Ther Adv Infectious Dis
2020, Vol. 7: 1–18
DOI: 10.1177/2049936120960646

Convalescent Blood Products in COVID-19: A Narrative Review

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***Abstract*:** The coronavirus disease 2019 (COVID-19) pandemic has left the world in a state of desolation with overburdening public health systems in a short period. Finding possible preventative and therapeutic measures to counter severe respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent of COVID-19, has been the priority. A possible solution is convalescent blood products (CBP), primarily convalescent plasma (CP) and immunoglobulins, as an adjunctive therapy. CBP has been tried on the previous coronavirus epidemics with severe acute respiratory syndrome coronavirus (SARS-CoV) and the Middle East Respiratory Syndrome Coronavirus (MERS-CoV). Therefore, we reviewed the clinical utility of CBP and available evidence in COVID-19. We found some of the current anecdotal studies demonstrate promising therapeutic potential, but many of these studies do not meet the academic rigours to substantiate its use with confidence. However, the compassionate use of CBP in critically ill COVID-19 patients can be an option while we await a definitive answer from ongoing randomised clinical trials.

Keywords: convalescent blood products, COVID-19, evidence, review, SARS-CoV-2

Received: 13 July 2020; revised manuscript accepted: 26 August 2020.

Introduction

Since the coronavirus disease 2019 (COVID-19) was first reported in December 2019 in Wuhan, China, the global pandemic has resulted in over 12.4 million confirmed cases, including 559,047 deaths as of 12 July 2020.[1] While dexamethasone and remdesivir have shown some promising results recently with a reduction in mortality and recovery time, we are still awaiting a definitive therapy against COVID-19.[2,3] An alternative therapeutic option for severe respiratory syndrome coronavirus 2 (SARS-CoV-2),[4] the pathogen responsible for COVID-19, could be the use of convalescent blood products (CBP), primarily convalescent plasma (CP) and immunoglobulins, as an adjunctive therapy based on previous experience with coronavirus epidemics with severe acute respiratory syndrome coronavirus (SARS-CoV) and the Middle East Respiratory Syndrome Coronavirus (MERS-CoV). Therefore, this study aims to discuss the clinical usage of CBP and review the existing evidence in COVID-19.

Method

A review of the literature was done through PubMed and Google Scholar databases to identify all relevant English language scientific studies based on the study objectives. Unspecified combinations of the search strings included, 'Coronavirus' OR 'Severe Acute Respiratory Syndrome' OR 'SARS' OR 'SARS-CoV' OR 'Middle Eastern Respiratory Syndrome' OR 'MERS' OR 'MERS-CoV' OR 'Severe Acute Respiratory Syndrome Coronavirus 2' OR 'SARS-CoV-2' OR '2019-nCoV' OR 'Coronavirus disease' OR 'COVID-19' AND 'convalescent blood products' OR 'CBP' OR 'convalescent plasma' OR 'CP' AND 'intravenous human immunoglobulin' OR 'IVIG' in association with related physiology and efficacy. Included studies assessed the efficacy and safety of CBP in SARS, MERS, and COVID-19, including *in vivo* models. Owing to the scarcity of randomised control trials (RCT) and other relevant studies, including observational studies, case reports, case series and review

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articles were also involved. Studies carried out in the paediatric population were excluded. A separate assessment of the studies was executed for a secondary reference search on applicable supplementary research studies.

Convalescent blood products

CBP consists of[5]:

1. convalescent whole blood or convalescent plasma or convalescent serum;
2. pooled human immunoglobulin for intravenous or intramuscular administration;
3. high-titre human immunoglobulin; and
4. polyclonal or monoclonal antibodies.

CBP is obtained from an individual who has developed humoral immunity and recovered from an infection. It is suppose to have high-titres of neutralising antibodies (NAb) used either for prophylactic passive inoculation or supportive treatment with the intention of reducing symptoms and mortality.

CBP has been used throughout history to confer artificially acquired passive immunity against various pathogens. The first use can be traced back between 1918 and 1920 during the Spanish Flu pandemic.[6–11] A meta-analysis was conducted by Luke *et al.* regarding the effectiveness of CBP against Spanish influenza that involved eight studies and 1703 patients.[12] The study revealed significantly reduced mortality in CBP groups compared with untreated patients [16% *versus* 37% fatality; absolute risk difference 8% to 26%; pooled risk difference 21%, 95% confidence interval (CI): 15–27%].

CBP continued to be used prophylactically against viral infections such as measles, varicella-zoster, and cytomegalovirus to variable effects due to the nature of its preparation.[13–15] Pooled human plasma tends to have inconsistent titres of NAbs. However, in 1944, Stokes *et al.* argued that the efficacy of CBP could be improved through more potent preparations and intravenous administration.[16] But, as definitive preventative tactics, such as vaccines, emerged, CBP became marginalised. Presently, CBP is used as a replacement therapy for congenital or acquired immunoglobulin production deficiencies.

CBP against SARS

During the 2002 SARS-CoV epidemic, there were no specific therapies/vaccines available for treatment. CBP therapeutic potential was first observed by Wong *et al.*,[17] when a 57-year-old SARS-CoV infected woman received 200 ml CBP + 500 mg methylprednisolone and made an unremarkable recovery with no adverse drug reactions (ADRs). Similar recoveries were reported in three case series, including one pregnant female, and another woman, who subsequently became pregnant, without complications.[18–20] Separately, Soo *et al.*[21] found that patients ($n = 19$) receiving CBP + ribavirin-steroid had reduced admission lengths ($p = 0.001$) and mortality ($p = 0.049$) compared with patients ($n = 21$) receiving 1.5 g pulsed methylprednisolone. However, patients had a poor clinical response when CBP was given beyond 16 days post-symptom onset. Cheng *et al.* reported similar findings in 80 SARS-CoV infected patients with 279.3 ± 127.1 ml CBP (range:160–640 ml), with a greater 22-day discharge rate when CBP was given within 14 days of illness (58.3% *versus* 15.6%; $p < 0.001$).[22] A systematic review by Mair-Jenkins *et al.* analysed 32 studies regarding the efficacy of CBP against SARS and influenza and reported that mortality declined significantly in CBP patients [odds ratio (OR): 0.25; 95% CI: 0.14–*0.*45; I2 = 0%].[23] They concluded that CBP is a safe therapeutic option with decreased mortality against SARS-CoV.

CBP against MERS

Similar to the 2002 SARS-CoV epidemic, no proven therapy was found during the 2012 MERS-CoV outbreak. By July 2014, 12 MAbs were identified to have prophylactic or therapeutic potential against MERS-CoV.[24–26] Subsequent rapid and affordable production of NAb LCA60, exhibiting MERS-CoV S protein interaction, demonstrated MAb/NAb as a viable option to combat emerging viral infections with low ADR risk.[27,28] Of the 12 NAbs identified, m336 underwent further *in vivo* studies. Houser *et al.* reported that m336 significantly reduced viral titres (40–9000 fold) in rabbit lung tissue,[29] and these results were replicated in mouse models by Agrawal *et al.*[30] However, the therapeutic predictive value remains limited compared with non-human primate models.[31] As such, Doremalen *et al.* began examining MERS-CoV infected common marmosets, given either high-titre hyperimmune

plasma (1:3840) or m336.[32] The m336 conferred better clinical recovery, and hyperimmune plasma reduced respiratory tract viral load. Separately, Ko *et al.* examined three MERS-CoV infected patients, who received four CBP transfusions.[33] They showed significant serologic CBP response with plaque reduction neutralisation test (PRNT) titres of 1:80, and concluded that PRNT titre >1:80 could be effective against MERS-CoV. However, as per Choe *et al.*,[34] it was challenging to obtain high CBP titre. They followed 11 MERS-CoV patients (five severe and six mild) for 12 months post-recovery, and found that severe patients tend to exhibit higher acute (0–6 months) and maintenance (6–12 months) PRNT90 titres, suggesting the possibility of obtaining effective high titre CBP only within the initial months of severe disease.

Overall, the quality of clinical evidence of CBP in SARS and MERS was low and lacked substantial support from RCTs for a definitive conclusion.

CBP against COVID-19

CBP has been used frequently against COVID-19 due to the existing therapeutic inertia. Here, we discuss the evidence concerning CBP in COVID-19 (summarised in Table 1).[35-48] On 2 February 2020, a study by Zhou *et al.* examined the full-length genome sequences of SARS-CoV-2 isolated from five patients.[49] SARS-CoV-2 was 79.6% and 96.0% similar to SARS-CoV and a bat coronavirus, respectively. This study encouraged clinicians to repurpose the therapeutic options tried and tested in SARS and MERS outbreaks. Subsequently, Zhou *et al.* conducted a serum-neutralisation assay in Vero E6 cells using IgG-positive sera from five human donors.[49] At a dilution of 1:40–1:80, the sera were able to neutralise SARS-CoV-2 samples of 100 $TCID_{50}$ (50% tissue-culture-infective dose). Also, they found horse anti-SARS-CoV-2 serum to effectively cross-neutralise the virus, indicating the therapeutic potential of CBP against COVID-19.

On 21 March 2020, a case series by Cao *et al.* investigated the use of intravenous immunoglobulins (IVIG) as a therapy against COVID-19 patients.[38] They described three case studies reporting administration of 25 g/d of IVIG for 5 days along with empiric treatment (oseltamivir and lopinavir-ritonavir). All three cases showed clinical improvement after the infusion and were subsequently discharged at 8, 5 and 11 days post infusion. The outcome suggested that CBP may be effective against early-stage COVID-19, inhibiting disease progression.

On 26 March 2020, an *in vivo* study by Chan *et al.* assessed the use of convalescent serum as an immunoprophylactic agent against COVID-19.[35] Groups of Syrian hamsters were either given SARS-CoV-2 suspended in phosphate-buffered saline (PBS) (10^5 plaque-forming units/100 µl) or just 100 µl PBS. Compared with the control group, the SARS-CoV-2 challenged group had a weight loss of up to 11%, 1–6 days post inoculation (dpi). By 14 dpi, a high serum NAb titre >1:427 was achieved, weight was regained, but mild pulmonary congestion and infiltration were still detectable. Viral loads progressively declined in airway tissues between 2 and 7 dpi. The authors concluded that the prophylactic use of this high-titre CBP resulted in a significant decrease in viral lung load but no pathological changes in the lung.

By 27 March 2020, a case series by Shen *et al.* assessed the benefit of the CBP transfusion in five critically ill SARS-CoV-2 infected patients.[39] Each patient was infused with 400 ml CBP with a SARS-CoV-2 specific antibody binding titre >1:1000 and a neutralisation titre >1:40, between 10 and 22 days after admission. Following CBP therapy, the sequential organ failure assessment (SOFA) score decreased, and the ratio of arterial oxygen partial pressure to fractional inspired oxygen (PaO_2/FiO_2) increased within 12 days. Furthermore, 12 days post transfusion, the viral load became negative, NAb titres increased, and there was a resolution of acute respiratory distress syndrome (ARDS) in four patients. They concluded that administration of CBP with NAbs showed some potential as an effective treatment; however, their study was limited by small sample size and subordinate design. Subsequently, Zhang *et al.*[40] examined anti-SARS-CoV-2 antibody levels in six CBP donors and all donors had high IgG titres (>1:320) except for one (<1:40). Subsequently, 200 ml of CBP from one of the donors was given to a SARS-CoV-2 infected female. Following CBP transfusion, the CBP recipient exhibited clinical improvement and no longer required mechanical ventilation 11 days post transfusion. It was concluded that, although the outcome was favourable, further research is

Table 1. Summary of evidence on CBP usage in COVID-19.

Author	Study type	Patient	Intervention	Outcome	Conclusion
Chan *et al.*[35]	*In-vivo*	Syrian hamsters	SARS-CoV-2 challenge (10^5 plaque-forming units/100 µl)	High serum titre developed (⩾1:427) 14 days post-challenge. Progressive decrease of viral load in airway tissue from 2dpi–7dpi. Mild pulmonary congestion and infiltration still detectable 14 dpi.	Prophylactic use of high-titre CBP can significantly decrease lung viral load but not lung pathology.
Rogers *et al.*[36]	*In-vivo*	Syrian hamsters	MAb CC12.1 and CC12.23	CC12.1 dosages of 8 µg, 31 µg, 125 µg, 500 µg and 2 mg: 16.7%, 15.8%, 8.0%, 0.0% and 0.0% body weight loss. Similar viral loads were observed in dosages 125 µg, 500 µg, and 2 mg. Statistically insignificant weight loss + viral load was seen with 8µg and 31 µg MAb CC12.1. CC12.23 had no evidence of protection.	Passive NAb transfer has potential for protection and prophylactic role in SARS-CoV 2 hamsters.
Iwatsuki-Horimoto *et al.*[37]	*In-vivo*	Syrian hamsters	CBP	CBP (1 day post-infection: significantly lower viral titres in the nasal turbinates ($p < 0.05$) & lungs ($p < 0.01$). CBP (2 days post-infection): lower viral titres.	Passive immunity *via* convalescent serum can hinder virus replication in hamster lungs.
Cao *et al.*[38]	Case series	3	25 ⩾ g/d of IVIG + Oseltamivir + Lopinavir/Ritonavir (5 days)	Clinical improvement and patients discharged at 5, 8 and 11 days post-infusion.	CBP may be effective against the early stage of COVID-19.
Shen *et al.*[39]	Case Series	5 (critically ill patients)	400 ml CBP (Anti-SARS-CoV-2 titres >1:1000, Neutralisation titres of >1:40) Given between 10–22 days post-admission	SOFA score decreased, PaO2/FiO2 increased within 12 days. Four patients had negative viral load, increase in NAb titres and resolution of ARDS, 12 days post-transfusion.	Administration of CBP with NAbs shows potential as an effective treatment.
Zhang *et al.*[40]	Case Study	1 (64 years, female)	CBP from donor B, IgG titre (> 1:320) IgM weakly reactive (OD ratio 1.22)	Mechanical ventilation no longer required 11 days post-transfusion.	Although beneficial results were achieved, CBP efficacy is still indefinite.
Zhang *et al.*[41]	Case Series	4	200–2400 ml of CBP	Rapid decrease of viral load and eventual clearance of SARS-CoV-2.	CBP has a possible therapeutic potential in severe COVID-19 infection.

(Continued)

Table 1. (Continued)

Author	Study type	Patient	Intervention	Outcome	Conclusion
Wu *et al.*[42]	Cohort study	175 (Plasma collection from COVID-19 recovered patients)	–	SARS-CoV-2 specific NAb detectable within 10–15 days of disease onset. Higher NAb titres + spike binding antibodies positively correlated with age ($p < 0.0001 + p = 0.0003$). High NAb titres positively and negatively correlated with CRP ($r = -0.432$, $p < 0.0001$) and lymphocyte count ($r = -0.389$, $p < 0.0001$) respectively. In total, 30% of patients failed to develop high NAb titres after COVID-19 infection.	NAbs should be titrated before therapeutic use due to variable levels of NAbs.
Pei *et al.*[43]	Case series	3 (P1, P2, P3) (P3 was pregnant)	P1: CBP given on day 12 of admission P2: CBP given on day 27 of admission P3: 30 ml of IVIG. Unknown admission time	P1: Recovered and discharged by day 26 P2: Viral nucleic acid turned negative 4 days later. P3: Had anaphylactic shock and CBP was stopped. Recovery was unremarkable.	CBP use can lead to viral clearance but careful patient selection is advised to minimise ADRs.
Duan *et al.*[44]	Case series	10 (severely ill patients)	Antiviral + Supportive care + 200 ml of CBP NAb, titre >1:640 (Median time of infusion: 16.5 days)	Within 3 dpi: increased oxyhaemoglobin and lymphocyte count (0.65×10^9/L *versus* 0.76×10^9/L), CRP decreased (55.98 mg/L *versus* 18.13 mg/L). Within 7 dpi: 7 showed variable radiological improvements + undetectable viral loads. No reported ADRs.	Results suggest CBP is well-tolerable, associated with clinical improvement and neutralisation of viraemia in COVID-19 patients.
Zeng *et al.*[45]	Case series	6 (critically ill patients)	200–600 ml of CBP (Median volume: 300 ml) (Median transfusion time: 21.5 days)	Intervention ($n = 6$) *versus* control group ($n = 15$): 100% *versus* 21.4% viral clearance before death ($p = 0.005$), survival rate appears longer in the intervention group ($p = 0.03$). Eventually, 5 *versus* 14 deaths occurred in each group (intervention *versus* control).	CBP has the potential to halt viral shedding and lengthen survival in those without end-stage disease, provided it is given early in the disease course.
Liu *et al.*[46]	Matched control study	39 adult patients (Average age 55 ± 13 years, two-thirds are male, 54% are obese and 18% were smokers/ex-smokers)	2 units (250 ml each) of CBP transfusion (titre ⩾1:320 over 1–2 hours) Median days between admission and transfusion: 4 days + azithromycin ($n = 31$) + broad spectrum antibiotics ($n = 29$) + hydroxychloroquine ($n = 36$) + investigational anti-virals ($n = 1$) + therapeutic anticoagulation ($n = 26$) + corticosteroids ($n = 22$) + interleukin-6 inhibitors ($n = 3$)	Plasma group associated with improved survival (log-rank test: $p = 0.039$) (plasma *versus* 1:4 matched control *versus* 1:2 matched control: 12.8% *versus* 24.4% *versus* 21.6% died). Covariates-adjusted Cox model: Non-intubated patients (HR, 0.19; 95% CI, 0.05–0.72; $p = 0.015$) vs intubated patients (HR: 1.24; 95% CI: 0.33–4.67; $p = 0.752$).	CBP transfusion associated with higher survival rates. No suggestion that the effect of CBP relied on symptom duration.

(Continued)

Table 1. (Continued)

Author	Study type	Patient	Intervention	Outcome	Conclusion
Salazar *et al.*[47]	Case series	25 severe/ critically ill patient	300 ml of CBP (titre range 1:0–1:1350) Median day from admission to transfusion: 2 days (IQR: 2–4 days) (+ tocilizumab & steroids + hydroxychloroquine & azithromycin + ribavirin and/or lopinavir/ ritonavir + remdesivir)	Within 24 hours of transfusion: No ADRs, 1 case of morbilliform rash (not linked to serum sickness). Non-CBP associated vascular complications at 4–8 days post transfusion). Day-7: 36% improved from baseline, 52% remained unchanged, and 12% deteriorated. Seven of the nine improved patients subsequently discharged. Day-14: 76% improved from baseline, 4 additional patients were discharged, 8 improved from baseline, 3 remained unchanged, 3 deteriorated. One non-transfusion related death. Overall average length of stay: control vs intervention, 14.3 days (2–25) *versus* 11 days (1–21).	CBP was concluded to be a safe treatment for severe COVID-19 disease. Concomitant therapies prevent definitive conclusions to be made for CBP alone.
Li *et al.*[48]	Open-label, multicentre RCT	103 SARS-CoV-2 infected patients (45 severe, 58 life-threatening)	CBP with standard treatment ($n = 52$)	Clinical improvement (at 28-days): Non-significant (df: 8.8%, 95% CI: −10.4–28.0%; HR: 1.40, 95% CI: 0.79–2.49; $p = 0.26$). Mortality (28-day): Non significant (15.7% *versus* 24.0%; OR: 0.65, 95% CI: 0.29–1.46; $p = 0.30$). Duration from randomisation to discharge at 28 days: Non significant (51.0% *versus* 36.0%; HR: 1.61, 95% CI: 0.88–2.93; $p = 0.12$). Two ADR cases reported (recovered with supportive care).	CBP with standard treatment, and standard treatment alone: No statistically significant difference in clinical improvement. Trial terminated prematurely, which may have prevented the study from having significant results.

ADR, adverse drug reactions; ARDS, acute respiratory distress syndrome; CBP, convalescent blood products; CI, confidence interval; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; Dpi, days post-infusion; HR, hazard ratio; IQR, interquartile range; IVIG, intravenous immunoglobulins; MAb, monoclonal antibodies; NAb, neutralising antibodies; OR, odds ratio; SOFA, sequential organ failure assessment; TCM, traditional Chinese medicine.

Table 2. Summary of ongoing clinical trials of CBP in COVID-19.

ClinicalTrials.gov identifier*:	Study design	Country	Intervention	Comparator	Estimated date of completion
NCT04292340	Prospective, SC	China	Anti-SARS-Cov-2 Inactivated Convalescent Plasma	–	PCD: July 31, 2020 SCD: December 31, 2020
NCT04264858	Interventional NR, Parallel Assignment, SC, OL	China	Immunoglobulin Of Cured Patients (0.2 g/Kg, IV, OD, For 3 Days)	ɣ-Globulin (0.2 g/Kg, IV, OD, Over 3 Days)	PCD: April 30, 2020 SCD: May 31, 2020
NCT04321421	Interventional Single Group Assignment, Longitudinal Assessment, SC, OL	Italy	Hyperimmune Plasma (250–300 ml, TDS, For 5 Days)	–	PCD: April 28, 2020 SCD: May 7, 2020
NCT04323800	Interventional RCT, Parallel Assignment, TB, SC, Ph II	USA	Anti-SARS-Cov Plasma (200–250 ml, ⩾1:320 SARS-Cov-2 Antibody Titres)	Non-SARS-Cov-2 Immune Plasma	PCD: December 31, 2020 SCD: January 2023
NCT04327349	Interventional Single Group Assignment, OL, SC, Single Arm	Iran	Convalescent Plasma	–	PCD: May 20, 2020 SCD: September 30, 2020
NCT04345289	Interventional RCT, MC, QB, Ph III	Denmark	Convalescent Plasma (2 × 300 ml)	Infusion Placebo (600 ml 0.9% Saline IV, Single Dose)	PCD: June 15, 2021 SCD: June 15, 2021
NCT04345679	Interventional Single Group Assignment, OL, Ph I, SC, Single Arm	Hungary	Convalescent Plasma (200 ml, Over 4 H)	–	PCD: June 1, 2020 SCD: April 1, 2021
NCT04332380	Interventional Single Group Assignment, OL, SC, Ph II, Single Arm	Columbia	Convalescent Plasma (2 × 250 ml, For 2 Days)	–	PCD: August 31, 2020 SCD: December 31, 2020
NCT04332835	Interventional RCT, Parallel Assignment, OL, SC, Ph II/III	Columbia	Convalescent Plasma (2 × 250 ml, Over 2 Days), Hydroxychloroquine (400 mg Each 12 H, For 10 Days)	Hydroxychloroquine (400 mg Each 12 H, For 10 Days)	PCD: August 31, 2020 SCD: December 31, 2020
NCT04345991	Interventional RCT, Parallel Assignment, OL, SC, Ph II	France	Convalescent Plasma (200–220 ml, 2 Times, IV, As Early As Possible And No Later After Symptom Onset)	Standard Of Care	PCD: May 15, 2020 SCD: June 1, 2020
NCT04343755	Interventional Single Group Assignment, OL, SC, Ph II, Single Arm	USA	Convalescent Plasma	–	PCD: April 2021 SCD: April 2021
NCT04347681	Interventional NR, Parallel Assignment, OL, Ph II	Saudi Arabia	Convalescent Plasma (10–15 ml/Kg Body Weight)	–	PCD: December 31, 2020 SCD: April 11, 2021
NCT04345523	Interventional RCT, Parallel Assignment, MC, OL, Ph II	Spain	Convalescent Plasma	Standard Of Care	PCD: July 2020 SCD: July 2020
NCT04340050	Interventional Single Group Assignment, OL, SC, Ph I, Single Arm	USA	Anti-SARS-Cov-2 Plasma (300 ml, Over 4 H)	–	PCD: December 31, 2020 SCD: December 31, 2021

(Continued)

Table 2. (Continued)

ClinicalTrials.gov identifier*:	Study design	Country	Intervention	Comparator	Estimated date of completion
NCT04333355	Interventional Single Group Assignment, OL, Ph I, SC, Single Arm	Mexico	Convalescent Plasma, Supportive Standard of Care	–	PCD: December 20, 2020 SCD: April 30, 2021
NCT04342182	Interventional RCT, Parallel Assignment, SB, MC, Ph II/III	Netherlands	Convalescent Plasma (300 ml)	Standard Of Care (Supportive Care, Oxygen, Antibiotics)	PCD: July 1, 2020 SCD: July 1, 2020
NCT04343261	Interventional Single Group Assignment, OL, SC, Ph II, Single Arm	USA	Convalescent Plasma (2 Units)	–	PCD: December 1, 2020 SCD: April 1, 2021
NCT04346589	Interventional Single Group Assignment, OL, SC, Single Arm	Italy	Anti-Coronavirus Antibodies (Immunoglobulins)	–	PCD: August 2020 SCD: August 2020
NCT04344535	Interventional RCT, Parallel Assignment, OL, QB, SC, Ph I/II	USA	Convalescent Plasma (450–550 ml, >1:320 Anti-SARS-Cov-2 Antibody Titre)	Standard Plasma (450–550 ml Plasma With Low Titre Anti-SARS-Cov-2 Antibodies)	PCD: April 30, 2021 SCD: August 31, 2021
NCT04346446	Interventional RCT, Parallel Assignment, OL, SC, Ph II	India	Convalescent Plasma, Supportive Care	200–600 ml Random Donor Plasma, Supportive Care	PCD: May 30, 2020 SCD: May 30, 2020
NCT04333251	Interventional RCT, Parallel Assignment, OL, Ph I	USA	High Titre Anti-SARS-Cov-2 Plasma (1–2 Units Of ABO Matched Donor Plasma, Nab Titre >1:64)	Best Supportive Care (Oxygen Therapy)	PCD: December 31, 2022 SCD: December 31, 2022
NCT04355897	Interventional Single Group Assignment, OL, SC, Ph I, Single Arm	USA	Convalescent Plasma (500 ml)	–	PCD: July 2020 SCD: August 2020
NCT04365439	Interventional Single Group Assignment, OL, SC, Single Arm	Switzerland	Convalescent Plasma	–	PCD: May 30, 2020 SCD: June 30, 2020
NCT04372979	Interventional RCT, Parallel Assignment, TB, MC, Ph III, RCT	France	Convalescent Plasma (200–230 ml, 2 Units, Inactivated By Amotosalen)	Standard Plasma (200–230 ml, 2 Units, Inactivated By Amotosalen)	PCD: October 202 SCD: May 2021
NCT04353206	Interventional Single Group Assignment, OL, SC, Ph I, Single Arm	USA	Convalescent Plasma (1–2 Units On Day 0, Potentially Days 3 And 6)	–	PCD: May 2021 SCD: May 2021
NCT04356534	Interventional RCT, Parallel Assignment, OL, SC	Bahrain	Convalescent Plasma (2 × 200 ml, Over 2 H, In 2 Consecutive Days)	Standard Of Care	PCD: June 15, 2020 SCD: July 9, 2020
NCT04385043	Interventional RCT, Parallel Assignment, OL, MC, Ph II/III	Italy	Hyperimmune Plasma	Standard Therapy	PCD: October 15, 2020 SCD: May 15th, 2021
NCT04374487	Interventional RCT, Parallel Assignment, OL, SC, Ph II	India	Convalescent Plasma (200 ml ABO Matched Donor Plasma)	Standard Of Care	PCD: August 9, 2021 SCD: August 9, 2021

(Continued)

Table 2. (Continued)

ClinicalTrials.gov identifier*:	Study design	Country	Intervention	Comparator	Estimated date of completion
NCT04390178	Interventional NR, Single Group Assignment, OL, Ph I/II Single Arm	Sweden	Convalescent Plasma (180–200 ml)	–	PCD: June 2020 SCD: December 2020
NCT04388410	Interventional RCT, Parallel Assignment, DB, MC, Ph II/III, Placebo-Controlled	Brazil	Convalescent Plasma (200 ml, With 24–72 H In Between)	Placebo (200 ml Normal Saline)	PCD: October 31, 2020 SCD: December 31, 2020
NCT04384497	Interventional NR Controlled, Single Group Assignment, OL, Ph I/II, Single Arm	Sweden	Convalescent Plasma (200 ml, Up To A Maximum Of 7 Infusions)	–	PCD: June 2020 SCD: December 2020
NCT04390503	Interventional RCT, Parallel Assignment, DB, Ph II	USA	Convalescent Plasma (200–250 ml)	Albumin (5%)	PCD: April 2021 SCD: April 2021
NCT04348656	Interventional RCT, Parallel Assignment, OL, MC, Ph III	USA, Canada	Convalescent Plasma (2 × 250 ml, Over 4 H)	Standard Of Care	PCD: October 31, 2020 SCD: December 31, 2020
NCT04348877	Interventional Single Group Assignment, OL, Single Arm	Egypt	Convalescent Plasma (400 ml)	–	PCD: October 2020 SCD: December 2020
NCT04384588	Interventional NR, Parallel Assignment, OL, MC, Ph II/III	Chile	Convalescent Plasma	–	PCD: April 6, 2021 SCD: April 6, 2021
NCT04389710	Interventional Single Group Assignment, OL, SC, Ph II, Single Arm	USA	Convalescent Plasma (200–600 ml, 100–250 ml/Hr, ABO Matched Donor Plasma)	–	PCD: April 14, 2021 SCD: April 14, 2021
NCT04354831	Interventional NR, Parallel Assignment, OL, SC, Ph II	USA	Convalescent Plasma To ICU Patients At Enrollment Time (1–2 Units, 200–400 ml Each)	Convalescent Plasma To Non-ICU Patients At Enrollment Time	PCD: May 1, 2023 SCD: May 1, 2023
NCT04383548	Interventional Single Group Assignment, OL, SC, Single Arm	Egypt	Hyperimmune Plasma	–	PCD: December 1, 2020 SCD: January 1, 2021
NCT04389944	Interventional Single Group Assignment OL, SC, Single Arm	Switzerland	Convalescent Plasma (200 ml At Enrolment, 200 ml At 12–24 H Follow-Up)	–	PCD: June 30, 2020 SCD: June 30, 2020
NCT04380935	Interventional RCT, Parallel Assignment, OL, MC, Ph II/III	Indonesia	Convalescent Plasma	Standard Of Care	PCD: August 31, 2020 SCD: August 31, 2020
NCT04373460	Interventional RCT, Parallel Assignment, TB, MC, Ph II, RCT	USA	Convalescent Plasma (200–250 ml, ⩾1:320 Anti-SARS-Cov-2 Antibody Titre)	Standard Plasma	PCD: December 21, 2022 SCD: January 31, 2023
NCT04388527	Interventional Single Group Assignment, OL, Ph I, Single Arm	USA	Convalescent Plasma (2 Units, ABO Matched Donor Plasma)	–	PCD: August 30, 2020 SCD: September 30, 2020

(Continued)

Table 2. (Continued)

ClinicalTrials.gov identifier*:	Study design	Country	Intervention	Comparator	Estimated date of completion
NCT04355767	Interventional RCT, Parallel Assignment, DB, Ph II	USA	Convalescent Plasma (1 Unit, ⩾1:160 Anti-SARS-Cov-2 Antibody Titres, IV Infusion)	Placebo (1 Unit, Saline With Multivitamin)	PCD: December 2022 SCD: December 2022
NCT04352751	Interventional Single Group Assignment, OL, SC, Single Arm	Pakistan	Convalescent Plasma (Children, 15 ml/Kg Over 4–6 H In Patients Under 35 kg Body Weight; Adult, Maximum 450–500 ml Over 4–6 H Once)	–	PCD: April 2021 SCD: April 2021
NCT04385199	Interventional RCT, Parallel Assignment, OL, SC, Ph II	USA	Convalescent Plasma (200 ml ABO Matched Donor Plasma, Over 3 H)	Standard Therapy	PCD: August 1, 2020 SCD: August 1, 2020
NCT04375098	Interventional RCT, Parallel Assignment, OL, SC, Ph II	Chile	Convalescent Plasma (200 ml Day 1 And Day 2)	Convalescent Plasma (200 ml Day 1 And Day 2 If Worsening Of Respiratory Function/ Persistence Of COVID Symptoms >7 Days After Enrolment)	PCD: December 2020 SCD: December 2021
NCT04377568	Interventional RCT, Parallel Assignment, OL, MC, Ph II	Canada	Convalescent Plasma (10 ml/Kg, Up To A Maximum of 500 ml)	Standard Of Care	PCD: December 1, 2021 SCD: May 1, 2022
NCT04383535	Interventional RCT, Parallel Assignment, QB, MC	Argentina	Convalescent Plasma (10–15 ml/Kg, 5–10 ml/ Hour)	Placebo (Saline Solution, 10–15 ml/Kg, 5–10 ml/ Hour)	PCD: August 15, 2020 SCD: September 20, 2020
NCT04374526	Interventional RCT, Parallel Assignment, OL, Ph II/III	Italy	Convalescent Plasma (200 ml ABO Matched Pathogen-Inactivated, Over 3 Days)	Standard Therapy	PCD: September 30, 2020 SCD: June 30, 2021
NCT04376788	Interventional RCT, Parallel Assignment, OL, SC, Ph II	Egypt	IV Methylene Blue (1 Mg/Kg IV In 30 Minutes) + Convalescent Plasma (200 CC) *versus* Exchange Transfusion + IV Methylene Blue + Convalescent Plasma	Exchange Blood Transfusion From Normal Donor (Venesection of 500cc Blood + Replacement of One Unit Packed Washed Rbcs)	PCD: July 1, 2020 SCD: September 1, 2020
NCT04381858	Interventional RCT, Parallel Assignment, DB, Ph III, RCT	Mexico	Convalescent Plasma (400 ml Of Plasma, >1:640 Igg Titre)	Human Immunoglobulin (0.3 gr/Kg/Day, 5 Does)	PCD: August 30, 2020 SCD: September 30, 2020
NCT04362176	Interventional RCT, Parallel Assignment, TB, Ph III	USA	Convalescent Plasma (500 ml Hours, Within 12 H of Randomisation)	Ringer's Solution With Multivitamins (250 ml)	PCD: April 2021 SCD: April 2021
NCT04361253	Interventional RCT, Parallel Assignment, DB, Ph III	USA	Convalescent Plasma (2 × 250 ml High-Titre)	Standard Plasma (2 × 250 ml Fresh Frozen Plasma)	PCD: June 2021 SCD: December 2021

(Continued)

Table 2. (Continued)

ClinicalTrials.gov identifier*:	Study design	Country	Intervention	Comparator	Estimated date of completion
NCT04356482	Interventional Single Group Assignment, OL, MC, Ph I/II, Single Arm	Mexico	Convalescent Plasma	–	PCD: November 2020 SCD: December 2020
NCT04366245	Interventional RCT, Parallel Assignment, OL, MC, Ph I/II	Spain	Hyperimmune Plasma	Standard of Care	PCD: December 2021 SCD: December 2021
NCT04374565	Interventional Single Group Assignment, OL, Ph II, Single Arm	USA	High-Titre Anti-SARS-Cov-2 Plasma (200–400 ml, Given Preferably In 1 Day But Allowed To Be Given Over 2 Days, Titre To Be Determined After Unit Has Been Infused)	–	PCD: April 5, 2021 SCD: April 5, 2021
NCT04357106	Interventional Single Group Assignment, OL, Ph II, Single Arm	Mexico	Convalescent Plasma (200 ml, Single Dose)	–	PCD: July 2020 SCD: August 2020
NCT04359810	Interventional RCT, Parallel Assignment, DB, Ph II	USA	Convalescent Plasma (200–250 ml)	Standard Plasma (200–250 ml)	PCD: December 2020 SCD: April 2021
NCT04385186	Interventional RCT, Parallel Assignment, SB, MC, Ph II	Colombia	Inactivated Convalescent Plasma (2 × 200 ml ABO -Rh, Over 2 Days), Supportive Treatment	Supportive Treatment	PCD: November 30, 2020 SCD: December 30, 2020
NCT04376034	Interventional NR, Sequential Assignment, OL, Ph III	USA	Convalescent Plasma (Moderate Severity; Adults, 200–250 ml; Paediatric, 10 ml/Kg Up To 1 Unit Of Plasma, And Severe/Critical; Adults, 1–2 Units; Paediatric, 10 ml/Kg Up To 2 Units)	Mild Severity Without Convalescent Plasma	PCD: March 30, 2021 SCD: March 30, 2021
NCT04377672	Interventional Single Group Assignment, OL, Ph I, Single Arm	USA	Convalescent Plasma (1–2 Units, 200–250 ml/Unit, ⩾1:320 Anti-SARS-Cov-2 Antibody Titre, 5 ml/Kg With A Maximum Of 500 ml)	–	PCD: May 28, 2022 SCD: May 28, 2022
NCT04358783	Interventional RCT, Parallel Assignment, QB, Ph II	Mexico	Convalescent Plasma (200 ml)	Best Available Therapy	PCD: February 1, 2021 SCD: May 30, 2021
NCT04381936	Interventional RCT, Factorial Assignment, OL	United Kingdom	Convalescent Plasma, Lopinavir-Ritonavir, Dexamethasone, Hydroxychloroquine, Azithromycin, Tocilizumab	Standard Of Care	PCD: December 2021 SCD: December 2031

*Source: 'Clinicaltrials.gov' (https://Clinicaltrials.gov/).
CBP, convalescent blood products; COVID-19, coronavirus disease 2019; DB, double-blinded; IV, intravenous; MC, multi-centred; NR; non-randomised; OD, once daily; OL, open label; Ph I-III, phase I-III; QB, quadruple-blinded; RCT, randomised control trial; SARS, severe acute respiratory syndrome; SB, single-blinded; SC, single-centred; TB, triple-blinded; TDS, ter die sumendum; PCD, primary completion data; SCD, study completion date.

needed with an emphasis on long-term complications and safety profile.

On 31 March 2020, a case series by Zhang *et al.* described clinical improvement in four COVID-19 patients following CBP administration.[41] Initially, all four patients were unresponsive to empiric treatment; however, after CBP transfusion (range: 200–2400 ml), the viral load decreased rapidly and all the patients were subsequently cleared of SARS-CoV-2 infection.

On 6 April 2020, Wu *et al.* reported the characteristics of SARS-CoV-2 specific NAb from plasma collected from 175 recovered COVID-19 patients in a preprint cohort study.[42] It was revealed that the detection of such NAbs is possible within 10–15 days after disease onset. Furthermore, higher plasma NAb titres and spike-binding antibodies were positively correlated with age ($p < 0.0001$ and $p = 0.0003$, respectively). NAb titres were also correlated to C-reactive protein (CRP) [correlation coefficient (r) = –0.432, $p < 0.0001$] and lymphocyte count (r = –0.389, $p < 0.0001$), respectively. However, 30% of patients failed to develop high NAbs titres after COVID-19 infection. It was concluded that CBP from donors should be titrated before use as a passive antibody therapy due to the highly variable levels of NAbs.

On 11 April 2020, a case series by Pei *et al.* described the effects of CBP in three COVID-19 patients.[43] The first patient received CBP on day 12 of admission and was discharged by day 26. The second patient received CBP by day 27 and the viral nucleic acid turned negative after 4 days. The third patient suffered severe anaphylactic shock after receiving 30 ml of convalescent plasma from a 51-year-old pregnant woman. CBP treatment was immediately stopped, and the patient ultimately recovered and was discharged. This case highlights the importance of patient selection. Overall, the study showed that CBP use could lead to viral clearance as demonstrated by a negative viral nucleic acid test with a significant reduction in symptoms; however, careful patient selection should be conducted to prevent any adverse reactions.

On 28 April 2020, a case series by Duan *et al.* investigated the efficacy of CBP therapy in 10 severely ill COVID-19 patients.[44] In addition to antivirals and supportive care, patients were given 200 ml of CBP, NAb titre >1:640, with a median time of infusion at 16.5 days of symptom onset. The primary and secondary endpoints were the safety profile of CBP use and symptomatic improvement, respectively. Within 3 days post transfusion, oxyhaemoglobin increased, lymphocyte count increased (0.65×109/l *versus* 0.76×109/l) and CRP decreased (55.98 mg/l *versus* 18.13 mg/l). Within 7 days post transfusion, a variable radiological improvement was observed, and viral load was undetectable in seven patients. No ADRs were observed. The authors concluded that CBP was well tolerated, and its use was associated with clinical improvement and neutralisation of viremia in COVID-19 patients.

On 29 April 2020, a case series by Zeng *et al.* assessed CBP efficacy in six critically ill COVID-19 patients.[45] The intervention group received 200–600 ml CBP (median volume: 300 ml) at a median infusion time of 21.5 days, following the first detection of viral shedding. The control and intervention group achieved 21.4% and 100% viral clearance before death ($p = 0.005$), with the intervention group all testing negative for SARS-CoV-2 RNA within 3 days of transfusion. Furthermore, the survival rate appeared to be longer in the intervention compared with the control group ($p = 0.03$); however, there were 5 deaths in the intervention and 14 in the control groups. Death in the intervention group was attributed to late CBP transfusion, and no immediate ADRs were reported. They concluded that CBP therapy has the potential to halt viral shedding and lengthen survival in patients without the end-stage disease if administered early in the course of the disease.

Rajendran *et al.* conducted a systematic review on 1 May 2020, with five eligible studies.[50] Based on the existing clinical evidence, they concluded that: (i) elevation in NAb titres with the disappearance of viral RNA was noted in nearly all patients following CBP administration, (ii) CBP had a beneficial effect on the clinical picture, and (iii) CBP might decrease mortality in critical COVID-19 patients. CBP was found to be safe and clinically effective, with a reduction in mortality. However, they recommended more extensive multicentre clinical trials to have conclusive evidence for efficacy.

On 22 May 2020, a preprint by Liu *et al.* described a matched control study comparing the outcomes

of severe to life-threatening COVID-19 cases receiving CBP ($n=39$).[46] All 39 patients were given two CBP units (250 ml per unit), with a SARS-CoV-2 anti-spike antibody titre of >1:320, over 1–2 h at a median of 4 days from admission to transfusion. Patients were also receiving concomitant therapy that included azithromycin ($n=31$), broad-spectrum antibiotics ($n=29$), hydroxychloroquine ($n=36$), non-specified investigational anti-virals ($n=1$), therapeutic anticoagulation ($n=26$), corticosteroids ($n=22$), and interleukin-6 inhibitors ($n=3$). By day 14, clinical conditions deteriorated in both groups (18.0% intervention *versus* 24.3% control, $p=0.167$). The effects of CBP seemed to be confounded by therapeutic anticoagulants (unadjusted *versus* adjusted OR: 0.90 *versus* 0.84). Furthermore, the plasma group was associated with improved survival (log-rank test: $p=0.039$) (plasma *versus* 1:4 matched control *versus* 1:2 matched control: 12.8% *versus* 24.4% *versus* 21.6% mortality). In a covariates-adjusted Cox model, CBP transfusion significantly improved survival in non-intubated patients [hazard ratio (HR): 0.19; 95% CI: 0.05–0.72; $p=0.015$] but not in intubated patients (HR: 1.24; 95% CI: 0.33–4.67; $p=0.752$). There was no evidence to suggest that the effect of CBP relied on symptom duration. Finally, it was concluded that CBP transfusion might be associated with higher survival rates; however, they also recommended a larger RCT to establish these findings.

On 26 May 2020, a case series by Salazar *et al.* enrolled 25 severe and/or life-threatening SARS-CoV-2 cases to evaluate clinical improvement following CBP therapy.[47] The primary outcome was clinical disease severity measured through modification of the World Health Organisation (WHO) six-point scale. The patients received 300 ml of CBP, with a titre ranging from 1:0 to 1:1350 for the receptor binding and ectodomain of the SARS-CoV-2 spike protein. One patient was noted to receive a second dose 6 days after the initial dose. Concomitantly, patients were also receiving other treatments; tocilizumab, steroids, hydroxychloroquine, azithromycin, ribavirin and/or lopinavir/ritonavir, and remdesivir. On day 7, 36% ($n=9$) improved from baseline, 52% ($n=13$) remained unchanged, and 12% ($n=3$) deteriorated. Seven amongst nine were discharged. On day 14, 76% ($n=19$) improved from baseline, and four additional patients were discharged, eight improved from baseline, three remained unchanged, three deteriorated, and one patient died due to non-transfusion related complications. Overall, the average length of hospital stay and post-transfusion length-of-stay were 14.3 days (range 2–25 days) and 11 days (range 1–21 days), respectively. The authors showed that CBP is a safe treatment option for severe COVID-19 disease, but concomitant therapy prevented definitive conclusions on CBP as a monotherapy.

An open-label multi-centre RCT by Li *et al.*, published on 3 June 2020, examined 103 SARS-CoV-2 infected patients to assess CBP efficacy.[48] The primary outcome was time to clinical improvement before day 28. Patients were stratified based on disease severity (45 severe and 58 life-threatening conditions) and separated into two groups: CBP with standard treatment ($n=52$) and standard treatment alone as a control ($n=51$). Within 28 days, clinical improvement was observed in 51.9% ($n=27$; 21 severe and 6 life-threatening groups) and 43.1% ($n=22$; 15 severe and 7 life-threatening groups) in both CBP and control group (diff: 8.8%, 95% CI: −10.4%–28.0%; HR: 1.40, 95% CI: 0.79–2.49; $p=0.26$). Comparing severe/life-threatening cases against their respective control groups, the hazard ratio was 2.15 (95% CI: 1.07–4.32; $p=0.03$) and 0.88 (95% CI: 0.30–2.63; $p=0.83$). Two patients developed ADRs; however, they improved with supportive care. CBP with standard treatment, when compared with the control, was not associated with a statistically significant clinical improvement within 28 days. However, the trial was discontinued early due to the drop in overall COVID-19 cases in China.

A systematic review by Pimenoff *et al.* on 8 June 2020, published as a preprint in medRxiv examined 10 studies evaluating CBP therapy in 61 severely infected COVID-19 patients.[51] Efficacy was measured through the time of recovery and the presence of viral RNA post-transfusion. Upon admission, 72.1% ($n=44$) had ARDS and fever, while the remaining 27.9% ($n=17$) had mild disease. In addition to CBP therapy, most patients received arbidol, lopinavir/ritonavir, and interferon-alpha-1b and corticosteroids ($n=46$; 75%). A total of 52 patients had between 200 ml and 500 ml of CBP each; however, 9 patients received an additional 300 ml ($n=1$), 400 ml ($n=4$), 600 ml ($n=2$), 900 ml ($n=1$) and 2400 ml ($n=1$)

within a week, following non-response to the initial CBP dose and the presence of clinical deterioration. The CBP titres were not specified. In total, 50.8% ($n=31$) recovered within the first week and 39.3% ($n=24$) recovered between 8 and 29 days following CBP transfusion. There were no available recovery data in 9.8% ($n=6$). Regarding prevalence of viral RNA post transfusion, 66.7% ($n=24$) and 30.6% ($n=11$) were negative within the first week and 8–29 days, respectively. There was no significant difference in recovery rate after CBP therapy between gender, or the presence of underlying comorbidities, receiving CBP within 3 weeks or beyond following symptom onset. It was concluded that CBP therapy was safe and had a positive recovery response in about half of patients, particularly those younger than 60 years. However, a definitive conclusion regarding the effectiveness of CBP was difficult due to the relatively small number of patients and multiple concomitant treatments.

On 15 June 2020, an *in vivo* study by Rogers *et al.* attempted to discover NAbs through the antibody response against SARS-CoV-2.[36] This was undertaken *via* two approaches: (i) the development of viral neutralisation assays using a replication-competent virus [SARS-CoV-2 Washington strain (USA-WA1/2020)] and a pseudovirus (PSV) (murine leukemia virus (MLV)-based PSV) in target cells (HeLa-ACE2), and (ii) the establishment of a SARS-CoV-2 cohort of 17 donors based on donor plasma receptor binding domain (RBD) in PSV assays. RBD-binding titres reached EC_{50} at 10^3 serum dilutions, with positive correlations observed between RBD binding and PSV neutralisation. A total of 33 antibodies were isolated from three donors (CC6, CC12 and CC25), where, ultimately, lineages MAb CC12.1 and CC12.23 were placed into Syrian hamster animal models. Both anti-SARS-CoV-2 NAbs were given at five different concentrations, starting at 8 μg/animal to 2 mg/animal for the two intervention groups. In contrast, the control group received a single dose of 2 mg anti-dengue virus antibody. Each group was then challenged intranasally with 1×10^6 PFU of USA-WA1/2020 12 h post infusion; 5 days following the SARS-CoV-2 challenge, the hamsters were weighed as a measure of disease, and lung tissue was collected to measure the viral load. The CC12.1 group had an average of 16.7%, 15.8%, 8.0%, 0.0% and 0.0% body weight loss for dosages of 8μg, 31 μg, 125 μg, 500 μg and 2 mg, respectively, against control (13.6%). Similar viral loads were observed for CC12.1 dosages of 2 mg, 500 μg and 125 μg, while the control and CC12.1 doses 8 μg and 31 μg exhibited higher viral loads. MAb 12.23 demonstrated no evidence of protection. Sera collected before the SARS-CoV-2 challenge suggest that approximately 22 μg/ml of NAb ($1160\times$PSV neutralisation IC_{50}) confers full protection, while 12 μg/ml ($630\times$PSV neutralisation IC_{50}) is sufficient for 50% reduced disease as measured by weight loss. They concluded that MAb CC12.1 directly competes with angiotensin converting enzyme 2 (ACE-2) with a potential for prophylactic, therapeutic, and vaccine applications. As evident, SARS-CoV-2 shows strong ACE-2 binding affinity due to modification of the functional receptor binding sequence as compared with other coronavirus families, and this improved binding pattern could be utilised to block viral cell entry.[52]

On 22 June 2020, another *in vivo* study by Iwatsuki-Horimoto *et al.* examined the replicative ability and pathogenesis of SARS-CoV-2 within Syrian hamsters.[37] Post-infection sera were collected from hamsters infected with either high ($10^{5.6}$ PFU) or low (10^3 PFU) dosages of the SARS-CoV-2 UT-NCGM02 strain. Infected sera were given either 1 or 2 days post-infection while two control groups received uninfected hamster sera. The hamsters receiving CBP 1 day post-infection were found to have significantly lower viral titres in the nasal turbinates ($p<0.05$) and lungs ($p<0.01$) compared with control groups. Similarly, statistically insignificant lower viral titres were reported in hamsters receiving CBP 2 days post infection compared with control (5.9 ± 1.8 log10 PFU $\pm$ SD/g *versus* 7.8 ± 0.1 PFU $\pm$ SD/g). Hamsters with SARS-CoV-2 infection had evoked NAbs resulting in the protection of hamsters from further infection, and viral replication was prevented more effectively in lungs than in nasal turbinates. The study concluded that anti-SARS-CoV-2 polyclonal hyperimmune globulin from CBP derived from COVID-19 patients and MAbs against SARS-CoV-2 could reduce viral loads in patients.

Can we trust existing studies?

As stated by Kalil *et al.*, we must be cautious in a fallacy on unproven drug efficacy.[53] It is not necessarily true that any death must be due to disease, and, likewise, any survival must be due

to therapeutic intervention. Past studies relating to SARS and MERS lend no substantial credibility to the efficacy of CBP. They were inconsistent, with vague methodology, and had several limitations like small sample sizes, lacked of large-scale trials, blinding, randomisation and control groups, and tested many concomitant treatments.[54] Although we did not perform quality assessment, we found the majority of existing CBP clinical studies in COVID-19 to be mainly case-based, lacking randomisation and standardisation, with sub-standard quality of methodology, and thus having low applicability and generalisability. Selection bias may also significantly skew the results, contributing to an already difficult interpretation.[48,55] Therefore, additional RCTs must be conducted to provide conclusive evidence.

Perks of CBP transfusion

CBP has the capacity for adverse reactions, similar to regular plasma transfusions.[56] Mild allergy is common, but serious adverse events like transfusion-associated circulatory overload (TACO) are possible, with an elevated risk in the elderly with acute lung damage under mechanical ventilation and those with viral myocarditis.[57] Furthermore, the risk of complement and coagulation pathways activation with CBP is also a concern, due mainly to a potential for complement-dependent antibody enhancement due to COVID-19.[58] Also, the potential of blood-borne infection cannot be ignored. The Pathogen Reduction Technology (PRT) system, using ultraviolet light and riboflavin, have shown an effective reduction of the SARS-CoV-2 in plasma and blood products without decreasing the quality of the blood products, which could be utilised to reduce the risk of transfusion-related viral transmission.[59] However, CBP is thoroughly tested before its use and specially screened for hepatitis B/C, human immunodeficiency virus (HIV), and other infections. Notably, SARS-CoV-2 is not a blood-borne pathogen; therefore, CBP is safe and theoretically the risk of SARS-CoV-2 transmission from donor CBP is not possible.[60]

Recommendations

We found some potential limitations of the clinical utility of CBP as a viable therapy in COVID-19, notably, (i) lack of robust clinical evidence, (ii) sufficient production of CBP, and (iii) production of CBP with consistent standard and safety. However, given the antiviral history of CBP and the absence of a definitive therapy against COVID-19, certain authorities such as the United States (US) Food and Drug Administration (FDA) have urgently authorised the therapeutic use of CBP, albeit within the framework of the strict guidelines suggested by scientific entities.[58,61,62] This is to standardise treatment, minimise any unforeseen ADRs and allow for subsequent academic investigations.

As of 11 June 2020, 63 interventional trials investigating the efficacy of CBP against COVID-19 were listed on the 'ClinicalTrials.gov' (https://clinicaltrials.gov/) (Table 2). Therefore, it would be interesting to wait for their outcomes to have a definitive conclusion.

Finally, we can say that CBP, either as a monotherapy or in combination with other antiviral drugs, could be an option. Although the optimal antibody titre is unknown, the FDA recommends titer of 1:160, which could be as low as 1:80 if higher titres are unavailable.[63] Similarly, while there are uncertainties regarding the timing of CBP delivery during the course of the disease, studies have shown greater clinical recovery and discharge rate when given within 14 days of illness and poor clinical response after 16 days post-symptoms.[19,20] Therefore, the CBP infusion should be of high titre, serologically screened for blood-borne pathogens, administered within 14 days of symptom onset, and the patient should be monitored during and after infusion to observe for any potential ADRs.

Conclusion

The clinical evidence for CBP against COVID-19 is insufficient. Some current anecdotal studies demonstrate promising therapeutic potential, but these studies do not meet the academic rigours to substantiate its use with confidence. However, the compassionate use of CBP in critically ill COVID-19 patients can be an option while we are awaiting a definitive answer from ongoing RCTs.

Study highlights

1. Currently, clinical evidence on CBP is limited to observational studies and further RCTs or large prospective studies are necessary to provide conclusive evidence.

2. Given encouraging early *in vivo* evidence and predicaments in therapeutic options, the compassionate use of CBP against COVID-19 can be an option in the ongoing crisis.
3. Clinicians and researchers should regularly update and adhere to the available credible evidence and findings of ongoing clinical trials.

Author contributions

KCVL, AS and YA made substantial contributions to the conception and study design, data acquisition and interpretation. All authors were involved in drafting the manuscript as well as the revision process. All authors have approved the final version of the manuscript.

Conflict of interest statement

The authors declare that there is no conflict of interest.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

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