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BRIEF REPORT

TRANSFUSION

Passive transfer of SARS-CoV-2 antibodies with platelet transfusions

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Abstract

Background: Although over 5000 platelet transfusions occur daily in the United States, the presence of SARS-CoV-2 antibodies in platelet units is not commonly evaluated for. The effects of platelet transfusions with SARS-CoV-2 antibodies remain largely unknown. We evaluated single-donor (apheresis) platelet units for SARS-CoV-2 antibodies and determined if platelet transfusions passively transferred antibodies to seronegative recipients.

Study Design and Methods: We conducted a retrospective analysis as part of a quality assurance initiative during February to March 2021 at a tertiary referral academic center in suburban New York. Platelet units and platelet recipients were evaluated for the presence of SARS-CoV-2 antibodies using the DiaSorin LIASON SARS-CoV-2 S1/S2 IgG assay. There were 47 platelet recipients eligible for study inclusion. The primary outcome was the presence of SARS-CoV-2 spike protein IgG antibodies in the recipient's blood after platelet transfusion.

Results: Twenty-three patients received platelets with SARS-CoV-2 spike protein IgG antibodies; 13 recipients had detection of SARS-COV-2 antibodies (56.5%), and 10 recipients did not. The median antibody titer in the platelet units given to the group with passive antibodies detected was significantly higher compared to the median antibody titer in the platelet units given to the group without antibodies detected (median [interquartile range]: 306 AU/ml [132, 400] vs. 96.1 AU/ml [30.6, 186], $p = .027$).

Conclusions: Our study demonstrated a significant rate of passive transfer of SARS-CoV-2 spike protein IgG antibodies through platelet transfusions. Considering the volume of daily platelet transfusions, this is something all clinicians should be aware of.

KEYWORDS

antibodies, covid-19, platelets, Sars-CoV-2, transfusion

1 | INTRODUCTION

Several studies have described the utility of convalescent plasma in transferring protective antibodies against coronavirus disease 2019 (COVID-19).[1–3] Convalescent plasma, the blood plasma of recovered COVID-19 patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) antibodies, has been transfused to symptomatic COVID-19 patients for the purpose of viral neutralization and immunomodulation.[3] In patients with hematologic cancers, COVID-19 convalescent plasma therapy was associated with a significant 30-day mortality benefit.[4] In August 2020, the US Food and Drug Administration issued an Emergency Use Authorization for COVID-19 convalescent plasma, with a subsequent revision (February 2021) to limit the authorization only to high-titer convalescent plasma.[5]

While there are national efforts to evaluate the prevalence of SARS-CoV-2 antibodies in the general population, evaluation of all blood components for these antibodies is not routine.[6] Dodd et al. and the American Red Cross reported a 1.82% seropositivity for SARS-CoV-2 antibodies in blood donations over a 10-week period during June to August 2020, with seroprevalence increasing over the same period.[7] Bajema et al. found seroprevalence in the general US population in September 2020 ranging from 1.0% to 23.0% depending on location.[8]

Tests for SARS-CoV-2 antibodies are highly diverse, with assays detecting antibodies targeting the nucleocapsid antigen, the spike protein (SP), or the S2 subunit of the SP.[9] In the United States, nucleocapsid antibodies are solely a product of prior infection, while SP antibodies can be detected with prior infection or after vaccination.[10,11] The antibody isotype targets also vary, with some tests measuring only IgG, while others measure total antibodies (i.e., IgG, IgA, and IgM).[9] The performance of these assays has not been fully characterized, including their sensitivity for detecting passive antibody transfer.

In the fall of 2020, we observed that a small number of patients at our institution developed SARS-CoV-2 antibodies during hospitalization, despite negative SARS-CoV-2 antibody testing on admission and no clinical evidence of infection. These patients had all received either frozen plasma or platelets during hospitalization. Apheresis platelet units at our hospital typically contain 200–300 ml of plasma, and thus may inadvertently serve to transfer antibodies. Based on this observation, we aimed to evaluate whether platelet transfusions resulted in passive transfer of SARS-CoV-2 SP antibodies.

2 | METHODS

2.1 | Study design and sample

This retrospective study was part of a hematology laboratory quality assurance initiative at a tertiary referral academic center in suburban New York. All adult inpatient platelet transfusions that occurred Monday to Friday in February–March 2021 were evaluated for the study. Patients were eligible if they: (1) were at least 18 years old, (2) required hospital admission, (3) received single-donor (apheresis) platelets, (4) had negative SARS-CoV-2 antibodies prior to transfusion, (5) had a negative SARS-CoV-2 nasopharyngeal polymerase chain reaction test prior to transfusion, (6) and had a post-transfusion serum specimen.

Clinical and laboratory data were obtained from review of the electronic medical record database (Sunrise Clinical Manager, Allscripts, Chicago, IL, USA). The study was reviewed by the Institutional Review Board and was approved under expedited review. Given the retrospective nature of the study, the need for informed consent was waived.

2.2 | Lab collection and procedure

Per the Transfusion Medicine Service policy at the study institution, a platelet sample was routinely collected by the transfusion service from each platelet unit prior to transfusion and held for 7 days after a transfusion for possible evaluation in the event of a suspected transfusion reaction. The platelet sample contained approximately 5 ml of plasma and allowed for the evaluation of SARS-CoV-2 antibodies without compromising the platelet unit.

In collaboration with the Transfusion Medicine Service, the research team was notified of platelet recipients, who were subsequently evaluated for study inclusion. After confirming eligibility, the research team identified pre- and post-transfusion blood specimens. These specimens were previously collected during hospitalization for medical purposes (such as evaluation of electrolytes or renal function) and were routinely held by the central laboratory for 5 days for repeat or add-on testing.

After the required laboratory holding periods, the research team accessed the eligible platelet samples and blood specimens. All samples were transferred into de-identified specimen tubes and stored in a freezer at −90 to −70 degrees Celsius. All specimens (including pre-transfusion blood plasma, post-transfusion blood plasma, and platelet pouch samples) were tested for the presence

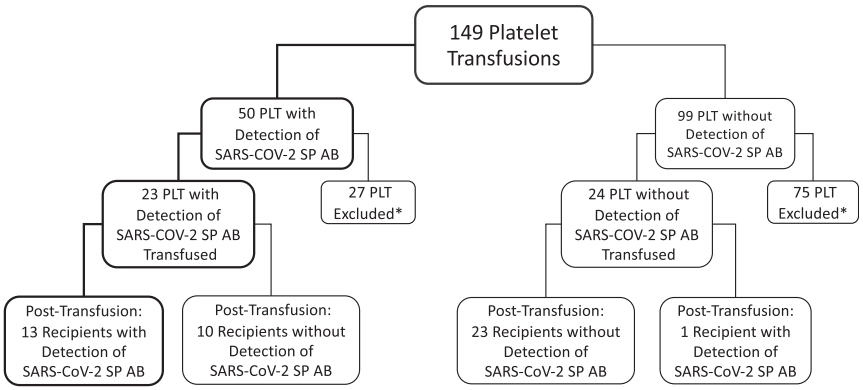

FIGURE 1 Flow diagram of platelet transfusions. PLT, platelet unit; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SP AB, spike protein antibody. *Exclusion due to: (1) Pre-transfusion specimen had antibodies detected with the DiaSorin. (2) Insufficient pre-tranfusion or post-tranfusion sample volume. (3) Multiple transfusions occurred for the same patient and the recipient had converted on prior transfusion

of SARS-CoV-2 SP IgG antibodies by a single assay, ensuring consistency in laboratory reporting. We utilized the DiaSorin LIASON SARS-CoV-2 S1/S2 IgG assay (DiaSorin S.p.A., Salvuggia [VC], Italy), which has been validated to identify antibodies from vaccine and/or natural disease.[12]

Ultimately, 79 individual patients were evaluated and 149 platelet samples were tested, of which 102 platelet samples were excluded due to: (1) recipient's pre-transfusion specimen had antibodies detected with the DiaSorin, (2) insufficient pre-transfusion or post-transfusion sample volume, or (3) multiple transfusions occurred for the same patient and recipient had converted on prior transfusion (see Figure 1).

2.3 | Outcome measures

The primary outcome was the presence of SARS-CoV-2 SP IgG antibodies in the recipient's blood after platelet transfusion in those with negative pre-transfusion serological testing. Secondary outcomes included the measurement of titers of SARS-CoV-2 SP IgG antibodies in the platelet units and in the blood plasma of the recipients with passive antibodies detected.

2.4 | Statistical analysis

Study variables were described by the presence of SARS-CoV-2 SP IgG antibodies in platelet units and by presence in the recipient's post-transfusion blood plasma. For categorical variables, frequency and percent were reported. For continuous variables, mean and standard deviation (SD) or median and interquartile range (IQR) were reported. Differences between other study variables and seropositivity were assessed by Fisher's exact test for categorical variables. For continuous study variables, Wilcoxon Rank Sum test or Kruskal-Wallis test were used. Analyses were generated using SAS/STAT® software, Version 9.4 of the SAS System (SAS Institute Inc., Cary, NC, USA).

3 | RESULTS

There were 149 platelet units evaluated during a 2-month study period. Of these, 50 platelet units showed the presence of SARS-CoV-2 SP IgG antibodies (Figure 1). Forty-seven patients were eligible for evaluation. Twenty patients received platelets due to hematologic disorders, including acute myeloid leukemia, immune thrombocytopenia, multiple myeloma, and lymphoma; 19 patients received platelets due to a surgery or procedure, including atrial fibrillation ablation, aortic aneurysm repair, coronary artery bypass graft, neurosurgery, cardiac valve repair, endoscopic retrograde cholangiopancreatography, and thoracentesis; and eight patients received platelets due to other reasons including subdural hemorrhage, hematemesis, hematoma, hematuria, and septic shock.

Of the 47 eligible patients, 23 received platelets with SP antibodies (study group) and 24 received platelets without SP antibodies (control group). Within the study group, 13 patients (56.5%) tested positive for SP antibodies after platelet transfusion. Mean age in those with passive antibodies detected was 64 years (SD, 13) and six (46.2%) were female (Table 1). Among the controls, one patient (4.2%) tested positive for SP antibodies after transfusion ($p < .001$). The patient was a 57-year-old white non-Hispanic male with hypertension who underwent coronary artery bypass graft surgery. During the surgery, he received three units of apheresis platelets (also negative for SP antibodies), three units of packed red blood cells, and 10 units of cryoprecipitate.

Of the 23 patients who received platelets with SP antibodies, median antibody titer in the platelet units was significantly higher in the group with passive antibodies detected compared to the group without antibodies detected (Med [IQR] = 306 AU/ml [132, 400] vs. 96.1 AU/mL [30.6, 186], $p = .027$) (Table 2). There were no statistically

TABLE 1 Demographics and clinical characteristics of patients who received platelets with SARS-CoV-2 SP IgG antibodies

	Passive antibodies detected ($n = 13$)	Passive antibodies NOT detected ($n = 10$)	p-Value[a]
Demographics and clinical characteristics			
Age, mean (SD), year	64 (13)	65 (15)	.828
Female sex, *n* (%)	6 (46)	5 (50)	1.000
Race, *n* (%)			.331
Asian	2 (15)	2 (20)	
Black or African American	1 (8)	3 (30)	
More than one race	5 (39)	1 (10)	
Unknown/not reported	0	1 (10)	
White	5 (39)	3 (30)	
Hispanic or Latino ethnicity	3 (23)	0	.229
Co-existing diseases, *n* (%)			
Type 2 diabetes mellitus	5 (39)	6 (60)	.414
Hypertension	8 (62)	8 (80)	.405
BMI 30.0 or greater	9 (69)	3 (30)	.100
Other blood products transfused, yes (%)	10 (76.9)	4 (40.0)	.102
Median time from transfusion to post-transfusion testing (hours)	11.2	16.9	.292

Abbreviations: BMI, body mass index; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SD, standard deviation; SP, spike protein.
[a]p-Value testing difference between study variables and post-transfusion antibody status among those given platelets with SARS-CoV-2 antibodies ($n = 23$) using Fisher's exact test or Wilcoxon two-sample test.

TABLE 2 Median SARS-CoV-2 SP IgG antibody titers

	Passive antibodies detected ($n = 13$)	Passive antibodies NOT detected ($n = 10$)	p-Value[a]
SARS-CoV-2 antibody titer, median (IQR), AU/ml			
Of platelet unit	306 (132–400)	96.1 (30.6–186)	.027
Of platelet recipient post-transfusion	53.7 (32.9–93.7)		

Abbreviations: IQR, interquartile range; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SP, spike protein.
[a]p-Value testing difference between study variables and post-transfusion antibody status among those given platelets with SARS-CoV-2 antibodies ($n = 23$) using Wilcoxon two-sample test.

significant differences in demographics and comorbidities between those with passive antibodies detected and those without passive antibodies detected (Table 1). Median time from transfusion to post-transfusion testing across post-transfusion antibody status was 11.2 and 16.9 hours, although there was no significant difference found (Table 1). There was also no significant difference in the median number of other blood products transfused when differed across post-transfusion antibody status (data not in tabular format, passive antibody detected median = 2, passive antibody not detected median = 1.5, p-value = .8794). Among the 13 patients with passive antibodies detected, six were patients with hematologic disorders.

4 | DISCUSSION

Our study demonstrated a significant rate of passive transfer of SARS-CoV-2 SP IgG antibodies through platelet transfusions—to the best of our knowledge, this has not been previously recognized or discussed in the literature. We found that platelet units with higher antibody titers were the most successful in the passive transfer of antibodies. We did not recognize any patient characteristic that significantly predisposed to the detection of passive antibodies. According to the US National Blood Collection and Utilization Survey in 2017, over 1.937 million platelet transfusions were given, or approximately

5300 units per day.[13] Considering the volume of platelet transfusions that occur daily, our findings may impact many patients and health-care providers in their interpretation of COVID-19 antibodies. Patients with previously negative serologies who received platelets may develop detectable antibodies after transfusion and this may lead to misconceptions among patients and clinicians regarding prior COVID-19 infection.

Our findings raise several pertinent follow-up questions. First, are these antibodies protective, and if so, for how long? This will need to be further studied with extended follow-up of platelet recipients after transfusion. Another question that arises: is there a critical SARS-CoV-2 antibody titer threshold that needs to be reached to ensure protection?

Lastly, our findings also raise the question about whether there are other antibodies passively transferred through platelet transfusions that may have clinical implications.

4.1 | Limitations

Our study is not without shortcomings. The study was conducted in a suburban region of New York during February to March 2021, with high prevalence of COVID-19 and lower overall vaccination rates.[14] Thus, the noted seroprevalence of 33% in the platelet units was likely reflective of the blood-donor population. Now that more people are vaccinated, seroprevalence may be very different among donor and recipient populations. To that point, the noted prevalence of SARS-CoV-2 antibodies is likely to exist among all blood products and possibly led to the detection of antibodies in one patient of the control group. This study did not test other transfused blood products, such as packed red blood cells, fresh frozen plasma, and cryoprecipitate.

Furthermore, the study was halted after 149 platelet transfusions due to changes in the laboratory protocol in which the Transfusion Medicine Service stopped routinely collecting platelet pouch samples. On April 1, 2021, the blood supplier implemented large volume delayed sampling of platelet products to mitigate the risk of bacterial contamination of platelet products and enhance their safety; hence, the previous practice of maintaining a pouch for each bag of platelets was discontinued. This prevented any further evaluation of platelet units.

Finally, there was insufficient blood plasma to test for nucleocapsid antibodies on many of the samples, thus limiting any conclusions about the differences between vaccine-induced antibodies and natural infection-induced antibodies.

5 | CONCLUSIONS

Despite the small sample, we demonstrated the ability to transfer SARS-CoV-2 antibodies through platelet transfusions. Our findings impact the interpretation of SARS-CoV-2 antibody testing in patients who received platelet transfusions. With the large volume of platelets transfusion that occurs daily, this is important for clinicians to recognize. Further studies are required to determine the protective efficacy and duration of these transfused antibodies, particularly as COVID-19 remains a serious global concern.

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CONFLICT OF INTEREST

The authors have disclosed no conflicts of interest.

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