Safety and Efficacy of Convalescent Plasma for Severe COVID-19: Interim Report of a Multicenter Phase II Study from Saudi Arabia

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Abstract

Objective: To present the interim findings from a national study investigating the safety and efficacy of convalescent plasma (CP) containing detectable IgG antibodies as a treatment strategy for severe coronavirus disease 2019 (COVID-19).

Trial Design and Participants: An open label, two-arm, phase-II clinical trial conducted across 22 hospitals from Saudi Arabia. The intervention group included 40 adults (aged ≥18 years) with confirmed severe COVID-19 and the control group included 124 patients matched using propensity score for age, gender, intubation status, and history of diabetes and/or hypertension. Intervention group included those (a) with severe symptoms (dyspnea; respiratory rate, ≥30/min; SpO2, ≤93%; PaO2/FiO2 ratio, <300; and/or lung infiltrates >50% within 24–48 h), (b) requiring intensive care unit (ICU) care or (c) experiencing life-threatening conditions. The control group included confirmed severe COVID-19 patients of similar characteristics who did not consent for CP infusion or were not able to receive CP due to its nonavailability.

Interventions: The intervention group participants were infused 300 ml (200–400 ml/treatment dose) CP at least once, and if required, daily for up to 5 sessions, along with receiving the best standard of care. The control group only received the best standard of care.

Outcomes: The primary endpoints were safety and ICU length of stay (LOS). The secondary endpoints included 30-day mortality, days on mechanical ventilation and days to clinical recovery.

Results: CP transfusion did not result in any adverse effects. There was no difference in the ICU LOS (median 8 days in both groups). The mortality risk was lower in the CP group: 13% absolute risk reduction (P = 0.147), hazard ratio (95% confidence interval): 0.554 (0.299–1.027; P = 0.061) by log-rank test. There was no significant difference in the days on mechanical ventilation and days to clinical recovery.

Conclusion: CP containing detectable antibodies is a safe strategy and may result in a decrease in mortality in patients with severe COVID-19. The results of the completed trial with a larger study sample would provide more clarity if this difference in mortality is significant.

Trial Registration: ClinicalTrials.gov Identifier: NCT04347681; Saudi Clinical Trials Registry No.: 20041102.

Keywords: Antibodies, convalescent plasma, COVID-19, SARS-CoV-2, Saudi Arabia

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**INTRODUCTION**

Coronavirus disease 2019 (COVID-19) has caused significant morbidity, mortality, and societal disruption globally. To date, there is neither a proven prophylaxis against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) nor therapy for patients who develop COVID-19, and currently, investigational drugs are being used for life-threatening cases.\(^1\)\(^2\) One of the investigational treatments evaluated for severe COVID-19 is the use of convalescent plasma (CP) collected from patients who have recovered from COVID-19. CP contains antibodies against SARS-CoV-2 that may be effective against the infection. The concept of the treatment is not new and has robust historical precedence and sound biological plausibility. It has been studied in previous outbreaks of other respiratory infections, including the 2003 SARS-CoV-1 epidemic, the 2009–2010 H1N1 influenza virus pandemic, the 2012 Middle East respiratory syndrome-CoV epidemic and the Ebola virus disease outbreak.\(^3\)\(^4\)

For the current study, a group of hematologists, intensivists and infectious disease specialists collaborated to develop a national protocol to investigate the safety, efficacy and feasibility of the administration of CP at a larger scale in different healthcare facilities in the Kingdom of Saudi Arabia (KSA).\(^5\)

**METHODS**

**Trial design and oversight**

This is an open label, two-arm, phase II national collaborative trial conducted at 22 centers in Saudi Arabia. The trial was reviewed and approved by the Ministry of Health (MOH) of the KSA (central Institutional Review Board [IRB] log no. 20-COVID-19-01M) and by the IRB or Ethics Committee at each participating center (Supplementary Data File) and was conducted according to the principles of the Declaration of Helsinki, 2013. The trial was registered at ClinicalTrials.gov (Identifier: NCT04347681) and Saudi Clinical Trials Registry (No. 20041102). Detailed bilingual informed consent forms approved by the MOH/IRBs were used for both CP donors and CP recipients. All the participants or their kin provided written informed consent at enrollment. A summary of the protocol is described here, and the complete protocol has previously been published.\(^6\)

**Study eligibility**

In terms of the donors, the trial included adult donors aged ≥18 years who had a prior confirmed COVID-19 diagnosis, as per the current MOH guidelines, and had a complete clinical recovery from COVID-19 before donation (at least 14 days from the last SARS-CoV-2–negative PCR or 28 days from the initial symptoms) and a positive rapid serology test for IgG antibodies against SARS-CoV-2 indicating immunity.\(^7\)\(^8\) All the MOH guidelines and criteria for routine blood donation and screening regulations were followed; for example, the transfusion of transfusable infection markers in the donor's blood must be negative. In addition, to minimize the risk of transfusion-related acute lung injury (TRALI), CP was only collected from male donors and nulliparous female donors.

Recipients with a negative or inconclusive real-time reverse transcription polymerase chain reaction (rRT-PCR) test for SARS-CoV-2, or with mild symptoms that did not require hospitalization or ICU care, were not included in the trial. The trial also excluded donors who are unfit for blood donation and multiparous or pregnant females.

In terms of the two arms of the study, the trial included adults aged ≥18 years with COVID-19 confirmed with a positive (rRT-PCR) test for SARS-CoV-2 using one of the Saudi Food and Drugs Authority (SFDA) approved kits, according to the current MOH guidelines. Patients in both arms (a) had severe symptoms (dyspnea; respiratory frequency, ≥30/min; blood oxygen saturation, ≤93%; partial pressure of arterial oxygen to fraction of inspired oxygen ratio, <300; and/or lung infiltrates >50% within 24–48 h), (b) required intensive care unit (ICU) care or (c) experienced life-threatening conditions (respiratory failure, septic shock, and/or multiple organ dysfunction or failure).

For the interventional arm, all patients admitted in the participating centers who met the inclusion criteria were approached and those who consented for CP infusion and the study were recruited to this arm. For the control group, participants were recruited in a 4:1 ratio (i.e., for each CP recipient, four controls were recruited). The control group included patients who did not consent to CP infusion but agreed for participation as well as those who were not able to receive CP due to its nonavailability. In addition, historical controls with matched propensity score (PS) were also included. To account for major confounding factors, the following variables were used to generate a PS: age, gender, intubation status, history of diabetes mellitus (DM) and hypertension (HTN); these variables for matching were selected according to the scientific agreement regarding the importance and effect on COVID-19 outcomes. In addition, both the controls and treatment groups were undergoing the same standard concurrent treatments, as recommended by the MOH.
Collection, transfusion of convalescent plasma and safety monitoring

The CP donors were managed according to the routine blood donation processes, including the completion of a donor history questionnaire, clinical examination and testing for the infectious marker (serology and NAT methods), ABO RhD blood grouping, antibody (Ab) screening and complete blood count. They were also tested for IgG and IgM antibodies against SARS-CoV-2.

The collected plasma underwent an additional pathogen reduction safety step, using Mirasol Pathogen Reduction Technology (Terumo BCT, Lakewood, CO, USA), which is Conformité Européenne marked and SFDA approved [Figure 1]. After passing through the pathogen reduction system, the CP was either sent for transfusion to the COVID-19 recipients or stored in a dedicated fresh frozen plasma (FFP) freezer at ≤−18°C. The CP units were labeled, stored and shipped according to the Central Board for Accreditation of Healthcare Institutes, American Association of Blood Banks and Joint Commission International guidelines for handling and managing blood products.[7,8]

Eligible patients with severe COVID-19 were infused after the consenting process with the donated CP, 300 ml (200–400 ml/treatment dose) at least once, and if required, daily for up to 5 sessions.[6] For plasma selection, the ABO compatibility was considered, regardless of the Rh status. The CP recipients were monitored for serious adverse effects (SAEs) of FFP transfusion, including anaphylaxis, TRALI and transfusion-associated circulatory overload (TACO). Other supportive and therapeutic measures were continued according to the locally approved protocols for both CP and control groups.

Data collection

Data collection forms were developed to collect the data of all participants (i.e., CP donors, recipients and controls) and included the clinical, radiological and laboratory information that was retrieved from the hospital electronic/paper records system. The data were cross-checked to ensure the minimization of data entry errors by two investigators per site of the clinical trial.

Study endpoint and outcome measures

The secondary endpoints were as follows:
1. Number of days on mechanical ventilation
2. 30-day mortality
3. Days to clinical recovery, as defined by the MOH.

Study size

For the completion of this study, a total sample size of 575 patients: 115 CP recipients and 460 matched controls (1:4 ratio), was considered to be sufficient to detect a clinically important difference of 11.6% between the two groups (CP recipients vs. matched controls) in the 30-day mortality, using a two-tailed z-test of proportions and a Chi-square test with 80% power and a 5% level of significance. The 11.6% difference represents a presumed 12.4% mortality in the CP recipient group and 24.4% mortality in the matched control patients.

Statistical analysis

We used descriptive and inferential statistics to characterize the study sample and test the hypotheses. Descriptive results for all the quantitative variables (e.g., age) are presented as mean ± standard deviation (for normally distributed data), or median with interquartile range (for data not normally distributed), while frequency (percentage) is reported for all the qualitative variables (e.g., gender).

The bivariate analysis was performed using an independent sample t-test, Mann–Whitney U-test, Pearson's chi-square test or Fisher’s exact test, whenever appropriate, to compare the demographic characteristics (e.g., age, gender) and clinical characteristics (history of DM, and HTN, length of hospital stay, ICU duration, days on mechanical ventilation and number of days to clinical recovery and 30-day mortality) between the two groups.

The time-to-event analysis was measured from the date of admission. The overall survival at 30 days was evaluated using the Kaplan–Meier estimator and compared between the two groups using the log-rank test. A Cox proportional hazard model was used to estimate the 30-day mortality hazard ratio (HR) for the CP group compared with the PS-matched group. P < 0.05 (two-tailed) was considered statistically significant. All statistical analyses were performed using SPSS version 24 (IBM, Armonk, NY, USA).

RESULTS

This Phase II national clinical trial was ongoing at the time of reporting these preliminary findings. In this interim finding, data of the first 40 CP recipients and their matched 124 controls are reported [Table 1]. These patients were
recruited from May 4 to June 30, 2020. No patients were excluded or lost after recruitment to the trial.

**Primary outcomes**
The CP transfusion was safe, with no adverse effects reported. All the mortalities in the CP group were reviewed by an independent committee and declared to be unrelated to the CP transfusion. The median ICU LOS was similar in both groups (8 days) [Table 2].

**Secondary outcomes**
There was also no statistical difference in the median number of days on mechanical ventilation between the treatment group (10 days; range 5–20 days) and control group (8.5 days; range: 5–13 days) ($P = 0.47$). Similarly, there was no statistical difference in the median number of days to clinical recovery between the treatment (16.5 days; range: 12–36.5 days) and control groups (15 days; range: 11–21 days) ($P = 0.1$) [Table 2].

The 30-day mortality in the CP group was 26.3% compared to 39.3% in the control group, but this was not statistically significant ($P = 0.15$) [Table 3], likely due to the small sample size. However, a 13% absolute reduction of death is clinically meaningful. The CP group showed improved survival, compared to the control group with the log-rank test: $P = 0.061$; HR (95% confidence interval): 0.554 (0.299–1.027) [Figure 2]. Transfusion of CP in the earlier stages of severity (i.e., before its progression to a life-threatening state) likely has a more pronounced beneficial effect [Figure 3].

**DISCUSSION**

Treatment options for COVID-19 are limited, and CP is the only Ab-based therapy currently available.[2] Duan et al., in the first study regarding the feasibility of CP therapy against COVID-19, found that 200 ml of CP (single dose) resulted in rapid improvements in the clinical symptoms within 3 days.[9] In addition, they found that the dose was well tolerated as well as led to viremia clearance in 7 of the 10 patients and lymphocyte elevation in all patients with lymphocytopenia. Similarly, Ahn et al. reported favorable outcomes in two COVID-19 patients with severe pneumonia treated with CP infusion and systemic corticosteroid.[10]

The current study highlights the safety of using CP as a concurrent treatment modality against COVID-19, as no transfusion-related mortality was reported in the CP group. This finding is consistent with several other studies. All four critically ill COVID-19 patients (including a pregnant woman) of Zhang et al.[3] who were treated with supportive care and CP had complete recovery. Wong and Lee also highlighted the pivotal role of CP in managing emerging infectious diseases, including severe COVID-19.[11] In addition, Liu et al. reported an improvement in survival, and Olivares-Gazca et al. reported an improvement in the pulmonary function of patients who received CP.[12,13] Joyner et al. analyzed key early safety metrics after the transfusion of ABO-compatible CP in 5000 hospitalized adults with severe or life-threatening COVID-19 and the incidence of all SAEs.[14] Of the 36 reported SAEs, there were 25 reported incidences of transfusion-related SAEs, including mortality ($n = 4$), TACO (TACO; $n = 7$), transfusion-related acute lung injury (TRALI; $n = 11$) and severe allergic transfusion reactions ($n = 3$). However, only 2 of the 36 SAEs were judged as definitely related to the CP transfusion. Given the fatal nature of COVID-19
and the large population of critically ill patients included in these analyses, the 7-day mortality rate of 14.9% was not considered to be excessive. Joyner et al recently reported more safety data related to 20,000 CP recipients, providing robust evidence regarding the safety of a CP transfusion for hospitalized COVID-19 patients.

It should be noted that plasma transfusion does carry the risk of viral transfer. Chang et al found the presence of SARS-CoV-2 RNA in the plasma sample of donors, highlighting the need to use a pathogen reduction strategy to increase the safety of CP. Duan et al had used methylene blue photochemistry for inactivating any residual virus before transfusion without compromising the neutralizing antibodies. For this study, we aimed at CP collection at least 14 days after the resolution of all clinical signs and symptoms. This strategy is supported by the findings in other studies. Zhao et al studied the Ab responses to SARS-CoV-2 in 173 patients of COVID-19 and found that the seroconversion rate for IgG was 64.7% (112/173), with a median time of 14 days. In addition, a higher titer of Ab was independently associated with a worse clinical severity ($P = 0.006$). Currently, neutralizing antibodies (Nabs) against SARS-CoV-2 are expected to correlate with the recovery and protection of this disease. Wu et al. collected plasma from 175 COVID-19–recovered patients who had mild symptoms and reported that the titers of Nabs were variable in the patients. The Nab titers showed a positive correlation with the plasma CRP levels but a negative correlation with the lymphocyte counts of the patients at the time of admission, indicating an association between the humoral response and cellular immune response. The variations of SARS-CoV-2–specific Nabs suggest that the titration of Nab may be useful before the use of CP. However, Ab titration testing facilities are currently not widely available in Saudi Arabia; therefore, we decided to use the SFDA-approved rapid test kits for the detection of the antibodies against SARS-CoV-2, and we saved aliquots of the CP samples for future testing whenever titration facilities become available.

In agreement with the findings of previous studies, the current study found that CP was less effective in life-threatening and other ICU admission patients. In a multicenter trial, where 103 severe COVID-19 patients were stratified by disease severity and randomized into CP + standard treatment or standard treatment alone (1:1 ratio), the clinical improvement within 28 days (i.e., discharged, alive or a 2-point reduction on a 6-point disease severity scale) was about 52% in the CP group and 43% in the control group. However, in patients with life-threatening COVID-19, such clinical improvements occurred in about 20% and 24% of those in the CP and control groups, respectively. In the life-threatening disease group, there was no significant difference in the 28-day mortality (15.7% vs. 24.0%) or at the time to discharge from randomization.

### Table 1: Demographic and clinical characteristics of the patients at baseline

| Matching variable | Overall (n=164), n (%) | CP recipients (n=40), n (%) | Controls (n=124), n (%) | $P^*$ |
|-------------------|------------------------|-----------------------------|-------------------------|-------|
| Gender            |                        |                             |                         |       |
| Female            | 27 (16.5)              | 7 (17.5)                    | 20 (16.1)               | 0.839 |
| Male              | 137 (83.5)             | 33 (82.5)                   | 104 (83.9)              |       |
| Age in years      | 52.02±13.33            | 50.25±14.90                 | 52.59±12.79             | 0.3355|
| Comorbidity       |                        |                             |                         |       |
| Diabetes          | 75 (45.7)              | 17 (42.5)                   | 58 (46.8)               | 0.637 |
| Hypertension      | 63 (38.4)              | 14 (35.0)                   | 49 (39.5)               | 0.610 |
| Intubation        |                        |                             |                         |       |
| Yes               | 104 (63.4)             | 25 (62.5)                   | 79 (63.7)               | 0.890 |
| No                | 60 (36.6)              | 15 (37.5)                   | 45 (36.3)               |       |

Results are expressed as mean±SD, number and percentage. $^1P$-value has been calculated using Pearson’s Chi-square test; $^2P$-value has been calculated using independent sample $t$-test. SD - Standard deviation; CP - Convalescent plasma.

### Table 2: Comparison of clinical outcomes between the recipients and matched control groups

| Outcomes (days) | Overall | CP recipients | Controls | $P^*$ |
|-----------------|---------|---------------|----------|-------|
| ICU length of stay | 8 (5-14) | 8 (5-20) | 8 (5-12.5) | 0.349 |
| Hospital length of stay | 15 (10-22) | 15.5 (11-31) | 14 (10-20) | 0.049 |
| Intubation duration | 9 (5-14.5) | 10 (5-20) | 8.5 (5-13) | 0.474 |
| Time to clinical recovery | 15 (11-24) | 16.5 (12-36.5) | 15 (11-21) | 0.101 |

Results are expressed as median with interquartile range (25th%-75th%). $^*P$-value has been calculated using nonparametric Mann-Whitney U-test. ICU - Intensive care unit; CP - Convalescent plasma.

![Figure 2: Survival probability between CP group and matched control patients](image-url)
However, the interpretation of this trial is limited by the early termination of the trial, which may have been underpowered to detect a clinically important difference.\cite{21} Despite these limitations, Casadevall et al. highlighted the importance of that study in furthering the understanding of the effects of CP independently from concurrently administered agents.\cite{23} Furthermore, they also highlighted the potential benefit of using high titer Ab in severely ill patients, paving the way for future such studies.

High titer of Ab and time from admission to transfusion may be important factors in maximizing the effects of Ab treatments. Very recently, Salazar et al. found that transfusion with anti-spike protein receptor-binding domain titer of $\geq 1:1350$ within 72 h of admission resulted in a significant reduction ($P = 0.047$) in mortality within 28 days compared with their matched controls.\cite{23}

Joyner et al.\cite{24} recently demonstrated relationships between reduced mortality and both an earlier time to CP transfusion and higher Ab levels in the CP in the treatment of 35,322 hospitalized COVID-19 patients. Of these, a high proportion were critically ill at the time of plasma transfusion, with 52.3% in the ICU and 27.5% receiving mechanical ventilation. The 7-day mortality rate was 8.7% in patients transfused within 3 days of COVID-19 diagnosis, but 11.9% in patients transfused 4 or more days after diagnosis ($P < 0.001$). Similar findings were observed in the 30-day mortality (21.6% vs. 26.7%, $P < 0.0001$). Notably, higher mortality on day 7 and day 30 was observed in relation to low IgG Ab levels in the transfused CP ($P = 0.048$ and $P = 0.021$, respectively). In the current study, the absolute risk reduction in the 30-day mortality for patients in the CP group had decreased compared with the PS-matched control group. Therefore, the collective evidence suggests that CP transfusion provides favorable mortality risk reductions, especially when carried out at the earlier stages of admission and disease progression. Expanding the patient cohort may explain this difference and the report on the complete study of 575 planned patients would provide more clarity.

**Limitations**

All patients included in this study (in both groups) received concurrent therapy, and thus, it is unclear whether a synergistic or combinatorial effect between these strategies of care and the CP transfusion had an impact on mortality and improvement of symptoms. Due to the perceived benefit of CP in the community, a randomized control trial could not be carried out, and consequently, a PS matching was used for best comparison. Another limitation is that a range rather than a fixed dose was used for each transfusion (based on CP availability); although this was done to maximize patient benefit, it could possibly have resulted in outcome differences between patients. This interim report also does not provide comparison in outcome between patients who received single and multiple doses of CP; we would attempt to analyze this in our final report. The final report would also include a regression analysis of all the variables. Furthermore, we could not do the neutralization titers of antibodies before the CP transfusion; nonetheless, we used an on-spot rapid antibodies test for IgG antibodies detection and saved aliquots for further characterization of antibodies in the future, whenever this facility is available.

**CONCLUSION**

The preliminary findings of this trial suggest that CP is a safe strategy for COVID-19 disease and that it results in a nonsignificant absolute risk reduction in the 30-day mortality for CP recipients, and its effects are likely to be more profound when carried out earlier in their disease course. The final report of this trial would provide more clarity on the outcomes reported here.

**Ethical considerations**

Ethical approval was obtained from the Ministry of Health, KS\textregistered; Central IRB log no. 20-COVID-19-01M. Approvals were also obtained from the IRBs of the 22 participating centers (Supplementary Data File). All the participants or their kin provided written informed consent at enrollment. The study was conducted in
accordance with the Declaration of Helsinki, as revised in 2013.

Peer review
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Conflicts of interest
There are no conflicts of interest.

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KSA COVID-19 CONVALESCENT PLASMA STUDY GROUP

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The affiliations of the above Group members are available in Supplementary Appendix 1.
### SUPPLEMENTARY APPENDIX 1

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### SUPPLEMENTARY DATA FILE

| Institutional name & its approval body | Approval number | Date of approval |
|----------------------------------------|-----------------|------------------|
| King Fahad Specialist Hospital - Dammam | HAEM0321 | 02/04/2020 |
| Qatif Central Hospital | 20-COVID-19-01M | 02/04/2020 |
| King Fahad General Hospital - Madinah | 20-COVID-19-01M | 02/04/2020 |
| Ohud Hospital - Madinah | 20-COVID-19-01M | 02/04/2020 |
| Dammam Medical Complex | 20-COVID-19-01M | 02/04/2020 |
| National Guard Hospital - Riyadh | RC20/163/R | 09/04/2020 |
| National Guard Hospital - Jeddah | RC20/163/R | 13/04/2020 |
| National Guard Hospital - Alahsa | RC20/163/R | 13/04/2020 |
| National Guard Hospital - Madinah | RC20/163/R | 13/04/2020 |
| International Medical Center - Jeddah | 2020-04-119 A1 | 15/04/2020 |
| King Faisal Specialist Hospital & Research Centre | C380/788/41 | 04/05/2020 |
| Madinah General Hospital | 20-COVID-19-01M | 02/04/2020 |
| John Hopkins Aramco Healthcare | 20-08 | 10/05/2020 |
| King Fahad Medical City | 20-198 | 15/04/2020 |
| King Abdullah Medical Complex | 20-COVID-19-01M | 02/04/2020 |
| Prince Mohammed bin Abdulaziz Hospital | 20-198 | 15/04/2020 |
| King Saud Medical City/King Khalid University Hospital | 20/0271/IRB | 20/04/2020 |
| Asir Central Hospital | 20-COVID-19-01M | 02/04/2020 |
| Prince Sultan Military Medical City | 2020-005 | 03/06/2020 |
| King Abdullah Medical City | 20-COVID-19-01M | 02/04/2020 |
| King Fahad Medical Complex | AFHER-IRB-2020-010 | 19/04/2020 |
| Imam Abdulrahman Bin Faisal University | 2020-01-128 | 23/04/2020 |