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Convalescent plasma as a therapeutic agent for SARS-CoV, MERS-CoV and SARS-CoV-2: A scoping review

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ABSTRACT

Severe acute respiratory syndrome coronavirus (SARS-CoV), Middle East respiratory syndrome coronavirus (MERS-CoV), and SARS-CoV-2 are three kinds of coronaviruses that are exceptionally pathogenic to humans *via* zoonotic infections. The outbreaks of SARS-CoV and MERS-CoV, and SARS-CoV-2, to some extent, posed a severe threat to human health, daily activities as well as the economic status of many countries. When faced with these emerging viruses and no accessible vaccines and drugs, convalescent plasma (CP) is required as passive immunotherapy, since CP has the potential to neutralize and eliminate the virus from blood circulation. The sources of CP are individuals who have recovered from the viruses. Currently, CP is administered as emergency use and investigational treatment. Some studies have shown that CP is effective to treat infected individuals with viral pandemics such as influenza A, Ebola virus, SARS-CoV, and MERS-CoV. Moreover, following the deadly outbreak of SARS-CoV-2 in 2019, plenty of non-randomized clinical studies have been done on the effectiveness of CP for the treatment of Coronavirus Disease 2019 (COVID-19), and most of these studies have indicated that CP therapy is promising and saved many critically-ill patients. Therefore, CP is a helpful immune therapeutic agent for the immediate response of such pandemics because of its clinical efficacy, immediate availability, cost-effectiveness, ease of production, delivery, and storage. This review aims to summarize the effectiveness of CP in the treatment of these three coronaviruses, *i.e.* SARS-CoV, MERS-CoV, and SARS-CoV-2.

KEYWORDS: Convalescent plasma; Coronaviruses; SARS-CoV; MERS-CoV; SARS-CoV-2; COVID-19

1. Introduction

Coronaviruses are known to cause adverse effects on the respiratory, intestinal, liver, and sensory systems of animals and humans. They are enveloped, positive-stranded RNA viruses[1,2]. Before the severe acute respiratory syndrome coronavirus (SARS-CoV)-2 come to be known, which is also a member of coronaviruses, there were just 6 human coronaviruses (HCOV) distinguished. Among these, HCOV-229E, HCOV-NL63, HCOV-OC43, and HCOV-HKU1 are primarily self-restricted respiratory diseases and usually affect babies, immunosuppressed patients, and old people; whereas, severe acute respiratory syndrome coronavirus (SARS-CoV) and middle east respiratory syndrome coronavirus (MERS-CoV) have a place with the B and C subclasses of β-coronavirus separately, and both can rapidly develop deadly respiratory infections[3]. SARS-CoV, MERS-CoV, and SARS-CoV-2 are zoonotic viruses that are exceptionally pathogenic for humans. The outbreaks of such viruses had been shown to affect health and daily activities of humans as well as the economic status of many countries[4].

The sources of convalescent plasma (CP) could be individuals who recovered from SARS-CoV, MERS-CoV, and SARS-CoV-2. It has the potential to neutralize and eliminate the virus from the blood circulation[5,6]. When new infectious diseases occur, and there is no confirmed treatment, CP is required as passive immunotherapy[6]. The research done by Yeh *et al.*[7] revealed an ideal result in the utilization of CP for the treatment of SARS-CoV infected humans. Further, the safety, clinical effectiveness, and feasibility of CP treatment were also well researched by Chen *et al.*[8] and Arabi *et al.*[9]

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in individuals who are infected with MERS-CoV. CP administration has also been proved efficient in improving the health status of SARS-Cov-2 patients[10,11].

CP treatments for SARS-CoV, MERS-CoV, and Ebola virus (EBOV) have been assessed[7,12-14]. Food and Drug Administration of the United States of America has permitted the utilization of CP treatment to patients who were severely infected with SARS-CoV-2[15]. Besides, because of a shortage of knowledge about the mechanism and the exact therapeutic components of CP, there are no common criteria to select blood donors. Thus, the world health organization (WHO) provided standard criteria on how to use the CP in a pandemic, internationalizing the selection of blood donors and strengthening the quality control of the CP to increase the treatment effectiveness[16]. Hence this review aims to summarize the potential therapeutic value of CP against SARS-CoV, MERS-CoV, and SARS-CoV-2.

2. Epidemiology

SARS-CoV is a coronavirus causing the twenty-first-century pandemic and certainly spreads to more than 30 nations in about months[17]. After ten years, a second coronavirus outbroke, MERS-CoV, beginning in the Middle East, and infected more than 2 000 people around the world, with a higher number of cases is reported in Saudi Arabia. Practically all MERS-CoV contaminated cases announced outside of the Middle East were identified with travel history in the Arabian Peninsula[18]. At the end of 2019, another global panic disease which is a type of pneumonia brought by a novel, exceptionally pathogenic human coronavirus, SARS-CoV-2 swept over the world[19].

The genomes of SARS-CoV and SARS-CoV-2 are comparative and have a 79.6% similarity. The SARS-CoV-2 and bat coronavirus RaTG13 have 96% similarities in their genome sequence. Due to the high homology between SARS-CoV-2 and bats coronaviruses, bats might be the first host of SARS-CoV-2 though it is still not confirmed[20,21]. The intermediate hosts differ among the three coronaviruses (Figure 1). SARS-CoV was confined in civets, cats, raccoons, and ferret badgers in the live animal market, suggesting that these animals may serve as intermediate hosts[22]. MERS-CoV on the other hand was isolated from fluid taken from the nose of a camel and the individuals who were contaminated through close contact with camels, indicating that camels serve as intermediate hosts for the transmission of MERS-CoV[23]. Studies on SARS-CoV-2, however, have indicated that the pangolin is an intermediate host for advancing the transmission of COVID-19 to people[24].

3. Historical background of CP therapy for viral infections

Different researches done during the Spanish flu pandemic from 1918 to 1920 suggested that the utilization of convalescent blood plasma may be an effective therapy[25-30]. In fact, at that time CP was recognized as a promising treatment for various viral diseases[31]. In the next decades, the administration of CP for the treatment of diseases caused by viruses has been declared in confidence with its feasibility and therapeutic capability[32-42]. Moreover, *in vivo*

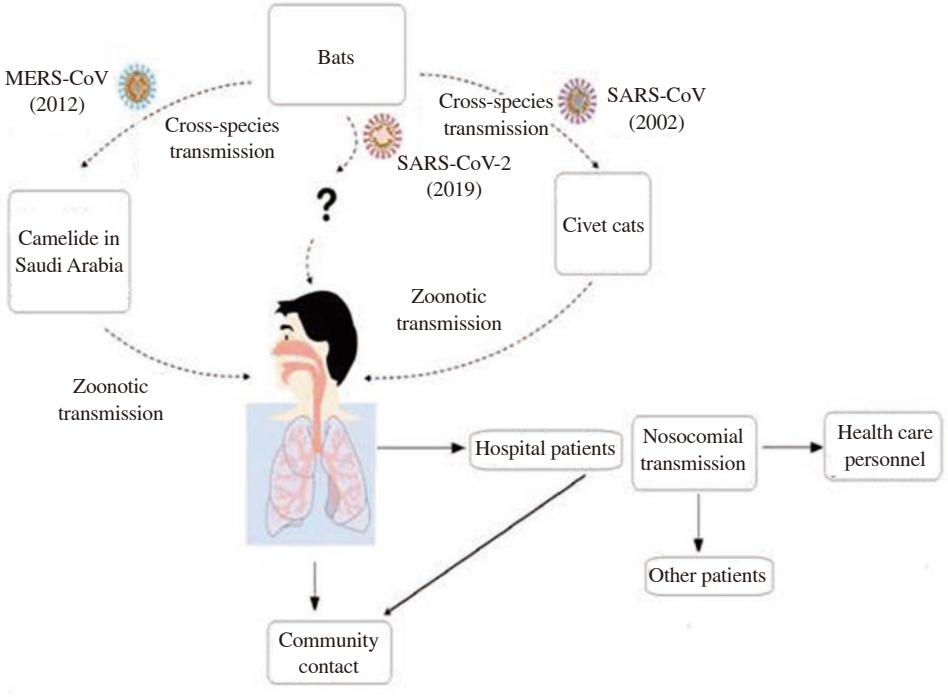

Figure 1. Possible intermediate hosts of the three zoonotic coronaviruses [severe acute respiratory syndrome coronavirus (SARS-CoV), Middle East respiratory syndrome coronavirus (MERS-CoV), and SARS-CoV-2] and their route of transmission to humans.

researches in animal models for flu pneumonia have indicated the advantage of CP: protection against H1 and H3 challenge; equine hyperimmune F(ab')2 globulin (protection against H5N1 challenge) and monoclonal antibodies (against H1, H3, and H5N challenge) [43-45]. Besides, the other interesting result of CP was found after its transfusion to hospitalized patients with Lassa fever, resulting in a better outcome[46]. Another eight studies included 1 703 individuals who were positive for Spanish flu revealed a significantly decreased risk for mortality after being treated by CP, therefore it is proposed that CP could be considered in the treatment of diseases similar to H5N1-infections[47].

In a study done by Mair-Jenkins *et al.*[48] focusing on the effectiveness of CP and hyperimmune Ig for the treatment of severe acute respiratory infection, it was reported that there was a statistically significant reduction (75%) in the risks of mortality among the patients who received CP treatment in contrast to the control groups who received no therapy. The study can show consistent evidence for a reduction in the risk of mortality, particularly with early CP transfusion. However, as many studies were usually low in their quality, even without control groups, and showed a moderate or high risk of bias, the authors strongly suggested that such therapy should be further studied with a well-designed clinical trial or other formal evaluation[48].

As far as the CP treatment for haemorrhagic fevers is concerned, in 1976 in the Democratic Republic of Congo, the treatment showed no advantage in one young lady infected with EBOV. The woman was treated with CP from an individual who had recovered from infection of a closely Marburg-related virus[49]. However, during the EBOV outbreak, 201 units of CP with a titer ⩾1:64 were collected from EBOV patients and frozen for later use and treatment. Two units were administered to EBOV-infected laboratory workers, and the patient's recovery suggested a credible therapeutic effect of CP on EBOV[50]. Besides, CP was also shown as a treatment for Argentine haemorrhagic fever patients infected by the Junin virus[51-54]. In 1979, a double-blind trial has carried out on the treatment of CP for Argentine haemorrhagic fever patients, and a lower mortality rate was recorded with patients treated with CP compared to the normal plasma-treated patients. From an analysis of 23 consecutive annual epidemics of Argentine haemorrhagic fever in a group of 4 433 patients observed from 1959-1983, it was found that CP treatment has a lower mortality rate (3.29%) than conventional treatment (42.85%)[55]. Immunotherapy with CP is also tried in the treatment of Crimean Congo haemorrhagic fever, though its effectiveness for this disease is still not clear[56].

Since the first EBOV outbreak in Congo, infected animals such as monkeys have been shown to acquire passive immunization *via* the administration of IgG preparations from horses hyper-vaccinated with EBOV, thus suggesting this therapy could likely be used in humans[57-60]. In 1995, following the EBOV outbreak in Kikwit, Zaire, out of the 8 patients who have received 150 mL-400 mL of convalescent whole blood, 7 were survived, resulting in a quite high reduction of mortality rate (12.5%) when compared with that of the untreated patients[61]. The authors recognized their study with a high risk of bias as well as its non-representativeness as their sample was small and lack of control subjects.

In 2007, Oswald *et al.* found that passive immunization with CP failed to protect macaques against EBOV infection in their study[62]. Such findings suggest the need for a better understanding of both the characteristics and titer of antibodies as well as the role of the recipient's immune response[61]. In 2012, a study by Dye *et al.*[63] showed that passive transfer of polyclonal IgG was able to provide a total protective potential in non-human primates infected with filo virus. Also, the study revealed that, following multiple administrations, a sufficiently high level of IgG was shown to be maintained until the host's adaptive immune responses could be recruited to clear the viral load. Moreover, studies done by Olinger *et al.*[64] and Qiu *et al.*[65] showed that administration of anti-EBOV glycoprotein monoclonal antibodies on EBOV infected monkeys was able to cure them from this lethal virus.

4. Clinical use of CP

The administration of convalescent blood products (CBP) is a known clinical strategy for the treatment of emerging infectious diseases. In the past, treatment of new emerging infectious diseases was focused on immune therapy by using passive immunization which includes (1) Convalescent whole blood (CWB), CP, and convalescent serum (CS); (2) Pooled human immunoglobulin (Ig) for intravenous or intramuscular administration; (3) High-titer human immunoglobulin(Ig); (4) Polyclonal or monoclonal antibodies. Nowadays, plasma gathered by apheresis is the favored treatment[66] (Figure 2). The utilization of blood products from recuperated patients goes back to the late 1800s[67]. It was during the Spanish flu pandemic (1918-1920) when CBP were found to be effective for patients' immune therapy during the clinical studies[25-31]. CBP reduced mortality rate as it is indicated in 8 studies with a total of 1 703 patients of Spanish influenza[47].

A mass application of CP for prevention and/or treatment of infectious diseases was during the recent West African Ebola outbreak, for the reason that the absence of vaccines for pre-immunizations and effective curing drugs, the exceptionally infectious nature of the virus, as well as high case-mortality rate[68]. Many other newly emerging infectious viruses such as West Nile Virus, MERS-CoV, SARS-CoV, and Influenza A virus (H1N1) have additionally been the target of possible passive immunity with CP. Even though CP has been used for a long time, rare studies concentrated on its clinical efficacy as well as conclusions were weak. The reason could be that the CP was only used in confronted with critical situations and serious pandemic outbreaks which require quick responses as much as possible. The effectiveness of CP treatment seems to vary from the pathogen and treatment procedures (timing, volume, and dosing of administration). Many studies have shown the administration of CP for the treatment of coronaviruses such as MERS-CoV and SARS-CoV[7,8,10,11,69]. In a study by Yeh *et al.*[7], it was reported that seriously-sick patients with SARS

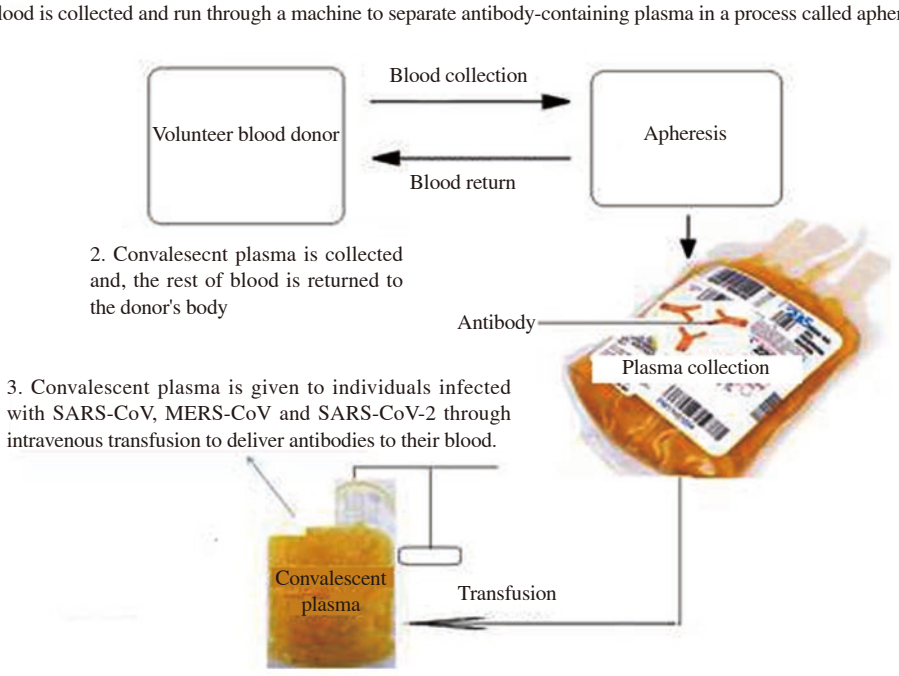

Figure 2. The collection process of convalescent plasma and its transfusion to SARS-CoV, MERS-CoV, and SARS-CoV-2 patients.

recovered after they were treated with CP with a serum antibody titer of >1:640. In this case, it has shown that the CP administration has demonstrated safety.

Moreover, for the current SARS-CoV-2 (COVID-19 pandemic coronaviruses) infection, CP is widely collected and being used as a clinical treatment along with other drugs and treatments for critically-ill patients[70-75].

5. Therapeutic guideline on CP

Authorities including the Blood Regulators Network, Food and Drug Administration (FDA), scientific associations such as the International Society of Blood Transfusion and the European Blood Alliance, have guided the whole handling and consideration of CP as an emergency treatment for SARS-CoV, MERS-CoV, and SARS-CoV-2. In these guidelines, it is specified that CP should be considered as experimental or investigational therapy. In August 2020, FDA issued an Emergency Use Authorization for CP in the treatment of hospitalized patients with COVID-19, provided that the doctors get approval over the telephone. Besides, the FDA has also instructed doctors to study the use of COVID-19 CP by following the usual system for investigational new drug application. The selection criteria for donors and recipients were also detailed in these guidelines[76-78].

6. CP transfusion for the treatment of SARS–CoV

Assessment of the effectiveness of CP for the treatment of SARS-CoV infection was conducted among 80 confirmed cases in Prince of Wales Hospital, Hong Kong, from March to May 2003. The result was considered as great if the patients recovered from the infection and released from the hospital within 22 days, and bad if death happened or hospitalization past 22 days. A higher rate of day-22 release from the hospital was seen among individuals who received CP before two weeks of sickness (58.3% *vs.*15.6%; $P<0.001$) and among the individuals who were PCR positive and seronegative for coronavirus during plasma transfusion (66.7% *vs.* 20%; $P=0.001$) [7,69,79-82].

7. CP transfusion for the treatment of MERS–CoV

The utilization of CP and whole blood treatment has been recommended to be a likely treatment for coronavirus illnesses, such as MERS, Ebola, and SARS. It is used as a treatment when there are no specific and effective drugs or vaccines[66]. Arabi and his group[9] examined the viability of CP treatment, its safety, clinical and laboratory effects in severely sick individuals with the MERS-CoV disease. They proposed that the CP and other defensive antibodies are immunotherapeutic (hyperimmune immunoglobulins and monoclonal antibodies) and possible agents for the treatment of MERS-CoV disease. At that time, the disadvantage of CP was its inaccessibility and absence of reports on the confirmation of the safety and viability[83].

CP has been utilized clinically since 1916 to treat challenging infectious diseases[84,85]. Convalescing serum was utilized at the time of SARS-CoV and EBOV outbreaks[61,12]. For studies conducted during that time, clinical trials were lack for characterizing the

safety and viability of the treatment. WHO considered CP as the most encouraging available treatment for the MERS in the WHO-International Severe Acute Respiratory and Emerging Infection Consortium MERS-CoV Outbreak Readiness Workshop 2013[86]. In any case, because of the absence of clinical trials, the article published by WHO as of March 2014 expressed that the clinical utilization of CP should be viewed as investigational[77].

8. Convalescent plasma as a potential therapy for SARS–CoV–2 infection (COVID–19)

Being an emerging variant of coronaviruses, SARS-CoV-2 takes accountability for the current global pandemic[11]. Human monoclonal antibody is a promising therapeutic product for cross-neutralization to target a communal epitope on SARS-CoV and SARS-CoV-2 viruses. Hence it has a potential for prevention and treatment of COVID-19. However, this possible therapy is not likely available soon[8]. Investigation of the possible mechanism of action of the virus is another concern. As it is hypothesized by Ling *et al.*[87], the organ of the patients which expresses angiotensin-converting enzyme 2 receptors are more venerable to the attack of the virus. Early in the disease, the virus affects the antibody production in patients, which may cause B lymphocyte reduction and IL-6 reduction. In the disease progression, lymphocytes may continue to decline while the inflammatory cytokines increase. Consider that, a therapy that focuses on the improvement of the immunity of patients and inhibition of the increased inflammatory cytokine production is very important. Hence, additional studies on the pathogenesis and immune response are needed for further development of improved CP and other therapies[87].

CP is a promising treatment since it enables immediate use, while specific vaccines and treatments must pass through a serious evaluation and scaling up. CP derived from the donors might be the most promising therapy either using it as prophylaxis or administrating after the onset of the symptoms within 14 days. Its protection potential ability may last from weeks to months[88].

Following the proliferating number of confirmed cases of COVID-19 and mortality throughout the world, the world enhanced the effort to collected CP from recovered patients. CP from recovered individuals at least 28 days after the resolution of their symptoms were collected in England (April 22-May 12, 2021), and CP containing minimum neutralizing antibody titer of 1:100 were provided for clinical use[89,90]. During the CP apheresis collection in these weeks, CP of the 254 (99%) out of 256 (who had been confirmed positive for SARS-CoV-2) cases developed a measurable antibody response and 88% (226/256) contained neutralizing antibodies, and this shows that the huge potential of CP as a therapy of COVID-19. However, antibody levels declined over 3 months after diagnosis suggesting that CP collection should be done as early as possible. Based on the binding antibody measurements, CP donors with high neutralizing antibody levels should be selected for CP collection[91]. Interestingly, the current enormous amount of SARS-CoV-2 infected (⩾31 million) and recovered (⩾24 million recovered) patients could be potential resources of CP[92].

Following the sudden outbreak of SARS-CoV-2 and flooding throughout the world, numerous studies were done on the capacity and efficacy of CP for the treatment of SARS-CoV-2. These studies showed that CP collected from recovered patients was effective to treat both moderately- and critically-ill patients with SARS-CoV-2 if it is administered during the early stage of the diseases[10,11,70-75, 93-96].

Researchers from China tried to treat SARS-CoV-2 infected patients *via* CP[87]. In one pilot study, administration of CP on some seriously-ill patients improved their oxygenation, reduced inflammation, and viral load. In the study, 1 dose of 200 mL CP with neutralizing antibody titers of >1:640 was administered for 9 patients. Transfusion of the CP for these patients was done after the beginning of illness [calculated as 16.5 days (median time)]. The patients have shown improvement in clinical signs and symptoms within 3 days. Their oxyhemoglobin saturation has increased. The lymphocyte counts increased from 0.65×10^9/L to 0.76×10^9/mL while the C-reactive protein decreased from 55.98 mg/L to 18.13 mg/L. The neutralizing antibody in all patients has increased. The viral load of 7 patients who had previous viremia was undetectable[97]. In another study, ABO-compatible CP was transfused for 6 laboratory-confirmed COVID-19 patients. The study showed that CP therapy is effective and specific for COVID-19. The efficacy of the intervention was determined by tests like the alleviation of symptoms, changes in radiologic abnormalities, and laboratory tests. During the treatment, no obvious adverse effect was observed. In 5 of the patients, CP transfusion resolved ground-glass opacities and consolidation. In one case, CP therapy stimulated an elimination of the virus, while in another two patients, the serologic analysis indicated an immediate increase in anti-SARS-CoV-2 antibody titers[95].

In a study of Abolghasemi *et al.*, the clinical efficacy of CP therapy was compared among 189 SARS-COV-2 positive patients (115 patients in CP therapy and 74 as the control group) based on the length of the total hospitalization and the need for intubation. Ninety-eight patients (98.2%) who received CP were discharged early from the hospital (9.54 days) when compared with 56 patients (78.7%) who did not receive CP (12.88 days for discharge). Only 8 (7%) of the patients under CP therapy needed intubation, while 20% from the control group need intubation[96]. The study provides strong evidence to conclude CP therapy is effective in the treatment of SARS-CoV-2 infected patients and can be recommended for future use.

CP therapy has been shown as an effective treatment for the elimination of viruses and shortening of the hospital stay for patients with prolonged positivity of SARS-CoV-2 RNA[98]. Wu *et al.* have conducted a retrospective observational study on the clinical effect of CP among 27 patients with prolonged positivity of SARS-CoV-2 RNA. After the administration of CP therapy, the qRT-PCR test of SARS-CoV-2 RNA was analyzed and become negative in 7 days for 15 patients (the early negative groups) and 12 patients were negative in 7 days (the late negative groups). Improvement in the pulmonary image was shown on 7 patients in the early negative groups and 8

patients in the late negative groups following the CP therapy. The viral load of the early negative group decreased compared with the late negative group. The median length of hospital stay was shorter for patients in the early negative group.

The effectiveness of CP on the treatment of critically-ill COVID-19 patients, as well as COVID-19 patients with co-morbidity, were also the concerns of some studies[73-75,94]. Zeng *et al.*, investigated, the effect of CP therapy on viral shedding and survival was studied in 6 patients with respiratory failure due to SARS-CoV-2 infection[73]. The study indicated that CP therapy can help stop viral shedding and could extend the survival rate in patients who are moderately-ill, while it could not reduce the mortality rate in critically-ill patients with end-stage diseases. To benefit critically-ill patients infected with SARS-CoV-2, the current study suggested that administration of CP should be done early in the course of the diseases. Similar to this study, Altuntas *et al.*[74] had investigated the potential of CP therapy on severe- and critically-ill COVID-19 patients, and the study suggested that CP has the potential for decreasing the course of diseases in these patients. The case fatality rate was 24.7% in the patients who received CP, while 27.7% for the control groups. A higher rate of mechanical ventilation support was needed when CP was administered 20 days after the COVID-19 diagnosis when compared with shorter time intervals (⩽5 days, 6-10 days, 11-15 days, P=0.001).

In one non-randomized pediatric trial, the safety and efficacy of CP treatment in 4 children who developed life-threatening COVID-19 was also studied[94]. The CP therapy was safe and effective. No effects had been observed on the endogenous antibody response of the children. Upon CP transfusion, the IgG, IgM, and IgA antibodies against the receptor-binding domain of 3 of the patients were improved eventually and continued for 7-26 days post-transfusion.

The potential of CP therapy on the treatment of severe COVID-19 infection had also studied in cancer patients[75]. Results of the current study showed that CP is also promising in the treatment of such risky patients while they are under life-threatening conditions. Out of the total 24 patients with cancer, including 14 of whom had hematological malignancy, 15 patients (62.5%) were on cancer-directed treatment at the time of SARS-CoV-2 infection. CP treatment of these patients showed that, after a median of 9 days of hospitalization, 13 patients (54.2%) had been discharged, while 1 patient (4.2%) was still hospitalized and 10 patients died (41.7%).

9. Pros and cons of CP as a treatment for SARS–CoV, MERS–CoV, and SARS–CoV–2

Various studies mentioned that the highlighted advantage of CP therapy is its effectiveness in confronting several infectious pathogens. Particularly, it has been used in the treatment of many viral infections like H1N1, SARS-CoV, MERS-CoV, Ebola, and the current COVID-19 outbreak[9,99-101]. CP therapy is considered as a ”stopgap measure” and as an immediate way to keep patients alive[100,102]. CP therapy has the aforementioned advantages such as high clinical efficacy, immediate availability and potential cost-effectiveness, ease of production, delivery, and storage. However, it must be noted that there may be concealed constraints as a risk and challenges of CP therapy. Cons related with CP therapy includes different reactions against the plasma constituents, unintended infections induced by pathogens present in the transfused plasma, antibody-dependent enhancement of infections, and adverse effects such as fever, anaphylactic reactions, chills, hemoptysis, transfusion-associated circulatory overload, and transfusion-related acute lung injury[11,88,103-105].

Therefore, the risk-benefit assessment should be considered before transfusion of CP. The criteria for effective CP are summarized as follows: (1) It should contain high-titer specific antibodies which bind and neutralize the viral particles; (2) Block the access of the virus to uninfected cells; and (3) Able to activate potential effector mechanisms[106].

10. Conclusions

The worldwide emerging of coronavirus disease has turned the spotlight onto the possible utilization of CP in the treatment of deadly infections that need immediate responses. Though numerous studies have detailed the suitability and safety of CP therapy in the treatment of SARS-CoV, MERS-CoV, and SARS-CoV-2, CP treatment is considered as an investigational treatment, because of the lack of enormous subjects and well-designed randomized clinical trials.

Conflict of interest statement

The authors report no conflict of interest.

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Authors’ contributions

The idea for the study was conceptualized and designed by A.H.M. A.H.M. and E.M.A search the literature. The manuscript was drafted and written by A.H.M. E.M.A did the critical review and edition. Both authors approved the final manuscript.

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