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Review

COVID 19 convalescent plasma: Is there still a place for CCP?

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ABSTRACT

Background: Convalescent plasma has been used for a long time for the treatment of various infectious diseases. The principle is to collect antibody-containing plasma from recovered patients and to transfuse the plasma to infectious patients thereby modifying their immune system. This approach was also used in the SARS-CoV-2 pandemic when no specific drugs were available for the treatment of the disease.
Design and methods: This short narrative review reports on relevant studies of collection and transfusion of Covid-19 convalescent plasma (CCP) from 2020 until August 2022. Clinical patients' outcome parameters such as need for ventilation, length of hospital stay and mortality were analysed.
Results: Heterogenous patient groups were studied resulting in difficult comparability of the studies. High titer of transfused neutralizing antibodies, early onset of CCP treatment and moderate disease activity were identified as key parameters for effective treatment. Special subgroups of patients were identified to benefit from CCP treatment. No relevant side effects were observed during and after collection and transfusion of CCP.
Conclusions: Transfusion of CCP plasma is an option for the treatment of special subgroups of patients suffering from SARS-CoV-2 infection. CCP can be easily used in low-to-middle income countries where no specific drugs are available for treatment of the disease. Further clinical trials are necessary to define the role of CCP in the treatment of SARS-CoV-2 disease.

1. Introduction

The history of convalescent plasma (CP) backdates to the end of the 19th century when Emil von Behring immunized horses to produce antibodies against diphtheria. Horse serum containing diphtheria antitoxin was successfully given to infected children thereby saving thousands of lives. During the Spanish influenza pandemic 1918 – 1920 CP was collected from patients recovered from influenza and the antibody containing plasma was infused to infected patients. Further on in the 20th century CP was used for the treatment of scarlet fever, pertussis and Argentine haemorrhagic fever. Nowadays CP was used to treat Ebola virus infection during the outbreaks of the disease.

At the end of 2019 the SARS-CoV-2 virus spread globally around the world and more than 200 million people were infected, of whom around 4 million died. At the beginning of the disease no effective drugs for treatment were available and CCP collection was initiated to treat the disease.

2. Collection and transfusion of CCP

The principle of CP is to collect plasma from recovered patients. In CCP plasma is collected from patients with a laboratory confirmed infection with SARS-CoV2 after at least 14 days of clinical recovery and a negative test result with NAT [1]. An adequate serum antibody titer of specific neutralizing antibodies $>$ 160 is of utmost importance for clinical efficacy of CCP. The CAPSID study showed a great variation of neutralizing antibodies and no correlation was found with gender, age, body weight and AB0 blood type [2]. A predefined subgroup analysis showed that patients receiving a larger amount of neutralizing antibodies had a shorter time to clinical improvement and better overall survival [3]. The optimal time point of administration of CCP was within 7 days of onset of SARS-CoV-2 symptoms and a volume of 400 – 600 mL of CCP should be transfused once per day on up to 3 consecutive days. Libister et al. found that early administration of high-titer CCP to mildly ill-infected patients reduced the progression of SARS-CoV-2 to severe illness [4].

There are contradictory results with CCP therapy due to different study designs, patient subgroups, transfused volumes, antibody titers, timing and end points which made it difficult to draw conclusions. One of the very first studies from China analysed the effect of CCP on time to clinical improvement in patients with severe and life-threatening COVID-19, the SARS-CoV-2 disease [5]. In this open-labelled

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multicenter study no statistically significant improvement was observed in patients receiving CCP compared to the standard treatment group. Results of 3 meta-analyses showed uncertain estimates on the efficacy of CCP [6], an effective therapeutic option in concomitant treatment with antiviral / antimicrobial drugs, steroids and other supportive care [7] and evidence favouring the efficacy as a therapeutic agent in hospitalized patients [8]. Thus, there was a lack of consensus in these meta-analyses due to different patient subgroups analysed.

An individualized approach can be used for the successful administration of CCP: patient's antibody level following transfusion can be predicted by the formula:

Total antibody dose / Patient's plasma volume.

The antibody dose can be calculated by multiplying donor's antibody level by the unit volume. Leon et al. found a high correlation between the predicted SARS-CoV-2 antibody level and the actual SARS-CoV-2 antibody level after transfusion [9].

The FDA published updated issues about CCP over the time of the pandemic: in August 2020 an Emergency Use Authorization (EUA) for CCP for the treatment of hospitalized patients with SARS-CoV-2 was released. Six months later the EUA was revised to limit the authorization to the use of high-titer CCP for the treatment of hospitalized patients with SARS-CoV-2 in the early phase of the disease or with impaired humoral immunity. In December 2021 the EUA was revised to the use of patients with immunosuppressive disease or under immunosuppressive therapy. When the Omicron variant appeared, the FDA recommended against the use of CCP that was collected prior to the emergence of Omicron variant.

Most studies reported no adverse events of CCP. Principally the well-known side effects of plasma transfusion such as TRALI, TACO, allergic / anaphylactic reactions, transmission of pathogens etc. may occur. To avoid transfusion-associated infections CCP should preferably be pathogen-reduced prior to transfusion.

3. Conclusion

To sum up, CCP was not intended as ultimate therapy for SARS-CoV-2 but to fill a gap until effective therapies and preventive measures were available. Today, modern drug treatment and supportive care are more effective than CCP. In the past CCP has been shown to be effective in the early phase of SARS-CoV-2 infection in certain patient subgroups. A high titer of neutralizing antibodies was a prerequisite for successful treatment.

CCP may serve as a model for implementation of future CP programs. Key elements of CP programs are identification of optimal patient population based on clinical grading systems, establishment of a donor registry, consensus on dosage (volume, timing, schedule) based on virus knowledge and rapid and timely implementation of randomized controlled studies with consensus on a list of key and homogenous clinical outcomes.

Statement of ethics

This narrative review did not require any Ethics Committee approval.

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Conflicts of interest

The author is employee of Octapharma Plasma GmbH.

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