JMedSci

Journal of the Medical Sciences
(Berkala Ilmu Kedokteran)

Volume 52, Number 3 (SI), 2020; 60-73
http://dx.doi.org/10.19106/JMedSciSI005203202007

Efficacy and safety of convalescent plasma therapy in patients with COVID-19: a rapid review of case series

David Dwi Putera[1], Mardiah Suci Hardianti[2*]

[1]Siloam Hospitals Labuan Bajo, Nusa Tenggara Timur, [2]Division of Hematology-Medical Oncology, Department of Internal Medicine, Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada, Yogyakarta, Indonesia

Submitted : 2020-05-01
Accepted : 2020-05-08

ABSTRACT

Coronavirus disease 2019 (COVID-19) has become a world pandemic since early 2020. Currently, there is no established treatment to combat this potentially fatal disease. Convalescent plasma (CP) therapy has a strong scientific basis and historical perspective to treat previous viral infections such as Ebola, Middle East respiratory syndrome (MERS) and severe acute respiratory syndrome (SARS). The aim of this review was to evaluate the efficacy and safety of convalescent plasma CP therapy in patients with COVID-19. We searched for every available study from major databases (CENTRAL, MEDLINE via Ovid, EMBASE) through 20th April 2020. We independently screened, extracted, assessed the risk of bias, analyzed the data using SPSS version 26, and narratively summarized the data. For the outcomes, we wanted to evaluate the changes of clinical parameters, radiological appearance, pulmonary function, the titer of neutralizing antibody, viral load, the disappearance of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) RNA, and adverse events.We found five case series from our literature searching. The overall methodological quality of the case series was moderate. We included 27 patients, and all patients received CP transfusion. All patients experienced improvement of clinical symptoms and pulmonary lesions after receiving 200 to 2400 mL (median 200 mL) of CP transfusion. All patients in reported studies had negative results of reverse transcriptase-polymerase chain reaction(RT-PCR) after 1 to 26 days of transfusion (median 3 days). There was one non-life threatening adverse event reported after CP transfusion (facial red spot). In conclusion, CP therapy in COVID-19 patients showed promising results as it improved clinical symptoms and parameters, and it is well-tolerated based on our included studies. However, further expanded clinical trials with better designs are still required to evaluate the efficacy of this treatment although suchidea will be quite challenging to be conducted in the era of an epidemic.

ABSTRAK

Coronavirus disease 2019 (COVID-19) menjadi pandemik dunia sejak awal tahun 2020. Hingga saat ini belum ada terapi yang efektif untuk penyakit yang berpotensi mematikan ini. Terapi plasma konvalesen (PK) atau plasma sembuh mempunyai landasan ilmiah yang kuat dan sejarah yang cukup panjang sebagai terapi infeksi virus seperti pada wabah Ebola, *Middle East respiratory syndrome* (MERS) dan *severe acute respiratory syndrome* (SARS). Tinjauan pustaka ini bertujuan mengevaluasi kemampuan dan keamanan terapi PK pada pasien COVID-19.Tinjauan pustaka secara cepat dilakukan dengan mencari literatur dari *database* penelitian besar, seperti CENTRAL, MEDLINE, dan EMBASE sampai tanggal 20 April 2020. Kami melakukan penyaringan abstrak, ekstraksi data, menganalisa kualitas penelitian, dan secara naratif menjelaskan data yang ada. Kami mengumpulkan data disesuaikan keluaran yang telah kami rumuskan sebelumnya, yaitu perubahan parameter klinis, perubahan gambaran radiologi paru-paru, perubahan fungsi paru-paru, titer *neutralizing antibody, viral load,* dan efek samping setelah transfusi PK. Kami memasukkan 5 studi *case-series* pada tinjauan ini, dengan total 27 pasien. Enam belas dari 27 pasien adalah pasien dengan kategori klinis berat. Semua pasien mendapatkan terapi PK dengan volume bervariasi dari 200 sampai 2400 mL (median 200 mL). Semua pasien mengalami perbaikan dari segi klinis, perbaikan gambaran radiologis, dan hasil negatif *reverse transcriptase-polymerase chain reaction* (RT-PCR) setelah 1 sampai 26 hari transfusi (median 3 hari). Dapat disimpulkan, terapi PK menunjukkan hasil yang menjanjikan dalam memperbaiki keadaan klinis, dan cukup aman untuk pasien COVID-19 berdasarkan berbagai penelitian. Namun demikian masih diperlukan penelitian yang melibatkan lebih banyak pasien dan dengan rancangan penelitian yang lebih baik untuk menilai efektifitas terapi PK yang sesungguhnya, meskipun hal ini menjadi hal yang sangat menantang dalam situasi pandemik.

Keywords:
COVID-19;
convalescent plasma;
therapy;
rapid review;
efficacy and safety;

*corresponding author: mardiah.suci@ugm.ac.id

INTRODUCTION

Coronavirus disease 2019 (COVID-19) is a disease that emerged from Wuhan Province in China in December 2019.[1] This disease became a world pandemic in early 2020 and already infected more than 2.4 million people in the world on the 20th of April 2020.[2] It is caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), an RNA virus, and belongs as a species from betacoronavirus genus. This virus is the seventh coronavirus that infects human.[3]

World Health Organization (WHO) and other clinical institutions have not yet established any definitive treatment for handling this disease, because specific treatment is still under research.[4] Antivirals, such as favipiravir, oseltamivir, are used, however, patients' responses while receiving this medication are still diverse. Furthermore, the mortality rate of COVID-19 remains around 5.21% from all cases.[2,5]

Convalescent plasma (CP) therapy is suggested to be used as an adjunctive treatment for this disease.[6] This approach was used in Ebola, Middle East respiratory syndrome (MERS) and severe acute respiratory coronavirus (SARS-CoV) infection, and several studies showed promising results. Convalescent plasma therapy works to decrease the viral load, cytokine response, and mortality rate. In addition, CP therapy also works by transferring antibody of a certain infectious agent from survivors to patients who are infected with the same agent of disease. This form of passive immunity helps the patient to fight the disease from getting worse immediately.[7] The CP had been used in a small population of severe COVID-19 patients, and the results were appeared promising from this population.[8] We conducted a rapid review to evaluate the efficacy and safety of CP therapy in patients with COVID-19.

MATERIALS AND METHODS

Type of participants

We included all patients who were confirmed with COVID-19 using throat swab SARS-CoV-2 reverse transcriptase-polymerase chain reaction (RT-PCR) in all ages, all clinical stages, and all sexes. We defined the clinical stages or severity of disease based on the WHOClinical Classification of COVID-19.[9] Asymptomatic patients were patients without any clinical symptoms of COVID-19. Patients with mild disease were patients without any specific symptoms, such as fever, weakness, cough, and malaise. Patients with moderate disease were those who had signs and symptoms of pneumonia, but did not require supplemental oxygen. Patients with severe disease were patients with clinical signs and symptoms of pneumonia, and had one form these conditions: respiratory rate ≥ 30 times per minute, severe respiratory distress, oxygen saturation (SpO_2) < 93% in room air, or PaO_2/ FiO_2 ratio <300. We defined critically ill patients as those who experienced acute respiratory distress syndrome (ARDS), septic shock, and/ or multiple organ failure. We also included those patients who were already treated with other regimens, such as antivirals, interferon-alpha (INFα), and other supportive treatments before receiving CP therapy.

Type of interventions

Patients received CP containing the SARS-CoV-2 antibody (IgG). The CP was drawn from individuals who had recovered from COVID-19, could donate blood, had no symptoms for 14 days, and had showed negative results on COVID-19 tests.

Treatment outcomes

Our primary outcomes were to evaluate the clinical responses in patients who were treated with CP, such as changes of clinical parameters, changes of radiological appearance, changes of PaO_2 / FiO_2, the titer of neutralizing antibody, viral load, the disappearance of SARS-COV-2 RNA, and adverse events if available. Our secondary outcome was to evaluate whether there was any variation of clinical response based on the severity of COVID-19 disease.

Type of studies

We wanted to include any types of publications regarding our clinical questions, except systematic reviews. We also excluded animal studies.

Search strategy and literature review

Two authors (DPP and MS) independently conducted literature searching through major databases, such as MEDLINE via Ovid, EMBASE, and Cochrane Controlled Register of Trials (CENTRAL) until 20th April 2020. We did not cover grey literature and limited the studies with English language only. We used keywords related to our clinical questions (COVID-19 and convalescent plasma therapy). Full search strategies are available in APPENDIX 1.

Selection of studies and data extraction

The process of searching and screening of abstracts of the relevant studies were done independently by DDP and MS. We extracted the data according to our outcomes into standardized tables.

Risk of bias assessment

We evaluated the risk of bias of our included studies using Cochrane risk-of-bias tool for controlled trials. For observational studies (cohort, cross-sectional or case-control studies), we used Strengthening the Reporting of Observational studies in Epidemiology (STROBE) checklist. For case reports or case-series, we assessed the quality of studies using a tool by Joanna Briggs Institute.[10]

Data synthesis

We narratively synthesized the data and collected the data in tabular fashion. We also summarized the patient's baseline characteristics and calculated the median of age, days of convalescent therapy initiation, days of negative RT-PCR results after CP administration, and other outcomes measured using SPSS version 26. For the uncontrolled studies and one-arm studies, we did not conduct meta-analysis since it would be inappropriate as there are no controlled arm as the comparisons. Therefore, all available data that we already had extracted were discussed narratively. The authors discussed the details of all the taken steps and analysis. The authors also discussed all the different opinions raised by the analysis result thoroughly before wrapping up the final opinion in the manuscript.

RESULTS

From the literature searching, in the beginning, we found 56 studies related to our keywords. After we eliminated the duplicates, we found 40 studies. We screened the abstracts and only included trials, observational studies, or case reports, and we found six studies, and all of the studies were case series. However, one study was lack of information regarding the patients' characteristics, therefore we excluded the study from our review.[11] Overall, the quality of the case series was of moderate quality. All of the studies defined the patients' characteristics, intervention given, length of follow-ups, and outcomes measured.

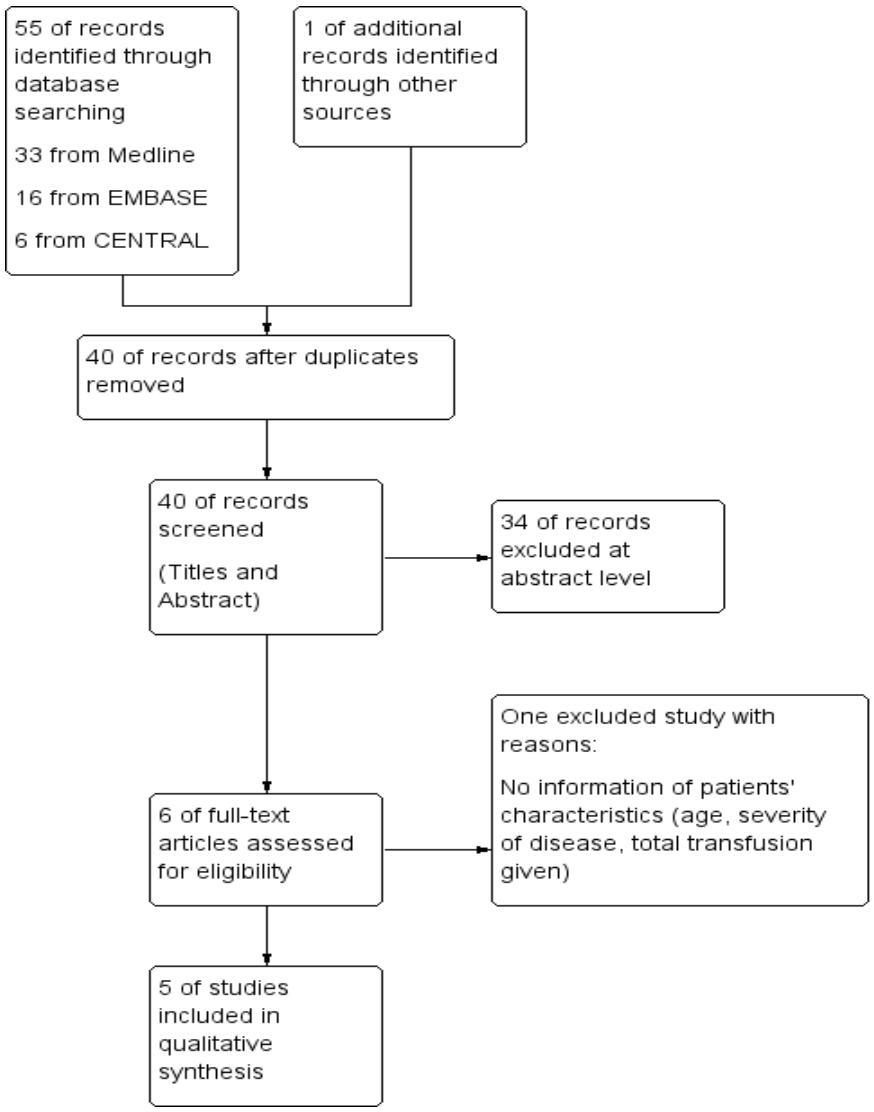

FIGURE 1. Study flow diagram.

TABLE 1.List of included studies

Authors	Publication type	No. of patients	Country	Patients characteristics	Intervention
Ahn,*et al.*[12]	Case Series	2	Korea	Two elderly patients (71-year-old man and a 67-year-old woman) with severe COVID-19	500 mL of plasma from recovered COVID-19 patients with Optical density ratio to IgG 0.586 and 0.532 divided into two doses.
Duan, *et al.*[13]	Case Series	10	China	10 severe COVID-19 patients confirmed with rtPCR, age 34-78 years old (median 52.5 years old), with varied comorbid conditions.	One dose of 200 mL of convalescent plasma (CP) from recently recovered donors with the neutralizing antibody titers above 1:640

Shen, *et al.*[8]	Case Series	5	China	5 critically ill patients (severe) confirmed with COVID-19 by rtPCR and ARDS, age range 36-65 years	Patients received transfusion with convalescent plasma with a SARS-CoV-2– (IgG) binding titer greater than 1:1000 and neutralization titer greater than 40)
Ye, *et al.*[14]	Case Series	6	China	6 COVID-19 patients confirmed by using throat swab SARS-CoV-2 real-time PCR, age 28-75 years old	Patients received at least one cycle of ABO-compatible convalescent plasma transfusion (200ml for each cycle, varied from 1-3 cyclers) and administered over 30 minutes.
Zhang, *et al.*[15]	Case Series	4	China	4 critically ill COVID 19 patients, age 31-73 years old.	Varied dosage of plasma convalescent was used (200 to 2400 mL divided into 1 to 8 cycles).

TABLE 2. Patients characteristics from 5 case series

Characteristics	n (%)	Median (IQR)
Age (years)		57 (20)
Sex		
• Male	15 (56)	
• Female	12 (44)	
Country		
• China	25 (93)	
• Korea	2 (7)	
Severity of disease		
• Asymptomatic	1 (4)	
• Mild	1 (4)	
• Severe	16 (59)	
• Critically III	9 (33)	
Comorbid		
• No Comorbid	15 (56)	
• Hypertension	7 (26)	
• Others	5 (18)	
Total dosage of CP transfusion (mL)		200 (200)
Initiation of CPtherapy after hospital admission (days)		11 (10)
Negative result of COVID-19 RNA after transfusion (days)		3 (8)

In total, there were 27 patients included in our review. The majority of the case series were reported in China, and only one study was reported from Korea. The patients' age ranged from 28 to 78 years old with a median age of the patients was 57 years old. Sixteen patients from the total 27 patients had severe disease, followed by nine patients with critically ill condition, and the rest

two patients were one asymptomatic and one with mild to moderate condition.

The initiation of CP therapy varied from 3 days to 28 days after hospital admission, with a median of 11 days. The dose of CP was varied from 200 to 2400 mL and the administration was divided into one up to nine cycles. Hypertension was the most common comorbid in our included patients, while other comorbid conditions were heart disease, pulmonary disease, end-stage renal disease, Sjögren disease, and pregnancy. All of the patients had already received antivirals therapy (lopinavir/ritonavir, arbidol, favipiravir, darunavir) and 14 (52%) patients received corticosteroids therapy prior to CP transfusion. Other treatments given to the patients were antibiotics, antifungals, and Interferon-α therapy.

Clinical symptoms

All studies reported the improvement of clinical symptoms after the administration of CP therapy, especially symptoms of fever, dyspnea, and cough.[8,12-15] Examples of clinical symptoms improvement can be seen from the number of patients who were successfully extubated (10 out of 13 patients). The study by Shen et al showed four out of five patients had their fever relieved 12 days after administration of CP therapy and had improvement of SOFA score.[8]

Improvement of chest radiology

All of the studies reported marked resolution of radiological findings. The study by Ahn et al showed two patients had marked improvement in bilateral infiltration.[12] These improvements occured in four to six days after the initiation of CP therapy, respectively. The study by Duan *et al.*[13] also showed different degrees of chest CT scan improvement after convalescent plasma transfusion, and two patients showed significant pulmonary lesions improvement in three to five days after transfusion.

Pulmonary function

Only two studies conducted by Ahn *et al.*[8] and Shen *et al.*[12] showed the changes in pulmonary function after CP transfusion. The mean of PaO_2/FiO_2 ratio increased after the administration of CP transfusion.[8,12]

TABLE 3. Changes of pulmonary function in sevenpatients

Out put	Before CP transfusion	After CP transfusion
Mean of pulmonary function (PaO2/FiO2 ratio)[a]	173.1 (70.9)	308.6 (43.8)

[a] In seven patients

Day of extubation

In total, there were 13 patients received mechanical ventilation, and 10 patients were successfully weaned and extubated.[8,12-15] Previous studies reported days of extubation after the patients were administered with the CP transfusion.[8,12,15] The day of extubation after CP therapy varied from two days to 39 days, with a median of 12 days. The study by Duan *et al.*[13] did not report the day of the extubation of the intubated patients, but the study reported the condition after the therapy. This study showed one out of three patients was still intubated. Shen *et al.*[8] reported that two patients were still intubated after

the administration of the CP therapy. However, the pulmonary function of these patients had improved and one patient was removed from an extracorporeal membrane oxygenation (ECMO) ventilation and was continued intubated. Whereas, Zhang *et al.*[15] reported that one patient was still intubated and transferred into an unfenced ICU due to multiple organ failure.[15]

Titer of viral neutralizing antibody

Viral neutralizing antibody assessment is important parameter that indicate the amount of antibody that is capable of neutralizing the viral. There was generally increased value of this parameter almost in all reported subjects as seen in TABLE 4.

TABLE 4. Change of viral neutralizing antibody before and after 1 to 7 days of CP transfusion in 15 patients.[8,13]

Patient No.	Before CP Transfusion	After CP Transfusion
1[a]	1/160	1/640
2[a]	Negative	Negative
3[a]	1/320	1/640
4[a]	1/160	1/640
5[a]	1/640	1/640
6[a]	1/640	1/640
7[a]	1/320	1/640
8[a]	1/640	1/640
9[a]	1/160	1/640
10[a]	1/640	1/640
11[b]	1/160	1/320
12[b]	1/40	1/160
13[b]	1/40	1/160
14[b]	1/80	1/240
15[b]	1/80	1/480

[a] Patients from Duan *et al.*[13] study; [b]Patients from Shen *et al.*[8] study

From the study by Duan *et al.*[13] nine patients had their neutralizing antibody detected before transfusion, and nine patients had neutralizing antibody titers of 1:640 after one to five days after transfusion. The study from Shen *et al.*[8] showed increased neutralizing antibody titers in all patients after seven days of transfusion.

Assessment of viral load

Assessment of qRT-PCR for SARS-CoV-2 from nasopharyngeal swabs indicated by Ct value indicates the viral load. Each RT-PCRassay provided a Ct value, which is the number of cycles required for the fluorescent signal to cross the threshold for a positive test: a higher Ct value is correlated with a lower viral load. The specimens were considered positive if the Ct value was 37.0 or lower and negative if the results were undetermined. Specimens with a Ct value higher than 37 were repeated. The specimen was considered positive if the repeated results were the same as

the initial result and between 37 and 40. If the repeated Ct was undetectable, the specimen was considered negative.

The viral load became negative in most of the cases after CP transfusion. The results of negative qRT-PCR were achieved between one day to 26 days after transfusion (median 3 days after CP transfusion) based on all included studies (Table 2).[8,12-15] Table 5 summarized the viral load change in 17 patients based on the three studies that reported Ct value before and after transfusion.[8,12,13] From this table, the negative qRT-PCR achieved after CP transfusion was similar, one to 26 days (median 2 days) after transfusion.

TABLE 5. Changes of SARS-CoV-2 RNA load in 17 observed patients before and after convalescent plasma transfusion

Patients No.	Ct value before CP transfusion	Ct value after CP transfusion	Days after transfusion
1[a]	25.0	Negative	26
2[a]	20.5	Negative	20
3[b]	37.3	Negative	1
4[b]	35.1	Negative	2
5[b]	38.1	Negative	1
6[b]	37.7	Negative	1
7[b]	Negative	Negative	2
8[b]	Negative	Negative	2
9[b]	34.6	Negative	2
10[b]	35.5	Negative	2
11[b]	Negative	Negative	2
12[b]	38.2	Negative	5
13[c]	28.5	Negative	12
14[c]	22.0	Negative	12
15[c]	33.0	Negative	3
16[c]	26.6	Negative	3
17[c]	35.9	Negative	1

[a]Study by Ahn *et al*.[12]; [b]Study by Duan *et al*.[13]; [c]Study by Shen *et al*.[8]; Ct value: cycle threshold value

Adverse events

There was only one mild side effect reported in the included studies. Duan et al showed one patient having a mild side effect from experiencing facial red spot, not a life-threatening condition.[13]

Mortality

All studies did not report any mortality after the transfusion.

Therapy response based on clinical severity

Only one asymptomatic and one patient with mild category of disease were included in our review, and they had negative RT-PCR results after transfusion. All 16 severe patients also had negative RT-PCR results and improvement in clinical parameters after transfusion. There were nine critically ill patients, three patients were still intubated until

the study end-point observation.[8,15] One critical ill patient from Zhang *et al.*[15] study received the highest total dose of CP therapy transfusion (2400 mL divided into nine cycles), and the patient remained intubated due to multiple organ failure.[15] The rest of six critically ill patients improved clinically and showed negative qRT-PCR result after CP transfusion.

DISCUSSION

Our review only included case series as until the end of our literature searching period, all studies we found with RCTs designs are still ongoing.This review shows CP therapy gave an improvement of overall clinical condition, radiological findings, improvement of pulmonary function, and negative PCR results after transfusion. This passive immunity helps to neutralize the virus as well as improving cytotoxicity and phagocytosis by harnessing the innate immunity.[16] Acute Respiratory distress syndrome condition was resolved in the majority of all cases probably due to the works of CP in subsiding the cytokine storm. This response might help to reduce mortality as there was no death reported from our included studies. This finding was similar to studies in SARS patients in 2005 (0% vs 24% mortality in patients without CP therapy, $p<0.05$)[17] and H1N1 patients in 2009 (Odds Ratio 0.20 [95% CI: 0.06–0·69], p=0.01).[18]

There were various initiation days of the transfusion and dose given in our review. The total dosage of CP therapy varied between studies, but the majority of the cases used 200 mL as a preferred dose and were repeated into several transfusion cycles. The dose of CP and the titer of antibodies either total IgG or viral neutralizing antibody given varied from the included studies as the standard of how this transfusion had to be given is still unavailable. Clinicians might have used the recommended dose of convalescent therapy based on the study of SARS patients. This study showed promising results in decreasing the mortality and length of hospitalization.[17] This study utilized 5 mL/kg of plasma with plasma titer of more than equal 1:160 and would result in 200-400 mL of plasma given.

The achievement of negative viral load required various duration from day one to 26 with median of two days, as presented in TABLE 5. The longer duration to achieve negative viral load inCase 1 may be explained by the fact of the later use of transfusion in the first case i.e after 22 days from the onset of symptoms, although for Case 2 it was admnistered only after seven days from the onset. In the study from Shen *et al*,[8] the convalescent plasma transfusion was administered 10 to 22 days after admission. Therefore whether a different timing of administration would have been associated with different outcomes cannot be determined so far. Furthermore, because the transfusion were not in the early phase of the disease, it is difficult to determine clearly that the decrease in the viral load shown in both cases is due to convalescent plasma or natural pathology of COVID-19. The first two cases in this table presented severe ARDS and the viral loads were in increasing trend at the time of plasma infusion regardless of the date of disease onset.[12]

This review shows only one case of side effect after transfusion due to allergic reaction. The side effects of CP transfusion are similar to any blood product transfusions, such as anaphylactic shock, transfusion-related lung injury (TRALI), and transfusion-associated circulatory overload (TACO).[19] Theoretically, CP transfusion may induce antibody-dependent enhancement of infection (ADE) phenomenon wherein normal mechanisms of antigen-antibody complex clearance fail, and instead provide an alternate route for host cell

infection and eventually worsen the disease. [19] This theoretical risk can be minimized by the measurement of viral neutralizing antibody titer in the plasma before given to the patient.

Our review only consisted of few patients with less severe COVID-19 disease, so we could not conclude if there were different responses based on the disease severity. However, we found that patients with severe comorbid needed more doses of the CP transfusion, as seen in one patient in the study by Zhang *et al.*[15]

The limitation of this review is that we only included found case series studies, and the patients' characteristics were heterogeneous. The patients in the included studies had different ages, comorbid conditions, and already received different medication (antivirals, antibiotics, and corticosteroids) before, during, and after the transfusion. Therefore, the true effect of CP therapy was unknown due to the influence of other therapies. We could not conduct pooled analysis and make comparisons with other interventions because of the study design of available studies (case series). Furthermore, our study is a rapid review, so we made limitations during the literature searching.

We suggest a clinical trial of CP therapy in COVID-19 patients with standardized methods and dosage of the plasma. So, the response after the therapy can be seen based on different clinical characteristics of the patients, such as sex, age, and severity of the disease.

CONCLUSION

Convalescent plasma therapy in COVID-19 patients shows promising results as it improved clinical symptoms, laboratory and imaging parameters. It is also well-tolerated based on our included studies. Although it is too early to be confident that all improvements are merely because of the transfusion due to diverse baseline clinical conditions, other treatments received, comorbidities and different day of transfusion after admission. Further clinical trials with expanded number of patients and comparable group of patient with similar characteristics and the same standard treatments are necessary to conclude a definitive statement about the efficacy of CP therapy. Although such idea will be quite challenging to be done in the era of an epidemic.

ACKNOWLEDGEMENTS

We would like to thank Irene Purnamawati from Siloam Hospitals Labuan Bajo, Yudha Nur Patria from the Clinical Epidemiology and Biostatistic Unit (CEBU) /Department of Child Health, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada, Yogyakarta, and Michael Dwinata from Depati Hamzah General Hospital, Pangkalpinang for their valuable feedbacks on the review.

REFERENCES

1. Ren LL, Wang YM, Wu ZQ, Xiang ZC, Guo L, Xu T, *et al.* Identification of a novel coronavirus causing severe pneumonia in human: a descriptive study. Chin Med J (Engl) 2020; 33(9):1015-24. https://doi.org/10.1097/CM9.0000000000000722
2. World Health Organization. Coronavirus disease 2019 (COVID-19) Situation Report – 77. Geneva: World Health Organization, 2020.
3. Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, *et al.* A novel coronavirus from patients with pneumonia in China, 2019. NEngl J Med 2020; 382(8):727-33. https://doi.org/10.1056/NEJMoa2001017
4. Chen L, Xiong J, Bao L, Shi Y. Convalescent plasma as a potential

therapy for COVID-19. Lancet Infec Dis 2020; 20(4):398-400. https://doi.org/10.1016/S1473-3099(20)30141-9
5. Beeching NJ, Fletcher TE, Fowler R. Coronavirus disease 2019 (COVID-19). BMJ Best Practice 2020. https://doi.org/bestpractice.bmj.com/topics/en-gb/3000168
6. Guan W, Ni Z, Hu Y, Liang W, Ou C, Ou J, *et al.* Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med 2020; 82:1708-20 https://doi.org/10.1056/nejmoa2002032
7. Bloch EM, Shoham S, Casadevall A, Sachais BS, Shaz B, Winters JL, *et al.* Deployment of convalescent plasma for the prevention and treatment of COVID-19. JClin Invest 2020; 138745. https://doi.org/10.1172/JCI138745
8. Shen C, Wang Z, Zhao F, Yang Y, Li J, Yuan J, *et al.* Treatment of 5 critically ill patients with COVID-19 with convalescent plasma. JAMA 2020; 323(16):1582-9. https://doi.org/10.1001/jama.2020.4783
9. World Health Organization. Clinical management of severe acute respiratory infection (SARI) when COVID-19 disease is suspected. Geneva: World Health Organization, 2020.
10. Joanna Briggs Institute. Critical appraisal checklist for case series. Available from: http://joannabriggs.org/research/critical-appraisal-tools.
11. Pei S, Yuan X, Zhang ZZ, Yao RR, Xie Y, Shen MM, *et al.* Convalescent plasma to treat COVID-19: Chinese strategy and experiences. medRxiv 2020. https://doi.org/10.1101/2020.04.07.20056440
12. Ahn JY, Sohn Y, Lee SH, Cho Y, Hyun JH, Baek YJ, *et al.* Use of convalescent plasma therapy in two COVID-19 patients with acute respiratory distress syndrome in Korea. JKorean Med Sci 2020; 35(14):e149. https://doi.org/10.3346/jkms.2020.35.e149
13. Duan K, Liu B, Li C, Zhang H, Yu T, Qu J, *et al.* Effectiveness of convalescent plasma therapy in severe COVID-19 patients. PNAS 2020; 117(17):9490-6. https://doi.org/10.1073/pnas.2004168117
14. Ye M, Fu D, Ren Y, Wang F, Wang D, Zhang F, *et al.* Treatment with convalescent plasma for COVID-19 patients in Wuhan, China. JMed Virol 2020. https://doi.org/10.1002/jmv.25882
15. Zhang B, Liu S, Tan T, Huang W, Dong Y, Chen L, *et al.* Treatment with convalescent plasma for critically ill patients with SARS-CoV-2 infection. Chest 2020; S0012-3692(20)30571-7.
16. Casadevall A, Pirofski LA. The convalescent sera option for containing COVID-19. J ClinInvest 2020; 130(4):1545-8. https://doi.org/10.1172/JCI138003
17. Cheng Y, Wong R, Soo YO, Wong WS, Lee CK, Ng MH, *et al.* Use of convalescent plasma therapy in SARS patients in Hong Kong. Eur J Clin Microbiol Infect Dis 2005; 24(1):44-6. http://doi.org/10.1007/s10096-004-1271-9
18. Hung IFN, To KKW, Lee CK, et al. Hyperimmune IV immunoglobulin treatment: a multicenter double-blind randomized controlled trial for patients with severe 2009 influenza A(H1N1) infection. Chest 2013; 144(2):464-73. https://doi.org/10.1378/chest.12-2907
19. Focosi D, Tang J, Anderson A, Tuccori M. Convalescent plasma therapy for Covid-19: state of the art. Preprints2020, 2020040097 https://doi.org/10.20944/preprints202004.0097.v1
20. Zand M, Wang J. Potential mechanisms of age related severity of COVID-19 infection: implications for vaccine development and convalescent serum therapy. Preprints 2020. http://doi.org/10.31219/osf.io/f3pze

Appendix 1

Search Strategies until April 20th 2020

MEDLINE via OVID	EMBASE via OVID	CENTRAL
Coronavirus Infections/ (5392)	Coronavirus Infections/ (1581)	COVID-19 (46)
Coronavirus/ (2003)	Coronavirus/ (6747)	SARS-COV-2 infection (2)
covid$19.tw. (4802)	covid$19.tw. (4774)	Coronavirus (144)
2019 coronavirus.tw. (52)	2019 coronavirus.tw. (43)	1 OR 2 OR 3 (156)
coronavirus disease 2019. tw. (797)	coronavirus disease 2019.tw. (543)	"convalescent plasma"(40)
sars-cov-2.tw. (1163)	sars-cov-2.tw. (790)	"immunoglobulin therapy" (7397)
1 or 2 or 3 or 4 or 5 or 6 (10804)	1 or 2 or 3 or 4 or 5 or 6 (12771)	5 OR 6 (7428)
convalescen* plasma.tw. (159)	convalescen* plasma.tw. (182)	4 AND 7 (6)
convalescen* therapy.tw. (8)	convalescen* therapy.tw. (8)	
8 or 9 (167)	8 or 9 (190)	
7 and 10 (33)	7 and 10 (16)	

Appendix 2

PRISMA Checklist

Section/topic		Checklist item	Reported on Page
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	1, 2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
METHODS			

Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	N/A
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4
Information sources	7	Describe all information sources in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	4
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	4
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	4
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	5
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	5
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	N/A
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	N/A
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	6, Figure 1

Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	6, Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment.	6, Appendix 3
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	7-11
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	N/A
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	N/A
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	11-13
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	13
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	13

Appendix 3

Summary of Critical Appraisal of Included Studies Using The Joanna Briggs Institute Critical Appraisal Tools for Case Series

Authors	Criteria for Inclusion	Measurement of Condition	Identification of Patients' Condition	Consecutive Inclusion of Participants	Complete Inclusion of Participants	Reporting of Participants' Demographic	Reporting of Clinical Information	Clear Report of Outcomes or Follow-ups	Reporting of Sites or Clinics Demographics	Appropriate Statistical Analysis
Ahn, 2020	Unclear	Yes	Yes	Unclear	Unclear	Yes	Yes	Yes	Unclear	Not Applicable
Duan, 2020	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Shen, 2020	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Ye, 2020	Unclear	Yes	Yes	Unclear	Unclear	Yes	Yes	Yes	Yes	Not Applicable
Zhang, 2020	Unclear	Yes	Yes	Unclear	Unclear	Yes	Yes	Yes	Unclear	Not Applicable