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ORIGINAL RESEARCH

Use of convalescent plasma in the treatment of critically ill COVID-19 patients: a study protocol

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Abstract

Use of convalescent plasma (CP) has shown promising results during early studies of COVID-19 patients. This study aims to prepare a protocol for the use of CP to treat critically ill COVID-19 patients. This will be a multicentre, double-blinded, controlled randomised trial. Subjects will be randomly assigned to the treatments, and evaluations will be taken at baseline and at intervals according to the protocol. Only those subjects who meet all inclusion criteria will be enrolled in the study. The experimental treatment group will receive CP at volume of 6 mL/kg divided into two doses separated by 24 hours, in addition to the standard treatment for COVID-19. The control group will receive only the standard treatments. The result assessed at the end of this trial will be the primary and secondary endpoints. The primary endpoints (efficacy indicators) will be the discharge from the ICU, discharge from the hospital, days of hospitalisation, days on mechanical ventilation and death. The main secondary endpoints (safety indicators) will be the severe transfusion reactions and transfusion-transmitted diseases. The authors developed the study protocol using standardised criteria for the development of a clinical trial protocol. This study protocol addressed all aspects that are necessary for the standardised implementation of CP for the treatment of COVID-19 patients, including CP collection, administration, evaluation, and follow up.

Keywords

COVID-19; Convalescent plasma; Study protocol; Efficacy; Safety

1. Introduction

In December 2019, an outbreak of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection was discovered in Wuhan, China, and rapidly spread globally [1]. The World Health Organization (WHO) named the disease caused by this infection coronavirus disease 2019 (COVID-19). On 31 January 2020, the WHO classified the COVID-19 outbreak as a pandemic [2]. COVID-19 remains a significant threat to global health and the global economy. The use of convalescent plasma (CP) has shown promise in early studies with COVID-19 patients. CP is the liquid portion of blood from patients who have recovered from confirmed SARS-CoV-2 infection, which can be collected using a cell separator machine (apheresis). CP is thought to act through classical adoptive immunotherapy because the plasma collected from donors who have recovered from COVID-19 likely contains antibodies (proteins) that might provide passive immunity. CP can mediate immune mechanisms such as the neutralisation of viremia, the initiation of antibody-dependent cellular toxicity, and the modification of the inflammatory response. CP can also serve a non-immune system role through the restoration of coagulation factors [3]. Many patients diagnosed with COVID-19 develop antibodies one to two weeks after the presentation of symptoms [4, 5]. According to the United States Food and Drug Administration (FDA) recommendations, the SARS-CoV-2 neutralising antibody titre should be at least 1:160 [6]. Most individuals with previous COVID-19 developed measurable antibody responses and neutralizing antibodies; however, antibody titre measurement can be variable. Therefore, comparative studies between serological assays are needed to reach a consensus. Recent studies [7–12] have indicated that the administration of CP to critically ill patients has resulted in improved clinical, laboratory, and radiological status of patients, accompanied by decreased mortality. There is a need for more information to guide the treatment of COVID-19 patients. Several drugs have not yet proven to be effective, and current treatment consists of supportive care. This study aims to help gain evidence on the effect of CP in the treatment of COVID-19 patients at their early stage of critical illness. Until medications are available, CP is a potential therapy for COVID-19 patients. However, the safety, efficacy, precise indications of use, optimal time, dose, and titre for CP therapy are not well characterized. Thus, a protocol regarding the use of CP could help to provide treating doctors with scientific evidence on a potential therapeutic option and

better clinical management of critically ill COVID-19 patients. Furthermore, COVID-19 is becoming more aggressive with increased numbers of critically ill patients. The objective of this study was to prepare a guiding protocol for the use of CP in the treatment of critically ill COVID-19 patients to assess efficacy and safety.

2. Methods

2.1 Study design

This study will be performed as a multicentre, double-blinded, controlled randomised trial. Patients will be randomised to receive (experimental arm) or not receive (standard arm) CP in a 1:2 ratio. Subjects will be randomly assigned to the treatments, and evaluations will be taken at baseline and at intervals according to the protocol. Screening data will be reviewed to determine subject eligibility. Only those subjects who meet all inclusion criteria and exhibit none of the exclusion criteria will be enrolled in the study. The experimental treatment group will receive CP at volume of 6 mL/kg [13] divided into two doses separated by 24 hours based on experience with previous use of convalescent plasma therapy in COVID-19, in addition to the standard treatment as usual for COVID-19. The control group will receive only the standard treatments as usual for COVID-19, without CP's addition.

2.2 Sampling

A total sample size of 300 patients: 100 CP recipients and 200 matched controls (1:2 ratio), to detect a clinically significant difference between two groups (CP recipients versus matched controls) in 30-day mortality using a two-tailed z-test of proportions/Chi-Square test with 80% power and a 5% level of significance. Assuming that approximately 80% of the enrolled participants will achieve improvement, we envisage an 80% power to achieve a decision.

2.3 Eligibility criteria

The selection of participants will be based on the following inclusion and exclusion criteria.

2.3.1 Inclusion criteria

2.3.1.1 Recipients

(1) Patients who are willing and able to provide written informed consent or who have an authorized representative who can sign informed consent.

(2) Patient age is $\geq$18 years.

(3) Evidence of COVID-19 infection, according to the PCR test results of a nasopharyngeal swab or oropharyngeal swab/tracheal aspirate sample.

(4) Patients with peripheral capillary oxygen saturation (SPO_2) $\leq$94% on room air.

(5) Patients that require oxygen or mechanical ventilation.

(6) Patients with infiltrates on chest X-ray.

(7) COVID-19 patients at their early stage of critical illness (within 14 days of disease onset and three days of hospital admission).

2.3.1.2 Donors

(1) Donors who are willing to provide written informed consent.

(2) Patient age is $\geq$18 years.

(3) Fully recovered from confirmed COVID-19, according to the WHO guidelines.

(4) Eligible for blood donation, according to the WHO criteria.

(5) Negative for transfusion transmissible infections.

(6) Positive for Immunoglobulin G (IgG) against SARS-CoV-2.

2.3.2 Exclusion criteria

2.3.2.1 Recipients

(1) Patients who are participating in any other clinical trial examining anti-viral agents for COVID-19.

(2) Patients who receive any anti-viral agents against COVID-19 fewer than 24 hours before starting plasma therapy.

(3) Prior history of transfusion reaction.

(4) Patients with immunodeficiency diseases and low Immunoglobulin A (IgA).

(5) Females who are pregnant or breastfeeding a child.

2.3.2.2 Donors

(1) Pregnant women.

(2) Donors who previously received a transfusion, unless they screen negative for human leukocyte antigen (HLA) antibodies.

2.4 Criteria for discontinuing or modifying the allocated interventions

Any serious adverse events (SAE's) occurrence should be reported by the research team immediately, and the subject will be taken out of the trial after receiving full medical care. If an adverse event (AE) develops during the CP infusion, the infusion may be stopped. Infusion is generally paused in cases of itching; the participant is treated, and the infusion is cautiously re-initiated. Severe allergic reactions that will generally require the discontinuation of the infusion include: respiratory embarrassment, associated with dyspnoea, wheezing, stridor or hypoxemia; systolic blood pressure falling $<$90 mmHg or decreasing $>$30% from baseline or a diastolic decrease of $>$30% from baseline; development of tachycardia, with an increase in resting heart rate to $>$130 bpm; bradycardia $<$40 bpm, associated with dizziness, nausea or feeling faint; syncope or deterioration to a confused state; or any other symptom observed by the study clinician that warrants halting the infusion.

2.5 Recruitment

Each hospital's COVID-19 unit is responsible for the identification and targeted recruitment of convalesced patients to serve as CP donors, according to the eligibility criteria. Patients participating in the study will be recruited on a voluntary basis. A variety of methods will be used to recruit CP donors. These include: recovered patients who fulfill the criteria for the donation will be selected and contacted via phone and

appointment will be scheduled for those willing to donate plasma; motivational messages will be delivered to the public through social media platforms to encourage the recovered patients to donate CP.

2.6 Intervention

Donor CP from fully recovered COVID-19 patients will be collected using a cell separator machine (Trima Accel, Automatic Blood Collection System) (Fig. 1). A fully recovered donor is defined as any healthy adult who has recently recovered a confirmed COVID-19 infection, who is clinically asymptomatic for a minimum of 14 days and who has tested negative for SARS-CoV-2 twice using a real-time reverse transcriptase-polymerase chain reaction (RT-PCR) assay on a respiratory tract sample, with a minimum of 24 hours between the two sample collections. The collection of plasma will occur a minimum of four weeks after the initial onset of symptoms and at least two weeks after disease recovery. In addition, we will adhere to the WHO blood donor selection criteria for the assessment of donor suitability for blood donation [14, 15]. The COVID-19 unit will be responsible for the identification and targeted recruitment of convalesced patients who qualify to serve as CP donors. The donor antibody titre will be measured by an IgG ELISA detecting spike receptor-binding domain (S-RBD). A cut-off of CP with anti-SARS-CoV-2 antibody titre $\geq$1:160 will be used according to FDA recommendations. The expert blood bank staff are responsible for donor selection, pre-donation screening, and CP collection using standard operating procedures and according to international guidelines. CP will be labelled (as CP for investigational use only) using a Zebra Designer 2 system, and product safety and distribution to the hospital will follow the same protocols that were established by our study hospital [16, 17]. Donors who have not previously received a transfusion are preferable, to avoid the occurrence of transfusion-related acute lung injury (TRALI). Six hundred ml of CP will be collected from each donor in a single sitting. Viral inactivation through irradiation is mandatory if the CP will be used within six hours of collection, without freezing, to reduce any possibility of infection transmission [18]. The 600 mL CP will be divided into 200 mL doses. Donors can donate twice each month for up to 12 months, based on the American Association of Blood Bank (AABB) guidelines. The CP will be tested for transfusion-transmitted infections, according to the standard procedure for blood transfusion. Finally, CP will be stored as fresh frozen plasma (FFP) at $\leq$–18 °C, separate from plasma for routine use [19]. Selection of blood groups, according to ABO compatibility, is illustrated in (Table 1). Based on published studies examining the use of CP to treat previous respiratory viral epidemics, the proposed volume of plasma that will be used for each patient is 6 mL/kg of compatible CP, from a single donor, divided into two doses separated by 24 hours. The decision to administer CP will be approved by the treating team doctors, including a pulmonologist, infectious disease specialist, intensive care specialist, and haematologist. The CP request will require that all study criteria are fulfilled, and the CP request form will include the patient's demographic and clinical information (Table 2). Other staff that will participate in the trial will include physicians, immunologists, nurses, laboratory scientists, statisticians, and infectious diseases experts.

TABLE 1. ABO group selection order for the transfusion of fresh frozen plasma.

Patient ABO group	Fresh frozen plasma
O	
First choice	O
Second choice	A or B
Third choice	AB
A	
First choice	A
Second choice	AB
Third choice	B*
B	
First choice	B
Second choice	AB
Third choice	A*
AB	
First choice	AB
Second choice	A*
Third choice	B*

** Tested and negative for high-titre anti-A and anti-B.*
Adapted from: Joint United Kingdom (UK) Blood Transfusion and Tissue Transplantation. Services Professional Advisory Committee. https://www.transfusionguidelines.org/transfusion-handbook/2-basics-of-blood-groups-and-antibodies/2-4-the-abo-system

2.6.1 Relevant concomitant care that will be permitted or prohibited during the trial

- Regular prescription medications will be permitted.
- Over-the-counter medications will be prohibited.
- Herbal treatments/nutritional supplements will be prohibited.
- Blood products, as prescribed by the trial, will be permitted.

2.6.2 Provisions for post-trial care and *monitoring subject compliance*

Recipients will be followed up at four hours, seven days, and 30 days after infusion. Follow-up will be mandatory, and AEs will be closely monitored and reported to the institutional review board (IRB) chairman [20]. A follow-up form will be generated and filled out by the treating doctor to evaluate the safety and efficacy of the trial (Table 3).

2.6.3 Outcomes measurements

The result assessed at the end of this trial will be as follows.

TABLE 2. Convalescent plasma request form.

Convalescent plasma request form			
Patient information			
MRNO……..……Name……...……			
Age……...			
Gender……..……..…..…			
Contact address……..……..…			
Blood group……...…..……..……			
Date of admission……			
Ward/ICU…….……...			
COVID-19 diagnosis:	Confirmed ( )	Suspected ( )	
IgA deficiency:	Yes ( )	No ( )	
Clinical history			
Pregnancy ( )	Breastfeeding ( )	Transfusion reaction ( )	Alloantibody ( )
Comorbidities			
Hypertension ( )	Diabetes mellitus ( )		
Cancer/other immunosuppressive states ( )	COPD ( )	Other ( )	
Factors associated with the severity			
Thrombocytopenia ( )	Lymphopenia ( )		
D-dimer >4 ng/mL ( )	CRP >30 mg/L ( )		
CP team			
Provided consent	from the patient ( )	from his/her first-degree relatives ( )	
The decision of the CP team	Approved ( )	Not approved ( )	
Number of CP units	One ( )	Two ( )	Three ( )
Date……			
Intensive Care Specialist	Pulmonologist	Haematologist	Infectious Disease Specialist
Name:	Name:	Name:	Name:
Signature:	Signature	Signature	Signature

Abbreviations: MRNO, medical record number; ICU, intensive care unit; COVID-19, coronavirus disease 2019; IgA, immunoglobulin A; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; SOFA, sequential organ failure assessment; CP, convalescent plasma.

TABLE 3. Convalescent plasma assessment and follow-up form.

Convalescent plasma assessment and follow-up form					
Patient information					
MRNO……..……					
Name……					
Age……					
Gender……..……..					
Contact address……					
Blood group……..……					
Date of admission……..……..					
Ward/ICU……					
COVID-19 diagnosis:	Confirmed ( )	Suspected ( )			
IgA deficiency:	Yes ( )	No ( )			
Clinical Assessment and follow-up					
Parameters	Pre-infusion of CP	Four hours after the first dose	Seven days after the first dose	30 days after the first dose	On discharge day
Breathlessness					
Temperature					
Respiratory rate					
Pulse rate					
Blood pressure					
O2 saturation					
PaO2/Fio2					
Partial O2 pressure					
SOFA score					
CBC					
CRP					
D-dimer					
Chest X-ray					
Outcome					
CP team					
Date:					
Intensive Care Specialist	Pulmonologist	Haematologist	Infectious Disease Specialist		
Name:	Name:	Name:	Name:		
Signature:	Signature	Signature	Signature		

Abbreviations: MRNO, medical record number; ICU, intensive care unit; COVID-19, coronavirus disease 2019; IgA, immunoglobulin A; CP, convalescent plasma; SOFA, sequential organ failure assessment; CBC, complete blood count; CRP, C-reactive protein.

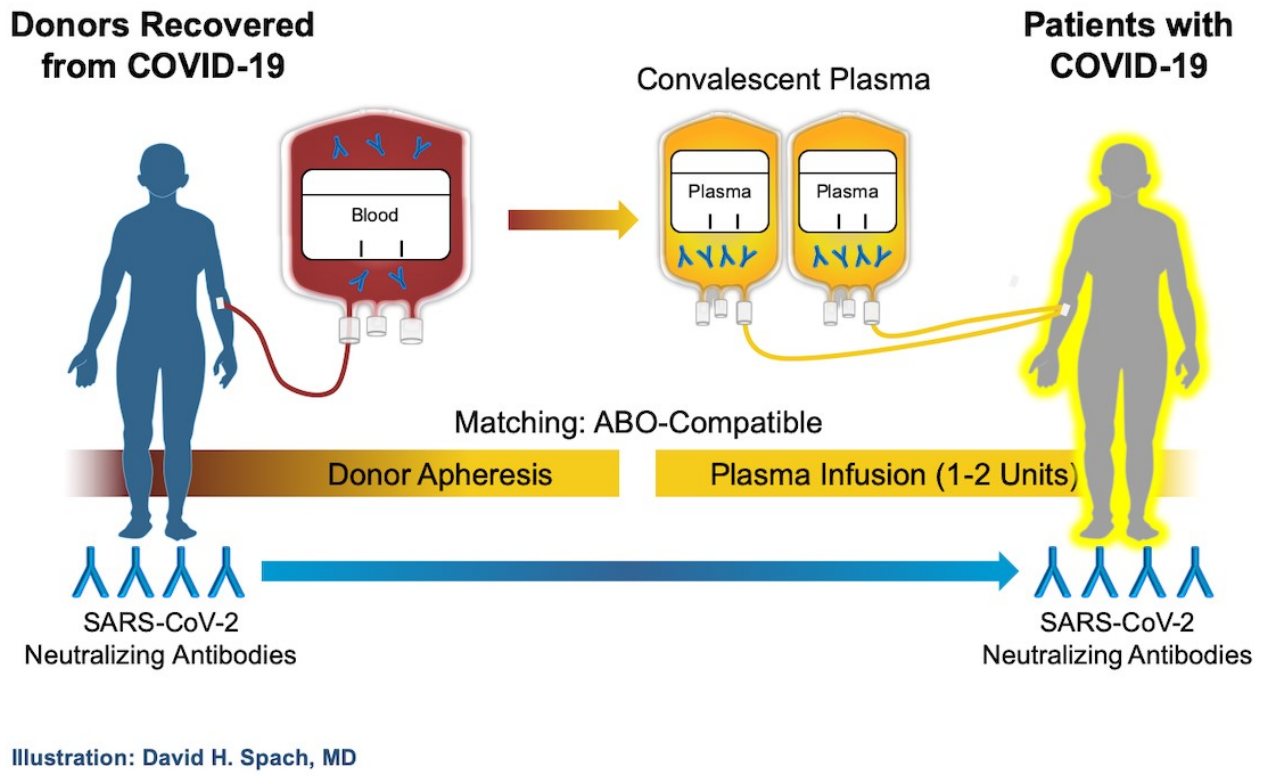

FIGURE 1. Collection and transfusion of two units of convalescent plasma.
The image was reproduced with the permission of David Spach, MD.

2.6.3.1 Efficacy indicators

The efficacy indicators include the primary endpoint parameters.

Primary endpoints will be:

- Discharge from the ICU
- Discharge from the hospital
- Days of hospitalisation
- Number of days on mechanical ventilation after the administration of CP
- Death
- SARS-CoV-2 viral clearance and viral load
- Inflammatory markers analyses
- Cytokine analyses
- Difference in oxygen saturation

2.6.3.2 Safety evaluation

The safety evaluation will include the secondary endpoints.

Secondary endpoints will be:

- Severe transfusion reactions
- Transfusion-transmitted diseases

2.6.4 Assignment of interventions

2.6.4.1 Allocation

The allocation to the intervention or control groups will occur in a randomised and blinded manner. The randomisation will be performed using computer-generated random numbers.

Patients who sign the informed consent will be randomised by the team into one of the two study arms:

- Experimental arm: will receive the standard treatment as usual, according to the local protocol, and two doses of compatible CP.
- Control arm: will receive only the standard treatment as usual, without the addition of CP (Fig. 2).

2.6.4.2 Blinding

Based on the objectives of the study, the identity of the intervention and control treatments will not be known to investigators, research staff, or patients to ensure the double-blinded administration of the study treatments. Access to the randomisation code will be strictly controlled to eliminate any forms of bias. The packaging of the CP concentrates and labelling will only be known to the principal investigator (PI). The clinical measurements obtained to describe the study results will be maintained confidential to avoid breaking the blind. The study blind will be broken upon completion of the clinical study after the study database has been locked. Only the PI will be aware of each subject's treatment assignments.

Double Blinding has taken care of the unanimity. High ethical standards will be maintained.

2.6.4.3 Procedure for unblinding if needed

During the study, the blind may be broken only in emergencies, when knowledge of the patient's treatment group becomes necessary for further patient management. In that case, the PI will discuss the emergency with the medical monitor before unblinding.

The study will be discontinued, and a review will be per-

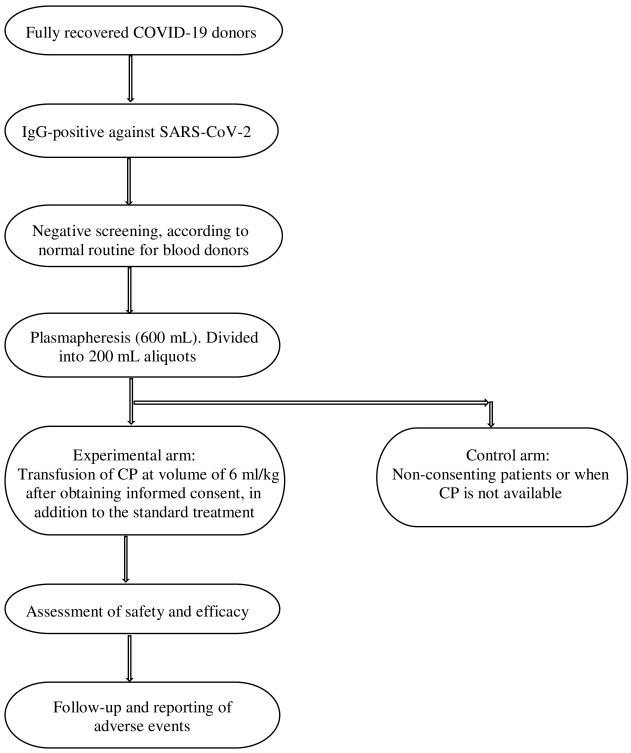

FIGURE 2. Diagram illustrating the steps for convalescent plasma donation and transfusion.

formed if any of the following events occur or if subject safety is at risk of becoming compromised:

(1) The unexpected death of any subject, in association with CP infusion.

(2) The occurrence of a life-threatening allergic/hypersensitivity reaction (anaphylaxis).

(3) Observed bronchospasm, urticaria, or angioedema requiring urgent support.

(4) At least one subject with an unexpected SAE associated with CP.

(5) An overall pattern of symptomatic, clinical, or laboratory events that the medical monitor considers to be associated with CP.

(6) Any other event that is considered to be an SAE in the good clinical judgment of the physician. All AEs will be appropriately documented.

Due to the risk of AEs associated with CP treatment, out of an abundance of caution, we will monitor the number of subjects in each trial arm that progress to an indication for the need for mechanical ventilation.

2.7 Data collection and management

2.7.1 Plans for the assessment and collection of outcomes

The data collected will be maintained secure and confidential. During the intervention, data from baseline and post-intervention will be verified for consistency during their entry and recorded for quality reasons into the main database.

2.7.2 Plans to promote participant retention and complete follow-up

Strict adherence to the protocol will enable us to retain the study subjects until the end of the study period. Loss to follow up will be minimised by ensuring the adequate maintenance of contact between the research team and the study subjects.

2.7.3 Data management

Collected data will be entered into a database and checked for consistencies upon entry by at least two members of the research team. At least 25% of the data will also be re-entered to check for inconsistencies.

2.7.4 Confidentiality

Personal information regarding each participant will be collected from the CP request form after obtaining informed consent. All personal information regarding participants will be shared only among the investigators, and confidentiality will be maintained through the use of a code for each patient, which will be only known to authorised individuals. The maintenance of confidentiality, as enshrined in the Nuremberg code, will be adhered to. This will protect the privacy of our clients, even after their deaths.

2.8 Statistical analysis plan

2.8.1 Statistical methods for primary and secondary outcomes

2.8.1.1 Primary Analysis, go/no-go decision, and power consideration

The time to one-point-improvement from randomisation will be compared in the framework of the Cox proportional hazards model. Specifically, the hazard ratio for improvement will be tested using a Wald test: if the one-sided *P*-value favouring the CP arm is less than 0.15, it will constitute a "go decision" during this proof-of-concept phase

2.8.1.2 The analysis will be intention-to-treat

Given the short study duration and the nature of the treatment, however, we anticipate minimal non-compliance or dropout.

Data collected and entered into records will be used in describing the study efficacy and safety. Categorical data will be presented in contingency tables with frequencies and percentages. Continuous data will be summarized with mean, median, quartiles, standard deviation, minimum and maximum. These will be presented as summary statistics by the amount and dosage of CP received, any dose modifications following observed toxicity, discontinuation or withdrawal from study treatment as the case may be, as well as drop-out.

The primary analysis will be assessed using the null hypothesis "the improvement observed for the primary endpoint among those with CP therapy versus those with standard treatment or the control arm are equal" as against the alternative hypothesis where the two groups are not equal at a two-sided significance level of α <5%. This will be determined by using the log-rank test stratified for the intervention group. The hazard ratio for those that receive the CP will also be determined using a Cox regression model stratifying for the factor together with a 95% confidence interval. The improvement

will be calculated and plotted using the Kaplan-Meier method together with 95% log-log-type confidence bands, for both study groups. In addition, cumulative improvement curves will also be calculated and produced separately for each individual group. Overall survival will be analyzed with a Cox regression model adjusting for treatment and patient group, determining hazard ratios with 95% confidence intervals and (descriptive) p-values. Survival estimates of the two groups will be determined using the Kaplan-Meier method together with 95% log-log-type confidence bands, and the 28-day survival rate will be given for both treatment groups together with 95% confidence intervals. Time until discharge will be assessed providing Kaplan-Meier estimates for the cumulative discharge rate for both groups and conducting a log-rank test stratified for the factor "patients receiving CP".

The secondary endpoint "requirement of mechanical ventilation (yes/no)" will be analyzed by means of a logistic regression model adjusting for the factors treatment and patient group. Also, absolute and relative frequencies will be given for this endpoint, together with 95% confidence intervals. The secondary endpoints SARS-CoV-2 viral load and antibody titres will be assessed over time with linear mixed models adjusting for the two study groups.

Adverse events will be reported and analyzed as absolute numbers and percentages as well as grading of individual toxicities. The most common AEs observed (at least in 10% of those receiving CP) will be determined. The assessment of safety will be based mainly on the frequency of adverse events and on the number of laboratory values that fall outside of pre-determined ranges and show progressive worsening from baseline during the study phase. Laboratory data will be summarized with summary statistics of raw data and any change from baseline values.

2.8.2 Interim analyses

All secondary efficacy analyses will be intention-to-treat. The Day-28 rating of the severity scale will be analysed using the Mann-Whitney U test. Longitudinal data collected over multiple days during the study period (e.g., PCR positivity, RNA) will be analysed using a generalised linear mixed model. Time-to-event variables (e.g., time to death) will be analysed using a Cox proportional hazards model. Continuous variables (e.g., duration of hospitalisation) will be analysed using the Mann Whitney U test. The treatment effects on these variables will be estimated with 95% confidence intervals.

2.8.3 Methods for additional analyses

We will compare the missing data patterns between the study arms and perform sensitivity analyses using different imputation approaches. However, due to the short study period, we anticipate minimal missing data. All efficacy analyses will be performed as intention-to-treat, although as-treated analyses will also be conducted to assess sensitivity.

2.9 Oversight and monitoring

2.9.1 Adverse event (AE)

An AE refers to any untoward or unfavourable medical occurrence in a human subject who has been administered an experimental product, including any abnormal signs, symptoms, or diseases, that is temporally associated with the subject's participation in research, regardless of whether it is believed to be related to the subject's participation in the research.

An AE does not include the following:

- Medical or surgical procedures, such as surgery, endoscopy, tooth extraction, and transfusion. The condition that led to the procedure may be an AE and must be reported.
- Pre-existing diseases, conditions, or laboratory abnormalities present or detected before the screening visit that do not worsen.
- Situations where an untoward medical occurrence has not occurred (e.g., hospitalisation for elective surgery, social and convenience admissions)
- Any medical condition or clinically significant laboratory abnormality with an onset date before the investigational product was administered to the subject and not related to a protocol-associated procedure is not considered to be an AE. These conditions are considered to be pre-existing and should be documented as medical history.

Pre-existing events or conditions that increase in severity or change in nature after the subject receives the investigational product will be considered AEs.

2.9.2 Serious Adverse Event (SAE)

Any AE temporally associated with the subject's participation in research that meets any of the following criteria:

- Results in death.
- Is life-threatening (places the subject at immediate risk of death from the event as it occurred).
- Requires inpatient hospitalisation or prolongs existing hospitalisation.
- Results in a persistent or significant disability/incapacity.
- Results in a congenital anomaly/birth defect.
- Any other AE that, based upon appropriate medical judgment, may jeopardise the subjects' health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

The AEs and SAEs related to CP are similar to those for standard plasma such as febrile/allergic reactions, transfusion-associated circulatory overload (TACO) and transfusion-related lung injury (TRALI) and blood transmitted infectious.

2.9.3 Investigator reporting requirements

The PI will report all AEs and SAEs to the Investigational New Drug (IND) sponsor within 48 hours of becoming aware of the event. The report to the IND sponsor will include the study investigator's preliminary assessment of seriousness, severity, and relatedness to the investigational treatment.

2.9.4 Plans for communicating significant protocol amendments to relevant parties

No deviation from the protocol is allowed, except in emergency cases to eliminate an immediate hazard to a research subject. However, the investigators will inform all stakeholders regarding any significant protocol modifications immediately.

2.10 Dissemination plans

The investigators and sponsor will disseminate the positive or negative results of the clinical trial by submitting it for publication in a peer-reviewed journal.

3. Results

The results assessed at the end of this trial will be the primary and secondary endpoints. The primary endpoints (efficacy indicators) will be the discharge from the ICU, discharge from the hospital, days of hospitalisation, days on mechanical ventilation and death. The main secondary endpoints (safety indicators) will be the severe transfusion reactions and transfusion-transmitted diseases.

4. Discussion

The presented study protocol was developed by the authors using standardised criteria for the development of a clinical trial protocol. This manuscript describes a study protocol to assess the effectiveness and safety of a CP treatment program that can be used during both the current and future pandemics. Because of the current worldwide COVID-19 outbreak a wide range of solutions must be explored to treat the increasing numbers of critically ill patients. The Food and Drug Administration (FDA) recently announced that CP is among the therapeutic approaches that are being actively considered until the successful development of specific treatment drugs. Many authors have explored this concept recently. The current study considers critically ill patients to represent the appropriate target treatment group for the designed CP protocol. Strict criteria for the enrolment of critically ill patients were considered and are in agreement with the available literature [21, 22]. The use of CP is a well-established technique that has been applied with varying success to treat several viral respiratory epidemics. Based on recently published trial studies, the administration of CP is expected to be safe and efficient, and critically ill patients who received CP have been associated with better outcomes than matched control patients. Preparation of a detailed protocol is essential before the implementation of this technique. The protocol that has been developed by the current study is feasible, with satisfactory outcomes, due to collaboration and teamwork, and the availability of potential donors. Our protocol aligns with other published protocols that have been released to address the current pandemic [20, 22, 23]. The present protocol is consistent with the protocol developed by Eckhardt and his team. The only differences are: Eckhardt's was a single-centre randomised, controlled trial and the study participants will receive one unit (200–250 mL) of CP versus one unit (200–250 mL) of the control plasma [22]. Our protocol is aligned with the protocol developed by Albalawi *et al*. [23] but differs in the sense that in Albalawi *et al*. [23] protocol, the volume of the CP will be 300 ml (200-400 ml/ treatment dose) at least once, and if needed daily for up to 5 sessions. Furthermore the anti-SARS-CoV-2 antibody titre was not determined [23]. The current protocol is also consistent with the recently published protocol apart from the source of CP [24]. In the recently published protocol, the CP will be from different donors, while in the present study the CP will be from a single donor [24]. The slight variation between the published study protocols and the present study allows a comparison between different protocols to reach a consensus about several variables such as the precise indications of use, the optimal time of CP infusion, dose, the concentration of anti-SARS-CoV-2 antibody titre.

This study protocol had some limitations. The generalizability of the results may be limited, as the patients participating in the study will include only critically ill patients.

5. Conclusions

The developed protocol will be used in a clinical trial to evaluate the efficacy and safety of CP used in the treatment of critically ill COVID-19 patients. The details that will be obtained from this study protocol can support its application in similar environments. This study protocol addressed all aspects that are necessary for the standardised implementation of CP for the treatment of COVID-19 patients, including CP collection, administration, evaluation, and follow up.

AUTHOR CONTRIBUTIONS

Conceptualization—AIOY, AYA, AMJ, EIM, HKK. Methodology—AIOY, AJ. Validation—AIOY, AJ. Investigation—AIOY. Data curation—AIOY, AJ. Writing original draft—AIOY. Writing-review and editing—AIOY, AYA, AJ, EM, HK. Project administration—AIOY. Supervision—AIOY. All authors approved the final version of the manuscript for publication.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study protocol was reviewed and approved by the institutional review board of the King Abdullah Hospital, Saudi Arabia (IRB NO. 002/07/21). Written informed consent will be obtained from the subject or the subject's legal representative, and the ability for the subject to comply with the requirements of the study will be evaluated (see supplementary files). Participants recruited to a study will be informed of the objectives, methodology and interventions that they may receive if they agree to participate. Only those who give their informed consent in writing will be included in the study. Participants will be allowed to withdraw at any time in the study. However, follow-up will continue for withdrawn recipients to ensure their safety and to document any SAEs.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

SUPPLEMENTARY MATERIAL

Supplementary material associated with this article can be found, in the online version, at https://oss.signavitae.com/mre-signavitae/article/1443153896320974848/attachment/Supplementary_Files.docx.

DATA AVAILABILITY

The data used in this study are available from the corresponding author upon request.

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