Convalescent Plasma Therapy: An Aspiring Option for COVID-19 Treatment?

Akhil Ranjon Biswas1*, Md. Mahbubur Rahman2

1Department of Haematology and BMT, Dhaka Medical College, Dhaka, Bangladesh.
2Department of Haematology, National Institute of Cancer Research & Hospital, Mohakhali, Dhaka, Bangladesh.

ABSTRACT

COVID-19 is a cause of life threatening severe acute respiratory syndrome (SARS) caused by a novel corona virus named as SARS-Cov-2. Since it has 1st been identified in the city of Wuhan in China in December, 2019, it has spread rapidly all over the world. As it is a newly emerged viral infection and any vaccine or specific therapy yet to be proven as clearly effective, multiple therapeutic option with supportive intent as well as search for specific therapy to combat the virus are under vigorous trial around the world. Convalescent plasma therapy is one such investigational therapeutic option for COVID-19 with hope that neutralizing antibodies present in plasma of persons recovered from COVID-19 would be able to neutralize the virus in infected person.

Key wards: COVID 19, Convalescent Plasma Therapy.

Introduction

Controlling a newly emerging infectious disease is historically, probably, the biggest challenge faced by healthcare system and medical science. The challenge is still high even with the tremendous advancement of modern medical science. COVID-19 (Corona virus disease-19) is such a newly emerged respiratory infection resulting in severe acute respiratory syndrome (SARS) in a significant number of cases, caused by a previously unknown novel coronavirus named as SARS-Cov-2. Due to lack of any well-established prophylactic or therapeutic option for an emerging infection, a number of proactive and reactive measures which include preventive, curative and supportive measures, are warranted.1 Endeavor to develop specific vaccine is virtually one of the earliest initiative which usually needs long time and, most importantly, may not be successful always. So, for such emergent infection a number of supportive treatment to protect organ or tissue function and specific treatment without evident clinical efficacy but based on evidence from similar previous infections and in vitro data are tried which need regular updating of recommendation from ongoing experience.1,2 Those expectant specific therapeutic agents for COVID-19 includes antiviral agents like lopinavir/ritonavir, remdesivir etc; other agents with in vitro anti SARS-Cov-2 activity like chloroquine/
hydroxychloroquine alone or in combination with azithromycin and host modifier/immunotherapy with expected antiviral activity like convalescent plasma or specific immunoglobulin and interferons.2 Some other immunomodulatory agents are thought to have no direct antiviral activity but postulated to ease life threatening cytokine storm in COVID-19.2,3 Recommendation for most of these agent are off-label and preferably under clinical trial.2 Convalescent plasma therapy is generally considered as option of last resort.4

Background

Convalescent plasma is the plasma collected from persons who have been previously infected/exposed to an infection and recovered subsequently. It generally contains antibodies, both neutralizing and non-neutralizing, against antigens expressed in infective agents. Though non neutralizing antibodies against a virus does not suppress or neutralize virus rather may enhance infectivity, neutralizing antibodies are directed against viral infection and replication.5 This fact is principle for the expectant use of convalescent plasma in a number of emergent viral infection over a century. 1st available experience of therapeutic use of convalescent blood products comes from devastating Spanish Influenza pandemic in 1918-19, caused by H1N1 virus, infected about 30% of world population and killed about 50 million people. Whole blood, serum as well as plasma from convalescent patients were used in different settings.6 Since then convalescent blood products/plasmas has been tried in a number of emergent epidemic or pandemic of viral infections like Lass fever, Ebola, SARS-Cov-1, MERS, H5N1 etc. Due to practical challenges related to convalescent plasma therapy like, availability of right plasma donor, timely availability, universal safety concern regarding blood product and uncertainty about presence of sufficient neutralizing antibodies, the size and quality of data about this therapeutic approach remain low. However, variable degree of efficacy has been observed in almost all reported literatures.7-11 Results of some small early studies about the usefulness of convalescent plasma in COVID-19 showing promising result in China has already been reported.4,12,13 Both FDA and EU have also been issued approval and guidelines to use convalescent plasma under clinical trial.14,15

Earlier Experiences

A meta-analysis of data extracted from experiences of Spanish flue pandemic showed that overall crude case fatality rate was 16% (54 of 336) among treated patients and 37% (452 of 1219) among controls who were not treated with convalescent blood or blood product. Different sets of data in that meta-analysis also showed overall crude case fatality rate was 19% (28 of 148) for the patients treated earlier (within 4 days) of pneumonia complications and 59% (49 of 83) for patients treated at 4 days or later.6 4,433 patients with Argentine haemorrhagic fever was treated at Junin, Argentina over the period of 1959 to 1983; the overall mortality rate was 3.29%. In 1958, before convalescent plasma was used, the mortality rate in 448 patients treated with conventional treatment was 42.85%. That was probably the largest but, at the same time, probably most poorly controlled study experience of therapeutic use of convalescent plasma.16 Overall case fatality rate of Ebola haemorrhagic fever (EHF) outbreak between January and June 1995, in Kikwit, a city in Democratic Republic of Congo was 80% (249 out of 311), comparable to fatality of other EHF outbreaks. In the same year between June 6 and 22, 8 patients of EHF received convalescent blood transfusion, along with best available supportive care including fluid replacement. 7 out of them were survived. Important to note that before that intervention EHF patients in Kikwit hardly received any supportive or specific treatment rather all effort was given to prevent the spread of infection especially within healthcare providers. Even fluid replacement was rarely given.8

During SARS outbreak in 2003, 80 patients in Prince of Wales Hospital in Hong Kong was treated with convalescent plasma upon clinical deterioration, postulating that convalescent plasma of SARS patients contain antibody against corona virus which may suppress virus. Overall mortality was 12.5% among the 80 patients given convalescent plasma. Overall mortality in Hong Kong from that epidemic was 17% (299/1755) over the period of 6 march to 24 may. Though fatality was numerically lower in convalescent plasma treated group, statistical significance of that value could not be evaluated. One more factor to note is that convalescent plasma treated patients received their care in Prince of Wales Hospital which most likely provided better care than that provided to overall patients in Hong Kong that time.9 One of a very few reasonably well controlled study result of convalescent plasma therapy came from H1N1 influenza A outbreak in Hong Kong in 2009. Neutralizing antibody titre was tested and plasma
collections with value >1:160 were used. That report revealed significant reduction in mortality (odd ratio 0.20, p= 0.011) in convalescent plasma treated cohort, which was 20% (4 of 20) compared to that of control group, which was 54.8% (20 of 73) in severely ill patients.17

40.9% (9 out of 22) virologically or serologically confirmed or clinically suspected Lassa fever cases in Nigeria, treated with convalescent plasma, were died, in contrast to 26.6% (4 out of 15) fatality in control group. However, fatality was 9.1% (1 out of 11) in early treatment (before D10) in comparison to 72.7% (8 out of 11) in late treatment group.18

Though most of the experiences of use of convalescent blood products in emerging outbreak of viral infections reported improved outcome, most of those evidences suffered lack of standard quality due mostly to small sample size, lack of randomization and safety concern. Efficacy of convalescent blood products were not compared with that of blood products from normal donor, which might have impact, especially in those viral infections which were haemorrhagic in nature.

**Current Scenario & Future Perspective**

Current pandemic of COVID-19 caused by a novel coronavirus identified as SARS-Cov-2 has affected more than 12.5 million people in 188 countries or regions around the globe till date and the number is still rising rapidly adding more than 0.2 million new cases daily. Till date 7.52% of total outcome (death + recovery) resulted in death globally.19 Since it’s 1st emergence in the city of Wuhan in China it has rapidly spread all over the world. Till date no treatment option has been clearly proven to be specifically effective to combat this virus and supportive measures still remain the mainstay of treatment. Any antiviral agent yet to be proven as effective in vivo and corticosteroid, an important component of acute respiratory distress syndrome (ARDS) treatment, results in delayed clearance of virus.2 However, a recent multicentre randomized trial in UK revealed distinct supportive role of corticosteroid, dexamethasone, in reducing ARDS related death in severe and critical COVID-19 patients requiring supplemental oxygen.20 Another important revelation about COVID-19 is it’s unique propensity to a set of haemostatic abnormality mainly expressed as thrombosis and significant survival benefit with use of anticoagulation therapy in patients who have d-dimer level more than 3 times upper limit of normal.21 All these developments about COVID-19 are about supportive care and clearly effective therapy against its causative agent, SARS-Cov-2, is still far cry where convalescent plasma is an aspiring option. A few early reports of small-scale trial from China showed encouraging outcome of convalescent plasma/serum treatment in severe COVID-19 disease.12, 13 In one series, 10 severe COVID-19 patients received convalescent plasma treatment. Simultaneously all of them received different antiviral agent and antifungal and/or antibiotic as needed. Methylprednisolone was given to 6 patients. Till reporting date two patients were wane from mechanical ventilation to high flow nasal cannula, one patient from high flow nasal cannula to intermittent oxygen and one patient completely waned of from high flow nasal cannula. Antibody titre of convalescent plasma from 40 donors was tested which was at least 1:160 in 39 cases and 1:32 in one case.13 Another group reported 4 out of 5 severe COVID-19 cases has been waned from mechanical ventilation or extracorporeal membrane oxygenation (ECMO) by 9 days after plasma transfusion.12 Though the results of both these studies were encouraging but limitations were very small sample size, lacking randomization and having no control. According to recently published data from a randomized multicentre control trial in China, where severe and life threatening COVID-19 patients were enrolled, revealed no statistically significant clinical improvement benefit with convalescent plasma recipient (51.9%) compared with control group (43.1%) [HR, 1.40; p= .26]. Among the life-threatening disease clinical benefit was observed in 20.7% vs 24.1% in control group [HR, 0.88; p= .83], which was not statistically significant. However, in severe disease it was 91.3% vs 68.2% [HR, 2.15; p=.03], which was statistically significant. Clinical improvement was defined as 2 points improvement in disease severity scale where score 1 was for discharge and score 6 for death. Almost similar pattern of results was observed in mortality outcome.22 Considering the paucity of effective specific therapy and vaccine along with previous and current potentially encouraging experience about using convalescent blood products, both US FDA and Directorate-General of Health and Food Safety of European Commission (EC) have issued recommendations and guidelines for collection and use of convalescent plasma for laboratory confirmed severe or life threatening COVID-19 as investigational product. Both the guidelines recommend the donors.
should be male or nulliparous women to minimize the chance of life-threatening transfusion related lung injury (TRALI). Plasmapheresis is the preferred method of plasma collection, however, plasma would be separated after collecting whole blood, provided plasmapheresis facility is not available.\textsuperscript{14,15} Neutralizing antibody titration is also recommended and as per EC it should be 1:320 or more.\textsuperscript{15} However, according to FDA it should be at least 1:160 and 1:80 would also be acceptable if alternative unit is not available.\textsuperscript{14} In India, a clinical trial proposal for convalescent plasma therapy in COVID-19 patients submitted by Indian Council of Medical Research (ICMR) recently has been approved by Drug Controller General of India (DGCI).\textsuperscript{23}

**Conclusion and Recommendation for Bangladesh**

Encouraging results of convalescent blood product therapy in previous viral outbreaks and current COVID-19 pandemic are mostly not coming from high quality evidence and most recent randomized trial have shown a thin benefit of use of convalescent plasma only in a subgroup of patients (in severe disease but not in life threatening disease). There are a number of documented and theoretical benefit and risk of using convalescent plasma.\textsuperscript{24} Considering the devastation of the pandemic and paucity of clearly effective specific antiviral therapy, investigational use of convalescent plasma therapy mostly under clinical trial are being approved by regulatory authorities around the globe. Bangladesh is also affected by this pandemic since it’s 1st case detected on March 8, 2020 and till date total number of identified cases are 183,795 with 2.45% fatality in relation to total outcome 95,966 (death + recovery).\textsuperscript{25} Convalescent plasma therapy can be investigational option in Bangladesh as well and methodology appropriate for existing and probable capacity of transfusion services should be adopted. Additionally, comparison with normal random plasma could be a consideration to investigate probable nonspecific immunomodulatory and/or haemostatic effect of plasma components. Risks of transfusion associated hazards and probable adverse event related to non-neutralizing antibodies to be waited against potential benefit as well.

**References**


