Journal of Experimental and Clinical Medicine
https://dergipark.org.tr/omujecm

Research Article

J Exp Clin Med
2023; 40(2): 258-263
doi: 10.52142/omujecm.40.2.11

Convalescent plasma transfusion in severe covid-19 patients admitted to intensive care unit: A single center study

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Received: 14.11.2022 • **Accepted/Published Online:** 02.03.2023 • **Final Version:** 19.05.2023

Abstract

Initial difficult times of novel coronavirus disease 2019 (COVID-19) had clinicians actively seeking appropriate treatment. Convalescent plasma (CP) has been studied for treatment of past coronavirus pandemics and was successful with promising efficacy and safety. This study aims to measure the efficacy of convalescent plasma transfusion in severe COVID-19 patients, determined by alleviation of symptoms, improvement in radiologic findings, and laboratory parameters. Cross-sectional study conducted involving 23 severe COVID-19 patients admitted to Udayana University Hospital intensive care unit in 2020. Patients received a minimum 200 cc CP transfusion, dexamethasone, and remdesivir. Data were retrieved from patient's medical records. Patients mean age was 54.04 years. Mean time from onset of illness to transfusion and length of stay were 11.09 and 16.70 days respectively. No adverse effects were observed during treatment. Twelve patients (52.2%) showed alleviation of symptoms and recovered, with 15 days median time from transfusion to recovery. Post-transfusion chest x-ray examination showed varying degrees of absorption of lung lesions in 10 patients (43.5%) and was associated with the patient's outcome (p=0.001). Significant changes in c-reactive protein (p=0.000) and procalcitonin level (p=0.024) was found as compared to pretransfusion. Despite these findings, almost half the patients (47.8%) did not receive benefits from CP transfusion and dead. CP transfusion has shown remarkable improvement in radiologic, inflammatory, and prognostic parameters but was unable to improve patient clinical outcomes and mortality rate.

Keywords: Convalescent plasma therapy, COVID-19, critical care, outcome

1. Introduction

Indonesia has reported a total of 1,012,350 cases and 24,468 deaths (2.8% confirmed case fatality rate) up to January 26, 2021, since the first two laboratory-confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections were reported on early March 2020, of which 25% (254,580) of cases and 17% (4077) of deaths were in the capital city of Jakarta. The number of novel coronavirus disease 2019 (COVID-19) cases and fatalities in Jakarta rapidly increased during the first two months of the outbreak (March–April 2020), and they have continued to rise steadily through January 2021 (1). The COVID-19 pandemic has had a massive negative impact on the Indonesian economy, particularly in Bali Province, where tourism is the primary source of income (2), and tourism, on the other hand, poses a risk of COVID-19 spreading. The increasing death rates and such impact on the economy caused by the pandemic have led to high demands to develop new potential therapies and made clinicians actively seek appropriate treatments.

During this early COVID-19 pandemic, clinicians still lacked evidence, especially randomized controlled trial (RCT) studies, to support which drugs would be helpful (3). Indonesia's second edition of the COVID-19 management guideline has included convalescent plasma (CP) transfusion for consideration in severe COVID-19 patients (4). For more than a century, CP transfusion as a traditional adaptive immunotherapy has been used to prevent and treat a variety of infectious diseases, including severe acute respiratory syndrome (SARS), middle east respiratory syndrome (MERS), and the 2009 H1N1 pandemic, have all been successfully treated with CP therapy over the past 20 years with satisfying efficacy and safety (5–8). Compared to placebo or no treatment, CP transfusion significantly reduced the pooled odds of mortality (odds ratio, 0.25; 95% confidence interval, 0.14-0.45) in a meta-analysis of 32 studies on SARS

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coronavirus infection and severe influenza (9). SARS, MERS, and COVID-19 have similar virological and clinical traits. Therefore, CP transfusion was a promising treatment for managing severe COVID-19 cases (10). However, in the middle of 2020, it was unclear whether using convalescent blood products during COVID-19 would be clinically advantageous or harmful. In the absence of a well-designed large multicenter RCT, a systematic review published in April 2020 has shown that CP transfusion appears safe, clinically effective, and reduces COVID-19-related mortality (11). Although numerous studies have been reported since then, the World Health Organization (WHO), on its seventh update of WHO's living guidelines on COVID-19 therapeutics, recommends against the use of CP to treat COVID-19. CP transfusions were found to cause significant costs and neither increase survival nor decrease the need for mechanical ventilation. While there is no question that convalescent plasma has no benefit for non-severe COVID-29 patients, this is not yet clear in the case of severe and critically ill patients (12).

Considering the potential benefit of CP transfusion in managing severe COVID-19 patients back in early 2020, one of the referral hospitals for managing severe COVID-19 in Bali Province, Udayana University Hospital, has done CP transfusion to severe COVID-19 patients admitted to the intensive care unit (ICU). In this study, we aim to report the efficacy and safety of CP transfusion for severe COVID-19 patients admitted to the ICU of Udayana University Hospital.

2. Materials and Methods

2.1. Study Population, Setting, and Data Collection

We did this study on 23 severe COVID-19 patients admitted to the ICU of Udayana University Hospital, Bali Province, Indonesia, in 2020. Research participants were laboratory-confirmed COVID-19 patients using nasopharyngeal swabs of SARS-CoV-2 real-time polymerase chain reaction (RT-PCR). Severe COVID-19 patients in the ICU have been empirically treated with dexamethasone (6 mg/day for ten days) and remdesivir [200 mg intravenous drip (day 1) continued by 100 mg intravenous drip (day 2-10)], which was recommended by the COVID-19 management guideline in Indonesia (4). The inclusion criteria were severe COVID-19 patients admitted to the ICU. Patients were defined as having severe COVID-19 by referring to Indonesia's COVID-19 management guidelines (4), which were patients that show clinical signs of pneumonia (fever, cough, shortness of breath, rapid breathing) plus one of: respiratory rate >30 breaths/minute, severe respiratory distress, or <93% oxygen saturation in room air. Exclusion criteria were (a) patients allergic to plasma products; (b) pregnancy; (c) breastfeeding mother; (d) patients with known thrombosis; (e) severe heart failure with risk of volume overload; (f) septic shock; and (g) kidney failure with ongoing dialysis. Demographic data, medical history, length of stay, laboratory, and radiology examination results were taken from medical records retrospectively. The Ethical Review Board of the Faculty of Medicine, Udayana University, has approved this study with an ethical clearance letter number 1010/UN14.2.2.VII.14/LT/2020. Written informed consent was obtained from each participant.

2.2. Convalescent plasma donors and transfusion

Convalescent plasma was obtained from patients who had recovered from COVID-19 through plasmapheresis. Relief from symptoms and negative results for SARS-CoV-2 nucleic acid in at least one RT-PCR test were considered signs of recovery. The donor recruitment was done by contacting previously recovered severe COVID-19 patients through voluntary participation. Donor criteria were 18-59 years old male or female who has never pregnant. The donors must test seropositive for anti-SARS-CoV-2 and seronegative for hepatitis B virus, hepatitis C virus, human immunodeficiency virus, and syphilis. The CP was also found free of any remaining SARS-CoV-2 by RT-PCR. As soon as we had access to available ABO-compatible CP, transfusion to eligible patients was initiated. Patients received a minimum of 200 mL CP transfusion, with each transfusion given over 30 minutes.

2.3. Safety and outcome measurements

Adverse events associated with convalescent plasma transfusion were assessed before and at 15, 30, and 60 minutes after CP transfusion. The safety measurements in CP transfusion included vital signs and transfusion reaction symptoms (fever, dyspnea, chest pain, cyanosis, wheal/urticaria, bleeding, and changes in urine color). The efficacy of CP transfusion for severe COVID-19 patients was determined by alleviation of symptoms and improvement in chest x-ray findings and laboratory parameters during 24 hours pre-CP transfusion and 48 hours post-CP transfusion. Laboratory parameters included in the analysis were hemoglobin, white blood cell count (WBC), differential neutrophil percentage, differential lymphocyte percentage, neutrophil-to-lymphocyte ratio (NLR), platelet count, prothrombin time (PT), c-reactive protein (CRP), D-Dimer, procalcitonin, alanine aminotransferase (ALT or SGPT), aspartate aminotransferase (AST or SGOT), blood urea nitrogen (BUN), and serum creatinine (SC). Normal references from the hematology analyzer were also recorded. The NLR value was counted from the differential neutrophil and lymphocyte count, and the normal reference range was set to 0.78-3.53 according to the study by Forget et al. (13). Chest x-ray findings pre and post-CP transfusion were categorized as "decreased lesions," "persistent lesions," and "increased lesions."

2.4. Statistical Analysis

Variables with categorical scales were reported in the frequency and percentage distribution, while numerical variables were reported as mean (± standard deviation) if the data were normally distributed or median (and interquartile range) if the data were not normally distributed. The numerical data normality of distribution test was performed using the Shapiro-Wilk test. The data distribution is not normal if the p-value <0.05. Mean differences between pre-CP transfusion and post-CP transfusion laboratory parameters were analyzed with Paired sample T-test in normally distributed data; otherwise, analysis was carried out using the Wilcoxon test. Chi-square analysis was used to evaluate the association between variables with categorical scales. Statistical analysis was performed using the IBM Statistical Package for the Social Sciences® software version 17.

3. Results

3.1. Patient's Characteristics

The patient's mean age was 54.04 (±13.07) years, ranging from 26 to 76 years old, and more than half were male (65.2%). Most patients had the O blood group (47.8%), while the AB blood group was the least common (8.7%). Patient's initial symptoms before ICU admission were mostly dyspnea (100%), fever (91.3%), and cough (95.7%), while the less common symptoms were rhinorrhea (13%), nausea and vomiting (17.4%), headache (8.7%), odynophagia (8.7%), lethargy (17.4%), and diarrhea (4.3%). The mean time from initial symptoms to ICU admission was 6.74 (±4) days. Patients were reported to have several comorbidities during treatment, including a history of type 2 diabetes mellitus, hypertension, obesity, bronchial asthma, hypokalemia, hyponatremia, pregnancy, and pulmonary edema.

Patients received CP transfusion with a median time of 4 (IQR=2) days from ICU admission (ranging from 0-13 days) or a mean of 11.09 (±4.28) days from initial symptoms. Most of the mean or median of the laboratory parameters value before CP transfusion was abnormal. Pre-transfusion median white blood cell count was 10.78 $\times 10^3/\mu L$ (interquartile range (IQR)=2.92), neutrophil differential percentage 90.80% (IQR=5.80), lymphocyte differential percentage 5.1% (IQR=3.80), D-Dimer 1889 ng/mL FEU (IQR=2921), procalcitonin 0.29 ng/mL (IQR=0.4), SGOT 49 U/L (IQR=48), SGPT 71 U/L (IQR=74), and SC 0.64 mg/dL (IQR=0.20). The mean NLR was 17.57 (±7.54) and CRP 129.40 mg/L (± 87.95). Baseline characteristics were further compared between the recovered and dead patients, as shown in Table 1 and 2.

Table 1. Patient baseline characteristics

Patient characteristics at ICU admission	Recovered (n=12)	Dead (n=11)
Age[a] - years	50.92±12.78	57.45±13.11
Sex – N (%)		
Male	9 (60)	6 (40)
Female	3 (37.5)	5 (62.5)
Comorbidities – N (%)		
Type 2 Diabetes Mellitus	2 (40)	3 (60)
Hypertension	1 (25)	3 (75)
Obesity	1 (33.3)	2 (66.7)
Pulmonary Tuberculosis	0 (0)	1 (100)
Pneumonia	2 (66.7)	1 (33.3)
Bronchial Asthma	1 (33.3)	2 (66.7)
Hypokalemia	0 (0)	1 (100)
Hyponatremia	0 (0)	1 (100)
Pregnancy	0 (0)	1 (100)
Lung Edema	0 (0)	1 (100)
Initial symptoms – N (%)		
Fever	10 (47.6)	11 (52.4)
Cough	11 (50)	11 (50)
Rhinorrhea	2 (66.7)	1 (33.3)
Nausea and vomiting	2 (50)	2 (50)
Headache	0 (0)	2 (100)
Odinophagia	2 (100)	0 (0)
Lethargy	1 (25)	3 (75)
Diarrhea	1 (100)	0 (0)
Interval from initial symptoms to ICU admission – days	1-14	1-14
Interval from ICU admission to CP transfusion – days	0-13	1-5
Interval from CP transfusion to outcome – days	8-22	3-22

[a]Mean±SD

3.2. Outcomes of Therapy

The mean overall length of ICU stay was 16.70 (±6.09) days. The mortality rate in this study reached 47.8%. Almost half of the patients did not receive the benefit of CP transfusion. Alleviation of symptoms was found in the recovered groups (52.2%), with median times 15 days (IQR=9) from transfusion to recovery. Post-transfusion statistically significant changes were observed in WBC (p=0.002), CRP (p=0.000), and procalcitonin value (p=0.024), as compared to pre-transfusion. Further detailed data on laboratory parameter changes are presented in Table 3. Improvement in radiological findings was found only in 10 patients (43.5%) and was associated with patient outcomes (p=0.003). No adverse events related to CP transfusion were found in this study. Comorbidities were not associated with the patient's mortality rate (p=0.278)

Table 2. Pre and post-CP transfusion changes between outcome groups

Parameters	Pre CP Transfusion		Post CP Transfusion		Normal References
	Recovered	Dead	Recovered	Dead	
Laboratory parameters					
Hemoglobin[a] – g/dL	13.15 (±1.29)	12.65 (±1.74)	12.33 (±1.63)	12.50 (±2.46)	13.2-17.3
WBC[b] – x10^3/µL	10.45 (4.49)	10.79 (2.85)	12.48 (6.34)	17.30 (7.08)	3.80-10.6
Differential neutrophil[b] – %	91.15 (4.35)	90.20 (6)	86.45 (7.38)	92.40 (3.60)	50-70
Differential lymphocyte[b] – %	5.05 (3.07)	6.10 (5.40)	8.70 (7.23)	3.20 (4.40)	25-40
NLR[a]	18.42 (±6.74)	16.64 (±8.55)	12.58 (±7.44)	27.45 (±12.25)	0.78-3.53
Platelet count[a] – x10^3/µL	312 (±123.02)	270.55 (±133.06)	335.58 (±121.45)	310.64 (±147.95)	150-450
PT[b] – seconds	9.75 (1.10)	9.20 (1.70)	9.50 (1.15)	10.10 (4.40)	7.9-10.3
CRP[b] – mg/L	69.30 (133.40)	146.10 (87.40)	4.30 (3.50)	54.80 (51.10)	≤10
D-Dimer[b] – ng/mL FEU	2104.50 (3148)	1111 (2991)	1112.50 (1738)	3195 (8250)	<500
Procalcitonin[b] – ng/mL	0.35 (1.20)	0.24 (0.44)	0.04 (0.14)	0.21 (1.14)	<0.05
SGPT[b] – U/L	85.50 (147)	59 (59)	92 (146)	65 (282)	<40
SGOT[b] – U/L	53.50 (76)	44 (26)	44.50 (43)	32 (66)	<41
BUN[b] – mg/dL	22 (12)	14 (10)	17.50 (15)	20 (13)	6-20
SC[b] – mg/dL	0.65 (0.38)	0.58 (0.28)	0.59 (0.45)	0.66 (0.56)	0.67-1.17
Radiologic changes – n (%)					
Decreased lesions			9 (90)	1 (10)	
Persistent lesions			2 (50)	2 (50)	
Increased lesions			1 (11.1)	8 (88.9)	

WBC, white blood cell count; NLR, neutrophil-to-lymphocyte ratio; PT, prothrombin time; CRP, c-reactive protein; SGPT, alanine aminotransferase; SGOT, aspartate aminotransferase; BUN, blood urea nitrogen; SC, serum creatinine

[a]Mean (±SD); [b]Median (IQR)

Table 3. Pre and post-CP transfusion changes in laboratory parameters

Parameters	Median (Min-Max)	Mean ± SD	Mean Differences (95% CI)	p
Hemoglobin – g/dL				
Pre-transfusion	12.60 (9.90-16.40)	12.91 ± 1.51	0.50 (-0.10 – 1.10)	0.099[a]
Post-transfusion	12.40 (7.40-16.70)	12.41 ± 2.02		
WBC – x10^3/µL				
Pre-transfusion	10.78 (4.36-23.69)	11.25 ± 3.66		**0.002**[b]
Post-transfusion	15.47 (5.77-47.09)	16.60 ± 8.48		
Differential neutrophil – %				
Pre-transfusion	90.80 (81.60-93.60)	89.59 ± 3.54		0.976[b]
Post-transfusion	90.50 (67.90-94.40)	88.18 ± 6.97		
Differential lymphocyte – %				
Pre-transfusion	5.10 (2.90-16.40)	6.30 ± 3.27	-0.39 (-2.76–1.97)	0.732[a]
Post-transfusion	5.50 (2.10-20.20)	6.70 ± 4.41		
NLR				
Pre-transfusion	18 (5-32)	17.57 ± 7.54		0.843[b]
Post-transfusion	17 (3-44)	19.70 ± 12.39		
Platelet count – x10^3/µL				
Pre-transfusion	260 (88-523)	292.17 ± 126.74	-31.47 (-76.40–13.44)	0.160[a]
Post-transfusion	322 (122-549)	323.65 ± 132.24		
PT – seconds				
Pre-transfusion	9.70 (7.80-13.90)	9.89 ± 1.36		0.314[b]
Post-transfusion	9.60 (8.20-17.50)	10.45 ± 2.46		
CRP – mg/L				
Pre-transfusion	116.40 (5.10-360)	129.40 ± 87.95		**0.000**[b]
Post-transfusion	15.20 (0.60-162.70)	33.82 ± 41.12		
D-Dimer – ng/mL FEU				
Pre-transfusion	1889 (283-50322)	5728.96 ± 11089.62		0.412[b]
Post-transfusion	1542 (323-50381)	5307.22 ± 10939.68		

Table 3. Pre and post-CP transfusion changes in laboratory parameters (Continue)

Parameters	Median (Min-Max)	Mean ± SD	Mean Differences (95% CI)	p
Procalcitonin – ng/mL				
Pre-transfusion	0.29 (0.07-4.81)	0.64 ± 1.02		**0.024**[b]
Post-transfusion	0.07 (0.01-19.73)	1.90 ± 5.62		
SGPT – U/L				
Pre-transfusion	71 (25-538)	105.52 ± 117.70		0.855[b]
Post-transfusion	70.20 (22-520)	131.14 ± 127.23		
SGOT – U/L				
Pre-transfusion	49 (24-138)	60.57 ± 32.71		0.191[b]
Post-transfusion	36 (8-830)	107.98 ± 203.42		
BUN – mg/dL				
Pre-transfusion	17 (6-48)	18.91 ± 9.38	-2.69 (-8.32–2.93)	0.331[a]
Post-transfusion	19 (6-54)	21.61 ± 12.38		
SC – mg/dL				
Pre-transfusion	0.64 (0.28-1.11)	0.65 ± 0.20		0.681[b]
Post-transfusion	0.60 (0.27-25)	1.87 ± 5.12		

WBC, white blood cell count; NLR, neutrophil-to-lymphocyte ratio; PT, prothrombin time; CRP, c-reactive protein; SGPT, alanine aminotransferase; SGOT, aspartate aminotransferase; BUN, blood urea nitrogen; SC, serum creatinine

[a]Paired sample t-test; [b]Wilcoxon test

4. Discussion

This study has found that convalescent plasma transfusion, along with dexamethasone and remdesivir, causes a significant decrease in inflammatory and prognostic markers, CRP and procalcitonin. Aside from these satisfactory changes, the mortality rate was still high. This study result demonstrated that CP transfusion could not improve overall outcomes in severe COVID-19 patients. Initial RCTs have also shown no statistically significant reduction in mortality compared to standard treatment alone or placebo. Despite the negative results, the characteristics of CP used in these RCTs were heterogenous, particularly its antibody content and the stratification of the recipient's serologic status (14–16). In a recent Cochrane living systematic review with a varying dose and total volume of plasma administered in 11 RCTs, there is a high certainty of evidence that CP transfusion to moderate-severe COVID-19 patients does not reduce all-cause mortality at up to 28 days, little to no impact on clinical improvement, and does not reduce the need for invasive mechanical ventilation (17). Therefore, the result of this study is in line with available evidence against the transfusion of CP for severe COVID-19 patients.

Transfusion of CP in this study appeared to be safe. There have been raised concerns in the early pandemic about the potential harm of CP transfusion to COVID-19, including transfusion-associated circulatory overload (TACO), coagulation, and antibody-dependent enhancement of COVID-19 (18). However, no recognized risk of plasma transfusion has been reported in the early RCTs (14–16). Although it has been reported to be safe, it is still difficult to draw a concrete conclusion due to the heterogeneous characteristics of CP. Cochrane's systematic review stated that there is uncertainty about whether CP reduces or increases the risk of serious adverse events (17). There was insufficient high-quality evidence reported to conclude the safety of CP.

Given the absence of benefits of CP transfusion to severe COVID-19, it is reasonable to recommend against its use in clinical settings. While it has undeniably high costs, applying CP transfusion outside the research context will shift healthcare resources away from other priorities in managing severe COVID-19 cases and offering false hope to patients (18).

Although this study revealed that CP transfusion has little to no benefit in severe COVID-19 patients, this study has several limitations to consider. First, this study has no control group; therefore, we could not see if the mortality rate would be the same or higher than the treatment group. Second, the number of samples in this study was relatively small, and study results were obtained from a single center. Third, the participants in this study had several comorbidities with varying fatality present during the observation; although chi-square analysis revealed no significant association, they may have affected the outcome of this study.

Ethical statement

The Ethical Review Board of the Faculty of Medicine, Udayana University, has approved this study with an ethical clearance letter number 1010/UN14.2.2.VII.14/LT/2020. Written informed consent was obtained from each participant

Conflict of interest

The authors declare no conflict of interest.

Funding
None to declare.

Acknowledgments
The authors wish to thank Professor Dewa Putu Gde Purwa Samatra as the former chief director and Professor I Dewa Made Sukrama as the current chief director of Udayana University Hospital, Professor I Ketut Suyasa as the former Dean, and Doctor Komang Januartha Putra Pinatih as the current Dean of Udayana University Faculty of Medicine, for the permission to conduct this study.

Authors' contributions
Concept: I.B.Y.B., C.A.W.P., Design: I.B.Y.B., C.A.W.P. Data Collection or Processing: I.B.Y.B., Analysis or Interpretation: I.B.Y.B., C.A.W.P., N.M.D.D.S., A.A.A.Y.G., I.M.S.U., I.K.A.S., I.G.N.M.A., K.T.P.M., Literature Search: I.B.Y.B., Writing: I.B.Y.B.

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