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Review Article

## Convalescent plasma therapy for COVID-19: a review of old therapy against new disease

Utshav Chapagain\*, Gajendra Prasad Rauniar, Kumud Chapagain, Rakesh Verma

Department of Clinical Pharmacology and Therapeutics, B. P. Koirala Institute of Health Sciences, Dharan, Nepal

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**\*Correspondence:**

Dr. Utshav Chapagain,

Email: [utshavchapagain08@gmail.com](mailto:utshavchapagain08@gmail.com)

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### ABSTRACT

Currently, novel coronavirus disease 2019 (COVID-19) is a big threat to global health which has revived the potential beneficial effect of ancient convalescent plasma therapy (CPT). This review was conducted to evaluate the effectiveness and adverse drug reactions associated with convalescent plasma therapy in COVID-19 patients, based on articles available to date. PubMed, Google Scholar, Cochrane library, and Hinari databases were searched until 15th September 2020. Every country across the globe today is encountered with a virus that has impacted millions of lives today and for generations to come. Nonetheless recommended antiviral drugs and vaccines are not evident and specified for novel coronavirus disease. This is now very well known that scientists and medical experts across the world are vigilant about recommending the use of CPT and call it an investigational treatment that may help in assisting recovery. The World health organization has perpetuated that there is not enough proof that plasma therapy works in treating those fighting the novel coronavirus. Therefore, convalescent plasma therapy is a feasible and immediate option for alleviating the impact of the disease. Comparing the effectiveness of convalescent plasma therapy with SARS-CoV, MERS-CoV, and COVID-19 would help in deriving proper outcomes for COVID-19 infected cases.

**Keywords:** Antibodies, COVID-19, Convalescent plasma therapy, SARS-CoV-2

### INTRODUCTION

Since December 2019, an outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection named, coronavirus disease 2019 (COVID-19) by the World health organization (WHO) has spread rapidly around the world, with high rates of transmission and considerable mortality. Its symptoms range from mild, self-limited respiratory disease to severe progressive pneumonia, multiple organ failure, and even death.<sup>1,2</sup> As of 15 September 2020, the World Health Organization has reported 29,730,066 confirmed cases of COVID-9, with 939,192 deaths worldwide.<sup>3</sup> The severity and epidemic potential of COVID-19 has paralyzed the world's health care system and threatened economic stability. Unfortunately, to date, apart from symptomatic

treatment and supportive care, there is no effective treatment or vaccine available to cure the disease.<sup>4</sup>

Convalescent plasma is obtained from the blood of a recovered patient. Plasma is the protein-rich component of blood, and the word convalescence comes from Latin words for “together” and “to grow strong”.<sup>5</sup> A patient has “convalesced” when they recover from an infection.<sup>5</sup> In the 1890s, passive immunization therapy was used successfully to treat individuals with infectious diseases. Such individuals after recovery have particular microorganisms neutralizing antibodies when blood samples are drawn and screened. Following the identification of individuals with high titers of neutralizing antibody, convalescent plasma could be administered in individuals with specified clinical disease

to reduce symptoms and mortality. Therefore, convalescent plasma therapy (CPT) has been one of the centres of attraction and burning topic in the global pandemic.<sup>6</sup>

The United States food and drug administration (US FDA) has suggested that administration and study of investigational convalescent plasma therapy may provide therapeutic benefit for the treatment of COVID-19.<sup>7</sup> Although the use of convalescent plasma shows promise, the evidence supporting its use in the treatment of COVID-19 remains limited as the interim resort and thus needs further investigation.

The purpose of this review was to evaluate true efficacy and adverse drug reactions associated with the administration of convalescent plasma therapy.

## HISTORY OF CONVALESCENT PLASMA THERAPY FOR INFECTIOUS DISEASES

Before the antibiotic era, infectious diseases like scarlet fever and pneumococcal pneumonia were treated using serum (plasma minus clotting factors) therapy. In 1890, blood serum was collected from immunized animals and was used to treat diphtheria and tetanus.<sup>8</sup>

**Table 1: Classical uses of antibody therapy against infectious diseases from ancient to modern period.**

Period	Infectious diseases
1890 A.D.	<ul style="list-style-type: none"> <li>• Diphtheria</li> <li>• Tetanus</li> </ul>
1900 A.D.	<ul style="list-style-type: none"> <li>• Meningococcal infection</li> <li>• Rheumatic Fever</li> </ul>
1910 A.D.	<ul style="list-style-type: none"> <li>• Mumps</li> <li>• Measles</li> </ul>
1917 A.D.	<ul style="list-style-type: none"> <li>• Scarlet fever</li> </ul>
1918 A.D.	<ul style="list-style-type: none"> <li>• Spanish Flu</li> </ul>
1920 A.D.	<ul style="list-style-type: none"> <li>• Pneumococcal Pneumonia</li> <li>• Chickenpox</li> </ul>
1930 A.D.	<ul style="list-style-type: none"> <li>• Anthrax</li> </ul>
1940 A.D.	<ul style="list-style-type: none"> <li>• Tularemia</li> </ul>
1950 A.D.	<ul style="list-style-type: none"> <li>• Rabies</li> </ul>
1976 A.D.	<ul style="list-style-type: none"> <li>• Ebola</li> </ul>
1979 A.D.	<ul style="list-style-type: none"> <li>• Argentine Hemorrhagic Fever</li> </ul>
2003 A.D.	<ul style="list-style-type: none"> <li>• SARS-CoV</li> <li>• Avian Flu (H5N1)</li> </ul>
2009 A.D.	<ul style="list-style-type: none"> <li>• Swine Flu (H1N1)</li> </ul>
2012 A.D.	<ul style="list-style-type: none"> <li>• MERS-CoV</li> </ul>
2013 A.D.	<ul style="list-style-type: none"> <li>• Ebola</li> </ul>
2019 A.D.	<ul style="list-style-type: none"> <li>• COVID-19</li> </ul>

There are numerous examples throughout history where convalescent serum was used to treat various diseases, like rheumatic fever, scarlet fever, mumps, measles, chickenpox, and meningococcal infections (Table 1).<sup>8-13</sup> Between 1918 to 1920, convalescent serum was used in

the treatment of the Spanish Flu pandemic where a meta-analysis study showed a significant reduction in mortality risk in patients treated with convalescent serum.<sup>14,15</sup>

Later in the mid-20th century, after the arrival of antimicrobials agents, the use of convalescent plasma therapy had been reduced. Yet whenever new epidemics or pandemics emerged, the interest in convalescent plasma therapy is renewed.

In 1979, convalescent plasma was used to treat patients with Argentine hemorrhagic fever virus and a lower mortality rate was seen in patients receiving convalescent plasma when compared to patients receiving normal plasma.<sup>16</sup> Similar outcomes were reported for successive epidemics of the disease.<sup>16</sup>

Since, past two decades, CPT was successfully used in the treatment of SARS in 2003, MERS in 2012, and H1N1 swine influenza pandemic (2009) with satisfactory efficacy and safety as well as during the Ebola virus outbreak in West Africa in 2013.<sup>17-20</sup> Due to the similarity in virological and clinical characteristics among SARS, MERS, and COVID-19, CPT might be a promising treatment option for COVID-19 rescue.<sup>21,22</sup>

## USE OF PLASMA THERAPY FOR SARS

Cheng et al conducted a study to evaluate the efficacy of convalescent plasma therapy in patients with severe acute respiratory syndrome (SARS).<sup>17</sup> Eighty SARS patients were given convalescent plasma, between 20 March and 26 May 2003 at Prince of Wales Hospital, Hong Kong.

Patients with suspected SARS were given cefotaxime and levofloxacin (or clarithromycin) on the day of admission.<sup>17</sup> If fever persisted, ribavirin and prednisolone were started on day 3. Patients with radiographic progression and hypoxemia were given pulsed methylprednisolone.<sup>17</sup> Patients whose condition continued to deteriorate, SaO<sub>2</sub><90% on 0.5 FiO<sub>2</sub>, were given 200–400 ml of ABO compatible convalescent plasma at the discretion of the attending clinicians and according to convalescent plasma availability. A higher day 22 discharge rate was observed in patients who were given convalescent plasma before day 14 of illness (58.3% vs 15.6%; P<0.001) and among those who were PCR positive and seronegative for coronavirus at the time of plasma infusion (66.7% vs 20%; P=0.001). There were no immediate adverse effects following plasma infusion.

The data suggests that it was not a randomized trial where recipients of convalescent plasma therapy were at the discretion of the attending physicians and according to plasma availability. Non-standardized amount of antibody might have contributed to the variations in clinical outcomes. A potential risk of transfusion-transmitted infection was present. No placebo group for comparison was evident during the trial.

Henceforth, it may be worthwhile for future researchers to test the effectiveness of therapy with convalescent plasma or SARS-specific hyperimmune globulin in patients in the early phase of SARS during the next outbreak. The randomized control trial with a placebo group should be conducted for comparison and to illustrate the effectiveness of CP in patients with SARS.

### USE OF PLASMA THERAPY FOR MERS

The coronavirus outbreak of SARS-CoV was followed by the MERS-CoV outbreak which occurred in 2012. It caused severe infection in the respiratory tract of infected persons in Saudi Arabia and other Middle East countries.<sup>23</sup>

In vitro study showed cross-reactive antibodies in convalescent SARS patients sera, which act against other beta-coronavirus including MERS-CoV.<sup>24</sup> Out of 28 sera, 7 had anti-MERS-CoV neutralizing antibodies at low titers.<sup>24</sup>

Convalescent sera were recommended in a study by the International severe acute respiratory and emerging infection consortium (ISARIC).<sup>25</sup> Since there is a lack of high-quality clinical evidence, protocols must be developed to use it in randomized-controlled trials to determine the most effective therapy for this MERS-CoV.

### USE OF PLASMA THERAPY FOR COVID-19

Currently, convalescent plasma with neutralizing antibodies is being explored as it can be used for investigational purposes in the COVID-19 pandemic. It is multifaceted in applicability as it can be used for prophylaxis or treatment as illustrated in (Figure 1).

In case of prophylaxis, an individual at high risk of infection (due to age or underlying medical conditions or those likely to be in contact with a confirmed case of COVID-19) could be administered convalescent plasma for protection against infection. Alternatively, it can be administered to treat individuals who have contracted the infection but have not made sufficient antibodies to augment their immune response, improve disease course, and enhance recovery.<sup>26</sup>

Shen et al published the first preliminary case series of convalescent plasma therapy against COVID-19 in about 5 critically ill patients with COVID-19 who were treated using plasma from recovered individuals.<sup>27</sup>

All 5 patients had severe acute respiratory distress syndrome and were receiving mechanical ventilation. 2 had bacterial pneumonia and 1 needed extracorporeal membrane oxygenation (ECMO). Plasma was transfused to four patients without coexisting diseases around hospital day 20 and in a patient with hypertension and mitral valve insufficiency, was transfused at day 10.<sup>28</sup> These patients also received antiviral treatment with

lopinavir/ ritonavir and interferon.<sup>28</sup> The use of convalescent plasma may have contributed to their recovery as clinical status of all patients had improved just about 1 week after transfusion, as indicated by normalization of body temperature, improvements in sequential organ failure assessment (SOFA) scores, and PAO<sub>2</sub>/FIO<sub>2</sub> ratio.<sup>28</sup> Also, the patients' neutralizing antibody titers increased and respiratory samples tested negative for SARS-CoV-2 between 1 and 12 days after transfusion.<sup>28</sup>

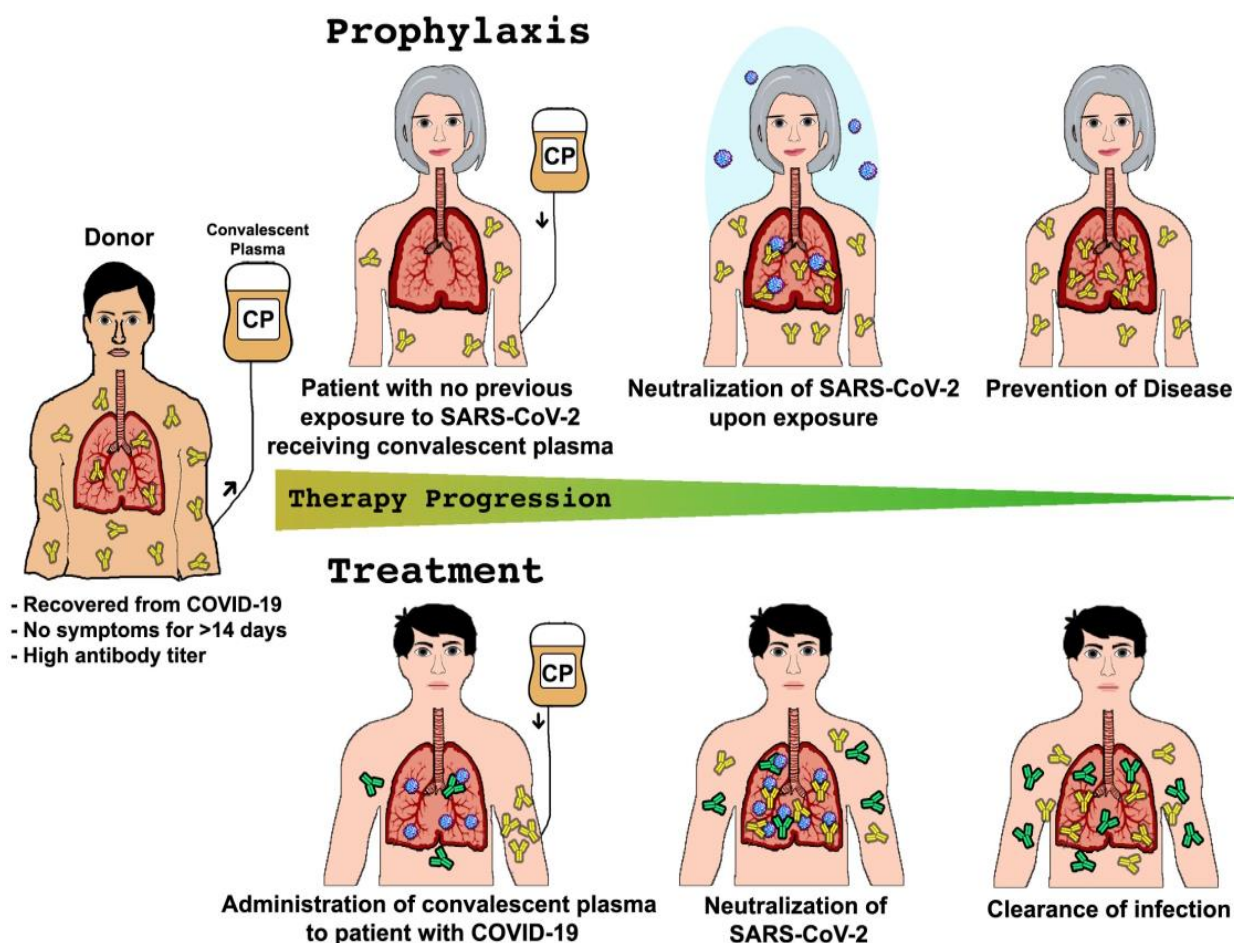
These data suggest that intervention, administration of convalescent plasma was not evaluated in a randomized clinical trial. The outcomes in the treatment group were not compared with a control group who did not receive the intervention. Hence, it is not possible to determine the true clinical effect of this intervention. It is also unclear whether the timing of administration of convalescent plasma is optimal or if earlier administration might have different clinical outcomes.

Despite these limitations, the study provides some evidence to support the possibility of evaluating plasma therapy in patients with COVID-19. Henceforth, future researchers should focus on conducting a randomized clinical trial for convalescent plasma therapy against COVID-19 where outcomes in the treatment group could be compared with the control group. These trials should be performed with early administration of convalescent plasma along with other clinical interventions as a treatment group and only clinical intervention as a control group to determine the true efficacy of ongoing trials.

Li et al conducted the first randomized clinical trial of convalescent plasma therapy against COVID-19. In the primary analysis, 52 patients were randomized to receive convalescent plasma along with standard treatment (intervention) and 51 patients to receive standard treatment alone (control).<sup>29</sup>

The primary outcome (time to clinical improvement within 28 days) was 2.15 days shorter (95% CI, -5.28 to 0.99 days) in the intervention arm compared to control arm. Similarly, clinical improvement at 28 days occurred in 27 patients (51.9%) in the intervention arm vs 22 patients (43.1%) in the control arm (difference, 8.8%; 95% CI, -10.4% to 28%; hazard ratio, 1.40 [95% CI, 0.79-2.49]; P=0.26).<sup>30</sup>

In patients with severe disease (23 in the intervention group and 22 in the control group), time to clinical improvement within 28 days was 4.94 days shorter (95% CI, -9.33 to -0.54 days) in the intervention arm compared with the control arm, and clinical improvement at 28 days occurred in 21 patients (91.3%) in the intervention arm vs 15 patients (68.2%) in the control arm (hazard ratio, 2.15 [95% CI, 1.07-4.32]; P=0.03).<sup>30</sup> In patients with the life-threatening disease (29 in the intervention arm and 29 in the control arm), there were no significant differences in the primary outcome. Following plasma transfusion, two patients experienced adverse events which improved with supportive care.<sup>30</sup>



**Figure 1: Overview of the use and applications of CP therapy.<sup>16</sup>**

Virus-neutralizing antibodies in the plasma of a patient who recovered from COVID-19 can be administered prophylactically to prevent infection in vulnerable individuals and those with known exposure to the virus (Prophylaxis).<sup>16</sup> Convalescent plasma can also be administered to infected individuals to improve the clinical outcome (Treatment).<sup>16</sup> CP, convalescent plasma; COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

**Table 2: Characteristics of the studies on convalescent plasma therapy**

Author & reference	Study type	Regimen	# Patients With Indications	Time of administration of CP	Outcome and adverse effect
Cheng et al. <sup>17</sup>	Cohort	200-400 ml (4-5 ml/kg) of ABO compatible CP	80 patients (SARS)	On day 14 of starting symptoms	Overall, the mortality rate was 12.5% compared to 17% of SARS patient. No immediate adverse effects were observed
Shen et al. <sup>27</sup>	Case series	Two consecutive transfusions of 200-250ml (400ml net.) of ABO compatible CP	Five critically ill patients with laboratory confirmed COVID-19 and ARDS (SARS-CoV-2)	Between 10-22 days after admission	Three patients were discharged (length of hospital stay: 53, 51, and 55 days), and Two were in stable condition at 37 days after transfusion.
Li et al. <sup>29</sup>	Open-label, Multicenter Randomize	Approximately 4-13 ml/kg of recipient	103 patients with severe or life-	14 days after onset of symptoms in	CP Group (n=52) Control Group (n=52) P value

Continued.

Author & reference	Study type	Regimen	# Patients With Indications	Time of administration of CP	Outcome and adverse effect			
	Randomized Clinical trial	body weight	threatening COVID-19 (SARS-CoV-2)	most cases	Clinical improvement Within 28 days	51.9 %	43.1%	0.26
					28 days mortality	15.7%	24.0%	0.36
					Negative conversion rate of viral PCR at 72 hours	87.2%	37.5%	< .001
					Two patients in the CP group experienced adverse events, 1 <sup>st</sup> patient: chills, rashes within 2 hours of transfusion. 2 <sup>nd</sup> patient: shortness of breath, cyanosis, severe, dyspnea within 6 hours of transfusion.			
<b>Duan et al.</b> <sup>14</sup>	Pilot study	One dose of 200 mL of CP	10 severe patients (SARS-CoV-2)	The Median time of 16.5 days from onset of illness to CP transfusion	CP could significantly increase or maintain neutralizing antibodies at a high level, which could lead to the disappearance of viremia in seven days. An evanescent facial red spot was seen in a single patient only.			
						Intervention Arm (n=235)	Control Arm (n=235)	
					Composite primary outcome	44 (18.7%)	41 (17.9%)	
					Progression to severe disease	17 (7.2%)	17 (7.4%)	
					All-cause Mortality	34 (14.5%)	31 (13.5%)	
<b>Mukherje et al.</b> <sup>31</sup>	Open-label, RCT	Two doses of 200 ml CP was transfused 24 hours apart	Moderately ill 464 patients (SARS-CoV-2)		In one patient: Pain in local infusion site, chills, nausea, bradycardia, and dizziness. In three patients: Fever, tachycardia. In two participants: dyspnoea and intravenous catheter blockage			

CP: Convalescent plasma, SARS: Severe acute respiratory syndrome, SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2, COVID-19: Coronavirus disease 2019, ARDS: Acute respiratory distress syndrome.

These data suggest that it was an open-label study with a smaller sample size as well as the early termination of the study. The study was underpowered to detect a clinically important benefit of convalescent plasma therapy.<sup>29</sup> It is unclear whether earlier treatment would have resulted in greater benefit.<sup>29</sup> No specific protocol was mentioned for using standard therapy in both groups which could have potentially influenced outcomes. Plasma was not used for the control group which would have been more ideal in making blinded design possible.<sup>29</sup>

To sum it up, this study used a randomized trial design and well-characterized plasma units with a high titer of antibody to SARS-CoV-2. The study findings should be analyzed cautiously since standard treatment and supportive care may vary from hospital to hospital across the globe. Future researchers should focus on conducting a close level study with a greater sample size and plasma as a control group. Specified protocol for standard therapy as well as early treatment with convalescent plasma therapy could influence outcomes.

Duan et al conducted a pilot study in three hospitals to explore the feasibility of convalescent plasma therapy in a group of 10 patients with severe disease.

All patients received antiviral agents, other supportive care, and 200ml of convalescent plasma with high neutralizing antibody titers. The primary and secondary endpoints were the safety of convalescent plasma transfusion and improvement of clinical symptoms and laboratory parameters within 3 days of convalescent plasma transfusion respectively. The median time from the start of symptoms to CP transfusion was 16.5 days. CP was well tolerated and could increase or maintain neutralizing antibodies at high levels, leading to the disappearance of viremia in 7 days and improved clinical symptoms in all patients within one to three days of administration.<sup>14</sup> There were no severe adverse events after convalescent plasma transfusion.

This study suggests that the patients also received other standard care. All patients received antiviral treatment and these antiviral agents could contribute to the recovery of patients, or synergize with the therapeutic effect of CP which could not be ruled out. Some patients also received glucocorticoid therapy, which might interfere with immune response and delay virus clearance.

Although the kinetics of viremia during natural history remains unclear, the relationship between SARS-CoV-2 RNA reduction, CP therapy, the optimal concentration of neutralizing antibodies, and treatment schedule, should have been further clarified. Dynamic changes of cytokines during treatment were not investigated.<sup>14</sup>

Despite various limitations, the study provides evidence that convalescent plasma therapy shows a potential therapeutic effect and low risk in the treatment of severe COVID-19 patients. The optimal dose and treatment time point and definite clinical benefits of convalescent plasma therapy owing to dynamic changes of cytokines can be further investigated in randomized clinical studies.

Mukherjee et al conducted an open-label, parallel-arm, phase II, multicentric randomized controlled trial in 464 hospitalized, moderately ill confirmed COVID-19 patients (PaO<sub>2</sub>/FiO<sub>2</sub>: 200-300 or respiratory rate >24/min and SpO<sub>2</sub> ≤ 93% on room air) in 39 tertiary care hospitals across India.<sup>31</sup>

A total of 235 patients were randomized to receive Convalescent Plasma with the best standard of care (BSC) (intervention group) and 229 patients received BSC alone (control group). Patients in the intervention arm received two doses of 200 ml of CP, 24 hours apart. Thirty-four patients (14.5%) in the intervention arm and 31 (13.5%) in the control arm died (adjusted odds ratio (aOR) was 1.06 [95% CI: 0.61 to 1.83]). In both arm 17 patients progressed to severe disease (7.2% vs. 7.4%; aOR: 1.04; 95% CI: 0.51 to 2.11). The Composite primary outcome was achieved in 44 (18.7%) and 41

(17.9%) patients in the intervention group and the control group respectively.<sup>31</sup>

In moderately ill, hospitalized COVID-19 patients the convalescent plasma therapy did not reduce 28-day mortality or progression to severe disease.<sup>31</sup> On days three and five, there was a reduction in supplemental oxygen requirement. On day seven, there was a resolution of shortness of breath and fatigue. Convalescent plasma therapy was associated with the early negative conversion of SARS-CoV-2 viral RNA. Convalescent plasma therapy as an effective treatment modality for moderately ill COVID-19 patients is limited. These data suggest that it was an open-label study with anchoring bias to the clinician with no initial measurement of neutralizing antibodies titers in donors and participants. Since more patients with shortness of breath and fatigue were enrolled in the intervention group compared to the control group, it is unclear to justify the similarities in the result of the two groups.

Future researchers should focus on minimizing any type of bias associated with randomized control trial and prior measurement of neutralizing antibody titers in donors and participants may further clarify the role of CP in the management of COVID-19.

## CONCLUSION

The aforementioned studies suggest that the greatest global health crisis caused by the COVID-19 outbreak needs to be controlled. Convalescent Plasma therapy for SARS-CoV-2 and other viruses have shown promising results. While evaluating existing drugs and developing new specific vaccines, convalescent plasma therapy has the potential to provide an effective therapeutic option with promising evidence on safety, improvement of clinical symptoms, and reduction of mortality rate in severe or life-threatening COVID-19 infected cases. Further studies are needed to optimize patient selection by enrolling a greater sample size for moderate to severely infected cases of COVID-19. Early administration of convalescent plasma during the trial will prove to evaluate its beneficial effect and true efficacy. Specific protocol for standard therapy and supportive care should be simplified as guidelines at health institutions across the globe. Research is still being worked on regarding the effectiveness of convalescent plasma for treating COVID-19.

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