Convalescent plasma therapy prevents acute respiratory distress syndrome in patients with SARS-CoV-2 virus disease

Terapia con plasma convaleciente previene el síndrome de dificultad respiratoria aguda en pacientes con enfermedad por el virus del SARS-CoV-2

Consuelo Macias Abraham,[1*] https://orcid.org/0000-0001-5484-096X

Delia Esther Porto González,[2] https://orcid.org/0000-0002-8111-2930

Ariel Legrá Ayala,[3] https://orcid.org/ 0000-0001-5003-4864

Mariela Forrellat Barrios, [1] https://orcid.org/0000-0002-1590-9191

Rosa María Lam Díaz,[1] https://orcid.org/0000-0002-9909-3862

Damisela Cordoví Rodríguez,[3] https://orcid.org/0000-0002-5411-5722

Lillebit Ortega León[1], https://orcid.org/0000-0001-5736-4305

Laura Ballester Planes,[3] https://orcid.org/ 0000-0002-4892-7003

Kalina García Domínguez,[3] https://orcid.org/0000-0002-8145-3807

Zuleidi González Maldonado,[3] https://orcid.org/0000-0003-3426-1551

Zunilda FrómetaTolón,[3] https://orcid.org/0000-0001-8949-3523

Milaidys Rodríguez Hernández,[4] https://orcid.org/0000-0001-8620-7309

Judith Rodriguez Alonso,[5] https://orcid.org/0000-0003-2359-4588

Tania Morales Quiñones,[5] https://orcid.org/0000-0001-8677-9374

Thalia Valdivia Valido,[5] https://orcid.org/0000-0002-8083-9644

Irinia Valdivia Alvarez,[6] https://orcid.org/ 0000-0002-1450-941X

Aurora Delahanty Fernández,[6] https://orcid.org/ 0000-0002-3780-215X

Darien Ortega León,[6] https://orcid.org/0000-0002-4711-6479

Ariel Palenzuela Díaz, [6] https://orcid.org/0000-0001-5930-7849

Vivian Kourí Cardellá[7] https://orcid.org/0000-0001-7878-7542

[1]Instituto de Hematología e Inmunología, La Habana, Cuba
[2]Ministerio de Salud Pública de Cuba, La Habana, Cuba

[3]Banco de Sangre Provincial de La Habana, La Habana, Cuba

[4]Banco de Sangre Municipal de Diez de Octubre, La Habana, Cuba

[5]Hospital Militar Central Luis Díaz Soto, La Habana, Cuba

[6]Centro de Inmunoensayos, La Habana, Cuba

[7]Instituto de Medicina Tropical Pedro Kourí La Habana, Cuba

* Autor para la correspondencia: rchematologia@infomed.sld.cu

ABSTRACT

Background: SARS-CoV-2 disease 2019 is a pandemic with no specific therapeutic agents and substantial mortality. The success of convalescent plasma therapy is based on the transfused plasma had high concentrations of anti-SARS-CoV-2 antibodies, and on the safe preparation of serum to eliminate potential risk factors, such as the transmission of viruses via transfusion.

Methods: Five patients laboratory confirmed COVID-19, diagnosed using reverse transcriptase–polymerase chain reaction (RT-PCR) classified like of care and seriously non-ventilated patients with moderate hypoxemia were received 300 mL convalescent plasma treatment. Each donation was tested for antibody titers IgG class anti-SARS-CoV-2 by UMELISA. The transfused plasma units had an average antibody titer of 836.00 ± 617.155. The time interval between the onset of symptoms and transfusion was 9 days (7.20± 3). Before and after each transfusion, clinical and laboratory parameters were evaluated.

Results: At 24-hour after the plasma transfusion, oxygen partial pressure increased from medium value of 70.4 to 101.6 mm Hg, C-reactive protein and lactate dehydrogenase enzyme values decreased in 3 of 5 patients; however, the ferritin values increased in all the patients. Post-transfusion hospital discharge time was from 48 hours to 12 days and the SARS-CoV-2 PCR was negative between 3 and 5 days. No adverse transfusion reactions were reported.

Conclusion: This report emphasis about the efficacy and security of convalescent plasma transfusion to care and seriously non-ventilated patients infected like a preventive therapy for severe respiratory distress for SARS-CoV-2 virus disease.

RESUMEN

antecedentes: La enfermedad por el nuevo coronavirus SARS-CoV-2 es una pandemia sin agentes terapéuticos específicos y con una alta mortalidad. El éxito de la terapia con plasma de convalecientes se basa en que el plasma transfundido tiene altas concentraciones de anticuerpos anti-SARS-CoV-2, y en la preparación segura del plasma para eliminar posibles factores de riesgo, como la transmisión de virus por transfusión.

Métodos: Cinco pacientes COVID-19 confirmados por laboratorio, diagnosticados mediante reacción en cadena de la polimerasa con transcriptasa inversa (RT-PCR) clasificados como de cuidado y graves no ventilados con hipoxemia moderada recibieron tratamiento con 300 ml plasma de convalescientes. Cada donación se probó para los títulos de anticuerpos de clase IgG anti-SARS-CoV-2 mediante UMELISA. Las unidades de plasma transfundidas tenían un título medio de anticuerpos de 836.00 ± 617.155. El intervalo entre el inicio de los síntomas y la transfusión fue de 9 días (7.20 ± 3). Antes y después de cada transfusión, se evaluaron los parámetros clínicos y de laboratorio.

Resultados: Veinticuatro horas después de la transfusión de plasma, la presión parcial de oxígeno aumentó de un valor medio de 70.4 a 101.6 mm Hg; los valores de la proteína C reactiva y de la enzima lactato deshidrogenasa disminuyeron en 3 de los 5 pacientes; sin embargo, los valores de ferritina aumentaron en todos los pacientes. Después de la transfusión, el tiempo hasta el alta hospitalaria fue desde 48 horas hasta 12 días y la RT-PCR del SARS-CoV-2 fue negativa entre 3 y 5 días. No se informaron reacciones adversas a la transfusión.

Conclusión: Este informe enfatiza la eficacia y seguridad de la transfusión de plasma convaleciente para pacientes infectados, reportados de cuidado y grave no ventilados, como una terapia preventiva para la dificultad respiratoria grave de la enfermedad por el virus del SARS-CoV-2.

Palabras clave: plasma de convalecencia, virus SARS-CoV-2, COVID-19, coronavirus, SDRA.

INTRODUCTION

Currently, humanity internationally is facing a pandemic whose main cause of death is an acute respiratory syndrome caused by coronavirus 2 (SARS-CoV-2) COVID-19, which is affecting billions of people worldwide and with thousands of confirmed cases in Cuba to date. [1-7]

This virus is a new human pathogen and there are no vaccines, monoclonal antibodies, or drugs available for the specific treatment of SARS-CoV-2, so the serum of convalescent patients becomesan eligible option for its specificity, rapid availability and increasing number of immunized individuals cured of infection. [2-4]

Passive administration of antibodies against an infectious agent has been a very old procedure, used for more than 2 centuries, which has allowed the improvement and healing of patients and, in general, retrospective meta-analyses carried out indicate favourable effects, such as lower mortality. In previous epidemics with other coronaviruses, such as SARS-CoV-1 (2003) and MERS (2012), the presence of neutralizing antibodies in convalescent serum was demonstrated. Transfusion of plasma immune compatible for COVID-19 patients could provide neutralizing antibodies and other protective immune defence mechanisms mediated by IgM and IgG type antibodies produced in the primary immune response, such as antibody-dependent cytotoxicity, complement haemolysis and phagocytosis. [3-7]

The administration of this treatment is more effective when the application is closer to the onset of symptoms, probably because it involves neutralization of the initial inoculum of the smallest virus and early modification of the inflammatory response. Its most favourable indication is prophylaxis to avoid viral infection and not treatment of the infectious process. However, there is evidence of clinical improvement in previous epidemics and the current one in the treatment of seriously ill patients. [2, 3-6]

The risks of this therapy consist of transfer plasma infectious agents, [1-7] and non-infectious immunological adverse reactions, such transfusion reaction acute lung injury, called TRALI, due to the pre-existence of antibodies against class I and II antigens of Major Histocompatibility System and donor plasma anti-neutrophil antibodies.[4,5] It cannot exclude a state of neutrophil activation at the level of the pulmonary alveoli in the critically ill patient that could aggravate the clinical picture. Also, there is a theoretical risk of increased antibody-dependent infection that occurs in various viral diseases and that would be potentiated by previous coronavirus infections. [1-3] However, the available evidence of the use of convalescent serum in patients with SARS-CoV-1 and MERS, and previous use in patients with COVID-19, suggest that it is a safe practice.

METHODS

Selection criteria for patients

Patients laboratory confirmed COVID-19, diagnosed using reverse transcriptase–polymerase chain reaction (RT-PCR), infected with COVID-19, classified like of care were eligible to receive convalescent plasma treatment if they fulfilled the following criteria: 1) without history of anaphylaxis to blood components, 2) not contraindications for transfusion, 3) hypoxemia and moderate to severe respiratory symptoms, and 4) the patient or his family gave their informed consent. The ABO blood types of the patients were determined for potential compatibility with the convalescent plasma donor.

Selection criteria for convalescent donors

Convalescent SARS-CoV-2 patient, between 18 and 60 years old, with 4 weeks of the infection diagnosis, negative test for SARS-CoV-2 infection by RT-PCR and the presence of antibodies, without other criteria that exclude as a donor according regulation by the Cuban procedures of blood banks and transfusion services. The female donor requires the absence of HLA antibodies or anti-granulocyte realized previously. Screening for Hepatitis B, C, HIV were performed by nucleic acid detection using molecular biology techniques by Cobas Systems 201(*Roche Diagnostic*) at the Havana Blood Bank. The antibodies versus *Treponema pallidum*

was performed by the Rapid Reagin Plasma Carbon Test (*Isotope Center(CENTIS), Cuba*). The patients were invited to donate their convalescent plasma after written informed consent was obtained.

Exclusion criteria

Convalescent patients who were considered as polytransfused donors (4 or more blood component), female donor with a history of more than 3 alloimmune sensitization events such as pregnancy, interruption, abortion and transfusion, and the presence of decompensated comorbidities were excluded.

Procedure for obtaining immune plasma

600mL of plasma were obtained in 2 bags of 300 mL/unit by automated plasma apheresis. The serum of each donation was tested for antibody titersIgG class anti SARS-CoV-2 by enzyme-linked immunosorbent assay ultramicroanalytic (UMELISA SA-CoV-2 IgG) at the Immunoassay Center and RT-PCR for the SARS-CoV-2 virus [8]at the Tropical Medicine Institute "Pedro Kourí". The plasma bags were stored at -20ºC in the Havana Blood Bank.

UMELISA SARS-CoV-2 IgG

Ultramicroelisa plates were coated 4 hours at 45°C with synthetic peptides of the immune dominant regions of the protein N of the virus (15 µL per well). Plasma samples were diluted from 1 to 20 initial concentrations in double dilutions into buffer solution sheep serum (in other plate). 10 µL plasma diluted were added to the wells and incubated at 37°C for 30 minutes. After 4 wash with buffer solution, 10 µL of anti–human IgG antibodies conjugate/alkaline phosphatase (for IgG antibody titer detection) were added to each plate and incubated at 37°C for 30 minutes. After 4 wash, 10 µL of 4-methyl-umberiferyl phosphate was added and incubated at 20-25°C for 30 minutes in the dark and the substrate was hydrolysed. The fluorescence intensity detected the presence of antibodies. All samples were run in duplicate. The antibodies titers were determined by end dilution.

Blood count, Pressure of O_2 and Serumproteins

The blood count was performed using a Mindray 3200 and 5800 Haematology Complex (*Shenzhen Mindray Bio-medical Electronics Co. Ltd*). The partial pressure of oxygen(PO2) was measured in arterial blood using a Coba 121b gasometer (*Roche Diagnostics*). The serum proteins: C-reactive protein, LDH, and ferritin were measured using a BS 400 Chemical Autoanalyser (*Diamond Diagnostic*).

Characteristics of transfused patients

The patients are 50.80±13.30years old (1 female and 4 man). The blood groups were one patient A+, other B- y three O+. The chronic diseases associated are the arterial hypertension, bronchial asthma and epilepsy. The initial symptoms were dyspnoea, fever, cough and headache. Others symptoms were asthenia, decay, chills and sneeze (some of them related with disease progression). The specific treatment received before the transfusion by Cuban therapeutic protocol was the triad: Lopinavir (5 patients), Chloroquine (4) and Recombinant alpha 2Interferon (1), (*Center for Genetic Engineering and Biotechnology, CIGB*). Others drugs were: Omeprazole (2), Ceftriaxone (2), Carbamazepine (1), Low Molecular Weight Heparin (1) and CIGB 258 (1). The complications prior to plasma transfusion were sustained hypoxemia, cerebral stroke and hypotension. The average interval between symptom onset and admission was 2.75 days and the average interval between admission and transfusion was 5 days. The interval between the onset of symptoms and transfusion was 9 days (7.20± 3) (table1).

Table 1. Clinical characteristics of SARS-CoV-2-infected patients andcharacteristics and antibody titer of convalescent plasma donors

Patient	1	2	3	4	5
Sex	Male	Male	Male	Female	Male
Age (years)	54	68	33	42	56
Weight (kg)	80	100	85	60	100
Smoking	Non	Non	Non	Yes	Non
Blood Type	O+	O+	A+	O+	B -
Coexisting chronic diseases	Hypertension	Epilepsy	Non	Hypertension,	Hypertension

				Bronchialasthma	
Disease presentation and course	Dyspnoea, Fever	Cough, Dyspnoea, Fever, Asthenia	Fever, Dyspnoea	Fever, Headache, Asthenia	Dyspnoea, Fever, Chill
Interval between symptom onset and admission(d)	4	3	1	1	3
Interval between admission and plasma transfusion (d)	2	4	10	3	6
Complications prior to plasma transfusion	Sustained hypoxemia	Cerebral stroke	Sustainedhypoxemia	Hypotension	Hypoxemia
Most severe disease classification	Serious	Serious	Serious	Care	Care
Treatments	Lopinavir/ Interferonα2r/Chloroquine/ Ceftriazone	Lopinavir/ Chloroquine/ Carbamazepine	Lopinavir/ Chloroquine/ Ceftriazone/ Heparin/ Omeprazole	Lopinavir/ Chloroquine/ Omeprazole	Lopinavir/ CIGB258
Characteristics and Antibody Titer of Convalescent Plasma Donors					
Blood type	O	O	A	O	O
[a] Volume of transfused plasma (mL)	300	300	300	300	300
[b] Specific IgG UMELISA Titer	1280	1280	320	1280	320
Time betweentransfusion and discharge(d)	12	6	5	12	4

[a]Donor-patients were paired by the donor plasma codes and the patient code.

[b]UMELISA end point dilution titers (IgG antibody).

Patient treatment

Five ill care and seriously non-ventilated patients were transfused with 300 mL/transfusion according to clinical criteria. Before and after each transfusion, clinical and laboratory parameters were evaluated: PO2 (mm Hg), quantitative reactive protein C (CRP) (mg/L), lactate dehydrogenase enzyme (LDH) (U/L), Ferritin(μg/L), erythrocyte sedimentation rate (mm/h) and complete blood count.

Statistical analysis

Median was used as a summary measure for the quantitative variables, and absolute and relative frequencies were used for the qualitative variables. For data processing, was used the SPSS version 15.0 for Windows program.

Ethical aspects

This research has complied with all the ethical aspects described in the Declaration of Helsinki for medical research involving human beings. Both donors and patients and their relatives gave informed consent before donation and transfusion, respectively. This clinical research was approved by the Research Ethics Committee of the Institute of Haematology and Immunology, and by CECMED (Center for State Control of Drugs, Equipment and Medical Devices) as well as complying with the regulations described by PAHO / WHO.

RESULTS

At 24-hour after the plasma transfusion, PO2 increased medium value from 70.4 to 101.6; CRP decreased medium value from 26.8 to 5.95, and LDH increased in 3/5 patients from 513.0 to 611.8. Ferritin was increased in all patients from 578 to 833 at 24 hours after transfusion too (figure and table 2).
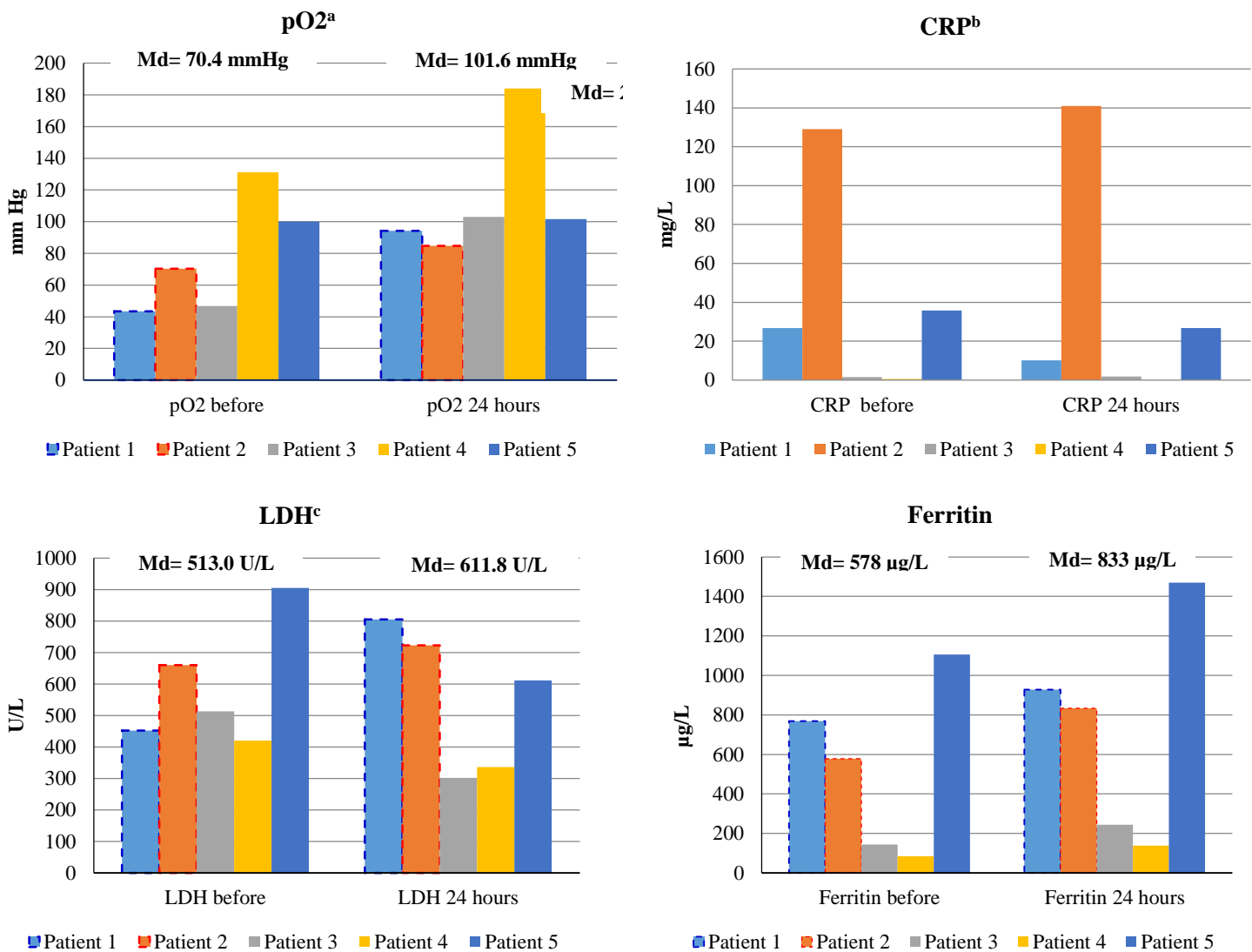
Fig. Values for partial pressure of oxygen, C-reactive protein, lactate dehydrogenase enzyme and ferritin before and after covalent plasma transfusion in 5 patients infected with COVID 19.

[a]pO2; partial pressure of oxygen, [b]CPR; C-reactive protein, [c] LDH; lactatedehydrogenaseenzyme

Table 2. Median of clinical and laboratory parameters before and 24 hours after of convalescent plasma transfusion

Parameter	Before	After 24 hours	Referencesvalues
Temperature (ºC)	36.3	37	36.1 - 37.2
Oxygen partial pressure(mm Hg)	70.4	101.6	95 - 105
C reactive protein (CRP)(mg/L)	26.8	5.95	0-5
Lactate deshydrogenase (LDH)(U/L)	513.0	611.8	230 - 460
Ferritin(µg/L)	578	833	12.5-350

At automatized blood count, the haematological and immunological parameters not showed abnormal values. There were not differences between the parameters before and after the convalescent plasma transfusion (tabla 3).

Table3. Hematological and immunological parameters (median) before and 24 hours after convalescent plasma transfusion in 5 patients infected with SARS-CoV-2.

Parameters	BEFORE	24 HOURS	REFERENCE VALUES
Hemoglobin**(g/dL)**	12.8	13.3	Men:13.0 – 15.0 Women: 12.0 – 14.0
Hematocrit **(v/v)**	0.38	0.40	0.42 - 0.52
White blood cells **(x10⁹/L)**	4.9	4.8	4 - 11
Lymphocyte s**(x10⁹/L)**	0.37	0.33	0.2 - 0.4
Neutrophils**(x10⁹/L)**	0.51	0.60	0.5 - 0.7
Monocytes **(x10⁹/L)**	0.07	0.11	0.03 - 0.12
Platelets**(x10⁹/L)**	220	201	150 - 450
Erythrocyte sedimentation rates **(mm/h)**	50	50	Men: ≤ 10 Women: ≤ 20

Post-transfusion hospital discharge time was between 2 and 12 days, and the SARS-CoV-2 RT-PCR was negative between 3 and 5 days. No adverse transfusion reactions were reported. All patients are alive.

DISCUSSION

Previous studies have reported the use of convalescent plasma transfusion in the therapy of infected patients with SARS, MERS and influenza A(H1N1). These treatments have shown higher significant percentage of patients with medical discharge and less critical cases and fewer deaths.[9-11] In the present study, the patients improve hypoxemia with increased levels of PO2at 24 hours after plasma transfusion and decreased CRP which shows an improvement in the clinical picture. In some patients it has been report that RT-PCR confirmation of the absence of the virus takes 30 days or more.[12-14]However, in this study it is observed that after transfusion of convalescent plasma the PCR was confirmed as negative in less than 5 days, corresponding to discharge of the hospital of a maximum number of 12 days post-transfusion. This suggests that the transfer of viral specific antibodies in the convalescent plasma neutralizes the viral inoculum and helps to eliminate the infection more quickly.

Acute phase proteins such as LDH and ferritin were increased, which could be explained by the complications before the transfusion and its measurement only 24 hours after it.

In addition to the antiviral treatment, has been shown that virus-specific antibodies could accelerate virus clearance and prevent entry into target cells host. [15]In the current study, all plasma from the donors had high virus-specific IgG determined by UMELISA may have contributed to the clearance of the virus and also the improvement of symptoms.

In the current study, all patients received antiviral agents by the trial of the Cuban therapeutic protocol that including Interferon alpha 2 recombinant and Lopinavir during and following convalescent plasma treatment, which also may have contributed to the viral clearance observed.

Limitations

This study has several limitations: First, the case series is just 5 patients representing a small sample and does not include a control group. Second, it is unclear if these patients had improved without transfusion of convalescent plasma,

although the change in PO2 at 24 hours after the plasma transfusion represents encouraging findings. Third, all patients were treated with other drugs (including antiviral medications), and it is not possible to determine whether the improvement observed could have been related to other therapies than convalescent plasma.

Conclusions

In this preliminary uncontrolled case series of 5 ill care patients with COVID-19, administration of convalescent plasma containing specific SARS-CoV-2 IgG antibody was followed the improvement in the patients' clinical status and the possible prevention of ARDS.

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REFERENCES

1. Cunningham AC, Goh HP, Koh D. Treatment of COVID-19: old tricks for new challenges. Crit Care.2020; 24:91. doi: 10.1186/s13054-020-2818-6

2. Shen C, Wang Z, Zhao F, et al. Treatment of 5 Critically Ill Patients With COVID-19 With Convalescent Plasma. JAMA. 2020;323(16):1582-9. doi: http://10.1001/jama.2020.4783

3. Sohrabi C, Alsafi Z, O'Neill N, et al. World Health Organization declares Global Emergency: A review of the 2019 Novel Coronavirus (COVID-19). Int J Surg. 2020 Apr;76:71 – 6. doi: http://10.1016/j.ijsu.2020.02.034

4. Wang J, Zand MS. Potential mechanisms of age related severity of COVID-19 infection: implications for development of vaccines, convalescent serum, and antibody therapies. A Preprint · March 2020. OSF Preprints - DOI: http://10.31219/osf.io/f3pze

5. Pedersen SF, Ho Y. SARS-CoV-2: a storm is raging. J Clin Invest. 2020; In-Press Preview DOI: http://10.1172/JCI137647.

6. Casadevall A, Pirofski L. The convalescent sera option for containing COVID-1 9. J Clin Invest. 2020;130(4):1545-8. DOI: http://10.1172/JCI138003.

7. Mair-Jenkins J, Saavedra-Campos M, Baillie JK, et al. The Effectiveness of Convalescent Plasma and Hyperimmune Immunoglobulin or the Treatment of Severe Acute Respiratory Infections of Viral Etiology: A Systematic Review and Exploratory Meta-analysis. J Infect Dis. 2015 Jan;211(1):80–90.

8. Corman VM, Landt O, Kaiser M, et al.Detection of 2019 novel coronavirus (2019-nCoV) by real-time RT-PCR. Euro Surveill. 2020 Jan;25(3):pii=2000045. doi: http://10.2807/1560-917.ES.2020.25.3.2000045

9. Kraft CS, Hewlett AL, Koepsell S, et al; The use ofTKM-100802 and convalescent plasma in2patients with Ebola virus disease in the UnitedStates. Clin Infect Dis. 2015 Apr;61(4):496-502. DOI: http://10.1093/cid/civ334

10. Hung IF, To KK, Lee CK, et al. Convalescentplasma treatment reduced mortality in patientswith severe pandemic influenza A (H1N1) 2009virus infection. Clin Infect Dis. 2011;52(4):447-56.

11. Yeh KM, Chiueh TS, Siu LK, et al. Experience ofusing convalescent plasma for severe acuterespiratory syndrome among healthcare workers ina Taiwan hospital. J Antimicrob Chemother. 2005 Sep;56(5):919-22.DOI: http://10.1093/jac/dki346

12. McIntosh K. Coronavirus disease 2019 (COVID-19). Up to Date13/3/2020. Available: https://www.cmim.org/PDF_covid/Coronavirus_disease2019_COVID-19_UpToDate2.pdf (Visited 26/5/2020).

13. Tan W, Lu Y, Zhang J, et al. Viral Kinetics and Antibody Responses in Patients with COVID-19. MedrXiv. 2020.03.24.20042382; DOI http://10.1101/2020.03.24.20042382

14. Tan L, Kang X, Zhang B, et al. A special case of COVID-19 with long duration of viral shedding for 49 days. MedrXiv. 2020.03.22.20040071; DOI: http://10.1101/2020.03.22.20040071

15. Shen C, Chen J, Li R, et al. A multimechanistic antibody targeting the receptor binding site potently cross-protects against influenza B viruses. Sci Transl Med.2017;9(412):eaam5752. DOI: http://10.1126/scitranslmed.aam5752

Conflicto de intereses

Los autores declaran que no existe conflicto de interés

Contribución de autoría

Consuelo Macías Abraham: concepción de la idea, realizó el diseño general y coordinación del estudio, interpretación de datos, redacción del borrador inicial del artículo, corrección y revisión crítica del manuscrito. Aprobación de versión final.

Delia Esther Porto González: participó en la concepción y coordinación del estudio, coordinó la actividad de donación de plasma del Banco Provincial de Sangre de La Habana, aprobó la versión final que va a publicarse.

Ariel Legrá Ayala: contribuyó a la realización del estudio, coordinó la actividad de plasmaféresis del Banco de Sangre de Diez de Octubre y el envío de muestras para estudios, aprobó la versión final que va a publicarse.

Mariela Forrellat Barrios: apoyó la recolección de datos y la elaracióa n de ilustraciones, la escritura del borrador inicial del artículo, corrección y revisión del manuscrito. Aprobación de versión final.

Rosa María Lam Díaz: análisis estadístico e interpretación de datos, redacción del borrador del artículo, aprobación de versión final.

Damisela Cordovi Rodríguez: participó en la coordinación y la actividad de plasmaféresis del Banco de Sangre de Diez de Octubre, aprobó la versión final que va a publicarse

Lillebit Ortega León: contribuyó a la realización del estudio participó en la coordinación y recolección de datos; aprobó la versión final.

Laura Ballester Planes: contribuyó a la realización del estudio, adiestró y participó en la puesta en marcha de las plasmaféresis Banco de Sangre de Diez de Octubre.

Kalina García Domínguez: participó en la realización estudio, elaboró los procedimientos normalizados de operación asociados al proyecto para los bancos de sangre participantes

Zuleidi Gonzales Maldonado: participó en la realización del proyecto, procesó las muestras por biología molecular de los pacientes incluidos en el estudio.

Zunilda FrómetaTolón: participó en la realización del proyecto, coordinó y realizó el traslado de muestras al Instituto de Medicina Tropical "Pedro Kourí" y al Centro de Inmunoesayos.

Milaidys Rodríguez Hernández: participó en la realización del estudio, realizó las palasmaféresis de donantes en el Banco Provincial de Sangre de La Habana.

Judith Rodriguez Alonso: participó en la realización del estudio, tuvo a su cargo la coordinación el proyecto con la terapia intensiva del Hospital Militar "Luis Díaz Soto".*Tania Morales Quiñones*: participó en la realización del estudio, participó en la coordinación y aseguramiento de las transfusiones en el Banco de Sangre del Hospital Militar "Luis Díaz Soto".

Participó en la coordinación de las transfusiones y aseguramiento del Banco de Sangre del Hospital Militar "Luis Díaz Soto".

Thalia Valdivia Valido: participó en la realización del estudio, participó en la coordinación y aseguramiento de las transfusiones en el Banco de Sangre del Hospital Militar "Luis Díaz Soto".

Irinia Valdivia Álvarez: realizó estudios de anticuerpos y títulos de plasmas de los donantes incluidos en el estudio.

Aurora Delahanty Fernández: realizó estudios de anticuerpos y títulos de plasmas de los donantes incluidos en el estudio.

Darien Ortega León: realizó estudios de anticuerpos y títulos de plasmas de los donantes incluidos en el estudio.

Ariel Palenzuela Díaz: realizó estudios de anticuerpos y títulos de plasmas de los donantes incluidos en el estudio.

Vivian Kourí Cardellá: colaboró con la realización del estudio, coordinó la realización de los estudios de RT-PCR SARS-COV-2