Convalescent plasma: possible therapy for novel coronavirus disease 2019

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The recent coronavirus disease 2019 (COVID-19) epidemic is spreading all over the world. By March 23, over 300,000 patients had been confirmed and almost 15,000 died because of COVID-19. More than 200,000 cases have been confirmed in other countries and regions outside China. Italy is the worst affected country in Europe. So far, no specific effective treatment has been developed for COVID-19 except for meticulous supportive care including critical care and organ support when necessary. Convalescent plasma might be a potential treatment for COVID-19.[1] Convalescent plasma refers to a plasma therapy based on plasma or plasma derivatives obtained from donors who have survived previous infections by developing antibodies and infusing into newly infected individuals.[2]

The precise action mechanism of convalescent plasma therapy is not fully stated. There are some assumptions: First and foremost, the assumption is that convalescent plasma contains protective antibodies by neutralizing the pathogen, eventually leading to its eradication from the blood circulation. Rapid viral clearance would prevent further replication and the stimulus for the cytokine cascade. The level of anti-Ebola virus immunoglobulin G (IgG) titers was found to be associated with a delay in the peak of viral replication in a lethal Ebola virus–infected mouse model.[3] Another assumption is that convalescent plasma can convey other healing factors, such as preventing excess vascular leakage, procoagulant or antifibrinolytic factors, restoring the endothelium glycocalyx.[2,4] Convalescent plasma plays an important role as one of the treatments for many viral infections when vaccines or other specific treatments are not available.

RISE OF CONVALESCENT PLASMA

Convalescent plasma has been applied more than 100 years (the first well documented was the Spanish flu in 1917-1919).[2] Recently, severe acute respiratory syndrome (SARS) coronavirus epidemics (2003), A (H5N1) flu epidemics (2005-2015), A (H1N1) flu epidemics (2009-2010), and the Ebola virus epidemics (2013-2015) have been proved exceedingly lethal and a threat to global health systems. There is an urgent need to have protective measures for nonexposed populations, prophylaxis for exposed but not yet infected populations, and experimental therapy for attacked individuals.[5–12] Each of those situations including the early Spanish flu have proposed the use of convalescent plasma therapy. Evidence shows that it is also effective in infectious diseases such as Lassa fever,[13] Argentine hemorrhagic fever,[14] measles,[15] and Sin Nombre virus.[16] Public Health of England and the International Severe Acute Respiratory and Emerging Infection Consortium[17] put forward that convalescent plasma could be a promising specific treatment for serious Middle East respiratory syndrome (MERS), and further evaluation is needed in human clinical trials.[18] The World Health Organization (WHO) announced in September 2014 that serum from people who are convalescing from infection with the Ebola virus can be used to treat new patients.[19]

PRINCIPLE OF CONVALESCENT PLASMA

According to the WHO's criteria, only clinically asymptomatic survivors, 28 days after being discharged and who have

ABBREVIATIONS: COVID-19 = coronavirus disease 2019; MERS = Middle East respiratory syndrome; SARS = severe acute respiratory syndrome; WHO = World Health Organization.

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twice tested negative for Ebola virus RNA by molecular techniques (the two samples for Ebola virus RNA testing should be taken at least 48 hours apart, and the test results should be negative on each sample), and aged between 18 years old and 55 years old, could be considered as potential convalescent plasma donors. A dosage of 400 to 500 mL of convalescent plasma was given in two doses of 200 to 250 mL each, separated from two different whole blood donations. For pediatric convalescent plasma transfusion, a dose of 10 mL/kg could be used based on the considerations of blood volume. Donors needed to be seronegative of HIV, hepatitis B virus, hepatitis C virus, syphilis, and other locally transmitted infections.[19]

CLINICAL TRIAL OF CONVALESCENT PLASMA

Convalescent plasma has been used to treat several viral infections, including SARS, avian influenza A (H5N1), influenza A (H1N1), MERS, and Ebola virus. Although many studies have reported the efficacy and safety of convalescent plasma infusion in the treatment of various infections, due to the lack of large-scale, randomized, well-designed, and prospective clinical trials, we tend to consider convalescent plasma as an "empirical" therapy.[20] Many studies have shown that convalescent plasma can effectively reduce viral load and increase antibodies to inhibit virus replication. Nevertheless, subsequent trials about convalescent plasma showed different results.[13] The characteristics of primary study are described in Table 1. See Table **S1** (available as supporting information in the online version of this paper) for detailed data (https://data.mendeley.com/datasets/n8w9n7rgz3/1).

SARS infection

A retrospective comparative study showed a shorter hospital stay after convalescent plasma therapy in SARS patients who deteriorated despite ribavirin and high-dose steroid therapy (74% vs. 19%; p = 0.001). Compared with five people who died in the continuing high-dose methylprednisolone group, there were no deaths in the plasma group (p = 0.049).[6] A case report by Wong et al.[21] stated that a 57-year-old woman infected with SARS improved gradually in clinical signs and symptoms after receiving a single 200-mL dose of convalescent plasma by 15 days after symptoms onset, suggesting that convalescent plasma combined with antiviral drugs and a corticosteroid may be an available option for the treatment of SARS infection.[21] A study reported recovery of three patients infected with SARS who developed severe progression and failed to respond to the ribavirin or methylprednisone. The study shows that viral load dropped from 495×10^3, 76×10^3, or 65×010^3 copies/mL to zero or one copy/mL 1 day after transfusion, and anti–SARS-Cov immunoglobulin M (IgM) and IgG also increased in a time-dependent manner following convalescent plasma transfusion.[22]

Influenza A/B infection

Two cases of convalescent plasma were reported. Both showed absolute reductions in viral load. One shows that the H7N9 virus was undetectable, the number of lymphocytes had been normalized by 4 days after infusing 200 mL of convalescent plasma with a titer of 80, and a computed tomography scan of the consolidation in the left lung had improved markedly after 12 days.[23] Another case report provided by Zhou et al., found that the virus load was reduced from 1.68×105 to 1.42×104 copies per milliliter during the first 8 hours and was undetectable within 32 hours after infusing convalescent plasma.[9] A look-back study suggests that patients with Spanish influenza pneumonia who received transfusion with influenza-convalescent human blood products may have experienced a clinical reduction in the risk of death. The overall crude case fatality rate was 16% (54/336) among treated patients and 37% (452/1219) among controls. A significant absolute reduction in the case fatality rate was observed in the patients treated within 4 days (19%; 28/) compared with 4 days or later (59%; 49/83). Therefore early definitive therapy is of great significance for pneumonia and hypoxia.[24] In 2012, Rockman et al.[8] conducted an animal experiment in which ferrets were exposed to lethal doses of highly pathogenic influenza H5N1, infused with hyperimmune serum at three different times (24 hr before or 24 hr after virus exposure at the onset of fever [>40°C] or immediately before the earliest expected onset of significant clinical signs [estimated from previous studies as Day 3 after exposure]). A total of 12 ferrets were included in the treatment group. The purpose of this study was to investigate the effects of convalescent plasma infusion at different time periods on survival. All four animals transfused hyperimmune serum 24 hours before virus exposure survived and were generally well, with slight weight loss. We can conclude that the greatest benefit was derived from passive immunization provided immediately before contact with an infectious dose of virus, compared to buffer controls or H3N2 nonhomologous hyperimmune serum. A prospective cohort study designed by Hung et al.[25] in which patients received a single 500-mL dose of convalescent plasma with an antibody titer greater than 160. Mortality in the treatment group was significantly lower than in the nontreatment group (20.0% vs. 54.8%; p = 0.01). Multivariate analysis showed that treatment with convalescent plasma reduced mortality (odds ratio [OR], 0.20; 95% confidence interval [CI], 0.06-0.69; p = 0.011). Subgroup analysis of 44 patients with serial respiratory tract viral load and cytokine level demonstrated that plasma treatment was associated with significantly lower Day 3, 5, and 7 viral load, compared with the control group ($p < 0.05$). Nevertheless, there is research showing different results. A randomized

TABLE 1. Characteristics of 13 studies

Virus	Author	Journal	Days of CP transfusion	Dose and frequency	Titer	Outcome
SARS	Soo[6]	*Clinical Microbiology and Infection*	Mean 11.42 days after symptom onset	200-400 mL	Titer 160-2560	Patients in the plasma group had a shorter hospital stay (p=0.001) and lower mortality (p=0.049) than control group.
	Wong[21]	*Hong Kong Medical Journal*	15 days after symptom onset	200 mL	Unknown	CP was demonstrated effective for SARS.
	Yeh[23]	*Journal of Antimicrobial Chemotherapy*	Unknown	500 mL	>640	CP can decrease the viral load and increase Anti-SARS-CoV IgM and IgG
Influenza A/B	Wu[22]	*International Journal of Infectious Diseases*	10 days after symptom onset	200 mL	80	CP significantly decreased the viral load and improved clinical symptoms and signs.
	Luke[24]	*Annals of Internal Medicine*	…	…	…	Early transfusion can significantly reduce the mortality.
	Hung[25]	*Clinical Infectious Diseases*	Day 2 of ICU admission	500 mL	>160	CP reduced respiratory tract viral load, serum cytokine response, and mortality.
	Xu[28]	…	…	0.25-0.40 g/kg (H-IVIG)	>80	CP/H-IVIG had no significant benefit on mortality in patients with severe influenza.
	Beigel[26]	*Lancet Respiratory Medicine*	<24 hours after randomization	Two units (225-350 mL/unit)	>80	CP was associated with a lower mortality and improved clinical symptoms, but no statistical significance.
	Beigel[27]	*Lancet Respiratory Medicine*	<12 hours after randomization (2.2 hours [IQR, 1.7-3.3])	450-700 mL >30 kg 8 mL/kg <30 kg 4 mL/kg	>80	High-titer (> = 1:80) anti-influenza plasma was not superior to low-titer (<=1:10).
	Rockman[8]	*Critical Care Medicine*	24 hours before exposure or 1-3 days after exposure	10 mL (in animals)	128	Passive immunization had most benefit when provided before contact with virus.
	Zhou[9]	*New England Journal of Medicine*	12 days after symptom onset	Three 200 mL	80	The viral load of patients can be quickly removed after transfusion.
Ebola	van Griensven[4]	*New England Journal of Medicine*	Up to 2 days after symptom onset	Two 200-250 mL	Unknown	CP was not associated with a significant improvement in survival in 84 patients with confirmed EBV.
	Mupapa[29]	*Journal of Infectious Diseases*	4-15 days after symptom onset	150-450 mL	Unknown	Transfusion can result in distinct reduction in mortality.

CP = convalescent plasma; H-IVIG) = hyperimmune intravenous immunoglobulin; ICU = intensive care unit; IQR = interquartile range.
See Table S1 for detailed data.

controlled trial reported that patients who received immune plasma and standard care for severe influenza showed a nonsignificant reduction in the mortality rate.[26] One death (2%) from the plasma plus standard care group and five (10%) from the standard care group (hazard ratio, 0-19; 95% CI, 0·02-1·65; p = 0·093). Twenty-eight of 42 (67%) patients in the plasma plus standard care group normalized their respiratory status by Day 28 compared with 24 of 45 (53%) participants on standard care alone (p = 0·069). Moreover, the sequent study with patients suffering influenza A has suggested that there is no significant benefit from high-titer (80) anti-influenza plasma. There is no significant reduction in the discharge rate at Day 7 (95% CI, 0.65-2.29; p = 0·54), mortality (six [7%] in the high-titer group vs. four [9%] in the low-titer group; p = 0·73).[27] Both of the randomized controlled trials focused on influenza A and B. These studies contradict what we know about the theory and previous research work. Meanwhile, a meta-analysis showed that convalescent plasma may not have a clinically relevant impact in reducing the rate of mortality in patients with influenza (OR, 1.06; 95% CI, 0.51-2.23; p = 0.87; I^2 = 35%). There were nonsignificant reductions in days in the intensive care unit, days in the hospital, and days on mechanical ventilation. Nevertheless, there was evidence of a benefit of decreasing influenza B virus loads and cytokines after convalescent plasma treatment.[28]

Ebola virus infection

In 1995, a small study reported that eight patients received 150 to 400 mL of convalescent plasma and seven survived, for a case fatality rate of 12.5% in comparison to 80% in patients without convalescent plasma treatment.[29] However, van Griensven et al.[4] performed a nonrandomized comparison study in which patients received two consecutive transfusions of 200 mL to 250 mL with unknown levels of antibody titer. Eighty-four patients received convalescent plasma was not associated with a significant improvement in survival. From Day 3 to Day 16 after diagnosis, the risk of death was 31% (26/84 patients) in the convalescent plasma group and 38% (158/418 patients) in the control group (risk difference, −7 percentage points; 95% CI, −18 to 4). In conclusion, the transfusion of up to 500 mL of convalescent plasma with unknown levels of neutralizing antibodies in 84 patients with confirmed Ebola virus infection was not associated with a significant improvement in survival. Further clinical trial is worth performing.

COVID-19 infection

COVID-19 belongs to the same coronavirus family as SARS and MERS. Many life-threatening complications, such as acute respiratory distress syndrome, can occur during the viral mass replication phase. None of them had specific and effective treatment. According to previous studies and WHO recommendations, convalescent plasma might be used when a specific treatment is not available. According to the press conference of the Joint Prevention and Control Mechanism of the State Council on February 28 (Guangming Net of China), up to 544 doses of plasma from convalescent COVID-19 patients have been collected across the country and applied to 245 COVID-19 patients. Of the 157 COVID-19 patients who received convalescent plasma therapy and were closely monitored for more than 48 hours, 91 cases showed improvement in clinical indicators and symptoms. The plasma therapy has proved to be safe and effective. Neutralizing antibodies against the novel coronavirus have been identified in the plasma of convalescent patients. A pilot study that has just been reported shows that the convalescent plasma (titer ≥ 640) therapy was safe and could improve clinical symptoms and laboratory parameters.[30] We look forward to the release of relevant data about convalescent plasma applied in COVID-19. More prospective comparative studies are needed to confirm the efficacy of convalescent plasma.

ADVERSE EVENTS

No serious adverse events were associated with convalescent plasma treatment.[4,5,31] The most commonly reported mild adverse event was a brief "chill" reaction with a transient hyperpyrexia after the convalescent plasma transfusion. Few patients develop transfusion-related adverse events such as phlebitis, generalized jaundice, or anaphylaxis.[24] A case report raised an association between transfusion-related acute lung injury and convalescent plasma.[32]

OPTIMAL TIMING OF CONVALESCENT PLASMA TREATMENT

In most viral illnesses, viremia peaks in the first week of infection. The patient then develops a primary immune response by Day 10 to Day 14, followed by virus clearance. Arabi et al.[18] studied the time course of specific antibody response and found that those antibodies peaked 1 week after the inoculation and then began declining. Therefore, convalescent plasma should be more effective when given early during the course of infections. SARS patients whose clinical condition deteriorated after receiving ribavirin and methylprednisolone had a higher discharge rate by Day 22, a shorter hospital stay, and a lower mortality rate when convalescent plasma was administered before Day14 of illness onset.[5] In a study of patients with Lassa fever in Nigeria, all eight patients who received convalescent plasma before Day 10 of illness recovered and survived, while only three of eight patients who received plasma after Day 10 survived.[13] The latest research proved that the positive rate of IgG reached 100% at around 17 to 19 days after symptom onset, while the IgM seroconversion rate reached its peak of 94.1% at around 20 to 22 days after symptoms onset. During

the first 3 weeks of symptom onset, there was an increase in the titer of IgG and IgM antibodies to SARS-CoV-2. All those patients achieved a seroconversion of IgG or IgM within 20 days after symptom onset. The median day of seroconversion for both IgG and IgM was 13 days (after symptoms onset). The IgG levels in all the patients reached the platform in 6 days after the first positive points. It means that we should use convalescent plasma within 3 weeks after symptoms onset.[33] These findings suggest that early initiation of convalescent plasma treatment may be of critical importance to reduce mortality in patients with SARS or other pathogen infection.[31] However, a report showed that, when convalescent plasma transfusions were initiated on the day of diagnosis or up to 2 days later, the risk of death on Day 3 to Day 16 was nonsignificant.[4] Therefore, whether earlier use of convalescent plasma is better need more evidences.

FURTHER QUESTIONS NEEDED TO EXPLORE

There are still some issues to consider in determining the advisability of implementing a large-scale convalescent plasma transfusion program: What is the optimal timing for infusion? How long after clinical resolution of symptoms is there a chance to obtain neutralization antibodies if any? What is the most effective frequency of administration of convalescent plasma? Is clinical therapeutic effect related to antibody titer? Is it more likely to benefit young children and pregnant women? How do we make efficient use of convalescent plasma? More physiological studies are needed to explore why convalescent plasma is superior to fresh plasma and convalescent whole blood. Clinical research needs to explore the relationship between time (both extraction time and infusion time), volume, frequency, antibody titer and other healing factors, and clinical symptoms and signs of the patient. There is limited availability of eligible potential donors with sufficient levels of antibody. More large-scale, randomized, well-designed prospective studies are needed. Of note, eight studies, including a randomized controlled trial, have been registered in the Chinese Clinical Trial Registry (http://www.chictr.org.cn), preparing for clinical research (ChiCTR2000030690, ChiCTR2000030627, ChiCTR2000030557, ChiCTR2000030381, ChiCTR2000030312, ChiCTR2000030046, ChiCTR2000030039, ChiCTR2000029850).

CONCLUSION

Convalescent plasma is now used as an empirical treatment in the absence of specific treatment for COVID-19 and other dangerous viral infections, although its efficacy remains controversial. There are still some questions need to be explored. We look forward to more well-designed prospective studies.

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CONFLICT OF INTEREST

The authors have disclosed no conflicts of interest.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article.

Table S1. Characteristics of 13 studies that assessed the effect of convalescent blood products in patients with different pathogeny.