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ORIGINAL ARTICLE

Infection

Efficacy and safety of convalescent plasma therapy in SARS-CoV2 patients on hemodialysis

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Abstract

Background: The passive immunization of patients with SARS-CoV2 with convalescent plasma (CP) is theoretically beneficial in patients with end-stage renal disease who are immunosuppressed and unable to mount an adequate immune response. Hence, this study was conducted to evaluate the safety and efficacy of CP in patients with chronic kidney disease on hemodialysis with moderate-to-severe SARS-CoV2 infection.

Methods: A prospective observational cohort study was conducted in consecutive 68 moderate-to-severe SARS-CoV2 infected patients who were on maintenance hemodialysis or with acute worsening of chronic kidney disease which required initiation of hemodialysis. Patients who received CP were compared with those who did not. The primary outcome was death during hospitalization. Clinical characteristics, duration of hospitalization and inflammatory parameters were compared between the two groups. A subgroup analysis was done to find whether early initiation of plasma was associated with better outcome.

Results: Sixteen patients (44%) in the plasma group and 14 (45%) patients in the control group died during hospitalization ($p = 0.95$). The median duration of hospitalization was 9 (6–14) days in the plasma group and 9 (6–16) in the control group ($p = 0.60$). There was no difference in mortality or duration of hospitalization with respect to early initiation of CP ($p = 0.29$). Fistula thrombosis occurred in two patients (11.1%) in the plasma group.

Conclusion: Therapy with CP does not appear to confer any clinical benefit in moderate-to-severe SARS-CoV-2 infected patients with chronic kidney disease on hemodialysis.

KEYWORDS

chronic kidney disease, COVID 19, hemodialysis, plasma therapy

INTRODUCTION

The COVID-19 pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been an unprecedented challenge to the healthcare systems across the globe. Numerous therapeutic options have been tried for critically ill patients infected with SARS-CoV-2, but as on date, no drug other than corticosteroids has shown to improve outcomes in this patient population.[1] Convalescent plasma (CP) therapy is a form of passive immunization in which plasma obtained from convalescent patients is used therapeutically. Neutralizing antibodies present in CP block the entry of the virus into cells and also mediate the phagocytosis of microbes by immune cells.[2] CP therapy has been effective in treating diphtheria and tetanus since the late 19th century. It has also been used for the treatment of viral infections like Ebola and Middle East Respiratory Syndrome.[2] Considering the circumstances of the global pandemic, US Food and Drug Administration (FDA) has approved the use of CP as an investigational therapy for severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) infection.[3] Randomized controlled trials have evaluated the efficacy of CP in SARS-CoV-2 infections in the general population. A recently published RCT has demonstrated the benefit of CP in preventing disease progression among elderly patients with mild disease at time of study entry.[4]

A decline in renal function results in functional defects in the innate and adaptive immune responses and produces a pro-inflammatory milieu. This impaired immune cell function in end-stage renal disease (ESRD) causes increased susceptibility to bacterial and viral infections as well as poor immune responses to vaccination.[5] Therefore, passive immunization with neutralizing antibodies has been hypothesized to result in better outcomes in patients with ESRD, when compared to the general population. To the best of our knowledge, there is no data available on the use of CP in patients with chronic kidney disease patients on hemodialysis. Hence, this study was conducted to evaluate the safety and efficacy of CP in the treatment of SARS-CoV-2-infected patients with chronic kidney disease on hemodialysis.

MATERIALS AND METHODS

This is a prospective observational cohort study conducted at the Institute of Nephrology, Madras Medical College, after approval by the Institutional Ethics Committee. All patients with dialysis-requiring renal failure admitted with SARS-CoV-2 infection diagnosed by a positive reverse transcription-polymerase chain reaction (RT-PCR) of nasopharyngeal swab during September 2020 and October 2020 were screened for inclusion into the study. Patients with moderate and severe disease were included in the study after getting informed consent.

Demographic data were collected by direct interviews with the patient or care-giver, and a detailed clinical examination was performed. All study participants were subjected to a series of tests including complete hemogram, renal and liver function tests, noncontrast CT chest, serum lactate dehydrogenase (LDH), serum ferritin, and serum C-reactive protein (CRP). They were classified as having mild, moderate, and severe disease based on clinical and laboratory investigations according to the institutional protocol (S1). CT findings were graded based on lung involvement, with Grades 1, 2, 3, and 4 corresponding to involvement of <25%, 25%–50%, 50%–75%, and >75% of the lung fields, respectively.

Case definitions

Moderate disease was defined as having any two of the following:

Respiratory rate 24–30 per minute, oxygen saturation in room air 90%–94%, neutrophil-lymphocyte ratio 5–7, C-reactive protein 50–100 mg/dl, serum ferritin 600–1500 ng/ml in males and 500–1000 ng/ml in females, serum LDH 300–500 IU/ml, serum interleukin-6 20–100 pg/ml, CT chest Grades 2 and 3.

Severe infection was defined as having any two of the following:

Respiratory rate more than 30 per minute, oxygen saturation in room air less than 90%, neutrophil lymphocyte ratio more than 7, C-reactive protein more than 100 mg/dl, serum ferritin more than 1500 ng/ml in males and more than 1000 ng/ml in females, serum LDH more than 500 IU/ml, serum interleukin-6 more than 100 pg/ml, CT chest Grade 4.

Treatment protocols

All patients received enoxaparin 40 mg subcutaneously once daily and dexamethasone 8 mg intravenously once daily. Remdesivir was administered 4 h prior to each hemodialysis session, at a dose of 100 mg intravenously, for a total of two to five doses at the discretion of the treating physician.

CP was collected from individuals with microbiologically proven COVID-19 (by RT-PCR for SARS-CoV-2), who had clinical recovery, with detectable SARS-CoV-2 IgG antibodies in serum. The presence of IgG antibody is

determined using the Vitros®Anti SARS CoV2—Total test kit using chemiluminescence immuno assay. Plasma donation was done at least 28 days after the date of initial swab positivity. CP was collected using the Spectra Optia® Apheresis System. The apheresis was performed over 40 min in four cycles, with each cycle lasting for 10 min. Upto a maximum of 400 ml of plasma was harvested from each donor (with 100 ml of plasma being harvested during each 10-min cycle). This was then stored with acid citrate dextrose solution A (ACD-A) and immediately frozen in 200 ml aliquots at −30°C.

Patients meeting inclusion criteria were counselled regarding the use of CP as a supplementary therapy to the standard-of-care. Patients who provided informed consent for CP transfusion (plasma group) were compared with those who did not (control group). CP was transfused in an ABO-compatible fashion. One unit (200 ml) of frozen CP was thawed to room temperature and transfused over 4 h, under close monitoring for adverse effects. All patients were reviewed daily by the nephrology team until discharge, and data relating to clinical status and laboratory parameters were collected.

Statistical methods

Statistical analysis was performed using IBM® SPSS® Statistics version 23. Qualitative variables are expressed as absolute numbers and percentage. Quantitative variables are expressed as mean ± SD or as median (interquartile range). Appropriate tests for statistical significance were used for comparisons between various groups—the Chi-square test or Fisher's exact test for qualitative data, and the Independent samples t-test for continuous variables and Mann–Whitney U test for nonparametric data. Comparison of parameters before and after treatment was done by Wilcoxon rank sum test for nonparametric data. A two-sided p value < 0.05 was considered to be statistically significant.

RESULTS

Baseline characteristics

Among the 68 patients studied, 37 (54.4%) patients received CP in addition to the standard of care (plasma group), and 31 (45.6%) patients received only the standard care (control group). The mean age of patients in the plasma group and the control group was 52 (±13.6) years and 56.4 (±12.3) years, respectively. Males predominated in both groups, with 29 (80.6%) patients in the plasma group and 23 (74.2%) patients in the control group (Table 1).

Patients with comorbid conditions like diabetes, hypertension, hypothyroidism, and coronary artery disease were comparable in both groups. Thirty-three (48.5%) patients were diabetic, of whom 18 (54.5%) patients received CP therapy. Among the 58 (85.3%) patients with hypertension, 32 (55.2%) received CP (Table 1). Among the patients included in the study, 49 (72.1%) had end-stage renal disease on maintenance hemodialysis, and the remaining 19 patients (27.9%) had acute on chronic kidney disease. The median dialysis vintage of patients with ESRD was 25 months (IQR 6–48 months). Shortness of breath was the most common symptom at presentation, being present in 51 (76.1%) patients. Other common symptoms included cough and fever in 29 (42.6%) and 27 (39.7%) patients, respectively (Table 1).

Laboratory and radiological features

The median CRP, NLR, and ferritin levels of the study population was 154 mg/dl (IQR 102–269.5 mg/dl), 7.5 (IQR 4–14) and 1527 ng/ml (IQR 750–2406 ng/ml), respectively. The median CRP, NLR, and ferritin levels at admission were comparable between both the groups. Most inflammatory markers showed a significant reduction post-treatment in both groups (Table 2). However, no between-group difference was noted post-treatment (Table 1).

CT lung showed features of SARS-CoV-2 infection in 67 patients. One patient was too ill to be shifted for CT chest and was not done. Most of the patients had significant lung involvement as per our Institutional CT grading protocol. Twenty six (38.2%) patients had Grade 4 CT changes and 26 (38.2%) patients had Grade 3 CT changes. Two (2.9%) and 13 (19.1%) patients had lesser involvement of CT lung with Grade 1 and 2 changes, respectively. There was no significant difference in the severity of CT grading between the two groups. Grade 4 CT changes were higher in those who received plasma therapy compared to control group (47.2% vs. 29%), though it was not statistically significant ($p = 0.31$). (Table 1).

Outcome

The median duration of hospitalization of patients who received plasma was 9 (6–14) days and in the control group was 9 (6–16) days—a difference that was not statistically significant ($p = 0.60$). Sixteen patients (44%) in the plasma group and 14 (45%) patients in the control group died during hospitalization ($p = 0.95$) Respiratory failure was the major cause of death in both the study

TABLE 1 Baseline characteristics of study participants given plasma therapy (plasma group) or to best standard care (control group)

Characteristics	Total ($n = 68$)	Plasma group ($n = 37$)	Control group ($n = 31$)	p value
Age (mean ± SD)	54.1 ± 13.1	52.0 ± 13.6	56.4 ± 12.3	0.78
Sex: Male *n* (%)	52 (76.5)	29 (80.6)	23 (74.2)	0.53
Comorbidities				
Diabetes mellitus *n* (%)	33 (48.5)	18 (54.5)	15 (48.4)	0.56*
Hypertension *n* (%)	58 (85.3)	32 (55.2)	26 (38.2)	0.18*
Coronary artery disease *n* (%)	2 (2.9)	1	1	—
Hypothyroidism *n* (%)	2 (2.9)	1	1	—
CAD (coronary artery disease) *n* (%)	1 (1.5)	0	1	—
Steven Johnson Syndrome *n* (%)	1 (1.5)	0	1	—
Renal syndrome				0.65
CKDVD *n* (%)	49 (72.1)	26 (70.3)	23 (74.2)	
Acute on CKD requiring HD *n* (%)	19 (27.9.)	11 (29.7)	8 (25.8)	
Symptoms				1.00*
Fever *n* (%)	27 (39.7)	14 (38.9)	13 (41.9)	0.80
Cough *n* (%)	29 (42.6)	16 (44.4)	13 (41.9)	0.84
Shortness of breath *n* (%)	51 (76.1)	27 (75.0)	24 (77.4)	0.82
Laboratory values				
NLR (median [IQR])	4.6 (4–14)	7.5 (4.1–13.7)	9 (3.9–11.5)	0.06
CRP (mg/dl) (median [IQR])	154 (102–269.5)	148 (105–246)	171 (98–295)	0.77
S.ferritin (ng/ml) (median [IQR])	1983 (811–2017.2)	1527 (750–2406)	2000 (1111–2000)	0.96
NLR (after plasma) (median [IQR])		5.4 (3–10)	4.9 (2.2–11)	0.80
CRP (after plasma) mg/dl (median [IQR])		82.9 (34.8–164.0)	78 (33–242)	0.53
S.ferritin (after plasma) ng/ml (median [IQR])		1342 (601.5–2000)	1477 (600–2000)	0.52
Total hospitalization (median [IQR])	9 (6–16)	9 (6–14)	9 (6–16)	0.60
CT chest				0.31
Grade 1	2 (2.9)	1 (2.8)	1 (3.2)	
Grade 2	13 (19.1)	7 (19.4)	6 (19.4)	
Grade 3	26 (38.2)	11 (30.6)	15 ((48.4)	
Grade 4	26 (38.2)	17(47.2)	9(29.0)	
Death *n* (%)	30 (44.1)	16 (44.4)	14 (45.1)	0.95
Cause of death				
Respiratory failure *n* (%)	24 (80.0)	12 (75)	12 (85.8)	
Encephalopathy *n* (%)	2 (6.7)	1 (6.3)	1 (7.1)	
Septic shock *n* (%)	4 (13.3)	3 (18.8)	1 (7.1)	

Abbreviations: CRP, C-reactive protein; CT, computerized tomography; IQR, interquartile range; NLR, neutrophil lymhocyte ratio; SD, standard deviation.
*p value measured by Fischer exact test.

groups—12 patients (75%) in plasma group and 12 patients (85.8%) in the control group. Septic shock and encephalopathy were the other causes of mortality during hospitalization (as described in Table 1).The outcome was compared with the severity of disease in both the treatment groups, among the 54 (79.4%) severe cases 29 patients died, 15 (22%) in the plasma group, and 14 (20.6%)in the control group ($p = 0.78$). In the patients with moderate disease only one (1.4%) patient in the plasma group died. (Supplementary Table 2).

A total of 37 patients received CP. In this group of patients, the relationship between the time to initiation of CP and outcome (death) was studied as a subgroup analysis. Of the 16 patients (44%) who succumbed to the

TABLE 2 Comparison of laboratory parameters before and after treatment in plasma group and control group

	Plasma group			Control group		
	At admission	After plasma	*p* value	At admission	After treatment	*p* value
CRP (mg/dl) (median [IQR])	148.5 (105.5–246)	82.9 (34.8–164.0)	<0.001	171 (98.7–295.3)	78 (33–242)	0.005
Ferritin (ng/ml) (median[IQR])	1527.5 (750.2–2406.5)	1342 (601.5–2000)	0.009	2000 (1111–2000)	1477 (600–2000)	0.092
NLR (median[IQR])	7.6 (4.1–13.7)	5.4 (3–10)	0.001	8 (3.1–14)	4.9 (2.2–11)	0.007

Abbreviations: CRP, C-reactive protein; IQR, interquartile range; NLR, neutrophil lymhocyte ratio.

TABLE 3 Comparison of parameters between those who received plasma before 72 h and after 72 h of admission (n = 37)

Parameters	Initiation before 72 h	Initiation after 72 h	*p* value
Discharge *n* (%)	12 (32.4%)	9 (24.3%)	0.29
Death *n* (%)	10 (27.0%)	6 (16.2%)	

disease, 10 (27%) patients received CP within 3 days of admission and 6 (16.2%) patients received CP after 3 days of admission. Similarly, of the 21 patients (56%) who clinically recovered and were subsequently discharged, 12 (32.4%) patients received CP within 3 days of admission and 9 (24.3%) patients received CP after 3 days of admission. There was no statistically significant difference in mortality among those who received plasma therapy before and after 3 days of admission ($p = 0.29$) (Table 3).

Similarly, among the eight patients who required high levels of respiratory support in the form of high flow nasal oxygen (HFNO) and continuous positive airway pressure (CPAP), there was no statistically significant difference in mortality among those who received CP and those who did not (plasma group mortality—1 of 4 (25%); control group mortality—3 of 4 (75%); $P = 0.49$) (Table 4).

The outcome (death) was also compared in the two groups with CT grading of the 26 patients with Grade 3 CT change 7 (10.3%) patient in the plasma group and 9 (13.2%) patient in the control group died ($P = 1.0$). Among the 26 patients with Grade 4 CT changes 7 (10.3%) died in the plasma group and 5(7.6%) died in the control group ($p = 0.68$) (Supplementary Table 3).

Complications

Three patients (8.1%) developed minor transfusion reactions in the form of chills and rigors, which were managed symptomatically. Two of the 18 patients who had an AV fistula (11.1%) developed fistula thrombosis and closure immediately after transfusion.

TABLE 4 Comparison of mortality of patients with oxygen support among plasma group and control group

Oxygen requirement	Plasma group (*n* = 16)	Control group (*n* = 14)	*p* value
HFNO/CPAP *n* (%)	1 (25)	3 (75)	0.49*
NRM *n* (%)	12 (45.5)	8 (57)	0.88*
Oxygen by mask *n* (%)	3 (30)	3 (27)	1.00
Room air	Nil	Nil	—

Abbreviations: CPAP, continous positive airway pressure; HFNO, high flow nasal oxygen; NRM, nonrebreather mask.
**p* value measured by Fischer exact test.

28-day follow-up

All the 19 (27.9%) patients who were admitted as acute on chronic kidney disease necessitating initiation of dialysis via temporary HD catheter, at 28-day follow-up, remained dialysis dependent.

DISCUSSION

This prospective study was done on patients infected with SARS CoV2 requiring hemodialysis with an aim to assess the effects of CP therapy on patients with moderate and severe disease. Theoretically CP could have a beneficial effect in COVID patients with chronic kidney disease as they lack the ability to mount a strong immune response. CKD patients are at higher risk for severe SARS-CoV-2 infection.[6] Studies from various centers across the globe have reported a mortality rate of 20%–33.7% in CKD patients.[6,7] Mortality among patients receiving dialysis who have COVID-19 was approximately 20%.[6] This rate is very high compared to the mortality in general population which is approximately 4%.[6] In our center, the mortality due to COVID-19 in dialysis requiring renal failure patients was found to be 18.8%.[23] SARS-CoV2 is also known to affect the kidneys by causing acute kidney failure or worsening of the already existing chronic kidney disease.[8] All patients in our study who were newly

initiated on dialysis remained dialysis-dependent after 1 month, illustrating the long-term consequences of COVID-19 in this patient population.

Interim results from the Solidarity Therapeutics Trial, coordinated by the World Health Organization, indicate that remdesivir, hydroxychloroquine, lopinavir/ritonavir, and interferon regimens appeared to have little or no effect on 28-day mortality or the in-hospital course of COVID-19 among hospitalized patients.[9] The RECOVERY trial found that dexamethasone use resulted in lower 28-day mortality among those who were receiving either invasive mechanical ventilation or oxygen therapy.[1] The trial also showed no clinical benefit with the use of hydroxychloroquine or lopinavir-ritonavir on SARS CoV2 infection.[10,11] In a previous study from our center, the use of remdesivir on hemodialysis patients was not associated with any beneficial effect on mortality, though their time to recovery was shorter.[12] The meta-analysis on use of antivirals like ribavirin, chloroquine, hydroxychloroquine, umifenovir (arbidol), favipravir, interferon, and lopinavir/ritonavir showed no benefit in outcome in both nonsevere and severe SARS-Cov2 infection.[13] Meta analysis that analyzed 15 in vitro and 35 clinical studies found no favorable outcome with the use of lopinavir-ritonavir, remdesivir, and tocilizumab.[14]

Our study found no significant difference in mortality between patients who received CP transfusion therapy combined with standard treatment compared to those who received standard treatment alone. There was no significant difference in the mean duration of hospitalization between the two groups. Our data are consistent with the recently published results of the PLACID trial, a multicentre randomised controlled trial done in general population with moderate COVID-19 that showed no difference in mortality.[15] However, a meta-analysis on use of CP which analyzed two randomized controlled trials and five cohort study found low-quality evidence that CP is effective in viral clearance, mortality reduction, and clinical improvement.[16] Studies done on general population with COVID infection from China and the Netherlands showed no clinical benefit with plasma therapy.[17,18]

CP as a passive source of neutralizing antibodies and immunomodulators is a centuries-old therapeutic option used for the management of viral diseases. There is evidence that CP collected from COVID-19 survivors contains receptor binding domain specific antibodies with potent antiviral activity.[2] But the response of patients with chronic kidney disease to CP therapy has not been studied so far to the best of our knowledge. The administration of neutralizing antibodies in the form of CP alone may not be beneficial in patients with ESRD, as these patients show functional defects in all innate and adaptive immune responses.[5]Also the levels of specific protective antibody titers were uncertain as it was not measured prior to plasma administration in our cohort.

There was a significant fall in CRP as well as NLR in both the plasma and control groups following treatment. This could be because of the administration of remdesivir and dexamethasone in both the groups as a part of standard care. In a previous study done in a similar cohort from our center showed significant decrease in CRP level after the administration of remdesivir.[12] CP therapy does not appear to confer any additional benefit over the standard of care in our cohort. Prespecified subgroup analyses were done to detect the usefulness of early initiation of plasma therapy on clinical benefits. No differences in favor of CP were noted in outcomes in any of these subgroups including the 21 patients who received plasma early during hospitalization. A recent study conducted in general population found that early administration of high titer CP to older patients with mild disease reduced the progression of disease.[4] But in our study, CP therapy was given to patients with moderate and severe disease as the outcome of patients with milder disease was better with conservative management.

CP transfusion was associated with few adverse reactions. Spontaneous closure of AV fistula in two patients occurred during transfusion, despite the absence of hemodynamic compromise. None of the patients in the control group had any thrombotic episodes or failure of AV fistula. Both these patients succumbed within 1 week of admission and had severe disease. This could be attributed to the hypercoagulable state of the disease per se, though procoagulant property of plasma could not be ignored.[19,20] The laboratory pretreatment of CP for inactivating potential residual virus decreases its procoagulant effects but does not nullify it.[21] The hemo vigilance programs have not reported any thrombotic events in general population associated with transfusion of plasma so far. The use of CP did not increase the risk of thrombotic event in PLACID trial as well.[15] Failure of AV fistula should raise concern for patients on maintenance hemodialysis. Two patients experienced chills and one patient had itching during transfusion and were managed symptomatically. The long-term complications and transfusion related infectious complications were not studied due to short follow-up of 28 days.

Our study has several limitations. The antibody titers were not measured before infusion of CP. The study from Mexico showed that neutralizing antibody titers are variable in CP and could be dependent on severity of illness and/or time post-infection and could affect the response to CP.[22] In our study, volume of plasma infused was also constant and independent of the patient weight and plasma volume. Hence, there is a need for a randomized controlled trial with a larger sample size to ascertain the

effects of CP therapy on SARS-CoV2 infected patients on hemodialysis.

CONCLUSION

Our observational study showed that therapy with CP confers no benefit in chronic kidney disease patients on hemodialysis with moderate-to-severe SARS-CoV2 infection.

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CONFLICT OF INTEREST

The authors declared no competing interest.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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