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

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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, NCT04335251, 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 differentially expressed in the nine trials. Nevertheless, they can be summarized as changes in time, day, and number of a 7-point ordinal scale. There are 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, and the Cochrane Central Register of Controlled Trials.
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 |
| CTgov 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 | 1. Close-contact exposure within 96 h | 1. Age range: 18-60 years |
|                        | 2. Hospitalized with PCR + COVID-19 | 2. High-risk exposure | 2. Hospitalized with PCR + COVID-19 |
|                        |                               | 3. Days of hospitalization (days 7, 14, and 28) | 3. Days of hospitalization (days 7, 14, and 28) |
|                        |                               | 4. Contraindication to transfusion | 4. Contraindication to transfusion |
| Exclusion criteria for Plasma recipients | 1. Patient within 14 days of admission | 1. Receipt blood product in the previous 120 days | 1. Pregnant or breastfeeding |
|                        | 2. Unable to tolerate 450-550 mL of CCP | 2. Psychiatric or cognitive illness or recreational drug/alcohol use | 2. Contraindication to transfusion |
|                        | 3. Contraindication to transfusion | 3. Confirmed COVID-19 | 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. Pregnant or breastfeeding | 4. Inability to complete therapy | 4. Surgical procedures in the last 30 days |
|                        | 5. Inability to complete therapy | 5. Hospitalized, noninvasive ventilation or high flow oxygen | 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 | Changes of 7-point ordinal scale at day 28 | Changes of 7-point ordinal scale at day 28 | Changes of 7-point ordinal scale at day 28 |
|                        | 1. Not hospitalized, no activity limitation | 1. Not hospitalized, no activity limitation | 1. Changes in viral load at days 0, 4, 7, 14, and 28 |
|                        | 2. Not hospitalized, activity limitation | 2. Not hospitalized, activity limitation | 2. Changes in immunoglobulin M at days 0, 4, 7, 14, and 28 |
|                        | 3. Hospitalized, no requiring O2 | 3. Hospitalized, no requiring O2 | 3. Changes in immunoglobulin G at days 0, 4, 7, 14, and 28 |
|                        | 4. Hospitalized, requiring O2 | 4. Hospitalized, requiring O2 | 4. Changes in immunoglobulin G at days 0, 4, 7, 14, and 28 |
|                        | 5. Hospitalized, noninvasive ventilation or high flow oxygen | 5. Hospitalized, noninvasive ventilation or high flow oxygen | 5. Changes in immunoglobulin G at days 0, 4, 7, 14, and 28 |
|                        | 6. Hospitalized, invasive mechanical ventilation or Extracorporeal Membrane Oxygenation | 6. Hospitalized, invasive mechanical ventilation or Extracorporeal Membrane Oxygenation | 6. Hospitalized, invasive mechanical ventilation or Extracorporeal Membrane Oxygenation |
|                        | 7. Mortality | 7. Mortality | 7. Mortality |
| Secondary outcome measures | All-cause mortality up to 90 days after randomization | All-cause mortality up to 90 days after randomization | 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, 4, 7, 14, and 28 | 1. The proportion of patients in ICU (days 7, 14, and 28) |
|                        | 2. Rates of SARS-CoV-2 PCR positivity at days 0, 4, 7, 14, and 28 | 3. Duration of SARS-CoV-2 PCR positivity at days 0, 4, 7, 14, and 28 | 2. Days of ICU stay (days 7, 14, and 28) |
|                        | 3. Peak quantity levels of SARS-CoV-2 ribonucleic acid at days 0, 4, 7, 14, and 28 | 4. The number of patients with mechanical ventilation (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) | 4. The number of patients with mechanical ventilation (days 7, 14, and 28) |
|                        | 5. Clinical status | 6. Clinical status | 5. Clinical status |
|                        | 6. Clinical status | 7. Mortality (days 7, 14, and 28) | 6. Clinical status |

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
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), NCT0432835 in Colombia (13), NCT04348656 in Canada (14), NCT04345289 in Denmark (17), and NCT0433251 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-
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), NCT0433251 in US (18), and NCT04345523 in Spain (19) are without a positive drug in controlled groups.

NCT04332835 in Colombia (13) adds hydroxychloroquine (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 O₂; Hospitalized, requiring O₂; Hospitalized, noninvasive ventilation or high flow oxygen; Hospitalized, invasive mechanical ventilation or Extracorporeal Membrane Oxygenation; Mortality. In addition, there are □ 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 hydroxychloroquine 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.

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