Convalescent plasma therapy for managing infectious diseases: a narrative review

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Abstract: The coronavirus disease 2019 (COVID-19) pandemic in 2020 is one of the worst catastrophic events in human history. A number of therapeutic modalities have been utilized in order to fight the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), although the majority of them failed to demonstrate a beneficial clinical effect. Among the anti-COVID-19 agents being investigated, the convalescent plasma collected from recovered donors has gained a growing interest. Convalescent plasma has been employed for over a hundred years to treat severe acute viral infections when a vaccine or a specific antiviral treatment was not yet available. In this narrative review, we summarize the literature data on the use of convalescent plasma during previous viral outbreaks and pandemics, including influenza viruses, coronaviruses other than SARS-CoV-2 and Ebola virus. A literature search, using the Medline and PubMed electronic database, was performed to retrieve publications on the use of convalescent plasma in previous viral epidemics. In conclusion, the available literature data suggest the safety profile of convalescent plasma and its potential benefit in treating emerging viral infectious diseases. In addition, these data retrieved from previous viral epidemics provide a solid rationale for the employment of plasma from convalescent donors also in COVID-19 patients.

Keywords: Convalescent plasma; infectious diseases; coronavirus; influenza; Ebola

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Introduction

Coronavirus (CoV), an enveloped single-stranded RNA virus belonging to the family of Coronaviridae, which initially caused enzootic infections, has shown in the past to be capable of crossing the species barrier and infecting humans causing epidemics with different levels of severity (1). Two outbreaks of CoVs in humans have occurred in the last two decades, causing severe acute respiratory syndrome (SARS-CoV) in 2003 and Middle East Respiratory Syndrome (MERS-CoV) in 2012 (2–4). In December 2019, the third outbreak of a rapidly transmitted CoV, named SARS-CoV-2 and causing coronavirus disease 2019 (COVID-19), occurred and on March 11 2020, the World Health Organization (WHO) declared the CoV outbreak as a pandemic (5,6).

This new virus posed a major challenge among physicians because it had no specific pre-existing therapy. As a consequence, the therapeutic efforts were initially focused on optimizing respiratory care, managing thrombotic and inflammatory complications by using anticoagulation and corticosteroids, and repurposing existing antiviral therapies (7). Unfortunately, almost all these initially promising agents (i.e., hydroxychloroquine, lopinavir/ritonavir and remdesivir) failed to demonstrate a beneficial effect (8–10). Considering the lack of effective anti-SARS-CoV-2 drugs and the initial positive experience from China (11), convalescent plasma (CP, i.e., plasma collected from completely recovered patients), an old therapy used with apparent success in many epidemics and outbreaks since the Spanish 1918 flu (12–18), was proposed again also for COVID-19 (19). Although various immune and non-immune mechanisms have been hypothesized to explain the effect of passive immunotherapy...
by means of CP transfusion, the most important is likely due to the presence of neutralizing antibodies that, thanks to their capacity of inhibiting viral entry into target cells, prevent the deleterious consequences of viral replication.

In this narrative review, we summarize the main literature data on the use of CP as treatment for past viral epidemics other than COVID-19, focusing on severe acute respiratory epidemics and the most recent Ebola outbreak. We present the following article in accordance with the narrative review checklist (available at http://dx.doi.org/10.21037/aob-2020-cp-03).

**Search methods**

As a search literature strategy, the Medline and PubMed electronic database was searched for publications on CP in previous viral epidemics without time limits using English language as a restriction. The Medical Subject Heading and key words used were: “convalescent plasma”, “hyperimmune plasma”, “therapy”, “SARS-CoV-2”, “COVID-19”, “safety” and “efficacy”, “acute respiratory infections”, “viral infections”, “Ebola virus”, “SARS”, “MERS”, “Avian influenza”, “H5N1”, “Spanish influenza A”, “H1N1”. We also screened the reference lists of the most relevant review articles for additional studies not captured in our initial literature search.

**The use of CP for severe acute viral respiratory infections**

von Behring and Kišato were the first investigators in 1980 to provide the basis of passive immunization, then known as serum therapy. Given the early success in 1900s, which earned von Behring the Nobel Prize for Medicine in 1901, passive immunization was rapidly expanded and was used to treat several bacterial infections including *Corynebacterium diphtheriae*, *Streptococcus pneumoniae*, *Clostridium tetani*, *Haemophilus influenzae* and *Neisseria meningitidis* (18). In addition, CP was used to fight outbreaks of viral diseases such as poliomyelitis, measles, mumps and acute viral hepatitis A and B (12). Regarding the acute viral respiratory diseases, a meta-analysis by Luke and colleagues reported eight studies involving 1,703 patients with 1918 Spanish influenza pneumonia (H1N1) (14). Although with several methodologic limitations (no study was blinded or randomized and CP was used in many cases without measuring antibody titers), this review showed a pooled absolute reduction of 21% in the mortality rate in patients receiving CP compared to controls (14). During the influenza A (H1N1) pandemic in 2009, the results from a prospective cohort study conducted by Hung and colleagues showed that CP treatment reduced mortality (20.0% in CP-treated group versus 54.8% in control group) (20). Positive evidence was also reported for the 2006 avian influenza A (H5N1) outbreak although mostly based on case reports and case-series (15). Regarding the treatment of previous CoVs, CP was studied in the treatment of SARS during the 2003 outbreak originating in Hong Kong. In a retrospective study, Soo and colleagues compared CP with steroid treatment and observed a significant mortality reduction in CP-treated group which remained also after controlling for co-existing comorbidities (21). Interestingly, Cheng and colleagues retrospectively reviewed 80 patients with SARS infection who had been given CP transfusion and compared those who had been transfused before day 14 following the onset of symptoms to those who received plasma after day 14 (22). The results showed that the group receiving CP earlier had better outcomes (days of hospitalization and death) than the patients who received plasma later. A meta-analysis by Mair-Jenkins and colleagues, including 32 studies of SARS-CoV and severe influenza, reported that CP reduced mortality and it was safe (no relevant adverse events after CP treatment were reported). The reduction of mortality was higher when CP was administered earlier after symptom onset (16). The 2015 MERS-CoV outbreak in South Korea generated a few case reports and case-series that failed to show clinical improvement with the administration of CP (15). Nevertheless, a study conducted by Ko and colleagues found that donor CP containing high titers (>1:80) of MERS-CoV neutralizing antibody resulted in seroconversion of the recipient post-transfusion whereas seroconversion was not observed with transfusion of low-titer CP (23). This study highlights the importance of the quality of CP in terms of neutralization activity, which plays an important role in the effectiveness of CP.

**The use of CP for Ebola virus disease**

In addition to the respiratory viral diseases, the recent 2013–2016 West African Ebola virus disease outbreak provided another opportunity to assess the role of CP. A number of non-randomized trials have been published on this issue (17). A study conducted on 84 patients from Guinea receiving CP confirmed the safety of the blood component but failed to demonstrated a survival benefit in the CP treatment arm (24). Another study conducted in Sierra Leone evaluated CP for Ebola treatment in 44 subjects versus 25 non-treated
patients and showed an improvement in death rate in patients receiving CP compared to the control group (27.9% versus 44%) with a 2.3 odds ratio (OR) for survival in CP-treated arm (25). In 2014, the WHO has recommended the investigation of CP in the treatment of Ebola virus disease and provided specific protocol guidelines (26). A recent systematic review and meta-analysis on CP therapy for treating severe infectious diseases (SARS-CoV, influenza, Ebola, SARS-CoV-2) including 15 controlled studies showed a significantly lower mortality rate in the group treated with CP compared with the control groups (pooled OR 0.32; 95% CI: 0.19–0.52; P<0.001) (27).

Conclusions

Thanks to the presence of antibodies able to inhibit a specific pathogen, plasma collected from convalescent donors has been frequently used during the last century during several infectious epidemics or pandemics to provide an immediate treatment option while evaluating existing drugs and developing new specific vaccines and therapies. The analysis of the literature data on the use of CP for managing infectious diseases supports its beneficial effect with a high safety profile. In particular, its effectiveness appears to be optimal when administered early and with an adequate titer of neutralizing antibodies. These data have represented a solid rationale for the use of CP treatment during the current SARS-CoV-2 pandemic (28).

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