Convalescent plasma therapy as a conventional trick for treating COVID-19: a systematic review and meta-analysis study

M. Keikha[1,2] and M. Karbalaei[3]

1) *Department of Microbiology and Virology, Faculty of Medicine,* 2) *Student Research Committee, Mashhad University of Medical Sciences, Mashhad and* 3) *Department of Microbiology and Virology, School of Medicine, Jiroft University of Medical Sciences, Jiroft, Iran*

Abstract

Convalescent plasma therapy (CPT) is one of the well-known therapeutic protocols for treating infectious diseases that do not have special treatment or vaccine. Several documents confirm the clinical efficacy of this therapy for treating bacterial and viral infections. A comprehensive systematic search was conducted by August 2020 using global databases including PubMed, Scopus, Embase, Cochrane library, Google scholar, medRxiv and bioRxiv. The Joanna Briggs Institute critical appraisal checklist was used to evaluate the included studies. Using the Comprehensive Meta-Analysis software version 2.2 (Biostat, Englewood, NJ, USA), the pooled data analysis process was performed. A total of 15 eligible articles were enrolled in the current quantitative synthesis. The statistical analysis showed that clinical improvement in the group of patients who had received convalescent plasma was significantly increased compared with the control group (OR: 2.23; 1.12-4.45 with 95% CIs; p value: 0.022; Q-value: 6.11; I^2: 83.64; Eggers p value: 0.064; Beggs p value: 0.093). Furthermore, the rate of hospital discharge had increased in patients receiving CPT (OR: 2.92; 1.48-5.77 with 95% CIs; p value: 0.002; Q-Value: 4.32; I^2: 53.80; Eggers p value: 0.32; Beggs p value: 0.50). Because there is currently no fully effective antiviral drug against the virus and it will take time to confirm the effectiveness of new drugs, CPT can be used as an alternative treatment strategy to improve the severe clinical manifestations of COVID-19.
© 2021 The Author(s). Published by Elsevier Ltd.

Corresponding author: M. Karbalaei, Department of Microbiology and Virology, School of Medicine, Jiroft University of Medical Sciences, Jiroft, Iran.
E-mail: mohsen.karbalaei@jmu.ac.ir

Background

The family Coronaviridae is known as one of the most important etiologic factors for severe acute respiratory diseases for 21st-century human beings. The members of this family are enveloped, single-stranded, positive-sense RNA viruses (26-32 kbp length), and also have many spikes proteins on their surfaces that mediate virus entry into the cells [1,2].

Coronaviruses have a broad spectrum of the host including avian species, humans and several mammals such as bats, camels, mice, cats, dogs and anteaters [3]. Among them, several coronaviruses (CoVs) such as 229E, OC43, NL63, HKU1, severe acute respiratory syndrome coronavirus 1 (SARS-CoV-1), MERS-CoV and more recently SARS-CoV-2 can infect human [4]. Before 2002, CoVs were known only as of the causes of common cold; however, in the 21st century, the large pandemic of betacoronavirus revealed that these RNA viruses can cause the life-threatening severe respiratory diseases [5]. In 2002, the first pandemic, severe acute respiratory syndrome (SARS) was caused by SARS-CoV-1, so that had the mortality rate about 10% [6]. The second pandemic, Middle East respiratory syndrome (MERS), was occurred by MERS-CoV in 2012, with mortality rate about 35% [7]. In December 2019, a new member of betacoronavirus, 2019 novel coronavirus (2019-

nCoV) emerged in Wuhan, China, causing a severe pneumonia, that was called coronavirus disease 2019 (COVID-19) [8]. The clinical manifestations of COVID-19 are fever, dyspnoea, myalgia and invasive multilobular lesions (in chest radiological findings), and these are much like SARS and MERS diseases [5,9]. The nucleotide sequence of the 2019-nCoV genome is very similar (88%) with both bat-SL-CoVZC45 and bat-SL-CoVZXC21 genomes. In addition, the phylogenetic analysis revealed that the similarity of its genome with both SARS-CoV-1 and MERS-CoV is 79% and 50%, respectively [10]. SARS-CoV-2 is a highly contagious virus and rapidly spread worldwide. In March 2020, the World Health Organization announced the COVID-19 pandemic, and nowadays more than 13 million cases are infected by this virus [11]. Despite the rapid spread of the virus, so far there is no vaccine or drug approved by the Food and Drug Administration (FDA) against COVID-19 [12]. The lack of a protective vaccine and yet the need to avoid of spread of virus has been led to use of alternative strategies such as convalescent plasma therapy (CPT) for the treatment of patients [13]. Historically, passive immunisation is as one the therapeutic protocols against infectious agents, and first was used in 1880s [14]. In passive immunisation, the individuals who recover from an infectious disease are investigated, and the convalescent plasma (CP) with high titres of neutralising antibodies is used for other similar patients, so that leads to reduce the clinical sings, treatment duration and mortality rate [15]. As per review of literature, CP has been used for treating diseases such as diphtheria, Spanish influenza, Ebola, West Nile fever, SARS and MERS, and has been satisfactory results in amelioration and reduction of mortality rate [16–20]. Owing to advantages such as clinical efficacy, viral therapy, reducing death and low side effects, CPT is considered as a suitable therapeutic option in complications such infectious diseases, immune deficiencies, allergies and autoimmune diseases [14,21,22]. Furthermore, based on studies, it is demonstrated that CP has the satisfying results in improving and increasing the survival of COVID-19 patients [23]. CPT is one of the most reliable therapeutic options during the outbreaks of infectious agents, in particular in the absence of the appropriate vaccine [13]. Recently, FDA has announced that CP can be used as a trustworthy way in cases of widespread outbreak of COVID-19 [24]. In the present meta-analysis, we fulfilled a comprehensive evaluation study about the effects of CP on clinical improvement, increase of discharged cases, as well as reducing mortality of infected patients by viruses SARS-CoV-1, MERS-CoV and SARS-CoV-2.

Methods

Search strategy

Comprehensive systematic search was conducted independently by two authors (MK1 and MK2) using several databases including PubMed, Scopus, Embase, Cochrane library, Google scholar, medRxiv and bioRxiv. Our search strategy was based on MeSH and using keywords such as "convalescent plasma", "COVID-19", "SARS-CoV-1", "MERS-CoV", "SARS-CoV-2" and "Coronavirus". Next, we retrieved all relevant articles (up to August 2020) about the evaluation of CP effect on infected patients by SARS-CoV-1, MERS-CoV and SARS-CoV-2.
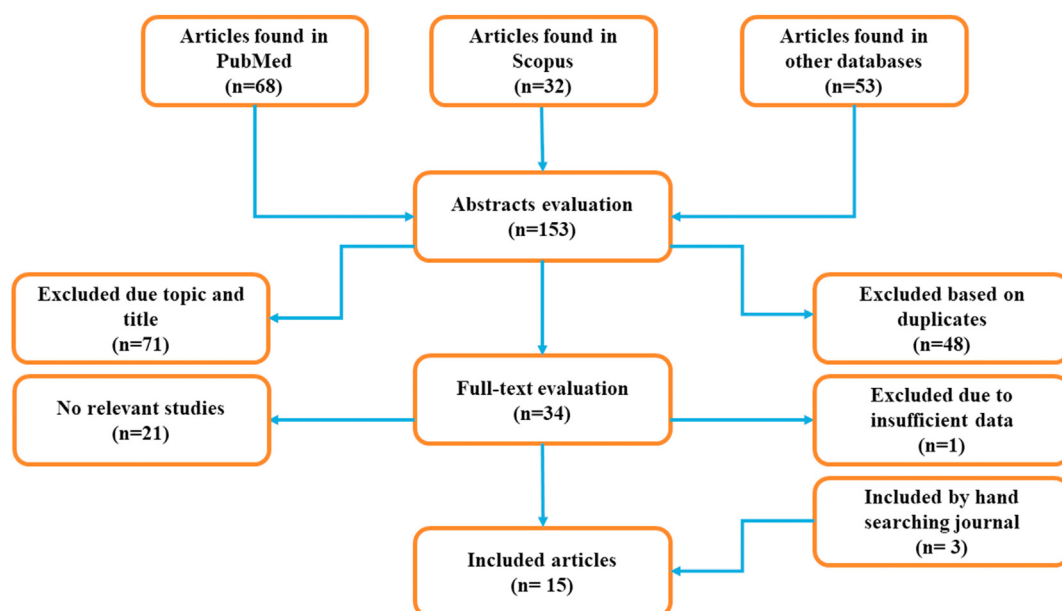
FIG. 1. The flowchart of search strategy.

The inclusion criteria were as follows: 1) articles containing the characteristics such as clinical improvement, viral therapy, mortality rate, the number of discharged cases and adverse event rate, in CP therapy patients; 3) patients infected by SARS-CoV-1, MERS-CoV and SARS-CoV-2; 3) articles containing the full text; 4) English articles. Also, duplicate studies were considered as exclusion criteria (Fig. 1). We reviewed all potentially relevant articles, and finally disagreements were resolved through discussion.

Quality assessment and data extraction

The Joanna Briggs Institute critical appraisal checklist was used for the evaluation of included studies. The main findings and characteristics of included studies include first author, country, viral aetiology, number of patients, CP dosages, outcome endpoint, number of improved patients, number of death, viral therapy rate, adverse event rate, number of cases weaned from the mechanical ventilation, number of discharged cases, therapeutic received drugs and reference number. The information is summarised in Table 1 [25–39]. The process of extracting the required data was also performed by both authors (MK1 and MK2).

Quantitative synthesis

Using the Comprehensive Meta-Analysis software version 2.2 (Biostat, Englewood, NJ, USA), the pooled data analysis was performed. In the present study, the cases who had received CP therapy were evaluated from aspects such as clinical improvement, discharged from hospital, weaned from mechanical ventilation, viral therapy, adverse events and mortality rate. For assessing the mentioned information, we used from event rate with 95% confidence intervals (CIs). Also, for evaluating, the clinical efficacy of CP therapy was used from the odds ratio (OR) with 95% CIs as well. Using the random-effects model, the pooled OR was estimated. It is noteworthy that, based on the Dersimonian and Laird method and random-effects model, the high heterogeneity cases included I^2 index >25% and Cochrane Q test p value $\leq$ 0.05.

Results

In the present meta-analysis, from all fifteen studies (5240 participants), eight studies were on SARS-CoV, while the other two and five were about MERS-CoV and SARS-CoV-1, respectively. The studies had been conducted in four countries China, Korea, Taiwan and the United States (USA). From all of the infected patients, 5151 were infected by SARS-CoV-2, while four patients were infected by MERS-CoV, as well as eighty-five were infected by SARS-CoV-1. The patients had received 200-900 mL of CP in addition to medication with steroids, antibiotics, anti-fungi drugs and also anti-viral drugs containing lopinavir/ritonavir, favipiravir, IFN-alpha 1b, arbidol, darunavir, ribavirin, remdesivir and peramivir. However, the parameters such as IgG titre, therapeutic regimens, disease status and outcome endpoint varied in different patients.

Overall, the results indicate that the CPT has good clinical effects on the patients infected by CoVs (SARS-CoV-1, MERS-CoV and SARS-CoV-2). Except for antiviral effects, the recovery rate in patients that had received CP was satisfying; adverse events or even mortality rate was low as well. The statistical analysis showed that clinical improvement in the group of patients who received CP significantly increased compared with the control group (OR: 2.23; 1.12-4.45 with 95% CIs; p value: 0.022; Q-value: 6.11; I^2: 83.64; Eggers p value: 0.064; Beggs p value: 0.093). Furthermore, discharge rate of patients from hospital in the group that were received CPT had increased (OR: 2.92; 1.48-5.77 with 95% CIs; p value: 0.002; Q-Value: 4.32; I^2: 53.80; Eggers p value: 0.32; Beggs p value: 0.50).

In the subgrouping analysis, we determined the efficacy of CPT in each patient separately. The statistical analysis on the eighty-five patients infected by SARS-CoV-1 demonstrated that the parameters such as clinical improvement, weaning from mechanical ventilation and discharging from the hospital in patients under the CPT significantly had increased (Table 2). On the other hand, the rate of mortality had a significant decrease in patients who had received CP compared with the control group (OR: 0.077; 0.004-1.497 with 95% CIs; p value: 0.090; Q-value: 0.00; I^2: 0.00; p value: 1.00).

In the group infected by MERS-CoV, we analysed the information of four patients. Although owing to the low sample size, we did not achieve significant results; however, using CPT had satisfying results in improving the clinical manifestations (Table 2). Interestingly, statistical analysis of information of 5151 COVID-19 patients confirmed the efficacy of CPT during the treatment. Improvement of clinical symptoms in patients who had received CP was more compared with the control group, although we observe the significant changes (OR: 1.66; 0.78-3.53 with 95% CIs; p value: 0.183; Q-value: 2.613; I^2: 61.72; p value: 0.106). Negative virus test for this disease in recipients of CP had the meaningful change (OR: 2.59; 1.65-3.52 with 95% CIs; p value: 0.001; Q-value: 0.67; I^2: 0.00; p value: 0.41). To discharge the patients in this group significantly increased as well (OR: 2.02; 0.94-4.35 with 95% CIs; p value: 0.07; Q-value:

TABLE 1. Characteristics of included studies

First author	Country	Viral Etiology	Patients	CP dose	Outcome endpoint	Clinical improvement	Death	Viral therapy	Adverse event	Weaned ventilation	Discharge	Drugs	Ref
Li	China	SARS-CoV-2	52 case 51 control	S-RBD−IgG 1:640 200 ml	28 days	27/52 22/51	15.7% 24%	87.2% 37.5%	2/0	NA	51% 36%	Antiviral, antibacterial, antifungal, interferon, steroids	[25]
Shen	China	SARS-CoV-2	5	IgG (1:1000) 200-250 ml	12 days	3	0	5	NA	3	3	Lopinavir/ritonavir, favipiravir, interferon alfa-1b, arbidol, darunavir	[26]
Joyner	USA	SARS-CoV-2	5000	IgG 500 ml	7 days	NA	602	NA	36	NA	NA	NA	[27]
Zeng	China	SARS-CoV-2	6/15	IgG 300 ml	22 days	6	5/6 14/15	6/3	0	NA	1/1	NA	[28]
Ahn	Korea	SARS-CoV-2	2	IgG 500 ml	26 days	2	0	2	0	2	2	Lopinavir/ritonavir, hydroxychloroquine, methylprednisolone, antibiotics	[29]
Ye	China	SARS-CoV-2	6	IgG 400-600 ml	33 days	5	0	2	0	NA	3	Arbidol, levofloxacin	[30]
Zhang	China	SARS-CoV-2	4	IgG 200-400 ml	NA	4	0	4	0	2	4	Arbidol, lopinavir-ritonavir, interferon alpha	[31]
Duan	China	SARS-CoV-2	10	IgG 1:640 200 ml	20 days	10	0	7	0	3	10	Arbidol, remdesivir, ribavirin, peramivir, antibacterial	[32]
Ko	Korea	MERS-CoV	3	IgG 1:80	3 days	3	0	2	NA	3	3	NA	[33]
Chun	Korea	MERS-CoV	1	IgG 500 ml	NA	1	0	NA	1	NA	1	Ribavirin, lopinavir/ritonavir, interferon alpha	[34]
Wong	China	SARS-CoV-1	1	IgG 200 ml	NA	1	0	NA	0	NA	0	Cefotaxime, levofloxacin, oseltamivir, ribavirin	[35]
Yeh	Taiwan	SARS-CoV-1	3	IgG 1:640 500 ml	NA	3	0	2	NA	1	3	Lopinavir, ritonavir, methylprednisolone	[36]
Soo	China	SARS-CoV-1	19/21	IgG 600-900 ml	22 days	14/4	0/5	NA	0	NA	74% 19%	Ribavirin, methylprednisolone	[37]
Kong	China	SARS-CoV-1	1	IgG 500 ml	7 days	1	0	NA	NA	1	1	Steroids, antiviral	[38]
Cheng	China	SARS-CoV-1	40	IgG 600-900 ml	22 days	40	13	NA	0	NA	26	Cefotaxime, levofloxacin, ribavirin, prednisolone, methylprednisolone	[39]

TABLE 2. Summarised events rate

Viral etiology	Clinical improvement Event rate (95% CIs)	Clinical improvement Heterogeneity	Clinical improvement Publication bias	Death Event rate (95% CIs)	Death Heterogeneity	Death Publication bias	Virological cure Event rate (95% CIs)	Virological cure Heterogeneity	Virological cure Publication bias	Adverse event Event rate (95% CIs)	Adverse event Heterogeneity	Adverse event Publication bias	Weaned ventilation Event rate (95% CIs)	Weaned ventilation Heterogeneity	Weaned ventilation Publication bias	Discharge Event rate (95% CIs)	Discharge Heterogeneity	Discharge Publication bias
Total CoVs	66.5% (56.7-75) p value: 0.001	Q: 18.28 I^2: 39.85 p value: 0.075	Eggers p value: 0.04 Beegs p value: 0.50	12.2% (11.3-13.1) p value: 0.001	Q: 29.98 I^2: 59.98 p value: 0.003	Eggers p value: 0.34 Beegs p value: 0.25	13.1% (12.2-14.1) p value: 0.001	Q: 158.96 I^2: 93.70 p value: 0.001	Eggers p value: 0.001 Beegs p value: 0.46	1% (0.7-1.3) p value: 0.001	Q: 28.98 I^2: 68.94 p value: 0.001	Eggers p value: 0.001 Beegs p value: 0.10	49.7% (38.6-0.8) p value: 0.95	Q: 4.75 I^2: 0.00 p value: 0.57	Eggers p value: 0.24 Beegs p value: 0.18	52.3% (44.4-0.2) p value: 0.56	Q: 20.31 I^2: 45.85 p value: 0.041	Eggers p value: 0.081 Beegs p value: 0.15
SARS-CoV 1	81% (64.9-91.4) p value: 0.001	Q: 5.04 I^2: 40.52 p value: 0.169	Eggers p value: 0.14 Beegs p value: 0.50	27.7% (17.1-41.5) p value: 0.001	Q: 4.62 I^2: 35.15 p value: 0.020	Eggers p value: 0.002 Beegs p value: 0.50	66.7% (15.4-56.6) p value: 0.57	Q: 8.96 I^2: 5.00 p value: 0.1	Eggers p value: 0.76 Beegs p value: 0.50	1.7% (0.2-1.13) p value: 0.001	Q: 0.14 I^2: 0.00 p value: 0.70	Eggers p value: NA Beegs p value: NA	40.0% (10-80) p value: 0.65	Q: 1.15 I^2: 0.00 p value: 0.97	Eggers p value: NA Beegs p value: NA	67.9% (55.5-8.2) p value: 0.006	Q: 1.35 I^2: 0.00 p value: 0.71	Egger p value: 0.33 Beegs p value: 0.15
MERS-CoV	85.6% (41.6-98) p value: 0.10	Q: 0.02 I^2: 0.00 p value: 0.87	Eggers p value: NA Beegs p value: NA	14.4% (2-58.4)	Q: 5.04 I^2: 40.52 p value: 0.169	Eggers p value: 0.100 Beegs p value: NA	66.7% (15.4-95.7) p value: 0.57	Q: 0.00 I^2: 0.00 p value: 1.0	Eggers p value: NA Beegs p value: NA	26% (5-69) p value: 0.276	Q: 0.215 I^2: 0.00 p value: 0.643	Eggers p value: NA Beegs p value: NA	55.3% (12-91) p value: 0.845	Q: 2.698 I^2: 62.931 p value: 0.100	Eggers p value: NA Beegs p value: NA	85.6% (41-98) p value: 0.100	Q: 0.24 I^2: 0.02 p value: 0.876	Eggers p value: NA Beegs p value: NA
SARS-CoV 2	60.4% (48-71) p value: 0.082	Q: 10.141 I^2: 40.83 p value: 0.119	Eggers p value: 0.082 Beegs p value: 0.183	12.1% (11–13) p value: 0.001	Q: 12.147 I^2: 42.371 p value: 0.096	Eggers p value: 0.002 Beegs p value: 0.19	80.6% (69-88) p value: 0.001	Q: 9.153 I^2: 34.44 p value: 0.165	Eggers p value: 0.24 Beegs p value: 0.27	0.9% (0.7-1.2) p value: 0.001	Q: 18.391 I^2: 67.37 p value: 0.05	Eggers p value: 0.46 Beegs p value: 0.08	46.7% (26-68) p value: 0.77	Q: 2.70 I^2: 0.00 p value: 0.44	Eggers p value: 0.003 Beegs p value: 0.15	54.5% (43-65) p value: 0.44	Q: 9.514 I^2: 36.93 P value: 0.147	Eggers p value: 0.154 Beegs p value: 0.11

0.049; I^2: 0.00; *p* value: 0.824). As well as, based on statistical analysis results, CP could be significantly decreased the mortality rate in COVID-19 patients (OR: 0.311; 0.12-0.76 with 95% CIs; p-value: 0.011; Q-value: 0.009; I^2: 0.00; p-value: 0.923). The mentioned data are listed in Table 2.

Discussion

So far, several genera of family Coronaviridae such as 229E, OC43, NL63, HKU1, SARS-CoV-1 and MERS-CoV have been known; however, in 2019, a new genus of this family, SARS-CoV-2, was considered as the etiologic agent of COVID-19 [40,41]. The first outbreak of COVID-19 occurred in more than 800 health care workers in Wuhan, China; however, the disease rapidly was spread in other countries, in particular Thailand, Japan, South Korea and the USA [5,42,43]. Today, various studies have shown that some underlying factors such as old age, pregnancy, cancer, diabetes, hypertension, as well as AIDS are specifically considered for the fatal outcomes and severity of this disease [44]. At the moment, several drugs such as teicoplanin, hydroxychloroquine, remdesivir, lopinavir, oseltamivir, ribavirin, favipiravir and tocilizumab are used for the treatment of COVID-19 [10,45]. Currently, regarding the importance of COVID-19 on one hand, and lack of the protective vaccine or effective drug, on the other hand, COVID-19 convalescent plasma (CCP) therapy can be considered as one of the fundamental ways for the treatment of this disease [46]. Studies show that the transfusion of plasma from patients who have recovered from COVID-19 infection to other SARS-CoV-2-infected patients can be led to their treatment without the occurrence of severe adverse events [47]. As per a study that Shen et al. conducted on five critically ill patients, following plasma transfusion, body temperature normalised during 3 days in four patients, the viral load became negative within two weeks after CCP therapy in all patients, and also, and 3 patients were weaned from mechanical ventilation [26]. Ye et al. conducted a study on six COVID-19 patients who had been admitted to Wuhan Huoshenshan Hospital from 11th February to 12th March 2020, and among them, there was a patient with Sjögren syndrome as well. They observed that the treatment of patients with CP had satisfying outcomes in all of them. Although the exact mechanism of action of CPT is not understood, they proposed that the antibodies IgM and IgG can directly neutralise the SARS-CoV-2, and probably, the anti-inflammatory contents of CP prevent cytokine storms [48]. In another study, Ahn et al. estimated the viral load of two cases that were affected by COVID-19 and acute respiratory distress syndrome by rRT-PCR technique, before and after CPT. In both cases, the value of the cycle threshold (Ct) had changed, which indicated a reduction in viral load after CP transfusion. In case 1 Ct changed from 24.98 on day 10 to 33.96 on day 20 after plasma transfusion, and in case 2 Ct changed from 20.51 on day 5 to 36.33 on day 9 after plasma transfusion [29]. Li et al. (2020) realised that CPT could be led to the negative conversion of SARS-CoV-2 in PCR (OR: 11.39; 3.91-33.18 with 95% CIs; p-value: 0.01) [49]. Based on studies, the exception with itching or skin rash and sometimes the little increase in body temperature, so far no serious adverse events have been reported with CPT [50]. Our present study had several limitations including 1) low population sample size, 2) evaluating limit published articles till August 2020, 3) significant heterogeneity in some cases, 4) presence of publication bias, 5) inaccessibility to raw data to evaluate several variables such as non-uniform details on interactions of medications, comorbidities, risk factors, morbidity, complications and randomised data. However, further investigations are necessary to examine the clinical benefit of CPT in CoVs with more sample size as well as randomised controlled studies to reduce certain sources of bias.

Conclusion

Based on different studies, it seems that in the absence of full effective antiviral drug or vaccine, CPT is an appropriate alternative for the treatment of patients infected by CoVs. The results of the present meta-analysis showed a reasonable conclusion about the clinical efficacy of CPT against COVID-19. In this study, we showed that CPT can be considered as a candidate for treating the patients who were infected by CoVs. This therapeutic protocol is an effective solution for characteristics such as clinical improvement, weaning from mechanical ventilation, hospital discharge, viral treatment and also prevention of mortality.

Ethics approval and consent to participate

Not applicable (this article was provided based on research in global databases).

Consent to publish

Not applicable.

Availability of data and materials

All data generated or analysed during this study are included in this published article and its supplementary information files.

Transparency declaration

There is no conflict of interest among all authors.

Funding

We have not received any funding for this research.

Authors' contributions

1. MK1 has contributed to the design of the work and analysis of data.
2. MK2 has drafted the work and substantively revised it.

All authors read and approved the final manuscript.

Acknowledgements

Abbreviations

CoVs   Coronaviruses
SARS-CoV-2   Severe acute respiratory syndrome coronavirus 2
MERS   Middle East respiratory syndrome
2019-nCoV   2019 novel coronavirus
COVID-19   Coronavirus disease 2019
WHO   World Health Organization
FDA   Food and Drug Administration
CPT   Convalescent plasma therapy
CP   Convalescent plasma
JBI   Joanna Briggs Institute
CMA   Comprehensive Meta-Analysis
CIs   Confidence intervals
OR   Odds Ratio
USA   United States
ARDS   Acute respiratory distress syndrome

References

[1] Su S, Wong G, Shi W, Liu J, Lai AC, Zhou J, et al. Epidemiology, genetic recombination, and pathogenesis of coronaviruses. Trend Microbiol 2016;24(6):490−502.

[2] Zare H, Aryan E, Meshkat Z, Gheybi F, Neshani A, Ghazvini K, et al. Development of biosensors for the detection of COVID-19. Nanomed Res J 2021;6(1):11−6.

[3] Singhal T. A review of coronavirus disease-2019 (COVID-19). Indian J Pediatrics 2020:1−6.

[4] Fehr AR, Perlman S. Coronaviruses: an overview of their replication and pathogenesis. Coronaviruses. Springer; 2015. p. 1−23.

[5] Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020;395(10223):497−506.

[6] Lee N, Hui D, Wu A, Chan P, Cameron P, Joynt GM, et al. A major outbreak of severe acute respiratory syndrome in Hong Kong. N Engl J Med 2003;348(20):1986−94.

[7] de Groot RJ, Baker SC, Baric RS, Brown CS, Drosten C, Enjuanes L, et al. Commentary: Middle east respiratory syndrome coronavirus (mers-cov): announcement of the coronavirus study group. J Virol 2013;87(14):7790−2.

[8] Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med 2020.

[9] Chan JF-W, Yuan S, Kok K-H, To KK-W, Chu H, Yang J, et al. A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. Lancet 2020;395(10223):514−23.

[10] Yousefi B, Valizadeh S, Ghaffari H, Vahedi A, Karbalaei M, Eslami M. A global treatments for coronaviruses including COVID-19. J Cell Physiol 2020.

[11] Wilder-Smith A, Chiew CJ, Lee VJ. Can we contain the COVID-19 outbreak with the same measures as for SARS? Lancet Infect Dis 2020.

[12] Rojas M, Rodríguez Y, Monsalve DM, Acosta-Ampudia Y, Camacho B, Gallo JE, et al. Convalescent plasma in Covid-19: possible mechanisms of action. Autoimmun Rev 2020:102554.

[13] Marano G, Vaglio S, Pupella S, Facco G, Catalano L, Liumbruno GM, et al. Convalescent plasma: new evidence for an old therapeutic tool? Blood Transfus 2016;14(2):152.

[14] Shahani L, Singh S, Khardori NM. Immunotherapy in clinical medicine: historical perspective and current status. Med Clin 2012;96(3):421−31.

[15] Casadevall A, Pirofski L-a. The convalescent sera option for containing COVID-19. J Clin Invest 2020;130(4):1545−8.

[16] Luke TC, Hoffman SL. Blood products for Spanish influenza: a future H5N1 treatment? Ann Inter Med 2007;146(9):687.

[17] Mair-Jenkins J, Saavedra-Campos M, Baillie JK, Cleary P, Khaw F-M, Lim WS, et al. The effectiveness of convalescent plasma and hyper-immune immunoglobulin for the treatment of severe acute respiratory infections of viral etiology: a systematic review and exploratory meta-analysis. J Infect Dis 2015;211(1):80−90.

[18] Rojas M, Monsalve DM, Pacheco Y, Acosta-Ampudia Y, Ramírez-Santana C, Ansari AA, et al. Ebola virus disease: an emerging and re-emerging viral threat. J Autoimmun 2020;106:102375.

[19] Planitzer CB, Modrof J, Kreil TR. West Nile virus neutralization by US plasma-derived immunoglobulin products. J Infect Dis 2007;196(3):435−40.

[20] Jean S-S, Lee P-I, Hsueh P-R. Treatment options for COVID-19: the reality and challenges. J Microbiol Immunol Infect 2020.

[21] Sherer Y, Levy Y, Shoenfeld Y. IVIG in autoimmunity and cancer−efficacy versus safety. Expet Opin Drug Saf 2002;1(2):153−8.

[22] Katz U, Achiron A, Sherer Y, Shoenfeld Y. Safety of intravenous immunoglobulin (IVIG) therapy. Autoimmun Rev 2007;6(4):257−9.

[23] 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. J Clin Invest 2020;130(6):2757−65.

[24] Food U. Recommendations for investigational COVID-19 convalescent plasma. 2020.

[25] Li L, Zhang W, Hu Y, Tong X, Zheng S, Yang J, et al. Effect of convalescent plasma therapy on time to clinical improvement in patients with severe and life-threatening COVID-19: a randomized clinical trial. JAMA 2020;324(5):460−70.

[26] 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.

[27] Joyner MJ, Wright RS, Fairweather D, Senefeld JW, Bruno KA, Klassen SA, et al. Early safety indicators of COVID-19 convalescent plasma in 5000 patients. J Clin Invest 2020;130(9).

[28] Zeng Q-L, Yu Z-J, Gou J-J, Li G-M, Ma S-H, Zhang G-F, et al. Effect of convalescent plasma therapy on viral shedding and survival in patients with coronavirus disease 2019. J Infect Dis 2020;222(1):38−43.

[29] 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. J Kor Med Sci 2020;35(14).

[30] 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. J Med Virol 2020;92(10):1890−901.

[31] Zhang B, Liu S, Tan T, Huang W, Dong Y, Chen L, et al. Treatment with convalescent plasma for critically ill patients with severe acute respiratory syndrome coronavirus 2 infection. Chest 2020;158(1):e9−13.

[32] Duan K, Liu B, Li C, Zhang H, Yu T, Qu J, et al. Effectiveness of convalescent plasma therapy in severe COVID-19 patients. Proc Nat Acad Sci 2020;117(17):9490−6.

[33] Ko J-H, Seok H, Cho SY, Ha YE, Baek JY, Kim SH, et al. Challenges of convalescent plasma infusion therapy in Middle East respiratory coronavirus infection: a single centre experience. Antivir Ther 2018;23(7):617−22.

[34] Chun S, Chung CR, Ha YE, Han TH, Ki C-S, Kang E-S, et al. Possible transfusion-related acute lung injury following convalescent plasma transfusion in a patient with Middle East respiratory syndrome. Ann Lab Med 2016;36(4):393.

[35] Wong V, Dai D, Wu A, Sung J. Treatment of severe acute respiratory syndrome with convalescent plasma. Hong Kong Med J 2003;9(3):199−201.

[36] Yeh K-M, Chiueh T-S, Siu L, Lin J-C, Chan PK, Peng M-Y, et al. Experience of using convalescent plasma for severe acute respiratory syndrome among healthcare workers in a Taiwan hospital. J Antimicrob Chemother 2005;56(5):919−22.

[37] Soo Y, Cheng Y, Wong R, Hui D, Lee C, Tsang K, et al. Retrospective comparison of convalescent plasma with continuing high-dose methylprednisolone treatment in SARS patients. Clin Microbiol Infect 2004;10(7):676−8.

[38] Kong L. Severe acute respiratory syndrome (SARS). Transfusion and apheresis science. Off J World Apher Assoc: Off J Eur Soc Haemapheresis 2003;29(1):101.

[39] Cheng Y, Wong R, Soo Y, Wong W, Lee C, Ng M, et al. Use of convalescent plasma therapy in SARS patients in Hong Kong. Eur J Clin Microbiol Infect Dis 2005;24(1):44−6.

[40] Decaro N, Lorusso A. Novel human coronavirus (SARS-CoV-2): a lesson from animal coronaviruses. Vet Microbiol 2020:108693.

[41] Kakhki RK, Kakhki MK, Neshani A. COVID-19 target: a specific target for novel coronavirus detection. Gene Rep 2020;20:100740.

[42] Wang C, Horby PW, Hayden FG, Gao GF. A novel coronavirus outbreak of global health concern. Lancet 2020;395(10223):470−3.

[43] Haynes B, Messonnier NE, Cetron MS. First travel-related case of 2019 novel coronavirus detected in United States. 2020. press release, Tuesday, January 21, 2020.

[44] Sahu KK, Mishra AK, Raturi M, Lal A. Current Perspectives of convalescent plasma therapy in COVID-19. Acta Bio Medica: Atenei Parmensis. 2020;91(4).

[45] Ghazvini K, Karbalaei M, Keikha M. What are the clinical benefits of tocilizumab for COVID-19 patients? Evidence from available case-control studies. Le Pharmacien Hospitalier & Clinicien 2020.

[46] Xia X, Li K, Wu L, Wang Z, Zhu M, Huang B, et al. Improved clinical symptoms and mortality on severe/critical COVID-19 patients utilizing convalescent plasma transfusion. Blood 2020.

[47] Chen L, Xiong J, Bao L, Shi Y. Convalescent plasma as a potential therapy for COVID-19. Lancet Infect Dis 2020;20(4):398−400.

[48] 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. J Med Virol 2020.

[49] Li L, Zhang W, Hu Y, Tong X, Zheng S, Yang J, et al. Effect of convalescent plasma therapy on time to clinical improvement in patients with severe and life-threatening COVID-19: a randomized clinical trial. JAMA 2020.

[50] Tiberghien P, de Lamballerie X, Morel P, Gallian P, Lacombe K, Yazdanpanah Y. Collecting and evaluating convalescent plasma for COVID-19 treatment: why and how? Vox sanguinis. 2020.