# Convalescent plasma as an adjunctive therapy for COVID-19: A single centre experience in Malaysia

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**ABSTRACT**

**Introduction: The coronavirus disease 2019 (COVID-19) pandemic posed a significant and urgent threat to global health and economy. Currently, there is no effective treatment known to alter the course of COVID-19. Convalescent plasma (CP) has been used previously to treat several types of infections during pandemics. The aim of our study is to evaluate the efficacy of CP in the treatment of severe COVID-19 infections at Hospital Sultanah Bahiyah, Kedah, Malaysia.**

**Materials and Methods: A retrospective cross-sectional study of all severe COVID-19 patients who received CP treatment from 1st August 2020 until 31st December 2020 was conducted. Clinical outcomes were compared before and after CP transfusion.**

**Results: Thirty-four patients were enrolled and received CP transfusion during the study period. The most common presenting complaints were fever (64.7%) and cough (58.8%). Fourteen patients showed improvement in oxygen support after CP transfusion. Several laboratory parameters also improved such as increased lymphocyte count (1.48 vs 1.98, p=0.008) and decreased C-reactive protein levels (28.1 vs 10.6, p=0.004), and these were statistically significant. Median time from symptoms onset to CP transfusion was 6 days (range 1-11) while median time from PCR diagnosis to CP transfusion was 5 days (range 1-11). One patient developed urticaria after CP transfusion and no severe adverse events were observed. Two of our patients passed away due to secondary causes.**

**Conclusion: This study showed CP treatment was well tolerated and could potentially prevent progression of COVID-19 to a severe disease if administered early during the viraemic phase. Further evaluation with randomized control trial should be conducted to help ascertain the optimal dose and effectiveness of CP treatment, in correlation with the IgG titer of the donated CP.**

**KEYWORDS:**
*COVID-19, coronavirus, convalescent plasma, antibody, IgG*

## INTRODUCTION

Coronavirus disease 2019 (COVID-19) is defined as an illness caused by a novel coronavirus, now called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It emerged in China in late 2019 from a zoonotic source.[1] The most common transmission modality includes droplet inhalation and contact transmission. Most cases are usually asymptomatic or result in only mild symptomatic disease. However, this infection can progress to a critical illness with hypoxemic respiratory failure requiring prolonged ventilator support in a substantial percentage of susceptible patients.[2] The pathophysiological features of severe COVID-19 are dominated by an acute pneumonic process with extensive chest radiological peripheral opacities; and on autopsy, diffuse alveolar damage, inflammatory infiltrates, and microvascular thromboses are seen.[3]

Severe COVID-19 infection remains a global crisis with limited treatment options. The available antivirals could only confer benefit if administered soon after onset of illness.[4] Until an effective vaccine is developed, convalescent plasma (CP) could be a mode of adjunctive therapy to neutralise the virus and to control the overactive immune response. This was shown to be effective in treatment of various infections, including during the H1N1 influenza virus pandemic.[5] It takes approximately two to three weeks for a normal individual to mount an antibody response against pathogens. It has been postulated that patients with COVID-19 may recover faster by administering virus-neutralising antibodies in the form of CP.[6] Observational studies have shown that CP treatment has an adequate safety profile in patients with COVID-19. Besides, few initial case series suggested that CP treatment is associated with faster clinical recovery and radiological improvement.[7-9] A matched controlled study by Liu et al. also showed that CP treatment improved survival of patients.[10]

To date, multiple observational and small randomized controlled trials have demonstrated that the use of CP in treatment of COVID-19 infection remains uncertain.[11] At the beginning of the present COVID-19 pandemic, CP was transfused in patients who are more critically ill, such as those hospitalized in intensive care units (ICU) and under invasive mechanical ventilation. A randomized controlled trial (RCT) by Li and colleagues, published in August 2020, failed to demonstrate a statistically significant difference in 28-day mortality between CP-treated and standard treatment groups. However, by stratifying disease severity, the researchers observed a statistically significant difference in time to clinical improvement within a 28-day period in the

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group treated with convalescent plasma. This study highlighted that CP must be administered at an early stage of the disease in order to achieve its maximum effect.[12]

An analysis of a cohort of 3082 patients in the United States of America Expanded Access Program found that high-titre CP given less than 72 hours after hospital admission conferred a survival benefit when compared to those receiving CP later in their hospital stay.[13] It is likely that early administration of CP would be able to block viral replication during the initial phase of COVID-19, preventing the activation of inflammatory and coagulative cascade, which is often an irreversible and prominent feature of the advanced stage of disease. Any viral anti-replicative activity of CP at this stage would likely be ineffective.

The aim of our study is to evaluate the efficacy of CP transfusion in COVID-19 infection to prevent progression of illness and to obviate the need of adding immunosuppressive agents and mechanical ventilation.

## MATERIALS AND METHODS

This was a single centre, retrospective cross-sectional study of 34 patients with severe COVID-19 infection who received CP treatment in Hospital Sultanah Bahiyah (HSB) Kedah, Malaysia from 1st August 2020 until 31st December 2020. All the patients were above the age of 12 years and had laboratory-confirmed SARS-CoV-2 infection by real-time reverse-transcription–polymerase chain reaction (RT-PCR) assay of either nasal or oropharyngeal swab.

In HSB, CP transfusion was given to patients with severe COVID-19 infection who had received standard of care yet noted progression of disease (e.g., >50% increase in lung infiltrates within 24-48 hours, respiratory rate more than 30/min, PaO2/FiO2 ratio of less than 300mmHg, oxygen saturation less than 93% on room air, rising CRP but < 80mg/L).

Consent was taken from all the patients prior to CP transfusion. Each patient received one (200-250ml) to two units of CP within a 12-hour interval. Corticosteroids were given to patients with rising CRP >80mg/L and worsening of PaO2/FiO2 ratio, its dose being titrated according to severity of illness. CPs were collected via apheresis method from donors who have recovered and tested positive for COVID-19 IgG, 28 days after onset of COVID-19 infection, using a point-of-care serology test, validated against the immunoassay serology.

Demographic data, clinical, radiological characteristics, co-morbidities, laboratory tests at admission and during hospitalization, treatment and outcome were retrieved from the medical records of patients. All the 34 patients were followed up during their hospitalization until they were discharged or died. Clinical symptoms (fever, cough, sore throat, anosmia, runny nose, shortness of breath, diarrhoea, and headache) and comorbidities (diabetes mellitus (DM), hypertension, chronic kidney disease, cardiovascular disease, respiratory diseases, chronic liver disease and malignancy) were also obtained. Drug treatment (antiviral, antibiotics, corticosteroid, interferon, anticoagulant), mode of oxygen therapy (standard nasal cannula, high flow oxygen, non-invasive ventilation, invasive mechanical ventilation) and need for renal replacement therapy were also collected and assessed.

Data were analysed using Statistical Package for Social Sciences software (version 21.0). Categorical data were expressed as frequencies and percentages. Wilcoxon signed-rank test were used to compare dependent variables and p value <0.05 was considered statistically significant.

## RESULTS

*Patient characteristics*

There were 34 severe COVID-19 patients who were enrolled and received CP transfusion from 1st August 2020 until 31st December 2020. Of these, 22 were males and 12 were females with median age of 53 years old (range 35-76). The most common symptom was fever in 22 patients (64.7%), cough in 20 patients (58.8%), shortness of breath in nine patients (26.5%) and sore throat in 8 patients (23.5%). Gastrointestinal symptoms were only reported in one patient. Most of the patients had comorbidities, majority had DM (41.2%), followed by hypertension (38.2%), cardiovascular disease (17.6%) and chronic lung disease (5.9%) (Table I).

*Treatment and clinical outcome*

Most of the patients received off-label therapy of antiviral, interferon, and anticoagulant before the enrollment. These patients were given one or two units of CP transfusion. More than two thirds (23/34) of patients received CP transfusion within seven days from symptoms onset and PCR diagnosis with median time of 5 days (range 1-11) from PCR diagnosis, median time of 6 days (range 1-11) from symptoms onset, median CRP of 28.1 mg/L (normal value: 0-5 mg/L) and median interleukin-6 (IL-6) level of 18 pg/mL (normal value: 0-4.4 pg/mL). Among these patients who received CP transfusion, 13 of them received corticosteroids treatment post transfusion with median time of two days (range 1-4 days).

Prior to CP transfusion, three patients were on mechanical ventilation, one on non-invasive ventilation (NIV), 20 patients received high flow oxygen while ten patients received standard nasal cannula oxygenation. Our patients achieved improvement in oxygen support after CP treatment in which 14 patients were able to wean down from mechanical ventilation/NIV/high flow oxygen to standard nasal cannula oxygenation/room air (Table III). Six patients had marked improvement of oxygen support from high flow supplemental oxygen to standard nasal cannula oxygenation within 24 hours after CP transfusion.

Our study showed improvement in absolute lymphocyte count (1.48 vs 1.98, p=0.008) and CRP levels (28.1 vs 10.6, p=0.004) post CP transfusions, which were statistically significant. The median absolute lymphocyte counts were 1.48 $x10^3$ prior to transfusion, and the counts repopulated after CP transfusion. Interestingly, the CRP levels continued to rise one to two days post-CP transfusion before it fell steadily towards normal level (Figure 1). There were two

**Table I: Demographic data and clinical presentation of severe COVID-19 patients who received convalescent plasma treatment**

| Characteristic | Value |
|---|---|
| Median age, years (range) | 53 (35-76) |
| Gender | |
| Male, n(%) | 22 (64.7) |
| Female, n(%) | 12 (35.3) |
| Co-morbidities | |
| Diabetes mellitus, n(%) | 14 (41.2) |
| Hypertension, n(%) | 13 (38 |
| Chronic kidney disease, n(%) | 0 (0) |
| Cardiovascular disease, n(%) | 6 (17.6) |
| Chronic lung disease, n(%) | 2 (5.9) |
| Malignancy, n(%) | 0 (0) |
| Presenting complaint | |
| Fever, n(%) | 22 (64.7) |
| Cough, n(%) | 20 (58.8) |
| Sorethroat, n(%) | 8 (23.5) |
| Anosmia, n(%) | 3 (8.8) |
| Runny nose, n(%) | 6 (17.6) |
| Shortness of breath, n(%) | 9 (26.5) |
| Diarrhoea, n(%) | 1 (2.9) |
| Headache, n(%) | 2 (5.9) |
| Treatment | |
| Antiviral, n(%) | 34 (100) |
| Interferon, n(%) | 24 (70.6) |
| Anticoagulant, n(%) | 34 (100 |
| Corticosteroids, n(%) | 13 (38.2) |
| Median time between PCR diagnosis and CP transfusion, days (range) | 5 (1-11) |
| Median time between symptoms onset and CP transfusion, days (range) | 6 (1-11) |
| Median duration of ICU stays, days (range) | 7 (0-34) |
| Outcome | |
| Alive, n(%) | 32 (94.1) |
| Death, n(%) | 2 (5.9) |

**Table II: Comparison of median laboratory parameters before and after CP transfusion**

| Variables | Before CP transfusion | After CP* transfusion | p value |
|---|---|---|---|
| Laboratory results | | | |
| Absolute lymphocyte count, 103/μL (range) | 1.48 (0.44-2.86) | 1.98 (0.43-4) | 0.008 |
| Ferritin, ng/mL (range) | 459.5 (34-2578) | 501 (45-1861) | 0.274 |
| C-reactive protein, mg/L (range) | 28.1 (3.61-129.62) | 10.6 (0.39-110.7) | 0.004 |
| Procalcitonin, ng/mL (range) | 0.04 (0.01-9.33) | 0.02 (0.01-3.3) | 0.033 |
| D-dimer, μg/mL (range) | 0.53 (0.27-3.62) | 0.76 (0.27-2.3) | 0.09 |
| IL-6 | 18 (2.7-692.2) | - | - |

*Day 7 post CP transfusion

**Table III: Comparison of oxygen requirement before and after CP transfusion**

| Variables | Before CP transfusion | After CP* transfusion |
|---|---|---|
| Oxygen supplementation | | |
| Room air | 0 | 15 |
| Standard nasal cannula | 10 | 9 |
| High flow oxygen | 20 | 8 |
| Non-invasive ventilation | 1 | 0 |
| Mechanical ventilation | 3 | 1 |

*Day7 post CP transfusion

patients who showed an increment in CRP levels after day seven due to superimposed bacterial pneumonia. The other inflammatory markers such as ferritin and D-dimer showed inconsistent response to CP treatment (Table II). Retrospectively, all stored serum were subjected to qualitative immunoassay analysis (Architect SARS-CoV2 IgG), where only three out of the 34 patients had SARS-Cov2 IgG detected prior to CP transfusion.

Thirty-two patients were discharged well from hospital, but the two others died. The two deaths were each due to hypoxic ischemic encephalopathy after a cardiac event, and a superimposed bacterial infection, respectively.

## DISCUSSION

This retrospective observational study explored the feasibility and efficacy of CP therapy in viraemic phase of COVID-19

infection. Majority of enrolled severe COVID-19 patients had significant clinical and laboratory improvement after CP transfusion. All investigated patients achieved improvement in oxygen saturation, lymphocyte counts and CRP after CP transfusion in our study. After CP transfusion, we noticed that there was a sharp drop in CRP concentration, but ferritin remained elevated for a few days before decreasing in trend. This is compatible with previous studies which showed that ferritin decreased at a slower rate compared to CRP after an episode of acute infection or inflammation.[14-15]

Both the ConCovid trial by Netherlands and PLACID Trial by India demonstrated 79% and 83% of patients had various titers of baseline neutralizing antibody on enrollment. This raises the question on the value of CP as a therapy of COVID-19 infection.[16,17] Nevertheless, in resource limited countries where highly effective antivirals are not easily available or affordable, CP therapy could be a substitution of antivirals during early viraemic phase of the disease.

One of the key factors that determine the efficacy of CP therapy in COVID-19 is the timing of CP transfusion. A previous study has shown that a better treatment outcome was observed among SARS patients who were given CP before 14 days post onset of illness (58.3% vs 15.6%; p-value < 0.01), highlighting the importance of timely rescue therapy.[18] Majority of our patients received CP transfusion within seven days from symptoms onset and PCR diagnosis. A large multicenter observational study by Mayo Clinic showed that early administration of CP associated with reduction in 7-day mortality and the result was most pronounced in patients administered with CP therapy within 3 days of diagnosis as compared with patients who received treatment 4 or more days after diagnosis (8.7% vs 11.9%, p <0.001).[19] Another RCT conducted by Libster and colleagues showed that older individuals with COVID-19 who were identified in the outpatient setting within 48 hours of symptom onset and who received CP transfusion within 72 hours of symptom onset had a 48% reduced risk of progression to severe respiratory disease.[20] The case fatality rate (CFR) in our study was 5.9% (2/34), which was comparable to the CFRs in SARS infection treated with CP transfusion, which varied from 0-12.5%.[21]

Studies have shown that CRP > 97mg/L and IL-6 >80pg/mL were associated with higher risk of respiratory failure, potentially requiring mechanical ventilation. In this scenario, alternative therapies, such as corticosteroids or IL-6 antagonist need to be considered.[22] In our study, 13 patients received corticosteroids treatment where the dosage ranged from 0.5mg-1.0mg/kg/day of methylprednisolone for 5 days after CP transfusion in view of no clinical, biochemical, and radiological improvements. Possible explanation for this would be that these 13 patients did not receive convalescent plasma with high titres of neutralising antibodies as we were unable to measure the titres of neutralising antibodies in the convalescent plasma that were being given to these patients. CP transfusion is relatively safe and rarely reported to cause adverse reactions. Our findings reported only one case of allergic reaction after being given CP. Although rare, plasma transfusion has been associated with a few complications, including transfusion-related infections and transfusion related acute lung injury (TRALI). TRALI had been previously reported in an Ebola virus disease woman who received convalescent plasma therapy.[23] TRALI could pose a significant morbidity, especially in critically ill patients with COVID-19 who are experiencing significant pulmonary injury.[24] CP therapy is also associated with theoretical risk of antibody-dependent infection enhancement, which typically occurs at subneutralising concentrations, which could further suppress innate antiviral systems, allowing intracellular growth of the virus.[25-26] Ideally, only donors with high titres of neutralizing COVID-19 IgG antibodies (> 1:160) should be recruited to ensure treatment efficacy.[27] Given that neutralization assays for SARS-CoV2 neutralising antibody is not readily available, the best available method is to predict the high titer of neutralising antibody using commercial serology tests. Current data shows moderate correlation between Architect SARS-CoV2 IgG and neutralizing antibody with sensitivity of 76% in predicting antibody titer ≥1:160 when the signal cut-off is above 4.57.[28-29] Observation by investigators in China showed that middle age and elderly patients had higher level of neutralizing antibodies, and the antibody levels correlate with CRP, which is a marker of severity of COVID-19 infection.[30] Selection criteria for CP donors should include the middle age group or the fit elderly who have recovered from COVID-19 pneumonia, preferable those who required oxygen therapy.

There were several limitations in the present study. Firstly, the number of patients described is small and lacks a control group, which limits the efficacy assessment of CP therapy. Secondly, most of our patients received antiviral and interferon treatment alongside CP transfusion. We could not exclude that our observation could be the end result of the antiviral effect. Furthermore, our study did not measure the serum neutralising antibody titers of SARS-CoV-2 of our patients before and after CP transfusion. Lastly, one study has demonstrated that higher IgG levels against spike protein S1 of SARS-CoV-2 in CP may confer improved outcomes to patients with COVID-19.[31] However, this was not done in our study prior to CP transfusion. Hence, the efficacy of CP therapy in our group of patients may be varied and heterogeneous.

## CONCLUSION

In our study of 34 patients with severe COVID-19, administration of CP was well tolerated, and we believe improved the clinical outcome. The optimization of CP transfusion treatment, i.e., the dose, time of administration, and established efficacy, as a potential therapy for patients with severe COVID-19 infections needs further evaluation with randomized control trials to provide a better understanding of the treatment outcomes.

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**DECLARATION OF CONFLICTING INTEREST**

The authors declare that there is no conflict of interest.

**APPROVAL**

Ethical approval of this study was obtained from Malaysia Medical Research & Ethics Committee (NMRR-20-2808-57126).

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