagulant) are required on consecutive days for viral load measurements. Residual serum from these blood samples should be stored in aliquots for retrospective antibody testing or any other tests, as required.[27-28]

Selection of convalescent whole blood or plasma units for transfusion ABO and RhD matched blood or plasma units should be selected for transfusion. RhD negative units should be used for transfusion to RhD negative women of child-bearing age, if feasible. If the RhD group of the patient is not known or in case of non-availability of RhD specific group, blood matched only for ABO group may be used. To reduce the risk associated with handling infectious blood samples, cross matching of patients' serum and donors' red cells, may be omitted if ABO group compatible CWB/CP is selected.

When it is not possible to test the patient's ABO group or if ABO matched CWB/CP is not available then:

- For whole blood transfusion: Group O convalescent whole blood, ideally from donors with low titre anti-A and anti-B, should be used;
- For plasma transfusion: Group AB convalescent plasma separated by centrifugation should be used. O
- Non ABO-matched CP separated by centrifugation could also be considered if group AB plasma is not available, but should preferably be group A or group B.
- CP prepared by 24-hour sedimentation should only be used for ABO group compatible recipients due to the higher red cell concentration.

Administration of convalescent whole blood or plasma CWB/CP units should be transfused to the COVID-19 patients using standard clinical transfusion procedures. One unit of CWB (collected in a 350/450 mL blood collection bag) should be transfused for adult patients. In the absence of evidence, 400-500 mL of CP in two doses of 200-250 mL each, separated from two different WB donations, should be considered for adult patients. For paediatric CWB/CP transfusion, a dose of 10 mL/kg could be used based on the considerations of blood volume. Slow intravenous transfusion should be given with careful monitoring of the patient for any acute transfusion reactions, particularly during the first 15-20 minutes. Transfusion should be completed within 1-4 hours of commencement with monitoring and recording of the patient's vital signs. If frozen plasma is being used for transfusion, it should be thawed in a water bath between +30°C and +37°C or other suitable thawing device before use and infused using a blood administration set as soon as possible after thawing. [27-29]

EFFECTIVENESS OF CONVALESCENT PLASMA THERAPY AGAINST COVID-19

CHINA - Earlier, a study in China found that this therapy was effective, albeit on small sample size, in treating coronavirus patients. In this trial, the research found that a 200 ml dose of convalescent plasma was infused in 10 adult patients with severe symptoms in Wuhan, China was well-tolerated. It could significantly increase or maintain neutralizing antibodies at a high level and patients showed improvement in their symptoms. A study published in The Lancet Magazine earlier this month citing another Chinese study said that a possible explanation for efficacy of convalescent plasma therapy is that the antibodies from convalescent plasma might suppress viraemia, or the presence of the novel coronavirus in the blood. The treatment has been successful in other disease outbreaks. However, it will not necessarily be effective for COVID-19. Scientists in China trialed the treatment on 245 coronavirus patients in February, the state-run Xinhua News Agency reported. Of these, 91 showed improvement in symptoms. In the March 27, 2020 issue of JAMA, researchers from China reported the results of 5 patients treated for severe COVID-19 infections with post convalescent serum taken from recovered patients.[18] All patients treated were on ventilators and were males, and they ranged in age from 36-73 years. Within 12 days of receiving convalescent serum, viral titers dropped dramatically to zero. The patients witnessed significant improvement with the disappearance of the virus reported without any severe adverse side-effects. Before and during treatment the patients also received interferon and lopinavir/ritonavir. It is questionable what role the addition of the antivirals played. The combination of lopinavir/ritonavir has now been discredited as a valid treatment for the COVID-19 infection.[32-33]

US - Five patients at Baylor St. Luke's Medical Center in Houston, part of the Baylor College of Medicine — have been treated with convalescent plasma and have found recently recovered donors with same blood groups for plasma transfusion. They are showing positive signs of recovery and waiting for more donors for new rounds of plasma transfusion. Another three critically ill COVID-19 Indian-American patients in Houston are also showing signs of recovery after they were transfused with the blood plasma from recovered patients.[34-35]

INDIA: Convalescent Plasma is an experimental procedure for COVID-19 patients. Hospitals and Institutions planning to provide this modality of treatment should do so in a clinical trial with protocols which are cleared by the Institutional Ethics Committee. The Indian Council of Medical Research (ICMR) has sought participation of researchers for conducting clinical trial of convalescent plasma therapy to treat critically ill COVID-19 patients and floated a protocol for it.The clinical trial is supposed to be two arm, open-label, randomized controlled trial, and meaning that patients will either be given convalescent plasma or any conventional therapy on a randomised-basis and each of the patients will know which treatment they are being gives. The Indian Council of Medical Research (ICMR) has given the nod to Kerala to conduct plasma therapy. Kerala is the first state in the country to have been given the nod to try this out, as a task force was already in place. Meanwhile, the Indian Council of Medical Research (ICMR) was begin a study on the efficacy of plasma therapy with involving 450 people. The experiments to use plasma therapy for treating a COVID-19 patient has been successful in Mumbai (Maharashtra), Chandigarh and New Delhi in month of May 2020.[36]

Japan's Takeda Pharmaceutical Company Limited also announced that it was working to develop a plasma-based therapy for COVID-19 at the start of March. Plasma-derived therapies are critical, life-saving medicines that thousands of people with rare and complex diseases rely on every day around the world.[37]

Globally, nearly five lakh positive cases have recovered completely. Therefore, a sufficient supply of antibodies could be available to critically ill patients if the therapy is proven effective. Through this therapy, the sick acquires only temporary passive immunization. It lasts only till the time the injected antibodies remain in the bloodstream—usually less than a week. On the other hand, a vaccine, if

developed, could provide life-long immunity against the pathogen. US Food and Drug Administration (FDA) stated on the bases of prior experience with respiratory viruses and on data that have emerged from China, the therapy has the potential to lessen the severity or shorten the length of illness caused by COVID-19.

CONCLUSION

The Food and Drug Administration is yet to approve the treatment but is allowing initial clinical trials. Because those trials are limited, doctors nationally can also request for the FDA's permission to use the treatment for severe COVID-19 cases. Instead, it could be used to treat people at high risk of getting the disease like nurses, physicians, and first responders exposed to known cases of COVID-19. This could allow them to continue their critical function as health care providers. As the world waits for a vaccine against COVID-19 with bated breath, it remains to be seen if this method can provide a much-needed short-cut in finding a cure.

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CONFLICTS OF INTEREST

Authors have declared that there is no conflict of interest.

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