

Rapid Review

Convalescent Plasma a Potential Therapy in Covid-19 Patients in Low Resource Setting

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Abstract

Background: The COVID-19 pandemic is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). At the time of writing, neither a cure nor a vaccine has been approved by the World health organization (WHO) for this disease. Given the fact that the severe acute respiratory syndrome coronavirus (SARS) and Middle East Respiratory Syndrome (MERS) viruses have a genetic sequencing similar to SARS-CoV-2, and since the use of convalescent plasma therapy (CP) has proved its efficacy in SARS and MERS virus infections, researchers are starting to focus more on it as a possible therapy for the COVID-19 disease. The main objective of this rapid review is to report and summarize the published evidence on the role of convalescent plasma therapy in the current COVID-19 pandemic.

Method: The PICO method was used to establish the review question. Moreover, papers were gathered from PubMed and Google scholar, critically appraised for the best evidence. Piersons 5-component scheme was used to check the quality of the review papers.

Results: After website screening: 10 papers in PubMed and 6 papers from Google scholars were retrieved. There were encouraging reports regarding the uses of CP in the previous viral outbreaks likes SARS and Ebola, yet there is still a doubt on the efficacy of this mode of therapy in the current COVID-19 pandemic.

Conclusion: CP is a very promising treatment approach for COVID-19 patients; however, more clinical trials are required to validate the effectiveness of this therapy.

Keywords: COVID-19, convalescent plasma therapy, SARS-CoV-2, therapy.

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1. Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), originating from Wuhan in China, has rapidly enveloped the world becoming a pandemic [1]. As of the 13th of April, 2020, there were 1,773,084 worldwide confirmed cases with 111,652 deaths as reported by the world health organization (WHO) [2]. The virus sequencing revealed a high similarity to SARS, making it the seventh virus discovered of this family. On the 11th of February, 2020, the WHO officially named the disease caused by this virus, COVID-19.

Many trials have assessed possible therapeutics and prevention methods for the disease. Nonetheless, to date, there are no drugs or vaccines specifically approved for the disease by the WHO [3]. Options of treatment such as antiviral drugs and corticosteroids are still under review by many agencies and are yet to be officially approved by the WHO [3, 4].

Serology testing of COVID-19 patients has revealed a notable rise in IgM antibodies in the acute setting, followed by rise in IgG antibodies as the patient entered the recovery phase. Therefore, many researchers have suggested using convalescent plasma from the recovered patient, and applying it as a passive antibody therapy for severe COVID-19 patients [5, 6]. Specific application of plasma therapy was similarly used during the EBOLA virus pandemic in 2014, when the WHO officially authorized the use of convalescent plasma as an empirical treatment therapy and published guidelines that specify the steps for donor selection, specimen collection and administration of this therapy to the Ebola infected patients [7]. Convalescent plasma therapy was also used successfully in managing diseases, caused by influenza virus and other pathogens [8, 9].

Closely related to the use of convalescent plasma therapy, is the use of monoclonal antibodies. The therapeutic potential of this mode of treatment has proved effective in the past in the treatment of many diseases. Some studies tested the effectiveness of monoclonal antibodies in vitro and in vivo against viral infections like SARS and MERS and they were found to yield positive results, yet like other types of treatment modalities, more clinical trials are needed to confirm the effectiveness of this method in the context of COVID-19 patients [10, 11].

When the patient is infected with a virus, his immune system starts to produce antibodies against the virus, which can later be harnessed in the form of convalescent plasma and transfused into a patient with a current infection, where it can neutralize and even induce antibody-dependent cellular cytotoxicity against the invading virus. This approach is usually used in conjunction with other antiviral and maintenance therapy [5, 12–16]. Mechanisms of convalescent plasma therapy illustrated in Fig 1.

CP therapy has been applied in clinical practice for a long time but its efficacy remains a point of debate between health professionals. Previous research proved this technique useful in the case of SARS1 and MERS infections, and since SARS-COV2 and SARS-COV1 and MERS viruses share clinical and genetic similarities, it is predicted that this type of therapy will have a good result in COVID-19 patients. Yet, some reports doubted the efficiency of this maneuver as the plasma will not be pure, and it may even contain other viral particles, which may cause patients to contract other diseases [17–19].

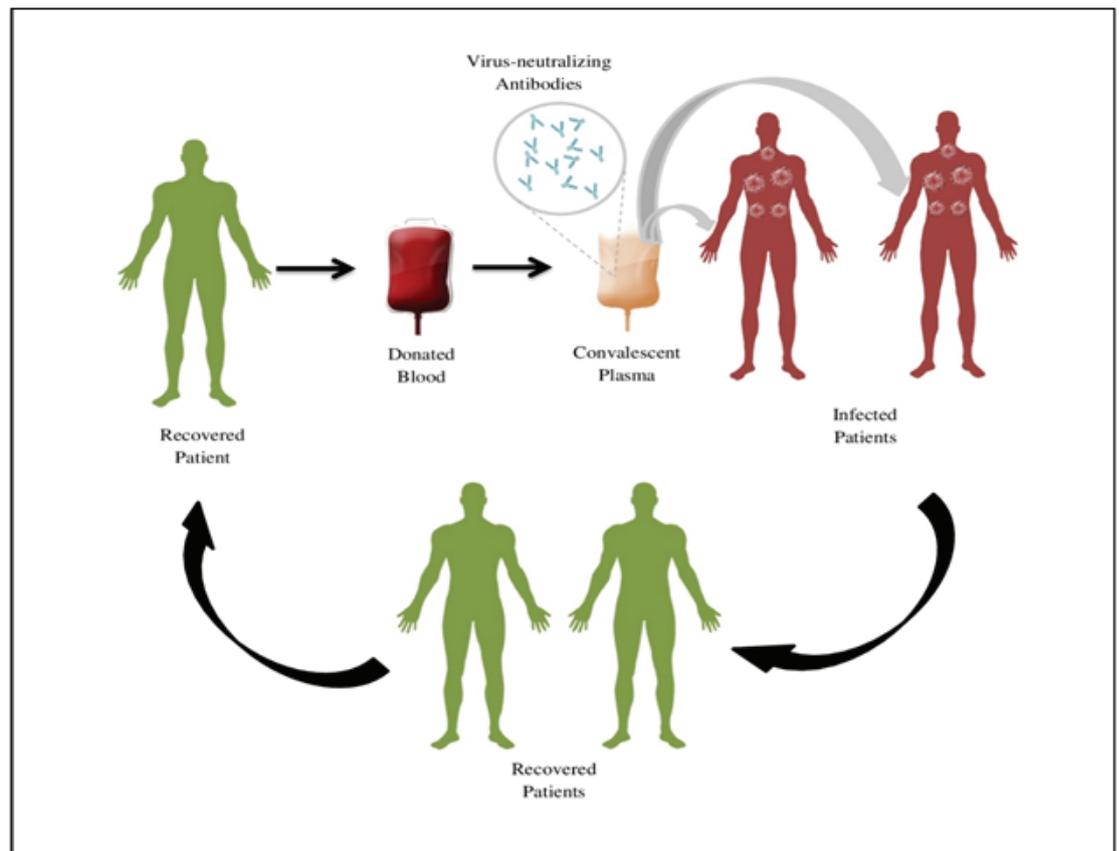


Figure 1: Mechanisms of convalescent plasma therapy (This image was created by author Mujahed I. Mustafa)

However, using antivirals may not be a cost-effective method for treatment in low income countries like Sudan, whereas plasma therapy extraction and preparation are more readily available and achievable in these countries making it a more reasonable choice of therapy [20]. The main objective of this rapid review is to clarify the conflicting evidence regarding the use of convalescent plasma therapy in COVID-19 patients, and to summarize the best evidence available.

2. Method

On the 10th of April 2020 the research databases PubMed, Google Scholar were screened for articles providing information on the use of convalescent plasma for the treatment of COVID-19 patients, (Fig.2). The inclusion criteria were any published (full text) articles written in English and all clinical study designs including case series. Furthermore, any articles published before 2019, and articles with no significant or duplicated information were excluded. Subsequently, reference lists of identified articles were searched to extract further relevant articles. Two reviewers conducted a detailed screening of the titles and abstracts. All authors independently performed full-text screening of identified articles and participated in the steps of manuscript preparation, writing and final revision. The PICO method was used to establish the review question in a standardized form (Table 1). The quality of each clinical report study was evaluated

using Piersons 5-component scheme, which composes of the following five components each with a score of zero to one (uniqueness, documentation, interpretation, objectivity, and educational value) with scores of 5 or less indicate of insufficient quality [21]

2.1. Data synthesis

The results were presented in a narrative format as the heterogeneity of outcomes and study designs made quantitative synthesis inappropriate.

TABLE 1: PICOS items: formation of the review question.

PICOS item	Description
Population	Patients with laboratory-confirmed SARS-COV-2 infection.
Intervention	Convalescent plasma therapy
Comparisons	Patients with COVID-19 disease who did not receive CP transfusion.
Outcome	Clinical outcomes of SARS-CoV-2 infection including but not limited to death, intensive care admission, ventilation, and SARS-CoV-2 viral shedding.

3. Results

A total of 16 articles were found after preliminary screening of the PubMed and Google Scholars databases. After title and abstract screening, a total of 9 articles were excluded. Full-text screening of the remaining 7 articles was conducted. Among these studies, after critical appraisal full-text screening, a total of 4 articles were included in the final review, all were published in respected journals. Three articles were excluded after full-text screen (1 review article, 1 letter to the editor, and 1one commentary) Fig 2. Details of studies included in this review are summarized in Table 2.

Pierson's assessment showed that the article produced by Duan *et al* [5] was the highest quality report with a score of 9 in comparison to only 8 in the other three reports (Shen *et al* [22], Jy Ahn *et al* [23], and Zhang *et al* [24]).

4. Discussion

Currently antiviral medication Remdesivir along with other antiviral drugs hold promising results in the fight against COVID-19. However, factors such as the high price and the unavailability of these medications in low resource setting countries coupled with the long time period needed to develop and test a vaccine (12 to 18 moths) [17], these factors make these medications inappropriate choices in low resource settings like Sudan and other similar countries. Therefore, searching for more reasonable treatment choices like convalesce plasma therapy [13], is appropriate since most countries already have the infrastructure, needed to prepare and perform this type of therapy.

TABLE 2: Summary of four clinical reports on the effectiveness of convalescent plasma therapy in COVID -19 patients.

Reference	Duan et al 2020 [5]	Shen et al 2020 [22]	JY Ahn et al 2020 [23]	Zhang et al 2020 [24]
No. of patients	10 patients	5 patients	2 patients	4 patients
Amount of Plasma received	200 ml	400 ml	500 ml	900 ml , 200 ml , 2400ml and 300 ml
Clinical Improvement	-Fever and respiratory signs largely improved within 1 to 3 days upon transfusion. -Two out of three patients were weaned from mechanical ventilation to high-flow nasal cannula, and one out of three patients discontinued high-flow nasal cannula. -In one patient treated with conventional nasal cannula oxygenation, continuous oxygenation was shifted to intermittent oxygenation.	-Body temperature normalized within 3 days in 4 of 5 patients. -ARDS resolved in 4 patients at 12 days after transfusion. -3 patients were weaned from mechanical ventilation within 2 weeks of treatment -The sofa score decreased -Pao2/FIO2 increased within 12 days	-Both patients showed improvement in the PaO2/FIO2 ratio -Both patients weaned from the mechanical ventilator	The clinical condition improved in the 4 cases and they were discharged from the ICU at (14, 7, 10, 27) days of plasma transfusion
Laboratory Improvement	-7 out of 10 patients showing an increase of lymphocyte counts. -C-reactive protein level reduced -Alanine Aminotransferase and Aspartate aminotransferase reduced. -The total bilirubin remained unchanged, except for an obvious increment in one patient. -The neutralizing antibody titers of five patients increased and four patients remained at the same level.	-SARS-CoV-2-specific ELISA and neutralizing antibody titers increased. -CRP, procalcitonin, decreased in all patients -IL 6 decreased in 4 out of 5 patients.	-The level of CRP and IL-6 reduced in both patients. -Leukocytosis and lymphopenia recovered in one patient.	Two out of four cases produced anti-SARS-CoV-2 IgG about 14 days after convalescent plasma transfusion
Radiological image improvement	All patients showed different degrees of absorption of pulmonary lesions after transfusion	CT scan showed improvement of the pulmonary lesion on one patient on the third day after the plasma transfusion and gradual resolution of pulmonary lesions of other patients at 3days after the plasma treatment	The density of bilateral infiltration on chest X-ray improved in both patients	The four patients showed resolution of the chest radiograph lesions
Time to V?..mnb irus clearance	SARS-CoV-2 RNA decreased to an undetectable level in three patients on day 2, three patients on day 3, and one patient on day 6 (the remaining 3 patients were negative before transfusion)	Viral loads became negative within 12 days after the transfusion	SARS-CoV-2 was negative after day 20 in one patient and day 26 in the second patient	The RT PCR became negative within 4 days of plasma infusion in 3 patients and within 3 weeks in the fourth patient
Piersons score	9	8	8	8

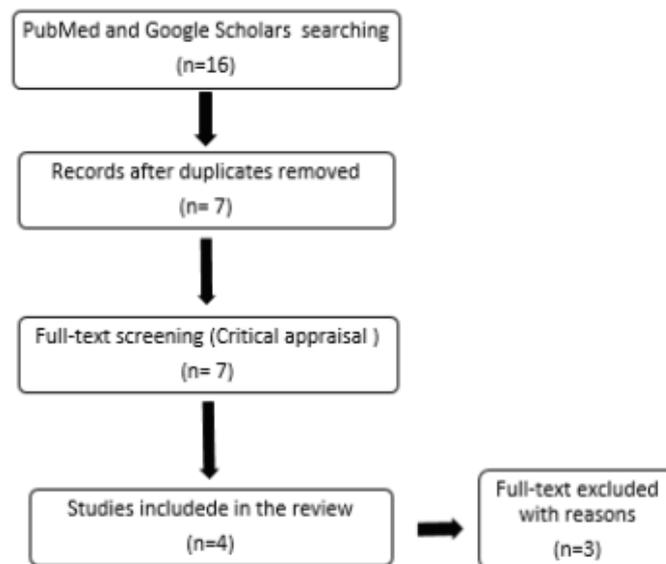


Figure 2: Flow-gram of search and selection of articles

4.1. The use of convalescent plasma against SARS-CoV-2

Plasma treatment is an old method of therapy that can be traced back for more than a century ago [14]. Furthermore, there are several examples where convalescent plasma has been used successfully as a treatment of infectious diseases like SARS, MERS, H1N1, H5N1 and Ebola. During SARS outbreak, patients who were treated with Plasma had more favorable prognosis and fewer side effects than those treated with antiviral drugs [25-32]. The largest study enrolled 80 patients in Hong Kong with SARS1. The patients who received treatment before day 14 had better outcomes as defined by the release from hospital before day 22 [28]. In comparison fewer studies were done in MERS outbreak possibly due to the limited numbers of donors [17]. In this current pandemic of SARS-CoV-2, several studies with limited data suggested that convalescent plasma is beneficial in extremely severe COVID-19 patients [5, 22-24].

Duan *et al* [5] in Wuhan performed a pilot study to explore the feasibility of CP treatment in 10 severe COVID-19 patients. 200 ml of convalescent plasma derived from recovered donors was transfused to the patients with neutralizing antibody titers more than 1:640. The patients were receiving maximal supportive treatment and antiviral therapy. After the transfusion, the neutralizing antibody titer was raised to 1:640 in five cases and maintained at a high level (1:640) in four cases. The clinical outcome showed dramatic improvement of symptoms within 1 to 3 days, and improved oxygen saturation within 3 days. Laboratory parameters also improved, the mean lymphocyte counts were raised from ($0.65 \times 10^9/L$) to ($0.76 \times 10^9/L$) and the mean C-reactive protein declined from (55.98 mg/L) to (18.13 mg/L). Radiological Imaging showed varying degrees of reduction of pulmonary lesions within 7 days. The viral load was undetectable in seven patients after transfusion who had previous viremia. No severe adverse effects were detected. The dose mention here is close to the therapeutic dose of 250 ml, recommended

in a review by Evan M. Bloch and colleagues [7]. Nevertheless, the optimal dose and treatment duration, as well as the clinical benefit of CP therapy need further investigation in larger well-controlled trials.

In addition, Shen *et al* [22] in Shenzhen, China, assessed the initial clinical experience with convalescent plasma transfusion administered to critically ill patients with COVID-19. The study involved five critically ill patients on mechanical. The patients were receiving antiviral treatment and methylprednisolone. Following convalescent plasma transfusion, the patients' body temperature improved in 4 out of 5 patients within three days. The SOFA (Sequential Organ Failure Assessment score) declined from (2-10) before transfusion to (1- 4) 12 days after the transfusion. The PAO₂/FIO₂ ratio was raised from (172-276) to (284-366) after 12 days, and the viral load became undetectable within the same period. The neutralizing antibody titers were raised from (40-60) to (80-320) on the seventh day after the transfusion. Within 2 weeks, four patients recovered from ARDS (Acute Respiratory Distress Syndrome), and three patients were weaned from mechanical ventilators. Two out of five patients were stable at 37 days, and three have been discharged within 2 months. These preliminary outcomes raise the probability that convalescent plasma transfusion may be supportive in the treatment of critically ill patients with COVID-19.

In Korea, JY Ahn *et al* [23] reported two cases of severe COVID-19 patients presenting acute respiratory distress syndrome (ARDS), who showed a favorable clinical course after the convalescent plasma infusion. In the first patient the fever normalized and oxygen demand declined one day after the transfusion. The patient's condition was much improved with decreased CRP and IL-6 to normal levels. After 8 days PaO₂/FiO₂ ratio became normal. Chest X-ray revealed disappearance of lung lesions after 3 days. The virus was undetectable after day 26. The patient had tracheostomy and was successfully weaned from mechanical ventilation. In the second case, Leukocytosis and lymphopenia recovered immediately after plasma transfusion. The density of pulmonary infiltrates on chest X-ray much improved 3 days after transfusion with increase in the PaO₂/FiO₂ ratio to 230. The level of CRP and IL-6 also normalized. SARS-CoV-2 was undetectable after day 20, and the patient was discharged on day 24.

This rapid improvement was witnessed again in a study done by Zhang *et al* [24]. They report the disease course on four critically ill patients infected with SARS-CoV-2 and treated with supportive care and convalescent plasma. They were confirmed positive by reverse transcriptase PCR. All of them received antiviral therapy and other supportive measures. The four patients developed ARDS during the first week of admission, and 3 of them received invasive ventilation. Three out of four developed septic shock, and 2 of them deteriorated to multi organ failure who received continuous renal replacement therapy (CRRT) and veno-venous extracorporeal membrane oxygenation (ECMO). The 4 patients received different doses of plasma therapy (900ml, 200 ml, 2400ml and 300 ml) respectively. The four patients showed resolution of the chest radiograph lesions. The RT PCR became negative within 4 days of plasma infusion in 3 patients and within 3 weeks in the fourth patient. The 4 patients were discharged from the ICU at (14, 7, 10, 27) days of plasma transfusion. The difference in the time of recovery between these groups of patients could be attributed to the difference in the doses and duration of

convalescent plasma used in these studies among other possible reasons. Furthermore, the absence of severe side effects in these reports supports the safety profile of this mode of therapy, although a more prolonged clinical trials are needed to confirm these results.

This improvement in patient condition and decrease in hospital stays are equivalent to what was noticed in the use of convalescent plasma therapy in SARS patients in 2004 in a retrospective study done by Soo Yo *et al.* Where they compare the clinical outcomes between two groups of SARS patients, one group on methyl prednisolone and the other on convalescent plasma, in which they reported a shorter hospital stay ($p < 0.001$) and lower mortality ($p < 0.049$) in the group receiving the plasma therapy [28].

The common factors in these four studies are the clinical benefit of convalescent plasma therapy and the very limited number of participants, which necessitates further investigation in larger well-controlled trials.

Despite the rapid improvement witnessed in these patients, animal studies in SARS COV virus, sometimes show an aggravation of clinical symptoms despite the reduction in viral load, possibly due to the role of passive plasma antibodies in shifting the burden of infections to macrophage which potentiates the dysregulated immune response against the virus [33].

4.2. Donor Eligibility

Zhang Dingyu, the director of Wuhan Jinyintan Hospital, has stated that to be a donor you have to be between 18 and 55 years old, and to have recovered for at least 14 days before blood donation. If the person is in good health, the age range could be extended to up to 60 years old.

Before donation, the donor has to screen for relevant transfusion-transmitted infections such as HIV, syphilis, Hepatitis B and C [34, 35].

4.3. Patient Eligibility

- Laboratory confirmed the COVID-19 status of the patient by RT-PCR.
- Severe or immediately life-threatening COVID-19. severe disease is defined as showing one or more of the following: shortness of breath, respiratory frequency $\geq 30/\text{min}$, blood oxygen saturation $\leq 93\%$, the partial pressure of arterial oxygen to fraction of inspired oxygen ratio < 300 , lung infiltrates $> 50\%$ within 24 to 48 hours.

The life-threatening disease is defined by the occurrence of one or more of the following: respiratory failure, septic shock and multiple organ failure.

- Informed consent provided by the patient who will receive the therapy [35].

4.4. Preparation of convalescent Plasma in low resource setting

The protocol for plasma preparation differs between countries but usually it contains two major parts: the first is the donor selection, which was previously mentioned; and the second is plasma preparations.

The plasma preparations start by separation the plasma from the blood by Plasma apheresis device or any other simple extraction methods (well within the remit of most blood banks) and then checking the antibodies level in the plasma by the enzyme-linked immunosorbent assay (ELISA). (In addition, checking and inactivation of the viral load will be undertaken to decrease the possibility of transmitting infection). And finally, freezing the plasma and storing it in aliquots of around 300ml [36]. These steps are summarized in Figure 3.

4.5. Convalescent Plasma Therapy Limitations

Although being a relatively available method of treatment yet, the recovered patients have to wait at least 14 days before they can donate their blood. Furthermore, the dose has to be high enough to be effective, as it was noticed in the clinical trials of convalescence plasma in MERS-CoV Infection, Saudi Arabia [17]. Other practical concerns in plasma donation may include difficulties in reaching the recovered patients by phone and the refusal of voluntary involvement in the donation [37].

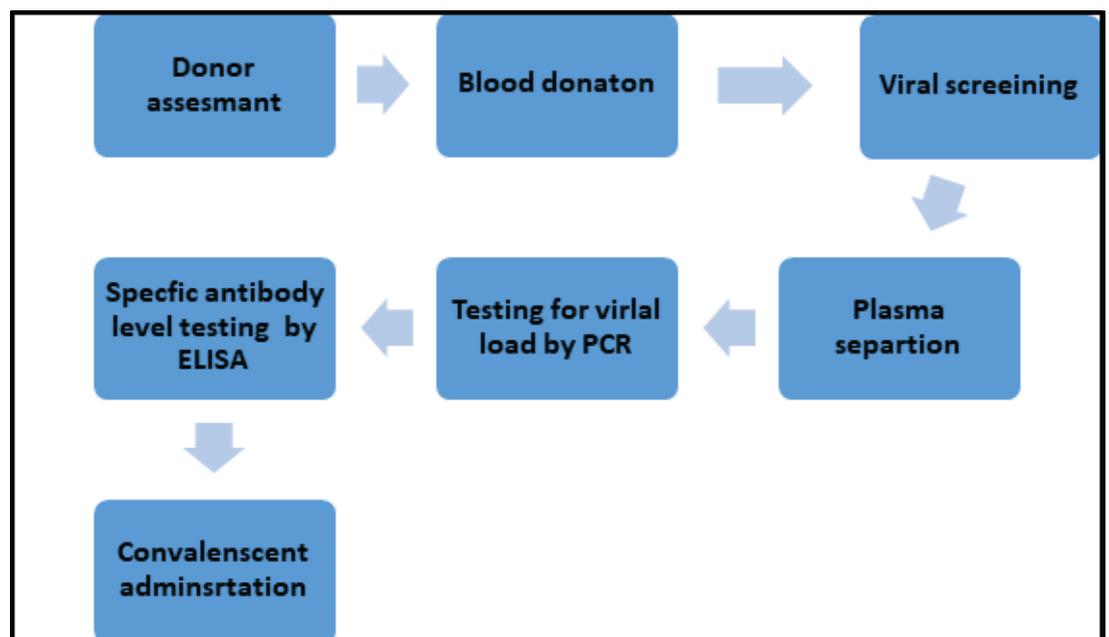


Figure 3: flow chart of convalescent plasma preparation in covid-19 patients showing the major steps from donor selection to the administration of screened plasma units. PCR: Polymerase chain reaction. ELISA: enzyme-linked immunosorbent assay

5. Conclusion

In summary, this rapid review shows a potential therapeutic effect of convalescent plasma in the treatment of COVID-19 patients. This is due to the fact that all the laboratory investigations come back to normal, as well as the clinical outcome, showed a dramatic improvement of symptoms within 1 to 3 days following convalescent plasma transfusion. Though convalescent plasma therapy has not yet been approved as a treatment for COVID-19 disease, there is growing evidence of its effectiveness in the previous SARS and MERS infection. Hence, we recommend plasma therapy to be used as treatment in the current COVID-19 pandemic in the form of clinical trials, especially in areas with low resource setting such as Sudan.

6. Limitations of the Reviewed Evidence

Several clinical trials reported enrolling small number of patients, which will be poorly representative of the general population, and hence it will be difficult to generalize the results of these studies. Another problem is the lack of long follow-up, which means that we are lacking the knowledge of the possible long side effects of this therapy [15, 16].

7. Strength and Limitations of the Current Paper

To our knowledge, this is the first rapid review, reporting the available evidence regarding the effectiveness and safety of convalescent plasma therapy in COVID-19 patients in low resource setting countries. In our attempt to spread the knowledge in a timely manner, we rapidly conducted this review in a duration of 14 days without strict adherence to systemic reviews guideline. Yet, we made sure that all reports used are published in well-respected journals and hence we believe this review will provide an invaluable asset in the fight against COVID-19 pandemic.

Conflict of Interest

The authors wish to declare that they have no conflict of interest regarding the publication of this study.

Ethical Clearance

Ethical clearance was not required for this paper.

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