

Convalescent Plasma Therapy in Severe COVID-19 Patients: Retrospective Study

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Abstract: *Background:* Covid-19 is infectious disease that caused by SARS-COV2 Virus. There is no definitive treatment for Covid-19 until now. Convalescent plasma therapy is one of therapy that considered to provide good outcome for Covid-19 patient. In developing country, convalescent plasma is difficult to obtain because there are requirements for donors. There is a time gap between patient's admission day and first day convalescent plasma administered to patient. The purpose of this article is to explore the association between timing of convalescent plasma therapy with outcome in severe covid-19 patient. *Method:* This study is retrospective study using secondary data of patient's medical record at Wangaya Hospital, Denpasar, between September 2020 and March 2021. Inclusion criteria is set in this study, include severe Covid-19 patient that had administered convalescent plasma therapy. *Result:* 32 sample was obtained in this study. Data was analyzed with Kolmogorov smirnov normality test, results is not normally distributed ($p=0.003$). Fisher exact analysis was performed. We found that there is no significant difference in outcome in severe Covid-19 patient that was given convalescent plasma before and after 3 days admission to hospital ($p=1.000$, CI 95%). We also found that there is no significant difference in outcome in severe Covid-19 patient that was given convalescent plasma before and after 5 days admission to hospital ($p=1.000$, CI 95%). *Conclusion:* There is no significant difference between timing of convalescent plasma therapy and outcome in severe Covid-19 patient. However, further research are needed to explain the effect of convalescent plasma therapy in severe Covid-19 patient.

Keywords: Convalescent plasma therapy, COVID-19, SARS-Cov2

1. Background

Covid-19 has become pandemic all over the world. First case of Covid 19 was found in Wuhan, China, in 2019. Until now, there is no definitive treatment for Covid-19. Many methods is tested to fight Covid-19, for example convalescent plasma therapy, stem cell therapy, and others. Convalescent plasma therapy is one of therapy which is expected can give good outcome for Covid-19 patient, especially in severe Covid-19 patient.

Convalescent plasma therapy was derived from blood donor of Covid-19 survivor. Convalescent plasma consists of neutralized antibodies, albumin, complement, coagulation factor and antithrombotic factor. Neutralized antibodies is expected to give some benefit, for example decrease viral load, decrease inflammation, decrease respiratory demand, and increase radiological improvement to severe Covid-19 patient.

There are several requirement to get convalescent plasma. Donor must have optimal antibody titer ≥ 160 , have recovered from Covid-19 at least 14 days following resolution of symptoms. Additional requirement for plasma donor are body weight ≥ 55 kg, 18-60 years old, man preferred, never got blood transfusion in last 6 months. Donors must fulfill all the requirement before eligible to donor their blood. In developing country, it is difficult to get donor that meet the requirement, consequently there is delay to get convalescent plasma and also delay the administration convalescent plasma to the patient.

There are procedures before we get convalescent plasma, administration convalescent plasma is also delayed. Because of that, this study will explore between first administration

of convalescent plasma and patient's outcome if it affects the outcome.

2. Method

This was retrospective study design using secondary data of patient's medical record. This study was placed at Wangaya Hospital, Denpasar in April 2021 to May 2021. Sample was obtained from patient that administered to Covid-19 intensive care unit (ICU) in September 2020 to March 2021. Inclusion criteria of this study was severe covid-19 patient, confirmed by RT-PCR who were hospitalized in intensive care unit in September 2020 to March 2021 and got convalescent plasma therapy during hospitalized.

Patient who did not get convalescent plasma therapy and patient with incomplete medical record were excluded from this study. time when patient was hospitalized to ICU Covid-19, first time convalescent plasma was administered, and outcome of patient were collected from medical records.

Statistical analysis was performed with SPSS 25.0. Data were expressed as mean. Data will be done with Kolmogorov-smirnov distribution test. If normally distributed, t-test dependent was used to analyse data. If data is not normally distribution, association analysis will be processed by *chi-square* association if there is no low expected count data. If there is low expected count data, the analyze will be done by *fisher-exact* test.

3. Result

Table 1: Baseline Characteristic of Covid-19 Patient

Characteristic	N
Age n (%)	
18- 60 years	8 (25)
> 60 years	24 (75)
Gender, n (%)	
Male	28 (87.5)
Female	4 (12.5)
Comorbidity, n (%)	
With comorbidity	23 (71.88)
No comorbidity	9 (28.12)
Time plasma administered mean (min-max)	6.06 (0-21)d
Outcome	
Improve clinical status	23 (71.88)
Passed away	9 (28.12)

Baseline characteristic of patient in this study can be seen in table 1. Total subjects of 32 that hospitalized in September 2020 to March 2021 was in this study. Majority of subjects in age was over 60 years, with 24 subjects (75%). 28 subjects (87.5%) were male and 4 subjects (12.5%) were female. Based on comorbidity in patient, there were 23 subjects (71.88%) with comorbidity and 9 (28.12%) with no comorbidity. All subjects were administered with convalescent plasma. Mean time difference between first day convalescent plasma was administered and the time patient was hospitalized to is 6.06 day.

Table 2: Fisher-exact Analysis of convalescent administration with outcome

Variable	Correlation coefficient	p value
Within and after 3 days	1.000	p< 0.05
Within and after 5 days	1.000	P < 0.05

Data were analysed with Kolmogorov-smirnov test to obtain normality of data. Data of this study were not normally distributed $p = 0.003$ ($p < 0.05$, CI 95%). Then, there were low expected count data, so data were tested with *fisher-exact* test to obtain the association. On association test we found no significant difference between administration convalescent plasma before and after 3 days admission to ICU Covid-19 and patient's outcome ($p=1.000$, $p < 0.05$, CI 95%). We also found that there is no significant difference between administration convalescent plasma before and after 5 days admission to ICU Covid-19 and patient's outcome ($p=1.000$, $p < 0.05$, CI 95%). Both data were tested with *Fisher-exact* association test. The test can be seen in table 3.

4. Discussion

Convalescent plasma therapy has become one of methods that is used to treat Covid-19 patient, with hope to improve clinical status of Covid-19 patient. Convalescent plasma contains of neutralizing antibody. This antibody is expected to give an improvement in clinical status in Covid-19 patient.

Mechanism of neutralizing antibody is bind with SARS-Cov2. It binds with spike 1 receptor binding protein (S1-RBD), S1-N-terminal domain, and S2 which inhibit the virus enters the host cell. This antibody also inhibits the replication of virus. Based on Tian, et al. study, there is no competition between antibody and Angiotensin Converting

Enzyme-2 (ACE-2) receptor to bind with virus. The amount of neutralizing antibody is different for each person. Approximately 30% people post Covid-19 infection did not have high titer of neutralizing antibody.

Other than neutralizing antibody, there are other antibodies, *Immunoglobulin M* (IgM) and *Immunoglobulin G* (IgG). These antibodies also bind with virus, but these antibodies are helpful in prophylaxis effect and improvement of recovery.

Study about convalescent study is still limited. A case study was conducted by ShenCG. Et al. There were 5 subjects that grouped in severe Covid-19 patients. All of the subject were treated with convalescent plasma therapy, approximately 10-22 days after hospitalized. Outcome was found no one of subjects that had improved clinical status after 28 days. 3 patients were discharged after approximately 50 days of inpatient care. 2 patients still treated in hospital when observation was completed.

A meta-analysis study was conducted in England about convalescent plasma therapy, called RECOVERY STUDY. This study had large sample, 11558 subjects that is divided in 2 group, convalescent plasma therapy group and control group. There is no differences in 28 days mortality between convalescent plasma therapy group and control group ($p=0.95$, CI 95%, RR=1.00).

There were different results in another study that was conducted by Gonzalez ES. et al. Aim of this study was to explore the effect of convalescent plasma if it is given before 3 days, 3 – 7 days, and after 7 days. In those study, there is significant difference between convalescent plasma administration within 3 days admission was associated with decrease in 28-day mortality ($p < 0.001$). In line with another study that was conducted by Duan K. et al. There were different outcome with convalescent plasma administration before 14 days onset of symptom than convalescent plasma administration after 14 days ($p < 0.01$).

There are many factors that responsible in patient Covid-19 outcome with convalescent plasma therapy. Antibody works and binds to virus specifically. Now, SARS-Cov2 are known to have mutated. Some variant of virus have been detected, for example Coronavirus B1.1.7, Coronavirus B1.3.51, Coronavirus P1, and etc. Difference in results in some studies may caused by mutation of the virus. Antibody could not bind with virus because the virus have changed their structure so it cannot be identified by antibody.

5. Conclusion

Covid-19 have become problem all over the world. Some treatment modalities have been tested to cure Covid-19 infection. Convalescent plasma therapy is one of modalities that is believed can give a good outcome in Covid-19 patient. Neutralized antibody plays a role in decreasing inflammation caused by Covid-19. Difficulty of getting donor for convalescent plasma affect time of administration convalescent plasma to patient. In This study we found that there is no association between administration convalescent plasma before and after 3 days since hospitalized in ICU Covid-19 and outcome in severe Covid-19 patient. And we

also found that there is no association between administration convalescent plasma before and after 5 days since hospitalized in ICU Covid-19 and outcome in severe Covid-19 patient. However, need further studies to explain the effect of convalescent plasma therapy in Covid-19 patient, especially in severe Covid-19 patient.

6. Ethical Clearance

This study was approved by ethical committee in Wangaya Regional General Hospital, Denpasar, Bali

7. Conflict of Interest

There is no conflict of interest in this study.

8. Author Contribution Statement

All of author contributed equally in this study.

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