Convalescent Plasma Therapy for COVID-19: Lessons from SARS-CoV, MERS-CoV, and H1N1 Infection

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ABSTRAK

Kematian global yang meluas setelah munculnya infeksi SARS-CoV-2 di China, telah menjadi perhatian kritis di seluruh dunia. Pemberian terapi convalescent plasma (CP) merupakan salah satu cara untuk meningkatkan survival rate kasus infeksi COVID-19. Teknik ini, sebagai terapi praktis, digunakan dalam kasus wabah virus sebelumnya termasuk influenza, SARS dan MERS. Dalam terapi CP, plasma darah dikumpulkan dari seseorang yang telah direhabilitasi dari infeksi spesifik tersebut untuk mengembangkan imunisasi pasif pada pasien lain. Oleh karena itu, ulasan ini bertujuan untuk menunjukkan peran terapi CP dalam infeksi virus yang disebutkan di atas dan menggambarkan berbagai faktor yang mempengaruhi kemanjuran terapi CP.

Kata kunci: *SARS-CoV-2, terapi plasma sembuh, COVID-19, MERS, SARS.*

ABSTRACT

The global widespread mortality after the emergence of SARS-CoV-2 infection in China, has become a critical concern all around the world. Convalescent plasma (CP) therapy is one of the methods elevating the survival rate for COVID-19 infection cases. This technique, as a practicable therapy, was used in previous viral outbreaks including influenza, SARS and MERS. In CP therapy, the blood plasma is collected from persons rehabilitated from that specific infection in order to develop a passive immunity in other patients. Therefore, this review aimed to point out the role of CP therapy in aforementioned viral infections and illustrate different factors influencing the efficacy of CP therapy.

Keywords: *SARS-CoV-2, convalescent plasma therapy, COVID-19, MERS, SARS.*

INTRODUCTION

The influenza virus belongs to the Orthomyxoviridae family[1] and can cause acute respiratory disease. An infection with the influenza virus can increase mortality worldwide and can cause an epidemic or pandemic.[2] In 2009, a modern swine-origin influenza A (H1N1) virus (S-OIV) developed among people in California and Mexico, spread rapidly around the globe through human-to-human transmission, and produced the primary flu widespread of the 21st century.[3]

Coronaviruses belong to the Coronaviridae family and can cause mild to severe respiratory disease in humans. The pathogenicity this family is of high importance in humans since some members of which have endangered human life. Severe acute respiratory syndrome coronavirus (SARS-CoV) infection occurred in 2002-2003 and middle East respiratory syndrome coronavirus (MERS-CoV) infection in 2011, which infected thousands of people.[4,5] Recently, in 2019, a new coronavirus infection was reported in Wuhan, China, called SARS-CoV-2,[6] leading to the novel 2019 coronavirus disease (COVID-19).[7] These zoonotic infections that are profoundly pathogenic. By 3 February 2021, COVID-19 infected over 104 million individuals and caused more than 2 million deaths worldwide[8] and there is currently no suitable antiviral treatment for coronavirus infection.[9,10]

SARS-CoV-2 has created a worldwide epidemic, which poses a significant risk to public health. Experience of treating patients with SARS-CoV, MERS-CoV and influenza A (H1N1) suggests that recovery plasma therapy may be helpful.[11-14] Several treatments have been reviewed, including: antiviral drugs, corticosteroids, and immune-regulating regulators. However, one potential treatment is convalescent plasma (CP) therapy.[14,15] In this study to the best of our knowledge for the first time, we review information available on the use of CP as a therapeutic option for patients with H1N1, SARS-CoV, MERS-CoV and SARS-CoV-2.

METHODS

We conducted a thorough search in online database such as Google scholar, Web of Science, PubMed, and Scopus to find all articles related to CP therapy in SARS, MERS, Influenza, and COVID-19 published from 2003 until 2020. We conducted no language limit and our search strategies for each database was independently designed. Our studies included all observational conducted on CP therapy in adult patients with SARS, MERS and COVID-19. Duplicate and Similar searches were excluded. Through screening the titles/abstracts of the articles we selected the relevant studies. We screened the references of the extracted articles to include all relevant studies.

CURRENT AVAILABLE THERAPIES FOR COVID-19

SARS-CoV-2 responsible for COVID-19 has spread globally and there is no effective therapy for this disease yet. The current treatment for COVID-19 is the therapeutic drugs based on different symptomatic conditions. In the case of acute respiratory distress, followed by other infections, antibiotic and corticosteroids as well as antiviral agents and anti-inflammatory drugs are used in suggested regimens.[16] Furthermore, cell therapy, traditional herbal medicine, and CP therapy have been used for these patients. Here in we will summarize available therapies for COVID-19.

Antiviral agents such as, Remdesivir Hydroxychloroquine ,Ribavirin and chloroquine are used for treatment.[17] Antibiotic agents like Azithromycin fight against many different types of infections. Currently the effect of Hydroxychloroquine combined with Azithromycin has been tested.[16] Gaurtred et al.[18] reported that subsequent to treatment of 6 patients with combination of Hydroxychloroquine and Azithromycin their nasopharyngeal swab was 100% clear from virus. Corticosteroids suppress inflammatory responses in host and prevent excessive inflammatory response. However, corticosteroids in combination with viral therapies may cause adverse effects including prolonged hospitalization without mortality benefits.[19] In cell therapy, Mesenchymal stem

cells can regulate immunity by inhibiting excessive inflammation caused by virus, therefore inhibiting damage of pulmonary, liver, kidney caused by excessive inflammation.[20]

Traditional herbal therapy has also been investigated for controlling and treating epidemic outbreak including SARS, H1N1 infuluenza.[21,22] At present south Korea and china have used traditional herbal therapy guidelines for COVID-19.[23]

CP therapy was an important treatment for previous infectious disease such as SARS-CoV, H1N1, MERS, EBOLA, and other viruses.[24,25] Plasma transfusion causes a fast and short-term immunity for individuals. CP, generally used prophylactically, also reduces infected patients clinical severity.[26,27] Mechanism of CP is through binding of transfused antibodies to several of pathogens resulting in neutralization of the pathogens directly.[28,29] According to previous studies, CP transfusion should occur early in patients with severe clinical symptoms ideally within 5 days. it is recommended to infuse one unit of plasma (200-250 ml) at first, then monitoring for adverse reactions such as allergic reactions and febrile reactions. If available repeat CP transfusion in next 24-48 hours according to how patients tolerated the 1st CP transfusion based on their clinical responses. CP donation is done by patients with history of COVID-19, confirmed by nasopharyngeal swab and present of plasma antibodies for SARS-CoV-2 and resolution of COVID-19 > 14 days without COVID-19 symptoms at donation (FDA, GUIDANCE, MAY 2020).[30]

CP THERAPY FOR SARS-CoV-2 INFECTION

Several studies have investigated the efficiency of CP in COVID-19 patients and various positive results have been reported: CP is evidenced to decrease viral load. In fact, it can bind to SARS-CoV-2 and neutralize viral particles. Another benefit of using CP is involved in inhibiting access to non-infected cells and also activating effective mechanisms.[31] Most importantly, CP therapy can have a positive effect on modulating the immune system in patients with COVID-19 via the infusion of antibodies and anti-inflammatory cytokines that inhibit complement system as well as autoantibodies and inflammatory cytokines.[32] There is also evidence of an increase in lymphocytes in patients with COVID-19 after CP injection.[33]

However, results of CP therapy are depending on multiple factors. Firstly, in an effective CP product there should be an optimum level of neutralizing antibody. Research on SARS-CoV-1 and MERS-Co-V infected patients indicated that the level of particular neutralizing antibodies reduced rapidly within months after infection, therefore, SARS-CoV-2 neutralizing antibodies may also wane; consequently, plasma from newly treated patients may be optimal for use in infected individuals undergoing active treatment.[34] Ahn et al in the first report of the use of CP therapy for COVID-19 in Korea described two cases of SARS-CoV-2 treated with CP infusion. Both cases showed severe pneumonia with acute respiratory distress syndrome and presented a desirable outcome subsequent to the use of CP together with systemic corticosteroids to lessen the possibility of excessive inflammatory response and also promoting the diminution of viral loads by CP simultaneously.[35]

Nisar et al studied the effect of plasma therapy on 4 patients with COVID-19 in Kerala, India with underlying diseases such as hypertension, diabetes, rheumatoid arthritis, and tuberculosis. The use of plasma therapy, significantly decreased the SARS-CoV-2 viral load and all patients were treated.[36] Furthermore, NEIL and SHREYANS evaluated the effect of plasma therapy on 8 patients infected with severe SARS-CoV-2 infection, hospitalized in a hospital ICU in Florida for two weeks. Each of these patients received 200 ml of plasma (1 dose). These patients were monitored for 1 day before the injection and one hour, 3 days and 7 days after the injection 6 patients were discharged from the hospital subsequent to the plasma injection and two patients died.[37] In another study Biju et al.[38] studied 5 critically ill COVID-19 patients admitted in ICU due to other organs' failure. Subsequent to CP therapy all patients showed significant improvement on day 12 compared to day 1. Therefore, the results of these studies shows that CP could function as an efficient therapeutic option also for late stage

COVID-19 patients.

Liu, S. T.H. et al.[39] study proposes much unique strength. Data of three different time points (including baseline, prior to transfusion, and the transfusion day) allowed controls matching of the cases to improve the similarity. During the 16 days of study enrollment (from March 24, 2020, to April 8, 2020), 4,152 patients were admitted to the Mount Sinai Health System (MSHS) with confirmed COVID-19. Thanks to this large group of patients, an aggressive patient matching was applicable considering treatment propensity and allowed 1 to 4 matching of cases to controls. Also, passive antibody transfer efficacy mainly depends on the donor's convalescent plasma quality. This study demonstrated that the titers of the serum neutralizing antibodies against a clinical isolate of SARS-CoV-2 is significantly correlated with the titer of the serum antibody (based on MSH-ELISA assay measurement, which was used for plasmapheresis reference prioritization for convalescent donors) in the presented donor group in the cohort of CP-recipient, no remarkable transfusion-related mortality or morbidity was observed, as well as the much larger cohort of national, multi-center CP-recipient.[39]

Moreover, some possible adverse effects could be proposed for plasma transfusion.[40-43] Pro-coagulants are present in plasma with unknown additive effects in COVID-19. COVID-19 is associated with hypercoagulability independently; thus, further cautions should be considered in patients suffering from acute thrombotic events. Typically, plasma transfusion's allergic reactions are mild and self-limited, though anaphylaxis may occur in rare cases. With these risks in mind, future studies should make more definitive conclusions on CP transfusion efficacy in COVID-19 treatment in different populations

CP THERAPY FOR SARS-CoV INFECTION

During severe acute respiratory syndrome (SARS) outbreaks, different studies were conducted to evaluate the CP therapy efficacy in the treatment of SARS patients. In a Retrospective comparison among 19 patients receiving CP and 21 patients receiving methylprednisolone, the plasma group showed better response to therapy (74% were discharged before day 22 in comparison with 19% of patients in the steroid group) and no deaths compared with five deaths in steroid group.[44] Additionally, in the case of CP, the earlier treatment is applied, the more effective the results especially after the first week of disease which viremia peaks.[24,44] Elimination of virus 1 day after plasma transfusion, pulmonary infiltrated resolution and reduction of fever were obtained as results for CP in a study on infected healthcare workers.[45] In a case report, combination of ribavirin, corticosteroids and CP was demonstrated as an ideal management having favorable results for SARS.[11] Although CP therapy appears to be a safe treatment reducing mortality, hospitalization duration, length of critical care support and viral load, this treatment should be evaluated by a well-designed clinical trial.[46]

CP THERAPY FOR MERS-CoV INFECTION

The feasibility of CP therapy for developing passive immunity in MERS-CoV patients has been explored in some studies. As WHO Blood Regulators Network recommended, scientific studies on the use and collection of CP are examined through clinical trials.[47] A protocol was suggested for identifying appropriate donors for CP in MERS conditions.[12] After being tested by the indirect fluorescent antibody (IFA) and the enzyme linked immunosorbent assay (ELISA) techniques, donors having anti-MERS-CoV antibodies IFA titer of ≥1:160 with no clinical evidence of active infection would be eligible for plasma donating.[12] However, the small group of potential donors with adequately high antibody titers would be a challenge for such clinical trials.[48] Of 443 serum samples in this research (including 196 patients with suspected or confirmed MERS-CoV infection, 230 healthcare workers, and 17 household contacts who exposed to MERS-CoV), only 12 (2.7%) had the result of a reactive ELISA and 9 of the 12 samples had reactive IFA and micro neutralization assay suitable titers.[48] During Korean MERS outbreak in 2015, three patients with high MERS-CoV infection resulting in respiratory failure received different CP infusions. Serologic responses of

recipients' samples were evaluated afterwards by different techniques include ELISA, IFA and PRNT (plaque reduction neutralization test).[49] In order to having effective CP infusion, the PRNT titer of donor plasma should be ≥1:80.[49] However, the possible adverse effects such as renal impairment in MERS-CoV should be considered in the use of passive immunotherapy.[47]

CP FOR H1N1 INFECTION

Different studies have been conducted in order to investigate clinical effectiveness of CP in influenza A (H1N1). In a cohort study, among ninety-three severely infected patients aged ≥18, twenty (21.5%) received plasma therapy with an antibody titer of ≥1:160. By comparing treatment and control groups, plasma treatment resulted in reduction of viral load, serum cytokine (interleukin 6, interleukin 10, and tumor necrosis factor α) and mortality rate.[13] However, a systematic review investigating the randomized controlled trials in the case of CP therapy for severe influenza demonstrated that CP might not have a definite clinical impact in diminishing the mortality rate, days on mechanical ventilation or days in intensive care unit and hospital for severe infected patients.[50] On the other hand, large-scale plasma samples collection has some practical limitations including lack of access to eligible donors (defeat in health blood history screening, inappropriate vein size, inadequate hemoglobin level and PLT count, etc.).[51]

CONCLUSION

CP therapy has been used to treat diseases caused by some viruses, such as the SARS-CoV, MERS-CoV, as well as H1N1. Although various drugs and even methods such as cell therapy have been used to treat patients with COVID-19, since there is no certain treatment for COVID-19, the use of CP for the treatment of patients with this disease has been investigated in various studies and positive results have been reported. **Table 1** summarizes the results of the studies investigating the efficiency of CP in COVID-19, SARS, MERS, and influenza patients. However, conducted studies have some limitations such as having been performed on a limited number of patients, or CP-drugs combination. Therefore, the effect of CP on patients has not been precisely evaluated, yet. On the other hand, the number of times and the exact dose of plasma per injection to the patient is still unknown. Yet, further randomized clinical trials with accurate study designs are required to investigate the safety and efficacy of CP transfusion and to assess the best candidates for CP donation who have highly specific antiviral antibodies, as well as CP therapy indications (including the optimal time point of transfusion, early warning indicators, and the required transfusion dose).

CONFLICTS OF INTEREST

None.

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Table 1. Summary of CP Trials in COVID-19, SARS, MERS, and Influenza Patients.

Number of cases		CP Dose	Titre	Administration Day	Other Antiviral Therapies	Disease Severity	Viral Load after Therapy	Reference
10		200 mL*1	< 1:640	after 6 d from onset of symptoms	Arbidol monotherapy or combination therapy with remdesivir , Ribavirin , peramivir , intravenous methylprednisolone , IFN-α , Oseltamivir	severe disease (All patients were admitted to the ICU)	Serum neutralizing antibody titers was 1:640 (in 1 case was Unavailable) ≤5 days Ct value was negative.	[14]
2	A	500 mL * 2	-	after 22 d from the onset of symptoms	Hydroxychloroquine lopinavir/ritonavir Methylprednisolone	severe disease - transferred to the tertiary-care hospital (on day 3)	the viral load estimated by Ct values showed an increasing trend just before plasma infusion but began to decrease right after the use of CP.	[35]
	B	-		after 7 d from the onset of symptoms	Hydroxychloroquine lopinavir/ritonavir methylprednisolone steroids			
3	A	CP unit (hd 7) *1	> 1:640	after 9 d from the onset of symptoms	Tacrolimus, prednisone, piperacillin-tazobactam, amoxicillin-clavulanate	admitted to the general medical service with surgery	-	[34]
	B	CP units (hd 4)*2		after 4 d from the onset of symptoms	Tacrolimus, prednisone, remdesivir, tocilizumab, ceftriaxone, azithromycin, vancomycin, piperacillin/ tazobactam	were admitted to the ICU		
	C	CP unit (hd 2) *1		after 7 d from the onset of symptoms	Tacrolimus, prednisone, azithromycin, vancomycin, piperacillin/ tazobactam, sulfamethoxazole trimethoprim, valganciclovir	Patient transfer to ICU for a higher level of care.		
4	A	200 ml*1	-	after 10 d from the onset of symptoms	Hydroxychloroquine Methyl prednisolone Lopinavir/ritonavir Tocilizumab	4 cases had underlying diseases and Severe Acute SARS CoV-2	viral shedding as indicated by negative RT-PCR varied from 4 to 30 days of plasma therapy	[36]
	B			after 12 d from the onset of symptoms				
	C			after 13 d from the onset of symptoms	Azithromycin Oseltamivir Hydroxychloroquine Methyl prednisolone Lopinavir/ritonavir Tocilizumab Low molecular weight heparin			
	D	200 ml*2		after 16 d from diagnosed to have TB from of abroad	Azithromycin Hydroxychloroquine Methyl prednisolone Lopinavir/ritonavir Tocilizumab Low molecular weight heparin			
8		200 ml*1	-	On average at 16.13 days post-admission	-	patients hospitalized in a hospital ICU	-	[37]

5	A	Male 70s	-	antibody titer higher than 1:1000 and neutralizing antibody titer greater than 40	CP transfusion was performed on the first day	Lopinavir/ritonavir Interferonalfa-1b, favipiravir	Intensive care admission	30.0 -ve	[38]
	B	Male 60s				Lopinavir/ritonavir Arbidol,darunavir		22.0 -ve	
	C	Female 50s				Lopinavir/ritonavir, Interferon alfa-1b		33.0 -ve	
	D	Female 30s				Interferon alfa-1b, favipiravir		26.6 -ve	
	E	Male 60s				Lopinavir/ritonavir, interferon alfa-1b		26.5 -ve	
888			200-600 ml*1	1:160	20 days after diagnosis or duration of MV support groups (≤5 days, 6− 10 days, 11− 15 days)	favipravir, lopinavir / ritonavir, hydroxychloroquine, high dose vitamin C, azithromycin	severe or critically disease	viral loads decreased and became negative within 12 days.	[52]
2	A		400 ml * 1	-	after 15 d from the onset of symptoms	Antiviral therapies	Non severe diesese	-	[53]
	B				after 11 d from the onset of symptoms				
8	A		400ml	≤1:64	7 d from symptom onset to admission	Lopinavir/ritonavir, arbidola, darunavira, interferon alfa-1ba	Severe	virus-specific IgG titer ratio (1.06 (0.99–1.54) >21 day	[54]
	B		400ml	≤1:64	3 d from symptom onset to admission	Lopinavir/ritonavir, arbidol[a], darunavir[a], interferon alfa-1b	Critical	virus-specific IgG titer ratio :1.20 (1.15–1.85) ≤21 day	
	C		400ml	≤1:64	4 d from symptom onset to admission	Lopinavir/ritonavir, interferon alfa-1b, arbidol, darunavir	Severe	virus-specific IgG titer ratio :1.20 (1.15–1.85) ≤21 day	
	D		300ml	≤1:64	10 d from symptom onset to admission	Arbidol, interferon alfa-1b	Critical	high neutralizing activity: virus-specific IgG titer ratio(1.06 (0.99–1.54) >21 day	
	E		400ml	≤1:64	3 d from symptom onset to admission	Lopinavir/ritonavir, arbidol, interferon alfa-1b	Severe	high neutralizing activity: virus-specific IgG titer ratio (1.06 (0.99–1.54) >21 day	
	F		200ml	≤1:64	2 d from symptom onset to admission	Lopinavir/ ritonavir, ribavirin, hydroxychloroquine sulfate[a], interferon alfa-1b[a]	Severe	virus-specific IgG titer ratio :1.20 (1.15–1.85)	
	G		200ml	≤1:64	-	Lopinavir/ritonavir, arbidol, interferon alfa-1b	Severe	1.20 (1.15–1.85) ≤21 day high neutralizing activity	
	H		200ml	≤1:64	13 d from symptom onset to admission	Lopinavir/ ritonavir, arbidol[a], interferon alfa-1b,hydroxychloroquine sulfate, lamivudine	Severe	virus-specific IgG titer ratio (1.06 (0.99–1.54) >21 day	

5000		200–500 mL *1-2	ABO compatible with no minimum neutralizing Ab titre	-	Not specified	adults with, or at high risk of, severe/ life-threatening disease	-	[55]
52		4–13 mL/ kg recipient BW	ABO compatible with ≥1:640 S-RBD-specific IgG titer	at least 14 d after the onset of symptoms in most cases	Varied, includes antibiotics, antivirals, steroids, human immunoglobulin, Chinese herbal medicines, interferon	Severe or life-threatening disease	-	[56]
19		200–400 mL	160–2560	the second week from the onset of symptoms (mean 11.42 days)	ribavirin therapy and 1.5 g of pulsed methylprednisolone and steroids	Having progressive disease after ribavirin-steroid therapy and receiving 1.5 g of pulsed methylprednisolone	-	[44]
80		200–400 ml	160–2560	after 14 d from the onset of symptoms	cefotaxime and levofloxacin (or clarithromycin), ribavirin, prednisolone and methylprednisolone	Deteriorative disease after antiviral treatments	-	[24]
3		-	>640	on days 11 and 10 after admission	ribavirin and methylprednisolone and moxifloxacin and intravenous immunoglobulin G	no respond to the available treatments	Viral load dropped from 495×1000, 76×1000 or 650×1000 copies/mL to zero or 1 copy/ mL one day after transfusion	[45]
1		200 mL	-	on days 15 after admission	intravenous cefotaxime, oral levofloxacin, oseltamivir, oral ribavirin, prednisolone, methylprednisolone	exacerbation of disease after oral antiviral and steroid agents	-	[11]
3	A	2 unit of CP	PRNT titer of 1:40 and 1:160	11- and 14-days post onset	-	Mechanical ventilation	Only patient C showed a meaningful antibody response after infusion	[49]
	B	1 unit of CP	ELISA IgG titer of 0.089, PRNT negative	8 days post onset				
	C	1 unit of CP	PRNT titer of 1:80	14 days post onset				
20		1 dose 500 mL	≥1:160	day 2 (median; IQR, day 1–2.5) of ICU admission	oseltamivir, intravenous peramivir or zanamivir, inhaled zanamivir, stress dose of intravenous hydrocortisone, antioxidant treatment with N-acetylcysteine	Requiring Intensive care and mechanical ventilation	respiratory tract viral load decreased by>3 log10 copies/mL within 48 h after plasma therapy	[13]
20		2 units of CP	≥1:160	-	corticosteroids, ribavirin, intravenous immunoglobulin and interferon	admission to ICU, partial pressure of oxygen to fraction of inspired oxygen ratio (PaO2:FiO2) of <300 mmHg and Mechanical ventilation	-	[12]

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