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Transfusing convalescent plasma as post-exposure prophylaxis against SARS-CoV-2 infection: a double-blinded, phase 2 randomized, controlled trial

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ABSTRACT

Background. The efficacy of SARS-CoV-2 convalescent plasma (CCP) for preventing infection in exposed, uninfected individuals is unknown. CCP might prevent infection when administered before symptoms or laboratory evidence of infection.

Methods. This double-blinded, phase 2 randomized, controlled trial (RCT) compared the efficacy and safety of prophylactic high titer (≥1:320 by Euroimmun ELISA) CCP with standard plasma. Asymptomatic participants aged ≥18 years with close contact exposure to a person with confirmed COVID-19 in the previous 120 hours and negative SARS-CoV-2 test within 24 hours before transfusion were eligible. The primary outcome was new SARS-CoV-2 infection.

Results. 180 participants were enrolled; 87 were assigned to CCP and 93 to control plasma, and 170 transfused at 19 sites across the United States from June 2020 to March 2021. Two were excluded for screening SARS-CoV-2 RT-PCR positivity. Of the remaining 168 participants, 12/81 (14·8%) CCP and 13/87 (14·9%) control recipients developed SARS-CoV-2 infection; 6 (7·4%) CCP and 7 (8%) control recipients developed COVID-19 (infection with symptoms). There were no COVID-19-related hospitalizations in CCP and 2 in control recipients. Efficacy by restricted mean infection free time (RMIFT) by 28 days for all SARS-CoV-2 infections (25·3 vs. 25·2 days; p=0·49) and COVID-19 (26·3 vs. 25·9 days; p=0·35) was similar for both groups.

Conclusions. Administration of high-titer CCP as post-exposure prophylaxis, while appearing safe, did not prevent SARS-CoV-2 infection.

Keywords

SARS-CoV-2, post-exposure-prophylaxis, convalescent plasma, transfusion, COVID-19

Running title: SARS-CoV-2 exposure plasma prophylaxis or SARS-C0V-2 PEP with convalescent plasma

Background

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is responsible for Coronavirus Disease 2019 (COVID-19) and the pandemic that has claimed millions of lives [1]. Especially at the pandemic's onset, effective preventive strategies were limited. Even by 2022, many have not been vaccinated, and some do not respond to vaccination [2, 3]. The urgency of effective prevention is highest within households of SARS-CoV-2 infected persons since 10-50% will be secondarily infected. Passive immunotherapy using preformed antibodies is effective as post-exposure prophylaxis (PEP) against many infections [4-7]. Combinations of monoclonal antibodies (mAb) are effective as COVID-19 PEP [8, 9]. COVID-19 convalescent plasma (CCP) may confer protection during early infection and in those without antibodies[10-12]. CCP has some advantages over mAb's, including ease of procurement, low cost, and resilience against viral variants [13]. This study sought to evaluate the safety and efficacy of CCP containing anti-SARS-CoV-2 antibodies as PEP.

Methods

Study design and Participants

A randomized, double-blind, placebo-controlled clinical trial was conducted to compare the safety and efficacy of transfusion of CCP (intervention) with SARS-CoV-2 non-immune control plasma.

Asymptomatic participants aged ≥18 years who had a close contact exposure to a person with confirmed COVID-19 in the previous 120 hours and did not have SARS-CoV-2 vaccination, and past or active SARS-CoV-2 infection were eligible.

The applied definition of close contact exposure was that used by Centers for Disease Control and Prevention (CDC) during the study period. Transfused participants positive by RT-PCR at screening were excluded from analyses. Participants were enrolled at 19 US centers between June 11, 2020 to June 23, 2021. Approval was obtained from the Institutional Review Boards at Johns Hopkins University School of Medicine functioning as single IRB for all participating sites. The protocol was additionally approved by the Department of Defense (DoD) Human Research Protection Office. An independent data and safety monitoring board provided oversight and reviewed efficacy and safety as the study was conducted. All participants provided written informed consent. Trial registration: Clinicaltrial.gov NCT04323800.

Randomization to treatment arm and masking

Eligible subjects were randomized 1:1 to receive a unit of CCP or control plasma using central interactive web-based systems. CCP and control plasma were in standard plasma bags, with identical labels.

Intervention

CCP donors were eligible for collection if they had a history of a positive molecular assay test result for SARS-CoV-2 infection, met standard criteria for blood donation, and had SARS-CoV-2 positive antibody levels after diluting 1:320 titer by Euroimmun ELISA, [Mountain Lakes, NJ] at screening. CCP was collected at various US locations. After qualification, the donor CCP antibody levels were later characterized in research laboratories by full length ancestral spike and receptor-binding domain (RBD) endpoint titers, live virus growth neutralization assays and Euroimmun arbitrary unit (AU) at the manufacturer's recommended dilution of 1:101[14]. Control was standard SARS-CoV-2 non-immune plasma collected before January 1, 2020, or seronegative for SARS-CoV-2. Transfusions were performed at outpatient clinical research facilities. Individuals were followed for 90 days with visits at days 0 (transfusion), 1, 3, 7, 14, 28, 60, and 90. Nasal swabs were collected at screening (days -1 to 0) and at days 1, 7, 14, and 28. Assessments for COVID-19

(symptomatic infection) were conducted at screening, transfusion, and days 1, 3, 7, 14, 28, and 60. Safety assessments were continued to day 90. Viral testing was performed using RT-PCR that targeted the SARS-CoV-2 nucleocapsid gene. Recipient antibody levels were measured by RBD endpoint titers.

Primary Outcome

The primary efficacy outcome was incident SARS-CoV-2 infection by study day 28 by positive RT-PCR testing conducted on collected nasal swabs or by clinical RT-PCR testing conducted outside the study.

Secondary efficacy outcomes

Disease severity was measured to day 28 using a clinical event scale (supplementary material) and evaluated using an ordinal logistic model. Efficacy for preventing SARS-CoV-2 infection and COVID-19 was examined based on donor antibody titer through characterization of donor IgG, including end point titers and area under the curve (AUC) using a standardized ELISA to measure IgG against the spike and receptor binding proteins and anti-SARS-CoV-2 IgG against recombinant S1 domain of the SARS-CoV-2 spike protein (Euroimmun) as previously described [14].

Safety assessments

The Common Terminology Criteria for Adverse Events (CTCAE) 5·0 was used for grading of adverse events (AE). The safety outcomes were monitored throughout the study, including transfusion-related serious AEs (SAEs) (i.e. severe transfusion reactions, acute respiratory distress syndrome and grade 3 or 4 adverse events). The masked independent medical monitor evaluated AEs, SAEs and changes in baseline safety laboratory values.

Data management and statistical analyses

The pre-specified primary analysis of cumulative SARS-CoV-2 infection was conducted using a time-to-event analysis to compare the restricted mean survival time, referred to henceforth as restricted mean infection free time (RMIFT).

We calculated and compared the restricted mean survival times by 28 days and risk difference (RD) by treatment arm in a modified intention to treat (mITT) analysis. We performed the primary analysis according to the participants' original randomized treatment groups excluding those who did not receive a transfusion of study plasma and those who were later found to have been test positive at transfusion [15]. Analyses were adjusted for variables potentially related to the outcome in order to increase estimate precision (statistical analysis plan; supplementary material) [15]. Demographic and clinical variables were measured at baseline. To determine which pre-specified candidate variables to include, we conducted variable selection by random survival forest in the entire sample (i.e., not including an indicator term for treatment arm) and masked to treatment allocation. This algorithm was implemented on the mITT sample to identify the prognostic baseline variables for the entire sample.

Baseline characteristics are reported as proportions or medians with interquartile ranges (IQR) for continuous variables. Time-to-event analysis was computed from the time of transfusion until development of a positive molecular test for infection. Analyses were repeated using only clinical illness with COVID-19 as the outcome. Targeted minimum loss-based estimation (TMLE) was used for difference in RMIFT by 28 days and risk of infection. Time scale was days from transfusion. A one-sided test with type I error of 0·05 was used to determine statistical significance.

A secondary outcome was disease severity by day 28 using a clinical event scale ranging from no infection to death. The most severe status by the day 28 visit was ascertained using a TMLE estimator for ordinal outcomes and adjusted for the pre-specified candidate variables selected by the algorithmic approach [16, 17].

A pre-specified sensitivity analysis was restricted to participants who remained infection-free up to day 4 to account for people with early and still undetectable infection when CCP was administered and for an expected lag between transfusion and effect from passive antibody transfer. Since protocolized RT-PCR testing was not performed on days 2 and 3, it is possible that infected asymptomatic patients were included in this analysis.

Donor antibody titers

Analysis for donor spike antibody titer was conducted for AUC as a continuous variable: controls were assigned a value of zero. To model antibody effect, a flexible Weibull time to event model was used[18] to estimate the hazard ratios. To allow for non-linearity, both natural cubic splines and fractional polynomials were assessed choosing the model with the lowest Akaike Information Criterion (AIC) [19]. Data on days from donation to transfusion were collected and compared in the CCP vs placebo group.

Safety

Rates of severe transfusion reactions, AEs, grade 3 or 4 AEs, and death were evaluated by treatment arm; 95% confidence intervals (CI) were calculated using skewness-corrected asymptotic score for exact CI[20], using the R package 'ratesci'.

Conditional Power Analysis

The trial did not meet the target sample of 500 participants as enrollment stopped with widespread vaccine availability. The sample size calculation is provided as supplementary material. A conditional power analysis, using the R package 'gsDesign', was conducted to assess the likelihood of providing evidence for the efficacy of convalescent plasma.

Results

Of 1,138 participants screened, 180 (15·8%) were eligible and consented to the study and 170 were transfused (82 CCP; 88 control plasma; Figure 1). Of those transfused, two were excluded from efficacy analyses for baseline SARS-CoV-2 RT-PCR positivity. Table 1 lists participants' demographic and baseline characteristics. Median time from exposure to transfusion was 2 days (IQR 1-4). Seven participants (3 CCP recipients) did not complete all study components.

CCP from 70 unique donations was transfused to 82 recipients; the IgG inverse endpoint titers to protein S were > 1,000 except for a single unit at 540. More than 85% of the plasma units were hospital qualified EUA high titer by Euroimmun Arbitrary units $\geq$3·5, international spike binding arbitrary units/mL $\geq$ 60, RBD AUC>900 and virus 3-day culture neutralization $\geq$ 8 International units/mL (appendix Figure S1).

Primary Outcomes

Of the 168 participants in the mITT analyses, 12/81 (14·8%) CCP and 13/87 (14·9%) control recipients tested positive for SARS-CoV-2 RNA. Three were positive on day 1 post-transfusion and 3 on days 2-3. The RMIFT by 28 days was 25·3 days for CCP and 25·2 for control recipients (p=0·47. The RD was 0·01 (p=0·42) lower for CCP. Excluding infections through day 3, the RMIFT was 26·6 days for CCP and 25·8 for control recipients (p=0·15). The RD was 0·04 (p=0·21) lower for CCP. Six (7·4%) CCP and 7 (8%) control recipients had COVID-19 (4 and 5 after day 3 from transfusion). The RMIFT by 28 days was 26·3 for the CCP and 25·9 days for the control recipients. The RD between groups was 0·012 lower for CCP. Excluding infections through day 3, the CCP group was consistently, but not significantly, better than control (difference in RMIFT =0·7 days, p=0·14; RD=0·017). Cumulative incidence of confirmed SARS-CoV-2 infections and of COVID-19, using a time-to-event analysis to compare the restricted mean survival (infection free) time are shown in figures 2 and 3.

Conditional power analyses were conducted since the target enrollment (500 transfused) was not reached. Had target enrollment been reached it is unlikely that statistically significant results would have been achieved, with chances for significant differences in RMIFT and RD calculated as 0·3% and 0·6% respectively.

Adverse Events

There were 86 reported AEs, of which 28 occurred with CCP and 58 with control plasma; 17/86 events were grade 3 or 4 Five participants required hospitalization (2 for COVID-19) all with control plasma (Supplemental Materials). CCP recipients had a lower proportion of any AEs (p=0·005), and severe AEs (p=0·06) (Table 2).

Clinical Severity Score

Two control participants required hospitalizations for COVID-19 (Table 3). The distribution of clinical severity was similar between the two groups for all events after transfusion (OR 0·99) and for events >3 days after transfusion (OR 0·94).

Relationship between donor antibody levels and infection

The donor antibody levels measured by binding to SARS-CoV-2 proteins or by virus neutralizations as well as the interval from plasma donation to transfusion was comparable in those infected or not infected when limiting analysis to those developing infection > 3 days after transfusion (Supplemental Figure 1 and 2). Pharmacokinetic analysis on 24 participants showed recipient antibody levels to be 4% or a 25-fold reduction from donor antibody levels with a 7-day recipient half-life measured over 14 days (Figure 4).

Discussion

This randomized, placebo-controlled, double-blinded trial evaluated the efficacy and safety of a unit of high antibody titer CCP for prevention of SARS-CoV-2 infection following recent, close contact exposure to a person with COVID-19. In this sample of outpatients, CCP did not reduce SARS-CoV-2 infection in participants transfused up to 120 hours following exposure.

The findings contrast with successful use of mAbs for PEP [8]. Inability of CCP to prevent infection cannot be ascribed to the absence of specific antibody to SARS-CoV-2, as both CCP and mAbs contain SARS-CoV-2 specific antibodies. Insufficient antibody dose in the CCP used is one explanation for lack of efficacy as PEP. The amount of immunoglobulin in the casirivimab/imdevimab dose is 12 grams, likely exceeding the amount of viral-specific antibodies in a unit of high-titer plasma. The concentration of antibodies in the casirivimab/imdevimab PEP trial was 22-25 mg/L which is about 150 times that needed for neutralization of many variants [21, 22]. CCP used in this study had geomean neutralizing international units/mL of 1:27, which when diluted about 30-fold after transfusion, resulted in 10-100 lower neutralizing capacity than mAbs. Neutralization potency of CCP may be impacted by multiple factors including time of plasma collection, distance from location of use, severity of illness and age. The impact of viral variants on efficacy of plasma collected earlier in the pandemic may be most profound with variants such as delta and omicron. Those would not have impacted the results of this trial. It is possible that low levels of the delta variant were present at the clinical sites during this trial, however, the treatment phase was completed prior to widespread circulation of those variants in the US. Qualitative differences between the products could also affect efficacy. For CCP, much of the neutralizing capacity is in IgM [23], a large molecule with poor tissue penetration; mAbs are entirely IgG, which has better tissue penetration[24].

Breakthrough SARS-CoV-2 infections despite vaccination provide insight as to why CCP did not prevent infection. Serum IgG is unlikely to prevent upper airways infection, presumably because of insufficient concentration within respiratory airway mucosa during initial infection when the epithelium is intact. As infection progresses an inflammatory response

permits transudation of serum (and IgG) into tissues. Our results contrast with those of a study using the same plasma supply, which found that CCP administered early in COVID-19 reduced hospitalization by 54% [25]. The large amount of immunoglobulin in plasma after prophylactic mAb administration or vaccination is presumably sufficient to prevent progression of infection to severe disease. However, the amount of specific antibody after a unit of CCP may be insufficient to affect the course of initial infection, especially if much of the neutralizing antibody is IgM. This is consistent with animal studies reporting antibodies' inefficiency at reducing virus in nasal tissues [26]. Notably, two control participants were hospitalized for COVID-19 (one with hematological disease and hypogammaglobulinemia). Though the numbers are small, none of those who received CCP progressed to hospitalization, which is consistent with findings that early treatment with passive immunotherapy (CCP or mAbs) reduces disease progression [10].

Our study affords insight into the optimal timing of CCP administration. Although numerous clinical trials and observational studies were initiated early in the pandemic, these —overwhelmingly— focused on hospitalized patients with severe COVID-19, collectively demonstrating little if any benefit in advanced disease [27]. By contrast, findings from large observational studies of hospitalized patients suggested a mortality benefit when CCP was administered early [11]. Two clinical trials of CCP in outpatients (i.e., those with early infection) have also shown benefit. One showed a significant reduction in progression of respiratory disease in older patients with COVID-19 who received CCP [10]. In the US, the largest trial to date of outpatient CCP use demonstrated a 54% relative risk reduction in hospitalization relative to controls [25]. Another trial enrolled patients with COVID-19 who presented to the emergency room (ER) [28]. It failed to show a significant difference between the CCP and control arms, but the high number of patients (n=25) who were hospitalized during the index visit, suggests that the trial may have selected for a population with more advanced disease [28]. Our study, which focused on PEP refines our understanding of when CCP is optimally effective, thus strengthening extant guidelines that recommend early use of qualified CCP following diagnosis [29].

Historically, convalescent serum was used for prophylaxis of measles [4] and mumps [5] where it was demonstrated to prevent measles and mumps-related orchitis. These viruses are acquired by the respiratory route, but disease manifestations are systemic [5]. For both measles and mumps, success of serum prophylaxis was measured by prevention of systemic disease (rash and orchitis). These experiences suggest that it may be easier to prevent systemic disease with antibodies than against respiratory tract-only disease. A similar pattern is found with pneumococcal vaccine, in which antibodies are more effective in preventing sterile site than respiratory tract disease [30].

In this study, CCP was associated with substantially fewer Grade 3/4 and severe AE's than control plasma. The reason for this finding is unclear. As there were two hospitalization for COVID-19 in control recipients and none in CCP a possible explanation could be protection from severe disease in those developing COVID-19 [25]. Early in the pandemic, there were concerns about antibody-dependent enhancement (ADE) of infection [31, 32]. While ADE has not been reported in CCP studies to date, almost all were conducted in hospitalized patients [33] and do not rule out the possibility of ADE in early infection when endogenous antibody responses are lacking. In this study, CCP was administered before or very early in the course of infection and there was no evidence of ADE. This strongly suggests that ADE is not a significant concern [31, 32, 34].

The study had limitations. The logistical challenges were formidable and frequently changed with the evolving pandemic. Enrollment declined precipitously with widespread vaccine availability. Previously vaccinated individuals were ineligible for participation, and guidance to defer vaccination until 90 days after receipt of CCP deterred potential subjects. The enrollment goal of 500 total participants was not achieved. However, conditional power analyses for the primary endpoint of infection suggest that results may not have significantly differed had the trial achieved target enrollment.

In conclusion, this RCT of high titer CCP given to participants exposed to, but not infected with SARS-CoV-2, within 120 hours demonstrated that CCP did not provide evidence of efficacy. Acknowledging the challenges of enrollment in the setting of vaccine availability, the ongoing evolution of SARS-CoV-2 with loss of multiple treatment and prevention options, could renew interest in new studies of CCP as PEP. Such studies should consider a higher dose of antibodies (i.e., collected from donors who have a history of SARS-CoV-2 infection and have also previously been vaccinated) and/or transfusion with multiple CCP units. Further, studies would best target populations most at risk, including the immunocompromised or elderly, with greater emphasis on clinical rather than laboratory outcomes.

NOTES

Supplementary Data

Supplementary materials are available at Clinical Infectious Diseases online.

Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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Potential conflicts of Interests.

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References

1. WHO. WHO (COVID-19) Homepage. Available at: https://covid19.who.int/. Accessed June 12, 2021.

2. Ritchie H, Ortiz-Ospina E, Beltekian D, et al. Coronavirus (COVID-19) Vaccinations. Available at: https://ourworldindata.org/covid-vaccinations. Accessed June 13, 2021.

3. Boyarsky BJ, Werbel WA, Avery RK, et al. Antibody Response to 2-Dose SARS-CoV-2 mRNA Vaccine Series in Solid Organ Transplant Recipients. JAMA **2021**; 325(21): 2204-6.

4. Gallagher JR. Use of Convalescent Measles Serum to Control Measles in a Preparatory School. Am J Public Health Nations Health **1935**; 25(5): 595-8.

5. Rambar AC. MUMPS: Use of Convalescent Serum in the Treatment and Prophylaxis of Orchitis. American Journal of Diseases of Children **1946**; 71(1): 1-13.

6. Luke TC, Casadevall A, Watowich SJ, Hoffman SL, Beigel JH, Burgess TH. Hark back: passive immunotherapy for influenza and other serious infections. Crit Care Med **2010**; 38(4 Suppl): e66-73.

7. Hemming VG. Use of intravenous immunoglobulins for prophylaxis or treatment of infectious diseases. Clin Diagn Lab Immunol **2001**; 8(5): 859-63.

8. O'Brien MP, Forleo-Neto E, Musser BJ, et al. Subcutaneous REGEN-COV Antibody Combination to Prevent Covid-19. New England Journal of Medicine **2021**; 385(13): 1184-95.

9. Cohen MS, Nirula A, Mulligan MJ, et al. Effect of Bamlanivimab vs Placebo on Incidence of COVID-19 Among Residents and Staff of Skilled Nursing and Assisted Living Facilities: A Randomized Clinical Trial. JAMA **2021**; 326(1): 46-55.

10. Libster R, Pérez Marc G, Wappner D, et al. Early High-Titer Plasma Therapy to Prevent Severe Covid-19 in Older Adults. New England Journal of Medicine **2021**.

11. Joyner MJ, Carter RE, Senefeld JW, et al. Convalescent Plasma Antibody Levels and the Risk of Death from Covid-19. N Engl J Med **2021**; 384(11): 1015-27.

12. Thompson MA, Henderson JP, Shah PK, et al. Association of Convalescent Plasma Therapy With Survival in Patients With Hematologic Cancers and COVID-19. JAMA Oncology **2021**; 7(8): 1167-75.

13. Casadevall A, Henderson JP, Joyner MJ, Pirofski LA. SARS-CoV-2 variants and convalescent plasma: reality, fallacies, and opportunities. J Clin Invest **2021**; 131(7).

14. Klein SL, Pekosz A, Park HS, et al. Sex, age, and hospitalization drive antibody responses in a COVID-19 convalescent plasma donor population. J Clin Invest **2020**; 130(11): 6141-50.

15. Diaz I, Colantuoni E, Hanley DF, Rosenblum M. Improved precision in the analysis of randomized trials with survival outcomes, without assuming proportional hazards. Lifetime Data Anal **2019**; 25(3): 439-68.

16. Benkeser D, Diaz I, Luedtke A, Segal J, Scharfstein D, Rosenblum M. Improving precision and power in randomized trials for COVID-19 treatments using covariate adjustment, for binary, ordinal, and time-to-event outcomes. Biometrics **2020**.

17. Diaz I, Colantuoni E, Rosenblum M. Enhanced precision in the analysis of randomized trials with ordinal outcomes. Biometrics **2016**; 72(2): 422-31.

18. Royston P, Parmar MK. Flexible parametric proportional-hazards and proportional-odds models for censored survival data, with application to prognostic modelling and estimation of treatment effects. Stat Med **2002**; 21(15): 2175-97.

19. Royston P. Model selection for univariable fractional polynomials. Stata J **2017**; 17(3): 619-29.

20. Laud PJ. Equal-tailed confidence intervals for comparison of rates. Pharm Stat **2017**; 16(5): 334-48.

21. Weinreich DM, Sivapalasingam S, Norton T, et al. REGEN-COV Antibody Combination and Outcomes in Outpatients with Covid-19. N Engl J Med **2021**.

22. Copin R, Baum A, Wloga E, et al. The monoclonal antibody combination REGEN-COV protects against SARS-CoV-2 mutational escape in preclinical and human studies. Cell **2021**; 184(15): 3949-61.e11.

23. Gasser R, Cloutier M, Prévost J, et al. Major role of IgM in the neutralizing activity of convalescent plasma against SARS-CoV-2. Cell Rep **2021**; 34(9): 108790.

24. Burnett D. Immunoglobulins in the lung. Thorax **1986**; 41(5): 337-44.

25. Sullivan DJ, Gebo KA, Shoham S, et al. Randomized Controlled Trial of Early Outpatient COVID-19 Treatment with High-Titer Convalescent Plasma. N Engl J Med. 2022 Mar 30. Epub ahead of print.

26. Zhou D, Chan JF, Zhou B, et al. Robust SARS-CoV-2 infection in nasal turbinates after treatment with systemic neutralizing antibodies. Cell Host Microbe **2021**; 29(4): 551-63.e5.

27. Piechotta V, Iannizzi C, Chai KL, et al. Convalescent plasma or hyperimmune immunoglobulin for people with COVID-19: a living systematic review. Cochrane Database Syst Rev **2021**; 5(5): Cd013600.

28. Korley FK, Durkalski-Mauldin V, Yeatts SD, et al. Early Convalescent Plasma for High-Risk Outpatients with Covid-19. New England Journal of Medicine **2021**; 385(21): 1951-60.

29. Cohn CS, Estcourt L, Grossman BJ, et al. COVID-19 convalescent plasma: Interim recommendations from the AABB. Transfusion **2021**; 61(4): 1313-23.

30. Webber C, Patton M, Patterson S, Schmoele-Thoma B, Huijts SM, Bonten MJ. Exploratory efficacy endpoints in the Community-Acquired Pneumonia Immunization Trial in Adults (CAPiTA). Vaccine **2017**; 35(9): 1266-72.

31. Yager EJ. Antibody-dependent enhancement and COVID-19: Moving toward acquittal. Clin Immunol **2020**; 217: 108496.

32. Dzik S. COVID-19 Convalescent Plasma: Now Is the Time for Better Science. Transfus Med Rev **2020**; 34(3): 141-4.

33. Joyner MJ, Wright RS, Fairweather D, et al. Early safety indicators of COVID-19 convalescent plasma in 5000 patients. J Clin Invest **2020**; 130(9): 4791-7.

34. Joyner MJ, Bruno KA, Klassen SA, et al. Safety Update: COVID-19 Convalescent Plasma in 20,000 Hospitalized Patients. Mayo Clin Proc **2020**; 95(9): 1888-97.

1 Table 1: Demographics and Medical Conditions at Randomization

	Control Plasma (N=93)	Convalescent Plasma (N=87)
Male, N (%)	53 (57·0)	46 (52·9)
Race, N (%)		
White	78 (83·9)	80 (92·0)
Black	6 (6·5)	4 (4·6)
Asian	7 (7·5)	2 (2·3)
Native American	0 (0)	0 (0)
Pacific Islander	0 (0)	1 (1·1)
Other race	2 (2·2)	0 (0)
Ethnicity, N (%)		
Hispanic/Latino	16 (17·2)	15 (17·2)
Age, median [min, max]	46·0 [18·0, 91·0]	48·0 [19·0, 82·0]
Age category, N (%)		
18-34	26 (28·0)	18 (20·7)
35-44	18 (19·4)	19 (218)
45-54	19 (20·4)	22 (25·3)
55-64	16 (17·2)	14 (16·1)
≥65	14 (15·1)	14 (16·1)
BMI category, N (%)		
<18	0 (0)	2 (2·3)
≥18-24·9	34 (36·6)	23 (26·4)
>25-29·9	14 (15·1)	30 (34·5)
≥30-34·9	16 (17·2)	10 (11·5)
≥35-39·9	11 (11·8)	6 (6·9)
≥40	5 (5·4)	3 (3·4)
Missing	13 (14·0)	13 (14·9)
Number in household, N (%)		
1	26 (28·0)	18 (20·7)
2	21 (22·6)	19 (218)
3	15 (16·1)	17 (19·5)
4	10 (10·8)	17 (19·5)
>5	17 (18·3)	12 (13·8)
missing	4 (4·3)	4 (4·6)
Number of household positives, N (%)		
1	54 (58·1)	54 (62·1)
2	5 (5·4)	8 (9·2)
3	3 (3·2)	1 (1·1)
≥4	1 (1·1)	0 (0)
missing	30 (32·3)	24 (27·6)
Median time from last exposure to transfusion (IQR)	3 (1,4)	2 (1,4)
Days from last exposure to transfusion (170), N (%)		

	7 (8·0)	7 (8·5)
0	16 (18·2)	24 (29·3)
1	14 (15·9)	12 (14·6)
2	17 (19·3)	11 (13·4)
3	16 (18·2)	12 (14·6)
4	9 (10·2)	7 (8·5)
≥5	9 (10·2)	9 (11·0)
Missing		
Cancer, N (%)		
Active cancer	1 (1·1)	1 (1·1)
Active cancer on chemotherapy	1 (1·1)	0 (0)
Cancer in remission	5 (5·4)	6 (6·8)
Leukemia/Lymphoma	6 (6·5)	2 (2·3)
Cardiac Condition, N (%)		
Arrhythmia	1 (1·1)	2 (2·3)
Atrial fibrillation, on anticoagulation	0 (0)	1 (1·1)
Cardiomyopathy	0 (0)	1 (1·1)
Coronary artery disease	3 (3·2)	1 (1·1)
Myocardial infarction	2 (2·2)	0 (0)
Immunologic Condition, N (%)		
Allergic rhinitis	10 (10·8)	12 (13·8)
Inflammatory bowel disease	3 (3·2)	0 (0)
HIV on antiretroviral treatment	6 (6·5)	4 (4·6)
Psoriasis	0 (0)	2 (2·3)
Immunosuppression on other immune modulator	0 (0)	1 (1·1)
Metabolic Condition, N (%)		
Diabetes mellitus	5 (5·4)	6 (6·8)
Vitamin D deficiency	1 (1·1)	1 (1·1)
Respiratory Conditions, N (%)		
Asthma	5 (5·4)	4 (4·6)
Chronic Bronchitis	2 (2·2)	0 (0)
Chronic sinusitis	1 (1·1)	0 (0)
Cough	1 (1·1)	1 (1·1)
Pulmonary fibrosis	1 (1·1)	0 (0)
Pulmonary hypertension	1 (1·1)	1 (1·1)
Tobacco User, N (%)		
Current tobacco user	1 (1·1)	2 (2·3)
Past tobacco user	4 (4·3)	1 (1·1)

Table 2: Adverse events

	Control Plasma		Convalescent Plasma			
	N	Incidence Rate per 100 person-years (95% CI)	N	Incidence Rate per 100 person-years (95% CI)	Rate Difference (95% CI)	P-Value
Severe transfusion reaction	1	5 (<0·001, 31)	0	0 (0, 23)	-5 (-31, 19)	0·67
Any adverse event	58	311 (236, 402)	28	164 (109, 238)	-147 (-254, -43)	0·005
Grade 3 or 4 adverse event	13	70 (37, 120)	4	23 (6, 61)	-47 (-100, 2)	0·06
Death	0	0 (0, 21)	0	0 (0, 23)	0 (-21, 23)	1

Table 3: Clinical severity in those receiving allocated intervention

	Control Plasma N=88	Convalescent Plasma N=82	Odds Ratio (P-value)	Odds Ratio Model excluding events through day 3 (P-value)
Hospitalization for COVID-19	2	0		
No hospitalization, COVID-19	5	6		
No hospitalization, asymptomatic SARS-CoV-2 infection	6	6	0·99 (0·98)	0·94 (0·90)
No SARS-CoV-2 infection	75	70		

Figure Legends

Figure 1: Consort Diagram: Intention to treat analysis, including all transfused individuals. Those lost to follow-up between transfusion to end of follow-up contributed to the time at risk. Individuals with positive RT-PCR on day of transfusion were removed from analysis. * One randomized participant was found ineligible after randomization.

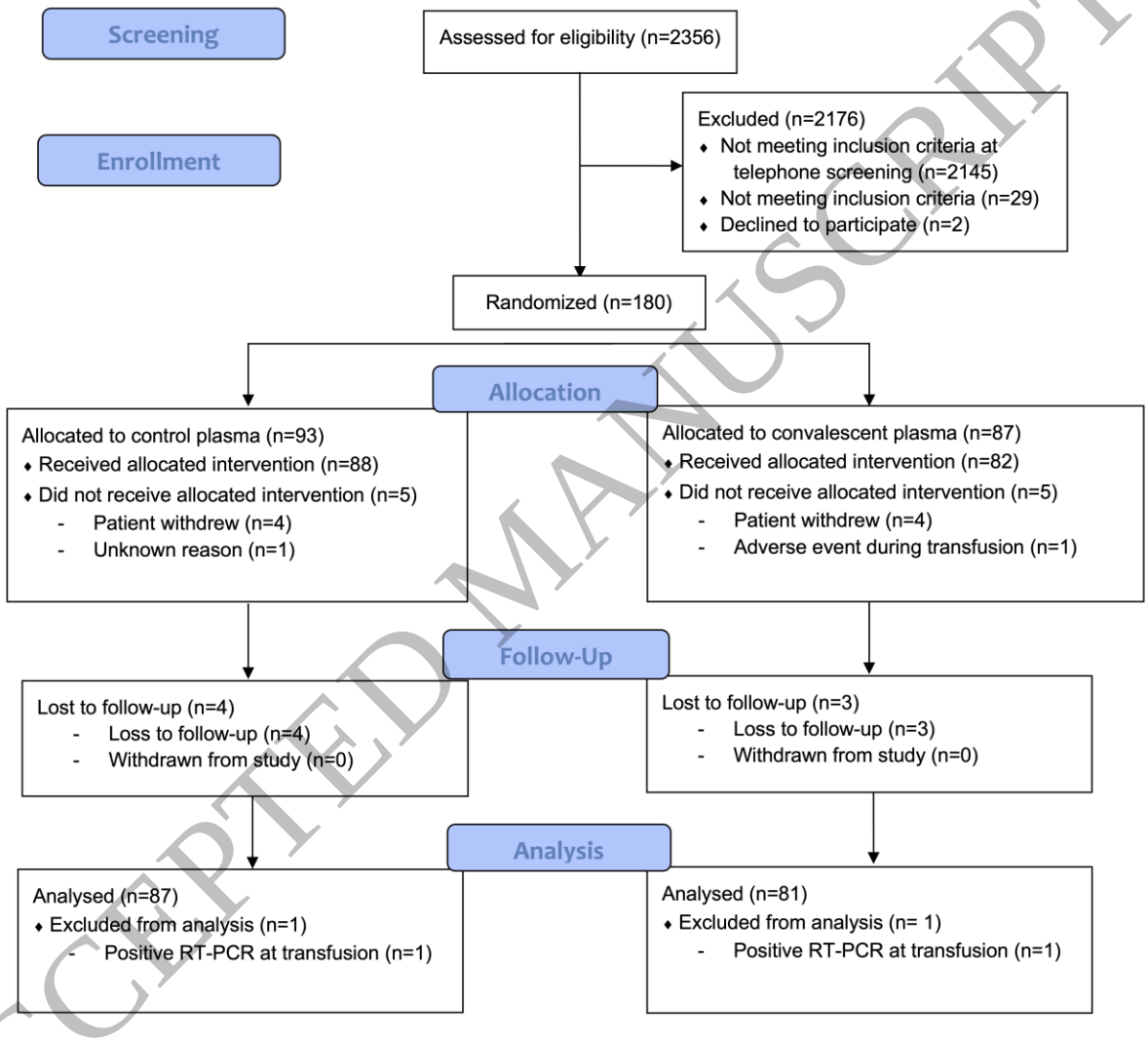
Figure 2: Cumulative incidence of confirmed infections and COVID-19.

Figure 3: Cumulative incidence confirmed SARS-CoV-2 infections and COVID-19 occurring after day 3.

Figure 4: The RBD AUC in the 24 donor plasma units were graphed at Day 0. Recipient participants (n=24) who were seronegative at screening and who did not acquire infection were measured for RBD protein antibody area under the curve (AUC) levels at day 1 (n=24), 7 (n=21) and 14 (n=20) after infection. Geometric means are shown. The recipient day 1 RBD levels were 4% of donor plasma levels. The half-life over days 1-14 is 7 days, half-life from day 1-7 is 4·5 days and over day 7 to 14 is 11·3 days.

Figure 1: CONSORT Diagram

(as of 23 June 2021)



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2 Figure 1

3 165x214 mm (.97 x DPI)

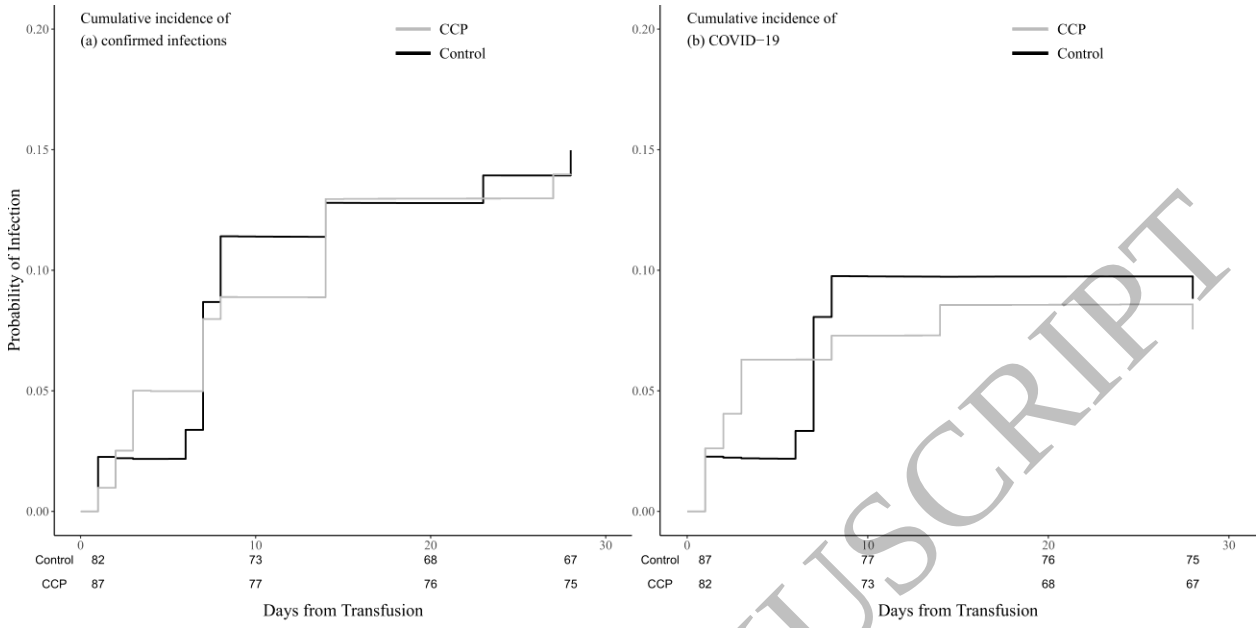


Figure 2

165x83 mm (.97 x DPI)

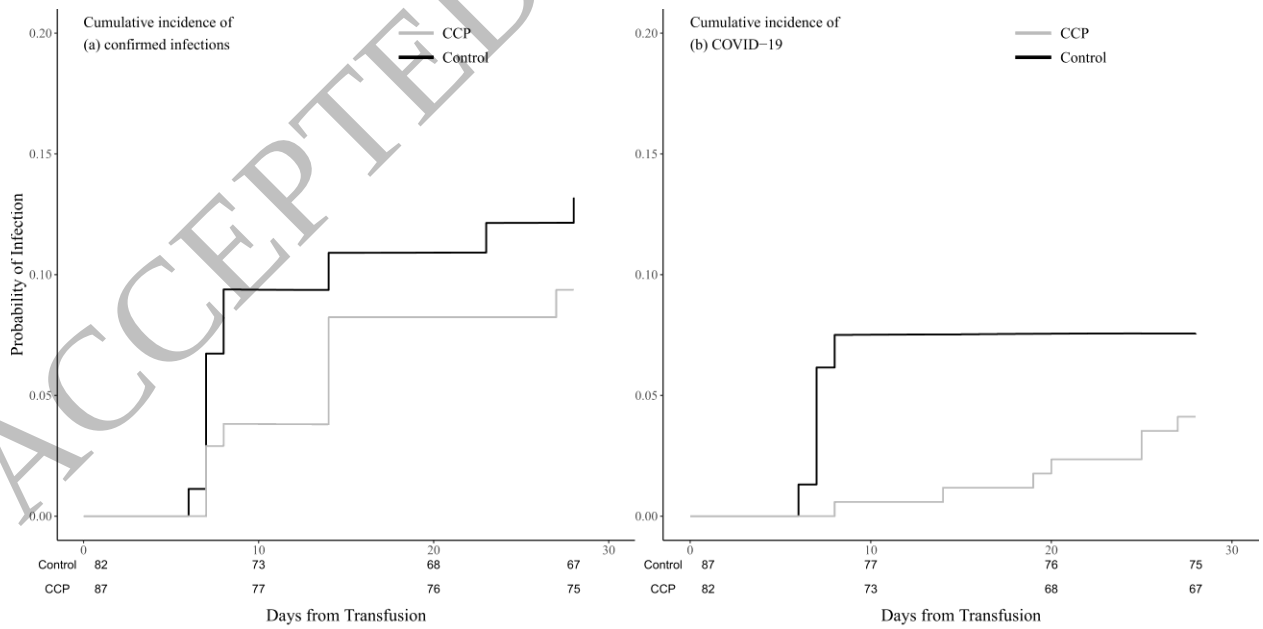
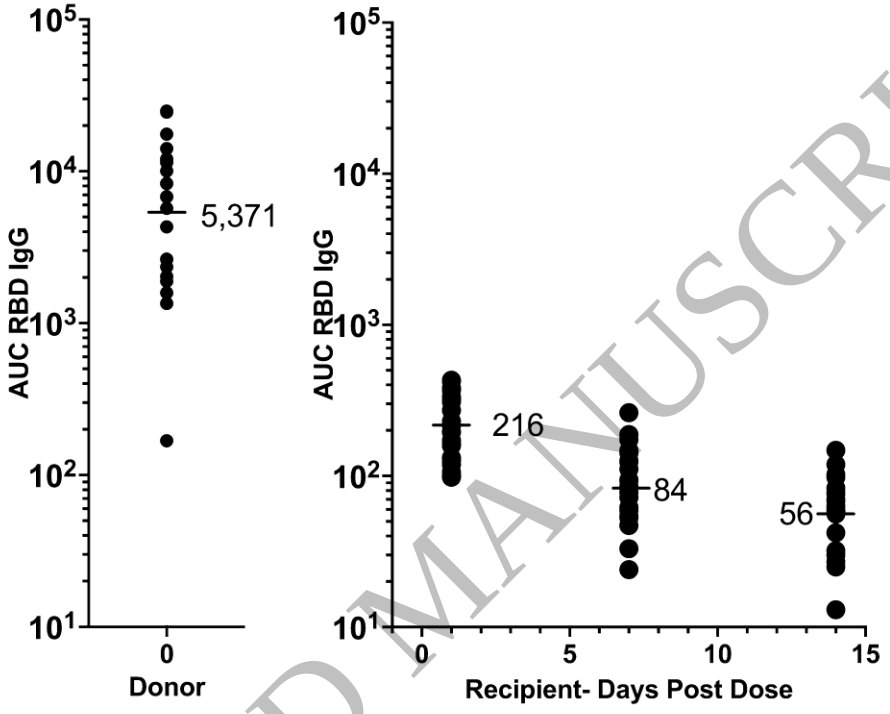


Figure 3

165x83 mm (.97 x DPI)



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2 Figure 4

3 165x214 mm (.97 x DPI)