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Convalescent Plasma Therapy in SARS-COV-2 Infection, Experience in Tucumán Argentina: An Observational Study

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ABSTRACT

Background: Therapies based on different drugs and corticosteroids have been employed to stop the SARS-COV-2 virus infection. The administration of convalescent plasma (CP) is other therapy used to control COVID-19 disease. **Aim:** To evaluate the efficacy of the CP therapy on the recovery of SARS-COV-2 infection in 189 hospitalized patients who received this treatment during July to October 2020. **Material and Methods:** 189 patients with COVID-19 requiring hospitalization in the Intensive Care Unit (ICU) or mechanical ventilation, from the public hospital dependent on the Health Ministry of Tucumán, Argentina, were selected to receive plasma. The Convalescent Plasma to be use in the transfusion therapy, was selected according the nucelocapside specific IgG antibody titer, measured by Abbott Architect SARS-CoV-2 assay. **Results:** We observed that early administration of CP, between3 to 5 days after hospitalization, to patients with moderate disease, was associated with a decrease in the mortality. In 27 patients from the Intensive Care Unit which required mechanical ventilation and 28 patients that presented several comorbidities, plasma administration was effective in 14 and 60% respectively. **Conclusion:** The results suggest that the favorable effect of CP would be related with the the period of time when plasma was administered to hospitalized patients and the severity of the disease. Early administration was a critical point to decrease the deaths of SARS-COV-2 infected patients.

Keywords: *Convalescent Plasma; SARS-COV-2; Therapy*

Introduction

At the end of 2019, a severe acute respiratory syndrome coronavirus 2 (SARS-COV-2) emerged in Wuhan, China, was spread worldwide, infecting millions of people. Coronavirus disease 2019 (Covid-19), has clinical manifestations ranging from no symptoms to a severe respiratory failure depending of the host immune response. The interplay between SARS-COV-2 and host antiviral defense determines the course and pathogenesis of the infection. Convalescent plasma neutralizing antibodies transfusion has been one of the treatments used against infectious diseases, for more than a century, considering that passive immunization can help the immune system to control the evolution of the infection, allowing the specific immune response be induced in the host (Luke *et al*., 2006). Convalescent plasma has also been used as a compassionate treatment for critically ill patients with COVID-19 (Abdullah *et al*., 2020). However, the results for convalescent plasma in COVID-19 were inconclusive regarding its efficacy against mortality in hospitalized patients, due to the fact that not all the trials were performed with a placebo group, and to the different therapies receiving. Several studies suggested that the benefit of receiving convalescent plasma was determined by the transfusion of high antibody titers, in the early stage of the disease (Cheng *et al*., 2005; Chen *et al*, 2020)

In that regards, convalescent plasma has been clearly demonstrated to be effective in Argentina for hemorrhagic fever (Maiztegui *et al*., 1979). Even more, the transfusion of immune plasma in defined doses of neutralizing antibodies during different phase of the illness is a currently specific therapy in this illness.

Others non-randomized trials have also shown the efficacy of convalescent plasma in several infections: Severe Acute Respiratory Syndrome (SARS), Middle East Respiratory Syndrome (MERS), Influenza A (H1N1), Avian Influenza (H5N1) and Ebola. (Hung *et al*., 2011, Zhou *et al*., 2007; van Griensven *et al*., 2016). However conclusive data from randomized, controlled trials are still an outstanding debt. It is also well documented that there are a number of risks for the use of convalescent plasma. These risks are associated with any blood product, such as transmission of infectious diseases or others like serum sickness (Casadevall and Pirofski, 2020; Benson *et al*., 2009). Nonetheless, transfusion-related acute lung injury is a life-threatening complication, especially in those due to a lung injury critical illness (Tiberghien *et al*., 2020). In COVID-19 disease, theoretical risks include antibody-dependent enhancement of infection, because the presence of antibodies elicited by one coronavirus strain can fail to neutralize, another coronavirus strain (Wooding and Bach, 2020). In addition, the safety assessment of patients who received convalescent plasma therapy demonstrated less than a 1% rate of serious adverse events immediately following treatment. This mean the risks of convalescent plasma therapy are likely not excessive in relation to the risks of severe COVID-19 itself (Abdullah *et al*., 2020; Erkurt *et al*., 2020).

This therapy is important because the vaccines are still in an experimental phase.

Recently, Libster, *et al*. (2020), in Argentina showed the efficacy of early plasma administration in severe forms of COVID-19 in older adults. The study was developed under the hypothesis that convalescent plasma contains neutralizing antibodies against the coronavirus, can be passively transferred to patients. The Food and Drug Administration (FDA) in 2020 approved the use of convalescent plasma to treat severe COVID-19 infection (Hopkins Tanne *et al*., 2020). The FDA recommends collecting convalescent plasma from patients at least 28 days after resolving COVID-19 symptoms, after two negative molecular tests, to ensure the eradication of the virus and having neutralizing antibodies. It is also demonstrated that the circulating antibody decays rapidly over the first 2–3 months of the infection, leaving a limited window to collect high-titer plasma from donors, as was pointed for H5N1 and SARS infection (Zhou *et al*., 2007; CaoW *et al*., 2007).

In our City Tucumán-Argentina, the Health Ministry of the Tucumán created the Centralized Registry of Convalescent Plasma Donors with the aim of collecting, processing and distributing convalescent plasma to be used in patients with COVID-19 disease (Agreement: N° 206/ from Health Province System HPS).

The potential benefit of post-COVID-19 convalescent plasma administration depends on many factors as: the severity disease, comorbidities, concurrent treatments, neutralizing antibody titers, and the time in the course of the illness that is administrated (Li *et al*., 2020; Jiang and Du, 2020; Janiaud *et al*., 2020). The earlier administration of CP from COVID-19 disease give the higher chance to block the entry of SARS-COV-2 into the host cell and prevent a severe disease. Late administration of CP in SARS-COV-2 infection could be less effective due to the intracellular location of the virus and/or the damages produced by the cytokine storm elicited by the virus infection (Shi *et al*., 2020).

The aim of the present study was to evaluate in hospitalized patients from the public health system of Tucumán, the efficacy of convalescent plasma administration to patients with moderate or severe COVID-19 illness, and its relation with different comorbidities during July to October 2020 when the number of hospitalized patients increased in Tucumán

Material and Methods

Immunoglobulin G (IgG) Antibody Titer

The IgG was measured using an Abbott Architect SARS-COV-2 assay to detect nucelocapside antibodies with high sensitivity and specificity (Bryan *et al*., 2020). Anti-nucleocapside antibodies from

SARS-COV-2 was determined in the serum from people recovery from the virus infection on the days 28-30 after the onset of the symptoms, by CMIA-Architect, Abbot test, according to manufacturer's instructions. The results were expressed as an anti-N IgG index, calculated as the relation between the result of the sample (S) and the calibrator (C). The cut-off point corresponds to an Index (S/C) of 1.4. The indexes below 1.4 were considered negative for IgG anti-N antibodies, while an index above 1.4 were considered a positive result. The plasma titters used as CP for therapy were between the index 4 to 7.

Patient's Intervention

Between July and October 2020, 48,243 nasopharyngeal swabs samples tested were positive for the polymerase chain reaction (PCR) against SARS-COV-2. The most of these patients (95.72 %) did not required hospitalization, but 4.28 % of them (n=2,069) were hospitalized in public hospitals. A total of 241 patients were included to receive plasma, from the Intensive Care Unit (ICU), or with requirement of mechanical ventilation. From the total of patients 52 of them left the public hospital to go to private institution, the rest 189 patient were included in the present study. The study was approved according protocol stated: 3131-410-DBS-2020 from Health Province System (HPS) and by the Research Department and Ethics Committee (SIPROSA-Tucumán Health Ministry): 12/2020 EC Nº 3131-410.

The hospitalized patients were between 23 and 84 years old with a median age of 54; some presented several comorbidities as arterial hypertension, diabetes, preexistent cardiovascular disease, chronic obstructive pulmonary disease. For the use of convalescent plasma patients with lung infiltrates determined by Pulmonary Infiltrates (X-Ray and Computed Tomography), dyspnea with respiratory rate >30 breaths/minute, oxygen saturation <93%, oxygen requirement, PaFiO2 <300 mmHg, alteration of the conscious or patients that presented the comorbidities mentioned above were considered.

Patients received a volume of 200-250 ml of convalescent plasma (Tiberghien *et al*., 2020; Rasheed *et al*., 2020) with IgG-anti N antibodies, determined by (CMIA-Architect, Abbot).

A group of patients (n=16) requiring mechanical ventilation and comorbidities received a second dose of plasma as a therapeutic strategy due to the lack of improvement to the previous treatment (Marano *et al*., 2016). This second dose was administered in the same conditions that the first dose. In these patients the interval of time was 1.66 +/- 0.97 days between the first and the second dose for the CP administration.

Statistical Analysis

Continuous variables were expressed as the Mean ± Standard Deviation (SD). Categorical variables

were expressed as percentages. Survival, severity of COVID-19 disease and time to convalescent plasma administration, were analyzed with XLSTAT Excel Statistical Software. Non statistical model was used because this study is an observational approach.

Results

From 48,243 patients with COVID-19 diagnosis, by PCR positive reaction with average of 42 years old, we observed no differences in the total of infected persons in the percentage between female or male patients (50 and 49%, respectively).

From 48,243 infected persons, we focused only on 189 patients hospitalized in public institutions. The convalescent plasma administration was according the parameters described in Table 1. The transfusion of CP was on days 3.14 ± 1.77 after the hospital admission (Table 2).

Table 1: Admission criteria for plasma therapy

Parameters	Pre- Convalescent Plasma Transfusion
Fever	42.33 % with fever (n=102)
Respiratory Rate	23.64 breaths/min +/- 5.93
Heart Rate	86.12 beats/min +/- 12.37
Platelet Count	231447 µl +/- 86645
PaFi O_2 (Blood Pressure O_2/Inspired Fraction O_2) <300 mmHg	76,76% (n=185)
KPTT (Kaolin Activated Partial Tromboplastine)	33.71 sec +/- 8.13
Oxygen Saturation while Breathing Ambient Air	<93%
Ferritine	1283 µg +/- 96.4
D-Dimer (DD)	1511 ng +/- 226.9
Lactate Dehydrogenase (LDH)	801 U/L +/- 354.19
Pulmonary Infiltrates (X-Ray and Computed Tomography)	71.36% (n=172)

Table 2: Time scheme for admission to the hospital and plasma therapy and discharge

From	To	
Onset of Symptoms	Intervention with plasma	8,55 Day +/- 4,33
Admission to the Hospital	Intervention with plasma	3,14 Day +/- 1,77
Admission to the Hospital	Time of discharge from the hospital	13.87 Day +/- 8,75

As regard to the gender the patients who required convalescent plasma 72.49% were male n=137 and 27.51% were female n=52. The ages of both groups were 57 and 53 years old for male and female, respectively (Table 3).

Table 3: Percentage of patients receiving plasma according gender and age (n=189)

Sex	Number	Percentage	Rate of Age
Female	52	27.51	57
Male	137	72.49	53
	189	100,00	

Evolution of Covid-19 Disease After Convalescent Plasma Administration

From 189 patients hospitalized that received convalescent plasma transfusion, 48.02% of them resolved the illness and left the hospital. By contrast, 34.46% of the patients were not able to control the infection and died. A rate of 17.51% of patients that received CP, left the public hospital to continuous their treatment in a private institution. As regard the gender and mortality after CP in severe COVID-19 disease, we observed that 25.40% of them were female and 74.60% were male (Fig. 1A and 1B).

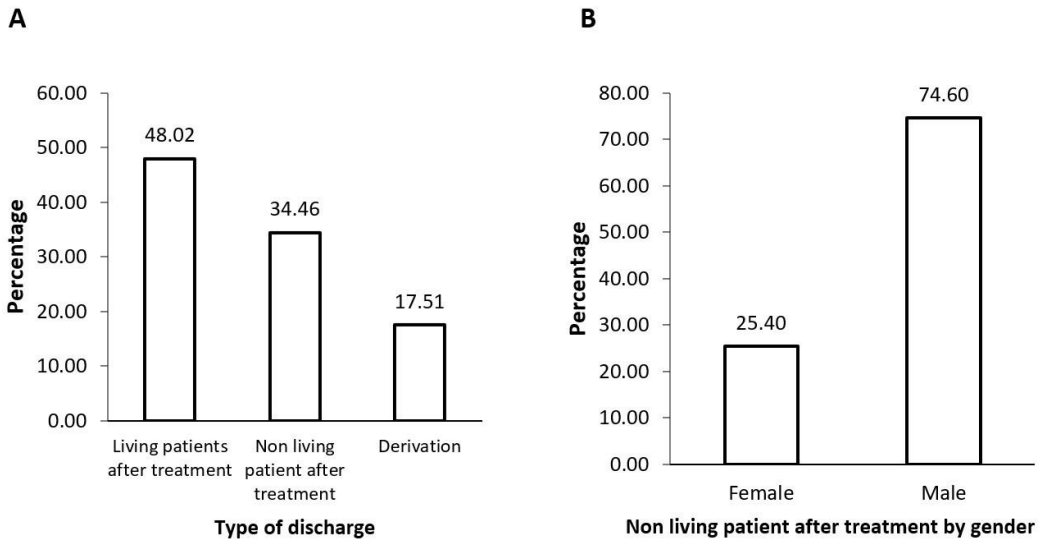

Figure 1: Type of discharge from hospital and mortality according to the A) the graphic represent the percentage of the patients live or non-living after CP administration and derivation to private hospital B) graphic represent the percentage of mortality between gender (n=189)

Analysis of Plasma Intervention with One or Two Doses

Table 4 shows that only 27 patients with severe illness and mechanical ventilation received CP and a total of 4 were recovery and could left the hospital. As shown in Fig. 2A the 92% of hospitalized patients required one dose of convalescent plasma and only an 8% received two doses. Fig. 2B shows the numbers of patients who required one or two doses of convalescent plasma with respect to the months July to November of 2020. The patients that received convalescent plasma were in accordance with the increase of COVID-19 infection registered in the Health Provincial System (HPS).

Table 4: Patients with mechanical ventilation that received plasma and died (n=27)

	Mechanical Ventilation Patients	Percentage
Living	4	14.81
Dead	23	85.19
	27	100

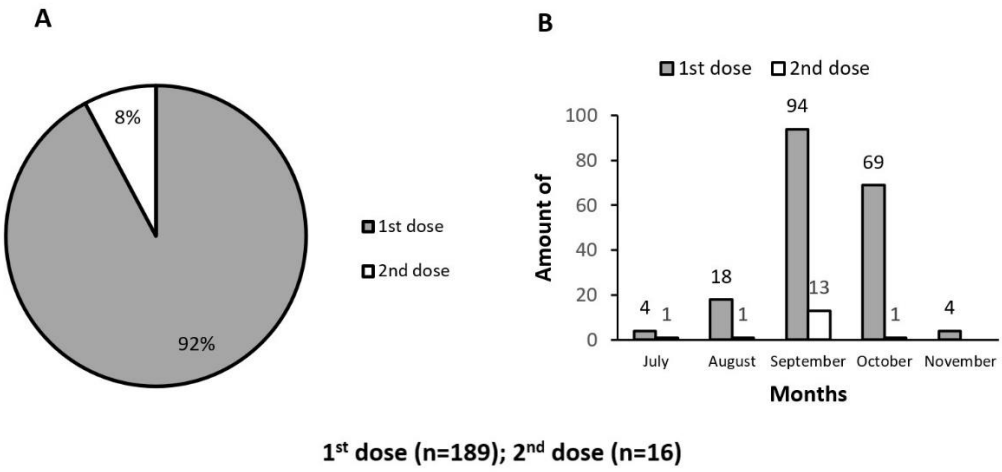

Figure 2: Percentage of patients receiving one or two doses between the months July to November A) Represent the percentage of patients receiving one or two dose of CP (n=189). B) The graphic shows the evolution of the disease through the year 2020 in Tucuman Argentina being the top on September

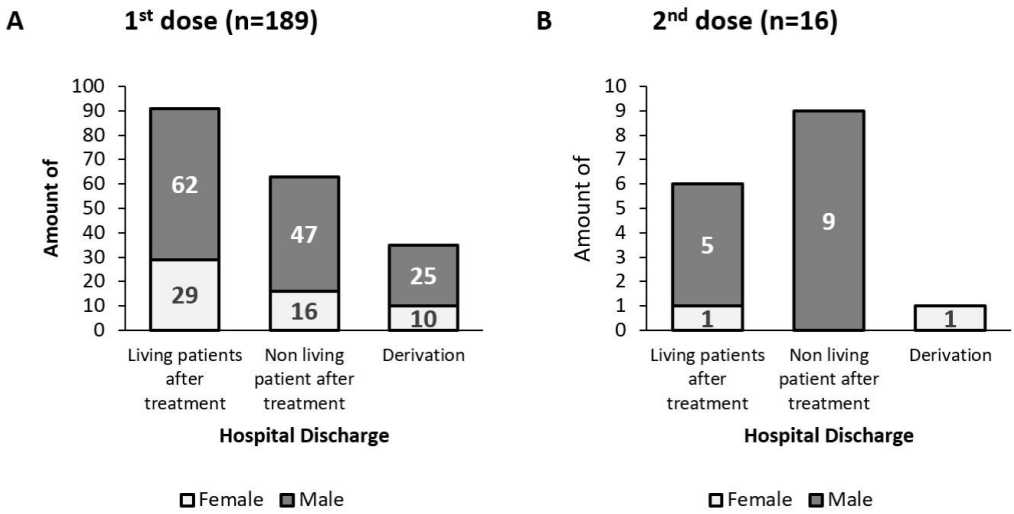

Figure 3: Number of patients recovered and mortality after one and two doses of CP according sex A) the graphic shows the number of patients live or non-living after one dose of CP (n=189) B) the graphic represents the number of patients live or non-living after the 2nd dose in relation to gender (n=16)

Fig. 3 shows the outcome of people receiving 1 or 2 doses of convalescent SARS-COV-2 plasma in female and male patients, and the number of patients recovered and death after one and two dose according to gender.

Requirement of Convalescent Plasma in Patients with COVID-19 that Display Comorbidities

We analyzed the requirement of CP in presence of different comorbidities. From a total of 28 patients, we observed that a 75% that received CP presented diabetes disease, followed by those who suffer both diabetes and obesity (14.29 %) with neurologic disease and 10.71% of autoimmune disease. Fig. 4 and Table 5 show the number of living and non-living patients with comorbidities.

Table 5: Patients living and dead with comorbidities after CP treatment (n=28)

	Comorbidities Patients	Percentage
Living	18	64.29
Dead	10	35.71
	28	100

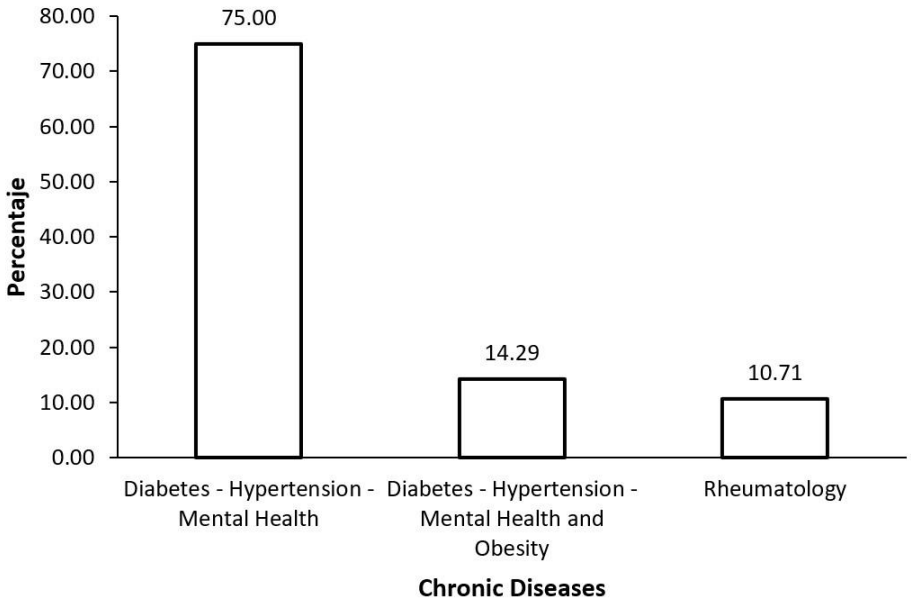

Figure 4: Percentage of patients with different comorbidities who received one dose of convalescent plasma. The figure shows the percentage of patients suffering different comorbidities being diabetes and hypertension the 75% of them, (n=28), who received only one dose of CP

Discussion

The use of convalescent plasma in critical patients, as a tool to combat COVID-19 infection, was a therapy in many countries (Tiberghien *et al*., 2020; Abdullah *et al*., 2020; Erkurt *et al*., 2020; Libster *et al*., 2021). The use of convalescent plasma in humans has been stated in a review from Wooding and Bach (2020) whose summarize 16 COVID-19 reports, with available evidence in human studies for treatment to coronavirus infection. According to these authors most of the reports described a potential benefit of convalescent plasma on clinical trials in severe or critically ill patients without adverse effects (Li *et al*.,

2020; Rasheed *et al*., 2020; Enzmann *et al*., 2020). The authors remark the limitations to evaluate properly the efficacy of the convalescent plasma, due to the use of antivirals, steroids and other treatments, the small sample sizes and the lack of randomization or control groups. One important point was that results published suggest an early administration of CP to have better outcomes. Other important point was to determine the dose of CP for transfusion. There are reports (Tiberghien *et al*., 2020; Rasheed *et al*., 2020; Marano *et al*., 2016) that use different doses between 200 to 1200 ml, being the most used 200 ml. High dose of plasma could have a potential effect on infectivity of severe acute respiratory syndrome Coronavirus 2 (SARS-COV-2), because the virus may also enter the host cells by binding to Fc receptor (FcR) on the cell membrane, resulting in antibody-dependent enhancement (ADE) effect on SARS-COV-2 infection. In the same way low neutralizing titers, may cause harmful effects (Shibo and Lanying, 2020).

In the present observational study, we report the results obtained using convalescent plasma in patients suffering COVID-19 infection. SARS-COV-2 convalescent plasma was administered in different stages of the disease according to the severity of the illness. All patients who required plasma maintained the treatment that was being administered according to medical criteria. We observed that the effectiveness of the treatment with CP was related to the early administration after admission to the hospital and with the days of the onset of the symptoms (8 and 12).

Even when the efficacy of convalescent plasma remains controversial, we demonstrated that in 48% of the interventions was effective (Fig 1A). The mortality observed related to the gender is shown in Fig 1B, where the mortality was higher in male than in female (75% vs 25%). This fact would be attributed that testosterone increase the immunosuppressive cytokine IL-10, which can act directly via androgen receptors on CD4 T lymphocytes to increase IL-10 gene expression (Liva and Voskuhl, 2001). Besides, angiotensin-converting enzyme-2 (ACE2) and trans membrane protease, serine 2 (TMPRSS2) act as receptors to bind the virus. Both ACE2 and TMPRSS2 have been proposed as modulators of the different susceptibility to SARS-COV-2 in both sexes (Penna *et al*., 2020). TMPRSS2 is a testosterone regulated gene and may have a higher expression in men than in women (Tomlins *et al*., 2005). Nevertheless, a number of non-genetic factors can change the susceptibility and mortality related to the gender, and they likely to be considered including cultural habits in different countries (Chen *et al*., 2020; Ghosh S and Klein RS, 2017).

With respect to the patients with comorbidities, the obesity and diabetes were predominant, these patients had more risk, because in obesity there is an elevated level of leptin circulating that predispose to morbidity and mortality in SARS-COV-2 infection. This fact is due to an immune response diminished with high levels of pro-inflammatory cytokines, which fails to control the viral replication (Shi *et al*.,

2020). The virus can bind to other receptors as Toll Like Receptors (TLRs) to increase the pathway of internalization into the cells (Rebello *et al*., 2020).

In diabetes is well described the effect of glucose on the immune system; an inflammatory response occurs as a result to high blood glucose levels, as well as the presence of inflammatory mediators produced by adipocytes and macrophages in fat tissue. Hyperglycemia in diabetes causes dysfunction of the immune response, which fails to control the spread of invading pathogens. The increased prevalence of type2 diabetes will increase the incidence of infectious diseases and related comorbidities (Berbudi Afiat *et al*., 2020).

Clinical trials published for CP showed to be beneficial, without side effects. As regards to the time of intervention, Li, *et al*. (2020) did not find difference on time to clinical improvement between groups in 93.9% of patients receiving the intervention, the median time elapsing between symptom onset and randomization was more than 14 days, as well as others reports (Avendano-Sola *et al*., 2020; Agarwal *et al*., 2020). Simonovich, *et al*. (2020) and others authors (Long *et al*., 2020; Chen *et al*., 2020) found that convalescent plasma administered between 8 to 12 days from the onset of Covid-19 symptoms was effective. However, there is a report from Janiaud Perrine, *et al*. (2021) that shows that convalescent plasma therapy compared with placebo or standard of care, was not significantly associated with a decrease in the mortality or with any benefit for other clinical outcomes. The evidence found in this study was low to moderate as regard the nonliving patients after CP administration.

In our study we found that the effective time to recovery was 13.87 days ± 8.75 between the hospitalization until discharge (Table 2) after CP administration. Our results showed that early administration (3 to 5 days) of convalescent plasma had a favorable effect in the hospitalized patients. This treatment was an option in these patients suffering COVID-19 infection, where the prior or concurrent treatments were no effective. The CP administration diminished the number of the deaths. This practice should continue as it was suggested in other clinical trials (Casadevall and Piroski, 2020; Wooding and Bach, 2020). The limitation of this observational study was a risk of bias, due to non-randomization. Control trials are necessary to determine the efficacy of this therapeutic option.

Conclusions

Our observational study showed CP administration as a potential therapeutic, with a diminution of 48% of the deaths associated to the disease, but only a decrease of 15% in deaths in critical patients with mechanical ventilation. The early CP intervention (3 to 5 days) was critical to obtain the therapeutic benefit reported.

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Author Contributions

ChR, PM, VJ, BG, MN, and FM designed and coordinated clinical studies SM, DGG, SW and TR established the criteria for convalescent plasma treatment. AM, CD and AF conceived dose for the plasma intervention. AN and AG compiled and analyzed the data. PD VPE and TGR were involved in the bibliography recruitment MC, CSI, CR, PG and PM wrote and discusses the manuscript. All authors participated equally in data analysis and interpretation.

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Competing Interests: The authors have no conflicts of interest to declare.

Ethics Statement

The protocol for use of Convalescent Plasma as therapy in COVID-19 disease (PAE CC19) is stated in administrative record: 3131-410-DBS-2020 from Health Province System HPS. The protocol was also approved by the Research Department and Ethics Committee (SIPROSA-Tucumán Health Ministry). Identification: Dictate12/2020 EC Nº 3131-410

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