Convalescent Plasma Treatment for Moderate to Critical Ill COVID-19 Patients – A Safe but Futile Treatment: A Non-Randomized Comparative Study

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ABSTRACT

Background: In a number of cases of viral infection, convalescent plasma therapy has been effective. Reportedly, the use of convalescent plasma as a therapy for COVID-19 patients with severe and life-threatening disorders is beneficial at this time. This study aims to assess the effectiveness and safety of convalescent plasma transfusions in hospitalized COVID-19 patients.

Subjects and Method: This was a clinical trial employing a non-randomized comparative study. A historical control group (21 samples) and convalescent plasma transfusions (21 samples) was selected consecutively from hospitalized Covid-19 patients between May 6th, 2020 and May 6th, 2021 at Dr. Moewardi General Hospital. We assessed and quantified viral clearance in the laboratory. Statistical analysis is performed in SPSS version 20.0.

Results: Plasma was taken from fifteen convalescent donors. In the plasma convalescent treatment group, there was a statistically significant difference between outcome and severity degree (p = 0.005). In addition, there was a substantial discrepancy between the result group and the control group (p 0.005). Significant differences in post-treatment NLR between the control and treatment groups (p 0.005). In addition, there were statistically significant differences between the control and treatment groups in post-treatment hsCRP levels (p 0.005). In addition, there were statistically significant differences (p 0.005) between all groups' inflammatory markers and outcomes.

Conclusion: Using convalescent plasma to treat patients with COVID-19 is a rather safe practice. Our analysis demonstrated that the administration of convalescent plasma did not enhance survival or clinical outcomes for COVID-19 patients with moderate to severe disease.

Keywords: COVID-19, convalescent therapy, critical ill

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BACKGROUND

Coronavirus Disease 2019 (Covid-19) is an infection of the respiratory tract caused by the Sars-CoV-2 virus, with an average incubation time of 5-6 days and a maximum incubation duration of 14 days. fever, cough, and shortness of breath are the symptoms. Covid-19 has the potential to cause pneumonia, acute respiratory syndrome, renal failure, and even death in severe cases. Wuhan, China announced its first case of coronavirus on December 31, 2019. There were other reports of fatalities and the disease's spread beyond China. The World Health Organization (WHO) named Covid-19 a Public Health Emergency of International Concern on January 30, 2020. Due of its fast worldwide spread, the World Health Organization (WHO) proclaimed the coronavirus pandemic on March 11, 2022 (Maulana, 2020).

The coronaviruses are classified by the subfamilies Coronavirus, family Coronaviridae, and order Nidovirales. Alphacoronavirus (CoV), Betacoronavirus (CoV), Deltacoronavirus (CoV), and Gammacoronavirus are the four generations of the Corona virus (CoV). COVID-19 patients exhibit a wide range of clinical symptoms, from asymptomatic to severe pneumonia, ARDS, sepsis, and septic shock. About 80% of patients were categorized as mild or moderate, 13.8% presented with acute illness, and 6.1% reached a critical stage.

The globe is now experiencing an outbreak of the Covid-19 pandemic, which is caused by the Coronavirus, spreads rapidly, and results in a modest mortality toll. This pandemic outbreak has resulted in deaths, astronomical medical bills, a decline in the nation's economy, and substantial societal effects (World Health Organization, 2020) Indonesia has detected more than 2,000 instances of Covid-19 in the last two months, including 191 deaths, making Covid-19 a severe public health concern in Indonesia. To date, however, there is no proven treatment for Covid-19 (Kementerian Kesehatan RI, 2020)

In an effort to halt the spread of COVID-19, the United States and a number of other governments have temporarily banned system travel in China. The COVID-19 epidemic has sparked global fear, yet there are currently no particular treatments or immunizations to treat COVID-19. Worldwide, feasible therapeutic research is continuing. In the meanwhile, it was reported that convalescent plasma was effectively provided to a COVID-19-infected patient in China. On the basis of the diagnosis of pneumonitis and the Treatment Program for SARS-CoV-2 infection, Chinese physicians' resort to convalescent plasma infusions if pharmaceutical therapy is inadequate. Convalescent plasma is used to enhance the survival of patients with acute infectious respiratory illnesses. Even though the effects of antivirals and immune-modulators on COVID-19 patients are still being assessed, physiopathology shows that convalescent plasma treatment may reduce mortality.

Convalescent Plasma is blood plasma collected from a patient diagnosed with Covid 19 and declared cured of COVID-19 infection for 14 days, as demonstrated by a single negative Swab examination utilizing RT-PCR. In an effort to provide COVID-19 patients with quick passive immune therapy, convalescent plasma therapy involves the infusion of plasma from recovered COVID-19 patients that is rich in polyclonal antibodies (Hung et al., 2011)

Convalescent plasma has been used to successfully treat multiple viral infections, such as SARS-CoV, H5N1 avian influenza, Ebola, Middle East Respiratory Syndrome (MERS), and H1N1 influenza.(Florescu et al., 2015; Hung et al., 2011b; Kraft et al.,

2015; Sall et al., 2020; Zhou et al., 2007) Convalescent plasma delivery in patients with severe H1N1 influenza can reduce viral load in the respiratory tract, serum cytokine response, and mortality (20% versus 54.8%; p=0.01), according to a 2009 study. (Hung et al., 2011). In a previous clinical research involving 80 SARS-CoV patients in Hong Kong, the injection of convalescent plasma lowered hospitalization duration (73.4% versus 19.0%; p.001) and mortality (0% versus 23.0%; p=0.049) (Casadevall & Pirofski, 2020; Duan et al., 2020)

This research investigates the efficacy of convalescent plasma as a therapy for COVID-19 patients with life-threatening illnesses. In an investigation done in China on 10 very sick COVID-19 patients, the viral load dropped until it became negative on the second and on the third day following transfusion. Three patients were discharged from the hospital, and seven patients exhibited symptoms of improvement as a result of this study (Duan et al., 2020)

SUBJECTS AND METHOD

1. Study Design
This study is a clinical trial employing a non-randomized comparative study design with a historical control group from May 6th 2020 to May 6th 2021 at Dr. Moewardi General Hospital.

2. Population and Sample
Hospitalized Covid-19 patients divide into control group (21 sample) and plasma recipient convalescent group (21 sample) with a consecutive sampling. The control group will consist of Covid-19 patients who received standard hospital treatment and whose data were retrospectively obtained (historical control). The control group will be randomly selected and stratified by gender, age (18 to 40 years, 40 to 60 years, and 60 years), and illness severity (moderate, severe/critically ill).

The plasma recipient convalescent group will consist of COVID-19 patients who have severe pneumonia with a rising viral load despite antiviral therapy, a PAO2 / FIO2 of 300 (PAO2 is measured in mmHg and FIO2 is the percentage of inspired oxygen), and artificial breathing. All patient blood was screened a day before transfusion using an enzyme-linked immunosorbent test (ELISA) kit (Sangon Biotech) and neutralizing antibody titers (Costar). In addition to the antiviral medication, each patient received two 200-250 ml transfusions.

COVID-19 convalescent plasma shall be obtained from a blood transfusion unit that satisfies all standards for conventional plasma and all BPOM rules for Covid-19 convalescent plasma. Information gathered following the administration of convalescent plasma will include effectiveness and safety indicators, patient demographics, treatment resources, and characteristics of the administered convalescent plasma. Convalescent plasma used for treatment is taken from COVID-19-free, totally recovered people. or symptomless (Berkhout et al., 2023). The donor must be a man between the ages of 18 and 60 who has recovered from COVID-19 infection and has a negative laboratory result for the SARS-CoV-2 virus using an RT-PCR special kit (GeneoDX Co) and a Viral QIAmp RNA kit for nucleic acid extraction (Qiagen). In addition, the donor must be free from a variety of respiratory illnesses, hepatitis B and C viruses, HIV, and syphilis. Donors must be asymptomatic for a minimum of ten days and have IgG antibody titers over 1:320. Exclusion criteria included those with incompatible cross-matches, anemia (Hb 12.5 g/dL), and cancer. Donor plasma was extracted by apheresis and delivered to the recipient on the same day.

3. Study Variables

The variable consist of the mortality, recovery, and ICU/hospitalization length, qRT-PCR, laboratory evaluation (white blood cell count, differential cell count, C-Reaction protein, procalcitonin, Interleukin-6, ALT, AST, ureum, creatinine, D-Dimer, and peripheral blood morphology) and clinical progress (recovered, returned home, stable, or worsening).

4. Operational definition of variables

Convalescent plasma is an independent variable in this study, with a definition of a treatment likely mediated by antibodies through direct viral neutralization and Fc-dependent functions such as a phagocytosis, complement activation, and antibody-dependent cellular cytotoxicity

Moderate ill is a dependent variable in this study, with definition of a moderate ill based on the sign and symptomp.

Critical ill is a dependent variable in this study, with definition of a critical ill based on the sign and symptomp.

5. Study Instruments

The effect of using of convalescent plasma for COVID-19 infection was measured by the sign and symptoms. Data was tested by descriptive study. Correlation between convalescent plasma and degree of COVID-19 infection was measured by the sign and symptoms. Data was tested by descriptive study.

6. Data analysis

The analysis in this study is presented with the distribution of frequencies and percentages for categorical data.

7. Research Ethics

This clinical study inquiry was permitted by the ethics council of Dr. Moewardi General Hospital Surakarta with a number of 88/-F1/PKS-KCOVID-19.E/VI/2020.

RESULTS

1. Sample Characteristics

There were two groups: the plasma recipient convalescent group (21) and the control group (21). The convalescent plasma was received from fifteen donors. In the control group of 21 patients, there were 3 patients with moderate illness, 14 with severe illness, and 4 with critical illness. In patients with a moderate degree of severity, two patients recovered, while twelve patients died. All four individuals in the critical illness group had died. (See figure 1). In the plasma convalescent group, there are 8 moderately ill patients and 3 critically ill individuals. All eight patients in the somewhat recovered group were cured. In severe degree group, 7 patients were recovered and 3 patients were deceased. In critically ill patients, all three were deceased. (See Figure 2).

There was a significant difference between outcome and severity degree in the plasma convalescent therapy group (p= 0.005). There was also a significant difference between the outcome group and the control group (p=0.005).

There are no statistically significant differences in outcome between moderate-degree patients in the control group and those in the therapy group. There are no significant differences in outcome between the control group and the treatment group in patients with severe disease (p>0.005). There is no significant difference in outcome between the control group and the treatment group in critically sick patients (all patients dead). However, there are substantial differences between the control group and treatment group in terms of overall patient outcome severity (p=0.005).

Laboratory evaluation of the ratio of neutrophils to lymphocytes as an indicator of inflammation (NLR). There are no significant differences in NLR between day-

1, day-2, and day-7 pre-treatment and post-treatment (p>0.005). The hsCRP marker does not alter significantly between pre-treatment and post-treatment on days 1, 2, or 7 (p>0.005). There are no statistically significant differences between pre-treatment and post-treatment day-1, day-2, or day-7 for IL-6 treatment (p>0.005).

Inflammatory markers (NLR and hsCRP) before to treatment were not substantially different between the treatment and control groups (p>0.005). How-ever, the NLR of the control group after treatment was substantially different from that of the treatment group (p=0.005). In addition, there were statistically significant differences between the control and treatment groups in post-treatment hsCRP levels (p=0.005). In addition, there were statistically significant differences (p= 0.005) between all groups' inflammatory markers and outcomes.
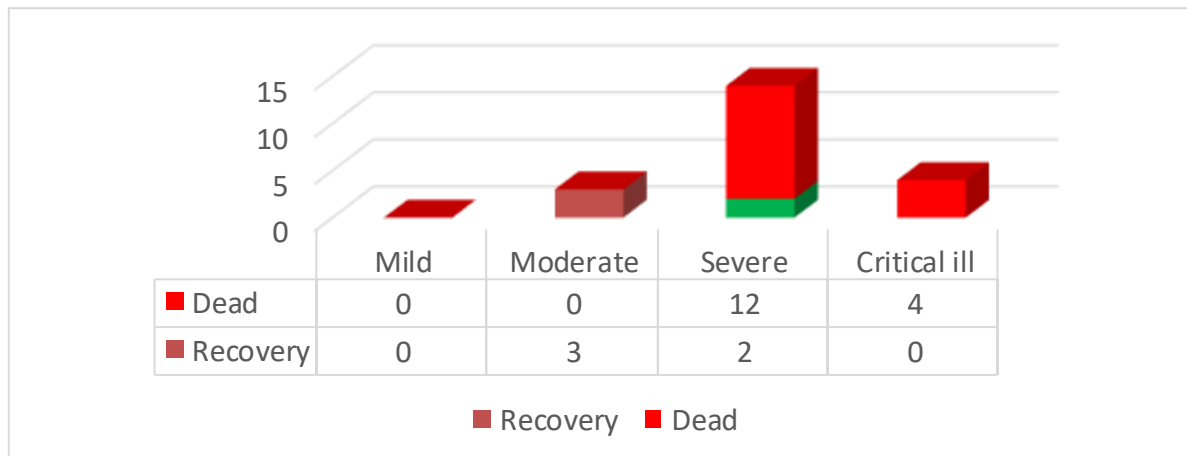

	Mild	Moderate	Severe	Critical ill
Dead	0	0	12	4
Recovery	0	3	2	0

Figure 1. Patient's outcome of Control group according to degree of severity

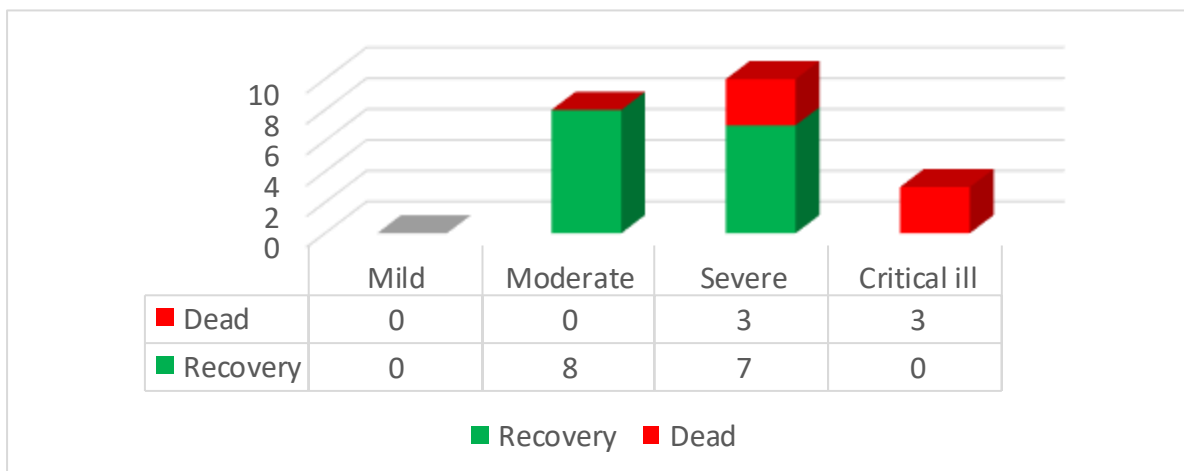|	Mild	Moderate	Severe	Critical ill
Dead	0	0	3	3
Recovery	0	8	7	0

Figure 2. Patient's Outcome in Treatment Group

DISCUSSION

In Wuhan, Hubei Province, China, the novel coronavirus 2019 (2019-nCoV) was iden-tified in a case of pneumonia in December 2019. The WHO then classifies the case as COVID-19 on March 11, 2020. The SARS-0V-2 virus is a member of the -coronavirus family. Clinical picture from asymptomatic

through respiratory failure, septic shock, and multiorgan failure, the outcomes varied (Chavda et al., 2023).

The majority of COVID-19-infected patients exhibit common symptoms such as fever, cough, lethargy, gastrointestinal symptoms, and comorbidities like hypertension and diabetes mellitus. On the radiological imaging, there is an image of ground glass opacity or bilateral patchy, however on the results, there is no such image. Lymphopenia and eosinopenia were detected in the laboratory.

The COVID-19 pandemic causes a global taste panic. Specific medications and vaccinations are available to treat COVID-19. Oxygen supplementation, fluid treatment, vasopressor medications, empiric antibiotics, symptomatic therapy, and systemic corticosteroids may be administered to COVID-19 patients in Indonesia, although they are not regularly administered. In China, convalescent plasma therapy is used as a last option if the present therapeutic strategy is ineffective. Priority is given to critically ill patients in order to enhance patient survival (Chavda et al., 2023).

Convalescent plasma therapy has been found to drastically lower the risk of death, inhibit the virus, clear viral infections, and eliminate infected cells. Several studies indicate that the administration of convalescent plasma can normalize body temperature, increase Pao2/Fio2, relieve clinical symptoms and conditions associated with ARDS, reduce viral load, and enhance the radiological picture.

A donor must complete several eligibility requirements, including required ones, in order to donate plasma after recovering from a disease. Donors must adhere to several WHO Blood Regulatory Network (BRN) regulations pertaining to weight, age, vital signs, sample frequency, and other parameters.

Selection of donors during pandemics. Appropriate nucleic acid testing or serological testing will identify if the sample is positive for HBV, HIV, Syphilis, HCV, and specific local diseases, and the sample must comply with local blood collection regulations in order to be transfused. To minimize the presence of antibodies against human leukocyte antigens (HLA) or granulocyte antigens in plasma, it is preferred to utilize plasma from both male and nonpregnant female donors. This approach minimizes the risk of transfusion-associated acute lung injury (TRALI) (Chavda et al., 2023).

There is a substantial relationship between illness severity and patient outcome in both the control and therapy groups. This conclusion is comparable to that of a prior cohort research in the United States that analyzed children infected with COVID-19 and found a high connection between disease severity and patient outcome (Martin et al., 2022) The severity of the disease was also related to the existence of risk factors and comorbidities. (Shoaib et al., 2021). Numerous clinical research investigations have examined clinical characteristics, illness development, and risk factors, which have become prognostic factors related with the severity of COVID-19 disease (Sharma et al., 2021).

The literature search findings according to Ye et al. and Shen et al. Convalescent plasma therapy refers to the provision of plasma infusions for Covid-19 patients taken from patients Covid-19 around 14 days (two weeks) after being declared cured, without exhibiting symptoms in the previous 10 days, and satisfying blood donor conditions. The use of convalescent plasma as a treatment has been prevalent for a very long time, with some estimates dating as far back as a century ago. Plasma therapy convalescent has been used prophylactically or delivery of plasma to destination passive

immunity enhancement treatment for a variety of infectious diseases, particularly during epidemics such as polio, measles, and Ebola, and when pandemic infectious diseases such as HIV, SARS, MERS, H1N1, and H1N2 occur.

In intermediate severity patients, there were no clinically significant changes between the control group and the convalescent plasma treatment group. In this study, each and every patient recovered. This study is comparable to clinical trials including hospitalized COVID-19-mild US veterans (K. Cho et al., 2021). They evaluated 402 patients assigned to receive convalescent plasma and found no significant differences in 30-day mortality between COVID-19 patients who were not seriously unwell and patients who were not ill (Cho et al., 2021). A phase II randomized controlled trial enrolling 235 patients with intermediate severity COVID-19 in India indicated that convalescent plasma therapy was not associated with a reduction in progression to severe COVID-19. Convalescent plasma transfusion in hospitalized patients with mild COVID-19 disease at the Gatot Soebroto Central Army Hospital in Indonesia was well tolerated and resulted in excellent clinical improvement in all patients, according to supplementary research (Rejeki et al., 2021). However, the researchers were unable to conclude that the effects were predominantly due to the convalescent plasma treatment. Several case reports exhibiting clinical and laboratory improvement substantiated the efficacy of convalescent plasma therapy for COVID-19 infection of moderate severity. (Mada & Setiawan, 2020) To achieve a more conclusive result, it is important to conduct more extensive clinical trials with a higher number of participants. In December 2021, the WHO will recommend against utilizing convalescent plasma to treat COVID-19 in COVID-19 patients who are not very unwell.

However, the World Health Organization recommends its use in clinical trials for COVID-19 individuals who are severely and critically unwell (World Health Organization, 2022).

It is anticipated that the use of convalescent plasma in Covid-19 cases will also serve as an alternative method for treating and conquering Covid-19 patients. The majority of Covid-19 patients are recovering at age 50 or older, are in severe condition, and have comorbidities or associated conditions, according to the findings of a meta-analysis of prior studies. Referring to the clinical results of convalescent plasma in SARS patients in Hong Kong and other countries in 2003, earlier therapy was associated with improved clinical outcomes. Because there is a greater chance of recovery while a patient's disease is severe than after they are treated. It is probable that policymakers may consider this when defining the procedure for convalescent plasma therapy. Regardless of age, convalescent plasma has a better therapeutic effect on patients of all ages.

Convalescent plasma therapy is a safe treatment option for COVID-19 infection, according to numerous studies. There are however a variety of potential side effects, such as transfusion-related events such as allergies, mild allergic reactions, hemolysis, and acute lung injury, physicochemical reactions such as fluid overload and citrate toxicity, drug reactions, and infection risk.

Infrequent anaphylaxis reactions are potentially lethal. Because multiple articles describe equivalent reactions in COVID-19 patients receiving convalescent plasma therapy. Mild itching, urticaria, and flushing are examples of the signs of an allergic reaction. Plasma transfusions having significant quantities of anti-A and anti-B antibodies have been related to instances of acute hemolysis and death.

Due to the presence of antibodies from transfused blood components to leukocyte antigens (mainly HLA) in donor plasma, a large number (1 in 5,000 to 50,000) of acute respiratory responses are referred to as TRALI. Non-lethal physicochemical responses, including as pulmonary edema, fluid overload, citrate toxicity, and drug reactions, may occur if the medication is present in donor plasma. The likelihood of developing HIV, HBV, or HCV.

In this trial, there was no significant difference between the control and treatment groups for patients with severe and life-threatening disorders who received convalescent plasma. This is comparable to a recent comparative cohort study including severely and critically ill COVID-19 patients, in which it was determined that the convalescent plasma treatment had no effect on death and was safe (Paul et al., 2021). Experience with previous coronaviruses has shown that antibodies in convalescents have a short half-life; therefore, patients who begin their recovery sooner may be more likely to have sufficient antibodies. (Wooding & Bach, 2020a) Multiple trials have revealed the potential benefit of convalescent plasma treatment for extremely ill COVID-19 patients. Convalescent plasma treatment has been reported to be well tolerated and to improve clinical results (Duan et al., 2020). In a previous open-label, non-randomized, comparative clinical study conducted at the Kariadi Hospital in Indonesia, the convalescent plasma treatment significantly enhanced clinical outcomes and survival rates compared to local standards of care. In addition to the findings of clinical studies done in Seoul, Korea, patients who received convalescent plasma had a greater increase in Ct values and better clinical outcomes. Even though the majority of COVID-19 reports suggest a possible benefit of convalescent plasma, there were several limitations, such as the concurrent use of antivirals, steroids, and other treatments, small sample sizes, lack of randomization, absence of control groups, short follow-up time, and the absence of ideal recipients and donors (Wooding & Bach, 2020).

The levels of the inflammatory markers NLR and hsCRP were substantially different between the control and treatment groups in this experiment. This is analogous to earlier research and clinical trials that shown an improvement in the clinical outcome of patients treated with convalescent plasma (Cho et al., 2021; Failure, 2023). According to our findings, the increase in clinical result was followed by improvements in laboratory indicators, viral loads, and antibody titers.

AUTHOR CONTRIBUTION

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CONFLICT OF INTEREST

There is no conflict of Interest in this study.

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