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Management of COVID-19 Virus Infection by Convalescent Plasma

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TO THE EDITOR

SARS-CoV-2, the virus that causes COVID-19 created a global challenge, particularly due to its rapid increase of critically ill patients with Acute Respiratory Distress Syndrome (ARDS). The mortality is high and a considerable percentage of the patients require ICU admission and develop ARDS. There is no vaccine or specific antiviral drug therapy yet to treat critically ill patients. Therefore, the management of patients mainly depends on supportive care in ICU.

Passive immunization which has been successfully used to treat infectious diseases could be considered as an effective strategy to treat COVID-19 patients. Convalescent plasma has been used for the severe acute respiratory syndrome (SARS), pandemic 2009 influenza A (H1N1),[1] avian influenza A (H5N1),[2] Ebola[3] to improve the survival rate of patients.

Studies demonstrated a significant reduction in mortality and viral load and shorter hospital stay in studies using convalescent plasma for the treatment of severe ARDS infections without any serious adverse events.

In one study in 2005, patients who received convalescent plasma had a lower mortality rate compared with the overall SARS-related mortality for admitted patients.[4] In 2009 influenza A H1N1 pandemic, a cohort study showed a significant reduction in viral load and reduced mortality for patients treated with convalescent plasma[3]. A meta-analysis involving 1703 patients with 1918 influenza pneumonia from 1918 to 1925 who influenza-convalescent blood products, showed a reduction of the overall mortality rate[5].

A key advantage of convalescent plasma is that this treatment is available immediately. It is also very cost-effective for resource-limited medical centers. If it is infused at the proper time, it may reduce the possibility of hospitalization in ICU. Therefore, convalescent plasma from patients who have recovered from COVID-19 infections could be used as a treatment without the occurrence of severe adverse events.

COVID-19 Convalescent Plasma Therapy

Deploying passive antibody therapies against the rapidly increasing number of COVID-19 cases provides an opportunity for the treatment of patients.[6] Although antibodies from convalescent plasma might suppress viremia, antibody might not only speed viral clearance and blocking new infection, but also accelerate infected cell clearance. Based on current data, viremia peaks in the first week of infection in most viral illnesses. The patient usually develops a primary immune response by days 10–14. Therefore, probably, the administration of convalescent plasma at the early stage of disease would create more benefits for the patients.

The convalescent plasma modality has been used by Chinese doctors in COVID-19 infected patients. A pilot

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study explored the feasibility of convalescent plasma therapy in 10 severe COVID-19 patients, aged 34-78 years. Within 3 days of convalescent plasma transfusion, clinical symptoms, such as fever, cough, shortness of breath, and chest pain, significantly improved, and patients exhibited increased lymphocyte counts, improved liver and lung function, and reduced inflammation without any serious adverse reactions.[7]

In a case series study 5 critically ill COVID-19 patients were treated with convalescent plasma. As assessed by CT Scan, viral load declined within days of treatment and the clinical conditions. Four patients no longer required respiratory support by 9 days after plasma transfusion.[8]

In another case series study, 10 severe patients were received one dose of 200 mL of convalescent plasma with the neutralizing antibody titers above 1:640. After convalescent plasma therapy, the clinical symptoms were significantly improved along with the increase of oxyhemoglobin saturation within 3 days.[9] A case series of two cases of COVID-19 treated with convalescent plasma infusion in Korea showed a favorable outcome after the use of convalescent plasma.[10]

Despite the low number of reported cases with COVID-19 convalescent plasma therapy on April 13, 2020, FDA has issued guidance to provide recommendations to health care providers and investigators on the administration of convalescent plasma for management of the patients with COVID-19 disease.[11]

EU also issued its program for the collection and use of convalescent plasma in the COVID-19 pandemic. It is stated that "the COVID-19 pandemic is a clear situation where plasma from recovered patients might be a valuable resource to support the disease treatment. Transfusion of convalescent plasma, as an immediately available experimental therapy with low risk, should be considered as an urgent priority and its outcome monitored".[12]

Compared with developing new drugs and vaccines for COVID-19 which may take months or years, convalescent plasma is readily available and could be used immediately in almost any health care facility. Blood and plasma collecting centers could start collecting plasma from convalescent donors. Within days of collection, clinicians could transfuse convalescent plasma to infected patients before they develop a humoral response to COVID-19.

Iran Experience

Iran is one of the countries with high numbers of infected cases of COVID-19 virus. The official statistics issued by Iran's health ministry about the coronavirus epidemic, reports 80,868 infected people and 5,031 deaths across the country as of April 19. Among many other medical interventions currently used in Iran medical centers, since March 19 Iranian researchers initiated a clinical trial to use convalescent plasma obtained from patients with previous confirmed COVID-19 virus infection, for management of current patients hospitalized in medical centers.

The clinical trial which was approved by Iran Ministry Health and the ethical committee started in three major hospitals receiving COVID-19 infected patients including Baqiyatallah and Masih Daneshvari hospitals in Tehran and Beheshti Hospital in Qom.

Convalescent plasma obtained from volunteers who have carefully been screened to meet strict criteria for plasma donation based on guidelines of Iran national Blood Transfusion Organization. The donors include people who tested positive for the virus by RT-PCR when they were ill, recovered, and discharged from the hospital and now tested negative for the virus.

The plasma would be tested for possible Transfusions Transmitted Disease such as hepatitis or HIV and also the COVID-19 virus. Convalescent plasma would be frozen and If it passes the quality tests, it will be distributed to the hospitals for use. The obtained convalescent plasma also tests for the presence of antibodies (IgG) against COVID-19 using rapid tests before giving them to the patients. Each patient infused one unit of 500 mL convalescent plasma. So far, in this clinical trial convalescent plasma has been used for management of 150 patients with COVID-19 infections including severely ill and mechanically ventilated, with promising results and substantial improvement in their respiratory tract functions.

Fortunately, so far the trail receiving a good number of volunteers to donate plasma. Fixed and mobile plasma pheresis units prepared through the collaboration of Iran National Blood Transfusion Organization and a private company specialized in plasmapheresis. Investigators hope to reach about 200 patients receiving convalescent plasma in the coming weeks and would be able to finalize the results of the clinical trial based on reduction in all causes mortality and hospital stay of COVID-19 infected patients.

Limitations of Convalescent Plasma Therapy

Convalescent plasma has the advantage that while its antibodies limit viral replication, other plasma components can also exert beneficial effects such as replenishing coagulation factors. However, despite the potential utility of passive antibody treatments, the absence of large clinical trials contributed to the lack of large scale employment of this treatment. In most cases, the administration of convalescent plasma was not evaluated in a randomized clinical trial, and the outcomes in the treatment group were not compared with a control group. Therefore, it is not possible to determine the true clinical effect of this intervention. The fact that patients received numerous other therapies including antiviral agents making it difficult to allocate the specific contribution of convalescent plasma to the outcome of the patient.

Nowadays, academic and industry groups are beginning to investigate the efficacy of convalescent plasma therapy for COVID-19 infection to find robust evidence from well-designed clinical trials to establishes its effectiveness. Although in most of the cases convalescent plasma administered within 14 days of onset of symptoms, it is unclear whether this timing is optimal or if earlier administration might have been associated with different clinical outcomes. Although most of the reports have been administrated 200-500 ml of convalescent plasma, the optimal volume of plasma should also be determined.

Another obstacle in plasma therapy is providing convalescent plasma in large numbers to enable medical centers to use them routinely. Therefore, even if shown to work, scalability to treat large numbers of patients may become an issue. To tackle the logistical challenge of providing convalescent plasma, guidance would be needed to encourage and regulate blood and plasma centers to collect COVID-19 convalescent plasma. Therefore, the construction of a stockpile of frozen convalescent plasma would be a precious asset in the fight against COVID-19. Funding to expand plasma collection capabilities at the national level could potentiate these efforts.

In addition, plasma transfusions could also cause adverse events ranging from mild fever and allergic reactions to life-threatening bronchospasm and volume overload especially in patients with cardiorespiratory disorders. There is also a negligible risk of infectious disease transmission.

Despite the limitations, the published data so far provide some pieces of evidence to support the efficacy of this fairly old therapy in the management of COVID-19 infections especially in patients with moderate to severe symptoms.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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Nothing to declare.

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