JOURNAL OF HEALTH SCIENCE AND PREVENTION
http://jurnalfpk.uinsby.ac.id/index.php/jhsp
ISSN 2549-919X (e)

Effectiveness of Convalescent Plasma Therapy in Severe and Critical COVID-19 Patients from Case Report and Case Series: A Systematic Review

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DOI: http://doi.org/10.29080/jhsp.v7i1.805

Received : Mei 2022, Accepted : Desember 2022, Published : April 2023

Kata Kunci

Plasma konvanlesen;
Perbaikan klinis;
COVID-19 derajat berat;
COVID-19 derajat kritis

Abstrak

Severe acute respiratory syndrome (SARS-CoV-2) menyebabkan pandemi Coronavirus Disease 2019. Plasma konvalesen merupakan pilihan pertama dalam situasi saat ini, karena telah berhasil digunakan dalam wabah virus corona lainnya. Pemberian plasma konvalesen mempunyai efek imunomodulator pada paru-paru melalui induksi sitokin anti-inflamasi dan antibodi yang menghambat kaskade komplemen (C3a, C5a) dan Efek antivirus dari NAbs. IgG dan IgM adalah isotipe utama, dan respon imun humoral terutama pada protein spike (S). Efek anti-inflamasinya mengontrol sistem kekebalan yang terlalu aktif (badai sitokin, rasio Th1/Th17, aktivasi komplemen dan regulasi keadaan hiperkoagulan) dan bersinergis dengan terapi standar menyebabkan perkembangan primary clinical outcome. Penggunaan plasma konvalensen berdampak turunkan angka kesakitan penderita COVID-19 derajat berat atau kritis.

Keywords

Convalescent plasma;
Clinical improvement;
Severe COVID-19;
Critical COVID-19

Abstract

Severe acute respiratory syndrome (SARS-CoV-2) causes the 2019 Coronavirus Disease pandemic. Convalescent plasma is the first choice in the current situation because it has been used successfully in other coronavirus outbreaks. Convalescent plasma administration has an immunomodulatory effect on the lungs through the induction of anti-inflammatory cytokines and antibodies that inhibit the complement cascade (C3a, C5a) and the antiviral effect of NAbs. IgG and IgM are the main isotypes, and the humoral immune response is primarily the spike protein (S). Its anti-inflammatory effect controls an overactive immune system (cytokine storm, Th1/Th17 ratio, complement activation and regulation of hypercoagulable states) and synergistically with standard therapy leads to the development of primary clinical outcomes. The use of convalescent plasma has an impact on reducing the morbidity of patients with severe or critical COVID-19.

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the cause of the outbreak of the coronavirus disease 2019 (COVID-19) pandemic. In 2020, therapeutic options including antimalarials, antivirals, and vaccines are in the process of clinical trials. Meanwhile, the current pandemic has attracted attention with the graph of new confirmed cases of COVID-19 spreading to a high point with increasing mortality rates and the focus of attention on old therapeutics to treat infectious diseases(1,2). Convalescent plasma containing SARS-CoV 2 specific IgG is the first choice in the current situation, as it has been used successfully in other coronavirus outbreaks. Indications for use are currently only for patients with severe or critical COVID-19 (2–5).

Some of the results of case series and case reports discuss the administration of convalescent plasma therapy with antiviral, corticosteroid, antibiotic therapy and others according to the protocol, showing

changes in clinical development after convalescent plasma administration such as decreased and normal body temperature, decreased SOFA score, PAO2 /FIO2 increases and laboratory results such as viral load become negative, biomarkers decrease and chest radiology results show improvement.(6–16)

Possible mechanisms of action of convalescent plasma prevent the inflammatory response in the pathogenesis of COVID-19, such as neutralizing antibodies, control of an overactive immune system (cytokine storm, Th1/Th17 ratio, complement activation) and immunomodulating hypercoagulable states(2,17–19).

Should convalescent plasma be considered routine therapy for COVID-19 patients? Hence, this study aims to further examine the effectiveness of convalescent plasma specifically in patients with severe or critical COVID-19, with a meta-analysis to evaluate it systematically. Are the benefits of convalescent plasma expected to improve clinical conditions if used in severe or critical patients in hospital care and can reduce morbidity and mortality?

Methods

Information Source

A literature review was conducted using the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines for systematic reviews. This is followed by the extracted data. We used electronic databases such as PubMed®, ScienceDirect®, and Google Scholar® to search using case reports, case series and observational methodologies for December 2020 - April 2022. Two search themes were used for the literature review and joined using the boolean operator "AND". The keywords used were “convalescent plasma” AND “effectiveness” OR “efficacy” AND “severe covid 19” OR “critical COVID-19” AND “clinical improvement” OR “Length of stay” OR “laboratory”.

Data Extraction and Study Selection

After the literature review was completed, the results were compared to 540 studies. The review excluded were 428 studies because the title did not match the researcher's question, 10 studies because they did not match the title, and 72 included Norwegian language, paid article, and not peer-reviewed yet, so the remaining 30 studies were eligible. The final results synthesized were 9 studies which were to be reviewed(Fig.1).

Included studies:

We identified case reports and case series in patients with severe or critical COVID-19 who received convalescent plasma therapy as recommended by the FDA and BPOM, the results after administration of convalescent plasma: improvement in clinical condition, improvement in the laboratory or radiological biomarkers compared to before in adult patients, single/double dose with comorbid/non-comorbid, together with standard management and the use of invasive mechanical ventilation or High Flow Nasal Canul (HFCN) or Extra Corporeal Membrane Oxygenation (EMCO)

Excluded studies:

We identified convalescent plasma transfusions in patients with moderate COVID-19, no comparison of primary clinical outcomes was reported.

Limitations

This study has several limitations which are the sample size is small and the study did not access paid articles.

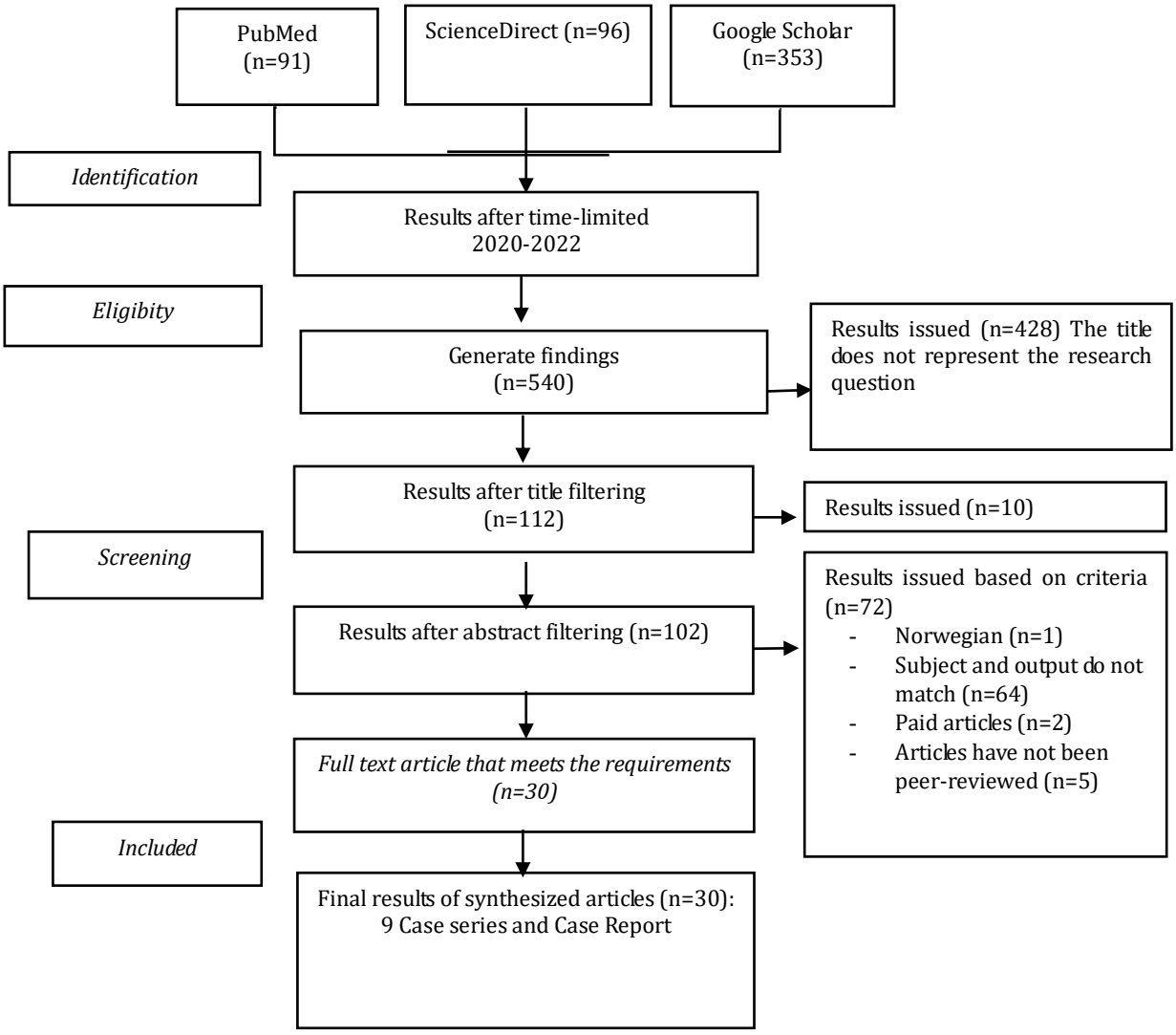

Figure.1: Prism Tracing Chart

Results

Table 1. Analysis Synthesis

No.	Author/ Year	Title	Study Design, Sample, Setting	Results
1.	Shen, Chenguang, et al (2021)	Treatment CP of 5 Critically Ill Patients With COVID-19 With Convalescent Plasma	Design: Case Series Sample: 5 Covid patients with critical 19 degrees on ventilator, aged 30-70 years; 2 women and 3 men). Weight between 41.5-87 kg. No-smoker. 1 patient with hypertension and mitral insufficiency. All patients were given corticosteroids and antivirals. Setting: Jan-March 2020RS Schenzen, China Intervention: Corticosteroids, antiviral, CP transfusion on day 11-13 in patients with critically COVID-19 dose of 400 mg	• Body temperature before CP transfusion: 37.6-39 degrees Celsius and after that the temperature is normal • CT value increased on the first day after transfusion. For patients 1 of 5 was negative on day 1, for 2 patients were negative on day 3 and 7, and all patients were negative on day 12 after CP transfusion. • SOFA score ranged from 2-10 points before CP transfusion and decreased to 1-4 on day 12 after CP transfusion. • PAO2/FIO2 before CP transfusion ranged from 172-276, on day 1 to day 12 ranged from 284-366 after CP transfusion. • CRP biomarkers, procalcitonin, IL-6 decreased in 4 patients while in 1

No.	Author/ Year	Title	Study Design, Sample, Setting	Results
				patient, only CRP and procalcitonin values decreased. • LOS: around 51-55 days for 3 patients and LOS for 2 patients about 88-92 days • Three days post-transfusion and persisted on day 7, IgM titer increased in the range 5400-437400, while IgG titer increased in the range 5400-145800. IgG and IgM titers. • After CP transfusion on days 2 and 9, 3 patients after intubation, one of them received ECMO after ECMO after 5 days and 2 patients were still on the ventilator without ECMO administration. (LOS: 53, 51, and 55 days). Patients 1 and 2 had lengths of stay 88 and 92. • Adverse effect (-)
2,	Rahardjo, Theresia M, et al (2021)	Effectiveness of Convalescent Plasma Therapy in Eight Non-Intubated Coronavirus Disease 2019 Patients in Indonesia: A Case Series	Design: Case Series Samples: 8 severe COVID-19 patients, non-intubated, age, 40-74 years; 3 women and 5 men). 6 non-intubated severe COVID-19 patients had comorbidities including DM, hypertension, CV disease, respiratory disease, and blood disorders. Setting: April 2020, Primaya Hospital Tangerang, Indonesia Intervention: CP therapy on day 14. And standard therapy includes antivirals, antibiotics, and corticosteroids.	• RR before giving CP transfusion: between 17-40x/minute, after that between 16-24x/minute • Oxygen saturation before CP transfusion between 90-98 and after transfusion to 95-99 • Oxygen support before CP transfusion using NRM/NC between 3-15 l/minute and 1 patient using HFNC 40 l/minute after CP transfusion on day 7 only 3 patients using NC 3-4 l/minute and 5 patients with room water • Chest X-ray improved on the 7th day after CP transfusion • 8 PCR positive patients after CP transfusion 6 patients with negative PCR and 1 patient appeared comorbid and 1 patient with comorbid remained positive until day 10 with RDRP gene 39.70 and 35.93 • All patients in the study received their first dose of CP within 14 days of first symptom onset, with a median time of 13 days. Most patients had at least one comorbid condition, including age, and the median time from admission to RT to administration of first CP was 6.5 days. • Two doses of CP tended to produce better and faster recovery than one dose of CP, including fewer days of decreased respiratory rate (mean days were 1.5 versus 2.75 days) and decreased oxygen supplementation (median days were) mean was 3 versus 3.75 days). • Adverse effect (-)
3.	Zeng Hao, et al (2020)	The Efficacy Assessment of Convalescent Plasma Therapy for	Design: Case Series, Retrospective Observational Study Sample: 8 patients with critical or severe COVID-19 with oxygen support, aged 46-70 years, (4 women and 4 men). 5 patients	• After given CP transfusion normal changes include body temperature, heart rate and blood pressure • After given the CP transfusion, there was clinical improvement marked by an increase in oxygen saturation and

No.	Author/ Year	Title	Study Design, Sample, Setting	Results
		COVID-19 Patients: A Multi-Center Case Series	had comorbidities (including DM + CHD and COPD, hypertension,). 1 patient is a smoker. Setting: Feb 2020,4 hospitals in Southwest Region of China Intervention: CP transfusion on day 9-34 days after the appearance of symptoms. Each patient also received other treatments including antivirals, antibiotics, antifungals, and corticosteroids.	a CT value = 7 which was not detected after the 7th day of giving CP transfusion. • There was an increase in CRP and procalcitonin before CP transfusion in 4 of 5 patients, and a decrease in CRP and procalcitonin after CP transfusion in 5 of 6 patients. • All patients were discharged from the hospital with a mean LOS of 28.0 days (IQR, 24-32.5 days), except for patient 4, who remained hospitalized to receive further treatment of the underlying disease (LOS 45 days) • Adverse effect (-) Patients who received a CP transfusion before 21 days of symptom onset tended to have a faster negative nucleic acid test and a shorter hospital stay.
4.	Zhang Bin, et al (2020)	Treatment With Convalescent Plasma for Critically Ill Patients With Severe Acute Respiratory Syndrome Coronavirus 2 Infection	Design: Case Report Sample: 4 critical COVID-19 patients, 3 patients on ventilator and 1 using supportive oxygen. Age: 31-73 years, 2 women and 2 men). Setting: Jan 2020, Dongguan Ninth People's Hospital, Xiangtan Central Hospital, Xiaolan People's Hospital. Intervention: Convalescent plasma transfusion. Each patient also received other treatments including antivirals, antibiotics, antifungals, and corticosteroids.	In the four patients with severe and critical grades including 3 patients on a ventilator and 1 patient with HFNC. The time from CP transfusion until the RT-PCR test showed a negative result ranged from 3 -22 days. In the first case, the viral load of SARS-CoV-2 after CP transfusion dropped significantly (from 55-105 to 3.9-104 to 180 copies/mL). In the third and fourth cases, anti-SARS-CoV-2 IgG was detected 14 days after convalescent transfusion. CP transfusion was given in critical cases (ventilator) between days 11-18. The dosage for using CP is 1 dose, 2 doses and 3 doses. The duration of CP administration is 1-8 days. 3 patients were able to go home only 1 remained in non-ICU care. Adverse effect (-)
5.	Azim, Dazil, et al (2021)	Utility of Convalescent Plasma for Addressing The COVID-19 Infection: Brief Review and Case Reports	Design: Case Report Sample: 2 male patients with severe COVID-19 with Non Breathing Mask and HFCN, male, age 54 and 62 years, respectively. The second patient had comorbid hypertension and obesity. Setting: Hayatabad Medical Complex Hospital, Peshawar and Dhaka Medical College Hospital, Bangladesh Intervention: CP transfusion. The first patient was not given antivirals, but received antibiotics, anticoagulants, symptomatic corticosteroids and acetaminophen. The second patient received antiviral, anti-inflammatory (tocilizumab), antibiotics and antivirals	The results of the study of the two patients who received CP transfusions on day 5 of admission to the hospital (patient 1) and day 9 of symptoms (patient 2) were as follows: • In the first patient, on day 5 after hospital admission, the patient received 500 ml of CP transfusion in two doses along with conservative COVID-19 treatment. After 3 days of plasma transfusion, the patient switched to non-invasive ventilation to a nasal cannula. The 15th day the patient was declared cured • In the second patient, a CP transfusion was given. Supplemental high pressure oxygen (HNCF) and oxygen saturation increased to 92% at 3 days after transfusion. The patient's condition was much better with a decrease in CRP by 90 mg/L and then gradually became normal on day 15. Chest X-ray showed resolution of both pulmonary infiltrates and follow-up rRT-PCR performed on day 14 was negative.

No.	Author/ Year	Title	Study Design, Sample, Setting	Results
6.	Hartman, William R, Hess, aaron S, & Connor, Joseph S (2020)	Hospitalized COVID-19 Patients Treated with Convalescent Plasma in a Mid-Size City in The Midwest	Design: Case Report Sample: 31 patients, 16 severe or 15 life-threatening COVID-19 (10 women, 21 men) Setting: April-June 2020,Hospital in Mid-Size City in the Midwest Intervention: CP transfusion and respiratory support.	• There was clinical improvement in patients receiving mechanical ventilation and CP transfusions. Although, 4 patients (29%) with life-threatening disease died, 9 patients (64%) experienced improved breathing 14 days after CP transfusion. • Among the 16 patients transfused with CP in severe disease (6%) developed progressive respiratory dysfunction and eventually required intubation five days after the CP transfusion (eight days after hospital admission, 13 days after symptoms). • Only one of the 12 ventilated patients received a CP transfusion prior to intubation. The patient used 100% O2 via a high-flow nasal cannula at the time of the transfusion and was intubated 15 hours later. Ultimately, 8 (67%) were extubated, after a median of 10 days since the CP transfusion. Severe LOS: 9 days and critical LOS 22 days.
7.	Haleli, Aber A, et al (2020)	Radiological and Clinical Improvement in A Patient with COVID-19 Pneumonia Post Convalescent Plasma Transfusion: A Case Report	Design: Case Report Sample: 1 male patient (55 years) with severe COVID-19, on ventilator. Non-smoker.. Settings: - Intervention: CP transfusion, antiviral, antibiotic, and other symptomatic drugs.	• In less than 48 hours, the patient's laboratory parameters improved, COVID RT-PCR was negative, and Ferritin decreased to 515; but CRP is still high at 315 mg/L. • After 2 weeks of CP transfusion, the CRP level decreased to 1.99 mg/L, the ferritin value to 385 mcg/L. • After, CP transfusion, CXR showed gradual improvement starting from day 2, the patient was extubated on day 6, chest CT scan was performed on day 12 which showed significant improvement and the patient was discharged on the same day.
8.	Ahn, Jin Y, et al (2020)	Use of Convalescent Plasma Therapy in Two COVID-19 Patients with Acute Respiratory Distress Syndrome in Korea	Design: Case Report Sample: 2 severe COVID-19 patients, on ventilator, male and female aged 71 and 67 years, respectively). The second patient has comorbid hypertension Setting: Feb 2022 Korea Intervention: CP transfusion was given on day 10 in the first patient, and on day 6 in the second patient. And both were given corticosteroids, antivirals, antibiotics, and respiratory support.	• The first patient who needs oxygen with severe COVID-19 is referred to a tertiary hospital. 9th day Blood gas analysis as severe covid 19. 9th day on ventilator and corticosteroid therapy. Day 10 received a CP transfusion. fever and decreased oxygen demand since day 11. Day 20 after the CP transfusion the patient's condition was much better with a decrease in CRP and IL-6 to the normal range (5.7 mg/L and <1.5 pg/mL). On day 18, PaO2/FiO2 increased to 300. Chest X-ray showed resolution of both pulmonary infiltrates. The cycle threshold value (Ct) changed from 24.98 to 33.96. SARS-CoV-2 was negative after 26 days. • In the second patient, leukocytosis and lymphopenia, CRP and IL-6, increased LDH and put on a ventilator. + corticosteroids. Day 6.

No.	Author/ Year	Title	Study Design, Sample, Setting	Results
				given CP transfusion. On day 9, bilateral infiltration on chest X-ray improved with an increase in PaO2/FiO2 to 230. CRP and IL-6 levels also decreased to the normal range. The patient was finally extubated and discharged from the hospital on day 24. SARS-CoV-2 was negative after day 20.
9.	Salazar, Eric, et al (2020)	Treatment of coronavirus Disease 2019(COVID-19)Patient's with Convalescent Plasma	Design: Case Report Sample: 25 patients with severe or life-threatening COVID-19 (age range: 19-77 years, 14 women and 11 men). Weight range 58-133 kg. BMI Range: 22.6-29). 2 former smoker patients. 5 patients were coinfected. 16 patients had comorbidities. Setting: April 2020 Houston Methodist Hospitals Intervention: CP transfusion, antiviral, antibiotics, and oxygen support.	• One patient developed a morbilliform rash 1 day after CP transfusion. Two patients developed deep vein thrombosis 8 days after CP transfusion, and one patient developed deep vein thrombosis and pulmonary embolism 4 days after CP transfusion. • On day 7 after CP transfusion, 9 patients had clinical improvement, and 7 of them were discharged. On day 14 after the CP transfusion, 19 had clinical improvement, and 11 of them were discharged. • Average LOS at the hospital was 14.3 days (range, 2 to 25 days). The mean posttransfusion LOS was 11 days (range, 1 to 21 days). • CRP decreased from 14.66 mg/dL on day 0 to 2.9 mg/dL on day 7 and to 0.45 mg/dL on day 14 after CP transfusion. Ferritin increased on the 3rd day, but tended to decrease on the 7th day. There was no significant increase in liver enzymes. • Of the 25 patients, 9 patients experienced improvement on day k-7, and an increase of 12 patients on day 14.

Annotatiion:
CP: Convalescent Plasma, CP: Convalescent Plasma Therapy, SOFA: Score Sequential Organ Failure Assessment , CRP: C-Reactive Protein, IL-6: Interleukin-6, LOS: Length of Stay, ECMO: Extracorporeal Membrane Oxygenation, DM: Diabetes Mellitus, CV: Cardiovascular, CHD: Coronary Heart Disease, RR: Respiratory Rate, CP: Convalescent Plasma Therapy, NRM: Non-Rebreathing Mask, NC: Nasal Cannula, HFNC: High Flow Nasal Cannula, RT-PCR: Real Time-Polymerase Chain Reaction, RDRP: RNA-Dependent RNA Polymerase, IQR, CXR: Chest X-Ray, BMI: Body Mass Index

Discussion

Convalescent plasma can be a therapeutic option during the COVID-19 pandemic, where standard treatment and vaccination are still in clinical trials. Convalescent plasma is a passive immunization containing SARS-CoV-2 specific IgG from recovered COVID-19 patients. The Food and Drug Administration (FDA), USA and the Drug and Beverage Control Agency (BPOM), Indonesia recommend the use of convalescent plasma as the emergency use authorization (EUA) for patients with severe/critical COVID-19. Convalescent plasma is highly effective with promising evidence of safety and reduced mortality in the treatment of severe and critically ill COVID-19 when coadministered with antiviral/antimicrobial drugs, steroids, and other supportive care (1,4,19–21).

The timing of convalescent plasma therapy varies between 2-14 days depending on the protocol and the doctor's decision and can be adjusted to the condition of the COVID-19 patient at that time. The use of a double dose is better than a single dose. According to Rojas.M's theory, the mechanism of action of convalescent plasma in patients with severe or critical COVID-19 is through an immunomodulatory effect on the lungs through the induction of anti-inflammatory cytokines and antibodies that inhibit the complement cascade (C3a, C5a) and the antiviral effect of NAbs. IgG and IgM are the main isotypes, and IgA may exert a protective effect. Humoral immune response mainly to spike protein (S). Its anti-inflammatory

effects include autoantibodies and control of an overactive immune system in the form of cytokine storm, Th1/Th17 ratio, complement activation and regulation of hypercoagulable states (13).

The effectiveness after giving convalescent plasma to all patients with age groups, male and female, accompanied by comorbid or non-comorbid diseases, showed improvement in primary clinical outcomes, including a decrease in body temperature to normal, SOFA score from score 2-10 decreased to score 1- 4, PAO2/FIO2 increased from 284-366, and oxygen saturation to 95-99. Similarly, the use of a high flow nasal cannula (HFNC) from 40 litres/minute to a nasal cannula of 3-4 litres/minute. Laboratory changes such as viral load decreased significantly (from 55-105 to 3.9-104 to 180 copies/mL SARS CoV-2 PCR decreased to negative. CRP, IL-6 and procalcitonin decreased. There was a change in chest radiography showing the resolution of both pulmonary infiltrates. Development also occurs in patients on invasive mechanical ventilation, where ECMO can be discontinued so that the length of stay is shorter than those who do not receive convalescent plasma therapy and the patient can be discharged from the hospital (2,3,10,19,21).

It was found different opinions from other researchers that the male sex hormone (testosterone) makes men susceptible to COVID-19 and worsens the prognosis of the disease because it provides an immunosuppressive effect resulting in a decrease in antibody response. Mortality rates in severe/critical COVID-19 patients with comorbidities receiving convalescent plasma therapy were as follows: hypertension (50%), diabetes (7.3%) and ischemic heart disease (18.5%).

There is a relationship between age and severity where the age of 50 years is more vulnerable due to weak immunity and other organ dysfunction. There was no significant difference in mortality in patients with COVID-19 who received or did not receive convalescent plasma therapy or delayed administration (14–16,22–26). By the theory of Hussin, 2020[15] that convalescent plasma is an adjuvant therapy and has no impact on the degree of severity resulting in death, whereas the severity is determined by how severe the patient's systemic and respiratory disorders are. COVID-19.

Conclusion

Implications for practice, we found no secondary clinical outcome (adverse effect) in the use of convalescent plasma with standard therapy resulting in the development of a primary clinical outcome. Implications for research, this study was conducted on small subjects, it requires an evaluation approach to large-scale randomized clinical trials, randomized by comparison to determine the effectiveness of convalescent plasma (primary clinical outcome) as a single treatment or with other therapies.

Acknowledgements

The authors thank NQ and FP for useful contributions and discussions.

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