*Case Report*

# Convalescent Plasma Therapy: The Early Use in Moderate to Severe COVID-19 Patients in Hospitals with Limited Resources

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### ABSTRACT

*COVID-19 cases in Indonesia in the period of June-July 2021 showed a catastrophic spike. During this period, a recently discovered variant, the delta variant, appeared to be one of the sources of COVID-19 infection. Treatment modalities are limited due to reduced stock of drugs. A case of a 63-year-old man has been reported, with a history of having been vaccinated with two doses of Sinovac, experiencing moderate-to-severe symptoms of COVID-19 infection then given convalescent plasma therapy since his initial admission to the hospital. Three days after being given convalescent plasma therapy, the improvement was noticeable. Shortness of breath, cough, fever, and weakness were less complained. On the seventh day the patient fully recovered and got discharged. Convalescent plasma therapy was e ective in early stage and was able to improve outcomes. Indonesia needs su cient stocks of convalescent plasma as a therapy to overcome the limitations of medicines.*

**Keywords**: *convalescent plasma therapy, COVID-19,infectious disease,health,*

### ABSTRAK

*Kasus COVID-19 di Indonesia pada periode Juni-Juli 2021 menunjukkan lonjakan katastropik. Selama periode ini, varian yang baru ditemukan, varian delta, tampaknya menjadi salah satu sumber infeksi COVID-19. Modalitas pengobatan terbatas karena berkurangnya stok obat. Dilaporkan kasus seorang laki-laki berusia 63 tahun, dengan riwayat pernah divaksinasi dengan dua dosis Sinovac, mengalami gejala infeksi COVID-19 sedang sampai berat kemudian diberikan terapi plasma konvalesen sejak pertama kali masuk rumah sakit. Tiga hari setelah diberikan terapi plasma konvalesen, terlihat perbaikan pada pasien. Sesak nafas, batuk, demam, dan lemas berkurang. Pada hari ketujuh pasien sembuh total dan diperbolehkan pulang. Terapi plasma konvalesen efektif pada tahap awal dan mampu meningkatkan hasil. Indonesia membutuhkan stok plasma konvalesen yang cukup sebagai terapi untuk mengatasi keterbatasan obat-obatan*

**Kata kunci:** *terapi plasma konvalens, COVID-19, penyakit infeksi, kesehatan*

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## INTRODUCTION

COVID-19 has turned out to be a global pandemic, with new variants currently emerging causing a spike in cases. In India, it was reported that since April 2021, there has been a massive escalation of new cases caused by delta variant, which has led to an increase of incidences, reaching more than 100,000 new cases with new deaths hitting almost 1000 cases per day. In Indonesia during June-July 2021, there also was a huge rise in COVID-19 cases and a delta variant was seemingly detected. New cases in Indonesia in mid-July 2021 have reached more than 40,000 cases per day with death cases reaching 1000 cases per day. Vaccination had been done to 5.5% Indonesian population per July 2021. Through the new wave of COVID-19 delta variant, Indonesia reported an average 919 deaths within first half of July 2021, statistically it is the same peak death rate in India at mid-May about 3.32 deaths per million people per day. Despite Indonesia new cases reached 56767 cases on July, it has low test positivity rate, 26%, that will mislead to many undiscovered cases.[1]

Many researches had been held across the globe to find the definite therapy for COVID-19. The therapeutic modalities in the COVID-19 treatment guidelines include symptomatic drugs, antivirals, steroids, and anti-IL6 blockers. On the other hand, there is still no guideline available in conduct the administration of convalescent plasma. IgG and IgM antibodies collected from patients who have been recovered from COVID-19, later it will be transfused to COVID-19 patient. The target therapy is increasing the chance to obtain neutralizing antibodies (Nab) against the virus.[2] Several studies have stated that convalescent plasma administration gives no significant result, otherwise, other studies and case reports announced that convalescent plasma is significant in moderate cases and should be given early.

In the following, we report a case of early administration of convalescent plasma therapy due to the limited availability drugs.
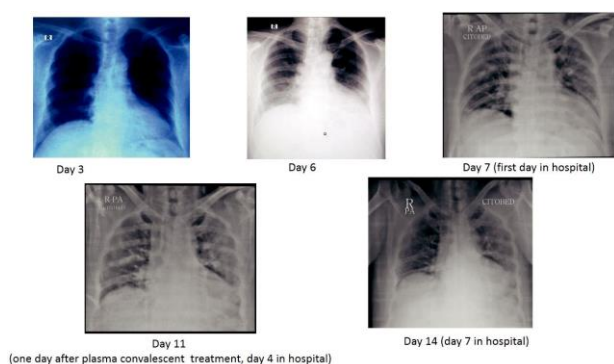
## CASE

A man, age 63, initially complained of fever accompanied by sore throat. The patient then complained of nausea, vomiting, and diarrhea. The COVID-19 antigen test on the second day showed a positive result. On the third day, the patient had a cough and also complained of shortness of breath. Oxygen level on the third day of self-examination showed 97-98% room air, on the fourth day through the sixth day, the saturation slowly dropped from 93-94% to eventually become 88-91% along with worsening body temperature, cough and shortness of breath. The vital signs on admission: BP 120/80, pulse 110/minute, respiration rate 24 times/minute, body temperature 38.8°C, $O_2$ Sat 92-93% free air, then given oxygen support with a 6 lpm simple mask and resulted $O_2$ Sat 97-98 %. The patient had no previous history of diabetes mellitus, heart disease, and hypertension.

The patient's medication history since the first day of symptoms was only symptomatic drugs plus Azithromycin 500 mg QD, Rebamipide 100 mg TID, Dexamethasone tablets 0.5 mg TID on the fourth day to the sixth day, and N-Acetylcysteine tablets 200 mg TID. The patient has been vaccinated with two doses of Sinovac vaccine. Laboratory examinations showed Hb 14.2 g/dl, lymphocyte 11%, neutrophil 82%, thrombocyte 171.000, leucocyte 6.260 u/L. AST 35u/L, ALT 37 u/L; blood sugar 113 mg/dl,urea 29.4 mg / dL, creatinine 1.16 mg / dL, C-Reactive protein (CRP) 20 mg/dl;IL-6 58.2 pg/ml; D-dimer < 0.2 mg/l. Blood gas analysis showed moderate to severe hypoxia; pH 7.45, pCO2 32, pO2 94, HCO3 22.2, BE - 1.0, $SaO_2$ 99%, P/F ratio 235 (see Table 1). Chest x ray in ER showed ground glass opacity in both lung fields giving the impression of pneumonia. PCR test showed positive result.

**Table 1**. Initial Laboratory Result in Emergency Room and Day 6 in Hospital

| Variable | | Result day 1 | Result day 6 | Variable | | Result day 1 | Result day 6 | Variable | | Result day 1 | Result day 6 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Hb | g/dL | 14,2 | 12,8 | D-dimer | mg/L | <0,2 | <0,2 | Blood gas analysis | | | |
| WBC | 10^3/uL | 6,26 | 6,16 | Blood glucose | mg/dL | 113 | 110 | pH | | 7,45 | 7,4 |
| RBC | 10^6/uL | 4,42 | 4,13 | AST | U/L | 35 | 22 | pCO2 | mmHg | 32 | 35 |
| HCT | % | 43 | 38 | ALT | U/L | 37 | 20 | pO2 | mmHg | 94 | 88 |
| PLT | 10^3/UL | 171 | 235 | Urea | mg/dL | 29,4 | 20 | HCO3 | mmol/L | 22,2 | 25 |
| MCV | fL | 89,4 | 88 | Serum Creatinin | mg/dL | 1,16 | 1,1 | BE | mmol/L | -1 | -1 |
| MCH | pg | 29,5 | 28 | Electrolycte serum | | | | SO2 | % | 98 | 98% |
| MCHC | g/dL | 33 | 32 | Na | mmol/l | 132 | 131 | P/F Ratio | | 235 | 440 |
| Limfosit | % | 12 | 7 | K | mmol/l | 3,49 | 3,8 | FiO2 | | 40% | 20% |
| Monosit | % | 5,8 | 5 | Cl | mmol/l | 102,9 | 103 | | | | |
| Eosinofil | % | 0,1 | 0,1 | IL6 | pg/L | 58,2 | | | | | |
| Basofi | % | 0,1 | 0,1 | CRP | mg/l | 20 | 10 | | | | |
| Neutrofil | % | 82 | 88 | | | | | | | | |

On the first day of care, The patient received Favirapir 1600 mg BID, intravenous Dexamethasone 6 mg QD, and symptomatic drugs. On the second day, antiviral drugs were no longer available, so the patient was given convalescent plasma therapy. Three days after convalescent plasma therapy, the breathing di culty and cough started to get resolved. The chest x-ray evaluastion was done that day. On the sixth day, the patient had no complaints, chest x-ray and laboratory examination was evaluated again (see Figure 1). The seventh day of treatment at the hospital, the patient was discharged with oxygen saturation 97-98% free air.



**Figure 1.** Chest X-Ray progression

## DISCUSSION

COVID-19 has expanded globally. WHO recorded 190,770,507 confirmed cases of COVID-19 with 4,095,924 deaths in the world as of July 20, 2021. Meanwhile, Indonesia ever announced 2,877,476 confirmed cases of COVID-19 with 73,582 deaths and 2,261,658 patients who recovered from COVID-19[3]. Thus far, there is no yet definitive therapy for COVID-19. The management of COVID-19 currently focuses more on general supportive therapy and treatment of critical conditions.[4]

Numerous researches have been conducted to examine the therapeutic e ect of existing drugs on the severity of COVID-19, where previously these drugs were used to treat other diseases. Some drugs do not have a significant therapeutic e ect on the progression of COVID-19. The idea of passive immunization using convalescent plasma therapy emerged as a therapeutic option for COVID-19. Convalescent plasma is processed from the blood of donors who have been infected with a specific pathogen, such as SARS-CoV-2, whose plasma has formed humoral immunity and specific antibodies against that pathogen. This blood plasma also contains anti-inflammatory

cytokines, blood clotting factors, and other neutralizing antibodies (NABs) that are beneficial for regulating recipient immunomodulation. A study in China involving 10 patients with severe COVID-19 showed a decrease in viral load and clinically significant improvement in patients transfused with convalescent plasma concurrently with antiviral and other supportive therapy.[5] Another study conducted in Indonesia on 5 moderate COVID-19 patients and 5 severe COVID-19 patients manifested clinical improvement after three convalescent plasma transfusions at a dose of 3 ml/kg recipient's body weight at 2-days interval. Convalescent plasma therapy is more e ective when given early in disease progression. [6-10]

The main mechanism of the pathogenesis of COVID-19 is the occurrence of SARS-CoV-2 replication in the early phase and the occurrence of immune system dysregulation or inflammatory response to SARS-CoV-2, which results in tissue damage which occurs in the late phase. Based on this comprehension, the NIH recommends that COVID-19 treatment aims to destroy SARS-CoV-2 directly in the early stages, while administration of immunosuppressants or anti-inflammatory therapy will provide better e cacy if given in the later stages of COVID-19. The severity of COVID-19 will a ect the e ect of the therapy; inpatients without oxygen supplementation are not recommended to receive dexamethasone or other corticosteroids, in hospitalized patients with supplemental oxygen, remdesivir and/or dexamethasone may be considered [11]. Patients with a very rapid increase in oxygen demand may be given Baricitinib or Tocilizumab. Convalescent plasma therapy has not yet been included in the NIH recommendations.[12] The Food and Drug Administration (FDA) once issued a recommendation regarding the provision of convalescent plasma therapy in Emergency Use Authorization (EUA), which was then renewed again in February 2021. The FDA does not recommend giving convalescent plasma therapy with low antibody titers. This therapy is also not recommended in mechanically ventilated patients except in clinical trials. However, several observational studies have demonstrated a favorable therapeutic response to the use of high-titer convalescent plasma in patients with primary and secondary humoral immunodeficiency, including patients with haematological malignancies, agammaglobulinemia, and organ transplants.[13-16]

The current guidelines of COVID-19 treatments are formulated based on the recommendations of the WHO, CDC or medical organizations in each country. The University Hospital Birmingham Foundation Trust (UHBFT) in the UK developed the COVID-19 Quick Glance Guide in adults, which was updated in February 2021. UHBFT recommends general therapy such as empiric antibiotics for bacterial co-infection, thromboplophylaxis, fluid administration, antiviral remdesivir, single dose tocilizumab, and administration of dexamethasone. Dexamethasone can be given 6 mg orally or intravenously in patients who require oxygen supplementation or are on a ventilator, with the administration of gastroprotectant drugs. UHBFT also recommends supplemental oxygen and the proning position [17]. The Australian COVID-19 treatment guidelines do not recommend convalescent plasma therapy as standard COVID-19 therapy in pediatric patients, adolescents, adults, pregnant and lactating women, geriatrics and palliative patients, due to the finding that convalescent plasma therapy did not provide a more prominent therapeutic e ect than standard COVID-19 therapy.[18]

Guidelines for the management of COVID-19 in Indonesia have undergone various emendations along with the emergence of new studies during this pandemic. Five professional organizations consisting of the Indonesian Pulmonologist Association/*Perhimpunan Dokter Paru Indonesia* (PDPI), the Indonesian Cardiologist Association/ *Perhimpunan Dokter Spesialis Kardiovaskular Indonesia* (PERKI), the Indonesian Internist Association/P*erhimpunan Dokter Penyakit Dalam Indonesia* (PAPDI), the Indonesian Association of Anesthesiologists and Intensive Therapists/ *Perhimpunan Dokter Anestesi dan Terapi Intensif Indonesia* (PERDATIN), and the Indonesian Pediatrician Association/ *Ikatan Dokter Spesialis Anak Indonesia* (IDAI) issued a recently revised protocol for the management of COVID-19 on July

14th, 2021. The therapy given is still adjusted to the severity of COVID-19. Recommendations are given in the form of supportive therapy, oxygen supplementation as needed, proning position, administration of pharmacological therapy in the form of: administration of vitamin C, vitamin B, vitamin D, antiviral favipiravir or remdesivir, dexamethasone or other corticosteroids in severe cases and requiring oxygen therapy, anti-interleukin 6 such as Tocilizumab or Sarilumab especially in severe or critically ill patients, as well as LMWH or UFH anticoagulants. Other therapies can also be given such as antibiotics for cases with bacterial coinfection, as well as convalescent plasma therapy. By far, convalescent plasma therapy has not been included in the main COVID-19 therapeutic guidelines because it is still in the clinical trial stage.[19]

A study was conducted in the United States involving 3082 COVID-19 patients. The patient was given a convalescent plasma transfusion with three different titers. The signal-to-cut-off ratio of anti-SARS-CoV-2 IgG antibody was categorized into: low titer (<4.62), medium titer (4.62-18.45) and high titer (>18.45). The study evaluated the mortality rate of patients after 30 days of convalescent plasma administration, discovered 115 deaths from 515 patients (22.3%) in the high titer group, 549 deaths from 2006 patients (27.4%) in the moderate titer group, and 166 deaths from 561 patients (29.6%) in the low titer group. In patients not on mechanical ventilation, administration of low-titer convalescent plasma had a higher risk of death than administration of high-titer convalescent plasma (relative risk 0.66; 95% CI 0.48 or 0.91). Convalescent plasma therapy had no effect on the risk of death in patients on mechanical ventilation (relative risk 1.02; 95% CI 0.78 to 1.32). Patients who received convalescent plasma therapy within three days after being COVID-19-confirmed had a lower risk of mortality than patients who received transfusions at a later stage.[20] With some research data showing a fairly good response to high-titer convalescent plasma therapy, it can be considered as one of the recommendations for COVID-19 therapy.[21-25]

## CONCLUSION

The administration of convalescent plasma at early stage of moderate-to-severe condition offers ameliorate outcome. Therefore, in the midst of multiplying cases of COVID-19 in Indonesia as the consequence of new variants, it is considered principal to prepare convalescent plasma stocks as one of treatment options in addition to other medicines.

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## CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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