International Journal of Applied Pharmaceutics

ISSN- 0975-7058 Vol 14, Issue 1, 2022

Original Article

LESSONS AND NEW PERSPECTIVES: IS CONVALESCENT PLASMA THERAPY EFFECTIVE ON COVID-19 PATIENTS?

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Received: 17 Jun 2021, Revised and Accepted: 19 Oct 2021

ABSTRACT

Objective: Recently, convalescent plasma (CP) therapy has shown promising evidence in the treatment of several serious contagious diseases, including SARS-CoV, Influenza and Ebola. We conducted a systematic review to extract data about using CP treatment for COVID-19 patients and it's effectively.

Methods: The retrieval of studies was conducted according to Cochrane Collaboration and from electronic databases including PubMed, Medline, and others (medRxiv and BioRxiv). Searching of the available evidence concerning CP treatment of COVID-19 patients was conducted in journal articles published between December 2019 and October 2020. The articles were further screened based on inclusion and exclusion criteria to identify the high-quality studies for analysis.

Results: A total of 18 CP studies were included in this review. We found variance regarding the effectiveness of CP in the reduction of mortality rate, length of stay, and increased discharging rate. Several findings show CP therapy is effective in increasing viral negativity, neutralizing antibodies to recipients, does not cause harmful adverse reactions and in some cases can improve clinical symptoms. This therapy is presently considered effective for generating good clinical outcomes when given early in the course of the disease.

Conclusion: The effectiveness of CP in terms of mortality, length of stay, and increased discharging patients is still debatable. However, CP therapy is effective in increasing the negativity of SARS-CoV-2 test, neutralizing antibody titer and is safe so it can be considered for COVID-19 patients. CP should not be given in the initial disease course but is recommended for the early disease course.

Keywords: Convalescent plasma, COVID-19, Effectivity, Neutralizing antibody, SARS-CoV-2, therapy

DOI: https://dx.doi.org/10.22159/ijap.2022v14i1.42452. Journal homepage: https://innovareacademics.in/journals/index.php/ijap

INTRODUCTION

The COVID-19 pandemic is currently a major public health concern and has become a significant and credible threat to economies around the world because the mortality and morbidity rates from this disease are still high. Coronavirus is a family of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) and Middle East Respiratory Syndrome-related Coronavirus (MERS-CoV) [1-6]. SARS-CoV-2 is a type of respiratory virus that can cause pneumonia in sufferers, and the first cases appeared in the city of Wuhan, China since December 2019. The World Health Organization (WHO) recently reported the virus had infected 194 million people and caused 4.16 million deaths [6-8]. The high incidence, worsening of disease, increasing death rate and the severe impacts caused by the disease have shown few signs of decreasing in most areas of the world. Accordingly, many leading scientists have proposed to change the term of the outbreak from pandemic to syndemic [9, 10]. Aimed toward accelerated development and distribution, vaccines for the disease were rapidly passed through phase 3 clinical trials in several countries and approved under rushed research and unorthodox development protocols without any animal trials. Single therapy from Remdesivir is presently considered effective in treating people with COVID-19 with mild-moderate symptoms, but for COVID-19 sufferers with severe symptoms who use mechanical ventilation (MV) breathing aids, this current treatment is not effective in helping in recovery [11].

Convalescent therapy is considered efficient management that can be done with plasma transfusions. The use of plasma transfusions for the treatment of infectious diseases has long been used successfully. The efficacy of convalescent plasma (CP) therapy has shown conclusive evidence in the treatment of several infectious diseases that have occurred in the last few decades, such as SARS-CoV, Ebola virus, also in severe cases of Influenza, and recently in pneumonia disease caused by SARS-CoV-2 infection. While still controversial, several studies regarding the effectiveness and safety of these CP treatments have provided promising evidence in improving clinical symptoms, the negativity of viral test rates, as well as reducing discharge times and mortality while bringing some hope in the handling of COVID-19, which has continued to ravage the world [12-16].

We conducted a systematic review to extract available data on recovery and mortality from CP for the treatment of people with COVID-19. This study may help clinicians and scientists identify more effective therapy options based on current scientific evidence for potential treatment and better clinical management in COVID-19 patients with severe symptoms.

MATERIALS AND METHODS

Study inclusion criteria

The retrieval of studies was conducted using electronic databases (PubMed, Medline and others (medRxiv, and BioRxiv) to comprehensively identify journal articles. Using "Convalescent plasma","SARS-CoV-2", "COVID-19" and "Coronavirus Disease 2019", relevant articles were searched by abstract and title. The papers included were the original research reports about the effects of giving CP therapy to patients with COVID-19, including patients' discharge and length of stay, improvements in laboratory and radiological findings, viral rate, mortality outcome, clinical benefits and adverse events with study designs including randomized controlled trials, prospective and retrospective comparative cohort studies that were published in scientific journals. Removal of duplicates of identified studies was done manually.

Exclusion criteria

There were some exclusion criteria in this review to exclude the identified data from searching, which excluded reviews and guiding statements about clinical guidelines and expert consensus papers;

case series and case reports of CP therapy either animal or *in vitro* cell studies; any article not available in full text; and studies not having complete data concerning treatment outcome, effectivity and safety of CP therapy.

Screening, Data extraction and quality assessment

Identified papers obtained from searching based on abstracts and titles using the keywords were screened based on the inclusion and exclusion criteria. Data from the included studies were further extracted for the following information: first author's name and year of publication, country, number of patients, diagnosing method, disease severity, age, concentration and frequency administration of CP, and other drugs administrated and summarized in table 1. Further, information about outcome, negativity rate of SARS-CoV-2 test, improvements in laboratory and radiological finding and adverse reactions are shown in table 1.

Outcomes

The outcomes we looked at and analyzed in the review included mortality outcome, discharge rate, length of stay after CPT therapy, improvements in laboratory and radiological findings, viral rate, mortality outcome, clinical benefits and adverse events**.**

Reduction of risk of bias

The assessment criteria for the journals were conducted independently by three authors to reduce the risk of bias in this systematic review. We used the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for use in JBI Systematic Reviews to apply the criteria. Disagreements were discussed to reach consensus while assessing all of the selected article.

RESULTS

Study Inclusion and characteristics

Based on the search results using titles and abstracts, we obtained 483 articles about CP therapy for Coronavirus Disease 2019 in the PubMed and Medline database and 521 additional articles were identified from other sources, namely medRxiv.

A total of 18 article were included in this systematic review including 8 randomized controlled trials (RCT) [11, 17-23], 5 prospective studies [11, 17-23], 5 prospective studies [24-28], 1 nonrandomized multi-center clinical trial [29], and 4 retrospective studies [30-33]. We further summarized the data of all the studies into two tables. Table 1 shows the study characteristics and patients in each study, including location of the study, study type, number of participants, diagnosed tools, the severity of patients, age, dosage of transfusion, and other drug administration.

Outcomes of the studies, including discharging and mortality rates, length of stay, negative rate after convalescent plasma transfusion, improvement disease progression, improvements of laboratory and radiological findings and adverse events of CP therapy, are presented in table 2. From our review, all patients with COVID-19 receiving conventional plasma therapy were generally adults (>18 y) with a mean and median age above 48 y.

There were studies conducted in different countries worldwide. Eight of the RCTs were conducted in various countries, including one in China that was conducted by Li *et al.* with 103 patients with severe and life-threatening COVID-19. They compared clinical improvements of CP therapy (n=52) vs standard treatment (n=51) [23]. In Iraq, an RCT was conducted with 49 patients, including 21 patients in the CP therapy group vs 28 in the control group. Comorbidities between the two groups, including diabetes mellitus, hypertension, heart disease, obesity and cancer, did not differ significantly [11]. Another two RCT were conducted in India by Agarwal *et al.*, and Bajpai among 464 and 29 patients, respectively. Agarway *et al.* and Bajpai conducted their studies on moderate and severe COVID-19 adult patients, respectively. The two studies each aimed to assess the effect of adding CP therapy intervention (n = 235)+best standard of care (SOC) in the management of COVID-19 compared with the best SOC as the control arm (n = 229) and aimed to compare the efficacy of CP therapy to fresh frozen plasma [17, 20].

Furthermore, two multicenter RCT studies were conducted by Avendaño-Solà on 81 early or mild COVID-19 patients in Spain, with 38 in the CP group (CP+SOC) vs 43 in the control group (received SOC) and the other by Gharbharan *et al.* in the Netherlands. However, since the study conducted in Holland was halted prematurely after 86 patients were enrolled, the analysis was only performed on patients from that number including 43 in the SOC arm vs 43 in the CP arm [19, 22]. The last two RCTs were randomized, open label pilot trials in Bahrain and a phase II RCT in Chile. Concerning the clinical trial in Bahrain, the study conducted by AlQahtani reported outcomes of 20 pilot trial patients who received SOC+two 200 ml CP transfusion compared to 20 patients who received routine care alone. Meanwhile, Balcells *et al.* assessed patient outcomes to compare the effectiveness of early CP therapy (n = 28) versus deferred CP therapy (n = 30) in patients with severe COVID-19 [18, 21].

In addition to RCTs, a non-randomized multi-center clinical trial was included. A study was conducted in Iran and involved 189 severe COVID-19 patients and involved 115 in the CP group vs 74 in the control group. To eliminate the risk of bias, the patients that were included in this study had no differing ages, gender, comorbidity, nor radiological and clinical findings on admission [29]. We also included several prospective studies that were conducted in different countries. Duan *et al.*, Erkurt *et al.*, Salazar *et al.*, and Olivares-Gazca, *et al.* did studies in China, Turkey, USA and Mexico, respectively, with 10, 26, 387, and 10 patients diagnosed with COVID-19 using quantitative reverse transcription-polymerase chain reaction (qRT-PCR) who had entered the severe stage of the disease [24-27]. A prospective phase II clinical trial study comparing the effectiveness of using CP in 16 patients with transfusion in the early disease course versus 22 patients with late transfusion (in disease progression) was also included in this review [28].

Other data were collected from several retrospective studies of CP therapy in some other countries worldwide. They include the retrospective observational study done by Altuntas *et al.* in Turkey with a total of 1,776 severe or critically ill COVID-19 patients (888 in the CP group vs 888 in the control group). Those participants who were included in these two groups have characteristics that were not different in gender, age, comorbidities, chronic liver diseases, and antiviral treatment, making it easier for the researchers to analyze the outcome of CP [30]. Additionally, the retrospective studies of Omrani *et al.* with 80 patients (40 vs 40), Zeng *et al.* with 21 patients (6 vs 15) and Wu *et al.* with 27 patients all had similar subject characteristics that did not differ in gender, age, comorbidities, nor symptoms and clinical laboratory findings before transfusion, making it easier for the researchers to analyze the outcome of CP. Specifically, for the retrospective study by Wu *et al.*, they compared the effectiveness of CP in early negative patients and late negative patients (n = 15 vs n = 12) [31-33].

CPT dosage

In the transfusion, the administration of CP therapy must be adjusted to the patient's ABO type of the recipient [23]. The optimal CP plasma transfusion dose that can be used varies, ranging from 200 to 600 ml. We found a single dose of 200 ml was the minimum dose of CP transfusion [24-26]. One RCT demonstrated that this treatment approach could be based on the patient's body weight of approximately 4 to 13 ml/kg of recipient body mass and median volume was 200 ml (IQR, 200-300 ml) per patient [23]. The administration can be repeated for the second or third transfusions if needed, both when clinical changes are seen in patients and to patients without clinical response and a persistently positive RT-PCR [22]. A dosage of 400 ml per administration was also given by some researchers to patients with severe COVID-19. However, the usual administration is at a dose of 200 ml or 250 ml per unit of administration and repeated once for a secondary transfusion with the same dosage (400 or 500 ml as two 2 units). This is recommended by the majority of authors in our compiled study in both retrospective, prospective and RCTs. Meanwhile, the maximum dose of CP therapy as stated in the two retrospective observational studies, is 600 ml [30, 32].

Table 1: Characteristic of patients given convalescent plasma

Authors	Study type	Disease severity	Age (year)	Concentration and frequency administration	Other drug administrated	Iral negative rate	Outcome
[11]	Randomized multicenter clinical trial	Severe	55.6± 17.83[a]	400 ml (was given only once for all of the patients)	Hydroxychloquine, azithromycin, oxygen therapy, methylprednisolone	Duration of infection 19.33±6.90 vs 23.42±6.39 (p=0.037)	There were significant differences in recovery time from critical illness ((RTCI) of CP group and control group 4.52±2.35 d vs 8.45±1.87 d (<0.0001). RTCI of patients received CP from IgM donor were lower than negative IgM donors. 3.18±1.4 vs 6±2.3 (p=0.003). and RTCI from donor with strongly IgG had lower than moderately (p=0.048). Mortality rates of CP group were lower than control group 1/21 (4.8%) vs 8/28 (28.5%) (p<0.05).
[29]	Nonrandomized multi-center clinical trial	Severe	54.41 ±13.71[a] vs 56.83 ±14.98[a]	500 ml (within 4 h)	Lopinavir-Ritonavir, Hydroxychloroquine and anti-inflammatory agent	Negative rate of CP group 98 (98.2 %) vs control 56 (78.7 %)	There were significant differences in length of stay 6.25±4.33 12.88±7.19 (p=0.000), intubation 7% vs 20.3% (p=0.006)., discharged from hospital in less than 5 d after transfusion between CP group versus control group 27(28.1 %) vs 5(8.9 %) (p=0.010) and total discharged were 98 (98.2 %) vs 56 (78.7 %), and no difference in both groups in all-cause mortality (p=0.09)
[25]	Cohort study	Severe	67.4± 15.5[a]	200 ml	Favipiravir, hydroxychloroquine and azithromycin	NA	Of 26 patients included, 20 were alive and 6 died after 1 w of CPT
[24]	Prospective observational study	Severe	52.5 (IQR 45.0-59.5)[b]	200 ml	Arbidol, remdesivir, ribavirin, peramivir, cefoperazone, moxifloxacin, linezolid, tazobactam, levofloxacin, imipenem-sitastatin, fluconazole, and methylprednisolone.	All patients were negative for SARS-CoV-2 RNA following CP therapy.	All patients in CP group were alive at the time of follow-up. There were significant differences in clinical outcome including three of patients were discharged, seven cases seem much improved status and ready for discharge in CP group, while three deaths, six cases in stabilized status, and one case in improvement in the control group (p<0.001)
[33]	Retrospective observational study	Severe (end stage)	61.5 vs 73[b]	300 ml	Antiviral, antibiotics, traditional chinese medicine, Ig therapy, and glucocorticoids	Viral clearance was higher than control group 6(100%) vs 4(26.7%) (p=0.004)	There were no differences of death rate in both groups with 5 of 6 in CP group versus 14 of 16 in control (p=0.18). Survival periods of CP group were longer than control (p=0.03)
[27]	Prospective observational study	Severe	<30-≥80	one or two units	Lopinavir/ritonavir, remdesivir, ribavirin, tocilizumab, pednisone, dexamethasone, methylprednisolone, hydrocortisone, hydroxychloroquine, azithromycin,	Discharge rate 98(87.5) vs 107(95.5) (p=0.04)	CP Therapy were significantly decreases in mortality (p=0.047). CP group (with anti-RBD IgG titer of 1:1350) had lower risk of overall mortality and mortality within 28 d compared to control (RR, 7.53; 95% CI, 1.12-50.46; p=0.04; and RR, 5.92; 95% CI, 0.90-38.84; p=0.06, respectively). Transfusion within 72 h and anti-RBD IgG titer of ≥1:1350 had lower risk of mortality compared to>72 h and titer<1:1350. Discharge rate 98(87.5) vs 107(95.5) (p=0.04)
[31]	Retrospective observational study	Severe	53.5 (IQR 42-60.5)[b]	400 ml	lopinavir-ritonavir, azithromycin, hydroxychloroquine tocilizumab, methylprednisolone, mechanical ventilation,	There were differences in viral clearance between CP and SOC group 65% versus 55%, (p=0.49).	There were no statistical differences in improvements of respiratory support (p=0.32), discharged alive from ICU within 28 d and all-cause mortality at 28 d (p>0.05).
[23]	Randomized Controlled Trial	Severe or life threatening COVID-19	70 (IQR 62-78))[b]	4 to 13 ml/kg of recipient body weight (median volume was 200 ml (IQR, 200-300 ml) each patients)	Antiviral, antibacterial, Chinese herbal medicine, herbal medicine, steroids, antifungal, human immunoglobulin, and interferon	There were significant differences in negative rate of viral in both severe disease and life-threatening patients in CPT group vs Control 90.5%(19/21) vs 41.2 (7/17) (OR, 13.57[95%CI, 2.36-77.95]; p<.001) and 84.6 (22/26) vs 34.8 (8/23)(OR, 10.31[95%CI, 2.63-40.50]; p<.001)	• There was no significant difference in 28-day mortality (15.7%vs 24.0%; OR, 0.65 [95%CI, 0.29-1.46]; p =.30) or time from randomization to discharge (51.0% vs 36.0%discharged by day 28; HR, 1.61 [95%CI, 0.88-2.93]; p =.12). • There were significantly improvements at primary outcome at severe patients of CPT group vs control group 91.3%(21/23) vs 68.2%(15/22) (HR, 2.15 [95%CI, 1.07-4.32]; p =.03) but did not occur in life-threatening patients
[32]	Retrospective observational study	NA	64 (IQR, 57.0–72.0)[b]	400 (IQR 200-600) ml	Ribavirin, lopinavir, favipiravir, mechanical ventilation, broad-spectrum antibiotic therapy, corticoid therapy, and immunoglobulin therapy.		Treatment CP had length of hospital stay and interval between first transfusion and discharge in early negative patients shorter than with late negative patients with prolonged positivity of SARS-CoV-2 RNA. Early negative had a lower mortality rate than late positive 0(0%) vs 3(25%).
[26]	Prospective, longitudinal, single-arm, and quasi	Severe	53 (range 27-72)[b]	200 ml	Lopinavir/ritonavir, azithromycin, tocilizumab, hydroxychloroquine,	Giving CP in early negative patients had significantly decrease viral load compare late	There was a significant decreasing of SOFA score in 8 d therapy from 3 to 1.5 (p=0.014), increasing Kirby index (PaO2/FiO2) score from 124 to 255 (p<0.0001), Overall survival

Authors	Study type	Disease severity	Age (year)	Concentration and frequency administration	Other drug administrated	Iral negative rate	Outcome
	experimental				steroids	negative of prolonged positivity of SARS-CoV-2 RNA at days 3, 5 and 7 post-transfusion (p<0.05)	of patient was 77% in 24 d after CPT, 5 on mechanical ventilation were extubated and only two patients were dead
[17]	Randomized controlled trial	Moderate	52 (IQR 41 and 42-60)[b]	200 ml in twice	remdesivir, lopinavir/ritonavir, oseltamivir, hydroxychloroquine, spectrum antibiotics, steroids, and tocilizumab	NA	There was higher improved resolution of shortness of breath and fatigue in the intervention arm. There was no significant difference in WHO ordinal scale scores and reduction in progression to severe, mechanical ventilation, and all-cause mortality of patients at 28 d after CP therapy with the risk difference 0.008 (95% confidence interval −0.062 to 0.078); risk ratio 1.04, 95% confidence interval 0.71 to 1.54 compared to control arm.
[19]	Randomized controlled trial	Mild	59[b]	250-300 ml	No Mentioned detail	There was a significant difference of viral clearance at day 7 with 117/173 (68%) in intervention arm versus 93/169 (55%) (RR 1.2 (1.04 to 1.5) of control arm. However, at day 3 it was 79/184 (43%) versus 67/183 (37%) 1.2 (RR (0.9 to 1.5)).	Progression of CPT patient were lower than SOC (0 of 38; 0% vs 7 of 43 patients, 14% (p=0.03), mortality rates were 0% vs 9.3% at days 15 and 29 for CPT. There was no significant in overall survival (p=0.06), first clinical deterioration (p=0.07), discharging duration, and time of improvements.
[22]	Randomized controlled trial	mild and moderate	63 (IQR 56–74)[b]	300 ml and can be repeated if needed	chloroquine, azithromycin, lopinavir/ritonavir, tocilizumab, and anakinra	viral negativity rate was 79.7% in CP group versus 66.54% in control at 29 d	There was no significantly difference in overall mortality (CI 0.20–4.67, p=0.95), time to discharge (HR 0.88 CI 0.49; 1.60, p=0.68) or day-15 disease severity (p=0.58) was observed in both of CPT and SOC
[21]	Randomized controlled trial	Severe	65.8 (27-92)[a]	400 ml as two 200 ml unit	Lopinavir/ritonavir, hydroxychloroquine, tocilizumab, Steroids, Thromboprophylaxis, and Anticoagulation	NA	There were no significant differences in both groups of early and deferred therapy of CP in primary outcome 32.1% (9/28) vs 33.3% (10/30) (OR 0.95, 95%CI 0.32-2.84). They are including death in hospital (5/28) vs 6.7% (2/30) (OR 3.04, 95%CI 0.54-17.2), mechanical ventilation 17.9% (5/28) vs 6.7% (2/30) (OR 3.04, 95% CI 0.54-17.2), and hospitalization>14 d 21.4% (6/28) vs 30% (9/30) (OR 0.64, 95%CI 0.19-2.1)
[18]	Randomized controlled trial	severe and/or life-threatening	52.6 (14.9) vs 50.7 (12.5)[a]	400 ml as two 200 ml unit	Lopinavir/ritonavir, Ribavirin, Hydroxychloroquine, Azithromycin, Peginterferon, tocilizumab, Methyl Prednisolone, Antibiotics, Anticoagulation	Rate of negative both of group early and deferred therapy of CP on day 3 (26% vs 8%, p=0.20) nor on day 7 (38% vs 19%, p=0.37)	There were no significant differences on ventilation time 10.5 d vs 8.2 (P>0.81) and discharge alive (19 vs 18), total death 1 vs 2 both of CPT and dead
[20]	Randomized controlled trial	Severe	48.2± 9.8[a]	500 ml as two unit	Hydroxychloroquine, Azithromycin,	NA	There were no significant improvements in both of CPT and FFP including needed of mechanical ventilation (p=0.26), mortality rate, ICU stay and Vasopressors requirement till 28 d. CPT showed significant benefits in the secondary outcome of this research, including reduction of respiratory rate per min [p=0.004] and [p=0.008], O2 saturation p<0.001 and p=0.026, SOFA p=0.01 and p=0.04, improvements of PaO2/FiO2 p=0.009 and p=<0.001 at 48 h and at day 7 respectively.
[30]	Retrospective observational study	severe or critically	60(19 ±96)[b] vs 61(21 ±91)[b]	200-600 ml	favipiravir, lopinavir+ritonavir, hydroxychloroquine, high dose vitamin C, azithromycin	There was no significantly difference in improvements of Ct value at 7 d both of group CPT and FFP	CPT could reduce time in ICU, rate of MV support and vasopressor support than control group (p = 0.001, p = 0.02, p = 0.001). Although CFR of CP group was lower than control 24.7 % vs 27.7 %, but it was not statistically significant (p = 0.150), the same with duration in hospital. Administration of CP 20 d after diagnosis of COVID-19 increases the rate of MV support more than when administrated in ≤5 d, 6-10 d, 11-15 d) (p = 0.001)
[28]	A Prospective Phase II Clinical Trial	moderate, severe and critically	63 (12)[a]	200 ml or 400 ml as two 200 ml unit	Renal replacement therapy, Antibiotics, Antifungals, Azithromycin, Hydroxychloroquine, IL-6 Inhibitors, Remdesivir, Vasopressors, Steroids, Anticoagulants, and Zinc	NA	Giving CP therapy early in the disease course as compare with late administration when the disease of patients had progress had significantly lower mean hospital length of stay 15.4 vs 33 d (p<0.01) and shorter hospital mortality 13% vs 55% (p<0.02).

Other therapy (Antiviral, antifungal/antibiotic, steroid drug and others)

Hydroxychloquine (HCQ) or chloquine (CQ) is one drug that is almost always used in COVID-19 therapy as SOC as recommended by the WHO in the COVID-19 Treatment Guidelines. In these guidelines, it is recommended that the drug is administrated at a dose of 800 mg of HCQ or 1 g CQ PO in 1 d then HCQ 400 mg or 500 mg CQ PO once daily for 4–7 d of total treatment based on clinical evaluation. Together with the two quinone drugs, the antiviral combination of lopinavir/ritonavir (LPV/RTV) is rarely absent in any therapy for COVID-19 patients in our compiled studies. Based on the guidelines issued by the WHO, the recommended dosage of LPV 400 mg/RTV 100 mg PO is given twice daily for 10–14 d in adults. Other antiviral drugs that we found used in the treatment of the disease symptoms caused by the SARS-CoV-2 virus are ribavirin, remdesivir, oseltamivir, favipiravir, and peramivir [17, 24, 25, 29].

Antibiotic and anti-inflammatory drugs are also the most commonly prescribed therapy for COVID-19 patients, including azithromycin, cefoperazone, moxifloxacin, linezolid, tazobactam, levofloxacin, imipenem-cytastatin, broad-spectrum antibiotics, dexamethasone, methylprednisolone, hydrocortazole, and anakinra antifunctions. Monoclonal antibodies are also frequently prescribed in the treatment of pneumonia caused by the novel coronavirus, such as tocilizumab and peginterferon. Other adjunctive drugs such as traditional Chinese medicine, anticoagulants and vasopressors have been reported in some studies as effective treatment regimens for the disease [11, 18, 22-24, 27, 28, 32].

Improvements in laboratory and radiological findings

Improvement in laboratory and radiological findings is one of the important aspects measured after COVID-19 treatment as parameters of the effectiveness of CP treatment in patients (table 1). Most of the studies we compiled indicated that IgG and IgM titers increased post-transfusion with CP. The immunoglobulin is a neutralizing antibody that comes from donor plasma that has previously been formed due to exposure to the SARS-CoV-2 virus. This increase in immunoglobulin levels was also followed by several other clinical laboratory findings that are considered markers of improvement in the patient's condition. From several studies that we analyzed, the other laboratory parameters, which we found changed from the baseline condition when the patient was treated, included decreased hemoglobin levels, increased lymphocyte counts, decreased C-reactive protein (CRP), alanine aminotransferase (ALT), and aspartate aminotransferase (AST), as well as changes (delta) in ferritin and fibrinogen [24, 27].

The clinical laboratory change in serological components was found to be associated with improved radiological findings as described in the study conducted by Duan *et al.* that found CP generated increased lymphocyte counts, as well as decreased CRP, ALT, and AST. These were associated with improvement in pulmonary infiltrates, gradual absorption of lung lesions and disappearing massive infiltration and ground-glass attenuation following CP therapy [24]. A prospective single-arm study conducted by Olivares-Gazca *et al.* in 2020 also demonstrated that there were decreasing of body temperature 38.1 °C to 36.9 °C (p=0.0058) and serum ferritin (p<0.05) after patients received treatment. Even though there were no significant differences in CRP and D-dimer levels, improvements were found in both chest X-rays of 7 of 10 patients and computerized tomography (CT) scans showing improvements of lung injury post-therapy [23].

However, several laboratory parameters such as levels of CRP, inflammatory cytokines: Interleukin (IL)-1β, IL-6, IL-10 and tumor necrosis factor (TNF)-α), D-dimer, lymphocyte count, lactate dehydrogenase (LDH), procalcitonin, ALT, and AST, which most studies included in the review that demonstrated CP therapy was not significantly different from SOC [17, 20, 25, 27, 31]. For example, the randomized controlled study by AlQahtani *et al.* in 2020 found there were no significant differences of laboratory findings in both the CPT group and controls in white blood cell (WBC), LDH, troponin, D-Dimer and procalcitonin levels. The same results were demonstrated by Balcells *et al.* in their RCT. They found there were no differences between study groups (CP vs control group) in levels of CRP (p = 0.39 and 0.94), IL-6 (p = 0.86 and 1.00), ferritin (p = 0.78 and 0.92), LDH (p = 0.78) and 0.58), D-dimer (0.87 and 0.68), procalcitonin (p = 0.82 and 0.96) nor lymphocyte count (p = 0.15 and 0.66) at days 3 and 7 [18, 21].

Viral negative rate

Viral load is one indication of the severity and progression of the disease caused by SARS-CoV-2, which is tested before and after treatment [34]. Administration of CP containing neutralizing antibodies is expected to reduce the amount of the virus, relieve symptoms and even cure infected patients. Some studies always include this parameter to assess the effectiveness of therapy. Agarwal *et al.* in their RCT found no statistically significant difference between the CP arms vs the SOC arm in negative viral rate with 79/184 (43%) versus 67/183 (37%) 1.2 (RR (0.9 to 1.5)) and 117/173 (68%) versus 93/169 (55%) (RR 1.2 (1.04 to 1.5) at both days 3 and 7 after transfusion. The similar RCT finding was found in a study conducted by Balcells *et al.* on the same day post-transfusion showing that the percentage for the negative rate of patients receiving early and deferred therapy did not differ (26% vs 8%, p = 0.20) in day 3 nor on day 7 (38% vs 19%, p = 0.37). This finding was also demonstrated in the pilot RCT results by Bajpai *et al.* in severely ill COVID-19 patients post 7 d CP therapy versus fresh frozen plasma.

Another finding by Wu *et al.* in 2020 demonstrated that patients given CP therapy had significantly reduced viral load in early negative compared to late negative in days 3, 5 or 7 after transfusion. An RCT conducted by Li *et al.* also stated that the administration of CP therapy led to higher negative rates of SARS-CoV-2 compared with the SOC at 72 h with a percentage 87.2% vs 37.5% (OR, 11.39 [95% CI, 3.91-33.18]; p<0.001). The studies conducted by Avendaño-Solà *et al.* and Zeng *et al.* also found that CP can increase the clearance of SARS-CoV-2 higher than the SOC at 29 d after therapy (79.7% vs 66.54%) with 6 (100) vs. 4 (26.7) (p = 0.004), respectively. Similarly, one RCT found that CP therapy could significantly reduce infection duration when compared with standard therapy with a mean of 19.33±6.90 vs 23.42±6.39 (p = 0.037).

Clinical benefits, length of stay and patients' discharge after CP therapy

Concerning these outcome parameters, we found a variance of the findings in the studies that we compiled. Several studies demonstrated that adding CP therapy to the SOC for COVID-19 patients was effective in increasing recovery time from critical illness, reducing time in the intensive care unit (ICU), rate of reducing mechanical ventilator (MV) support, with lesser length of stay and vasopressor support than the control group [11, 26, 29, 30]. One RCT showed that there were significantly improved primary outcomes of severe patients of the CP treatment group compared to the control group with 91.3% (21/23) vs 68.2% (15/22) (HR, 2.15 [95% CI: 1.07-4.32]; p = 0.03) at 28 d. Although the rate of discharging and mortality did not differ significantly between the two arms, however, this study showed a positive result in patients receiving this therapy [23].

The administration of CP therapy also generated an increase in discharging rate within 5 d, which was associated with an increase in the negativity rate of the SARS-CoV-2 RNA test when compared to the control group [29]. The association of better results with the use of CP compared to the SOC in the discharge rate of patients was also demonstrated by the studies conducted by both Duan *et al.* and Salazar *et al.* [24, 27]. Wu *et al.* recommended that this therapy be done in the early disease course because giving CP at that time is more effective in reducing the length of hospital stay and the interval between first transfusion and improving patient discharge time when compared to late negative patients [32]. The same result was demonstrated by Ibrahim *et al.* that recommended that this therapy should be given at the beginning of the disease course to achieve the desired effect, which cannot be separated from their findings that there was a significantly lower mean hospital length of stay 15.4 vs 33. days (p<0.01) when compared to giving CP after the disease has progressed while extending the survival period when

compared to the control group (p = 0.03) [28, 33]. In addition to some of the clinical effects mentioned above, other clinical benefits reported by patients after this therapy include a significant decreasing of Sequential Organ Failure Assessment (SOFA) score, decreasing patient disease progression, increasing Kirby index (PaO2/FiO2) score and improving the resolution of shortness of breath and fatigue in the intervention arm [17, 19, 26].

Contrary to these results, a retrospective study involving 1,776 moderate, severe and critically ill COVID-19 patients concluded that the administration of CP therapy could not change the CFR or duration in hospital of patients when compared to the SOC of 24.7% or 219 patients in the CP group vs 27.7% or 246 patients in the control group (p = 0.150) [30]. The same finding was stated by Gharbharan *et al.* in 2020, demonstrating there was no difference in-hospital stay (p = 0.68) nor day-15 disease severity (p = 0.58) observed between CP-treated patients and SOC, nor in time to discharge [22]. The absence of association between CP and length of stay, discharge and mortality rate day was also found in several other studies that we included in our review [17, 23, 33].

Mortality outcome

The effectiveness of CP therapy is also assessed by its ability to reduce mortality in patients diagnosed with pneumonia-related SAR-CoV-2 infection. Several studies have reported that this therapy is not effective in reducing patient mortality, especially in the severe stage. For example, the nonrandomized multicenter clinical trial by Omrani *et al.* as well as several RCT studies conducted by researchers in China, India and the Netherlands stated that adding this therapy into the SOC was not effective enough in reducing the mortality rate of severe COVID-19 patients when compared to the SOC alone (table 2) [17, 20, 22, 23, 31, 32].

However, several other studies refute these findings. For example, an RCT conducted by Rasheed *et al.* stated that CP therapy was able to reduce the mortality rate of patients when compared to controls in this case the SOC [25, 27]. Other findings also confirm the positive effect of CP and provide recommendations regarding deciding the timing of CP transfusion given to patients. The authors found that this therapy generates 77% higher overall survival rates in patients and also confirms that CP therapy in the early disease course had lower hospital mortality of 13% vs 55% (p<0.02) when compared to disease progress in untreated patients. Accordingly, they recommended that therapy be given in the early disease course [26, 28, 32, 33].

Adverse events

There were no serious adverse events associated with CP therapy in most of the included studies. Some of the side effects that appeared in patients are mild allergic reactions, evanescent facial red spots and one had transient transfusion reactions. However, they are very rare and usually improve before the therapy ends [11, 24, 30]. Mild allergic reactions involved the development of skin redness and itching lasted for one hour after receiving CP and subsequent injected intramuscular antihistamine terminated the allergic cutaneous manifestations [11]. Reports of minor side effects also came from a RCT of 464 patients in India that reported similar events, namely the findings of a voluntary intervention group had minor adverse events of pain at the infusion site, chills, nausea, bradycardia, and dizziness, while 3 patients reported fever and tachycardia and 2 each had dyspnea and blockage of an intravenous catheter [17]. Additionally, a pilot RCT reported a case of mild urticaria in both the control and CP arms [20].

Two other studies involving 81 and 58 patients, respectively, also reported a small proportion of their participants suffered from side effects, namely 2 patients with suspected TRALI who gradually recovered before the study was done and 3 with fever, 1 rash, 3 serious adverse events (2 developed to severe respiratory deterioration within<6 h, and 1 TRALI type II). One of the patients later developed severe thrombocytopenia within 48h post-transfusion [19, 21].

DISCUSSION

The highly varied findings from the existing CP therapies that we included in this review make it difficult for the researchers to determine whether these therapies are effective in curing COVID-19 patients. Several studies stated that this therapy could not reduce the mortality rate when compared with the SOC, but some also stated that this therapy could reduce the length of stay, discharge time and relieve clinical symptoms of patients, such as increasing the rate of viral negativity, with improvements in clinical and radiological findings.

The most common outcome found was an increase in the viral negativity rate of post-receiving CP patients compared to the SOC group. This negative rate cannot be separated from the role of neutralizing antibodies in donor plasma which is transfused into sick patients. The presence of Nabs is crucial in viral clearance and is associated with the efficacy of this therapy. An RCT conducted by Bajpai demonstrated the presence of a significantly increasing of S1 RBD IgG antibody titer post-transfusion (p =<0.001). Furthermore, the study conducted by Rasheed demonstrated that an increase in the level of neutralizing antibody was associated with a decrease in the duration of viral infection. The antibodies in the transfused plasma bind to the receptor-binding domain of SARS-CoV-2 and prevent the virus from attacking the ACE2 receptors [35].

The SARS-CoV-2 antibodies that can bind to the SARS-CoV-2 are generally IgM, IgG1, IgG3, and IgA. In the binding of Nabs-virus, antibodies will recognize the virus and activate the antiviral effector of innate immune cells. The Fab region of an antibody will bind to Fcγ receptors of NK cells and trigger antiviral activation to eradicate viruses or virus-infected cells through the induction of antibody-dependent cellular cytotoxicity. The presence of these antibodies will also bind to FcR of macrophages and trigger phagocytosis. Two key antibodies, IgG1 and 3, are opsonin molecules that can bind directly to SARS-CoV-2. The binding of IgG1 and 3-SARS-CoV-2 will also generate opsonophagocytosis of virus particles by plasmacytoid dendritic cells and conventional dendritic cells and activate responses directly and/or via NK cells and T cells [36, 37]. The mechanism might explain the high negativity rate of patients after convalescent plasma transfusion. Therefore, it is important to consider the timing of the plasma collection as well as the symptoms of the donor to ensure a high antibody titer is effective when transfused into a patient. Li *et al.* recommended that retrieval be done at 28 d post-onset of symptoms in recovery for COVID-19 patients with a history of fever with more than 38.5 °C of body temperature longer than 3 d. This is based on their findings that at that time, the S-RBD-specific IgG antibody levels were higher to donate [13, 38]. CP transfusion is highly recommended in the early of disease course. Administration of CP therapy in recent symptoms of onset can be effective in reducing the mortality rate compared with late transfusion [27, 28]. Early transfusion allows for an increase of the level and binding ability of IgG and generates improvement to humoral immune responses, prevents unwanted immune responses, avoids the cytokine storm, and prevents worsening of the patient's disease condition to a critical stage [13].

In terms of the dose of transfusion, although CP transfusion appears to be safe because there have not been any serious adverse events in most of the studies, transfusion dosing needs to be done carefully. In the articles we included in this review, CP transfusion is recommended to be done per 200-400 ml for each administration and can be repeated if the patient has not shown signs of improvement or is still a positive SARS-CoV-2 test. They also suggest 600 ml as the highest dose to avoid the side effects of this CP, since it is known that, apart from neutralizing antibodies, in the plasma received from donor patients, there are several other products such as pro-inflammatory cytokines, clotting factors, defensins, and pentraxins. Excessive presence of pro-inflammatory proteins such as IL-1β, IL-2, IL-6, IL-17, IL-8, TNFα and CCL2 may indicate worsening of the cytokine storm and generate pulmonary damage, and decreasing of pulmonary capacity [13, 39].

Increased viral negative rates and clinical finding have been associated with reduction of length of hospital stay, mortality rate, increased discharging rate and reduction of recovery time. The RCT by Li *et al.* found that an increase in negative viral rate was associated with significant improvements to the primary outcome in severe COVID-19 patients. The same result was also found by

several other researches that showed this therapy was able to decrease the duration of the infection and increase the negative test result of the patients causing them to be discharged from the hospital faster, increasing their time to recovery and recovery rate and reducing the mortality rate [11, 23, 29].

These results cannot fully generalize the findings that adding CP therapy to the SOC is effective in improving the clinical mortality, discharging rates, improvements of the clinical finding of patients. This is because contrarily, there were findings of existing studies that have stated that there are no significant differences between CP and SOC while other studies claim CP to be effective comparing it to the SOC alone. However, this therapy is worth considering because plasma transfusion is generally not associated with any adverse reaction events. Further research on a large scale and with a better design is needed to assess the effectiveness of this therapy and confirm these findings.

CONCLUSION

In summary, the results of this review related to the effectiveness of convalescent plasma cannot be completely concluded to apply in the general population and it is necessary to conduct RCT research on a larger scale. The studies that we included in this review have various conclusions regarding the effectiveness of convalescent plasma. Although the majority of RCTs state that CP does not reduce mortality and increase discharging rate, it is effective in increasing viral negativity and the Nabs titer. Most RCTs and several other studies stated that this therapy can increase recovery time, negativity rate, discharging rate and survival period. These findings provide evidence that this therapy needs to be considered in the management of COVID-19 patients, given that there is no therapy that effectively treats the diseases caused by SARS-CoV-2 infection. Moreover, according to the data we included in this study, most found that this therapy is safe to use and does not cause any serious adverse reactions that endanger users. In addition, from the results of the various studies, they recommended that plasma collection from donors be done from the appropriate donor, namely from recovered COVID-19 patients within the 28 d period post-onset of symptoms with a history of fever of more than 38.5 ° C of body temperature longer than 3 d. The convalescent plasma treatment is recommended to be done in the early disease course for maximum therapeutic effect.

ACKNOWLEDGEMENT

The authors would like to thank the support from the Faculty of Medicine and Health Sciences University of Bengkulu.

FUNDING

Nil

AUTHORS CONTRIBUTIONS

All authors have contributed equally.

CONFLICT OF INTERESTS

The authors declare that there are no conflicts of interests.

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