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Review on COVID-19 Treatment: Convalescent Plasma (CCP) Therapy

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ABSTRACT

The corona virus 2 (SARS-CoV-2) epidemic is evolving into a global threatening worldwide and no effectively proven therapeutic agents or vaccines for COVID-19 are available as of now. Historically convalescent plasma has been used as an empirical treatment for SARS-CoV, H1N1 influenza, H5N1 avian influenza etc. Convalescent plasma obtained from the recovered corona virus patients will be having these antibodies which can be utilized for passive immunization therapy against SARS-CoV-2 antigen. The plasma can be obtained either through plasmapheresis or by separation from the whole blood. The supposed mechanism of action by which passive antibody therapy provides protection against SARS-CoV-2 is viral neutralization, Phagocytosis or antibody-dependent cellular cytotoxicity. Uses of COVID-19 convalescent sera are either prophylaxis of infection or treatment of disease. But there are known and theoretical Risks of passive administration of convalescent sera also. There are certain national guidelines for collection of blood and plasma from healthy volunteer donors which need to be followed by all blood banks. COVID-19 convalescent plasma donation guidelines include different steps like donor search, ABO and Rh (D) blood type compatibility, eligibility criteria for the COVID-19 convalescent plasma donor, pre-donation health screening and testing, plasmapheresis procedure, storage of the CCP product, receiving of cross-match request and patient's sample and thawing and cross-matching the CCP unit. Studies on CCP with the limited sample size and study design preclude a definitive statement about the potential effectiveness of this treatment, and these observations require evaluation in clinical trials.

Key words: corona virus 2 (SARS-CoV-2), COVID-19, Covid convalescent plasma (CCP), passive immunization therapy, plasmapheresis, convalescent plasma therapy (CPT)

INTRODUCTION

The severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) epidemic which originated from Wuhan, China in December 2019, has swiftly evolved into a global phenomenon.[1] The World Health Organization named it as corona virus disease 2019 (COVID-19) and declared it as a pandemic on 11th March 2020. As of 4th Nov 2020, approximately 48,030,398 Corona virus Cases have been reported worldwide (219 countries) with about 1,223,172 deaths.[2]

In spite of the massive worldwide efforts, no effectively proven therapeutic agents or vaccines for COVID-19 are available as of now.[3] Initially a number of antiviral drugs seemed promising like remdesivir and favipiravir,[3,4] however their efficacy is not yet conclusively proven in any of the studies. Historically convalescent plasma has been used as an empirical treatment during the Ebola virus outbreaks

in 2014, and later on in 2015 during the Middle East respiratory syndrome coronavirus spread. [5] Similar approach with other viral infections such as SARS-CoV, H1N1 influenza, and H5N1 avian influenza also supported the effectiveness of convalescent plasma transfusion. [5,7-10] These findings point to the hypothesis that the use of convalescent plasma transfusion could be a beneficial treatment modality in SARS-CoV-2 patients.

Convalescent Plasma / Passive Antibody Therapy

The host immune system is triggered to form antibodies when it gets challenged by foreign pathogens like virus, bacteria, etc. These antibodies are produced by B lymphocytes which can specifically recognize the antigen. These then evolve into a clone of plasma cells which can generate antibodies whenever again exposed to the same pathogen thus providing life-long immunity.

Convalescent plasma obtained from the recovered coronavirus patients will be having these antibodies which can be utilized for passive immunization therapy against SARS-CoV-2 antigen. This is the only way of providing an immediate immune cover. A COVID-19 convalescent person can become a plasma donor when there is no evidence of viremia while having the protective antibodies. The plasma can be obtained either through plasmapheresis procedure or by separation of plasma from the whole blood donation. Even though the antibodies against SARS-CoV-2 can also be obtained from various sources like synthetic monoclonal antibodies or preparations of human antibody from genetically modified animal hosts, but these are currently under development. [11] The supposed mechanism of action by which passive antibody therapy provides protection against SARS-CoV-2 is viral neutralization. Phagocytosis or antibody-dependent cellular cytotoxicity are also the other possible mechanisms. [11]

Figure 1 shows schematic of the use of convalescent sera for COVID-19. [12] A consenting individual who has recovered from COVID-19 is identified as convalescent donor. Blood is drawn and screened for virus-neutralizing antibodies. Following identification of those with high titers of neutralizing antibody, serum containing these virus-neutralizing antibodies can be administered in a prophylactic manner to prevent infection in high-risk cases or as treatment of critical patients.

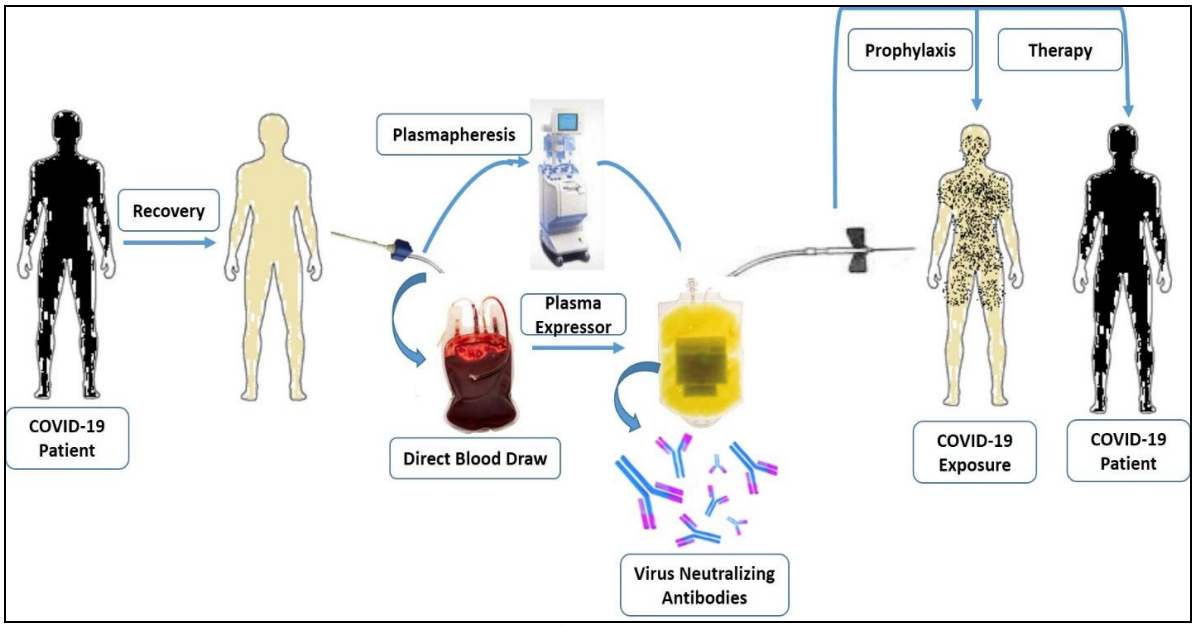

Figure 1: Schematic diagram of convalescent plasma collection and use

Usually passive antibody therapy is more efficacious when used for prophylaxis rather than for treatment of disease. When used for therapy, antibody is most effective when administered shortly after the onset of symptoms. The reasons for temporal variation in efficacy is not well understood but could explain that passive antibody neutralize the initial inoculum, which is smaller than that of established disease. [13] Another explanation is that antibody works by modifying the inflammatory response, which is additionally more easily achieved during the initial immune reaction, a stage which will be asymptomatic. [14]

A sufficient amount of antibody has to be administered for passive antibody therapy to be effective. When given to a susceptible person, this antibody will reach tissues by circulating with blood, and provide protection. Depending on the antibody titre and composition, the duration of protection conferred by the transferred immunoglobulin can last from weeks to months.

History

In the early twentieth century convalescent sera was used to stem outbreaks of viral diseases such as poliomyelitis, [15] measles, [16,17] mumps,[18] and influenza. [19] It is noteworthy that historically, convalescent sera were developed and utilized in many cases without the means to live antibody titers or knowledge about viral serotypes.

Recently, convalescent serum was used for viral epidemics. In the 2009-2010, H1N1 influenza virus pandemic, convalescent serum antibody preparations obtained by apheresis were used to treat individuals with severe H1N1 2009 infection requiring medical aid 20. Serum-treated individuals manifested reduced respiratory viral burden, serum cytokine responses, and mortality. [20] Convalescent serum was also utilized in the 2013 West African Ebola epidemic. In one of the nonrandomized study in Sierra Leone showed that significantly longer survival for those patients treated with convalescent whole blood relative to those who received standard treatment. [21] Although every viral disease and epidemic is different, these experiences provide important historical precedents that are both reassuring and useful.

Use of Convalescent SERA against Corona virus Diseases from Literature

In the twenty-first century, there have been two other epidemics with corona viruses that were associated with high mortality, SARS1 in 2003 and Middle East respiratory syndrome (MERS) in 2012. In both cases, the high mortality and absence of effective therapies led to the utilization of convalescent serum. The largest study involved the treatment of 80 patients with SARS in Hong Kong. [22] Patients treated before day 14 had improved prognosis as discharge from hospital before day 22, according to the notion that earlier administration is more effective. Those patients who were PCR positive with seronegative result for corona virus at the time of therapy had improved prognosis. Three patients with SARS in Taiwan were treated with 500 mL convalescent serum, resulting in a reduction in serum virus titer, and each survived. [23] Antibody declines with time and/or that few patients make high-titer responses. It is also possible that non-neutralizing antibodies are produced that contribute to protection and recovery, as described for other viral diseases. [24-26]

There are some reports that showed convalescent serum was used for therapy of patients with COVID-19 in China during the present outbreak. [27] From one study in china, [28] all 5 patients (age range, 36-65 years) who were receiving mechanical ventilation at the time of treatment and all had received antiviral agents and methylprednisolone. Following plasma transfusion, body temperature normalized within 3 days in 4 of 5 patients, the SOFA (Sequential Organ Failure Assessment) score decreased, and PAO2/FIO2 increased within 12 days (range, 172-276 before and

284-366 after). Viral loads were also coming down and have become negative within 12 days after the transfusion. SARS-CoV-2–specific ELISA and neutralizing antibody titers increased following the transfusion (titre: 40-60 before and 80-320 on day 7). ARDS resolved in 4 patients within 12 days after transfusion, and three 3 patients were removed from mechanical ventilation within 2 weeks of treatment. Of the 5 patients, 3 have been discharged from the hospital (length of stay: 53, 51, and 55 days), and 2 are in stable condition at 37 days after transfusion. A working group of the Italian Society of Haemapheresis and Cell Manipulation (SIdEM) and the Italian Society of Transfusion Medicine and Immunohaematology (SIMTI), has written a position paper on convalescent plasma therapy for COVID-19 patients. [29,30] The available anecdotal evidence from its use in 245 patients with COVID-19,[31] suggest it is safe.

Initially few case series and a prematurely terminated RCT in China, [28]38 had indicated usefulness of CCP as a beneficial therapy. Later the interim results of a RCT by a Netherlands group concluded COVID patients already have high neutralizing antibody titers at hospital admission. [40] Similarly the completed PLACID trial done in India CCP has no benefit in treatment of patients with moderate COVID 19 disease. [37] PLACID is that the world's largest pragmatic trial on CPT conducted in 464 moderately ill laboratory confirmed COVID-19 affected adult patients in world setting wherein no advantage of use of CPT could be established. Similar studies conducted in China and Netherlands have also documented no significant benefit of CPT in improving the clinical outcomes of hospitalised COVID-19 patients.[38,39]

Risks and Benefits

Uses of COVID-19 convalescent sera are either prophylaxis of infection or treatment of disease. In a prophylactic mode, the advantage of convalescent serum administration is the prevention of infection and subsequent disease in high risk individuals for disease, like vulnerable individuals with underlying medical conditions, health care providers, and those with exposure to confirmed cases of COVID-19. Passive antibody administration with CCP to stop disease is already utilized in clinical practice worldwide. For example, patients exposed to hepatitis B and rabies viruses are treated with hepatitis B immunoglobulin (HBIG) and human rabies immunoglobulin (HRIG), respectively and it became successful. In addition, passive antibody is used for the prevention of severe respiratory syncytial virus (RSV) disease in high-risk infants. The efficacy of these approaches cannot be inferred without carrying out a controlled clinical trial.

Risks of passive administration of convalescent sera fall under two categories - known and theoretical. Known risks are those associated with transfer of blood components, like inadvertent infection with another infectious disease agent , reactions to serum constituents (immunological reactions such as serum sickness), transfusion related acute lung injury (TRALI).[32] With modern blood banking techniques, the risks of inadvertently transferring known infectious agents or triggering transfusion reactions are low.

The theoretical risk involves the phenomenon of antibody dependent enhancement of infection (ADE). ADE can occur in several viral diseases and involves an enhancement of disease within the presence of certain antibodies. For corona viruses, several mechanisms for ADE have been described, and there is the theoretical concern that antibodies to one type of corona virus could enhance infection to another viral strain. [33] Since the proposed use of convalescent sera within the COVID-19 epidemic would believe preparations with high titers of neutralizing antibody against an equivalent virus, SARS2-CoV-2 ADE could also be unlikely. Nevertheless, in convalescent serum trials, caution and

vigilance to spot any evidence of enhanced infection are going to be required.

Another theoretical risk is that antibody administration to those exposed to SARS-CoV-2 may prevent disease in a manner that attenuates the immune response, leaving such individuals vulnerable to subsequent reinfection. In this regard, passive antibody administration before vaccination with respiratory syncytial virus was reported to attenuate humoral but not cellular immunity. [34] This concern might be investigated as a part of a clinical test by measuring immune responses.

There are however a couple of hurdles in plasma collection too. There are certain national guidelines for collection of blood and plasma from healthy volunteer donors which need to be followed by all blood banks. Going by these guidelines of donor selection, recovered patients aren't eligible to donate. These guidelines are laid down by three bodies under the Ministry of Health and Family Welfare - CDSCO (Central Drug Standards Control Organisation), DGHS (Director General of Health Services) and the National Blood Transfusion Council.

Deployment and Proposed Use

To deploy convalescent serum administration for COVID-19 the subsequent six conditions must be met [12]:

(i) Availability of a population of donors who have recovered from the disease and can donate convalescent serum
(ii) Blood banking facilities to process the serum donations
(iii) Availability of assays, including serological assays, to detect SARS-CoV-2 in serum and virological assays to live viral neutralization
(iv) virology laboratory support to perform these assays
(v) Prophylaxis and therapeutic protocols, which should ideally include randomized clinical trials to assess the efficacy of any intervention and measure immune responses
(vi) Regulatory compliance, including institutional review board approval, which can vary counting on location. Ideally, the utilization of convalescent serum would involve multiple centers, follow randomized control protocols, and have one center as an administration. Each of those conditions should be available in developed areas suffering from COVID-19.

CCP DONORS

- **Donor Search**

Blood center should identify potential CCP donors from the list of COVID-19 recovered patients and recruit them as plasma donors. Blood centers should seek help and coordination of NGO (non-government organization) working for this "cause". Patient's family could also be advised to look voluntary non-remunerated. COVID-19 recovered patient willing for CCP donation through social media platforms amongst their 'near and dear ones' or/and through various NGO which are maintaining a data-base of the persons who have recovered from COVID-19 disease. We might then approach the recovered patients and counsel them if they're found fit donate. The plasma collected could then be distributed to the varied COVID-19 care clinics. The remaining criteria still need to be fulfilled by the donor. Extreme alertness and care need to be exercised by the blood center to stop paid/professional donations. [35]

- **ABO and RH (D) blood type compatibility**

Only ABO blood type compatibility is required in plasma donation. Rh (D) blood groups are often ignored, provided anti-D antibodies aren't present in Rh (D) Negative donor.

- **Additional Material/Facility Required**

Written consent for donation of convalescent plasma from the donor additionally to regular donor health questionnaire cum consent form. Blood bank should possess license for

plasmapheresis, have facility to live serum protein and live anti-SARS-CoV-2 IgG antibodies.

- **Eligibility Criteria for the CCP Donor**

Males or nulliparous (to mitigate the danger of TRALI) female donors of weight > 50 kg. The donor shall be within the age bracket of 18 to 65 years. Recovered patient (CCP donor) should preferably have had symptoms (fever, cold, cough, etc.) since there's a greater probability of presence of anti-SARS-CoV-2 IgG antibodies as compared to an asymptomatic patient. A possible donor for convalescent plasma should have sufficient concentration of antibody working against COVID19. However, even asymptomatic donors could also be accepted, if anti-SARS-CoV-2 IgG antibodies are present. Complete resolution of symptoms a minimum of 14 days before donation, testing negative for COVID-19 isn't necessary. Donor should be advised to donate less than twice a month. Additionally, donor eligibility criteria for whole blood/Apheresis donation are going to be followed in accordance to the Drugs & Cosmetics Act 1940 and rules therein (as amended till March 2020).

BLOOD CENTER

- **Pre-Donation Health Screening And Testing**

Once the donor has been administered medical history questionnaire and physical examination has been completed; donor has been found eligible, the pre-donation samples collected. Blood samples are tested for complete blood counts (CBC), ABO and Rh D blood group and antibody screen, routine TTI (transfusion transmitted infections) serum proteins and anti SARS-CoV-2 IgG antibodies. The latter two tests are specifically for CCP plasmapheresis donation. Total serum protein > 6gm/dl and presence of anti-SARS-CoV-2 IgG antibodies are pre-requisite for CCP plasmapheresis donation. Though the latest ICMR guideline mentions a titer of 1:640 (in ELISA) or 13 AU (Absorbance unit/ ml) (in Chemiluminescence Immunoassay) or neutralizing antibody titer of 1:80 (in plaque reduction neutralization test or in microneutralization test), [6] but the DCGI working group recommends that in absence of quantitative test kits, at least the qualitative test (Yes/No) should be used for deciding upon donor eligibility. It is recommended to keep a donor serum sample frozen at < -30° C for a possible later date testing of titer, etc. [35]

- **Plasmapheresis Procedure**

Any automated cell separator (apheresis machine) may be used. Maximum CCP Volume collection that is allowed is 500ml. If the apheresis machine doesn't have dedicated plasmapheresis program, the plateletpheresis procedure could also be modified during a manner that a minimum of 400 ml (two therapeutic doses of 200 ml each) plasma is obtained and these is minimum possible number (and volume) of platelets are collected. This by-product (where platelets are collected separately and later on suspended in the plasma) may be discarded or returned to the donor (depending on the cell separator). The maximum volume that can be collected in one session is 500 ml.

- **Storage of the CCP Product**

CCP has to be stored at temperature < -30° C. Separate shelf of deep freezer or if possible, separate deep freezer may be dedicated for CCP.

CPT therefore should only be used, as advised by ICMR NTF, for management of COVID-19 when specific criteria as mentioned below are met. [6]

CCP RECIPIENT

- **Receiving of Cross-Match Request and Patient's Sample**

Patient's request form for CCP is received. The blood group is performed. A separate consent form (besides regular consent that is part of hospital/blood bank protocol) is required .The request form should mention "off-label" use of CCP. A

blood component requisition by a qualified physician, from another designated COVID-19 treatment hospital or a hospital treating COVID-19 patient may also be accepted. Appropriate documentation should be maintained. [35]

- **Thawing and Cross-Matching the CCP Unit**

The plasma unit is thawed at 37^0 C and the plasma bag segment is used for minor cross match with patient's RBC (red blood cells). If the unit is cross match compatible, the unit is issued. If not used for a COVID-19 patients, it should be discarded. As soon because the clearance is issued, we will start treatment immediately. In fact, from the very next day itself. Depending on the volumes needed and therefore the neutralizing activity of donated convalescent sera, these might be pooled or used individually, and preparations for clinical use would be treated for pathogen attenuation.

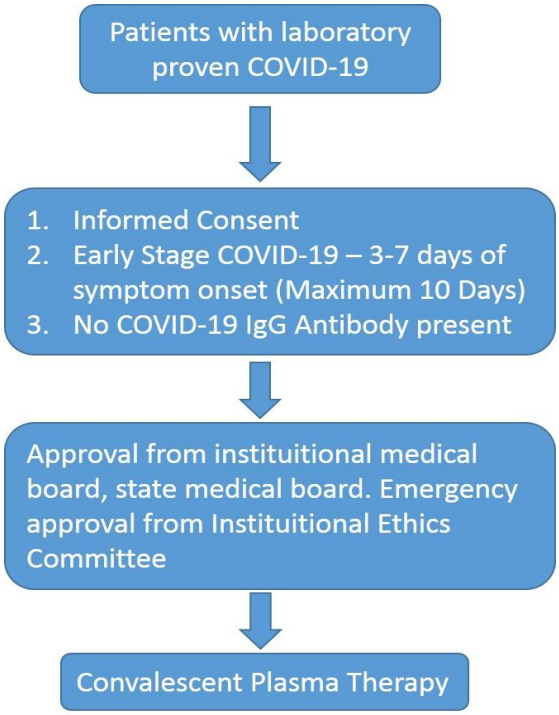

Figure 2: Flow chart on COVID-19 convalescent plasma collection

Clinical Use of CCP Therapy

It is important to select the patient appropriately. Only moderately affected patient have been shown to benefit from the CCP therapy. Patient should be provided CCP therapy if [35]:

- ICMR definition: Patients admitted with RT-PCR confirmed COVID-19 illness within 3-7 days of symptom onset (Maximum 10 days) with no presence of IgG COVID-19 antibody.
- MOHFW definition: Adolescent or adult with presence of clinical features of dyspnea and or hypoxia, fever, cough, including SpO2 on room air, rate of respiration more or adequate to 24 per minute. Moderate disease with increasing oxygen requirements not responding to steroids should receive CCP therapy should be instituted before the patient goes into multiple organ failure.

Patient should not have history of Ig A (immunoglobulin A) deficiency syndrome or allergy to immunoglobulins. One or two therapeutic units of 200-250 ml each should be administered to the patients on two consecutive days (24 hours apart and if, first is tolerated well), depending on the patient condition in early stage of COVID-19 disease. It is advised that donor CCP units provided to patient should rather be from two different donors. Patient should be closely monitored for adverse effects of plasma. CCP therapy may be given along with other therapies like, Remdesivir, Tocilizumab, etc. Patient should be monitored for improvement/deterioration after CCP therapy. [35]

CONCLUSIONS AND RELEVANCE

COVID-19 convalescent sera might be wont to treat individuals with early symptoms and stop disease in those exposed. It is anticipated that convalescent serum will prevent SARS-CoV-2 infection in those to whom it's administered. Clearly, the utilization of convalescent serum would be a stopgap measure that would be utilized in the midst of the present epidemic. However, even local deployment will entail considerable coordination between different entities, such as infectious disease specialists, hematologists, blood banking

specialists, and hospital administrators. Indiscriminate use of convalescent plasma therapy is not advisable. Studies on CCP with the limited sample size and study design preclude a definitive statement about the potential effectiveness of this treatment, and these observations require evaluation in clinical trials. Hence, as we are within the midst of a worldwide pandemic, we recommend that institutions consider the emergency use of convalescent sera and start preparations as soon as possible.

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