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Convalescent plasma transfusion for the treatment of COVID-19: Systematic review

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Short running title: CPT treatment for COVID-19

ABSTRACT

Background

The recent emergence of COVID-19 pandemic has reassessed the usefulness of historic convalescent plasma transfusion (CPT). This review was conducted to evaluate the effectiveness of CPT therapy in COVID-19 patients based on the publications reported till date. To our knowledge, this is the first systematic review on convalescent plasma on clinically relevant outcomes in individuals with COVID-19.

Methods

PubMed, EMBASE and Medline databases were searched upto 19 April 2020. All records were screened as per the protocol eligibility criteria.

Results

We included 5 studies reporting CPT to COVID-19 patients. The main findings from available data are as follows: (1) Convalescent plasma may reduce mortality in critically ill patients (2) Increase in neutralizing antibody titers and disappearance of SARS-CoV-2 RNA was observed in almost all the patients after CPT therapy (3) Beneficial effect on clinical symptoms after administration of convalescent plasma.

Conclusions

Based on the limited scientific data, CPT therapy in COVID-19 patient appears safe, clinically effective and reduces mortality. Well-designed large multi center clinical trial

studies should be conducted urgently to establish the efficacy of CPT to COVID-19 patients.

Key words: convalescent plasma transfusion (CPT), COVID-19, SARS-CoV-2, neutralizing antibody

INTRODUCTION

The recent Coronavirus disease 2019 (COVID-19) epidemic developed into an unprecedented global public health crisis with significant humanitarian consequences. As of 19 April 2020, the World Health Organization (WHO) has been informed of 2241359 confirmed cases of COVID-19, with 152551 deaths (6.8 %) documented worldwide.[1]

The current treatment of COVID-19 caused by novel coronavirus SARS-CoV-2 has been limited to general supportive care, with provision of critical care as no approved therapies or vaccines are available.[2]

The clinical data for the studies involving COVID-19, are still scarce and limited to data from China, Spain, Italy, United States of America, Germany, France, The United Kingdom and other international registries. This will be a problem when predicting treatment outcomes.

Passive immunization therapy has been successfully used to treat infectious diseases back to the 1890s. An individual who is sick with infectious diseases and recovers has blood drawn and screened for particular microorganism neutralizing antibodies. Following identification of those with high titers of neutralizing antibody, convalescent plasma containing these neutralizing antibodies can be administered in individuals with specified clinical disease to reduce symptoms and mortality. Hence, Convalescent Plasma Transfusion (CPT) has been the subject of increasing attention, especially in the wake of large-scale epidemics.[3] It has recently been suggested by Food and Drug Administration (FDA) that administration and study of investigational CPT may provide a clinical effect for treatment of COVID-19 during the public health emergency.[4]

We conducted a systematic review to evaluate available data for the clinical effectiveness of convalescent plasma for the treatment of COVID-19. This will help to provide clinicians and scientists with an overview of scientific evidence on a potential treatment option and better clinical management of critically ill COVID-19 patients.

METHODS

Protocol and registration:

This systematic search was carried out in major electronic databases (PubMed, Embase and Medline) to identify available evidence providing Information on the CPT for treatment of COVID-19 in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA-P) guidelines.[5] Due to the urgency of the matter and anticipated long waiting period, we were not able to wait for registration of this systematic review protocol (PROSPERO Submission id number: 179739).

Eligibility criteria

Study designs:

Study designs from the selected publication reported CPT in COVID-19 patients included clinical trials such as randomized controlled trials, controlled clinical trials, prospective and retrospective comparative cohort studies, case-control studies; cross-sectional studies, case series, and case reports.

Intervention:

We included clinical studies involving assessment of CPT treatment for the COVID-19 patients.

Study population, timing, and setting:

Published literatures were identified between 1st December 2019 and 19th April 2020 using "convalescent plasma AND COVID-19" as search term without restrictions on the study type of setting.

Comparators:

There were no restrictions on the type of comparator in the studies.

Outcomes:

The outcome of interest was clinical effects, survival benefits, viral load & antibody titer status and adverse events.

Languages:

We included articles without considering any restriction of language to identify potential published studies.

Publication status:

We included articles published in scientific journals.

Information sources:

This systematic search was carried out in major electronic databases (PubMed, Embase and Medline) to identify available evidence providing Information on the CPT for treatment of COVID-19. In addition, we also searched the reference lists of selected studies.

Search strategy:

The results of our database searches and records identified from other sources were documented. Removal of duplicates were also done manually and depicted in a PRISMA flow diagram.

Study selection:

A study screen was done minimum of 2 authors from the search results spreadsheet, authors independently screened the titles and abstracts of studies using the inclusion criteria. Studies selected at title and abstract levels were further screened with the full text of the

article for eligibility to include in our review. The studies exploring preclinical trials such as in vitro trials and studies on animal models and in silico drug screens were excluded.

Data extraction and data items:

A pre-conceived data extraction sheet was used to extract data from selected eligible studies. Any consensus in case of disagreement was resolved by opinion of a third reviewer. The Extracted information included mortality, viral load, viral antibody titers, clinical benefits and adverse events. Outcomes were extracted in all data forms (eg, dichotomous and continuous) as reported in the included studies. The results of our databases search were documented and described in a PRISMA flow diagram (Figure 1).

Risk of bias in individual studies:

To reduce risk of bias two authors independently assessed the included studies. Overall risk of bias was judged as low risk, unclear risk, and high risk.

RESULTS

The search identified 110 sources. Following screening of titles and abstracts and removing duplicates, we evaluated eight articles in full text. Among these, we found five relevant articles (one pilot study, one preliminary communication, one novel report, one case report, one descriptive study).[6-10] Extracted details for 5 studies are presented in Table 1, including the country of study, number of patients, dosage of CPT, mortality, length of hospital stay during transfusion, critical care interventions, clinical outcome, viral load, and adverse events. The 5 studies include a total of 27 patients who received CPT therapies for COVID-19.

All studies but one (South Korea) were conducted in China. In five studies, the male patients (n=15) were larger in number than the female patients (n=12). The age of the patients across the different studies varied from 28 to 75. Comorbidity was observed in some patients who were given CPT including COPD/Bronchitis (n=2), Cardiovascular and cerebrovascular diseases (n=1), hypertension (n=7). Among hypertensive patients, one had mitral insufficiency, another one had chronic renal failure. In addition, one 63 year old

female patient presented with Sjogren syndrome. Another 31 years aged female COVID-19 patient was pregnant with a gestation period of 35 wk & 2 d.

DISCUSSION

CPT has a very long history of use in the treatment of infectious disease. Its use has been well documented during the outbreak of many diseases at various periods, including spanish Influenza A (H1N1) infections in 1915-1917,[11] severe acute respiratory syndrome (SARS) in 2003,[12] pandemic 2009 influenza A (H1N1),[13] avian influenza A (H5N1),[14] several hemorrhagic fevers such as Ebola,[15] and other viral infections. In addition, studies show convalescent plasma antibodies can limit the virus reproduction in the acute phase of infection and help clear the virus, which is beneficial to the rapid recovery of the disease.[16]

Previous reviews have stated that the CPT may be considered for critically sick COVID-19 patients based on the earlier reported studies.[17,18] In this systematic review of CPT to the covid-19 patients, we identified and critically evaluated 5 studies that described about 27 patients. All studies reported good outcome after CPT performance, but all were considered to have risk of bias owing to a combination of non-randomized evaluations, confounding, predictor description and poor methodological conduct for participant selection, dosage of CPT and duration of therapy. This heterogeneity did not permit us to perform a meta-analysis. However, the important strength of this study is a comprehensive search of published clinical study data abstraction. Our review is the first to summarize all such literature in humans with COVID-19.

CPT Dosage

The doses of CPT used as described by the different studies is varied. A Chinese pilot study showed a minimal use of a single dose of 200 mL convalescent plasma with neutralizing antibody titers >1:640. Another study by Bin Zhang et al. reported a maximum of 2400 mL of convalescent plasma administered to a 73 years old male patient. Due to variability of CPT doses in reports, the optimal dose of CPT for COVID-19 could not be determined. All 27 survivors received CPT between Day 6 and Day 50 after the onset of symptoms or admission to hospitals.

Antiviral, antibacterial/antifungal Medications addition to CPT

All 27 COVID-19 patients described in these 5 studies received more than one antiviral drug including CPT, in addition, 10 patients received antibacterial/antifungal drugs for co-infection.

ICU Admission, Mechanical Ventilation, Length of Stay

Most of the patients are considered critically ill who received ICU admission (n=21) and most of patients received mechanical ventilation during the CPT (n=14). However six patients received nasal cannula oxygenation in which three received HFNO and two received conventional LFNO. ARDS were reported in 17 patients in which 7 received ECMO during CPT. The length of stay was not specified but most studies revealed data of discharge from hospital (n=15).

Viral load and antibody titer levels after CPT

All 5 studies found that CPT significantly reduces the viral load and increase the level of neutralizing antibody over time. Viral loads also decreased and became negative between day 1 and 30 days after the CPT. Chenguang Shen et al described that IgG titers of the treated patients increased upto 145800 and the IgM titers also increased upto 145800 after CPT.

Clinical benefits

After receiving convalescent plasma transfusion, almost all the patients showed improvements of symptoms including their body temperature normalized, varying degrees of absorption of lung lesions, ARDS resolved, weaned from ventilation within 1 day to maximum of 35 days post transfusion.

Survival

All studies reported unanimously positive findings of zero mortality after patients received CPT in varying doses. However, it was not clearly determined that whether the high percentage of survival was due to the treatment of patients with multiple other agents

(including antiviral medications) or CPT treatment or a combinatorial/synergistic effect of both. Bin Zhang et al. referred that one patient (73/Male) was transferred to unfenced ICU for further treatment due to underlying diseases and multiple organ failure.

Severe adverse events & treatment complications

CPT was well tolerated by the participants in all studies. No fatality occurred in SARS CoV2-infected individuals administered with convalescent plasma. Duan et al. mentioned a minor side effect of evanescent facial red spot in one patient administered with convalescent plasma but it was very minimal with no adverse events.

Limitations

A lack of high-quality RCT studies and relevant literature paucity limited our analyses. All the reported studies were predominately case reports or series, had no proper control groups and had a moderate to high risk of bias.

CONCLUSION

There is a compelling need to control the greatest global health crisis by COVID-19 outbreak. Currently there is no reliable therapeutic options for critically ill COVID-19 contracted patients. Based on the consolidated clinical data derived from 5 independent studies of 27 patients suggests, in addition to antiviral/antimicrobial drugs, CPT could be an effective therapeutic option with promising evidence on safety, improvement of clinical symptoms and reduced mortality. We recognize that a definitive conclusion cannot be drawn on optimal doses and treatment time point for the CPT to COVID-19, a large multicenter clinical trials are urgently needed to tackle this pandemic.

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Conflicts of interest

All authors declare no conflict of interest.

Authors' contribution

KR conceived the content, retrieved the data, wrote the manuscript and approved the final version. KN retrieved the data and approved the final version. JaR, JeR retrieved the data, wrote the manuscript. MN, AR helped in data extraction, revised the manuscript critically and approved the final version.

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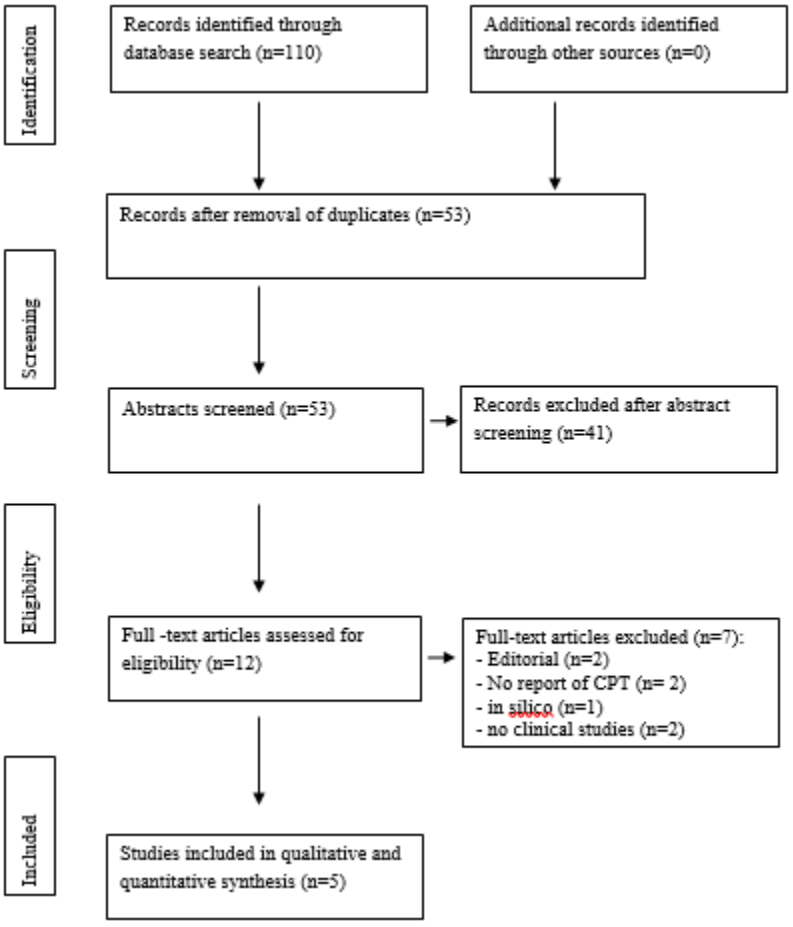
Figure

Figure 1. PRISMA Flow chart of study selection.



Table

Table 1: The efficacy and safety of Convalescent plasma transfusion (CPT) in patients with COVID-19

Author	Country	Study period	Study Population	CPT Dosage	Antiviral, antimicrobial drugs	Administrated day	Status during CPT	Outcome	Viral load	Severe adverse events & treatment complications
Duan et al.	China	January 23, 2020 to February 19, 2020	10, 6M:4F, Age ($\tilde{x}$ - 52.5 yrs), Cardiovascular and/or cerebrovascular diseases and HTN (n=4).	200 mL within 4 hr, antibody titer >1:640	arbidol or/and remdesivir/ ribavirin/peramivir (n=9), ribavirin (n=1), Antibacterial/antifungal for coninfecion (n=8)	Onset to CPT ($\tilde{x}$ - 16.5 d)	All at ICU, Mechanical ventilation (n=3), HFNO (n=3), Conventional LFNO (n=2)	Clinical symptoms, paraclinical improved, Increase of oxyhemoglobin saturation within 3 d, CP well tolerated, increase/ maintain the neutralizing	Viral load undetectable (n=7), Neutralizing antibody increased rapidly up to 1:640 (n=5), maintained at	No severe adverse effects, Evanescent facial red spot (n=1)

								antibodies, Varying degrees of absorption of lung lesions within 7 d.	a high level (1:640) (n=4)	
Chenguang Shen et al	China	January 20, 2020, to March 25, 2020	5, Age (range, 36-73 yrs), 3M:2F HTN; mitral insufficiency (n=1)	400 mL of CP in 2 doses on the same day, antibody titer >1:1000	interferon alfa-1b + Lopinavir/ritonavir (n=4) + favipiravir (n=1), arbidol + darunavir + Lopinavir/ritonavir (n=1)	After admission between 10 and 22 d	All 5 critical severe ARDS on mechanical ventilation, ECMO (n=1)	Temp normalized within 3 d (n=4), SOFA score decreased, and PAO2/FIO2 increased within 12 d (range, 172-276 before and 284-366 after), Neutralizing antibody titers increased (range, 40-60 before and 80-320 on 7th d),	Decreased and became negative with in 12 d	No severe adverse effects

								ARDS resolved (n=4) at 12 d, Weaned from mechanical ventilation (n=3) within 2 weeks		
Bin Zhang et al.,	China	February 16 2020 to March 15 2020.	69 yrs/F, HTN	900 ml in 3 doses	arbidol, lopinavir-ritonavir, interferon alpha	After admission 19th d	Critically ill invasive mechanical ventilation	Extubated and non-invasion ventilation was given on 34th d, Chest CT persistent absorption of consolidation, discharged on 44^{h} d.	Decreased 55 × 10^5 copies/ml (20th d) - 3.9 × 10^4 copies/ml (30th d) - 180 copies/ml (36th d). Negative (40th, 42th d).	No severe adverse effects

			55 yrs/M, COPD	200 ml	arbidol, lopinavir-ritonavir, interferon alfa-2b	After admission 12th d	Critically ill ARDS invasive mechanical ventilation	pO2 increased to 97 mmHg with OI of 198 mmHg in 1 d, All drugs discontinued except methylprednisolone, Chest images absorption of interstitial pneumonia (13th d – 17th d), Discharged on (19th d)	Negative (18th d)	No adverse reactions
			73yrs/M, HTN & chronic renal failure.	2400 ml in 8 doses	arbidol, lopinavir-ritonavir, oseltamivir, ribavirin, interferon alpha-2b	After admission 15th d	Critically ill Acute respiratory failure invasive mechani	Positive anti-SARS-CoV-2 IgG (26th d). Chest x-rays absorbed infiltrative lesions but	Negative (45th d, 46th d)	No adverse reactions

							cal venti latio n in V-V EC MO	pneumot horax, Serum IgM level decrease d to normal range (45th d, 46th d), Transferr ed to unfenced ICU for underlyi ng diseases, multiple organ failure (50th d)		
			31yrs/ F, pregn ant (35 wk & 2 d)	30 0 ml	lopinavir-ritonavir and ribavirin, Imipenem, vancomycin for coinfection	After admis sion 19th d	Criti cally ill ARD S, invas ive mec hani cal venti latio n in V-V EC MO	Remove d CRRT, ECMO (27th d), anti-SARS-CoV-2 IgM changed from positive to weakly positive to negative, anti-SARS-CoV-2 IgG was	Neg ative (40th d, 43th d),	No adver se reacti ons

								persistently positive (35th d 37th d), Chest CT showed near-complete absorption of opacities. Trachea cannula removed, nasal oxygen given (40th d), Discharged (46th d)		
Jin Young Ahn et al.	South Korea	February 22 2020 and March 6 2020	71yrs/M	500 mL in 2 doses at 12 hrs interval	hydroxychloroquine, lopinavir/ritonavir	After admission 10th d	Severe ARDS, mechanical ventilation,	Weaned from the mechanical ventilator, underwent a tracheostomy	Ct changed 24.98 (10th d) - 33.96 (20th d), Negative (after 26th d)	No adverse reaction

			67 yrs/F, HTN			After admission 6th d		Extubated and discharged on 24th d.	Negative (after 20th d). Ct changed 20.51 (5th d) - 36.33 (9th d)	
Mingxiang Ye et al.	China	February 11 2020 to March 18 2020	69/M	600ml in 3 doses	arbidol, levofloxacin	After symptom 33th d	Myalgia, Chest CT - patchy areas of GGOs	Symptoms improved, GGOs resolved 37th d, Cured and ready to discharge	Negative	No adverse reaction
			75/F	400ml in 2 doses	arbidol,		Fatigue, shortness of breath, oxygen therapy	Symptoms improved, alleviation of respiratory distress,	Negative	

							through nasal catheter, respiratory distress, Multiple consolidation	two-fold increase in IgM and IgG titers, consolidation gradually reduced, turned into scattered GGOs, Cured and under further clinical monitoring		
			56/M, Bronchitis	600ml in 3 doses			Fever, non-productive cough, shortness of breath, Chest CT - Multiple GGOs,	Symptoms improved, complete resolution consolidation,gradually resolution of GGOs, IgM and IgG titers increased,	Not mentioned	

							retic ular opac ities and fibro sis strea k,	Discharg ed		
			63/F Sjogr en syndr ome	20 0m l		After sympt om 40th d	Feve r, coug h, short ness of breat h, decr ease d exer cise toler ance, Ches t CT - Mult iple GG Os with cons olida tion and fibro sis strea k	Sympto ms improve d, GGOs tended to reduce, anti-SARS-CoV-2 IgM and IgG, Discharg ed 46th d	Neg ative 41th d	

			28/F	200ml		After symptom 33th d	Fatigue and myalgia, other symptoms	Discharged 39th d	Negative	
			57/M	200ml		After symptom 50th d	Fever, cough, shortness of breath and myalgia, Chest CT - Extensive bilateral GGOs, respiratory distress	Symptoms improved, GGOs resolved, discharged 54th d		

Abbreviations:

LFNO: low-flow nasal cannula oxygenation, HFNC: high-flow nasal cannula oxygenation, COPD:chronic obstructive pulmonary disease, HTN: hypertension