Convalescent Plasma Therapy in Critically Ill COVID-19 Patients: An Open Label Trial

Faryal Khamis[1*], Zainab Al Arimi[2], Hamed Al Naamani[3], Maher Al Bahrani[4], Nenad Pandak[1], Zakaryia Al Bolushi[1], Stephan S. Deenadayalan[5], Adil Al Lawati[5], Issa Al Salmi[6], Ibrahim Al-Zakwani[7,8]

[1]*Infectious Diseases Unit, Department of Internal Medicine, The Royal Hospital, Muscat, Oman*

[2]*Department of Blood Bank Services, Ministry of Health, Muscat, Oman*

[3]*Department of Pharmacy, The Royal Hospital, Muscat, Oman*

[4]*Department of Anesthesia and Critical Care, The Royal Hospital*

[5]*Acute Medicine Unit, Department of Medicine, Royal Hospital Muscat, Sultanate of Oman*

[6]*Department of Nephrology, The Royal Hospital, Muscat, Oman*

[7]*Department of Pharmacology & Clinical Pharmacy, College of Medicine & Health Sciences, Sultan Qaboos University, Muscat, Oman*

[8]*Gulf Health Research, Muscat, Oman*

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***Corresponding author:** khami001@gmail.com*

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Abstract

Objective: To evaluate the effectiveness of convalescent plasma (CP) therapy for patients with COVID-19 on mechanical ventilation (MV) and/or acute respiratory distress syndrome (ARDS).

Background: The novel coronavirus (SARS-CoV-2) pandemic continues to spread globally without availability of an effective treatment. In search for the cure, convalescent plasma containing protective antibodies from survivors of COVID-19 infection has shown potential benefit in non-ICU setting.

Methods: An open label trial performed in a single center, The Royal Hospital, in Oman. The study was conducted from April 14, 2020, to June 17, 2020. The trial included 94 participants with laboratory-confirmed COVID-19. The primary outcomes included extubation rates/ discharges from the hospital and overall mortality, while secondary outcomes were length of stay (LOS) and improvement in respiratory and laboratory parameters. Analyses were performed using univariate statistics.

***Results*:** The overall mean age of the cohort was 50±15 years and 90% (n=85) were males. A total of 78% (n=73) of the patients received CP. Those on CP were associated with higher extubation rate (42% *vs* 33%; $p < 0.001$), higher extubation/home discharges rate (64% *vs* 24%; $p = 0.001$) and tendency towards lower overall mortality (19% *vs* 29%; $p = 0.354$; *study power* = 11%) when compared to COVID-19 patients that did not receive CP.

Conclusions: CP was associated with higher extubation/home discharges and tendency towards lower overall mortality when compared to those that did not receive CP in COVID-19 patients on MV or in those with ARDS. Further studies are warranted to corroborate our findings.

Keywords: Convalescent plasma therapy, COVID-19, coronavirus, acute respiratory distress syndrome, mortality.

Introduction

The number of cases affected by coronavirus disease 2019 (COVID-19) and related complications and deaths is dramatically increasing worldwide.[1] Currently, COVID-19 pandemic has affected 77,169,291 individuals and has caused 1,699,560 deaths globally.[2] To date, there is no single effective therapeutic agent for COVID-19 infection. Standard supportive care including oxygen supply and intensive care unit (ICU) admission are the main management modalities provided for critically ill patients and several other investigational therapeutic options are currently being evaluated as potential therapies to be added to supportive care.[3]

Providing passive immunization in the form of convalescent plasma (CP) infusion that contains adequate neutralizing antibodies against severe acute respiratory syndrome coronavirus 2 (SARS-COV-2), is one of the potential therapeutic options that are currently being evaluated in various clinical trials.[3-5] CP therapy has been used in the past for the treatment of several other viral diseases and has been effective in the treatment of severe acute respiratory syndrome (SARS), Ebola virus (EBOV), Middle East respiratory syndrome (MERS), and H1N1 influenza.[6-8] Similarly, evidence from earlier un-controlled case-series from China on the use of CP in patients with COVID-19 infection has shown encouraging results favoring its use for severely ill patients. These studies have demonstrated clinical and laboratory improvements measured by reduction of oxygen requirements and mechanical ventilation (MV), improvement of the radiological findings, clearance of the virus and normalization of laboratory parameters.[4,5]

Given the public health emergency of the COVID-19 pandemic, the Food and Drug Administration (FDA) permits the use of CP for COVID-19 patients through three pathways. As an investigational therapeutic option, via single patient emergency Investigations New Drug

(eIND) applications, and through expanded use.[9] Several studies are currently being conducted to evaluate the safety and efficacy of CP for the treatment of COVID-19 disease. Recent publications have demonstrated high safety profile of CP therapy for patients as no major untoward events have been reported.[10-13] Despite the methodological limitations of these studies, the data suggests some clinical benefits.

Nevertheless, the potential clinical benefit and risk of convalescent plasma in COVID-19 remains uncertain due to the use of several other supportive interventions and lack of widescale and well-designed randomized clinical trials. The purpose of this study was to describe the initial clinical experience with CP transfusion administered to critically ill patients on MV with COVID-19 infection in Oman.

Methods

Study design and participants

An open label trial was conducted in Royal Hospital, a tertiary care hospital in Muscat, Oman. The study was conducted from April 17th to June 20th, 2020, and it compared two different treatment modalities of COVID-19 patients, CP with standard of care *versus* standard of care alone. The standard care group was a historical control who were admitted at the same hospital from March 12th to April 16th, 2020. Both groups received the standard of care for ICU patients that included hydroxychloroquine and lopinavir /ritonavir as per the National Guidelines (National Clinical Management Pathways for Hospitalized Patients with COVID-19, Ministry of Health, Oman, April 2020).[14]

The study was approved by the Royal Hospital Research and Ethics Committee (SRC#36/2020) and a written informed consent was obtained from the patient or (if intubated) through their health proxy.

CP collection

CP was collected from patients who had recovered from SARS-COV-2 and completed 14 days free of symptoms. CP donors were selected based on the National Blood Donor Selection Criteria (NBDSC) that includes: weight >50 kg and age range between 18-65 years. Standard pre-donation assessment was conducted for each donor and pre-screening tests were performed including blood group, serological tests for transfusion transmitted infections (TTI) and SARS-COV-2 IgG level.

The collection was performed using apheresis procedure and the volume collected was adjusted by gender, height and weight and according to standard policy procedures. Each donor was tested again for the blood group and TTI by both nucleic acid amplification technique (NAT) and serology at the time of the donation. The plasma apheresis units were then processed in the laboratory and divided into two to three aliquots with a volume ranges from 200-250 mL and stored at -80◦C. CP units from all the blood groups were collected to meet the demands of patients. The units were stored at the blood service and were issued to the hospital blood bank on request. No neutralizing antibody titer of the donors or patients were measured due to global unavailability of the needed equipment's and reagents during the period from April to June,2020. However, all eligible donors were tested for the SARS-CoV-2 IgG antibodies by ELISA method that gives a semi-quantitative measurement of the IgG levels. Only units that tested positive for the SARS-

CoV-2 IgG were issued. In the cohort that received CP, 6 patients were excluded due to unavailability of matched plasma.

CP protocol

The study included patients ≥18 years of age admitted with PCR confirmed COVID-19 pneumonia with one of the following high-risk criteria:

- Critical respiratory condition or rapidly increasing oxygen requirement requiring MV.
- Severe pneumonia or ARDS with one of the following additional risk factors for complicated disease: age ≥60 years, immunodeficiency, hypertension, diabetes mellitus, coronary heart disease (CHD), chronic obstructive pulmonary disease (COPD), lymphocyte count <0.8 $x10^9$/L, lactate dehydrogenase (LDH) >250 U/L, D-dimer >1 µg/mL, serum ferritin >300 µg/L.

The study exclusion criteria were: patient's rejection of plasma therapy, known IgA deficiency, hypersensitivity reaction to blood or blood products, past history of severe transfusion reactions, unavailability of matching plasma and more than 14 days of illness. The patients received 200 mL of CP at enrollment (day 0). A second dose was given 24-48 hours after the first dose in case the patient did not significantly improve and /or remained in critical respiratory condition.

Data gathered included demographics, baseline characteristics, risk factors, sequential organ failure assessment (SOFA) score, respiratory parameters (fraction of inspired oxygen (FiO2), positive end-expiratory pressure (PEEP), partial pressure of arterial oxygen (PaO2)/FiO2) *pre*-intervention on day 0 and *post*-intervention on day 3, day 7 and day 14. In addition, data collected included laboratory parameters (absolute lymphocyte count (ALC), C-reactive protein

(CRP), LDH, serum ferritin, D-dimer, interleukin-6 (IL-6), pH and lactate) *pre*-intervention on day 0 and *post*-intervention on day 3, day 7 and day 14.

The primary outcomes included extubation rates/ discharges from hospital and mortality rates. Secondary outcomes included length of stay and improvements in respiratory and laboratory parameters.

Definitions

1. ARDS was defined as an acute-onset hypoxemia (the ratio of Pao2:Fio2 of <300) with >50% bilateral pulmonary opacities on chest imaging within 24 to 48 hours that were not fully explained by congestive heart failure.[15]
2. Pneumonia in adults was defined as evidence of lower respiratory tract infection, including difficulty in breathing, fast breathing >20 breaths/min, crackles on examination, or new infiltrates on chest x-ray.
3. Severe pneumonia in adults was defined as respiratory infection with fever and one of the following: respiratory rate of >30 breaths/ minute, severe respiratory distress and oxygen saturation (SpO2) of <90% on room air. **(***World Health Organization (WHO)/ 2019 – n CoV/clinical/2020.5*).
4. Pneumonia in adults was defined as evidence of lower respiratory tract infection, including difficulty in breathing, fast breathing >20 breaths/min, crackles on examination, or new infiltrates on chest x-ray.
5. Critical respiratory condition requiring high-flow nasal cannula, or non-invasive ventilation (NIV), MV, or rapidly increasing oxygen requirement.

6. Sepsis defined as life-threatening organ dysfunction caused by a dysregulated host response to infection.[16]
7. Septic shock in adults was defined as sepsis with persisting hypotension despite volume resuscitation, requiring vasopressors to maintain mean arterial pressure of ≥65 mmHg and serum lactate level of > 2 mmol/L.
8. Multiple organ dysfunction syndrome (MODS) was defined as the progressive, potentially reversible dysfunction of two or more organ systems following acute, life- threatening disruption of systemic homeostasis.

Statistical Analysis

Descriptive statistics was used to analyse the data. For categorical variables, frequencies and percentages were reported. Differences between groups were analyzed using Pearson's $\chi 2$ tests (or Fisher's exact tests for expected cells of <5). For continuous variables, mean and standard deviation were used to summarize the data while analyses were performed using Student's t-test. Laboratory investigations and ventilatory parameters of the cohort stratified by CP over the course of the hospital admission, as presented in Table 2, were analysed using the repeated measures analysis of variance (ANOVA) and the *p*-values for the differences over time were corrected using the Greenhouse-Geiser correction factor. Statistical analyses were conducted using STATA version 16.1 (STATA Corporation, College Station, TX, USA).

Results

A total of 94 critically ill COVID-19 patients were enrolled in the study, 94% (n = 88) of which were on MV while 71% (n = 67) had ARDS. Their overall mean age was 50 ± 15 years and

90% (n = 85) were males. A total of 78% (n = 73) of the patients had CP added to their medical management, in addition to the standard of care that was provided to all patients. The three most prominent symptoms observed were fever (86%; n = 81), shortness of breath (79%; n = 74) and cough (71%; n = 67). Other signs and symptoms as reported by the patients are shown in **Figure 1**.

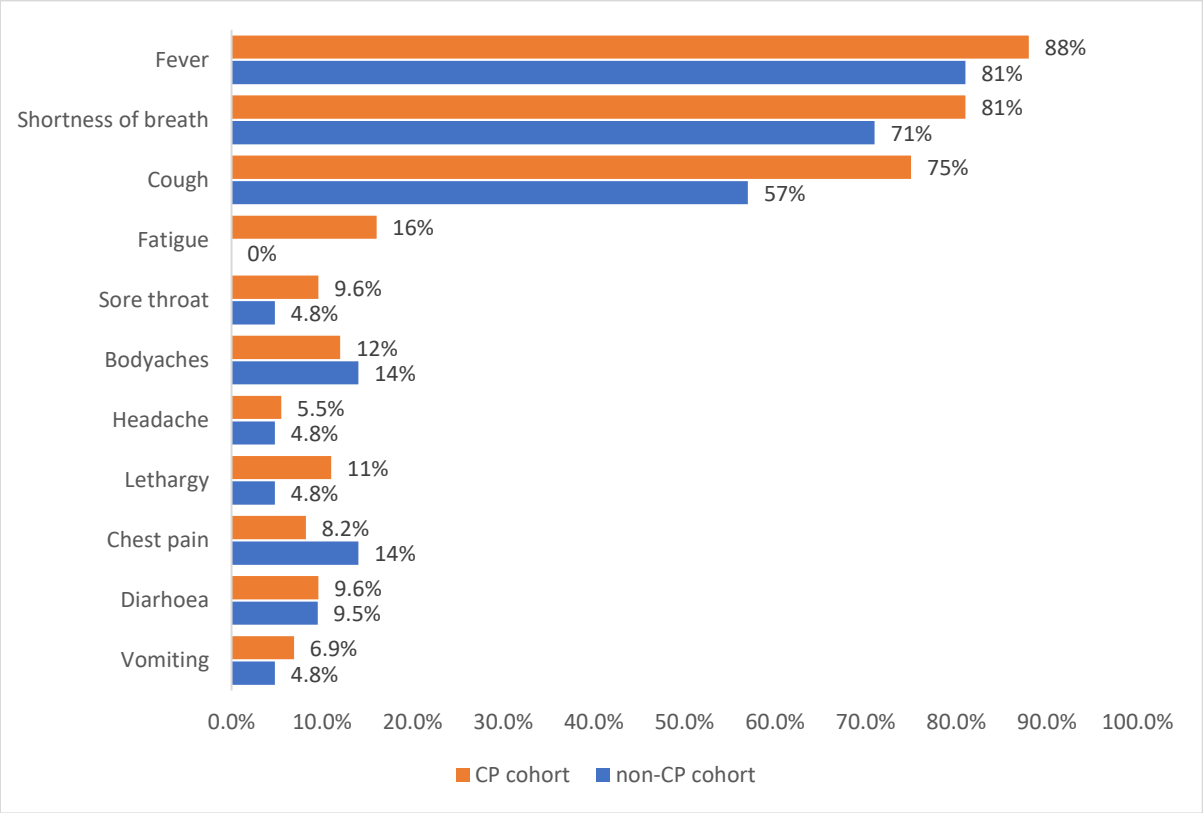

Figure 1: Signs and symptoms of the cohort stratified by convalescent plasma (CP).

Hypertension (37%; n = 35), diabetes mellitus (36%; n = 34), and chronic heart disease (7.5%; n = 7) were the three most prevalent comorbidities. The overall median sequential organ failure assessment (SOFA) score was 5 (3 - 7). A total of 7.5% (n = 7) and 8.5% (n = 8) of the patients had severe pneumonia and sepsis/septic shock, respectively. X-ray findings indicated major bilateral consolidation opacities in 73% (n = 69) of the patients with 23% (n = 22) showing

reticular interstitial patchy thickening in their X-rays. There were no significant differences among the demographic and clinical characteristics between the cohorts. Other details of the demographic and clinical characteristics are presented in **Table 1**.

Table 1: Demographic and clinical characteristics of the cohort with and without convalescent plasma.

Characteristic, *n (%) unless specified otherwise*	All (N = 94)	Convalescent plasma		*p*-value
		No (n = 21)	Yes (n = 73)	
Age, mean±SD, years	51±15	53±17	51±15	0.644
Male gender	85 (90%)	19 (90%)	66 (90%)	0.993
Smoking, past/present	4 (4.3%)	1 (4.8%)	3 (4.1%)	1.000
Hypertension	35 (37%)	8 (38%)	27 (37%)	0.926
Diabetes mellitus	34 (36%)	11 (52%)	23 (32%)	0.079
Chronic lung disease	1 (1.1%)	1 (4.8%)	0	0.223
Chronic heart disease	7 (7.5%)	1 (4.8%)	6 (8.2%)	1.000
Chronic renal disease	3 (3.2%)	1 (4.8%)	2 (2.7%)	0.536
Asthma	2 (2.1%)	0	2 (2.7%)	1.000
Pneumonia	20 (21%)	2 (9.5%)	18 (25%)	0.135
Severe pneumonia	7 (7.5%)	0	7 (9.6%)	0.343
Sepsis/septic shock	8 (8.5%)	0	8 (11%)	0.192
X-Ray findings				
Bilateral consolidations	69 (73%)	13 (62%)	56 (77%)	0.261
Patchy reticular infiltrations	22 (23%)	5 (24%)	17 (23%)	1.000
SOFA score	5 (3-7)	6 (2-9)	5 (3-7)	0.475

SD = standard deviation; SOFA = sequential organ failure assessment.

There were no significant differences among the laboratory investigations and ventilatory parameters between the two cohorts as shown in **Table 2**. However, there were significant changes over time in the CP cohort with regards to the white blood cell (WBC) count ($p < 0.001$; *increase*), CRP ($p = 0.005$; *decrease*), total bilirubin ($p < 0.001$; *decrease*), PEEP ($p = 0.007$; *decrease*) and FiO2 ($p < 0.001$; *decrease*).

Table 2: Laboratory investigations and ventilatory parameters of the cohort stratified by convalescent plasma (CP) use.

Investigation, mean±SD	Day 0 no CP vs CP	Day 3 no CP vs CP	Day 7 no CP vs CP	Day 14 no CP vs CP	Overall *p*-value over time	Overall *p*-value between groups
WBC count, $x10^9$/L	8.7 *vs* 10.2	11.8 *vs* 10.1	12.2 *vs* 11.9	15.9 *vs* 13.4	<0.001	0.693
ALC, $x10^9$/L	1.3 *vs* 0.9	1.5 *vs* 0.9	2.0 *vs* 1.2	2.0 *vs* 1.8	0.311	0.330
Hb, g/dL	13.2 *vs* 12.9	12.5 *vs* 11.8	11.5 *vs* 11.4	12.6 *vs* 10.1	0.119	0.288
Platelets, $x10^9$/L	310 *vs* 292	360 *vs* 344	376 *vs* 365	413 *vs* 322	0.141	0.836
D-dimer, μg/mL	7.1 *vs* 9.1	3.4 *vs* 8.4	3.9 *vs* 7.4	6.0 *vs* 8.5	0.970	0.915
CRP, mg/dL	171 *vs* 173	168 *vs* 120	101 *vs* 61	17 *vs* 19	0.005	0.365
Creatinine, μg/L	99 *vs* 95	122 *vs* 122	107 *vs* 140	53 *vs* 122	0.592	0.930
ALT, U/L	20 *vs* 85	54 *vs* 101	39 *vs* 149	31 *vs* 87	0.872	0.524
AST, U/L	33 *vs* 92	59 *vs* 104	61 *vs* 161	40 *vs* 61	0.876	0.776
Total bilirubin, mmol/L	16 *vs* 13	11 *vs* 22	9 *vs* 15	11 *vs* 9	<0.001	0.839
Ferritin, μg/L	1101 *vs* 2744	443 *vs* 1471	843 *vs* 1362	561 *vs* 942	0.979	0.780
LDH, U/L	759 *vs* 700	507 *vs* 594	472 *vs* 533	574 *vs* 526	0.210	0.529
Corrected calcium, mmol/L	2.1 *vs* 2.1	17.9 *vs* 4.2	2.3 *vs* 2.2	2.2 *vs* 2.2	0.066	0.482
IL-6, pg/mL	166 *vs* 427	577 *vs* 840	2925 *vs* 937	179 *vs* 923	0.051	0.865
PO4, mg/dL	1.6 *vs* 1.4	1.7 *vs* 1.2	1.7 *vs* 1.5	1.2 *vs* 1.6	0.785	0.321
PEEP, cm H_20	13 *vs* 12	13 *vs* 11	13 *vs* 10	10 *vs* 10	0.007	0.304
FiO2, mmHg	96 *vs* 69	41 *vs* 54	60 *vs* 48	55 *vs* 53	<0.001	0.256
PaO2, mmHg	86 *vs* 80	98 *vs* 88	67 *vs* 82	77 *vs* 88	0.662	0.793
pCO2, kPa	46 *vs* 44	50 *vs* 46	60 *vs* 46	-	0.234	0.887
SpO2, mmHg	86 *vs* 92	96 *vs* 93	90 *vs* 94	-	<0.001	<0.001

SD = standard deviation; WBC = white blood cell; ALC = absolute lymphocyte count; Hb = haemoglobin; CRP = C-reactive protein; ALT = alanine transminase; AST = aspartate aminotransferase; LDH = lactate dehydrogenase; IL-6 = interleukin 6; PO4 = phosphate; PEEP = positive end-expiratory pressure; FiO2 = fraction of inspired oxygen; PaO2 = partial pressure of arterial oxygen; pCO2 = partial pressure of carbon dioxide; SpO2 = oxygen saturation.

The analyses were performed using the repeated measures analysis of variance (ANOVA) and the *p*-values for the differences over time were corrected using the Greenhouse-Geiser correction factor.

Those on CP were less likely to be prescribed azithromycin (1.4% *vs* 57%; $p < 0.001$). Seventy percent (n = 66) of the patients in both groups received intravenous steroids. Patients in the CP group were less likely to be prescribed interferon beta 1B or peginterferon alpha-2a (6.9% *vs* 71%; $p < 0.001$) compared to those that were not on CP. They also had longer length of hospital stays compared to those not on CP (12 *vs* 8 days; $p = 0.047$). However, those on CP were more likely to be extubated (42% *vs* 33%; $p < 0.001$) as well the higher composite endpoint of extubation/discharged home alive (64% *vs* 24%; $p = 0.001$) when compared to those that did not received CP. Furthermore, those on CP had also the tendency for lower mortality when compared to COVID-19 patients that did not receive CP (19% *vs* 29%; $p = 0.354$; *study power* = 11%). The list of other medications and clinical outcomes are outlined in **Table 3**.

Table 3: Medications and clinical outcomes of the cohort stratified by convalescent plasma use.

Characteristic, *n (%) unless specified otherwise*	All (N=94)	Convalescent plasma		*p*-value
		No (n=21)	Yes (n=73)	
Antibiotic				
Ceftriaxone	62 (66%)	14 (67%)	48 (66%)	0.938
Piperacillin	69 (73%)	15 (71%)	54 (74%)	0.816
Meropenem	30 (27%)	4 (8.3%)	26 (42%)	1.000
Azithromycin	13 (14%)	12 (57%)	1 (1.4%)	<0.001
Antiviral				
Lopinavir/Ritonavir	79 (84%)	16 (76%)	63 (86%)	0.265
Antimalarial				
Hydroxychloroquine	76 (81%)	18 (86%)	58 (79%)	0.754
Intravenous steroids	66 (70%)	15 (71%)	71 (70%)	0.890
Interferons*	20 (21%)	15 (71%)	5 (6.9%)	<0.001
Outcomes				
Extubated	42 (38%)	16 (33%)	26 (42%)	<0.001
Remains hospitalized	39 (41%)	9 (43%)	30 (41%)	0.885
Discharged home	34 (36%)	5 (24%)	29 (40%)	0.181
Extubated/discharged home	52 (55%)	5 (24%)	47 (64%)	0.001

Died	20 (21%)	6 (29%)	14 (19%)	0.354

* included interferon beta 1B and peginterferon alpha-2a.

Discussion

We conducted an open label trial analysing the effectiveness of CP in COVID-19 infected patients that required mechanical ventilation and/or had ARDS. Both the groups had similar demographics, baseline characteristics and bilateral infiltrations on chest X-ray that is in accordance with the criteria for severe ARDS. In this study, a large number of COVID-19 patients had ARDS caused by cytokine storm and host immune responses.[17,18] CP was associated with higher rates of extubation as well as the composite endpoint of extubation/ home discharges. The benefit of CP that has been observed in these patients is partly hypothesized to be caused by neutralizing antibodies present in the donor CP that can provide high levels of passive antibodies titer until the host's immune responses activates and clears both the viral infection from the blood circulation and pulmonary tissue as well as the infected cell.[19-21]

In the CP group, serial oxygenation parameters and laboratory investigations showed gradual improvement over time including reduction in PaO2/FiO2 ratio, reduction in PEEP, increase in WBC count and reduction in CRP and bilirubin. This was seen despite receiving less immunomodulating therapies such as interferon and azithromycin. [22, 23] Early into the pandemic azithromycin was commonly used for bacterial respiratory infections and to treat or prevent co-infection with SARS-CoV-2. Azithromycin have shown in vitro antiviral activity against some RNA viruses including Zika, rhinoviruses and SARS-CoV-2. [24,25] The use of azithromycin became less as studies showed lack of efficacy and increase in adverse events when combined with

hydroxychloroquine.[26] Similarly, interferon beta 1B or peginterferon alpha-2a was considered early into the pandemic for severe cases with evidence of cytokine storm.[27]

Although the improvement of inflammatory markers and oxygenation could be contributed to the adjunction of steroids, there has been significant decrease in these markers in the CP group suggesting the additional potential role of the transfusion. The same observation was noted in previously published small case series studies.[28-30] where all investigated patients achieved serum SARS-CoV-2 RNA negativity after CP transfusion, accompanied by an increase of oxygen saturation and lymphocyte counts, and the improvement of liver function and CRP. The results suggested that the inflammation and overreaction of the immune system were alleviated by the antibodies contained in CP.[20]

In the present study, 42% of patients who had been receiving mechanical ventilation no longer required respiratory support after the CP transfusion. The beneficial effects could have been due to the transfusion of CP at the early stages of the disease as neutralizing antibodies can wean within short time.[19,20,31,32] In a recent multicenter study from Iran, the benefit from the CP transfusion was reported if CP was given early within 3 days of hospitalization and less than 7 days of onset of the illness.[10] In addition, all-cause mortality was reduced in the CP group in comparison to the standard care group (14.8% vs 24.3%). However, similar to our study this was not statistically significant probably due to low study power (11%).

In our study, patients that received CP were more likely to be extubated or discharged home than patients receiving the standard care only (24% *vs* 64% $p = 0.001$). Moreover, both groups equally received intravenous steroids (70% *vs* 71%; $p = 0.890$). The case fatality rates (CFRs) in the CP group was 19%, which is comparable to the CFRs in four noncomparative studies using

CP treatment.[4,33-36] Similar to other reports, in the current study, no severe adverse effects, such as transfusion-related acute lung injury or antibody-dependent infection enhancement were observed or reported after CP transfusion.[10,37-39]

In this study, collection and transfusion of the plasma was done as previously reported, but there have been several technical limitations: firstly, SARS-CoV-2 PCR was not repeated due to the limitation in availability of the testing early into the pandemic. Secondly, virus-specific neutralizing antibodies were not measured due to unavailability of the tests. Virus specific neutralizing antibodies are essential to accelerate the virus clearance and prevent further entry into target cells.[40,41] However, CP units were given only if COVID- IgG antibodies were adequate after semi-quantitative measurement of the IgG levels. Thirdly, CP was not transfused at the same day of the collection that potentially could affect the antibody levels. Nevertheless, the beneficial effects of CP were observed in the clinical outcomes and laboratory responses. This is probably due to the proper selection process of donors who had recovered from SARS-COV-2 and timing of their donation which was at least 4 weeks from the onset of symptoms; to ensure adequate antibody titers. Recent studies have shown that SARS-Cov-2 viral neutralization activity correlates with S protein receptor-binding domain (RBD); a key target for therapeutic antibodies that have plays major part in tropism and virus entry into host cells and produces neutralizing antibodies and protective immunity.[42,43] S-RBD-Specific IgG and are highest 4 weeks from the onset of symptoms , thus, we carefully selected the donors based both on this time period and on the IgG antibody levels that correlate well with neutralizing antibodies. Lastly, patients receiving CP were treated with other modalities of therapies including steroids. This could have potentially confounded the results although patients in CP group received less azithromycin and interferon, in fact both groups received steroids equally reflecting no major differences.

Conclusion

COVID-19 infected patients on mechanical ventilation and /or ARDS receiving CP tended to have better outcomes in terms of extubations and discharges. Based on our results, and in the absence of a specific treatment, CP therapy could have a clinical benefit in mechanically ventilated patients and could be a safe rescue option for severely ill COVID-19 patients. Large scale randomized clinical studies are required to demonstrate the safety and efficacy of CP in COVID-19 patients.

Conflicts of Interest

The authors declare no potential conflicts of interest with respect to research, authorship, and/or publication of this article.

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