Convalescent Plasma as Adjunctive Therapy for Hospitalized Patients with COVID-19: The Co-CLARITY Trial

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ABSTRACT

Background and Objective. Convalescent plasma therapy (CPT) may reduce the risk of disease progression among patients with COVID-19. This study was undertaken to evaluate the efficacy and safety of CPT in preventing ICU admission among hospitalized COVID-19 patients.

Methods. In this open-label randomized controlled trial, we randomly assigned hospitalized adult patients with COVID-19 in a 1:1 ratio to receive convalescent plasma as an adjunct to standard of care or standard of care alone. The primary endpoint was ICU admission within first 28 days of enrolment. Primary safety endpoints include rapid deterioration of respiratory or clinical status within four hours of convalescent plasma transfusion and cumulative incidence of serious adverse events during the study period including transfusion-related acute lung injury (TRALI), transfusion-associated circulatory overload (TACO), severe allergic reactions, and transfusion-related infections.

Results. A total of 22 patients were assigned to receive convalescent plasma as an adjunct to standard of care and 22 to receive standard of care alone. The median time from onset of COVID-19 symptoms to study enrolment was eight days (IQR, 4 to 10). Two patients (9.1%) in the CPT group and one patient (4.5%) in the control group were admitted to the ICU. The primary outcome measure, ICU admission, was not different between the two groups (q-value >0.9). No patient who received convalescent plasma had rapid deterioration of respiratory/clinical status within four hours of transfusion and none developed TRALI, TACO, anaphylaxis, severe allergic reactions, or transfusion-related infections. There was also no significant difference in the secondary outcomes of 28-day mortality (two patients in the CPT group and none in the control group, q-value >0.90), dialysis-free days, vasopressor-free days, and ICU-free days.

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Conclusions. Among hospitalized COVID-19 patients, no significant differences were observed in the need for ICU admission between patients given CPT as adjunct to standard of care and those who received standard of care alone. Interpretation is limited by early termination of the trial which may have been underpowered to detect a clinically important difference.

Keywords: convalescent plasma, COVID-19, COVID-19 serotherapy

INTRODUCTION

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was declared a global pandemic by the World Health Organization (WHO) on March 12, 2020.[1] As of July 5, 2021, there are at least 183 million confirmed cases worldwide, with 3.97 million dying due to the disease.[2] In the Philippines, about 5,300 new cases are still being recorded per day.[3] COVID-19 severity can range from mild, self-limited disease to severe progressive pneumonia leading to multi-organ failure and death.[4] Early data revealed that the rate of ICU admission in COVID-19 was between 26% and 38%, with ICU mortality rate as high as 39%.[5]

The treatment landscape for COVID-19 is rapidly evolving. Over the past months, there have been a number of reports of drugs with significant clinical impact on COVID-19.[6-8] However, despite these and the availability of several effective vaccines, the rate of COVID-19 disease and complications remain to be significant.

Convalescent plasma therapy (CPT) is a form of passive antibody therapy where protective antibodies from naturally infected convalescent humans are used prophylactically to prevent infection or therapeutically to neutralize viral load among infected individuals with the goal of symptom reduction and prevention of death.[9,10] Historically, CPT was found to have clinical use in severe acute respiratory syndrome[11], H1N1 influenza[12], and Ebola virus infection[13]. Since the start of the pandemic, thousands of COVID-19 patients worldwide received CPT under clinical trials and under compassionate use for settings without access to these clinical trials. In the University of the Philippines – Philippine General Hospital (UP-PGH), 51 patients with severe and 57 patients with life-threatening COVID-19 received CPT under compassionate use.[14] Of the 51 patients with severe disease, 44 (86.2%) were discharged improved while 7 (13.7%) expired. Among the 57 patients with life-threatening disease, only 20 (35.1%) were discharged while 37 (64.9%) died. CPT was generally well-tolerated and adverse events were seen only in four patients with life-threatening disease. Acute respiratory failure from COVID-19 pneumonia accounted for majority of deaths in both groups, followed by septic shock, and pulmonary embolism. CPT appeared to be more effective among patients with severe disease compared to those with life-threatening disease.

CPT use in COVID-19 showed beneficial effects on mortality in non-randomized studies.[15] Multiple randomized clinical trials were also published and released as preprints in the past months, the largest of which was the Randomised Evaluation of COVID-19 Therapy (RECOVERY) Trial.[6,16-24] Most of these trials included patients with severe to life-threatening COVID-19 disease. Although none of these trials report mortality benefits with use of CPT for COVID-19, one study reported prevention of development of severe respiratory disease when CPT is given early and at high titers.[19]

The primary objective of this study is to evaluate the efficacy and safety of COVID-19 convalescent plasma as adjunctive therapy in preventing disease progression among hospitalized patients with COVID-19. Secondary objectives include (a) to compare the anti-SARS-COV-2 IgG antibody titers between the convalescent plasma and control groups at days 0, 1, 7, and 14 (additional day 28, as needed) and (b) compare the rates, levels, and duration of SARS-CoV-2 RNA in nasopharyngeal swabs (or other specimen types as available, e.g., bronchoalveolar lavage fluid, tracheal secretions, sputum, etc.) using RT-PCR CT values between the COVID-19 convalescent plasma and control groups at days 0, 1, 7, and 14. This is the first randomized clinical trial investigating the clinical benefit of CPT in preventing COVID-19 disease progression and ICU admission in the Philippines and one of the few clinical trials investigating the use of CPT among patients with moderate to severe disease.

METHODS

Trial Design

This was a randomized, non-placebo-controlled, open-label, single center trial conducted at the University of the Philippines – Philippine General Hospital (UP-PGH), a designated COVID-19 referral center. The trial protocol was approved by the University of the Philippines Manila Research Ethics Board (UPMREB) and the Philippine Food and Drug Administration. Written consent was obtained from all participants, and the trial was conducted in accordance with the principles stated in the Declaration of Helsinki and Good Clinical Practice guidelines, and local regulations. The authors take full responsibility for the design and conduct of the trial and vouch for the accuracy and completeness of the data, the analysis of the data, and the adherence of the trial to the protocol. No one who is not an author contributed to the writing of the manuscript.

Participants

Patients admitted to the UP-PGH were recruited into the trial via convenience sampling. The study recruitment was from September 2020 to May 2021. Follow-up was completed on June 2021.

Inclusion Criteria

Inclusion criteria were the following: (1) aged at least 19 years old, (2) hospitalized for moderate or severe COVID-19 with positive SARS-CoV-2 RT-PCR testing, (3) signed informed consent, (4) and agreed to storage of specimen for future testing. The study may include participants enrolled in other clinical trials in UP-PGH.

Exclusion Criteria

Exclusion criteria were the following: (1) female subjects with positive pregnancy test, are breastfeeding, or planning to become pregnant during the study period, (2) symptomatic illness exceeding 14 days from onset of illness at the time of enrolment, (3) receipt of any blood products including pooled immunoglobulin or intravenous immunoglobin (IVIg) in the past 30 days prior to enrolment, (4) known IgA deficiency, (5) presence of any contraindication to transfusion or history of prior severe reactions to transfusion of blood products, and (6) ICU admission on initial presentation at the hospitals which also includes all patients with clinical indications for ICU admission as follows: (6.1) respiratory distress with requirement of oxygen >6 lpm to maintain oxygen saturations >92%, (6.2) rapid escalation of oxygen requirement or significant work of breathing, and (6.3) hemodynamic instability defined as systolic blood pressure <90 mmHg or mean arterial pressure <65 mmHg.

Randomization

Eligible patients underwent treatment allocation and concealment through randomization module using REDCap[25-27] and were assigned in a 1:1 ratio to receive either convalescent plasma or local standard of care (Figure 1). Patients and clinicians were not blinded to the treatment given.

Procurement of Convalescent Plasma

The criteria for convalescent plasma donors included: (1) must have passed standard Department of Health (DOH)-prescribed donor history questionnaire, (2) suitable for blood donation as per national standards, (3) evidence of prior COVID-19 disease and have recovered from the disease defined as any of the following: (3.1) previously diagnosed with COVID-19 by SARS-CoV-2 RT-PCR, absence of any clinical evidence of COVID-19 for at least 14 days, and with at least 1 negative SARS-CoV-2 RT-PCR result done on recovery, (3.2) previously diagnosed with COVID-19 by SARS-CoV-2 RT-PCR, absence of any clinical evidence of COVID-19 for at least 28 days, even without a negative SARS-CoV-2 RT-PCR result done on recovery, or (3.3) no SARS-CoV-2 RT-PCR test done to document disease, absence of any clinical evidence of COVID-19 for at least 28 days but with a positive result for anti-SARS-CoV-2 IgG antibody-based test.

Convalescent plasma collection was performed via plasmapheresis or via whole blood donation using standard operating procedures. COVID-19 convalescent plasma was collected and processed at the UP-PGH. Antibody levels were measured using the commercially available serological assay, Ortho VITROS® SARS-CoV-2 IgG Assay (Ortho Clinical Diagnostics, US) which targets antibodies to the S protein and are reported as signal-to-cutoff (S/Co) ratios. Additional details regarding plasma donation and processing can be found in the trial protocol.

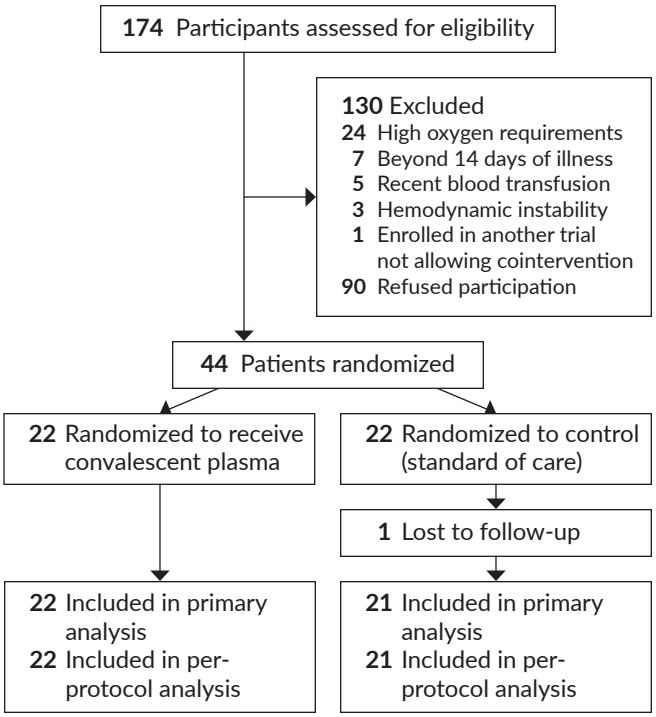

Figure 1. Patient enrolment and randomization.

Intervention

Patients randomized into the intervention group received one dose (~500 mL) of type-specific COVID-19 convalescent plasma within 24-48 hours of enrolment. Convalescent plasma was also crossmatched with the patient's red blood cells to ensure compatibility. Convalescent plasma was transfused intravenously as two aliquots of ~250 mL (or 3 aliquots totaling ~500 mL for some patients) as an adjunct to local standard of care. Each aliquot was transfused over 2-3 hours with an interval of 2 hours between each aliquot. Adjustments in infusion rates were allowed based on the patient's risk for volume overload and tolerance, at the discretion of the patient's clinical care team. Pretreatment with oral paracetamol and/or diphenhydramine to minimize transfusion reactions and post-transfusion intravenous diuretics may also be given as per clinical care team's discretion. As convalescent plasma in this study was considered adjunctive, other co-interventions such as antivirals, hydroxychloroquine/chloroquine, tocilizumab, and dexamethasone were allowed and documented for each

study participant. Patients included in the control group received local standard of care, guided by institutional care pathways, as deemed appropriate by the clinical care team and did not receive convalescent plasma.

Outcome Measures

The primary endpoint was ICU admission within first 28 days of enrolment. Pre-defined indications for ICU admission as per the institutional protocol includes any of the following: (1) respiratory distress requiring oxygen support >6 lpm to maintain oxygen saturation >92%, (2) rapid escalation of oxygen requirements/significant work of breathing, and (3) hemodynamic instability characterized by systolic blood pressure <90 mmHg or mean arterial pressures <65 mmHg. Primary safety endpoints include rapid deterioration of respiratory or clinical status within 4 hours of convalescent plasma transfusion and cumulative incidence of serious adverse events during the study period including transfusion-related acute lung injury (TRALI), transfusion-associated circulatory overload (TACO), severe allergic reactions, and transfusion-related infections.

Secondary outcomes were as follows: (1) 28-day mortality, (2) ventilator-free days, (3) dialysis-free days, (4) vasopressor-free days, (5) ICU-free days, (6) incidence of cardiopulmonary arrest, (7) ICU mortality and length of stay, (8) hospital mortality and length of stay, and (9) qSOFA scores on discharge. Additionally, anti-SARS-CoV-2 IgG antibody titers and SARS-CoV-2 RNA in nasopharyngeal swabs were also compared between groups at baseline and at 1, 7, and 14 (or on discharge) days after enrolment. Patients were followed up until 28 days. In the event that patients are already discharged from the hospital before 28 days, the investigators did telephone follow-up to assess clinical outcomes relevant to the study.

Data Handling and Statistical Analysis

Study data were collected from electronic medical records of the institution and these were manually inputted and managed using REDCap tools hosted at the University of the Philippines Los Baños College of Veterinary Medicine.[25-27] REDCap is a secure, web-based software platform designed to support data capture for research studies, providing 1) an intuitive interface for validated data capture; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages, and 4) procedures for data integration and interoperability with external sources. Clinical data entered into REDCap are password protected. REDCap includes internal quality checks to identify data that appear inconsistent, incomplete, or inaccurate. REDCap also features real time data validation which have been incorporated and tested in the alpha version of our form to ensure quality of data. This makes the tool useful with minimal guidance from the form creator/designer and usable even with minimal technical knowledge with REDCap. Discrepancies between source data and data entered into REDCap were addressed by qualified site personnel. When a data discrepancy warrants correction, the correction was made by the principal investigator.

The desired sample size was determined to be 68 for each group to test the null hypothesis of no difference, against the alternative that hospitalized adult COVID-19 patients given COVID-19 convalescent plasma, on top of local standard of care versus local standard of care alone, will have less need for ICU admission from 37% to 18%, at a one-sided level of significance of 0.05, power of 0.70, and a treatment-to-control ratio of 1:1. Calculations were performed using the simple asymptotic normal approximation of the binomial distribution.

Analyses were performed based on the intent-to-treat set defined as the set of all randomized subjects where each was analyzed according to their assigned treatment, regardless of the treatment actually received. Statistical analysis was performed on randomly assigned treatment groups. Continuous variables were summarized by presenting the median and interquartile range (IQR) for the total number of patients who contributed values. Categorical variables were summarized by presenting the frequency and proportion of patients in each category. Non-parametric statistical tests for continuous variables were done using Wilcoxon rank sum test, and the chi-square test or the Fisher exact test for categorical variables. P-values were adjusted to control for the false discovery rate due to multiple testing. Data analysis were performed in the R programming language for statistical analysis, and RStudio.

Early Study Termination

Despite UP-PGH being a COVID-19 referral center, COVID-19 admissions started to drop in the last quarter of 2020 (note that first recruitment date for the trial was September 28, 2020). March 2021 saw a surge in the number of COVID-19 admissions, however by April 2021 most of the patients being admitted at UP-PGH already had severe and critical COVID (i.e., most have baseline high oxygen requirements) precluding their enrolment in the clinical trial (Appendix). Furthermore, recruitment also became difficult as there were multiple ongoing interventional and observational studies in UP-PGH and most patients are less likely to consent to join another study if they are already part of another (Figure 1, n=90 refused participation). Due to these reasons, there was significant difficulty in completing study participant enrolment.

There was also a continuous decline in the number of successful convalescent plasma donations by October 2020 despite re-strengthened call for donors (this was also seen in other CP collection areas like the Philippine Red Cross and Philippine Blood Center; another reason is that a lot of other institutions are already doing their own CP collections). There was a rise in interested donors by March 2021 (coinciding with the surge), however, most of these donors did not have

sufficient anti-SARS-CoV-2 IgG antibodies to make them eligible for donation. Thus, there was a marked reduction in the pool of convalescent plasma available for potential study participants (incidentally, this is also the same pool being used for the compassionate use pathway of CPT in UP-PGH and also being shared with other institutions). There were times when there were potential study participants but no available type-specific blood and thus recruitment was not pursued. The roll-out of COVID-19 vaccines also posed another challenge as there was a deferral period post-vaccination leading to further drop in potential donors. Appendix also shows the graph of donors screened and bled in UP-PGH.

The last patient enrolled in this study was included on May 13, 2021 and we were unable to recruit more patients thereafter. Due to the above, and the results of the interim analysis mirroring that of bigger studies done in other centers, the study team decided early termination/non-extension.

RESULTS

Study Population

Between September 28, 2020 and May 31, 2021, a total of 174 patients were assessed for inclusion criteria and 44 were enrolled. Consequently, 22 patients were assigned to convalescent plasma and 22 to control (standard of care) (Figure 1). One patient in the control group was lost to follow-up.

The median age of the patient population was 60 years (IQR, 52 to 67); 50% of the patients were males. The median time from onset of COVID-19 symptoms to study enrolment was eight days (IQR, 4 to 10) and was not different between the two groups. Baseline qSOFA scores, systolic blood pressure, temperature, respiratory rate, and oxygen saturation were similar between the two groups. Overall, the convalescent plasma and control groups were similar in terms of demographic and clinical characteristics and baseline laboratory results (Table 1). The use of dexamethasone and other COVID-19 investigational drugs/modalities did not differ between groups (Table 2).

Efficacy and Safety of CPT

A total of two patients (9.1%) in the CPT group and one patient (4.5%) in the control group were admitted to the ICU (Table 3). The primary outcome measure, ICU admission, was not different between the two groups (q-value >0.9). No patient in the CPT group had rapid deterioration of respiratory/clinical status within four hours of transfusion. No patient who received CPT developed TRALI, TACO, anaphylaxis, severe allergic reactions, or transfusion-related infections. One patient developed mild allergic reaction after transfusion and one developed febrile non-hemolytic transfusion reaction.

There was no significant difference in the secondary outcome 28-day mortality (2 patients [9.1%] in the CPT group and none in the control group, q-value >0.90). There was also no significant difference between the two groups in terms of ventilator-free days (mode of 28 days in both groups), dialysis-free days (mode of 28 days in both groups), vasopressor-free days (mode of 28 days in both groups), and ICU-free days (mode of 28 days in both groups). Rates of cardiopulmonary arrest, ICU mortality, and hospital mortality were also similar in both groups (q-value >0.90 for all outcomes). Median hospital length of stay was 15 days (IQR, 13 to 18) in the CPT group and 14 days in the control group (IQR, 12 to 20 days); (q-value >0.90). There was also no significant difference in terms of discharge qSOFA scores in both groups (q-value >0.90). There were two deaths in the study and both were in the CPT group. The first patient expired on the 22nd hospital day (17 days from receipt of CPT) from hypovolemic shock secondary to massive intraabdominal and gastrointestinal bleeding in the context of warfarin anticoagulation for rheumatic heart disease. The second patient expired on the 22nd hospital day (21 days from receipt of CPT) from acute coronary syndrome in the context of chronic kidney disease and diabetes mellitus. These events were judged to be unlikely related to convalescent plasma therapy by the clinical team.

Anti-SARS-CoV-2 IgG Antibody Titers and SARS-CoV-2 RNA Viral Load

Baseline anti-SARS-CoV-2 IgG antibody levels were similar between the two groups (q-value >0.90) (Table 4). Anti-SARS-CoV-2 IgG antibodies were noted to increase from baseline until day 14 (or discharge, whichever is earlier). However, there was also no significant difference between both groups at each time point (q-value >0.9). There was also no significant difference between both groups in terms of SARS-CoV-2 RNA viral load (using cycle threshold [Ct] values) at baseline and at days 1, 7, and 14 (or discharge, whichever is earlier) (Table 4).

Convalescent Plasma Donors and Products

A total of 46 aliquots of convalescent plasma where transfused to those randomized to receive CPT. These came from 26 eligible donors. Of these 26, 20 (76.9%) were apheresis donors while 6 were whole blood donors. Most of the convalescent plasma donors were nulliparous females with no history of blood transfusion (n=14, 53%). The mean age of convalescent plasma donors is 36 years. Majority of donors had mild COVID-19 (n=15, 57%) while two had moderate disease. Nine donors had unrecalled disease severity. There were 19 units of B+ and O+ CP and 8 units of A+ CP used in the study. Of the 46 aliquots of CP available for the trial, 38 were at least 200 mL in volume. In terms of anti-SARS-CoV-2 IgG antibody levels, 14 (30%) aliquots were considered high-titer (≥9.5 S/Co, VITROS®) while 32 (70%) were considered low titer (<9.5 S/Co, VITROS®). All CP products have anti-SARS-CoV-2 IgG antibody levels of at least 5.0 S/Co.

DISCUSSION

In this randomized clinical trial of hospitalized COVID-19 patients, there was no significant difference in the rates of ICU admission between patients who received CPT within 14 days of symptom onset as an adjunct to local standard of care versus those who received standard treatment alone. There was also no significant difference in secondary outcomes of 28-day mortality, ventilator-free days, dialysis-free days, vasopressor-free days, ICU-free days, incidence of cardiopulmonary arrest, ICU mortality, hospital mortality and length of stay, and qSOFA scores on discharge. These findings are congruent to the results of bigger international trials involving patients with moderate COVID-19 severity like the PLACID trial which showed no difference in 28-day all-cause mortality and other clinical outcomes such as time to resolution of symptoms, total duration of respiratory support, proportion requiring ventilation, SOFA score, and

Table 1. Baseline Characteristics of the Study Population and Both Groups

Characteristic	Overall, n=44	CPT, n=22[1]	SOC, n=22[1]	p-value[2]	q-value[3]
***Age**, years*	60 (52, 67)	62 (57, 68)	57 (48, 64)	0.2	>0.9
Sex				0.8	>0.9
Female	22 (50%)	10 (45%)	12 (55%)		
Male	22 (50%)	12 (55%)	10 (45%)		
Day of illness from onset	8 (4, 10)	8 (5, 10)	8 (4, 10)	0.9	>0.9
Co-morbidities					
Hypertension	29 (66%)	17 (77%)	12 (55%)	0.2	>0.9
Diabetes	18 (41%)	12 (55%)	6 (27%)	0.13	>0.9
Heart failure	8 (18%)	3 (14%)	5 (23%)	0.7	>0.9
COPD	1 (2.3%)	0 (0%)	1 (4.5%)	>0.9	>0.9
Chronic liver disease	0 (0%)	0 (0%)	0 (0%)		
Chronic kidney disease	4 (9.1%)	3 (14%)	1 (4.5%)	0.6	>0.9
Malignancy	1 (2.3%)	0 (0%)	1 (4.5%)	>0.9	>0.9
***Temperature**, Celsius*	36.5 (36.10, 36.82)	36.55 (36.10, 36.80)	36.50 (36.15, 36.88)	0.7	>0.9
***Respiratory rate**, cpm*	20 (20, 20)	20 (19, 20)	20 (20, 20)	0.5	>0.9
***Systolic blood pressure**, mmHg*	124 (112, 138)	120 (119, 132)	125 (109, 140)	0.9	>0.9
Unknown	1	1	0		
***Peripheral O_2 saturation**, %*				0.7	>0.9
90	1 (2.3%)	0 (0%)	1 (4.5%)		
92	1 (2.3%)	1 (4.8%)	0 (0%)		
93	1 (2.3%)	1 (4.8%)	0 (0%)		
95	8 (19%)	2 (9.5%)	6 (27%)		
96	7 (16%)	4 (19%)	3 (14%)		
97	7 (16%)	3 (14%)	4 (18%)		
98	10 (23%)	6 (29%)	4 (18%)		
99	8 (19%)	4 (19%)	4 (18%)		
Unknown	1	1	0		
qSOFA score				0.2	>0.9
0	41 (93%)	19 (86%)	22 (100%)		
1	1 (2.3%)	1 (4.5%)	0 (0%)		
2	1 (2.3%)	1 (4.5%)	0 (0%)		
3	1 (2.3%)	1 (4.5%)	0 (0%)		
***Hemoglobin**, g/L*	131 (114, 141)	124 (112, 140)	133 (119, 144)	0.3	>0.9
***Platelet**, $x10^9$/L*	277 (205, 376)	244 (178, 359)	314 (251, 376)	0.2	>0.9
***WBC**, $x10^9$/L*	8.75 (6.45, 10.50)	8.75 (6.15, 10.38)	8.75 (6.78, 10.42)	>0.9	>0.9
***ANC**, cells/uL*	6105 (4357, 8313)	6105 (4782, 8246)	6051 (4043, 8178)	0.5	>0.9
***ALC**, cells/uL*	1029 (710, 1587)	920 (637, 1040)	1307 (978, 1866)	0.041	>0.9
***CRP**, mg/dL*	36 (7, 77)	48 (10, 96)	32 (5, 57)	0.5	>0.9
Unknown	1	1	0		
***LDH**, u/L*	297 (244, 372)	340 (274, 390)	264 (233, 341)	0.13	>0.9
Unknown	1	0	1		
***Ferritin**, ng/mL*	855 (568, 1258)	1028 (659, 1320)	742 (305, 938)	0.11	>0.9
Unknown	2	0	2		

[1]*Statistics presented: median (IQR); n (%)*
[2]*Statistical tests performed: Wilcoxon rank-sum test; chi-square test of independent; Fisher's exact test*
[3]*False discovery rate correction for multiple testing*

Table 2. Other COVID-19 Investigational Agents Received

Characteristic	Overall, n=44	CPT, n=22[1]	SOC, n=22[1]	p-value[2]	q-value[3]
Co-intervention				>0.9	>0.9
Dexamethasone	13 (46%)	6 (40%)	7 (54%)		
Interferon b1a	1 (3.6%)	1 (6.7%)	0 (0%)		
Remdesivir	3 (11%)	2 (13%)	1 (7.7%)		
Remdesivir, dexamethasone	3 (11%)	2 (13%)	1 (7.7%)		
Tocilizumab	1 (3.6%)	0 (0%)	1 (7.7%)		
Tocilizumab, dexamethasone, hemoperfusion	1 (3.6%)	0 (0%)	1 (7.7%)		
Tocilizumab, remdesivir	1 (3.6%)	1 (6.7%)	0 (0%)		
Tocilizumab, remdesivir, dexamethasone	5 (18%)	3 (20%)	2 (15%)		
None	16	7	9		

[1]Statistics presented: median (IQR); n (%)
[2]Statistical tests performed: Wilcoxon rank-sum test; chi-square test of independent; Fisher's exact test
[3]False discovery rate correction for multiple testing

requirement of vasopressors[17] and the ConPlas-19 Trial which showed no significant difference in proportion of patients requiring non-invasive and invasive ventilation as well as 15-day mortality.[23] Several local studies (retrospective cohorts and quasi-experimental study designs) also showed no significant difference in mortality, length of hospital stay, severity of illness, and need for critical care support among those who received CPT and those who did not.[28-30] Furthermore, a collaborative systematic review and meta-analysis of 33 ongoing, discontinued, and completed RCTs (both published and unpublished) with 15,476 patients showed that use of CPT is not associated with a reduction in all-cause mortality.[31]

In contrast, another RCT done in Argentina involving elderly patients with moderate disease severity showed lower rates of development of severe respiratory disease among those who received CPT less than 72 hours after onset of symptoms versus those who received placebo.[19] This underscores the importance of giving CPT as early as possible to maximize its potential in neutralizing viral load among those infected with COVID-19. The US FDA, in its Emergency Use Authorization (EUA) of COVID-19 convalescent plasma for treatment of hospitalized patients with COVID-19 emphasized that transfusion of CPT late in the course of illness has not been associated with any clinical benefit.[32]

Taking together the results of this study and the results of other large international clinical trials, CPT appears to have very limited clinical benefit among patients with moderate to severe COVID-19 disease. This is congruent with the latest living clinical practice guidelines of the Institute of Clinical Epidemiology of the UP Manila National Institutes of Health which recommends against the use of COVID-19 convalescent plasma in patients with COVID-19 infection (strong recommendation; moderate quality of evidence).[33] This is also parallel with the Infectious Disease Society of America (IDSA) guidelines which recommend against the use of COVID-19 convalescent plasma among hospitalized COVID-19 patients (conditional recommendation; low certainty of evidence).[34] Furthermore, the IDSA panel recommends use of CPT in mild-to-moderate COVID-19 only in the context of a clinical trial.

An inherent challenge in CPT is the wide variation in mean antibody levels between convalescent plasma products taken from different donors. In this study, majority of convalescent plasma units had anti-SARS-CoV-2 IgG antibody levels between 5.0 and 9.5 S/Co, and by US FDA definition, these are considered low-titer.[28] This may have underestimated the effect of CPT in this trial as other trials have shown a dose-dependent effect for anti-SARS-CoV-2 IgG titers (less risk for disease worsening with higher IgG antibody titers).[19]

In this study, there was also no significant difference in anti-SARS-CoV-2 IgG antibody levels between both groups at baseline, a day after convalescent plasma transfusion, seven days after transfusion, and at discharge (or 14 days, whichever is longer) between groups. It was notable in this study that baseline anti-SARS-CoV-2 IgG levels were already present and may actually be comparable to IgG antibody levels of convalescent plasma donors. This was reflective of an RCT done in Netherlands which showed that 80.3% (53/66) patients who have been symptomatic only for a median of 10 days (IQR, 6 to 15) already had anti-SARS-CoV-2 antibodies at baseline and that 79% (44/56) of patients had neutralizing antibody titers (using plaque reduction neutralization testing) comparable with their convalescent plasma donors (1:160 vs 1:160, p=0.40).[21] This trial showed no difference in mortality, length of hospital stay of day-15 disease severity between those who received CPT versus those who received standard of care only. This trial was terminated early due to these observations which brings into question the potential benefit of CPT in this specific study population. This study emphasized the possible need to screen for baseline antibodies to identify patients that may still benefit from convalescent plasma. Our RCT also showed no significant difference in the SARS-CoV-2 viral loads between both groups. This is in contrast with other studies which showed faster negative conversion rates of viral PCR among those who received CPT compared to those who only received standard of care.[18]

Table 3. Comparison of Outcomes between Groups

Characteristic	Overall, n=44	CPT, n=22[1]	SOC, n=22[1]	p-value[2]	q-value[3]
ICU admission				>0.9	>0.9
No	41 (93%)	20 (91%)	21 (95%)		
Yes	3 (6.8%)	2 (9.1%)	1 (4.5%)		
Cardiopulmonary arrest				0.5	>0.9
No	42 (95%)	20 (91%)	22 (100%)		
Yes	2 (4.5%)	2 (9.1%)	0 (0%)		
ICU Mortality				0.5	>0.9
No	42 (95%)	20 (91%)	22 (100%)		
Yes	2 (4.5%)	2 (9.1%)	0 (0%)		
Hospital Mortality				0.5	>0.9
No	42 (95%)	20 (91%)	22 (100%)		
Yes	2 (4.5%)	2 (9.1%)	0 (0%)		
Hospital length of stay, *days*	14 (12, 19)	15 (13, 18)	14 (12, 20)	0.7	>0.9
Ventilator-free days				>0.9	>0.9
17	1 (2.3%)	1 (4.5%)	0 (0%)		
21	1 (2.3%)	1 (4.5%)	0 (0%)		
28	41 (95%)	20 (91%)	21 (100%)		
Unknown	1	0	1		
Dialysis-free days				0.6	>0.9
0	1 (2.3%)	1 (4.5%)	0 (0%)		
17	1 (2.3%)	1 (4.5%)	0 (0%)		
21	1 (2.3%)	1 (4.5%)	0 (0%)		
28	40 (93%)	19 (86%)	21 (100%)		
Unknown	1	0	1		
ICU-free days				>0.9	>0.9
17	1 (2.3%)	1 (4.5%)	0 (0%)		
21	1 (2.3%)	1 (4.5%)	0 (0%)		
25	1 (2.3%)	0 (0%)	1 (4.8%)		
28	40 (93%)	20 (91%)	20 (95%)		
Unknown	1	0	1		
Vasopressor-free days				>0.9	>0.9
17	1 (2.3%)	1 (4.5%)	0 (0%)		
21	1 (2.3%)	1 (4.5%)	0 (0%)		
25	1 (2.3%)	0 (0%)	1 (4.8%)		
28	40 (93%)	20 (91%)	20 (95%)		
Unknown	1	0	1		
Mortality				0.5	>0.9
No	41 (95%)	20 (91%)	21 (100%)		
Yes	2 (4.7%)	2 (9.1%)	0 (0%)		
Unknown	1	0	1		
qSOFA score (on discharge)				0.2	>0.9
0	41 (93%)	19 (86%)	22 (100%)		
1	1 (2.3%)	1 (4.5%)	0 (0%)		
3	2 (4.5%)	2 (9.1%)	0 (0%)		

[1]*Statistics presented: median (IQR); n (%)*
[2]*Statistical tests performed: Wilcoxon rank-sum test; chi-square test of independent; Fisher's exact test*
[3]*False discovery rate correction for multiple testing*

This study shows that CPT is safe and well-tolerated with no documented immediate serious adverse events like TRALI, TACO, anaphylaxis, severe allergic reactions, or transfusion-related infections. The safety of convalescent plasma was first shown in an observational study involving 20,000 hospitalized COVID-19 patients in the United States which reported low incidence (<1%) of serious adverse events.[35]

This study has several limitations. The study was terminated early and the sample size was small which makes the study underpowered to detect a clinically important benefit of CPT. This study has an open-label design and not placebo-controlled, and this introduces a risk of reporting bias for adverse events and other outcomes. Convalescent plasma products are difficult to standardize and are intrinsically heterogenous, and these may have significantly affected the outcomes of this study. Further studies with larger study population, use of placebo, and use of COVID-19 convalescent plasma with more standardized antibody titers (neutralizing antibodies) are warranted to clearly elucidate the possible clinical benefit of CPT in COVID-19.

Table 4. Comparison of anti-SARS-CoV-2 IgG Antibody Levels (S/Co) and SARS-CoV-2 RNA Viral Load (Ct values) between Groups

Characteristic	Overall, n=44	CPT, n=22[1]	SOC, n=22[1]	p-value[2]	q-value[3]
IgG Day 0[4] Unknown	8 (0, 24) 1	9 (4, 46) 1	7 (0, 15) 0	0.3	>0.9
IgG Day 1	11 (6, 22)	12 (8, 48)	10 (1, 16)	0.11	>0.9
IgG Day 7 Unknown	15 (9, 33) 1	17 (11, 54) 1	15 (9, 22) 0	0.4	>0.9
IgG Day 14 *(or discharge)* Unknown	16 (13, 26) 5	17 (13, 28) 2	16 (11, 25) 3	>0.9	>0.9
ORF1ab Day 0[4] Unknown	36 (32, 45) 2	36 (32, 45) 2	45 (34, 45) 0	0.3	>0.9
ORF1ab Day 1	39 (31, 45)	36 (30, 45)	45 (37, 45)	0.1	>0.9
ORF1ab Day 7 Unknown	45 (36, 45) 1	45 (36, 45) 0	45 (37, 45) 1	0.4	>0.9
ORF1ab day 14 *(or discharge)* Unknown	45.0 (36.3, 45.0) 6	45.0 (35.6, 45.0) 1	45.0 (45.0, 45.0) 5	0.3	>0.9

[1]*Statistics presented: median (IQR); n (%)*
[2]*Statistical tests performed: Wilcoxon rank-sum test; chi-square test of independent; Fisher's exact test*
[3]*False discovery rate correction for multiple testing*
[4]*Day 0 refers to day of convalescent plasma transfusion for CPT group (test taken before transfusion)*

CONCLUSION

Among hospitalized COVID-19 patients, no significant differences were observed in the need for ICU admission between patients given CPT as adjunct to standard of care and those who received standard of care alone. Furthermore, there was also no significant difference between groups in secondary outcomes of 28-day mortality, ventilator-free days, dialysis-free days, vasopressor-free days, ICU-free days, incidence of cardiopulmonary arrest, ICU mortality, hospital mortality and length of stay, qSOFA scores on discharge, anti-SARS-CoV-2 IgG antibody titers, and SARS-CoV-2 RNA viral load. These findings highlight the limited clinical benefit of COVID-19 convalescent plasma among hospitalized COVID-19 patients. These findings are congruent with local clinical practice guidelines which also recommend against the use of convalescent plasma in patients with COVID-19 infection. Interpretation, however, is limited by early termination of the trial which may have been underpowered to detect a clinically important difference.

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Statement of Authorship

DTVG, TED, MACA and FMMC contributed in the conceptualization of work, acquisition and analysis of data, drafting and revising of manuscript, and final approval of the version to be published. CDD contributed in the conceptualization of work, acquisition and analysis of data, and final approval of the version to be published. SCM, RNA, AKHQ, JACL, CFNC, ALME, RANK, FMH, LBB, GJCJ, IMSE, MCMS, AFGM, AVM, JDV, JMCJ, PYT, JAL, MMA and MALM contributed in the conceptualization of work, acquisition of data, and final approval of the version to be published. SEAS contributed in the acquisition and analysis of data, and final approval of the version to be published.

Author Disclosure

All authors declared no conflicts of interest.

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APPENDIX

Study Participant and Convalescent Plasma Donor Recruitment

For the last quarter of 2020, there was also a decreasing number of COVID-19 hospitalizations in UP-PGH. By March 2021, there was a surge in number of COVID-19 admissions, however, these patients were already too toxic to be eligible for the trial. The UP-PGH is home to a lot of ongoing clinical trials (e.g., Solidarity, favipiravir, VCO, tocilizumab, etc.) and non-intervention studies. With the limited number of COVID-19 patients in UP-PGH, these could account for the decreasing number of patients allocated/referred to our clinical trial. All patients admitted in UP-PGH are invited to join these trials and most of them will consent to join. However, once they are already enrolled in another study (even if non-interventional), they are already less likely to consent to another study (especially RCTs). The following table summarizes the number of patients being referred to the trial (over time), the actual number of patients enrolled, and those deferred (and reasons for deferral).

	Sept	Oct	Nov	Dec	Jan	Feb	March	April	May
Enrolled	**3**	**7**	**7**	**4**	**5**	**1**	**13**	**3**	**1**
Deferred	**1**	**11**	**11**	**6**	**12**	**7**	**35**	**37**	**7**
No consent	1	9	7	5	10	5	29	17	5
Ineligible, recent BT	0	1	3	0	0	0	0	1	0
Ineligible, high O_2 needs	0	1	0	1	1	1	4	14	1
Ineligible, beyond 14 days	0	0	0	0	1	0	1	4	1
Ineligible, enrolled in another trial	0	0	0	0	0	1	0	0	0
Ineligible, hemodynamic instability	0	0	1	0	0	0	1	1	0
Total	**4**	**18**	**18**	**10**	**17**	**8**	**48**	**10**	**8**

Beginning October 2020, there was a drop in the number of donors being screened and eventually found eligible for donation (other collection areas like the Philippine Red Cross and Philippine Blood Center also experienced the same). There was a rise in interested donors by March 2021 which coincided with another surge in number of COVID-19 cases, however, most of these donors didn't have sufficient antibodies to make them eligible for donation. Thus, there was a marked reduction in the pool of convalescent plasma available for potential study participants (incidentally, this is also the same pool being used for compassionate use in the institution and also being shared to other institutions). There were times when there were potential study participants but no available type-specific blood and thus recruitment was not pursued. The roll-out of COVID-19 vaccines also caused a drop in potential donors (as there was a deferral period post-vaccination prior to being eligible for blood donation). Despite re-strengthening of our campaign to increase our donors (through release of promotional materials in social media and active campaign from our institution's spokesperson in mainstream media), there was a drop in potential donors. The following figure showed the number of recovered COVID-19 patients/donors screened and eventually bled.