Effectiveness of Convalescent Plasma Therapy in Treating COVID-19: an Evidence-based Case Report

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ABSTRACT

Background: *Convalescent plasma is a potentially beneficial, tolerable, and available additional treatment option for COVID-19. This study aims to evaluate whether the administration of convalescent plasma therapy leads to improved clinical outcomes in COVID-19 patients compared to standard medical therapy.* ***Methods:*** *We conducted a search of Pubmed, Cochrane, and EBSCO for studies assessing the clinical question using inclusion and exclusion criteria. Selected studies were critically appraised, and the results were summarized.* ***Results:*** *A meta-analysis of 10 randomized clinical trials (RCTs), an RCT, a case-control clinical study were selected and assessed. Only the case-control clinical study showed that convalescent plasma administration improved the clinical outcomes of patients with COVID-19, including all-cause mortality, hospital length of stay, and the need for mechanical ventilation. On the contrary, the other two studies of a higher level of evidence showed no significant clinical outcome improvement with convalescent plasma therapy.* ***Conclusion:*** *The effectiveness of convalescent plasma therapy in improving clinical outcomes of patients with COVID-19 was still inconclusive due to several study limitations and other possible causes.*

Keywords: *convalescent plasma, coronavirus, COVID-19, SARS-CoV-2*

INTRODUCTION

Coronavirus disease 2019 (COVID-19), caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), has been an ongoing pandemic for more than a year. According to current guidelines, the treatment of COVID-19 is still mainly supportive with additional drugs such as antibiotics or antiviral agents with limited evidence.[1,2] SARS-CoV-2 entry into host cells is facilitated by the spike (S) protein, which has two functional subunits (S1 and S2). The receptor-binding domain (RBD) within S1 binds the angiotensin-converting enzyme 2 (ACE2) receptor, enabling viral attachment to the target cell's surface.[3–5]

Convalescent Plasma (CP) is a type of passive immunization obtained through apheresis from survivors of prior infections by pathogens of interest. A key component of CP is the neutralizing antibodies (NAbs). NAbs in CP from COVID-19 survivors can bind S1-RBD, inhibiting viral attachment and entry to host cells.[3,6] In addition, complement activation, antibody-dependent cellular cytotoxicity, and phagocytosis are other antibody-mediated pathways thought to contribute to viral clearance

by CP.[6] CP also contains non-neutralizing antibodies (Non-NAbs) that may contribute to prophylaxis or even enhance recovery through mechanisms still unknown.[7] Apheresis may also yield other proteins including anti-inflammatory cytokines, coagulation factors, natural antibodies, and defensins, that might provide additional benefits such as immunomodulatory effects by relieving cytokine storm in severe COVID-19.[6]

CP has been considered an emergency intervention in pandemics in the past, such as the Spanish flu and SARS-CoV, where early administration of CP resulted in reduced mortality in severe acute respiratory infections with no adverse events.[6] CP is rapidly available, requires relatively low technology, is easily scalable as long as donors are available, and requires low cost compared to other options such as the interleukin-6 inhibitors.[8,9] Considering its potential benefit, tolerability, and availability, CP is a good candidate for COVID-19 therapy, especially in low-to-middle income countries.[3] This report aims to assess the effectiveness of CP therapy in treating COVID-19.

CASE ILLUSTRATION

Case 1

A 57-year-old female patient was admitted with a fever since four days before admission. She had shortness of breath, dry cough, throat discomfort, nausea, and a bitter taste in her mouth, leading to decreased appetite. The patient lived in an area with local transmission of COVID-19. The patient had type 2 diabetes mellitus and hypertension with routine oral medication of glibenclamide, acarbose, metformin, amlodipine. On initial examination, the patient was alert but had tachypnea, rales on bilateral lungs, and oxygen desaturation; then, she was confirmed to have COVID-19 by RT-PCR. On her third day of admission (day 7 of symptom onset), the patient had just been transferred to the high-care unit (HCU) due to oxygen desaturation and diabetic ketoacidosis (DKA). The DKA had resolved, but the difficulty breathing and a dry cough remained. The patient was alert with a blood pressure of 133/69 mmHg, pulse 91 bpm, respiratory rate 18 rpm, temperature 36°C, SpO_2 85% on 15 LPM oxygen via non-rebreathing mask (NRM).

Lab results showed leukocytosis (10580 / mcL) with high neutrophil (85.6%) and low lymphocyte (10.5%) counts (NLR 8.16), a respiratory alkalosis and oxygen desaturation (pH 7.508, pCO_2 23.4 mmHg, pO_2 43.7 mmHg, HCO_3 18.7 mmHg, SaO_2 85.1%). Prothrombin time (PT) was 10.6 s (control 11.4 s), aPTT was 34.4 s (control 31.1 s), and D-Dimer level was 420 ng/mL, IL-6 level was 207 pg/mL. Chest X-ray showed inhomogenous opacities, some nodular, at upper-middle-lower segments of both lungs suggestive of pneumonia.

The patient was assessed with the diagnoses below:

1. Confirmed severe COVID-19 (day 7 of symptom onset)
2. Moderate-severe Acute Respiratory Distress Syndrome (ARDS)
3. Type 2 Diabetes Mellitus on Insulin regulation with history of DKA
4. Controlled Hypertension
5. Hypercoagulable state

Therapies administered to the patient included 15 LPM oxygen via NRM, ceftriaxone 2 g i.v. q.d., levofloxacin 750 mg i.v. q.24h, remdesivir 200 mg i.v. (D1), then 100 m.g. i.v. q.d., Other therapies include IV insulin, a prophylactic dose of heparin, candesartan, vitamin D3, and acetylcysteine.

Case 2

A 49-year-old female patient was admitted with shortness of breath since three days before admission, accompanied by dry cough, fatigue, and nausea. She had no past medical history of other diseases. Physical examination and blood tests were done, and the patient was assessed with acute respiratory distress syndrome (ARDS), severe confirmed COVID-19, and had elevated liver transaminase levels. At the time of this report, the patient was in her third day of hospital stay in the standard COVID-19 ward and considered to be transferred to the HCU due to unresolved shortness of breath and desaturation after two days of standard therapy, including an antiviral agent, an antibiotic, and an intravenous corticosteroid (dexamethasone 5 mg

i.v. b.i.d.). The patient was alert; blood pressure was 140/100 mmHg, pulse 90 bpm, respiratory rate 22 rpm, temperature 36.5 °C. The patient was already on a high-flow nasal cannula (HFNC) with FiO2 90% 60 LPM and a SpO2 of 93-94%.

CLINICAL QUESTION

Does the administration of Convalescent Plasma (CP) Therapy lead to improved clinical outcomes (such as reduced mortality, length of hospital stay, and need for mechanical ventilation) in COVID-19 patients compared to standard medical therapy alone?

METHODS

A search of Pubmed, Cochrane, and EBSCO was performed on March 29, 2021, using the search terms "COVID-19" and "convalescent plasma" along with their synonymous and related terms. The search strategy used, results, inclusion criteria, and exclusion criteria can be seen in **Figure 1**. Selected articles include completed clinical trials performed on human subjects, systematic reviews or meta-analyses of these trials, published within two years. These articles were then critically appraised based on the appraisal tools from the Centre for Evidence-Based Medicine, University of Oxford.

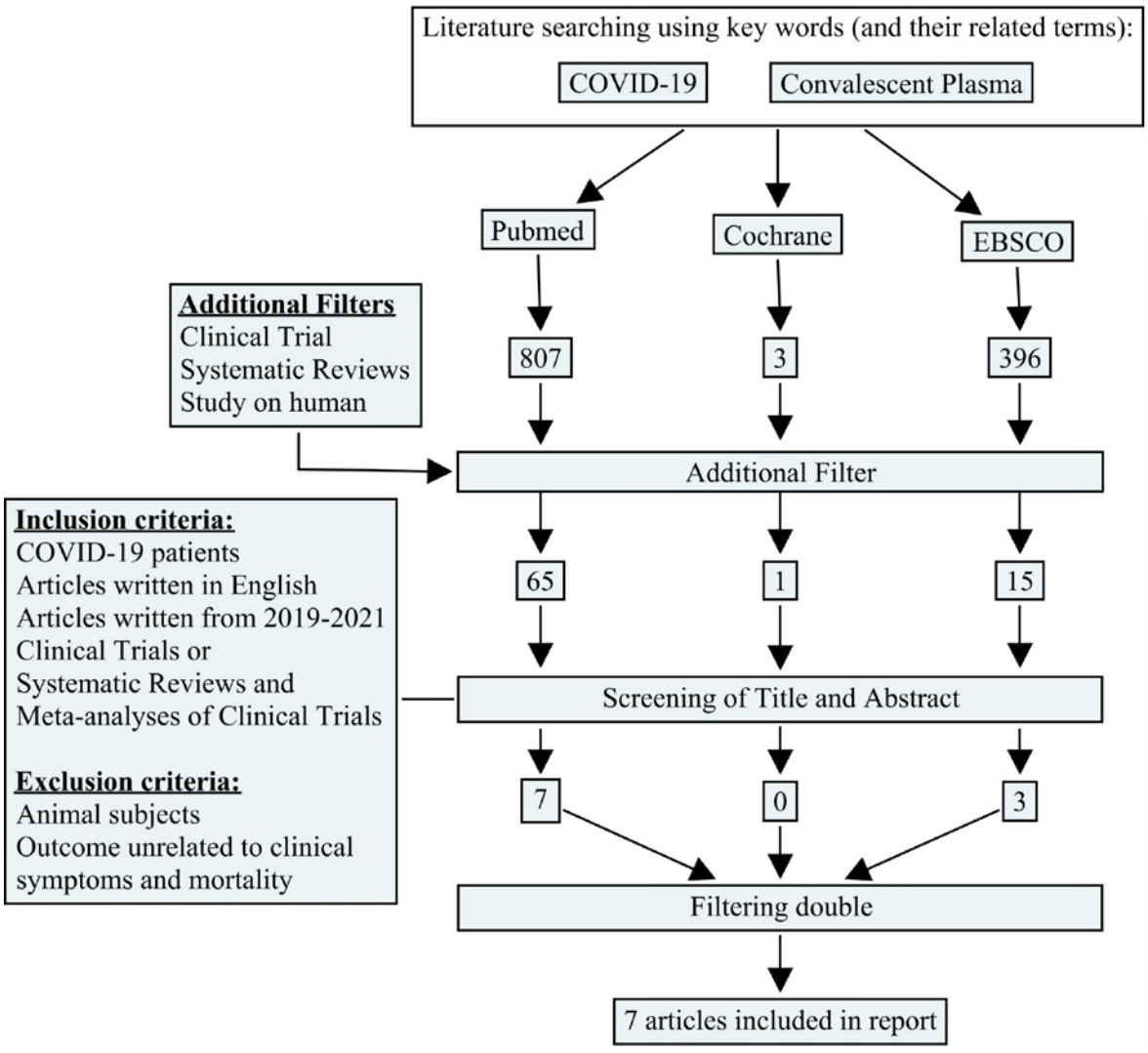

Figure 1. Flow chart of the search strategy.

RESULTS

The search criteria, additional filters, and screening of title and abstract described in **Figure 1**, 10 articles fulfilled the inclusion and did not meet the exclusion criteria. Three of the studies were duplicates; hence we only included seven articles in the report. The articles include a meta-analysis by Janiaud et al.[10], five randomized controlled trials (RCTs), and a non-randomized multicenter clinical trial. Four of the RCTs, written by Simonovich et al.[11], Libster et al.[12], Li et al.[13], and the PLACID trial by Agarwal et al.[14] were already reviewed and analyzed in the meta-analysis by Janiaud et al.[10], hence will not be discussed separately in this report as the two remaining studies by Balcells et al.[15] and Abolghasemi et al.[16] Critical Appraisal of the meta-analysis and clinical trials are described in **Table 1** and **Table 2**. The studies were considered applicable to the patient in this report with the same diagnosis of COVID-19, and the patient had agreed to the use of convalescent plasma with no contraindication of the therapy.

The meta-analysis by Janiaud et al.[10] consisted of primary analysis of 4 peer-reviewed RCTs and secondary analysis including additional 6 RCTs not published in peer-reviewed journals. The analyses were conducted for clinical outcomes of all-cause mortality, length of hospital stay, and mechanical ventilation use (**Figure 2**). Certainty of evidence in all-cause mortality was low in the primary analysis but moderate in the secondary analysis. The RECOVERY trial dominated the evidence since it accounted for most of the weight (90.2%) in the meta-analysis and the number of patients.[10] Results of the three studies are summarized in **Table 3**.

DISCUSSION

The treatment of COVID-19 has continued to be extensively studied since the start of its pandemic, but there is still limited evidence in therapies currently used in guidelines and clinical practice. Convalescent plasma (CP) therapy has proved to be a rapidly obtainable and useful emergency treatment option in previous

Table 1. Critical appraisal of the study by Janiaud et al.[10]

Articles	Validity					Level of Evidence
	PICO	Relevant studies included	Appropriate search criteria	Quality assessment of trials	Heterogeneity	
Jainaud et al.	+	+	+	+	+	1

Table 2. Critical appraisal of articles by Abolghasemi et al.[16] and Balcells et al.[15]

Articles	Time Published	Study Design	No. of Patients	Validity					Importance			Level of Evidence
				Randomization	Similarity at Start of Trial	Equal Treatment	Intention-to-treat	Blinding	Measurement of Outcome	Treatment Effect Result	Point Estimate (CI)	
Abolghasemi et al.14	Jul-20	Case control	189	-	+	+	+	-	Comparative study	+	-	4
Balcells et al.13	Mar-21	RCT	58	+	+	+	+	-	OR	+	+	2

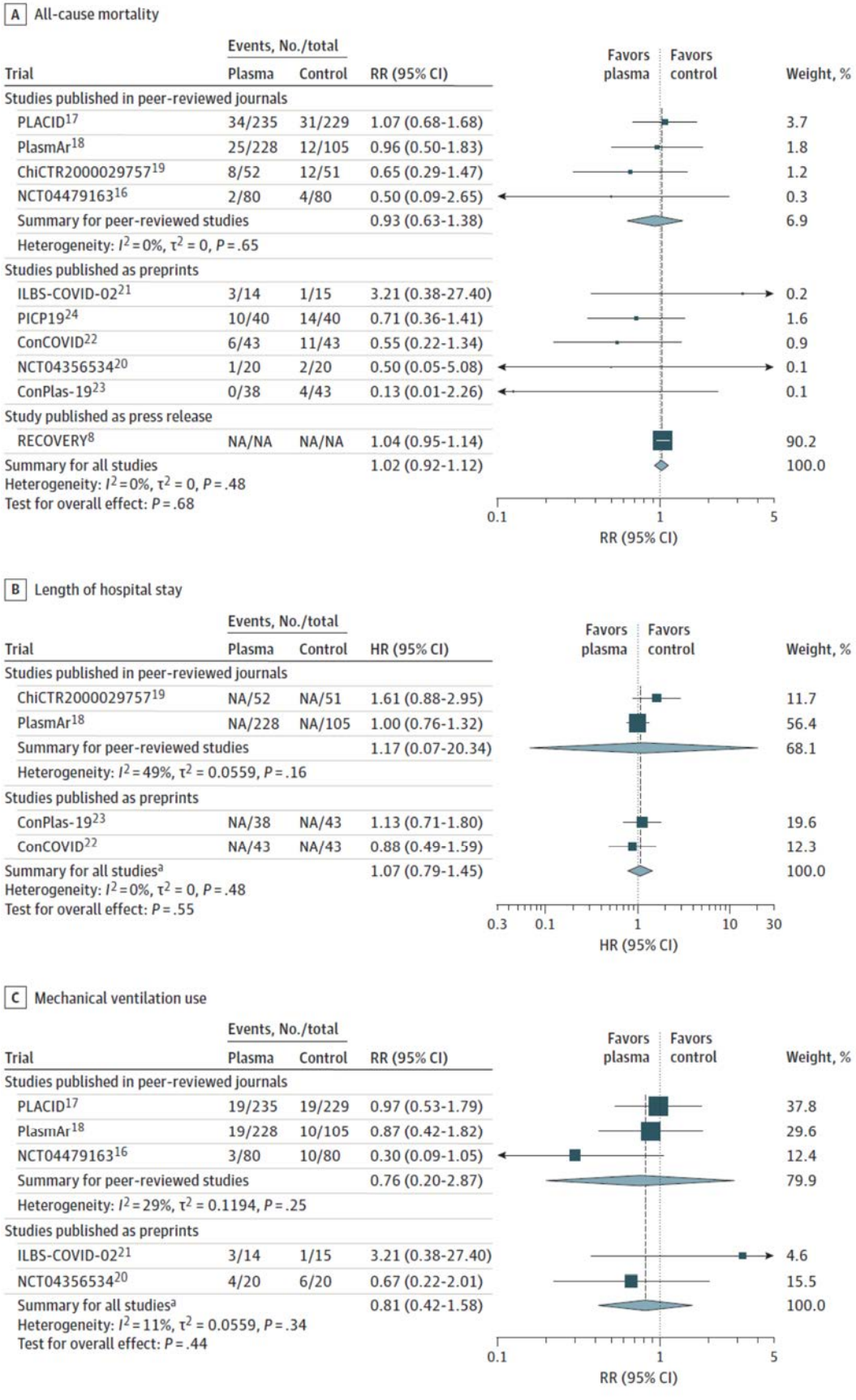

Figure 2. Forest plot of the association between convalescent plasma therapy and clinical outcomes in the meta-analysis by Janiaud et al.[10]

Table 3. Results of the three studies.

Authors	Endpoints	Result	Summary
Janiaud et al. [10]	All-cause mortality, length of hospital stay, mechanical ventilation use	Primary analysis of 4 peer-reviewed RCTs: - Relative risk (RR) for all-cause mortality with convalescent plasma: 0.93 (95% CI 0.63 to 1.38; P = 0.60), absolute risk difference: -1.21% (95% CI, -5.29% to 2.88%) - Hazard Ratio (HR) for length of hospital stay with convalescent plasma: 1.17 (95% CI 0.07 to 20.34; P = 0.61) - Relative risk (RR) for mechanical ventilation with convalescent plasma: 0.76 (95% CI 0.20 to 2.87; P = 0.35), absolute risk difference: -2.56% (95% CI, -13.16% to 8.05%) Secondary analysis including additional 6 pre-published RCTs (a total of 10 RCTs): - Relative risk (RR) for all-cause mortality with convalescent plasma: 1.02 (95% CI 0.92 to 1.12; P = 0.68) - Hazard Ratio (HR) for length of hospital stay with convalescent plasma: 1.07 (95% CI 0.79 to 1.45; P = 0.87) - Relative risk (RR) for mechanical ventilation with convalescent plasma: 0.81 (95% CI 0.42 to 1.58; P = 0.88), absolute risk difference: -2.21% (95% CI, -8.94% to 4.51%)	Treatment with convalescent plasma in addition to standard of care compared to standard of care only or standard placebo in addition to standard of care was not significantly associated with any of the clinical outcome benefits (all-cause mortality, length of hospital stay, mechanical ventilation use) among COVID-19 patients
Abolghasemi et al. [16]	All-cause mortality, length of hospital stay, need for mechanical ventilation	- All-cause mortality: plasma 14.8% vs control 24.3% (p = 0.09), absolute reduction of 9.5% - Length of hospital stay: plasma 9.54 days vs control 12.88 days (p = 0.002) - Need for mechanical ventilation: plasma 7% vs control 20.3% (p = 0.006)	Statistically significant reduction in length of hospital stay and need for mechanical ventilation in plasma group compared to control, but not in all-cause mortality
Balcells et al. [15]	Composite and individual outcomes of in-hospital death, use of mechanical ventilation, and length of hospitalization >14 days (prolonged hospital stay)	- Composite of the three outcomes of early vs deferred plasma group: 32.1% vs 33.3%, OR 0.95, 95% CI 0.32-2.84, p > 0.999 - In-hospital death of early vs deferred plasma group: 17.9% vs 6.7%, OR 3.04, 95% CI 0.54-17.17, p = 0.246 - Use of mechanical ventilation in early vs deferred plasma group: 17.9% vs 6.7%, OR 3.04, 95% CI 0.54-17.17, p = 0.246 - Length of hospital stay >14 days (prolonged hospital stay) in early vs deferred plasma group: 21.4% vs 30.0%, OR 0.64, 95% CI, 0.19-2.10, p = 0.554	No significant difference in either the composite or individual outcomes (in-hospital death, use of mechanical ventilation, and prolonged hospital stay) between the early and deferred plasma group

pandemics.[6] Studies have also shown that CP therapy has a good safety profile in patients with COVID-19.[17,18] More than a hundred ongoing clinical trials were still studying CP in COVID-19 patients.[19]

Based on the three studies we analyzed, only one study (a case-control clinical study) showed that CP therapy improved the clinical outcomes of patients with COVID-19, including all-cause mortality, hospital length of stay, and the need for mechanical ventilation.[16] On the other hand, a systematic review and meta-analysis of 10 RCTs and another open-label RCT not included in the prior study found no significant association between CP therapy and those clinical outcomes. The reasons for these results have been elaborated in the studies themselves.[10,15]

The meta-analysis by Janiaud et al. mentioned five of its limitations. First, three out of ten RCTs analyzed had some concerns or a high risk

of bias. Still, they only contributed to 10.8% of weight in all-cause mortality metanalysis (majority dominated by RECOVERY trial). Second, the RECOVERY trial was insufficient and inconsistent in using definitions and relevant details in reporting clinical outcomes besides all-cause-mortality. Third, the data were too limited for meaningful subgroup analyses. Fourth, in all but 1 RCT with outpatients, all patients were hospitalized, indicating moderate to critically ill COVID-19 patients. Therefore, results in patients with milder COVID-19 remained unclear. Lastly, the study also mentioned the many ongoing trials studying CP therapy in COVID-19 patients.[10]

The open-labeled RCT by Balcells et al. mentioned limitations that might also apply in other studies. The NAbs were not determined in donor plasma before transfusion. Evidence regarding the dose of CP needed to sufficiently increase antibodies to neutralize the virus was limited. The study found no significant difference in seropositivity conversion rates (measured by IgG titer at baseline, day 3, and day 7) in the early plasma and the deferred plasma group, suggesting insufficient dose. The study was also open-labeled; therefore, cointerventions such as steroids may unintendedly have influenced outcomes. They found it challenging to find patients admitted to the hospital in the early stages of the disease and stated that CP dose (volume and antibody titer levels) must be optimized.[15]

The two reported cases showed patients with severe COVID-19 with clinical conditions not improved after days of standard medical therapy alone, including an intravenous corticosteroid. In such patients, the use of additional therapy such as convalescent plasma (CP) therapy, IL6-inhibitors, and intravenous immunoglobulin therapy (IVIG) should be considered. However, IL-6 inhibitors and IVIG are not readily available and costly. Additionally, both patients were still within ten days of symptom onset. Considering these factors, we decided to administer convalescent plasma, with a dose of 400 mL divided into two administrations of 200 mL each on the same day, to both patients. The CP's antibody titer level was not known since the donor criteria did not include its measurement. Not more than one day after receiving CP, both patients showed clinical improvements, including decreased shortness of breath and a lowered supplemental oxygen needed to maintain SpO_2. The first patient, who had a high circulating IL-6 level (207 pg/mL) and initial SpO_2 85% with 15 LPM oxygen with standard therapy, could maintain SpO_2 of 96% with 15 LPM oxygen via NRM after CP therapy. The second patient who needed HFNC to reach SpO_2 of 93-94%, after CP therapy, only needed supplemental oxygen of 15 LPM via NRM to maintain SpO_2 of 98%. Both patients' oxygen supplementation could be titrated down to nasal cannula 3 to 4 days after CP therapy.

CONCLUSION

In conclusion, the results of studies assessing the effectiveness of convalescent plasma (CP) therapy in improving the clinical outcomes of patients with COVID-19 were still inconclusive. Differences in dose, interval of administration, time of administration since symptom onset, plasma titer level of convalescent plasma therapy may have caused the difference in outcomes of the patients. Limited data, inconsistency in details, and varying cointerventions may also have affected the studies' results. More than a hundred ongoing clinical trials studying CP therapy in COVID-19 patients may yield different and more conclusive results. Nevertheless, convalescent plasma therapy is still a widely and rapidly available, low-cost, and safe option of additional therapy in COVID-19 patients whose clinical conditions have not yet improved with standard medical therapy alone. CP therapy will continue to be used and studied in the COVID-19 pandemic, especially in countries where other high-cost therapies such as IL-6 inhibitors and IVIG might not be available.

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