Published online 2020 August 31 **Systematic Review**

Comparative Analysis of Nine COVID-19 Convalescent Plasma Protocols Registered by Cochrane Central Register of Controlled Trials

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Received 2020 May 22; **Revised** 2020 July 17; **Accepted** 2020 July 31.

Abstract

Context: Coronavirus disease 2019 (COVID-19) has progressed into a public health emergency of international concern. Passive immunotherapy has been successfully used for the treatment of infectious diseases since the 1890s. It is necessary and constructive to compare and analyze COVID-19 convalescent plasma (CCP) randomized controlled trials (RCTs) to help clinicians to have a potential option for COVID-19.

Evidence Acquisition: In this study, eight databases were searched on May 1, 2020, such as China National Knowledge Infrastructure, PubMed, and Cochrane Library, with the search fields of "Title Abstract Keyword" of "Convalescent plasma AND COVID-19" or " Convalescent plasma AND SARS-CoV-2". The outcome of interest was clinical RCTs for COVID-19.

Results: The search retrieved nine relevant CCP protocols for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). All nine trials were randomized, parallel assignment, interventional, clinical treatment studies with NCT04344535, NCT04345289, and NCT04323800 masking and the rest open-label. The estimated enrollment is within the range of 40-1,500 subjects, and five trials will be finished in 2020 as opposed to two in 2021 and two in 2022. Except for NCT04323800 on the prevention of COVID-19, other eight trials will test and verify the effectiveness and safety of CCP for the treatment of COVID-19.

The used dosage of CCP is within the range of 200-600 mL. NCT04344535, NCT04323800, and NCT04346446 use standard donor plasma in controlled groups in comparison to NCT04348656, NCT04342182, NCT04333251, and NCT04345523 without any positive drug in controlled groups. NCT04332835 adds hydroxychloroquine to both groups, and only NCT04345289 is a six-armed placebo-controlled trial.

Primary and secondary outcome measures are differently expressed in the nine trials. Nevertheless, they can be summarized as ㈠ changes in time, day, and number of a 7-point ordinal scale. There are ㈡ changes in SARS-CoV-2 ribonucleic acid (i.e., viral load), anti-SARS-CoV-2 antibody titers (i.e., immunoglobulin M and immunoglobulin G), C-reactive protein, lymphocyte count, lactate dehydrogenase, and interleukin 6 on a specified day or during a specific period.

Conclusion: The nine well-designed RCT trials will establish the efficacy of CCP for the treatment of SARS-CoV-2 from the perspective of evidence-based medicine.

Keywords: Convalescent plasma, COVID-19, Neutralizing antibody, Passive antibody transfer, SARS-CoV-2

1. Context

Coronavirus disease 2019 (COVID-19) has progressed into a public health emergency of international concern, with grave humanitarian consequences. Up to May 1, 2020, more than 3.2 million patients have been diagnosed with COVID-19 worldwide, and more than 240,000 individuals have died, affecting more than 200 countries and regions (1). At present, the treatment of COVID-19 is limited to supportive care, and there are no approved therapies or vaccines (2). However, there have been a limited number of clinical studies carried out on COVID-19.

Passive immunotherapy has already been successfully used for the treatment of infectious diseases since the 1890s. Convalescent plasma (CP) containing high titer neutralizing antibodies can be used for individuals with specific clinical diseases for the reduction of symptoms and mortality (3). For the treatment of COVID-19, medical studies have been recently applying COVID-19 convalescent plasma (CCP) to this pandemic (4, 5). The US Food and Drug Administration has recently recommended CCP for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (6, 7).

Several systematic reviews have detected that all completed studies were considered to have bias due to nonrandomized controlled trial methodology (8-10), along with some randomized controlled trials (RCTs) registered by Cochrane Central Register of Controlled Trials, which were not finished and did not publish any results. It is necessary and constructive to compare and analyze the CCP protocols to help clinicians to have a potential option for the treatment of COVID-19.

2. Evidence Acquisition

Eight databases were searched on May 1, 2020, including China National Knowledge Infrastructure, Wanfang Data, PubMed, Medline, EMBASE, Google

Scholar, Cochrane Library, and International Clinical Trials Registry Platform, with the search fields of "Title Abstract Keyword" of "Convalescent plasma AND COVID-19" or " Convalescent plasma AND SARS-CoV-2". The outcome of interest was the RCT methodology for the treatment of COVID-19.

3. Results

The search retrieved nine relevant CCP protocols for SARS-CoV-2 registered this year by the Cochrane Central Register of Controlled Trials (11-19) (Tables 1, 2, 3).

Table 1. Comparative analysis of nine coronavirus disease 2019 convalescent plasma protocols registered by Cochrane Central Register of Controlled Trials

Principal investigator	Elliott Bennett-Guerrero (11)	Shmuel Shoham (12)	Juan Manuel Anaya Cabrera (13)
Sponsor	Stony Brook University	Johns Hopkins University	Universidad del Rosario
Country	United States	United States	Colombia
CT gov accession no.	NCT04344535	NCT04323800	NCT04332835
Recruitment status	Enrolling by invitation	Not yet recruiting	Not yet recruiting
Research period	April 8, 2020-August 31, 2021	May 1, 2020-January 2023	May 1, 2020-December 31, 2020
Estimated enrollment	500	150	80
Study type	Interventional (Clinical trial)	Interventional (clinical trial)	Interventional (clinical trial)
Allocation	Randomized	Randomized	Randomized
Intervention model	Parallel assignment	Parallel assignment	Parallel assignment
Masking	Quadruple (i.e., participant, care provider, investigator, and outcome assessor)	Triple (i.e., participant, care provider, and investigator)	None (open-label)
Primary purpose	Treatment	Treatment	Treatment
Official title	Convalescent plasma for the reduction of complications associated with COVID-19 infection: A randomized trial comparing the effectiveness and safety of high-titer anti-SARS-CoV-2 plasma vs. standard plasma in hospitalized patients with COVID-19 infection	Convalescent plasma to stem coronavirus: A randomized blinded phase II study comparing the efficacy and safety of human coronavirus immune plasma vs. control (i.e., SARS-CoV-2 nonimmune plasma) in adults exposed to COVID-19	Convalescent plasma for patients with COVID-19: A randomized open-label parallel controlled clinical study
Inclusion criteria for plasma recipients	1. Age>18 years 2. Hospitalized with PCR + COVID-19	1. Age >18 years 2. Close-contact exposure within 96 h 3. High-risk exposure 4. age >65 years with chronic diseases	1. Age range: 18-60 years 2. Hospitalized with PCR + COVID-19
Exclusion criteria for Plasma recipients	1. Patient within 14 days of admission 2. Unable to tolerate 450-550 mL of CCP 3. Contraindication to transfusion 4. Pregnant or breastfeeding	1. Receipt blood product in the previous 120 days 2. Psychiatric or cognitive illness or recreational drug/alcohol use 3. Confirmed COVID-19 4. Contraindication to transfusion 5. Inability to complete therapy	1. Pregnant or breastfeeding 2. Contraindication to transfusion 3. Critical in ICU (confusion, urea, respiratory rate, blood pressure, and 65 years of age or older<2; Sequential Organ Failure Assessment score>6.6) 4. Surgical procedures in the last 30 days 5. Chronic diseases
Treatment group	450-550 mL of CCP antibody titer >1:320	200-250 mL of CCP antibody titer >1:64	CCP (500 mL) +hydroxychloroquine (400 mg Bid for 10 days)
Control group	450-550 mL of standard donor plasma	200-250 mL of standard donor plasma	Hydroxychloroquine (400 mg Bid for 10 days)
Primary outcome measures	1. The number of days a patient is receiving invasive mechanical ventilation during 28 days after randomization 2. Patients who die during 28 days after randomization are assigned at 0	Changes of 7-point ordinal scale at day 28 1. Not hospitalized, no activity limitation 2. Not hospitalized, activity limitation 3. Hospitalized, no requiring O2 4. Hospitalized, requiring O2 5. Hospitalized, noninvasive ventilation or high flow oxygen 6. Hospitalized, invasive mechanical ventilation or Extracorporeal Membrane Oxygenation 7. Mortality	1. Changes in viral load at days 0, 4, 7, 14, and 28 2. Changes in immunoglobulin M at days 0, 4, 7, 14, and 28 3. Changes in immunoglobulin G at days 0, 4, 7, 14, and 28
Secondary outcome measures	All-cause mortality up to 90 days after randomization	1. Anti-SARS-CoV-2 titers at days 0, 1, 3, 7, 14, and 90 2. Rates of SARS-CoV-2 PCR positivity at days 0, 7, 14, and 28 3. Duration of SARS-CoV-2 PCR positivity at days 0, 7, 14, and 28 4. Peak quantity levels of SARS-CoV-2 ribonucleic acid at days 0, 7, 14, and 28	1. The proportion of patients in ICU (days 7, 14, and 28) 2. Days of ICU stay (days 7, 14, and 28) 3. Days of hospitalization (days 7, 14, and 28) 4. The number of patients with mechanical ventilation (days 7, 14, and 28) 5. Days with mechanical ventilation (days 7, 14, and 28) 6. Clinical status 7. Mortality (days 7, 14, and 28)

COVID-19: Coronavirus disease 2019
SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2
PCR: Polymerase chain reaction
CCP: Coronavirus disease 2019 convalescent plasma
ICU: Intensive care unit

Table 2. Comparative analysis of nine coronavirus disease 2019 convalescent plasma protocols registered by Cochrane Central Register of Controlled Trials

Principal investigator	Donald M Arnold (14)	Bart Rijnders (15)	Shiv Kumar Sarin (16)
Sponsor	Hamilton Health Sciences Corporation	Erasmus Medical Center	Institute of Liver and Biliary Sciences
Country	Canada	Netherlands	India
CT gov accession no.	NCT04348656	NCT04342182	NCT04346446
Recruitment status	Not yet recruiting	Recruiting	Recruiting
Research period	April 27, 2020-December 31, 2020	April 8, 2020-July 1, 2020	April 21, 2020-June 30, 2020
Estimated enrollment	1200	426	40
Study type	Interventional (clinical trial)	Interventional (clinical trial)	Interventional (clinical trial)
Allocation	Randomized	Randomized	Randomized
Intervention model	Parallel assignment	Parallel assignment	Parallel assignment
Masking	None (open-label)	None (open-label)	None (open-label)
Primary purpose	Treatment	Treatment	Treatment
Official title	A randomized open-label trial of convalescent plasma for hospitalized adults with acute COVID-19 respiratory illness (CONCOR-1)	Convalescent plasma therapy from recovered COVID-19 patients as therapy for hospitalized patients with COVID-19	Efficacy of convalescent plasma therapy in severely sick COVID-19 Patients: A pilot randomized controlled trial
Inclusion criteria for plasma recipients	1. Age≥16 years 2. Hospitalized with PCR + COVID-19 3. Receiving O_2	1. Age>18 years 2. Hospitalized with PCR + COVID-19	1. Age>65 years 2. Respiratory distress, respiratory rate≥30 beats/min 3. Oxygen saturation level less than 93% 4. P_aO_2/FiO_2≤300 mmHg 5. Lung infiltrates>50% within 24-48 h 6. With comorbidities, such as chronic obstructive pulmonary disease and chronic kidney disease 7. Multiorgan failure
Exclusion criteria for plasma recipients	1. The onset of symptoms>12 days before randomization 2. Intubated or plan in place for intubation 3. Plasma is contraindicated 4. A decision in place for no active treatment	Participation in another intervention trial on the treatment of COVID-19	1. Age<18 years 2. Patients with known comorbidities 3. Multiorgan failure or requiring mechanical ventilation 4. Pregnancy 5. Human immunodeficiency viruses and hepatitis 6. Obesity: Body mass index>35 kg/m^2 7. Expected life expectancy less than 24 h 8. Failure to give informed consent 9. Hemodynamic instability requiring vasopressors 10. History of allergy to plasma
Treatment group	500 mL of CCP	300 mL of CCP	200-600 mL of CCP
Control group			200-600 mL of random donor plasma
Primary outcome measures	Intubation or mortality in 30 days	Mortality in 60 days or discharge	The number of patients free of mechanical ventilation in 7 days
Secondary outcome measures	1. Time in hours to intubation from randomization in 30 days 2. In-hospital mortality in 90 days 3. Length of ICU stay in 30 days 4. Need for Extracorporeal Membrane Oxygenation in 30 days 5. Renal replacement therapy in 30 days 6. Myocarditis in 30 days 7. Serious adverse events in 30 days	1. Hospital stay days 2. Weaning from oxygen therapy 3. Mortality 4. ICU stay days 5. Decrease in SARS-CoV2 shedding from airways (airway samples will be taken on days 1, 3, 5, 7, 10, and 14 and at discharge) 6. Cytotoxic T lymphocyte and natural killer cell immunity (blood will be drawn at days 1, 7, and 14) 7. Severe adverse events	1. Mortality at day 28 2. Improvement in P_aO_2/FiO_2 at days 2 and 7 3. Improvement in Sequential Organ Failure Assessment score at days 2 and 7 4. Duration of hospital stay at day 28 5. Duration of ICU stay at day 28 6. Requirement of vasopressor at day 28 7. Days free of dialysis at day 28

COVID-19: Coronavirus disease 2019
PCR: Polymerase chain reaction
CCP: Coronavirus disease 2019 convalescent plasma
ICU: Intensive care unit

NCT04344535 in US (11), NCT04342182 in the Netherlands (15), NCT04346446 in India (16), and NCT04345523 in Spain (19) have been recruiting patients; however, NCT04323800 in US (12), NCT04332835 in Colombia (13), NCT04348656 in Canada (14), NCT04345289 in Denmark (17), and NCT04333251 in US (18) have not yet been recruiting patients. Due to the delay between the starting date of the clinical study and date of registration information update, it is temporarily impossible to know whether these five RCT studies have been conducting.

All nine trials are randomized, parallel assignment, interventional, clinical treatment studies with NCT04344535 in US (11) and NCT04345289 in Denmark (17) in quadruple (i.e., participant, care provider, investigator, and outcome assessor) masking, NCT04323800 in US (12) in triple (i.e., participant, care provider, and investigator) masking, and the rest open-label. The estimated enrollment is within the range of 40-1,500 subjects, and five trials will be finished in 2020 as opposed to two in 2021 and two in 2022. Except for NCT04323800 in US (12) expected to use CCP for the prevention of COVID-19, other eight trials will test and verify the effectiveness and safety of CCP for the treatment of COVID-19. Inclusion and exclusion criteria for CCP are slightly different according to the different study populations and objectives.

The used dosage of CCP is within the range of 200-

Table 3. Comparative analysis of nine coronavirus disease 2019 convalescent plasma protocols registered by Cochrane Central Register of Controlled Trials

Principal investigator	Thomas Benfield (17)	Baylor Research Institute (18)	Cristina Avendaño Solá (19)
Sponsor	Hvidovre University Hospital	Baylor Research Institute	Puerta de Hierro University Hospital
Country	Denmark	United States	Spain
CT gov accession no.	NCT04345289	NCT04333251	NCT04345523
Recruitment status	Not yet recruiting	Not yet recruiting	Recruiting
Research period	April 20, 2020-June 15, 2021	April 1, 2020-December 31, 2022	April 3, 2020-July, 2020
Estimated enrollment	1500	115	278
Study type	Interventional (clinical trial)	Interventional (clinical trial)	Interventional (clinical trial)
Allocation	Randomized	Randomized	Randomized
Intervention model	Parallel assignment	Parallel assignment	Parallel assignment
Masking	Quadruple (i.e., participant, care provider, investigator, and outcomes assessor)	None (open-label)	None (open-label)
Primary purpose	Treatment	Treatment	Treatment
Official title	Efficacy and safety of novel treatment options for adults with COVID-19 pneumonia: A double-blinded randomized multi-stage six-armed placebo-controlled trial in the framework of an adaptive trial platform	Evaluating convalescent plasma to decrease coronavirus associated complications: A phase I study comparing the efficacy and safety of High-titer anti-Sars-CoV-2 plasma vs. best supportive care in hospitalized patients with interstitial pneumonia due to COVID-19	Multicenter randomized clinical trial of convalescent plasma therapy versus standard of care for the treatment of COVID-19 in hospitalized patients
Inclusion criteria for plasma recipients	1. Age≥18 years 2. Confirmed COVID-19 3. The onset of first experienced symptom no more than 10 days before admission	1. Age≥18 years 2. Hospitalized within 3-7 days from the onset of the illness	1. Age≥18 years (male or female) 2. Confirmed COVID-19 3. Hospitalization without mechanical ventilation or high flow oxygen devices
Exclusion criteria for plasma recipients	1. Inevitable mortality within 24 h 2. Allergy to study drug 3. Participation in other drug clinical trials 4. Pregnant or breastfeeding 5. eGFR<30 ml/min 6. Severe liver dysfunction 7. Tuberculosis, hepatitis B or C, retinopathy, maculopathy, neurogenic hearing loss 8. Absolute neutrophil count<1,000 mm^3 9. Alanine aminotransferase>5 times 10. Platelet count<50,000 per mm^3 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	1. Age<18 years 2. Receipt of pooled immunoglobulin in previous 30 days 3. Contraindication to transfusion	1. Requiring mechanical ventilation (invasive or noninvasive) or high flow oxygen devices 2. More than 12 days since onset 3. Participation in any other clinical trial 4. Inevitable mortality within 24 h 5. Any incompatibility or allergy to the administration of human plasma 6. eGFR<30 ml/min 7. More than 12 days after onset
Treatment group	600 mL of CCP infusion + 1.14 mL of saline injection (placebo)	1-2 units of CCP antibody CCP titer>1:64	
Control group	Group A: 600 ml of saline infusion (placebo) + 200 mg/1.14 mL of sarilumab injection Group B: 600 ml of saline infusion (placebo) + 1.14 mL of saline injection (placebo) Group C: 600 mg of hydroxychloroquine oral for 7 days Group D: 4 mg of baricitinib oral for 7 days Group E: 3 glucose monohydrate capsules for 7 days (placebo)		
Primary outcome measures	All-cause mortality or need for invasive mechanical ventilation in 28 days	Reduction in oxygen and ventilation support in 28 days	Changes of 7-point ordinal scale at day 15
Secondary outcome measures	1. Changes of 7-point ordinal scale at day 90 2. Number of days without organ-failure in 28 days 3. The mortality rate at days 7, 14, 21, 28, and 90 4. Length of hospital stay in 90 days 5. Days requiring O_2 in 90 days 6. Adverse events in 90 days	Not Available/Applicable	1. Changes of 7-point ordinal scale at day 29 2. Mortality of any cause at day 15 3. Neutralizing antibody activity against SARS-CoV-2 viral load at days 1, 3, 5, 8, 11, and 29 4. C-reactive protein, lymphocyte count, lactate dehydrogenase, D-dimer, interleukin 6, and coagulation tests at baseline and days 3, 5, 8, 11, 15, and 29 5. Adverse events at day 29

COVID-19: Coronavirus disease 2019
eGFR: Estimated glomerular filtration rate
CCP: Coronavirus disease 2019 convalescent plasma
SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2

600 mL. NCT04344535 in US (11), NCT04323800 in US (12), and NCT04346446 in India (16) use the corresponding amount of standard donor plasma in controlled groups; nevertheless, NCT04348656 in Canada (14), NCT04342182 in the Netherlands (15), NCT04333251 in US (18), and NCT04345523 in Spain (19) are without a positive drug in controlled groups. NCT04332835 in Colombia (13) adds hydroxyl-chloroquine (400 mg Bid for 10 days to both groups), and only NCT04345289 in Denmark (17) is a six-armed placebo-controlled trial.

Primary and secondary outcome measures are differently expressed in the nine trials. However, they can be summarized as (-) changes in time, day, and

number of 7-point ordinal scale on a specified day or during a specific period (i.e., Not hospitalized, no activity limitation; Not hospitalized, activity limitation; Hospitalized, no requiring O_2; Hospitalized, requiring O_2; Hospitalized, noninvasive ventilation or high flow oxygen; Hospitalized, invasive mechanical ventilation or Extracorporeal Membrane Oxygenation; Mortality. In addition, there are (二) changes in SARS-CoV-2 ribonucleic acid (i.e., viral load), anti-SARS-CoV-2 antibody titers (i.e., immunoglobulin M and immunoglobulin G), C-reactive protein, lymphocyte count, lactate dehydrogenase, and interleukin 6 on a specified day or during a specific period.

4. Discussion

The CP has been successfully applied for the treatment of infectious diseases, such as H1N1 (20, 21), severe acute respiratory syndrome (22), H5N1 (23), Ebola (24), and other viral infections. The results of studies have shown that CCP can limit virus reproduction and eliminate SARS-CoV-2 (4, 5). However, systematic reviews (25, 26) have demonstrated that all reported studies are case reports without a control group with a high risk of bias due to nonrandomized controlled trial methodology (10, 27).

Fortunately, the nine well-designed RCTs have been conducting to determine the effectiveness, dosage, and safety of CCP for the prevention and treatment of COVID-19, and whether hydroxyl-chloroquine is useful for the treatment of COVID-19. As the number of clinical studies in this regard continues to increase, the research protocols may adjust the CCP dosage and other research drugs based on the evidence.

5. Conclusion

The nine well-designed RCTs will determine the efficacy of CCP for the treatment of SARS-CoV-2 from the perspective of evidence-based medicine.

Footnotes

Authors' Contribution: The authors equally contributed to the present study.
Conflict of Interests: The authors declare that there is no conflict of interest.
Funding/Support: The present study was self-funded.

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