Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Battle against COVID-19: Efficacy of Convalescent Plasma as an emergency therapy

To the editor:

Convalescent Plasma (CP) is a form of adaptive immunization. It is an indirect way to protect a susceptible individual by providing immunity against a specific pathogen. Currently, the outbreak of highly infectious respiratory illness, i.e., novel coronavirus (COVID-19), has so far affected 2,471,136 individuals and has caused 169,006 deaths (WHO situation report-93; April 22, 2020). The USA alone reported 695,353 infected cases with the highest number of fatalities (n = 37,602). The outbreak is so dangerous that it has affected the entire world (213 countries/areas/territories). So far, scientists are struggling to develop an effective treatment strategy. The only preventive measures rely on supportive care, quarantine, and isolation of infected patients. CP therapy was effective during the outbreaks of SARS in 2002/2003, H1N1 in 2009, and MERS in 2012 [1-3]. CP transfusion improves clinical symptoms and reduces the mortality rate [4]. A previous exploratory study on SARS and severe influenza performed in 2014, which included 32 separate studies, identified a reduction in mortality rate after CP transfusion. The study showed pooled odds of mortality reduced after CP therapy compared to the placebo or no treatment (OR, 0.25; 95% CI, 0.14–0.45; I2 = 0%) [5]. A retrospective non-randomized study on 19 SARS infected patients showed reduced mortality as well as shorter hospital stay after CP transfusion [6].

Similarly, a meta-analysis study on 1703 Spanish influenza pneumonia patients reported improved clinical symptoms and reduction in mortality upon CP transfusion. Absolute mortality risk range between the groups (treatment vs. control) was 8% - 26% with a pooled difference of 21% [CI 95%: 15–27%] [7]. A 2015–16 MERS study on Marmosets, treated with mAb and CP, reported a reduction in clinical symptoms and viral load in the CP group [8]. During the Ebola outbreak, CP therapy was found to be effective [9,10], especially during the early phase of the epidemic and showed improved survival odds ratio (OR: 2.3; 95% CI: 0.8–6.5) [9].

Phylogenetic and molecular sequencing-based studies suggest the similarity between the present COVID-19 virus and previously reported SARS and MERS viruses. Therefore, CP transfusion could be an effective therapy against COVID-19 (Table 1). Recently published article on ten critically ill COVID-19 patients transfused with a single dose of 200 mL CP (neutralizing antibody (nAb) titer > 1:640) reported increased SO2,

Table 1
Previous studies describing the impact of CP therapy.

Sr. no	Title of the study	Year	Indication	No. of participants	Outcomes	References
1.	Retrospective comparison of convalescent plasma with continuing high-dose methylprednisolone treatment in SARS patients	2003	SARS	19 SARS patients (retrospective non-randomized study)	Short hospital stays and low mortality was observed in CP treated patients. CP therapy showed no adverse effects following treatment	[6]
2.	Use of convalescent plasma therapy in SARS patients in Hong Kong	2003	SARS	80	Early discharge rate from hospital was observed in CP treated patients	[3]
3.	Convalescent plasma treatment reduced mortality in patients with severe pandemic influenza A (H1N1) 2009 virus infection	2009–10	Severe influenza A virus (H1N1 2009)	93 HIN1 patients (prospective cohort study)	Viral load and cytokine response was reduced after the CP transfusion. Also the mortality rate was significantly lower in the CP transfusion group than the control group.	[2]
4.	Efficacy of antibody-based therapies against Middle East respiratory syndrome coronavirus (MERS-CoV) in common marmosets	2015–16	MERS	Common marmoset MERS-CoV infection model-3 groups	Common Marmosets treated with mAb and CP therapy, both the groups showed reduction in the clinical symptoms.	[8]
5.	Evaluation of convalescent whole blood for treating Ebola Virus Disease in Freetown, Sierra Leone.	2014–15	Ebola	69 patients	Increased recovery and clinical symptoms in CP treated group	[9]
6.	The Use of TKM-100802 and convalescent plasma in 2 patients with Ebola virus disease in the United States	2014	Ebola	2 (case reports)	Both patients recovered. One patient underwent multi-organ failure	[10]
7.	Effectiveness of convalescent plasma therapy in severe COVID-19 patients	2020	COVID-19	10 severe COVID-19 patients	Viral load decreased in the treatment group along with improvement in the clinical symptoms. Also lymphocyte count increased with reduction in CRP. Overall CP therapy showed promising results with no side effects.	[11]
8.	Treatment of 5 critically ill patients with COVID-19 with convalescent plasma	2020	COVID-19	5 critically ill COVID-19 patients (case series)	Body temperature normalized, SOFA (Sequential Organ Failure Assessment: with higher score indicating more illness) score decreased and PAO_2/FIO_2increased. Also viral load decreased and became negative within 12 days of CO transfusion.	[12]
9.	Use of convalescent plasma therapy in two COVID-19 patients with acute respiratory distress syndrome in Korea	2020	COVID-19	2 COVID-19 patients with multiple diseases (case reports)	After CP therapy fever subsided, and oxygen demand decreased in both the cases. CRP and IL-6 levels decreased to normal range. Both the patients showed a favorable outcome after the use of CP therapy in addition to systemic corticosteroid treatment.	[13]

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Table 2
Registered clinical trials (CT) to check the efficacy of CP therapy on COVID-19 patients.
(Source: ClinicalTrials.gov; dated April 23, 2020.)

CT no.	Title of the study	Country	Participants (n)	Intervention type	Phase	Status
NCT04343755	Convalescent plasma as treatment for hospitalized subjects with COVID-19 infection	USA	55	–	2	Recruiting
NCT04342182	Convalescent plasma as therapy for Covid-19 severe SARS-CoV-2 disease (CONCOVID Study) (ConCoVid-19)	Netherlands	426	Randomized	2/3	Recruiting
NCT04347681	Potential efficacy of convalescent plasma to treat severe COVID-19 and patients at high risk of developing severe COVID-19	Saudi Arabia	40	Non-Randomized	2	Recruiting
NCT04357106	COPLA Study: Treatment of severe forms of COronavirus Infection With Convalescent PLAsma (COPLA)	Mexico	10	–	2	Recruiting
NCT04346446	Efficacy of convalescent plasma therapy in severely sick COVID-19 patients	India	20	Randomized	2	Recruiting
NCT04345523	Convalescent plasma therapy vs. SOC for the treatment of COVID19 in hospitalized patients (ConPlas-19)	Spain	278	Randomized	2	Recruiting
NCT04340050	COVID-19 convalescent plasma	USA	10	Non-Randomized	1	Recruiting

lymphocyte count, and decreased C-reactive protein [11]. Another study on five severe COVID-19 patients found clinical improvement where nAb titers improved from 40 to 60 to 80–320 on the 7th day, and the patient recovered within 12 days of CP transfusion [12]. When used in combination with systemic corticosteroids, CP therapy reduces the inflammatory response and viral titer [13]. Currently, seven CP based clinical trials are undergoing on COVID-19 patients (Table 2). Recently FDA has approved the use of CP therapy for critically ill COVID-19 patients [14,15].

In CP therapy, passive immunization takes place where antibodies act as an active agent for a specific pathogen. CP antibodies exert their therapeutic effect through different mechanisms. Antibody neutralizes the viral pathogenesis by directly binding to the epitope of a virus. Other modes of action include antibody-dependent cellular cytotoxicity (ADCC), and activation of the complement system [16]. The serum of recovered patients will develop a humoral immune response in terms of the IgG antibody against various epitopes of the COVID-19 virus (Fig. 1). The receptor-binding domain (RBD) of this virus acts as both an antibody epitope and a binding site for ACE-2 (Angiotensin-converting enzyme-2) receptor, which is known as a significant entry receptor for COVID-19 to display its toxicity. The IgG derived from plasma of recovered patients has the potential to compete with ACE-2 receptors for binding with RBD of COVID-19, and it might neutralize the infection caused by the virus [17].

There are minimal studies to report the adverse events caused by CP therapy, and one such incident occurred during the Ebola outbreak. It could be due to a lack of the neutralizing antibody titration data. Of the 99 patients studied, 8% showed minor problems, with 5% having increased temperature, and 4% reported itching/body rash [18]. Two separate studies on patients of Ebola [18], and MERS [19] developed transfusion-related acute lung injury after CP transfusion. Amongst other studies, H5N1 Spanish influenza based meta-analysis constituting of 8 studies reported common adverse effects in 7 studies, including chill reactions and exacerbations of symptoms [7]. However, evaluation of risks and benefits could be done according to clinical features and patient history to prevent any hostile effect.

In conclusion, an increase in the number of deaths and a lack of potential effective antiviral therapy against COVID-19 urges an emergency approach that may contribute to saving lives. It is essential to check the required optimal doses, the concentration of nAb titers, treatment points, and the severity of the diseases before the transfusion.

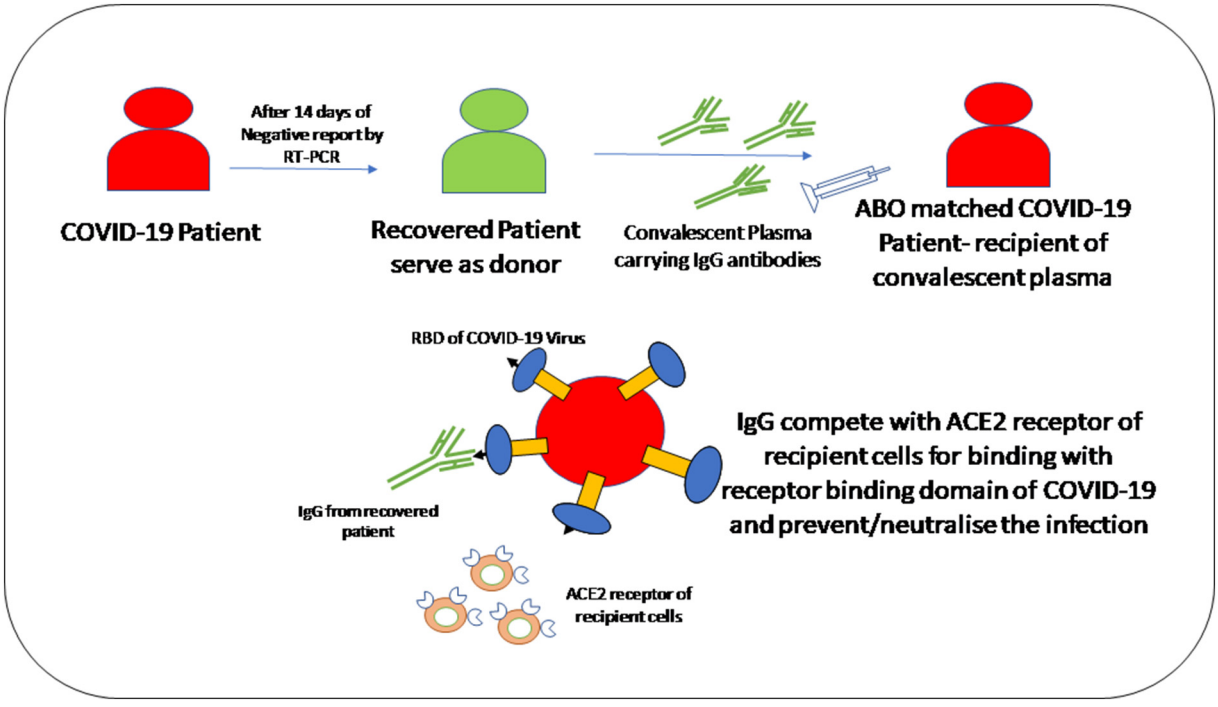

Fig. 1. Diagrammatic representation of CP therapy and its mode of action for treating COVID-19 patients. IgG antibodies from recovered patient could neutralize viral infection by blocking receptor-binding domain of COVID-19.

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SK: conceptualization, writing and editing; **VS**: writing, illustration, **KP**: writing.

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Declaration of competing interest

None.

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