Convalescent plasma in the treatment of moderate to severe COVID-19 pneumonia: a randomized controlled trial (PROTECT-Patient Trial)

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There is a need for effective therapy for COVID-19 pneumonia. Convalescent plasma has antiviral activity and early observational studies suggested benefit in reducing COVID-19 severity. We investigated the safety and efficacy of convalescent plasma in hospitalized patients with COVID-19 in a population with a high HIV prevalence and where few therapeutic options were available. We performed a double-blinded, multicenter, randomized controlled trial in one private and three public sector hospitals in South Africa. Adult participants with COVID-19 pneumonia requiring non-invasive oxygen were randomized 1:1 to receive a single transfusion of 200 mL of either convalescent plasma...
There are limited drugs with convincing evidence of efficacy for hospitalized patients with COVID-19. Host-directed therapies including dexamethasone⁴, tocilizumab⁵,⁶ and baricitinib⁷, and the monoclonal antibody casirivimab/imdevimab cocktail⁸, and anakinra⁹ are associated with survival benefit. Remdesivir, an antiviral agent, has modest impact on shortening the time to recovery⁶. Of these, only dexamethasone is widely available in resource-limited settings and there is an urgent need for accessible therapeutic options for COVID-19 pneumonia.

Transfusion with convalescent plasma (CP) provides antiviral activity through transfer of neutralizing antibodies and possibly other immune components⁹. Observational studies suggested CP therapy may improve outcomes in severe viral infections⁹, including lower mortality and earlier hospital discharge in SARS-CoV-2⁹. There have been no safety signals associated with CP use in the treatment of severe viral infections¹¹. CP is therefore an attractive potential therapy for COVID-19, particularly in resource-limited settings where access to other novel drugs is limited¹², given its potential for rapid and relative low cost local production¹³.

In the absence of other therapeutic options, COVID-19 convalescent plasma (CCP) was widely deployed outside of clinical trials in the first year of the pandemic. Early experience from uncontrolled observational studies suggested efficacy for CCP, including improved survival, decreased viral load, and radiological improvement¹⁴,¹⁵. There was a dose–response relationship in an analysis of a large expanded access programme, with reduced 30-day mortality among patients receiving CCP with higher titre anti-SARS-CoV-2 spike IgG compared with those who received lower titres, providing biological plausibility for clinical efficacy¹⁶. Encouraging results were also observed in a small randomised control trial (RCT) in India where CCP was associated with improvement in respiratory parameters and a shortened recovery time¹⁷. Another RCT from New York and Brazil found significantly improved survival at day 28 in participants treated with CCP¹⁸. By contrast, the RECOVERY trial, a large RCT with clinical endpoints, was halted prematurely as high titre CCP did not improve survival in hospitalized patients with COVID-19 in the UK¹⁹.

Prior to the announcement of the RECOVERY trial results and in the context of rapidly emerging observational data supporting potential efficacy and safety of CCP, we undertook a randomized controlled trial to test whether CCP improved clinical recovery for COVID-19 pneumonia in an African population with high HIV prevalence and limited available treatment options.

**Methods**

**Study design and population.** The PROTECT-Patient trial, A PROspective, randomised, placebo-controlled, double-blinded phase III clinical trial of the Therapeutic use of convaEsCenT plasma in the treatment of patients with moderate to severe COVID-19) evaluated the efficacy and safety of CCP for hospitalized patients with COVID-19 pneumonia. The trial took place at one private sector and three public sector hospitals in South Africa. The trial was first registered on 24/04/2020. The trial was sponsored by the South African National Blood Service (SANBS) and was conducted in accordance with the principles of the International Conference on Harmonisation–Good Clinical Practice guidelines, approved by the South African Health Products Regulatory Authority and the Human Research Ethics Committees of SANBS (2019/0524, 24/04/2020), University of Cape Town (312/2020, 14/07/2020), University of the Free State (UF52020/1253/2710, 22/09/2020), University of Walter Sizulu (086/2020, 04/11/2020) and the Life Hospital group (07052020/107/07/2020). The trial is registered on clinicaltrials.gov (NCT04516811 [https://clinicaltrials.gov/ct2/show/NCT04516811], 18/08/2020) and the protocol is available as part of Supplementary Information.

Informed consent was obtained from hospitalized patients ≥ 18 years of age were eligible for inclusion if they had laboratory confirmation of SARS-CoV-2 infection by reverse transcriptase polymerase chain reaction (RT-PCR) on any respiratory sample, radiologic evidence of pneumonia with pulmonary infiltrates on chest X-ray, oxygen saturation (SpO2) of < 94% on room air and requiring non-invasive oxygen therapy. We excluded patients who were mechanically ventilated or where survival for < 24 h was expected. Co-enrolment into another investigational therapy trial was not permitted.

**Randomization, blinding, and intervention.** Eligible and consenting participants were randomized (1:1) to receive either a single infusion of 200–250 mL CCP or 200 mL of placebo (0.9% normal saline), together with local standard of care. Random assignment was stratified by study site, age (≥ 65 years), and body mass index (BMI) (≥ 30 kg/m²). An electronic randomisation application (REDCap hosted by SANBS²⁰, was used to generate the treatment allocation. To mask treatment allocation, investigational product (IP) was
covered in opaque paper wrapping prior to dispatch from the blood bank. Participants were transfused within
24 h of randomization. CCP or placebo was administered over 20–30 min; vital signs were monitored at 15-min
intervals for one-hour post initiation of transfusion. Use of other treatments, including corticosteroids and anti-
cogulation, was at the discretion of treating clinicians; remdesivir was unavailable for routine use.

CCP was collected by SANBS and the Western Cape Blood Service (WCBS) from donors who had recovered
from SARS-CoV-2 infection, confirmed by positive nasopharyngeal swab RT-PCR (Supplementary Informa-
tion). SARS-CoV-2 antibody titre testing was performed by the National Institute of Communicable Diseases
(NICD) using an in-house enzyme-linked immunosorbent assay (ELISA) assay based on the assay developed
by Mount Sinai Hospital21, which detected the presence of anti-spike and -receptor binding domain antibod-
ies. Testing for neutralizing antibodies (nAb) was performed on stored samples once the assay was developed
and validated (methods described elsewhere)22. Initially we selected donor units with an anti-spike IgG optical
density (OD450nm) of ≥ 0.4, which was considered to be positive21. As more information emerged regarding the
importance of nAb titers, we aimed to transfuse CCP with nAb titres of 1:160 or higher based on findings from
other clinical trials22. However, in line with Food and Drug Administration (FDA) guidance24 on the use of anti-
spike binding antibody as a proxy for nAb, we moved to using CCP with anti-spike protein IgG OD450nm values
greater than 2.0, which correlated well with nAb titres ≥ 1:16025.

Clinical and laboratory monitoring. We performed daily in-person or medical record assessments for
adverse events, clinical status, and oxygen utilization during hospital admission. For participants discharged
prior to day 28, clinical status and adverse events were determined via telephone. Concomitant medication was
recorded at each clinical visit. Phlebotomy for safety and inflammatory markers was performed on the day of
transfusion and when possible, on days 2, 5, 10, 14 and 28 during hospitalisation. A nasopharyngeal swab for
SARS-CoV-2 genomic sequencing was collected at enrolment in a subset of patients and sent to the NICD for
RT-PCR testing using the 3 Allplex™ 2019-nCoV assay (Seegene Inc). Retained RNA samples were processed
using a commercially available version of the SARS CoV-2 ARTIC library preparation protocol (NEBNext
ARTIC SARS-CoV-2 FS Library Prep Kit, cat# E7658 (Illumina, San Diego, California, USA)). Following library
preparation, samples were sequenced on the NextSeq 500 platform (Illumina, San Diego, California, USA). A
minimum of one million 2 × 150 bp PE reads were generated per sample. Analysis of sequence data was performed
by the NICD. Whole genome assembly was conducted using the Exatype SARS-CoV-2 platform (https://sars-
cov-2.exatype.com/).

Outcomes. The primary outcome measure was successful treatment at Day 28 post-randomization, defined
as acute care hospital discharge or clinical improvement of ≥ 2 points on an ordinal scale recommended by the
World Health Organization25: 0 - uninfected; (1) ambulatory with no limitation of activities; (2) ambulatory with
greater than 2.0, which correlated well with nAb titres ≥ 1:16021.

Sample size. We hypothesized that a single transfusion of CCP would be associated with improved treat-
ment success compared with saline placebo in patients hospitalized with COVID-19 pneumonia. Based on
observational studies at the time of protocol development26–28, we assumed that approximately 30% of patients
with COVID-19 pneumonia would not reach the primary endpoint event of clinical improvement. We estimated
a sample size of 600 participants (300 per treatment group) would provide 80% power at 2-sided alpha to detect
a 33% difference in relative risk (10% absolute difference) in the primary outcome between the two arms.

Early trial termination and analysis. The trial management committee, in discussion with the trial
DSMB, paused recruitment on 14 January 2021 in response to evidence that convalescent plasma, collected
from people infected with ‘wild-type’ virus during the first wave in South Africa, had poor neutralizing activity
against the Beta (B.1.351/501Y.V2) SARS-CoV-2 variant presumed to have become the dominant variant in trial
participants29. The trial DSMB requested an unplanned interim analysis with futility calculations based on con-
ditional power. The 103 participants who received IP at the time of pausing provided an information fraction of
0.17 with observed event probabilities of 0.63 and 0.61. Conditional power for a significance difference at the end
of the trial based on the observed trend was 40%; if no effect was assumed from the time recruitment was paused to
the end of the trial, conditional power was 3%. Based on these low conditional probabilities, and emerging
data from the RECOVERY trial, the DSMB recommended that the trial be stopped for futility on 10 February
2021. To report findings, prevalence of endpoints in the intention to treat population were estimated at day 28
and/or date of discharge using risk ratios and 95% confidence intervals. Due to lack of power as a result of early
trial cessation, no formal statistical comparisons were done. We used Kaplan–Meier estimates to compare and
illustrate time to clinical improvement and death in the treatment groups. We used STATA V.17 (STATACORP,
Texas) to perform the statistical analysis.
Results

107 participants were enrolled between 30 September 2020 and 14 Jan 2021; 103 were transfused with IP (two participants withdrew consent and two were transferred to alternative facilities prior to transfusion): 52 participants received CCP and 51 were given placebo (Fig. 1).

The trial groups were well balanced in terms of baseline characteristics, disease severity, and routine management (Tables 1 and 2). Twenty-one (25%) of those with known HIV status (n = 84) were HIV positive, 16 (76%) of whom were on antiretroviral therapy (ART). Median CD4 count for the HIV positive participants was 596 (interquartile range (IQR) 242–1029). Co-morbidities, including a high prevalence of diabetes and hypertension, were present in 42 (80.8%) participants. More than half of participants (n = 56, 54.4%) were classified as obese.

The median time from symptom onset to IP infusion was 9 (IQR 6–11) days. Corticosteroids were used in 97 (94.2%); 98 (95.1%) participants were prescribed heparin prophylaxis, mostly with therapeutic doses.

Information on the primary endpoint was unavailable for six participants who were uncontactable after initial discharge or transfer, however sensitivity analysis did not change the findings. The primary outcome was therefore assessed in 97/103 (94.2%) participants: 31 (66.0%) in the CCP group and 32 (64.0%) in the placebo group experienced ≥ 2 point BOSCI improvement or discharge by Day 28, relative risk 1.03 (95% CI 0.77 to 1.38) (Table 3). All participants who were discharged demonstrated a clinical improvement (BOSCI improvement ≥ 2) (Fig. 2). There were 11 and 13 deaths in the CCP and placebo groups, respectively. Four participants required invasive mechanical ventilation, one in the CCP group and three in the placebo group. There was no difference in time to death or clinical improvement between treatment groups (Fig. 3). Among HIV positive participants, the primary outcome was achieved in two (33%) and nine (60%) participants in the CCP and placebo groups, respectively.
The total number of adverse events, including serious adverse events, was similar across treatment groups (Table 4). Two transfusion-related adverse events occurred, both grade 1 allergic reactions. Six grade 3 or higher adverse events were recorded among HIV-positive participants who were transfused CCP, all assessed as unrelated to the study drug.

In the transfused CCP, the median anti-spike protein IgG optical density (OD_{450nm}) was 2.7 AU/mL (IQR 2.0 to 3.0); and the median anti-SARS-CoV-2 neutralizing antibody titre was an inhibitory dilution at which 50% neutralization is attained (ID_{50}) of 1:234 AU/mL (IQR 194 to 304; range 71 to 1245). Participants who demonstrated clinical improvement received CCP transfusions with higher median anti-SARS-CoV-2 neutralizing antibody titres compared with those who did not: ID_{50} of 1:298 (IQR 212–374) versus 1:205 (IQR 181–254) (Fig. 4). Of those who showed clinical improvement, 21 (81%) had an antibody titre > 1:200 ID_{50} (Fig. 4).

SARS-CoV-2 genomic sequencing was performed on available baseline nasopharyngeal samples from 66 participants. SARS-CoV-2 variants were similarly distributed across treatment groups. The beta variant was detected in 45 (68.2%) samples. In the CCP group, 6/22 (27.7%) participants with the beta variant died and 1/10 (10.0%) participants with other SARS-CoV-2 variants died. Clinical improvement by day 28 occurred in 11/18 (61.1%) of participants with beta variant infection who received CCP, and in 7/10 (70.0%) of those infected with other variants.

### Discussion

Our trial showed that the use of therapeutic CCP for hospitalized patients with COVID-19 pneumonia was not associated with clinical improvement in a South African population with a high HIV-prevalence. Although our final sample size did not support formal hypothesis testing, the lack of any signal of benefit led to a conclusion of futility, and is consistent with findings from randomized controlled trials in other settings. Notwithstanding early trial termination, our study contributes additional evidence for recommendations against use of CCP for established COVID-19 pneumonia, especially in a high HIV-prevalence setting, and may provide some insights into reasons for the lack of clinical efficacy.

Observational studies suggest that the clinical effect of CCP is related to neutralizing antibody titre. There has been variability and lack of standardisation in transfused neutralizing titres across trials, which may explain some of the heterogeneity in outcomes with CCP. It is an operational challenge to perform neutralisation assays in real time, and similarly to other studies, we selected CCP units on anti-spike IgG antibodies that correlated with neutralizing titres. Consequently, we used a wide dosing range in transfused CCP in our trial, highlighting the challenge of CCP standardisation in future studies, or if implementation is contemplated. Informative subgroup

| Table 1. Participant characteristics at baseline in 103 participants with severe COVID-19 randomized to treatment with convalescent plasma versus placebo. |
|---------------------------------|----------------|----------------|----------------|
| Total                           | CCP, n (%)     | Placebo, n (%) | Total, n (%)   |
| Age group (years)               |                |                |                |
| < 40                            | 9 (17.3)       | 6 (11.8)       | 15 (14.5)      |
| 40–60                           | 26 (50.0)      | 26 (51.0)      | 52 (50.5)      |
| > 60                            | 17 (32.7)      | 19 (37.3)      | 36 (35.0)      |
| Age-median (IQR)               | 54 (46–62)     | 57 (47–64)     | 56 (46–63)     |
| Gender                          |                |                |                |
| Female                          | 31 (59.6)      | 30 (58.8)      | 61 (59.2)      |
| Male                            | 21 (40.4)      | 21 (41.2)      | 42 (40.8)      |
| HIV status                      |                |                |                |
| Positive                        | 6 (11.5)       | 15 (28.8)      | 21 (18.5)      |
| On ART                          | 5 (83.3)       | 11 (73.3)      | 16 (76.2)      |
| Not on ART                      | 1 (16.7)       | 4 (26.7)       | 5 (24.8)       |
| Negative                        | 37 (71.2)      | 26 (51.0)      | 63 (62.1)      |
| Unknown                         | 9 (17.3)       | 10 (19.6)      | 19 (19.4)      |
| Smoking                         |                |                |                |
| Current smoker                  | 5 (9.6)        | 6 (11.8)       | 11 (10.7)      |
| Ex-smoker                       | 11 (21.2)      | 11 (21.6)      | 22 (21.7)      |
| BMI                             |                |                |                |
| BMI ≥ 30 kg/m²                  | 29 (55.8)      | 27 (52.9)      | 56 (54.4)      |
| BMI-Median (IQR)               | 31.2 (26.8–37.6) | 31.0 (26.8–36.0) |                |
| SARS-CoV-2 clade on sequencing |                |                |                |
| 19A                             | 2 (5.9)        | 2 (6.3)        | 4 (6.1)        |
| 20A                             | 4 (11.8)       | 6 (18.8)       | 10 (15.2)      |
| 20B                             | 5 (14.7)       | 2 (6.3)        | 7 (10.6)       |
| 20H/501YV2                      | 23 (67.6)      | 22 (68.8)      | 45 (68.2)      |
analyses were not possible with our limited sample size, but we did observe higher neutralizing titres among participants with better outcomes. However, given the lack of clinical effect in the RECOVERY trial, which only transfused high anti-spike titre CCP, it is unlikely that selecting donor plasma with titres in accordance with current FDA guidelines would have altered our main finding.

The majority of CCP donations for the PROTECT trial were collected during the first COVID-19 wave in South Africa, during which donors were likely infected with the ‘wild type’ SARS-CoV-2. Due to delays in regulatory approvals, recruitment was unable to commence until the beginning of the second wave when the beta variant had become the predominant circulating SARS-CoV-2 strain. This was subsequently confirmed by sequencing in over two-thirds of our participants with available samples. In vitro experiments indicated that...
SARS-CoV-2 antibodies in convalescent plasma provided for the PROTECT trial, obtained from donors infected before the emergence of beta, was significantly less effective at neutralizing pseudovirus expressing beta variant spike protein. SARS-CoV-2 variants have also shown resistance to neutralisation by anti-receptor binding domain monoclonal antibodies, and antigenic variability of SARS-CoV-2 with emergence of new variants will be a major obstacle to deployment of these therapeutic strategies. Although CCP may contribute some indirect antiviral effect through non-neutralizing antibody activity, which is preserved in convalescent plasma against multiple variants, this appears unlikely to translate into clinical efficacy.

Clinical studies suggest CCP and monoclonal antibody therapy may provide benefit early in the course of COVID-19 when SARS-CoV-2 viral load is highest at around 3 days post-diagnosis, but this has been inconsistent. The median time from symptom onset to transfusion in our trial was 9 days, which is comparable to other negative trials of CCP for inpatients with COVID-19 pneumonia. The RECOVERY trial did not find benefit for earlier CCP administration on stratified analysis, and a trial evaluating monoclonal antibody therapy was stopped early for failing to demonstrate efficacy among hospitalized patients, even with low oxygen requirements, suggesting that antibody based therapies are unlikely to be effective after activation of excessive host inflammation associated with severe disease.

CCP may have therapeutic potential in other contexts and patient groups and more likely as a prophylactic for severe COVID-19 in individuals with comorbidities. A randomized controlled trial showed that transfusion of CCP within three days of symptom onset reduced progression to severe COVID-19 among older people in Argentina, and there are at least thirteen active trials evaluating CCP for treatment and prophylaxis of mild or moderate COVID-19. There is also accumulating evidence from case reports of good outcomes with CCP use in a heterogeneous group of patients with primary and secondary immunodeficiency, including those with haematological malignancy and solid organ transplantation. HIV may be a risk factor for worse outcomes with COVID-19, but data is scarce on the use of CCP in this patient group. Our trial included 21 HIV-positive participants, six of whom received CCP. Although this small number precludes

**Table 3.** Primary and secondary efficacy outcomes in 103 participants with severe COVID-19 randomized to treatment with convalescent plasma versus placebo. Six participants were discharged from primary acute care prior to Day 28 but were lost to follow up as they were uncontactable at Day 28. Clinical improvement is a composite of discharge from hospital and/or improvement in BOSCI score by ≥ 2 by Day 28.

| Primary outcome                                               | CCP: n (%) | Placebo: n (%) | RR (95% CI) |
|--------------------------------------------------------------|------------|----------------|-------------|
| Clinical improvement by D28                                  | 31/47 (66.0) | 32/50 (64.0)   | 1.03 (0.77 to 1.38) |
| Secondary efficacy outcomes                                  |            |                |             |
| Discharge from hospital by D28                               | 28/46 (60.9) | 31/50 (62.0)   | 1.21 (0.84 to 1.74) |
| BOSCI improvement: ≥ 2 by D28                               | 31/47 (66.0) | 32/50 (64.0)   | 1.03 (0.77 to 1.38) |
| Death by D28                                                 | 11/52 (21.5) | 13/51 (25.5)   | 0.83 (0.41 to 1.68) |
| Invasive mechanical ventilation                              | 1/52 (1.9)  | 3/51 (5.9)     | 0.33 (0.04 to 3.04) |

**Figure 2.** Proportion of clinical outcomes for 103 participants with moderate-severe COVID-19 randomized to treatment with convalescent plasma versus placebo at day 28 post recruitment.
definitive conclusions, absence of a major safety signal is somewhat reassuring. In line with experience in other settings, CCP use was safe in our overall cohort, supporting future evaluation for different indications in high HIV burden populations.

The premature termination of the PROTECT trial illustrates the complexity of undertaking clinical research in a rapidly evolving global pandemic. Inconsistent case numbers, viral evolution, and rapidly changing evidence during the trial period contributed to this challenge. Despite this, our trial demonstrated the feasibility of deploying CCP in a resource-limited setting and contributed knowledge on the use of this therapeutic strategy for COVID-19 pneumonia. Our experience highlights the necessity of globally networked clinical trial sites and harmonised study protocols to more efficiently evaluate interventions among diverse populations during a pandemic.

**Figure 3.** Kaplan–Meier survival analysis of time to death and separately for improvement by ≥ 2 BOSCI points in 103 participants with moderate-severe COVID-19 randomized treatment with convalescent plasma versus placebo. *BOSCI: World Health Organization Blueprint Ordinal Scale for Clinical Improvement.*

**Table 4.** Number of adverse events in 103 participants with severe COVID-19 randomized to treatment with convalescent plasma versus placebo.
Figure 4. Correlation of neutralizing antibody titer and spike optical density, partitioned by clinical improvement status in patients who received CCP.

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Author contributions

I confirm that the following authors have seen and approved the submitted manuscript, and that all have made substantial contributions to the work justifying authorship: K.B., T.G., M.V., E.L., R.S., C.B., R.C., M.B., C.N., A.S., C.M., T.C., G.K., J.N., P.S., J.C., T.M.-G., P.L.M., J.B., J.S., J.N.B., P.B., P.M., J.M., S.P., C.V., S.M., R.J.W., V.J.L., S.W.

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Competing interests
The authors declare no competing interests.

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