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Convalescent Plasma Therapy in Severe COVID-19: A Pilot Study at the Beginning of the Pandemic Outbreak in Southern Chile

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Terapia con plasma convaleciente en COVID-19 grave: Un estudio piloto al inicio del brote pandémico en el sur de Chile

ABSTRACT

Convalescent Plasma (CP) from patients who recovered from COVID-19 may present neutralizing antibodies against viral protein S of SARS-CoV-2 and emerged as a potential therapeutic alternative for patients with severe infection at the beginning of the COVID-19 pandemic breakout. Thus, this study aimed to evaluate the effect and safety of CP treatment in patients with severe COVID-19. ***Methods:*** *We designed a quasi-experimental study that included 156 patients with SARS-CoV-2 infection confirmed by RT-qPCR and severe symptoms who received CP. As a control group, we selected a historical cohort of 113 individuals admitted with COVID-19 and severe symptomatology before the starting date of the study. Clinical status and mortality during the study period were recorded.* ***Results:*** *There were no adverse reactions to CP administration. In the CP group, days on mechanical ventilation were significantly lower than the control group (2.8±5.08 days vs. 4.7±6.19 days; p= 0.0081). Moreover, a significant difference was observed in the number of days stayed in the critical patient unit (CPU) in CP vs. controls (4.2±5.47 vs. 5.8±6.39 days, p= 0.0281).* ***Conclusions:*** *We observed no association between CP administration and survival at 14 days. Treatment with CP was safe and not associated with adverse events. In addition, using CP was associated with a reduction in both stay at the CPU and connection to mechanical ventilation.*

Keywords: *SARS-CoV-2; COVID-19; Convalescent Plasma Therapy.*

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Statements and Declarations
Declaration of Interest: The authors have no conflicts of interest to declare.
Statement of Ethics: This study was conducted at the Hospital Dr. Hernán Henríquez Aravena of Temuco between May and December 2020, in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Servicio de Salud Araucania Sur (protocol code N°97 28/04/2020). Informed consent was obtained from all subjects involved in the study.

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RESUMEN

El plasma convaleciente (PC) de pacientes recuperados de COVID-19 puede presentar anticuerpos neutralizantes contra la proteína viral S del SARS-CoV-2, surgiendo como una posible alternativa terapéutica para pacientes con infección grave al comienzo de la pandemia de COVID-19. Por lo tanto, el objetivo de este estudio fue evaluar el efecto y la seguridad del tratamiento de PC en pacientes con COVID-19 grave. ***Métodos:*** *Se diseñó un estudio cuasi-experimental que incluyó a 156 pacientes con infección por SARS-CoV-2 confirmada por RT-qPCR y síntomas severos que recibieron PC. Además, se seleccionó como grupo control una cohorte histórica de 113 personas con COVID-19 y sintomatología severa ingresadas antes de la fecha de inicio del estudio. Se registró el estado clínico y la mortalidad durante el período de estudio.* ***Resultados:*** *No hubo reacciones adversas a la administración de PC. En el grupo PC, los días de ventilación mecánica fueron significativamente menores que en el grupo control (2,8±5,08 días frente a 4,7±6,19 días; p= 0,0081). Además, se observó una diferencia significativa en el número de días de estancia en la unidad de pacientes críticos (UCP) en PC vs controles (4,2±5,47 vs 5,8±6,39 días, p= 0,0281).* ***Conclusiones:*** *No se observó asociación entre la administración de PC y la supervivencia a los 14 días. El tratamiento con PC fue seguro y no se asoció a eventos adversos. Además, el uso de PC se asoció con una reducción tanto de la estancia en la UCP como de la conexión a ventilación mecánica.*

Palabras clave: *COVID-19; Terapia de Plasma Convaleciente; SARS-CoV-2.*

Coronavirus viral pneumonia (COVID-19) in most patients, produces mild and self-limited symptoms, whose clinical manifestations include fever, cough, sore throat, diarrhea, dyspnea, anosmia, ageusia and, in severe cases, can lead to respiratory failure, multiple organ failure and death[1].

The recovery rate and severity of the disease depend on the age and health determinants of the host, with an overall mortality rate reported for confirmed cases of 4.5%. Population over 80 years old has a higher mortality reaching 15%. In elderly people carrying comorbidities such as diabetes, hypertension or cardiovascular disease, SARS-CoV-2 infection can result in severe and fatal respiratory disease[2].

The COVID-19 disease lack of specific therapy, guidelines recommend the use of corticosteroids and antibiotics in patients with invasive mechanical ventilation (IMV), in addition to ventilatory or hemodynamic life support management. Pharmacological treatments, such as hydroxychloroquine, azithromycin and immunoglobulin, not shown effectiveness[3], excepting tocilizumab, with favorable results in cytokine storm. Remdesivir clinical trial did not show a significant difference in mortality rates[4]. The RECOVERY trial showed that dexamethasone reduce mortality in IMV patients[5]. A possible therapeutic alternative is the use of convalescent plasma (CP) from recovered of the infection[6]. This therapy has been used in severe acute respiratory syndrome (SARS) and pandemic influenza A (H1N1), avian influenza A (H5N1), Ebola and other viral infections[7].

Cheng, et al. reported CP use during SARS outbreak. CP receptors (n= 80) had a lower mortality rate (12.5%) compared to the overall SARS-related inpatient mortality (n= 299, 17%). Antibody titers and plasma transfusion volumes varied and did not appear to correlate with clinical response; however, CP transfused within 14 days of symptom onset (n= 33) showed better outcomes[8].

Most patients recovered from SARS-CoV-2 infection develop antibodies 2 to 3 weeks after infection. Previous experience with SARS virus suggested that CP exhibits a neutralizing antibody response against viral protein S. This antibody blocks SARS-CoV entry and can be detected even 24 months after infection[9,10]. In China, promising results were reported using CP with high titers of neutralizing antibodies in COVID-19 critical patients[11]. In our hospital, at the beginning of the health emergency, the use of CP was proposed as a therapeutic alternative considering its previous use on Hanta Virus infected patients[12]. Thus, the aim of this study was to evaluate the response to CP treatment in a selected population of COVID-19 patients.

Materials and Methods

Study design and patients

This study was performed at the beginning of pandemic outbreak using a quasi-experimental study design that analyzed the response to CP treatment in severe COVID-19 patients and controls selected from a historical cohort. The CP group included 156 individuals over 18 years old, with severe SARS CoV-2 infection confirmed by RT-qPCR testing from nasopharyngeal swabs and defined by any of the following criteria: dyspnea ≤ to 7 days, respiratory rate ≥ to 30 per minute, oxygen saturation ≤ to 93%, oxygen partial pressure/inspired oxygen fraction (PaFi) ratio < 300, or increase in pulmonary infiltrates >50% in 24 to 48 h. Patients with IgA deficiency or history of hypersensitivity and allergic reaction to blood components or immunoglobulins were excluded. All signed an informed consent form. Patients received two doses of 300 ml of ABO-compatible CP every 12 hours. Additionally, a historical cohort was retrospectively selected as control group from the records of admitted to the hospital with COVID-19 diagnosis before the starting of CP treatment protocol. Thus, 113 individuals over 18 years old were selected, matched for age and sex, meeting the same selection criteria as those who received CP transfusion.

Convalescent plasma donors

CP donors were older than 18 years with previous COVID-19 infection diagnosed by RT-qPCR, no history of transfusion, pregnancy or miscarriage. Donors were free of symptoms for at least 28 days and negative RT-qPCR test on nasopharyngeal swab 24/48 hours prior to donation. The selection criteria for blood donors in Chile were applied. IgG antibodies against to nucleocapsid protein of SARS-CoV-2 in plasma were determined by chemiluminescent microparticle immunoassay (CMIA) in Architect™ analyzer (Abbott®). The chemiluminescent reaction was measured as relative light units (RLU) and expressed as a calculated index. Results greater than 1.4 are interpreted as positive. Plasma was collected by apheresis with a Spectra Optia cell separator (Terumo BCT, Lakewood, CO) extracting a maximum volume of 600 mL, anticoagulated with Citrate Dextrose solution (ACD-A). All donors signed an informed consent form.

Concomitant pharmacological treatments

The management of SARS-CoV-2 was based on the early support measures recommended by the Chilean Society of Hematology (SOCHIHEM). Thus, some patients received oseltamivir until negative screening for Influenza A H1N1 was observed in both convalescent plasma and controls individuals. Drugs such as hydroxychloroquine was also administered in some patients prior to the recommendation for not to use due to adverse events and ineffectiveness[11]. Thus, the mainstay of pharmacological treatment was the use of corticosteroid therapy recommended by the World Health Organization (WHO). All patients received ceftriaxone and azithromycin antibiotic therapy on admission until infection was ruled out.

Clinical assessment

In CP group, the clinical status, presence of adverse events associated with the therapy and finally mortality 14 days after the intervention were recorded. In addition, time to extubating defined as days elapsed from intubation in patients connected to IMV; length of stay in the CPU considered as days elapsed from admission to discharge from the CPU; and time of use of Non-Invasive Mechanical Ventilation (NIV) counting days elapsed from the start of NIV to withdrawal of the device were determined.

Statistical analysis

Data were collected in an MSExcel spreadsheet and processed with the statistical software Stata v17. Descriptive analysis was performed using charts and summary measures. Fisher's exact test was used to compare percentages and the t-test for equal and different variances was used for averages, as appropriate. The calculation of RR was estimated with binomial regression. For the comparison of repeated measurements of laboratory variables, multilevel linear mixed-effects regression was used. The statistical significance level was 5%.

Results

Demographic characteristic

Demographic characteristics of control and CP group are summarized in table 1. No differences were observed in age, gender distribution and urban or rural precedence. Both groups presented similar frequencies of comorbidities.

Table 2 summarize the clinical characteristics of both groups. In relation to pharmacological treatment, 6.4% of CP group received hydroxychloroquine versus 92.1% of controls (p<0.001). In the case of glucocorticoids, 84.6% of CP group received treatment and only 10.5% of the group used as control (p<0.001). Oseltamivir was used more frequently in controls (54.0%) than in the CP group (p<0.001).

It is important to highlight that in 92.3% of the patients in CP group underwent pronation maneuvering as an additional support measure, compared to 25.7% in controls (p<0.001; Table 2). This is because this maneuver was incorporated some months after the pandemic beginning. Bronchoalveolar lavage culture was performed in 9 patients of CP group undergone IMV. Staphylococcus aureus in 3 cultures and Klebsiella pneumoniae in 1 culture were isolated. The remaining cultures were negative.

Time until extubation

At hospital admission, the control group had a significantly higher mean oxygen saturation (SpO2) value (93.5±4.4, p<0.001) than the CP group (89.3±6.6), revealing a more deteriorated clinical condition.

The average number of days on mechanical ventilation in CP group was significantly lower than the control group (2.8±5.1 days vs. 4.7±6.2 days; p= 0.0081). A significant difference was observed in the length of stay in the critical patient unit, which averaged 4.2 days (4.2±5.5 days) in the CP group and 5.8 days (5.8±6.4) in the controls (p= 0.0281).

Patient survival

No differences were observed according to sex or origin of the patients in relation to survival. Regarding morbidity variables, hypertensive patients presented 4.2 times more risk of death than those with normal blood pressure levels (RR 4.2, CI 1.3-14.2). Regarding obesity, there was a statistical but not clinical association between obesity and survival (p<0.0001). This controversial result may be because the number of deceased was low, and none had obesity. On the other hand, diabetes mellitus was associated with a worse prognosis, conferring 3.0 times more risk of death to a diabetic patient than to a non-diabetic patient (RR 3.0 CI 1.2-7.5).

In this study, no association was observed between the administration of CP and survival at 14 days. However, even though the clinical condition of CP recipients was more delicate, their mortality was similar.

The safety of CP administration was assessed by monitoring immediate and 24-hour post-transfusion adverse reactions. Two patients presented mild allergic rash associated with CP administration during the period of this study.

Table 1. Baseline characteristics of the convalescent plasma and control groups.

		Control group (n= 113)	Convalescent plasma group (n= 156)	p
Age, year		58±15.3	59.4±15.5	0.4842**
Sex, n (%)	Women	41 (36.3)	51 (32.7)	
	Men	72 (63.7)	105 (67.3)	0.603
Origin, n (%)	Urban	87 (78.4)	112 (71.8)	
	Rural	24 (21.6)	44 (28.2)	0.255*
Hypertension, n (%)	No	50 (44.3)	73 (46.8)	
	Yes	63 (55.7)	83 (53.2)	0.711*
Obesity, n (%)	No	73 (64.6)	101 (64.7)	
	Yes	40 (35.4)	55 (35.3)	1*
Diabetes, n (%)	No	76 (67.3)	101 (64.7)	
	Yes	37 (32.7)	55 (35.3)	0.698*
Tobacco, n (%)	No	107 (94.7)	147 (94.2)	
	Yes	6 (5.3)	9 (5.8)	1*
Body mass index, kg/m^2		29±4.9	28±6.8	0.4880***
Respiratory rate, breaths/minute		28.3±10.4	28.7±8.3	0.7550***
Heart Rate, beats/minute 98.1±17.8		91.7±16.1	0.0024**	
Systolic Blood Pressure, mm/Hg		129.8±22.4	132.3±20.8	0.3551**
Diastolic Blood Pressure, mm/Hg		75.8±13.1	76.4±11.7	0.6753**
Temperature, ºC		37.4±0.96	37.1±0.97	0.0167**
Oxygen Saturation, %		93.5±4.4	89.3±6.6	<0.0001***
Fraction of Inspired Oxygen, %		26.9±15.6	24.8±8.1	0.1818***
C Reactive Protein, mg/dL		144.3±110.5	110.7±81.5	0.004**
D-dimer, ng/mL		1.8±1.9	1.2±1.3	0.002**
Period from symptom onset to admission, days		7.7±6.0	4.7±3.1	<0.0001**

* Fisher's exact test; ** test for equal variances; *** test for different variances. Data expressed in frequencies, averages and standard deviation and frequencies (percentages).

Table 2. Clinical characteristics during follow-up period of the convalescent plasma and control groups.

		Control group (n= 113)	Convalescent plasma group (n= 156)	p
Hydroxychloroquine, n (%)	No	9 (7.9)	146 (93.6)	
	Yes	104 (92.1)	10 (6.4)	<0.001*
Azithromycin, n (%)	No	3 (2.6)	9 (5.8)	
	Yes	110 (97.4)	147 (94.2)	0.370*
Corticosteroids, n (%)	No	101 (89.4)	24 (15.4)	
	Yes	12 (10.6)	132 (84.6)	<0.001*
Oseltamivir, n (%)	No	52 (46)	141 (90.4)	
	Yes	61 (54)	15 (9.6)	<0.001*
Pronation, n (%)	No	84 (74.3)	12 (7.7)	
	Yes	29 (25.7)	143 (92.3)	<0.001*
Location, n (%)	Room	62 (54.9)	100 (64.1)	
	ICU	27 (23.9)	27 (17.3)	
	UTI	24 (21.2)	29 (18.6)	0.281*
Critical Patient Unit Stay, days		5.8±6.39	4.2±5.47	0.0281**
Mechanical Ventilation, days		4.7±6.19	2.8±5.08	0.0081***
High Flow Nasal Cannula, days		2.8±8.11	3.9±4.71	0.1842***
Vital Status, n (%)	Alive	106 (93.8)	145 (93)	
	Deceased	7 (6.2)	11 (7)	1*

* Fisher's exact test; ** test for equal variances; *** test for different variances. Data expressed in frequencies, averages and standard deviation and frequencies (percentages).

Conclusion

Previous reports indicate that CP could be an effective therapeutic option to improve clinical symptoms and reduce mortality associated with COVID-19[10]. However, Wang, et al.[13] conclude that despite the limited results of randomized clinical trials, the reduction in mortality is not significant.

Similarly, Simonovich, et al. observed no significant differences in clinical status or overall mortality between patients treated with CP and placebo at 30-day follow-up. However, the enrolled patients had a severe form of presentation, so their results are not extrapolable to patients with mild or moderate disease[14].

In our study, no association between CP administration and survival at 14 days was observed. However, CP use was associated with shorter CPU stay (4.2±5.47 vs. 5.9±6.39 p= 0.0281) and shorter MV connection time (2.8±5.08 vs. 4.7±6.19, p= 0.0081). This result agrees with that reported by Abolghasemi, et al. (2020), who point out that CP treated had a significantly shorter length of stay than the untreated and a shorter MV connection time[15]. Similarly, O`Donnell, et al. reported a better clinical condition of CP treated[16].

The CP group had a severe clinical condition, and, despite this, mortality was like than controls. This raises the question that if this group with an unfavorable clinical condition had not been treated with CP, would it have evolved in the same way. A possible explanation is provided by studies in which it is reported that CP treatment within the first days of illness can lead to an improvement in clinical symptoms, elimination of the virus and a reduction in mortality of patients with COVID-19[17]. In addition, it has been reported that the use of CP with high antibody titer in older adult patients treated within 72 hours of symptom onset significantly reduces progression to severe disease[18]. On the other hand, a trial of CP in Chilean hospitalized patients in the early stage of COVID-19, compared to giving plasma only at clinical deterioration, failed to demonstrate improvement in clinical outcomes[19]. However, is important to note the low number of events accounted in our study and the short period of follow might influence these findings.

Other randomized clinical trials suggesting a possible benefit of using high-titer CP[20]; or that SARS-CoV-2 patients treated with CP within the first week of symptom onset did not showed prevention of disease progression[21].

Our study was limited by the lack of screening and titration tests for neutralizing antibodies. Studies such as PLACID or ConCOVID, have shown that CP with low titers (1:40 or 1:160) are not useful in treatment[22,23]. The identification of donors with high titers of neutralizing antibodies and their use in early stages may be an alternative, especially in those patients who have not received vaccines. Neutralizing antibodies are crucial in virus clearance. Additionally, other antibody-mediated pathways, such as complement activation, antibody-dependent cellular cytotoxicity or phagocytosis, may also promote the therapeutic effect of CP[24].

In addition, patients who received CP were subjected to the pronation maneuver, unlike the untreated group, since this intervention was not performed as standard at the beginning of the current pandemic in our hospital. Pronation is a factor that may have contributed to a better clinical evolution in this group. The pronation maneuver improves pulmonary mechanics and gas exchange, mainly in the early stages of respiratory failure. Early implementation of prolonged ventilation in prone position decreases mortality among patients with severe acute respiratory distress syndrome (ARDS) caused by COVID-19[25]. Similarly, CP group received corticosteroids in a greater proportion than controls (84.6% vs 10.6%; p<0.001). This intervention could contribute to the better condition observed in CP group, since different studies conclude that corticosteroids probably reduce mortality and duration of mechanical ventilation in patients with ARDS[26].

Plasma transfusions can be associated with adverse events such as non-hemolytic febrile reactions, allergic reactions, circulatory overload, transfusion-associated acute lung injury (TRALI), among others. In our study, the safety of CP treatment was evaluated through the search for and follow-up of transfusion-associated adverse reactions. Of the 156 patients who received CP only two had an associated mild skin rash.

Regarding the possibility of transfusion transmission of SARS COV-2, the literature indicates that there is no risk of transmission by this route[27].

Currently, despite the pharmacological options, vaccines and public policies of each country, a high number of new cases continues. The increase in circulating mutations in the spike protein that have emerged independently in the United Kingdom, South Africa and Brazil[28], the low predictability of existing treatment failure scenarios[29], the asymptomatic course of some patients[30] and the potential for reinfection[31], promote the resurgence of this pandemic.

Thus, the use of CP is a possible therapy in

patients whose condition exposes them to a risk of early death due to COVID-19[32,33]. CP has characteristics such as having polyclonal antibodies and being easy and quick to obtain, which make it potentially useful in adverse scenarios, such as the context of emerging variants of SARS-CoV-2.

Current evidence on the use of CP is inconclusive due to the lack of studies of its effects in patients with different severities of COVID-19 as mild to moderate cases[34].

On the other hand, there is recent evidence of variants with increased resistance to hyperimmune plasma such as the beta variant or the Omicron variant, strengthening the perspective of the importance of periodic updates on the management of COVID-19 because of the impact seen so far on morbidity and mortality in populations[35].

In conclusion, our study did not show a significant association between CP use and survival of SARS-CoV2-infected individuals. However, patients who received CP treatment had a shorter length of stay in the critical patient unit and less time on mechanical ventilation despite having a more severe admission condition than the controls. CP therapy was safe.

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