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Brief report

Lessons learned from the use of COVID-19 convalescent plasma at Kaiser Permanente

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Background: In April 2020, the Mayo Clinic helped establish the US Food and Drug Administration Expanded Access Protocol for COVID-19 (coronavirus disease 2019) convalescent plasma (CCP). The effectiveness of CCP in the published literature is contradictory because some retrospective studies showed benefit in reducing mortality and severe illness, whereas prospective randomized controlled trials demonstrated no benefit of CCP.

Objectives: To discuss (1) the implementation of CCP across Kaiser Permanente Southern California between April 2020 and April 2021, (2) retrospective multivariable analysis of 2,831 patients with COVID-19 who were transfused with CCP compared with 18,475 patients with COVID-19 who did not receive CCP, (3) how to reconcile contradictory published data regarding the efficacy of CCP, and (4) guidance regarding the future use of convalescent plasma in a large community hospital setting.

Methods: Multivariable analysis was controlled for demographic characteristics, level of oxygen delivery, intensive care unit stay, selected laboratory findings, and other concurrent treatment-related variables. Tubing segments from 151 CCP units transfused between October 2020 and April 2021 were retrospectively tested for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) anti–spike protein receptor-binding domain IgG. Multivariable analysis showed that CCP transfusion did not affect mortality rates at 30 days and 5 months (odds ratio, 1.04, 95% CI, 0.87-1.25, and hazard ratio, 1.05, 95% CI, 0.93-1.19).

Conclusions: If convalescent plasma is offered as a therapeutic in a future viral pandemic, we recommend (1) transfusing only those patients who are negative for neutralizing antibodies, (2) transfusing very early during the disease course, (3) only using convalescent plasma with known levels of neutralizing antibodies, or (4) alternatively providing fractionated hyperimmune globulin. (J Allergy Clin Immunol Global 2022;■■■:■■■-■■■.)

Key words: *COVID-19, convalescent plasma*

INTRODUCTION

The use of COVID-19 (coronavirus disease 2019) convalescent plasma (CCP) for the treatment of patients with COVID-19 resulted in numerous publications with conflicting outcomes. In 2021, Joyner et al[1] published positive retrospective analyses using data gathered through the US Food and Drug Administration's (FDA's) Expanded Access Protocol. The study suggested a reduction in 30-day mortality in patients who received "very high titer" CCP (>80th percentile, >1:2560) versus "low titer" CCP (<20th percentile, <1:160).[1] However, several large prospective randomized controlled trials, including the investigation by Ortigoza et al,[2] the National Institutes of Health SIREN-C3PO trial,[3] and the UK RECOVERY trial,[4] did not show benefit in reducing overall mortality. On the basis of our experience at a large integrated health care system, we suspect the following factors contributed to these conflicting results and were also challenges to overcome in community hospitals: (1) insufficient neutralizing antibodies present in donor CCP; (2) minimum thresholds set for "high titer" varied widely between studies; and (3) emergent data, which suggests that CCP should be reserved only for patients with COVID-19 with undetectable neutralizing antibodies before transfusion.[5]

RESULTS AND DISCUSSION

Kaiser Permanente serves 12.4 million members in 8 states and Washington DC. Kaiser Permanente Southern California (KPSC) includes 15 hospitals in urban, suburban, and semirural areas serving 4.7 million members. KPSC provided CCP to eligible, consenting patients hospitalized for COVID-19 under the FDA Expanded Access Protocol (EAP) and Emergency Use

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This research was supported by a grant from the Regional Research Committee of Kaiser Permanente Southern California (RRC grant no. KP-RRC-20201002).

Disclosure of potential conflict of Interest: The authors declare that they have no relevant conflicts of interest.

Received for publication April 29, 2022; revised June 29, 2022; accepted for publication July 18, 2022.

Available online xxx.

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2772-8293

https://doi.org/10.1016/j.jacig.2022.07.003

TABLE I. Retrospective testing of donor plasma for SARS-COV-2 anti–spike protein receptor-binding domain IgG on Beckman DxI 800 instrument

S/Co ratio	Interpretation	N = 151
<0.8 S/Co	Nonreactive	24 (15.9%)
≥0.8 to <1.0 S/Co	Equivocal	6 (4%)
≥1.0 S/Co	Reactive	121 (80.1%)
>3.3 S/Co	Acceptable threshold for high titer CCP per FDA EUA Letter of Authorization in June 2021	67 (44.3%)
>6.6 S/Co	~80th percentile	30 (20%)

EUA, Emergency Use Authorization; *S/Co*, Signal to Cut-off.

TABLE II. Multivariable odds ratio and Cox-proportional hazard ratio for patients with COVID-19, 30-d and 5-mo mortality

	Overall cohort 30-d mortality (N = 21,195)			Overall cohort 5-mo mortality (N = 21,306)		
Patient characteristic	**Odds ratio**	**95% CI**		**Hazard ratio**	**95% CI**	
CCP (n = 2,831) vs no CCP (n = 18,475)	1.04	0.87	1.25	1.05	0.93	1.19
Male (n = 12,237) vs female (n = 9,069)	1.28	1.15	1.42	1.13	1.05	1.21
Race/ethnicity (ref White n = 4,094)						
Asian/Pacific Islander (n = 2,347)	0.69	0.55	0.87	0.80	0.69	0.93
Black (n = 1,802)	0.72	0.60	0.86	0.82	0.70	0.97
Hispanic (n = 12,840)	0.85	0.73	0.98	0.87	0.77	0.99
Other/unknown (n = 223)	1.17	0.67	2.07	1.17	0.78	1.74
Age (y) (ref 18-49, n = 5,172)						
50-65 (n = 6,911)	2.13	1.82	2.49	1.87	1.67	2.09
66-79 (n = 6,248)	4.75	3.86	5.85	3.16	2.75	3.64
≥80 (n = 2,975)	19.34	15.35	24.37	7.96	6.86	9.23
BMI (ref 18.5-24.9) (n = 4,272)						
Overweight (25-29.9) (n = 6,315)	0.71	0.61	0.82	0.78	0.70	0.87
Obese (30-39.9) (n = 8,034)	0.65	0.57	0.73	0.74	0.67	0.82
Morbidly obese (>40) (n = 2,685)	0.83	0.69	1.01	0.87	0.78	0.97
ICU (n = 3,565) vs no ICU (n = 17,741)	3.73	3.00	4.63	2.46	2.16	2.79
Dexamethasone (yes n = 15,573 vs no n = 5,733)	1.51	1.13	2.01	1.28	1.10	1.50
Remdesivir (yes n = 14,384 vs no n = 6,922)	0.63	0.47	0.83	0.74	0.63	0.87
Tocilizumab (yes n = 390 vs no n = 20,916)	0.99	0.76	1.29	1.04	0.92	1.18
Elixhauser comorbidity index	1.16	1.14	1.18	1.12	1.11	1.13
AST (ref = normal <35 U/L)						
High (>35 U/L) (n = 14,036)	1.50	1.29	1.75	1.27	1.15	1.41
Very high (>175 U/L) (n = 1,295)	2.72	2.31	3.21	1.77	1.56	2.00
Ferritin (ref = normal range given age/sex)						
Abnormal (n = 12,871)	1.52	1.27	1.82	1.24	1.13	1.37
D-Dimer (ref = normal <0.5 FEU μg/mL)						
Abnormal (>0.5 FEU μg/mL) (n = 16,386)	2.15	1.72	2.69	1.99	1.70	2.32
O_2 support (ref = room air, n = 2,898)						
Intubation (n = 4,134)	10.29	7.84	13.52	5.51	4.44	6.84
Noninvasive with pressure support (BIPAP/SIPAP/CPAP) (n = 807)	13.37	8.56	20.88	6.35	4.56	8.84
Noninvasive nonpressure support (HFNC/T-PIECE/Ventimask) (n = 1,280)	4.82	3.48	6.68	3.10	2.28	4.23
Low O_2-need (non-rebreather, nasal cannula) (n = 12,185)	1.42	1.05	1.90	1.29	1.06	1.57

For 30-d mortality, we used logistic regression and excluded 111 patients who lost membership within 30-d, because their mortality status was unknown. For 5-mo mortality, we used Cox-proportional hazards survival analysis, and those patients were considered censored and kept.

AST, Aspartate aminotransferase; *BIPAP*, bilevel positive airway pressure; *BMI*, body mass index; *CPAP*, continuous positive airway pressure; *FEU*, fibrinogen equivalent unit; *HFNC*, high flow nasal cannula; *ICU*, intensive care unit; *SIPAP*, synchronized inspiratory positive airway pressure.

Authorization (EUA) guidelines (see https://www.uscovidplasma.org), with additional internal recommendations to reserve transfusion for nonpregnant patients within 3 days of admission or within 7 days of symptom onset, and preferably negative for anti–severe acute respiratory syndrome coronavirus 2 (SARS-COV-2) antibodies before transfusion. We performed retrospective multivariable analyses of 2,831 patients with COVID-19 treated with CCP compared with 18,475 patients with COVID-19 who did not receive CCP in KPSC. Only 277 (10%) patients were tested for the presence of antinucleocapsid IgG antibodies before transfusion (Abbott SARS-COV-2 IgG Assay). Tubing segments from 151 CCP units transfused between October 2020 and April 2021 were retrospectively tested at the Southern California Permanente Medical Group (SCPMG) Regional Reference Laboratories for SARS-COV-2 anti–spike protein receptor-binding domain IgG on the Beckman DxI 800 instrument (ACCESS, Beckman Coulter, Brea, Calif). This period of time spanned the original "wild-type" SARS-CoV-2 and the subsequent "alpha variant." Of the 151 tested segments, only 67 (44%) met the FDA criteria for "high titer" (S/Co ≥ 3.3, FDA EUA Letter, June 2021); 24 (15.9%) were nonreactive; and 6 (4%) equivocal (Table I).

When adjusted for demographic characteristics, level of oxygen delivery, intensive care unit stay, selected laboratory findings, and other concurrent treatment-related variables, CCP transfusion did not affect mortality rates at 30 days and 5 months (odds ratio, 1.04, 95% CI, 0.87-1.25, and hazard ratio, 1.05, 95% CI, 0.93-1.19) (Table II). No significant increase in adverse transfusion reactions related to CCP was identified. Multivariable analysis showed no reduction in mortality rate at 30 days and 5 months for the subset of patients who received CCP with detectable neutralizing antibodies at S/Co greater than or equal to 3.3 or equivalent (odds ratio, 0.87, 95% CI, 0.58-1.31, and hazard ratio, 0.96, 95% CI, 0.74- 1.24), respectively. Although not statistically significant when adjusted by multivariable analysis, patients who received CCP with the upper 75th percentile of antibodies had a lower 30-day mortality compared with overall (9.1% vs 27.9%).

The American Red Cross provided CCP for most community hospitals, and when SARS-CoV-2 IgG antibody testing was still very limited, the American Red Cross used donor criteria such as full recovery from COVID-19 as a surrogate for antibody testing, which likely resulted in subtherapeutic and nontherapeutic convalescent plasma entering the supply inventory. Consistent with our findings, Clark et al[6] noted that the levels of antispike, antinucleocapsid, and neutralizing antibodies for SARS-CoV-2 in CCP donor plasma samples provided by the American Red Cross were highly variable, with some plasma containing subtherapeutic antibody levels (ie, S/Co of 0.02 for Abbot IgG, positive is ≥1.00). In retrospect, government agencies' initial recommendations for antibody thresholds that constituted "high titer" CCP were much too low. If convalescent plasma is offered as a therapeutic in a future viral pandemic, if at all, we raise consideration for (1) limiting transfusion to only those patients who are negative for neutralizing antibodies, (2) transfusing very early during the disease course, (3) only using convalescent plasma with known levels of neutralizing antibodies more than 80th percentile compared with the donor pool, and not offering convalescent plasma transfusion at all until such a verifiable quantity of antibodies can be measured, or (4) pooling convalescent plasma units to make fractionated hyperimmune globulin.

We thank the following for assistance with this study: Stephanie Tovar (Department of Research Evaluation, Southern California Permanente Medical Group), for study coordination.

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