Rev Chil Med Intensiv 2023; 38(1): 10-17.

ARTÍCULO ORIGINAL

Therapeutic plasma exchange in adults with COVID-19 associated hyperinflammatory syndrome and multiorgan failure case series

Plasmaféresis en falla orgánica múltiple y síndrome hiperinflamatorio asociado a COVID-19. Serie de casos

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Abtract: *We report therapeutic plasma exchange use (TPE) in six adults with COVID-19-associated hyperinflammatory syndrome (COVID-19-AIS) refractory to first line therapy, facing the biological therapies unavailability in a resource-limited setting. Patients age was 41 (34-54) and all had ARDS, septic shock, and multiorgan-failure (MOF). According to ASFA 2019 classification, one patient corresponded to category I (Thrombotic thrombocytopenic purpura), and the others were non-classifiable. 2 patients had Thrombocytopenia–Associated Multiple-Organ-Failure, 2 adult-multisystem-inflammatory-syndrome, and 1 COVID-19–related autoimmune-encephalitis. Over 21 sessions, exchange volume was 1 volume in 81%, isovolumetric in 76%, and 19% had mild complications (Hypotension 4pt, Bleeding 1pt). After TPE, there was significant increase in lymphocyte count and decrease in LDH, a trend in ferritin and CRP reduction, and a trend in improving organ failures. TPE response was complete in three patients and partial in one patient. Four patients (66%) survived ICU discharge. The causes of death were unrelated to the TPE procedure. This COVID-19 phenotype is infrequent, has a high mortality, and its pathophysiology is still poorly understood. Thus, the best therapies are not yet settled. Future studies may include TPE among immunomodulatory treatments for COVID-19-associated hyperinflammatory syndrome, especially in limited resource settings.*
Keywords: ARDS; COVID-19; SARS-CoV-2; Therapeutic Plasma Exchange.

Resumen: *Describimos el uso de Plasmaféresis (TPE) en seis adultos con síndrome hiperinflamatorio asociado a COVID-19 refractario al tratamiento de primera línea, ante la falta de disponibilidad de terapias biológicas en un contexto de recursos limitados. Los pacientes tenían 41 años (34-54) y todos presentaban síndrome de distrés respiratorio agudo,*

shock séptico y fallo multiorgánico (FOM). Según la clasificación ASFA 2019, un paciente correspondía a la categoría I (púrpura trombocitopénica trombótica), y los demás no eran clasificables. Dos pacientes presentaban fallo multiorgánico asociado a trombocitopenia (TAMOF), 2 síndrome inflamatorio multisistémico del adulto (MIS-A) y uno con encefalitis autoinmune relacionada con COVID-19. En 21 sesiones, el volumen de intercambio fue de 1 volemia en el 81%, isovolémico en 76%, y el 19% tuvo complicaciones leves (hipotensión 4 pacientes, hemorragia 1 paciente). Tras la TPE, se produjo un aumento significativo del recuento de linfocitos y una disminución de la LDH, una tendencia a la reducción de la ferritina y la PCR, y una tendencia a la mejora de la falla de órganos. La respuesta a TPE fue completa en tres pacientes y parcial en uno. Cuatro pacientes (66%) sobrevivieron al alta de la UCI. Las causas de muerte no estuvieron relacionadas con el procedimiento TPE. El fenotipo de hiperinflamación es infrecuente en COVID-19 crítico, tiene una elevada mortalidad y su fisiopatología es aún desconocida. Por lo tanto, aún no se han establecido las mejores terapias. Los estudios futuros podrían incluir el TPE entre los tratamientos inmunomoduladores para el síndrome hiperinflamatorio asociado a COVID-19, especialmente en entornos con recursos limitados.

Palabras clave: COVID-19; SARS-CoV-2; Plasmaféresis.

Background

Globally, more than 593 million cases of Coronavirus disease 2019 (COVID-19) have been recorded, with more than 6,4 million deaths[1]. Beyond supportive care, there are currently no proven effective treatment options for COVID-19, although a few treatment modalities have shown some efficacy.

SARS-CoV-2 is heterogeneous and may range from no symptoms to multiple organ failure (MOF) and death[2]. In addition to acute respiratory distress syndrome (ARDS), some patients develop severe hyperinflammatory syndrome (cHIS), which plays a pivotal role in the progression of COVID-19 to MOF and death[3,4,5,6,7,8,9,10]. Immunothrombosis and endothelial dysfunction are common pathways of the dysregulated inflammatory response, resulting in severe microvascular dysfunction and end-organ damage[11,12,13].

Several therapeutic strategies that target this dysregulated inflammatory response are proposed, like high-dose corticosteroids, immunoglobulins, anakinra®, or tocilizumab® and other anti-inflammatory and immunomodulatory treatments[2,5,14,15,16,17,18,19,20,21].

Therapeutic plasma exchange (TPE) is a well-known immunomodulatory therapy that removes high molecular weight substances, including cytokines and autoantibodies capable of rescuing these specific severe phenotypes of SARS-CoV-2[6,15,16,17]. We report the use of therapeutic plasma exchange in six critically ill adults with COVID-19-associated hyperinflammatory syndrome, facing the unavailability of biological therapies in a resource-limited setting.

Patients and methods

Local IRB approved the analysis of de-identified data prospectively collected between August 1st, 2020, and August 31st, 2021. Comité Ético Científico of Servicio de Salud Metropolitano Central, Santiago de Chile approved this report (Acta 423/2021).

We included critically ill adults admitted to a dedicated COVID-19 ICU due to respiratory

failure in a General Community Hospital. We included patients with severe COVID-19 related ARDS and COVID-19 associated hyperinflammatory syndrome (cHIS) refractory to steroids (first-line therapy), defined as cHIS score ≥3 or despite corticosteroid therapy[4]. After a multidisciplinary evaluation, TPE was proposed as rescue therapy considering the life-threatening condition. TPE indications were recorded according to ASFA categories[22]. Patients who received at least one TPE were considered for analysis and clinical follow-up until ICU discharge or death.

Demographic and clinical data were registered, including mechanical ventilation (MV), vasoactive support and renal replacement therapy (RRT), immunomodulation therapy used, ICU length of stay, and mortality (Table 1). In addition, inflammatory biomarkers, C-reactive protein (CRP, mg/L) and ferritin (ng/mL); nonspecific markers of endothelial dysfunction, lactate dehydrogenase (LDH, U/L), D-dimer (ng/mL), absolute lymphocyte's count (per mm^3) and platelets (per mm^3); and organ dysfunction data, gas exchange, respiratory system compliance (CRS, ml/cmH_2O), and the Vasoactive-Inotropic Score (VIS)[23] were also recorded before and after TPE.

Table 1. Clinical and demographic characteristics of patients, therapeutic plasma exchange prescription and outcome. (M, male; F, female; TTP, thrombotic thrombocytopenic purpura; TAMOF, thrombocytopenia associated multiorgan failure; MIS-A, Multisystem inflammatory syndrome in adults; Y, yes; N, no).

	Patient					
	1	**2**	**3**	**4**	**5**	**6**
Gender	**M**	**M**	**F**	**M**	**M**	**M**
Indication	**TTP**	**Encephalitis**	**TAMOF**	**MIS-A**	**MIS-A**	**TAMOF**
Comorbidities						
Obesity	Y	Y	Y	Y	N	N
Diabetes mellitus	Y	Y	Y	N	Y	N
Hypertension	Y	N	N	N	N	N
Clinical Severity						
ARDS	Y	Y	Y	Y	Y	Y
Shock	Y	Y	Y	Y	Y	Y
MODS	Y	Y	Y	Y	Y	Y
TPE prescription						
Sessions	3	3	3	2	5	5
Exchange volume (volemias)	1	1	1	1	1	1.5
Complications	N	N	N	hypotension	bleeding	hypotension
Therapy before TPE						
Steroids	Y	Y	Y	Y	Y	Y
IVIG	N	N	N	N	N	Y
Biologic Therapy	N	N	N	N	N	N
Alive	Y	Y	Y	N	Y	N

A 12 Fr double lumen hemodialysis catheter placed in the internal jugular vein was used for TPE. TPE was performed with a centrifuge apheresis system (Spectra Optia, Terumo BCT, Lakewood, CO). We aimed to exchange 1-1.5 times the estimated plasma volume according to the formula 80 × kg × (1 - Ht)/100. The replacement solution was a 1:1 ratio of fresh frozen plasma and 5% albumin. The technique's efficacy was determined using the criteria of Panglialonga et al[24]. Procedure complications were classified into those related to the circuit (coagulation, malfunction) and those related to the patient (hypotension, anaphylaxis, hypocalcemia).

Continuous data were presented as median (interquartile range), and categorical data were expressed as proportions. Comparisons among continuous variables were performed with the Wilcoxon signed-rank test. Significance was set at $p<0.05$.

Results

Twenty-one TPE sessions on six patients were analyzed during the study period. The median age was 41 years (range from 34 to 54), and all were male. One patient's ethnicity was Mapuche, and 5 had comorbidities (4 obesity, one diabetes mellitus, one epilepsy, one psoriasis, and one drug abuse). All patients met the ARDS and septic shock criteria. In addition, three had acute kidney injury, and four had multiple organ failure.

All patients received MV and vasoactive support, and two required continuous veno-venous hemodiafiltration. Methylprednisolone pulse of 30 mg/kg (maximun 1 g) for 3 consecutive days, was the first-line therapy in all patients. Biological therapies and intravenous immunoglobulin were not available.

According to ASFA classification, one patient corresponded to category I (Thrombotic thrombocytopenic purpura), and the others were not categorized since their diagnoses were not included in 2019. In addition, two patients had Thrombocytopenia–Associated Multiple Organ Failure (TAMOF), 2 had multisystem inflammatory syndrome in adults (MIS-A), and 1 presented severe COVID-19 related autoimmune encephalitis.

The exchange volume was one plasma volume in 17 sessions and 1.5 times the other four (all in the same patient). Sixteen sessions were isovolumetric, and the others were programmed for the depletion of 10-20% estimated plasma volume. The replacement solution was 50.7% fresh frozen plasma, and the remaining 49.3% consisted of 5% albumin. Three patients received three sessions of TPE, 2 received five sessions, and 1 received two sessions (died before the third session).

After TPE, patients increased absolute lymphocyte count (1223 [910-2512] vs 2306 per mm^3 [1133-4194], $p = 0.03$), decreased LDH (371 [303-408] vs 224 U/L [184-246], $p = 0.006$), and have a trend to decrease ferritin levels (1394 [730-3022] vs 860 ng/mL [747-951], $p = 0.15$), and CRP levels (102 [45-191] vs 22 mg/L [2.9-73], $p = 0.31$), without differences in D-dimer and platelet counts (Figure 1).

Regarding organ dysfunction, the patients have a trend to improve PaO2/FIO2 (170 [78-211] vs 218 mmHg [133-336], $p = 0.06$), respiratory system compliance (30 [25-36] vs 45 mmHg [28-50], $p = 0.18$), and VIS (16 [7.3-54] vs 0 [0-5.7], $p = 0.15$) (Figure 2).For the whole group, the response to TPE was complete in three patients and partial in one patient.

Complications of TPE occurred in 4 (19%) TPE sessions, none of them related to the circuit and machine. Arterial hypotension was observed in 3 sessions, requiring a fluid bolus administration and an increase in vasoactive support. Bleeding from the insertion site of a central venous line occurred in one procedure. None of these complications led to a discontinuation of the therapy. Per protocol, all patients receive 1 g of calcium chloride at the end of each session, and hypocalcemia was not observed.

Four patients (66%) survived ICU discharge. The causes of death were unrelated to the

TPE procedure: one patient suffered refractory septic shock, and one died due to refractory ARDS. The average ICU length of stay was 26 days (10-79).

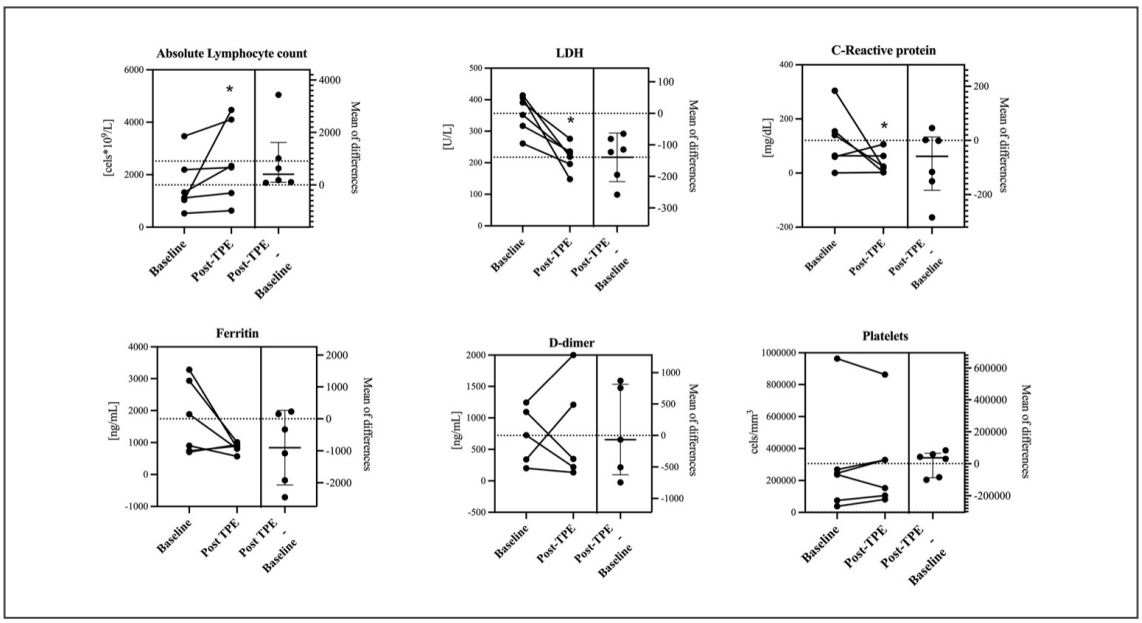

Figure 1: *Individual values of COVID-19-associated hyperinflammatory syndrome markers measured before and after Therapeutic Plasma Exchange (TPE). (LDH, Lactate dehydrogenase) * p< 0.05.*

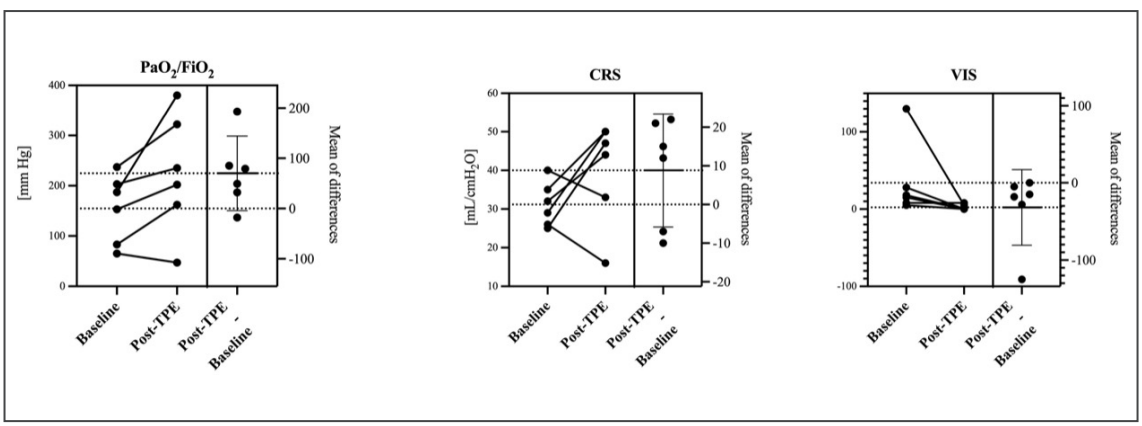

Figure 2: *Pulmonary and hemodynamic function before and after therapeutic plasma exchange (TPE) in COVID-19 associated hyperinflammatory syndrome.*

Discussion

We report six patients with COVID-19 associated hyperinflammatory syndrome, and multiorgan failure that received TPE for rescue immunomodulation, given the unavailability of biologic therapy in a limited resource setting. After TPE, there was a significant decrease in indirect markers of endothelial dysfunction, like LDH and lymphopenia. In addition, they tended to improve respiratory and hemodynamic dysfunction after TPE.

Severe COVID-19 cases are associated with a dysregulated immune response that triggers endothelial dysfunction and immunothrombosis, producing microcirculatory alterations leading to multiorgan dysfunction and death[2,3,4,5]. The cHIS phenotype manifests through various alterations in laboratory parameters that translate into a pro-inflammatory condition, such as lymphopenia, high levels of LDH, ferritin, CRP, D-dimer, and IL-64. There are many specific markers of endothelial injury, like von Willebrand factor levels and P-selectin. Still, they are limited to translational and experimental research and are unavailable in most centers taking care of severe COVID-19[25]. Thus, surrogate nonspecific markers of endothelial dysfunction, like LDH, lymphopenia, thrombocytopenia, and D-Dimer, are clinically useful[3,11,25].

In search of a different approach, it has been hypothesized that TPE may possess an immunomodulatory role in patients with cHIS refractory to high-dose corticosteroids through the removal of pro-and anti-inflammatory cytokines, stabilizing endothelial membranes, and resetting the hypercoagulable state as evidenced improvement of the hyperinflammatory state[7,19,20,21]. In COVID-19, it has been found that pro-inflammatory cytokines are significantly higher around the second week of illness[3,5]. Thus, the key to success is early recognition of hyperinflammatory phenotype, with early initiation of TPE during the fulminant stage of the viral infection, mainly because dysregulated immune system pathobiology is equally important as viral replication at this phase 12. Transient mild complications were observed in 1/5 of the TPE sessions, but therapy discontinuation was not required.

Regarding the improvement of inflammatory markers and organ dysfunctions, our results were comparable to the most relevant studies related to the use of TPE in severe COVID-19 patients, englobed in a recent systematic review[21,22]. In this study, lung dysfunction and some biomarkers improved significantly after TPE implementation. Reduction of the plasma level of inflammatory mediators due to TPE could be interpreted as simple remotion of the different molecules and not necessarily immunomodulation[26]. Still, the improvement of absolute lymphocyte account, lung and hemodynamic functions, and the trend to a higher survival can reflect hyperinflammation attenuation with this therapy and ultimately facilitate the resolution of the disease[29].

Our study has some limitations: 1. It is a single-center small cohort of patients. 2. Contrary to other studies, our patients did not have access to other expensive therapies, such as remdesivir, anakinra, tocilizumab, or IVIG, given a limited resource setting. TPE was the last rescue therapy to face cHIS patients in MOF, with a high risk of death without immunomodulation[27,28]. Given the limited resource setting, we could not quantify inflammatory cytokine levels before and after TPE.

Despite these limitations, we report TPE as a rescue therapy for critically ill patients with COVID-19 associated hyperinflammatory syndrome and MOF. This COVID-19 phenotype is infrequent, has a high mortality, and its pathophysiology is still poorly understood. Thus, the best therapies are not yet settled. Future studies may include TPE among immunomodulatory treatments for COVID-19 associated hyperinflammatory syndrome, especially in limited resource settings.

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