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Treatment with Convalescent Plasma for COVID-19 as an Immediate Option

Kaushal Kumar¹, Khushboo Kumari²

Ph.D. Student, Department of Botany, School of Life Science, Mahatma Gandhi Central University, Bihar, India¹

Ph.D. Student, Department of Botany, School of Life Science, Mahatma Gandhi Central University, Bihar, India²

ABSTRACT: As of Early 2020, Human in confronting with a global problem of COVID19 that paralysed the whole World. At the time of this writing SARS-CoV-2 is spreading in Multiple Countries with a high Fatality rates which somehow could leave a durable imprint. The Virus appear to be a new Pathogen so as we called novel. In a recent scenario there is no vaccine or monoclonal antibodies or drugs to combat COVID-19. Its need to be concludes that human Convalescent Serum is an immediate option for the prevention and treatment of COVID19 from recovered individual with rapid availability.

KEYWORDS: Convalescent Plasma ; COVID-19 ; Passive Antibody ; Serological Survey ; Neutralizing Antibodies ; SARS- CoV-2

I. INTRODUCTION

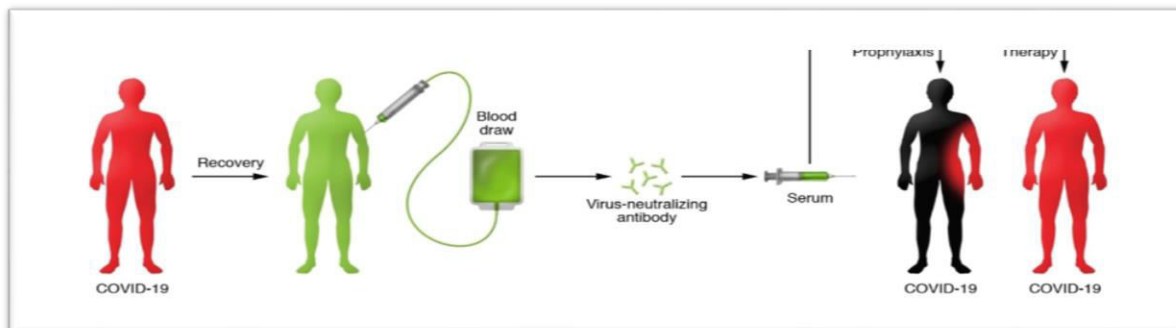
Convalescent sera or Convalescent Plasma is the fraction of blood that contains antibodies, but not red blood cells — from people who had recovered from COVID-19, considered to be especially rich in antibodies against the infectious agent of the diseases. It is some how possible that convalescent plasma that contains antibodies to SARS-CoV-2 (the virus that causes COVID-19) might be effective against the infection. Use of convalescent plasma has been studied in outbreaks of other respiratory infections, including the 1918 Spanish flu , 2009 H1N1 influenza virus pandemic, 2003 SARS-CoV-1 epidemic, and the 2012 MERS-CoV epidemic. The Immediate availability provide a key advantage to convalescent plasma , whereas drugs and vaccines take months or years to develop. It refer to this measure as ‘passive antibody therapy’ because a person receives external antibodies, rather than generating an immune response themselves, as they would following a vaccination. Through various clinical trials it is important to determine that before habitually administering convalescent plasma to patients with COVID-19, that it is safe and effective to do so. Convalescent serum might be replaced by modern therapies later this year if it works well enough.

The aim of this review article is to provide an overview as an immediate option to combat COVID-19 pandemic.

Passive Antibody Therapy

Antibodies for the prevention and treatment of infectious diseases have been used for a century. In various bacterial disease, facilitate opsonization while antibodies used to neutralize toxins and, with the help of complement promoting bacteriolysis; in viral disease, viral entry is being blocked by antibodies into uninfected cells, promote antibody-directed cell-mediated cytotoxicity by natural killer cells, and neutralize virus alone or with the participation of complement up to some extent.

But some times in various cases antibodies not able to neutralize the pathogen specifically in non immune individual. Throughout history, there have been a number of pandemics where it require Passive immunization to neutralize pathogen because of non availability of required antibodies in our blood circulation. Passive immunization for the prevention and treatment of various viral diseases traced back to the 20th century to acquire passive immunity. Passive antibody Therapy involves the administration of antibody to the hyper sensitive individual



(Figure a)

Various Animals like rabbit, horses contain required antibodies while human blood is also identify as a possible source of antibodies.[1,2] Convalescent Blood Product(CBP) obtained from a patient who has survived with previous infection and somehow developed humoral immunity against the pathogen by collecting the whole blood or Plasma. Transfusions of CBP resulting in neutralizing the pathogen and eventually eradicate out pathogen from the blood circulation.

Hitherto Different CBP have been used to a acquire passive immunity[1-4] : (i) convalescent whole blood (CWB), convalescent plasma (CP) or convalescent serum (CS); (ii) pooled human immunoglobulin (Ig) for intravenous or intramuscular administration; (iii) high-titre human Ig; and (iv) polyclonal or monoclonal antibodies. Regulation of Blood , Blood product and invitro diagnostic devices (IVD)monitored by Blood Regulators Network(BRN) one of the leading international authority of World Health Organization (WHO) which was established in 2006. Especially in the wake of large scale epidemics CP has been the subject of increasing attention.[5] The current therapeutic tool to combat various viral diseases by the significant use of Apheresis Plasma because of several reasons[6]: larger volumes collected per session, the possibility of more frequent donations, and the absence of impact on the donor's haemoglobin. Locations of Infectious diseases is also taken into consideration, The donor of CBP living in areas where epidemic has broken out can offer to provide specific , artificially acquired passive immunity against the local infectious agent while donor from other regions is comparatively having less effective CBP due to differ in strain variation of pathogen.[7,8]An individual who is suffer with COVID-19 and recovers has blood drawn and screened for virus-neutralizing antibodies subsequent identification of those with high titers of neutralizing antibody, serum containing these virus-neutralizing antibodies.An individual with underlying medical conditions should be administered in a prophylactic manner to prevent infection in high-risk cases.[Figure a] As convalescent subjects must also meet donor selection criteria, in compliance with national policies and routine procedures.

During outbreaks some donor selection criteria may be relaxed because of the potential importance of the treatment , as also suggested by World Health Organization (WHO)[9]. Hence for passive antibody therapy to be effective, 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.The protection conferred by the transferred immunoglobulin can last from weeks to months depend upon the antibody amount and composition. Convalescent plasma may be more effective in preventing disease than in the treatment of established disease by understanding some of the historical experiences while the efficacy of these viewpoint is not known.

Historical Precedents to use convalescent sera.

In the early twentieth century convalescent sera was used to hamper outbreaks of viral diseases such as poliomyelitis[9], measles (10 ,11), mumps (12), and influenza (13).During the 1918 Pandemic H5N1 influenza virus using of convalescent sera on 1703 patients suggested that those who received serum had lower mortality. Patients may have experienced a clinically important reduction in the risk of death with Spanish influenza pneumonia who received



influenza-convalescent human blood products Convalescent human H5N1 plasma could be an , emphatic, periodic, and widely available treatment that should be studied in clinical trials.[14]

During H1N1 influenza pandemic same sequel were proceed for the use of Convalescent sera with great efficacy where antibodies were obtained by apheresis.

A prospective cohort study by the researcher of University of Hong Kong concluded that Treatment with convalescent plasma of severe H1N1 2009 infection reduced respiratory tract viral load, serum cytokine response. In the treatment group the mortality rate was significantly lower than in the non-treatment group(20% vs 54.8%).[15]

During 2013 West African Ebola epidemic convalescent serum was also used.[16] A small nonrandomized study in Sierra Leone revealed significantly longer survival for those treated with convalescent whole blood relative Two patients with Ebola virus diseases transferred to the United States and treated with a combination of convalescent serum and an experimental drug also survived (17).

In Zhejiang Province, China, There was an outbreak of avian influenza A (H7N9) around January 2015 so that a patient with H7N9 symptoms was administered 3 days with convalescent plasma thereafter the patient was admitted to the hospital and led to a observable improvement. Results suggest that convalescent plasma combined with antiviral drugs may be a viable option for the treatment of H7N9.[18]

While Every epidemic and viral disease is different, such type of experiences provide important historical illustration that are both reassuring and useful as humanity now confronts the COVID-19 pandemic.

Past Experience using Convalescent sera on Corona virus

We have been experienced with last two epidemics one is SARS and other is MERS having high mortality rate. Both epidemics having high mortality rate as well as the absence of effective therapies. It led to use of convalescent serum during that time.About 80 patient were treated in Hong Kong by the use of convalescent plasma therapy[19]. Several other anecdotal information related the immediate use of convalescent serum on three patient in Taiwan resulting in each of the three patient survived. [20]. In South Korea three patients were treated with convalescent serum out of which two having neutralizing antibodies.[21] A Serological Survey showed that out of 99 samples 87 samples had neutralizing antibody with the geometric mean of 1:61.[22]. On the other hand In some cases Non- Neutralizing antibodies also contribute in the protection and recovery of other viral diseases.[23-25] Due to immediate unavailability of vaccine, drug or other specific treatment , somehow concludes that convalescent serum administration reduced viral load and was safe.

Proposed Use

Administration to deploy convalescent serum for COVID-19 the following six conditions must be met: (i) availableness of recovered population from the disease and subsequent donation of convalescent serum; (ii) serum donation processing by of blood banking facilities; (iii) availableness of serological assays, to detect SARS-CoV-2 in serum and virological assays to measure viral neutralization; (iv) Support of virology laboratory to accomplish these assays; (v) prophylaxis and therapeutic protocols to measure the efficacy of intervention and immune responses by randomly assessed clinical trials and (vi) regulation of established guidelines which may include approval from institutional review board. Ideally, all randomized protocol governed by a single centre as governing body to use convalescent serum by multiple centres, Once the necessary regulatory permissions are in place, individuals who recover from COVID-19 can be approached to donate blood for antibody isolation through apheresis. and recovered one will be examine clinically through which such individuals must be shown to free from SARS-CoV2

The Screening for Donated Blood Practices for Infectious agent according to current blood banking practices, and though differentially individual sera will be studied for specific antibody content and neutralizing activity to SARS-CoV-2. At this time, Effect of doses and neutralizingtiter in a susceptible individual for prophylaxis is unknown therapeutically. As in different precedent so far the amount of dosage is given at different intervals of time.

We do know in the treatment of measles and mumps the amount of dosage in the 10-40 cc which successfully prevent in such cases.[26,27]During World war I several soldiers were treated by using Convalescent serum given in the hundreds of millilitres. [28]

Without Any Knowledge and Experience of neutralizing titres such older studies claimed so much efficacy. Those experiences suggest that infection is being treated by a small amount of antibody. During severe disease infecting inoculum is likely to be much smaller than viral burden Hence, we can anticipate that effective prophylactic doses would be much smaller than therapeutic doses.

COVID-19 convalescent plasma could be used to treat individuals with early symptoms and prevent disease in those exposed. Health care system itself threatening in today's scenario in which nurses, sanitary workers, physicians, and first responders exposed to known cases of COVID-19, some of whom have developed disease, are being quarantined. It is anticipated that convalescent serum will prevent SARS-CoV-2 infection in those to whom it is administered. If this is established, period of quarantined may be avoided by those individuals who receive convalescent plasma. This could allow them to carry on their fundamental function as health care providers. Convalescent sera could also be used to prevent disease among family members caring for COVID-19 patients at home. Clearly, in the midst of current pandemic the use of convalescent serum would be act as standstill measure. However, even local deployment will entail considerable coordination between different entities, such as infectious disease specialists, haematologists, blood banking specialists, and hospital administrators. Hence, as we are in the midst of a worldwide pandemic, we recommend that institutions consider the emergency use of convalescent sera and begin preparations as soon as possible. Time is of the essence.

Possibilities and Challenges

In one of the recent preliminary study using Convalescent Plasma from recovered individuals on five severely ill patients with COVID-19 who were treated in the Shenzhen Third People's Hospital, China, [29] a patient with hypertension and mitral valve insufficiency received the plasma transfusion at day 10 while other four patients without coexisting diseases received convalescent plasma around hospital day 20. Subsequent administration of convalescent plasma containing neutralizing antibody was followed by Improvement in their clinical status is clearly seen in the preliminary uncontrolled case series of 5 critically ill patients with COVID19 and Acute respiratory distress syndrome (ARDS). In addition to this, Increment in the patients' neutralizing antibody titers and tested negative in respiratory samples for SARS-CoV-2 between 1 and 12 days after transfusion. Despite having potential utility of passive antibody treatments, there have been few convinced efforts to use them as initial therapies against emerging and pandemic infectious threats.

Due to the absence of large trials certainly contributes to the hesitancy to employ this treatment. Also, the concerned related to most effective formulations (convalescent plasma or hyper immune globulin, H-Ig or IV/IM administration or clonal antibodies) are unknown.

The antibodies of Convalescent plasma has the advantage to limit viral replication, while other beneficial effects exerted by other plasma components such as to replenish with coagulation factors when given to patients with haemorrhagic fevers such as Ebola.[30,31]. On the other hand, Donor- Dependent variability in antibody specificities and titers is being demonstrated by individual convalescent plasma units.

Although fractionation of H-Ig preparations which contain standardized antibody doses, removes IgM, which may be necessary against some viruses. However, pathogen reduced plasma collected from the Ebola Convalescent patients subsequently the construction of a strategic stockpile of frozen, demonstrated with well-characterized viral neutralization activities is one example of how to proceed with despite existing unknowns.[32]

The rapidly increasing rate of COVID-19 throughout the world cases provides an unprecedented opportunity to perform clinical studies of the efficacy of this treatment against a viral agent by deploying passive antibody therapies. If the results of rigorously conducted investigations, such as a large-scale randomized clinical trial, demonstrate efficacy, use of this therapy also could help change the course of this pandemic.[33]



How this increasing demands could be scaled to meet up? One approach would be the complementary way to combine the use of convalescent plasma and H-Ig to treat infected patients in the current COVID-19 pandemic, and subsequent infectious waves, perhaps with the following steps and considerations.

First, blood centres could start collecting plasma from convalescent donors, preferably at the leading edge of the infectious wave; health care workers could encourage COVID-19–infected patients to donate after hospital discharge. Plasma would be distributed to hospitals by subsequent testing and freezing and paired samples would be retained for concurrent investigations.

Second, Convalescent plasma could transfuse into infected patients within days of collection by clinicians because before they develop a humoral response to COVID-19 this approach would be expected to be most effective in patients ; and it would be beneficial to do serology tests that detect COVID-19 neutralizing antibodies to identify the best treatment candidates. Patient responses could be monitored by the comparison of clinical, laboratory, and imaging results against antibody titres on the other hand identification of patients to measure neutralizing activities in paired plasma samples to develop better algorithms.

Third, plasma collection capabilities expanded by funding agencies as well as mobilization of these efforts by the research initiatives of academic institution , industry, and government. Due to which transfusions are typically performed in hospital settings and may require large infusion volumes , the deployment of convalescent plasma will have limited reach despite having potentially rapid availability. In addition, Patients with cardiorespiratory disorders during plasma transfusions are also associated with adverse events ranging from mild fever and allergic reactions to life-threatening bronchospasm, transfusion-related acute lung injury, and circulatory overload which must be carefully tracked.[30] There is also a small, but nonzero, risk of infectious disease transmission.

Fourth, the distribution of convalescent plasma between blood centres and donor ,the source plasma industry could be informed by dynamic modelling of COVID-19 infection and factors that are associated with clinical efficacy so the former can manufacture concentrated COVID-19 H-Ig.

Fifth, due to which concentrated H-Ig preparations are injectable, time-tested treatment for viral (eg. Hepatitis A and B) and bacterial (eg, tetanus, diphtheria) diseases by using small volume H-Ig preparations could be possible for clinicians in ambulatory settings and drive-through clinics, as well as in hospitals within several months. Antibody preparation is logistically simpler than plasma to distribute world wide because it accurately determined specificities affinities and titres against COVID-19. It will be critical for convalescent plasma to identify factors that predict responses to COVID-19 H-Ig, and also to track adverse events while H-Ig (like plasma) can be stored for years,[34]

Due to the accumulation of viral mutation next season as especially passive antibody efficacy to be less intense so that a similar pathway may need to be reactivated. The investigations performed in parallel to clinical use will drive improvements, during each repetition for example the relative amounts of convalescent plasma vs H-Ig is being guided that are prepared, or these treatment to be benefited by identifying patients. The efficacy of passive antibody therapy for COVID-19 infection are begin to investigated by both academic and industry groups. substantial, robust evidence from rigorously conducted clinical trials clearly establishes effectiveness, and if tests could identify patients who could benefit from passive immunity, a national campaign could taken under consideration to provide such treatment by the India and other countries.

Although a logistical challenge, Develop vaccines and antiviral drugs so it will be important to accelerate just as executive direction was critical for rapid implementation of COVID-19 tests and could also synergize to protect high risk population with parallel efforts.

Specifically, Need to Prioritize Collections from COVID-19- convalescent donor which is being guided to direct the blood centres and plasma fractionators ;the products for therapeutic use should be speedy available ; Identify factors that predict therapeutic effectiveness by collecting, analysing the data and regulations of infrastructure ;the relative levels of convalescent plasma vs H-Ig production should be informed; and regulatory barriers like limit use of pathogen reduction technology for Convalescent sera or that most of the time require many months inventory hold on H-Ig pharmaceutical should be removed.



Concluding Remarks

As the proportion of patients infected with COVID-19 continues to rise, Convalescent plasma is used in patients with serious or immediately life-threatening COVID-19 infections. Use of convalescent plasma has been studied in outbreaks of other respiratory infections. It is possible that convalescent plasma that contains antibodies to SARS-CoV-2 (the virus that causes COVID-19) might be effective against the infection. The thought of using convalescent plasma makes total sense, because it's immediately available, and hence we can try to give Infected Individual convalescent plasma as a potential alternative to a yet-to-be-developed vaccine.

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