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A REVIEW OF COVID-19 CONVALESCENT PLASMA CLINICAL TRIALS AND PROTOCOLS FOR SARS-COV-2

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ABSTRACT

Context: COVID-19 has developed into a public health emergency of international concern. Treatment of COVID-19 is limited to supportive care with no therapies or vaccines approved. It is constructive to conduct a review of COVID-19 convalescent plasma (CCP) trials and protocols for SARS-CoV-2.

Evidence Acquisition: 8 databases were searched on May 1 2020, including CNKI, PubMed, Cochrane Library, *etc.* with search fields "Title Abstract Keyword" of "Convalescent plasma AND COVID-19". The outcome of interest was clinical benefits, mortality, viral load, viral antibody titers, adverse events as well as RCT trials protocols for COVID-19.

Results: The search retrieved five completed clinical trials and nine clinical research protocols for SARS-CoV-2. The five finished trials involved 27 patients with biases due to non-RCT methodology. All subjects after CCP demonstrated normalized temperature, absorbed lung lesions, resolved ARDS, removed ventilation with decreased viral load and increased antibody. The nine RCT protocols are randomized clinical studies with NCT04344535, NCT04345289 and NCT04323800 in masking, and the rest in open-label. The other eight trials will verify the efficacy and safety of CCP to treat COVID-19 apart from NCT04323800 to prevent COVID-19.

NCT04344535, NCT04323800, NCT04346446 employ standard donor plasma in controlled groups, in contrast to the standard of care with NCT04348656, NCT04342182, NCT04333251 and NCT04345523; NCT04332835 adds Hydroxychloroquine 800 mg for ten days to both treatment and control groups; NCT04345289 is a complicated 6-armed placebo-controlled trial.

Primary and secondary outcome measures can be summarized as (-) charges of 7-point ordinal scale; (=) charges in SARS-CoV-2 RNA, anti-SARS-CoV-2 titers, CRP, IL-6 etc.

Conclusions: CCP can normalize temperature, absorb lung lesions, resolve ARDS, remove ventilation, and is an effective and safe option to treat COVID-19. The nine RCT trials will establish the efficacy of CCP for COVID-19 from the perspective of evidence-based medicine.

KEYWORDS : SARS-CoV-2; COVID-19; Convalescent plasma; Passive antibody transfer; Neutralizing antibody

1. Context

COVID-19 has developed into a public health emergency of international concern. As of May 1 2020, more than 3.2 million patients have been diagnosed worldwide with more than 240,000 died, and more than 200 countries and regions affected[1]. Treatment of COVID-19 is limited to supportive care with no therapies or vaccines approved[2]. The clinical studies on COVID-19 are still few and limited.

Passive immunotherapy has been employed to treat infectious diseases since the 1890s. The convalescent plasma with high-titer neutralizing antibodies can be exploited to treat specific diseases to reduce symptoms and mortality[3]. **Medical researchers have been applying CCP to COVID-19 recently**[4,5]. The US FDA also recommended CCP for SARS-CoV-2[6,7]. Several reviews have found that all finished clinical trials were considered to be biased due to non-RCT methodology[8-10]. Moreover, several RCT Protocols registered by Cochrane Central Register of Controlled Trials do not finish and do not publish any results either.

It is constructive to conduct a review of CCP Clinical trials and protocols for SARS-CoV-2.

2. Evidence Acquisition

Eight databases were searched on May 1 2020, including China National Knowledge Infrastructure (CNKI), Wanfang Data, PubMed, Medline, EMBASE, Google Scholar, Cochrane Library, International Clinical Trials Registry Platform(ICTRP) with search fields "Title Abstract Keyword" of "Convalescent plasma AND COVID-19" or " Convalescent plasma AND SARS-CoV-2". The outcome of interest was clinical benefits, mortality, viral load, viral antibody titers, adverse events as well as RCT clinical trials protocols for COVID-19.

3. Results

The search retrieved five relevant completed clinical trials[11-15] and nine clinical research protocols[16-24] for SARS-CoV-2.

Table 1: The Efficacy and Safety of the Five CCP Clinical Trials for SARS-CoV-2

Researcher	Duan[11]	Shen[12]	Zhang[13]	Ahn[14]	Ye[15]
Country	China	China	China	South Korea	China
Date in 2020	January 23 to February 19	January 20 to March 25	February 16 to March 15	February 22 and March 6	February 11 to March 18
Cases	6 males 4 females, Age ($\tilde{x}$ =52.5 years), Cerebral cardiovascular diseases and Hypertension (n=4).	Three males Two females, Age (36-65 years), Hypertension with mitral insufficiency (n=1)	69 years/F, hypertension 55 years/M, COPD 73years/M, hypertension & chronic renal failure. 31years/F, pregnant 247 days	71years/M 67 years/F, hypertension	69 years /M, 75 years /F 56 years /M, Bronchitis 63 years /F, Sjogren syndrome 28 years /F, 57 years /M

CCP Dosage	200 mL, titer >1:640	400 mL, titer >1:1000	200-900-2400 ml	500 mL	200-400-600ml
Antiviral drugs	Arbidol, Remdesivir, Ribavirin Peramivir	Interferon 1b, Arbidol Lopinavir, Ritonavir Favipiravir, Darunavir	Arbidol, Lopinavir Ritonavir, Ribavirin Interferon or 2b Oseltamivir,	Hydroxychloroquine, Lopinavir Ritonavir	Arbidol
CCP date	Onset to CCP x =16.5 days	After admission 10^{th}- 22th days	After admission 12^{th}- 19^{th} days	After admission 10th days; After admission sixth days	After symptom 33^{rd} - 50^{th} days
Status	Mechanical ventilation or Nasal cannula oxygenation	Mechanical ventilation or ECMO	Mechanical ventilation or ECMO	Mechanical ventilation	Mechanical ventilation or Nasal cannula oxygenation
Outcome	Clinical symptoms improved, pO2 increased within 3 days, Neutralizing antibodies increased, Lung lesions absorbed gradually.	Temp normalized pO2 increased, Neutralizing antibody increased ARDS resolved, Mechanical ventilation removed.	pO2 increased IgM decreased to the normal range IgG was persistently positive Mechanical ventilation removed Lung lesions absorbed gradually.	Mechanical ventilation removed.	Symptoms improved, Alleviation of respiratory distress, IgM and IgG increased Lung lesions absorbed gradually.
Viral load	Decreased to negative (n=7), Neutralizing antibody increased to 1:640 (n=9)	Decreased to negative within 12 days	Decreased to negative 18^{th}- 46^{th}days	Decreased to negative 9^{th}- 26^{th} days	Five decreased to negative. One not mentioned
Side effect	evanescent facial red spot/ no severe side effect	No	No	No	No

Table 2: The Nine CCP Protocols Registered by Cochrane Central Register of Controlled Trials

RCT Trials	Inclusion and Exclusion Criteria for CCP	Treatment and Control Groups	Outcome Measures
NCT04344535 from US[16] April 8 2020--August 31 2021 Enrollment: 500 Masking: Quadruple	Inclusion: 1. Age >18 years; 2. Hospitalized with PCR+ COVID-19. Exclusion: 1.Patient within 14 days of admission. 2. Unable to tolerate a 450-550 mL CCP. 3. Contraindication to transfusion. 4. Pregnant or breastfeeding.	Treatment: 450-550 mL CCP antibody titer > 1:320 Control: 450-550 mL Standard Donor Plasma	Primary: 1.The number of days a patient is receiving invasive mechanical ventilation during 28 days post-randomization. 2. Patients who die during 28 days post-randomization are assigned 0 Secondary: All-cause mortality until 90 days post-randomization
NCT04323800 from US[17] May 1 2020-- January 2023 Enrollment: 150 Masking: Triple	Inclusion: 1. Age >18 years; 2.Close contact exposure within 96 hours. 3. High-risk exposure. 4. age >65 with Chronic diseases Exclusion: 1.Receipt blood product in the past 120 days. 2.Psychiatric or cognitive illness or recreational drug/alcohol use. 3. Confirmed COVID-19. 4. Contraindication to	Treatment: 200-250 mL CCP antibody titer >1:64 Control: 200-250 mL Standard Donor Plasma	Primary: Changes of 7-point ordinal scale at day 28 1.Not hospitalized, no activities limitation. 2.Not hospitalized, activities limitation. 3. Hospitalized, no requiring O2 4.Hospitalized, requiringO2. 5. Hospitalized, non-invasive ventilation or high flow oxygen. 6.Hospitalized, invasive mechanical ventilation or ECMO. 7.Death. Secondary: 1.Anti-SARS-CoV-2 titers at days 0,1,3,7,14,90; 2.Rates of SARS-CoV-2 PCR positivity at

	transfusion. 5. Inability to complete therapy.		days 0, 7, 14, 28; 3.Duration of SARS-CoV-2 PCR positivity at days 0, 7, 14, 28; 4.Peak quantity levels of SARS-CoV-2 RNA at days 0, 7, 14, 28.
NCT04332835 from Colombia[18] May 1 2020--December 31 2020 Enrollment: 80 Masking: Open Label	Inclusion: 1.Age=18--60 years 2. Hospitalized with PCR+ COVID-19. Exclusion: 1.Pregnant or breastfeeding. 2.Contraindication to transfusion. 3.Critical in ICU. (CURB-65 < 2; SOFA >6.6) 4.Surgical procedures in the last 30 days. 5 Chronic diseases	Treatment: CCP: 500 mL + Hydroxychloroquine: 400 mg Bid for 10 days Control: Hydroxychloroquine: 400 mg Bid for ten days	Primary: 1. Change in Viral Load at Days 0, 4, 7, 14,28. 2.Change in IgM at Days 0, 4, 7, 14 ,28. 3. Change in IgG at Days 0, 4, 7, 14, 28. Secondary: 1.The proportion of patients in ICU (days 7, 14, 28) 2.Days of ICU (days 7, 14, 28) 3.Days of Hospitalization (days 7, 14, 28) 4.The proportion of patients with mechanical ventilation (days 7, 14, 28). 5.Days with mechanical ventilation (days 7, 14, 28). 6.Clinical status. 7. Mortality (days 7, 14 ,28)
NCT04348656 from Canada[19] April 27 2020--December 31 2020 Enrollment: 1200 Masking: Open Label	Inclusion: 1. Age ≥16 2. Hospitalized with PCR+ COVID-19. 3.Receiving O2 Exclusion: The onset of symptoms >12 days before randomization Intubated or plan in place for intubation Plasma is contraindicated A decision in place for no active treatment	Treatment: 500 mL CCP Standard of care Control: Standard of care	Primary: Intubation or death in 30 days Secondary: 1.Time in hours to intubation from randomization in 30 days 2.In-hospital death in 90 days 3.Length of stay in ICU in 30 days 4.Need for ECMO in 30 days 5.Renal replacement therapy in 30 days 6.Myocarditis in 30 days 7.Serious adverse events in 30 days
NCT04342182 from Netherlands[20] April 8 2020--July 1 2020 Enrollment: 426 Masking: Open Label	Inclusion: 1. Age >18 2. Hospitalized with PCR+ COVID-19. Exclusion: Participation in another intervention trial on the treatment of COVID-19	Treatment: 300mL CCP Standard of care Control: Standard of care	Primary: Mortality in 60 days or discharge Secondary: 1.Hospital days 2. Weaning from oxygen therapy; 3.Mortality; 4.ICU days; 5. Decrease in SARS-CoV2 shedding from airways (airway samples will be taken on day 1, 3, 5, 7,10,14, and at discharge); 6.CTL and NK cell immunity (Blood will be drawn on day 1, 7, 14); 7. Severe Adverse Events.

Table 3: The Nine CCP Protocols Registered by Cochrane Central Register of Controlled Trials

RCT Trials	**Inclusion and Exclusion Criteria for CCP**	**Treatment and Control Groups**	**Outcome Measures**
NCT04346446 from India[21] April 21 2020--June 30 2020 Enrollment: 40 Masking: Open Label	Inclusion: 1. Age > 65 2.Respiratory distress, RR ≥30 beats/min 3.Oxygen saturation level less than 93% 4.PaO2/FiO2 ≤ 300 mmHg 5.Lung infiltrates > 50% within 24 to 48 hours 6.With comorbidities such as COPD, CKD, *etc*. 7.Multi-organ failure. Exclusion: 1.Age < 18 2.Patients with known comorbid	Treatment: 200--600 mL CCP Control: 200--600 mL Random Donor Plasma	Primary: The proportion of patients free of mechanical ventilation in 7 days Secondary: 1. Mortality in Day 28 2. Improvement in Pa02/Fi02 on Day 2,7 3.Improvement in SOFA score in Day 2,7 4.Duration of hospital Stay in Day 28 5. Duration of ICU stay in Day 28 6.Requirements of Vasopressor in Day 28

RCT Trials	Inclusion and Exclusion Criteria for CCP	Treatment and Control Groups	Outcome Measures
	3.Multi-organ failure or requiring mechanical ventilation 4.Pregnancy 5.HIV and Hepatitis 6. Obesity BMI>35 kg/m2 7.Expected life expectancy less than 24 hours 8.Failure to give informed consent. 9.Hemodynamic instability requiring vasopressors 10.Previous allergic history to plasma		7.Days free of dialysis in Day 28
NCT04345289 from Denmark[22] April 20 2020—June 15 2021 Enrollment: 1500 Masking: Quadruple	Inclusion: 1.age≥18 2.Confirmed COVID-19. 3. The onset of first experienced symptom no more than 10 days before admission Exclusion: 1.Inevitable death within 24 hours. 2.Allergic to study drug. 3.Participating in other drug clinical trials 4.Pregnant or breastfeeding 5.eGFR<30 ml/min 6.Severe liver dysfunction 7.TB, Hepatitis B or C, Retinopathy, Maculopathy, Neurogenic hearing loss. 8.Absolute neutrophil count <1000 mm3; 9.ALT> 5 times 10.Platelet count <50,000 per mm3 11.Chemotherapy or immunomodulatory drugs within 30 days before inclusion; 12.Corticosteroids in a dose higher than prednisolone 20 mg per day for 4 weeks;	Treatment: 600 mL CCP infusion + 1.14 mL saline injection(placebo) Control: Group A. 600 ml saline infusion (placebo) + 200 mg/1.14 mL sarilumab injection Group B. 600 ml saline infusion (placebo) + 1.14 mL saline injection(placebo) Group C. 600 mg Hydroxychloroquine oral for 7 days Group D. 4 mg baricitinib oral for 7 days Group E. 3 glucose monohydrate capsules for 7 days(placebo)	Primary: All-cause mortality or need for invasive mechanical ventilation in 28 days Secondary: Changes of 7-point ordinal scale at day 90. Number of days without organ-failure in 28 days The mortality rate at 7, 14, 21, 28, 90 days. Length of hospital stay in 90 days. Days requiring O2 in 90 days. Adverse events in 90 days
NCT04333251 from US[23] April 1 2020-- December 31 2022 Enrollment: 115 Masking: Open Label	Inclusion: 1.Age≥18 2.Hospitalized within 3 to 7 days from the beginning of the illness Exclusion: 1.Age <18 2.Receipt of pooled immunoglobulin in past 30 days 3.Contraindication to transfusion	Treatment: 1-2 units CCP antibody titer >1:64 Standard of care Control: Standard of care	Primary: Reduction in oxygen and ventilation support in 28 days. Secondary: N/A
NCT04345523 from Spain[24] April 3 2020—July 2020 Enrollment: 278 Masking: Open Label	Inclusion: 1.Age≥18 male or female 2. Confirmed COVID-19. 3.Hospitalization without mechanical ventilation or high flow oxygen devices. Exclusion: 1. Requiring mechanical ventilation (invasive or non-invasive) or high flow oxygen devices. 2.More than 12 days since onset 3.Participation in any other clinical trial. 4.Inevitable death within 24 hours. 5.Any incompatibility or allergy to the administration of human plasma. 6.eGFR <30 ml/min. 7. More than 12 days after onset	Treatment: CCP with no stated dosage Standard of care Control: Standard of care	Primary: Changes of 7-point ordinal scale at day 15 Secondary: Changes of 7-point ordinal scale at day 29 Mortality of any cause at day 15 Neutralizing antibody activity against SARS-CoV-2. Viral load at Days 1,3,5,8,11,29 CRP, lymphocyte count, LDH, D Dimer, IL-6, coagulation tests at baseline and days 3, 5, 8, 11, 15,29. Adverse Events at day 29

The five finished trials involved 27 patients with biases due to non-RCT methodology. All subjects after CCP transfusion demonstrated normalized temperature, absorbed lung lesions, resolved ARDS, removed ventilation with decreased viral load and increased antibody as well as zero mortality and no severe side effect[11-15].

The nine clinical research protocols are randomized clinical treatment studies with three trials in quadruple masking (participant, care provider, investigator, outcomes Assessor), one trial in triple masking (participant, care provider, investigator), and the rest 5 in open-label. Five trials will be finished in 2020 in contrast to two in 2021 and two in 2022. The other eight trials will verify the efficacy and safety of CCP to treat COVID-19 apart from NCT04323800 from US[17] to prevent COVID-19.

NCT04344535 from US[16], NCT04323800 from US[17], NCT04346446 from India[21] employ standard donor plasma in controlled groups in contrast to the standard of care with NCT04348656 from Canada[19], NCT04342182 from Netherlands[20], NCT04333251 from US[23] and NCT04345523 from Spain[24]; NCT04332835 from Colombia[18] adds Hydroxychloroquine 800 mg for ten days to both treatment and control groups; NCT04345289 from Denmark[22] is a complicated 6-armed placebo-controlled trial.

Primary and secondary outcome measures can be summarized as charges of 7-point ordinal scale on a specified day, or during a specific period: Not hospitalized, no activities limitation; Not hospitalized, activities limitation; Hospitalized, no requiring O_2; Hospitalized, requiring O_2; Hospitalized, non-invasive ventilation or high flow oxygen; Hospitalized, invasive mechanical ventilation or ECMO; Death. charges in SARS-CoV-2 RNA, anti-SARS-CoV-2 titers, CRP, IL-6 etc. on a specified day, or during a specific period.

4. Conclusions

CCP can normalize temperature, absorb lung lesions, resolve ARDS, remove ventilation, and is an effective and safe option to treat COVID-19. The nine RCT trials will establish the efficacy of CCP for COVID-19 from the perspective of evidence-based medicine.

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The authors contributed equally to the article.
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