Research Article

Safety of convalescent plasma to treat COVID-19: Systematic review

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Abstract

Background: Currently, Coronavirus disease (COVID-19) was reported in more than 204 countries. As of April 10, 2020, a total of 1,605,729 confirmed cases and 95,766 deaths had been reported worldwide. There are no approved specific antiviral agents targeting the novel virus. Convalescent plasma transfusion might be effective against the infection. Food and Drug Administration (FDA) has also approved the emergency use of investigational COVID-19 convalescent plasma to treat severely ill COVID-19 patients.

Objective: The aim of this study was to systematically review disease outcome and safety of convalescent plasma to treat COVID-19.

Method: We searched literature published in English from December 20 /2019 to April 10/2020 on electronic databases. Using R software we have conducted a systematic analysis, frequency, mean, standard deviation, and chi-square test.

Result: The average age of the participants in the included was 55.7 with a standard deviation of 13.9. The average days of recovery or test negative for the COVID-19 PCR test after convalescent plasma therapy were 9.6 days (95% CI 2- 30 days). About 43% (9/21) had a history of comorbidity. The average date of recovery of patients with co-existing chronic diseases infected by COVID-19 after convalescent plasma therapy was about 12 days relatively prolonged than patients without the co-existing disease (7.6 days). No series adverse effects have been demonstrated in patients who have received convalescent plasma transfusion.

Conclusions: This study indicated that convalescent plasma transfusion might be a potential treatment for critically ill patients with COVID-19 pneumonia. It could be helpful to reduce the risk of mortality of critically ill patients. We demonstrated no serious adverse reactions associated with the transfusion of convalescent plasma.

Background

The Severe Acute Respiratory Syndrome coronavirus 2 (SARS-CoV-2) is a novel strain of coronavirus that was first detected in the city of Wuhan, China [1,2]. It was named as coronavirus disease 2019 (COVID-19) by World Health Organization (WHO) [3,4]. The outbreak SARS-CoV-2 was named as a pandemic disease by WHO on March 11, 2020. Currently, the disease was reported in more than 204 countries. As of April 10, 2020, a total of 1,605,729 confirmed cases and 95,766 deaths had been reported worldwide [5]. Currently, due to an alarmingly spreading of the virus worldwide, the incidence and deaths are increasing. However several efforts made to treat COVID-19, there are no approved specific antiviral agents targeting the novel virus, and no vaccines have been fully tested for safety and efficacy while some drugs are still under investigation.

Convalescent Plasma (CP) therapy is an immunotherapy that has been applied to the prevention and treatment of many infectious diseases for more than one century. So, the use of convalescent plasma is not a new method rather it was used for poliomyelitis [6], measles [7], mumps [8], and influenza [9], Severe Acute Respiratory Syndrome (SARS), several hemorrhagic fevers such as Ebola, and other viral infections treatments [10]. Even more recently during H1N1 influenza virus pandemics in 2009–2010, convalescent serum antibody preparations obtained by apheresis were used to treat individuals with severe H1N1 infection requiring intensive care [11]. This was the baseline lesson for convalescent plasma to treat COVID-19.

Plasma from people who have recovered from COVID-19 may contain antibodies to the virus that causes the disease and might be effective against the infection [12]. Food and Drug Administration (FDA) has also approved the emergency use of investigational COVID-19 convalescent plasma to treat severely ill COVID-19 patients [12]. The general principle of passive antibody therapy is that it is more effective when used for prophylaxis than for treatment of disease [13]. When used for therapy, the antibody is most effective when administered shortly after the onset of symptoms [14]. So it is required to evaluate the effectiveness of convalescent plasma therapy. So this study planned to conduct systematic analysis of literatures on Convalescent plasma treatment in severely ill COVID-19 patients.

Objective

The main aim of this study is to systematically review the safety of convalescent plasma to treat COVID-19.

Materials and methods

Types of participants

The study population of interest was human subjects of any age or sexes who were hospitalized or were in ICU with COVID-19 infection. The intervention of interest was convalescent plasma transfusion. Outcomes of disease progress after Convalescent therapy that was extracted from included studies was used predict the clinical effectiveness of therapy.

Search strategy

We searched literatures published in English from December 20 /2019 to April 10/2020 on electronic data bases PubMed, Cochrane library, EMBASE, Escopus, Hinari, CINAHL, Open Access Journals (OAJ) and Google scholar, for studies conducted trial of convalescent plasma treatment of COVID-19. We simultaneously searched reference lists of all recovered articles for potentially eligible studies. All identified keywords, and mesh terms were combined using the "OR" operator and "AND" operator for searching literatures. Keywords used in the search included were those that explain infection of severe acute respiratory syndrome 2 (SARS CoV 2) (i.e., COVID-19, severe acute respiratory syndrome 2, SARS CoV 2, novel corona virus). Full-text articles were retrieved after review of the title and abstract.

Inclusion and exclusion criteria

Inclusion criteria: All studies published in English from December 20 /2019 to April 10/2020 were included in the review. There was no restriction to study design made.

Data extraction

Data were extracted from included study by two investigator (EA, and KD) using a standardized data extraction form. Then the extracted data were merged together for systematic analysis. Primary outcomes extracted from each study were, the citation details, sample size, number of cases, year of publication, location of study, method of identification of COVID-19. Secondary outcomes for this study included clinical data including the stage of disease, treatment received, co-morbidities, co-infection, and dates of recovery after convalescent plasma transfusion, progress opacities in the lung.

Statistical analysis

The R software was used to conduct systematic analysis, frequency, mean, standard deviation, and chi-square test.

Results

Identified studies

Following the initial search of data bases four eligible studies have been accessed and were reviewed by the authors. Following methodological quality assessment, all 4 articles were eligible [15-18] and included in this systematic review and meta-analysis. In the included studies the total of 21 patients infected with COVID-19 were obtained convalescent plasma therapy. All 4 papers were published in English.

Characteristics of included study

Of the 4 studies included in the Systematic review and Meta-analysis, all studies reported the detail case report of COVID-19 patients. All patients were severely ill and were put to Intensive Care Unit (ICU) (Table 1). All 4 studies included in the systematic review and Meta-analysis, infections of COVID-19 were examined using PCR which is of high quality diagnostic method. Most of the studies conducted are of higher quality because of method of diagnosis using highly sensitive and specific PCR techniques.

Systematic analysis outcome

The average age of the participants in the included was 55.7 with standard deviation of 13.9. From a total of 21 patients 12 of them were male. The average days between admissions to start of convalescent plasma therapy was 10 ± 4.5 days and the average days of recovery or test negative for CIVID-19 PCR test after convalescent plasma therapy was 9.6 days (95% CI 2- 30 days). About 43% (9/21) had history of comorbidity and about 24% (5/21) have co-infections, while 19% (4/21) patients are have both history of co-existing disease and co-infections (Figure 1).

Common sign and symptoms and complications of in patients of COVID-19

In this systematic review the most common symptoms at disease onset were fever, cough with clear sputum, and shortness of breath, while less commonly observed sign and symptoms were; chest pain, sore throat, myalgia and arthralgia (Figure 2). Majority of complications observed in the study participants were severe acute respiratory distress (85.7%), pneumorrhagia, cystorrhagia and gastrointestinal bleeding, myocardial damage, and cardiac dysfunction.

Co-morbidity, co-infection and rate recovery of patients with COVID-19 after treatment by CP

According to data of systematic review and meta-analysis

Table 1: Characteristics of patients in the included study.

Author	Age	sex	CPT	History of comorbidity	co-infection	days from CPT to negative viral test	Treatment received	Complication
patient 1	69	F	900ml	hypertension	Bacteria and fungi	21	arbodol, lopinavir-ritonavir, interferon alpha inhalation	bloody sputum
patient 2	55	M	200ml	None	None	8	arbidol, lopinavir-ritonavir, interferon alfa, methylprednisolone	
patient 3	73	M	2400ml	hypertension & chronic renal failure	aspergillus infection	30	arbidol, lopinavir-ritonavir, interferon alfa, oseltamivir, ribavirin	pneumorrhagia, cystorrhagia and gastrointestinal bleeding
patient 4	31	F	300ml	pregnancy	Gram-positive bacteria bacteremia	16	lopinavir-ritonavir, ribavirin,	Cardial dysfunction
patient 5	70	M	400ml	None	Bacterial pneumonia	14	Lopinavir-ritonavir; interferon alfa; favipiravir, Methylprednisolone	Severe ARDS; MODS
patient 6	60	M	400ml	Hypertension; mitral insufficiency	Bacterial pneumonia, fungal pneumonia	15	arbodol, lopinavir-ritonavir, darunavir, Methylprednisolone	Severe ARDS; myocardial damage
patient 7	50	F	400ml	None	None	13	Lopinavir-ritonavir; interferon alfa, Methylprednisolone	Severe ARDS
patient 8	30	F	400ml	None	None	12	Interferon alfa, favipiravir, Methylprednisolone	Severe ARDS
patient 9	60	M	400ml	None	None	12	Interferon alfa, favipiravir, Methylprednisolone	Severe ARDS
patient 10	71	M	500ml	None	None	16	hydroxychloroquine, Lopinavir-ritonavir, methylprednisolone	Severe ARDS
patient 11	67	F	500ml	hypertension	None	15	hydroxychloroquine, Lopinavir-ritonavir, methylprednisolone	Severe ARDS
patient 12	45	M	200ml	Hypertension	None	2	Arbidol, Ribavirin	Severe ARDS
patient 13	34	F	200ml	None	None	3	Arbidol	
patient 14	42	M	200ml	Hypertension	None	2	Arbidol	Severe ARDS
patient 15	55	F	200ml	None	None	2	Ribavirin	Severe ARDS
patient 16	57	M	200ml	None	None	3	Arbidol, Remdesivir, Interferon-α	Severe ARDS
patient 17	78	F	200ml	None	None	3	Arbidol	Severe ARDS
patient 18	56	M	200ml	None	None	3	Arbidol	None
patient 19	67	M	200ml	Cardiovascular, cerebrovascular diseases	None	3	Arbidol, Ribavirin	None
patient 20	49	F	200ml	None	None	3	Arbidol, Oseltamivir, Peramivir	Severe ARDS
patient 21	50	M	200ml	Hypertension	None	6	Arbidol, Interferon-α	Severe ARDS

there was significant rate of recovery between patients with co-morbidity and patients without co-morbidity. Patients without co-existing chronic diseases infected by COVID-19 relatively recovered earlier than those who have co-existing disease after convalescent therapy. They test negative for COVID-19 PCR test after an average of 7.6 days. The average date of recovery of patients with co-existing chronic diseases infected by COVID-19 after convalescent plasma therapy was about 12 days. On the other hand patients with COVID-19 infection and who have both co-existing chronic diseases and co-infection relatively have prolonged time of recovery or require relatively long time to test negative for COVID-19 PCR test (Table 1).

Reduction of pulmonary lesions on chest X ray examinations

According to chest CTs, all patients showed different degrees of absorption of pulmonary lesions after convalescent plasma transfusion. With average range of 1-10 days after convalescent plasma therapy, a chest X-ray revealed further resolution of lung infiltrates which is from partial to persistent absorption of consolidation or absorption of interstitial pneumonia was observed.

Major anti-viral agents used for treatment of COVID-19

Most frequently used antiviral agents were Arbodol 62% (13/21), Lopinavir-ritonavir 43% (9/21), and Interferon alpha 43% (9/21) and the other antiviral drugs used were: Oseltamivir, Ribavirin, Favipiravir, Hydroxychloroquine, Remdesivir and Peramivir. In more than 76% (16/21) patients antiviral agents were discontinued due to gradual recovery of patients after convalescent plasma transfusion. The other treatment given for the patients was anti-inflammatory drug Methylprednisolone 71% (15/21)

Convalescent plasma adverse effects

None of the studies analyzed in this systematic review reported serious adverse events. During convalescent plasma transfusion to severely ill COVID-19 patients, no serious adverse effects were reported. Only one patient (1/21) showed minor facial red spot.
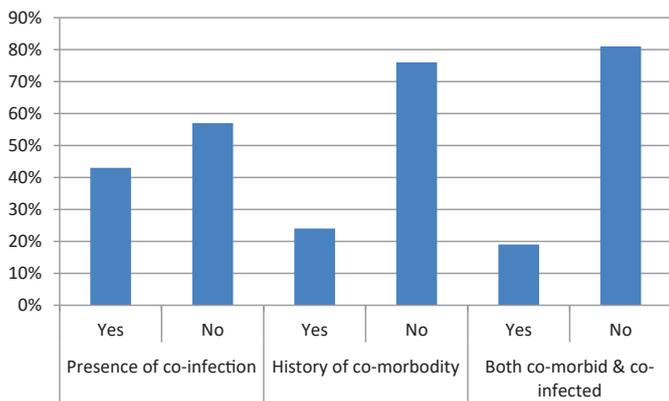
Figure 1: Presence of comorbidity and co-infection in patient with COVID-19.
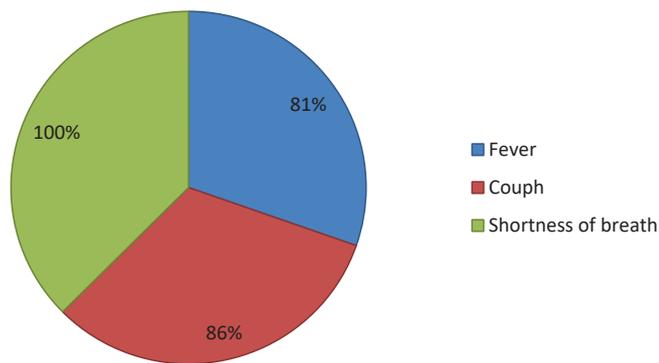

Figure 2: Most common clinical features for admission of COVID-19.

Discussion

The therapeutic benefits of convalescent plasma transfusion for infectious diseases began in the 20th century. Lesson learnt from proven effectiveness of convalescent plasma as a potential treatment of MERS-CoV, SARS-CoV and H5N1 influenza in the last decades (8, 9), can hold true that convalescent plasma transfusion can be an important optional treatment in patients with critical clinical disease stage in the absence of specific treatment of COVID-19 infection.

In this review we have demonstrated that there was significant difference of rate of recovery between patients with co-morbidity and patients without co-morbidity. Patients without co-existing chronic diseases infected by COVID-19 relatively recovered earlier than those who have co-existing disease after convalescent therapy.

Majority of complications observed in the study participants were severe acute respiratory distress, pneumorrhagia, cystorrhagia and gastrointestinal bleeding, myocardial damage, and cardiac dysfunction. This could be reason to death in patients infected by COVID-19.

According to data this systemic review to evaluate the clinical effects of convalescent plasma therapy after evidence recovery of patients, partial to persistent absorption of consolidation within the lung, ex-tubation of mechanical ventilation within

1–3 days of CPT showed that convalescent plasma can be a promising treatment option for severe COVID-19 patients.

As a limitation there is no well-designed study conducted to see effectiveness of convalescent plasma transfusion therapy we included systematic analysis of detail case reports of patients who have received convalescent plasma transfusion therapy for COVID-19 and the clinical outcome after transfusion. The other limitation is that this study is a systematic review of case series which does not have control.

Conclusions and recommendation

This study indicated that convalescent plasma transfusion might be a potential treatment for critically ill patients infected with COVID-19 and it can be helpful to reduce the risk of mortality of critically ill patients. We demonstrated no serious adverse reactions associated with the transfusion of convalescent plasma. This review suggests that convalescent plasma from patients who have recovered from COVID-19 infection might be an option to treat patients without causing severe adverse effects. Adequately assessing safety and efficacy of convalescent plasma therapy is essential. So, this study recommends that safety and efficacy of convalescent plasma transfusion in SARS-CoV-2-infected patients should be studied using well-designed clinical trial. The good outcome observed in critically ill patients; push us to recommend well organized trial of convalescent plasma transfusion in early infection before get in to critical illness stage.

Declarations

Availability of data and materials

All the datasets generated and analyzed during the review are included in this article.

Author's contribution

E. A, K. D, A. A and F. B designed the study, extracted, critically reviewed and analyzed data and wrote the first draft of the manuscript, and approved the manuscript.

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