



CONVALESCENT PLASMA FOR TREATMENT OF COVID-19

Based on available evidence up to 13 April 2020

INTRODUCTION

Convalescent plasma (CP) therapy, a classic adaptive immunotherapy, also known as passive antibody therapy, has been applied to the prevention and treatment of many infectious diseases for more than one century. Convalescent plasma therapy was successfully used in the treatment of SARS¹, MERS, and 2009 H1N1 pandemic with satisfactory efficacy and safety.²

Amid testing the already existing antiviral drugs and new ones, the researchers have come across the CP therapy, which could be a potential treatment for the virus. Several countries including China and the US have already started the clinical trials of the convalescent plasma therapy due to the absence of a coronavirus-specific treatment to cure the infected patients.^{2,3,4}

To date, no specific treatment was recommended for SARS-CoV-2 / COVID-19 infection except for meticulous supportive care and CP therapy has not yet been approved for use by FDA, so it is regulated as an investigational product under the US - Food & Drugs Administration. FDA is also facilitating access to COVID-19 convalescent plasma for use in patients with serious or immediately life-threatening COVID-19 infections through the process of Single Patient Emergency Investigational New Drug (IND). Health care providers may want to consider patient eligibility and donor eligibility before emergency use of COVID-19 CP to treat patients.⁵

EVIDENCE

There were 17 articles retrieved from the scientific databases such as Medline, EBM Reviews, EMBASE via OVID, PubMed, the general search engines [Google Scholar and US Food and Drug Administration (USFDA)] using the keywords of “*convalescent plasma*”, “*coronavirus*” and “*COVID-19*”. However, two relevant articles were retrieved from these scientific databases on convalescent plasma for the treatment of COVID-19 and were included in this review.

Duan K et al (2020) conducted a pilot case control study in three participating hospitals in China. In this study, ten severe patients (n=10) from January 23, 2020, to February 19, 2020 (six males and four females) were enrolled and received CP

transfusion. None of the patients had direct exposure to the Huanan Seafood Wholesale Market. All patients were confirmed by real-time viral RNA tests and received one dose of 200 mL of convalescent plasma (CP) derived from recently recovered donors with the neutralizing antibody titers above 1:640. The CP therapy was transfused to the patients as an addition to maximal supportive care and antiviral agents. Nine patients received arbidol monotherapy or combination therapy with remdesivir or ribavirin or peramivir, while one patient received ribavirin monotherapy. Antibacterial or antifungal treatment was used when patients had co-infection. Six patients received intravenous (i.v.) methylprednisolone (20 mg every 24 h). A computerized tomography investigation showed that all patients presented with bilateral ground-glass opacity and/or pulmonary parenchymal consolidation with predominantly subpleural and bronchovascular bundles distribution in the lungs. Seven patients had multiple lobe involvement, and four patients had interlobular septal thickening.²

All clinical symptoms in the ten patients, especially fever, cough, shortness of breath, and chest pain, disappeared or significantly improved within Day 1 to Day 3 upon CP transfusion. Two patients were able to wean off from mechanical ventilation to high-flow nasal cannula, and one patient discontinued high-flow nasal cannula after receiving CP. Lymphocytopenia, an important index for prognosis in COVID-19, tended to be improved after CP transfusion (median: 0.65×10^9 per L vs. 0.76×10^9 per L) with seven out of 10 patients showing an increase of lymphocyte counts. Several other parameters tended to improve as compared to pre-transfusion, including increased lymphocyte counts (0.65×10^9 /L vs. 0.76×10^9 /L) and decreased C-reactive protein (55.98 mg/L vs. 18.13 mg/L). Radiological imaging showed varying degrees of absorption of lung lesions within seven days in reduction of pulmonary lesions on chest CT. There were no serious adverse reactions or safety events were recorded after CP transfusion.²

The study also compared a historic control group of ten (n=10) patients which was randomly selected from the cohort treated in the same hospitals and matched by age, gender, and severity of the diseases. Baseline characteristics of patients between CP treatment group and control group showed no significant differences, while clinical outcomes of these two groups were different. Three cases were discharged while seven cases were in much improved status and ready for discharge in CP group, as compared to three deaths, six cases in stabilised status, and one case in improvement in the control group ($p < 0.001$).²

The authors concluded that this pilot study on CP therapy shows a potential therapeutic effect and low risk in the treatment of severe COVID-19 patients. One dose of CP with a high concentration of neutralising antibodies can rapidly reduce the viral load and tends to improve clinical outcomes. The optimal dose and treatment time point, as well as the definite clinical benefits of CP therapy, need to be further investigated in randomised clinical studies.²

Shen C et al (2020) reported their clinical experience in a case series of five critically ill COVID-19 patients treated with convalescent plasma transfusion in Shenzhen Third People's Hospital, China. All patients presented with acute respiratory distress syndrome (ARDS) and met these three following criteria: 1) severe pneumonia with rapid progression and continuously high viral load despite antiviral treatment; 2) $PAO_2/FIO_2 < 300$; and 3) requiring mechanical ventilation. Each patient received two consecutive transfusions of 200 to 250 mL of ABO-compatible convalescent plasma (400 mL of convalescent plasma in total) on the same day it was obtained from the donor. Convalescent plasma was administered between 10 and 22 days after admission. The patients also received antiviral agents (*combination of two or three of these drugs : lopinavir/ritonavir; interferon alfa-1b; favipiravir; arbidol; darunavir*) continuously until the SARS-CoV-2 viral loads became negative. **Following plasma transfusion**, body temperature normalized within three days (4 of 5 patients), the SOFA score decreased, and PAO_2/FIO_2 increased within 12 days. Viral loads decreased and tested negative within 12 days after the transfusion. SARS-CoV-2-specific ELISA and neutralizing antibody titers increased following the transfusion. Clinically, ARDS resolved in four patients at 12 days after transfusion, and three patients were weaned from mechanical ventilation within two weeks of treatment. Of the five patients, three have been discharged from the hospital (length of stay: 51 to 55 days), and two were in stable condition at 37 days after transfusion. The authors concluded that administration of convalescent plasma containing neutralizing antibodies may improve the clinical conditions of critically ill COVID-19 patients with ARDS. However, the limited sample size and study design preclude a definitive statement about the potential effectiveness of this treatment, and these observations require evaluation in clinical trials.⁶

The details of patients and convalescent plasma donors are described in **Annex 1**.

CONCLUSION

Convalescent plasma therapy is a potential therapeutic effect with improved clinical symptoms of the severe/critically ill patients with COVID-19. It is also reported that from the studies observed, no serious adverse reactions associated with the transfusion of convalescent plasma. However, optimal dose and treatment time point, as well as the definitive statement of this therapy, need to be further investigated in randomised controlled clinical studies.

REFERENCE

1. Mair-Jenkins J, Saavedra-Campos M, Baillie JK, et al. The effectiveness of convalescent plasma and hyperimmune immunoglobulin for the treatment of severe acute respiratory infections of viral etiology: a systematic review and exploratory meta-analysis. *J Infect Dis.* 2015;211(1):80–90
2. Duan K, Liu B, Li C, et al. Effectiveness of convalescent plasma therapy in severe COVID-19 patients [published online ahead of print, 2020 Apr 6]. *Proc Natl Acad Sci USA.* 2020;202004168. Available at: <https://www.pnas.org/content/early/2020/04/02/2004168117> (accessed online on 13 April 2020)
3. Dana Sparks. Convalescent plasma: A therapy for COVID-19? <https://newsnetwork.mayoclinic.org/discussion/convalescent-plasma-a-therapy-for-covid-19/> (accessed online on 13 April 2020)
4. Roback JD, Guarner J. Convalescent Plasma to Treat COVID-19: Possibilities and Challenges. *JAMA.* Published online March 27, 2020. doi:10.1001/jama.2020.4940
5. US-FDA Recommendations for Investigational COVID-19 Convalescent Plasma, update April 8, 2020. Available at: <https://www.fda.gov/vaccines-blood-biologics/investigational-new-drug-ind-or-device-exemption-ide-process-cber/recommendations-investigational-covid-19-convalescent-plasma> (accessed online on 13 April 2020)
6. Shen C, Wang Z, Zhao F, et al. Treatment of 5 critically ill patients with COVID-19 with convalescent plasma. *JAMA.* 2020 Mar 27. Available at : <https://jamanetwork.com/journals/jama/fullarticle/2763983> (accessed online on 13 April 2020)

Based on available evidence up to 13th April 2020.

Disclosure: The authors of this report has no competing interest in this subject and the preparation of this report is totally funded by the Ministry of Health, Malaysia.

Disclaimer: This rapid assessment was prepared to provide urgent evidence-based input during COVID-19 pandemic. The report is prepared based on information available at the time of research and a limited literature. It is not a definitive statement on the safety, effectiveness or cost effectiveness of the health technology covered. Additionally, other relevant scientific findings may have been reported since completion of this report.

Malaysian Health Technology Assessment Section (MaHTAS),
Medical Development Division,
Ministry of Health, Malaysia.

Annex 1 : Characteristics of patients and convalescent plasma donors

Study	Patients	Donors
<p>Duan K et al, 2020 (n=10)</p>	<p>Enrollment criteria were one of the conditions 2 to 4 plus condition 1:</p> <ol style="list-style-type: none"> 1) age \geq 18 years 2) respiratory distress, RR \geq30 beats/min 3) oxygen saturation level less than 93% in resting state; and 4) partial pressure of oxygen (PaO₂)/oxygen concentration (FiO₂) \leq 300 mmHg (1 mmHg = 0.133 kPa). <p>Exclusion criteria were as follows:</p> <ol style="list-style-type: none"> 1) previous allergic history to plasma or ingredients (sodium citrate) 2) cases with serious general conditions, such as severe organ dysfunction, who were not suitable for CP transfusion. 	<p>10 donor patients who recovered from COVID-19 were recruited from three participating hospitals. The recovery criteria were as follows:</p> <ol style="list-style-type: none"> 1) normality of body temperature for more than 3 d, 2) resolution of respiratory tract symptoms, and 3) two consecutively negative results of sputum SARS-CoV-2 by RT-PCR assay (1-d sampling interval). The donor's blood was collected after 3 wk post onset of illness and 4 d post discharge. Written informed consent was obtained from each patient.
<p>Shen C et al, 2020 (n=5)</p>	<p>- Enrollment criteria :</p> <ol style="list-style-type: none"> 1) severe pneumonia with rapid progression and continuously high viral load despite antiviral treatment; 2) PAO₂/FIO₂ of <300 mmHg 3) currently or had been supported with mechanical ventilation <ul style="list-style-type: none"> - Age range: 36-73 years - 3 men, 2 women - None were smokers - 4 of 5 had no pre-existing medical conditions (1 patient with hypertension and mitral insufficiency) - All patients received methylprednisolone 	<ul style="list-style-type: none"> - Age range : 18-60 years. - All donors had been diagnosed with COVID-19 (laboratory confirmed) and subsequently tested negative for SARS-CoV-2 and other respiratory viruses, as well as hepatitis B virus, hepatitis C virus, HIV, and syphilis - Donors were asymptomatic and well for at least 10 days - Serum SARS-CoV-2-specific ELISA antibody titer higher than 1:1000 and a neutralizing antibody titer greater than 40

