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Transfusion Clinique et Biologique 29 (2022) 107–111

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Original article

SARS-CoV-2 neutralizing capacity among blood donors without prior COVID-19 symptomatic history vs. blood donors with prior COVID-19 symptomatic history: A comparative study

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ARTICLE INFO

Article history:
Available online 12 February 2022

Keywords:
SARS-CoV-2
Neutralizing antibodies
COVID convalescent plasma

ABSTRACT

Introduction. – Though moderate to severely ill COVID-19 patients are being treated using COVID Convalescent plasma across the world, there is a lack of standardization or information about the relative neutralizing capacity of antibodies from convalescent plasma donors. The current study aimed to compare the neutralizing antibody inhibition levels between COVID-Convalescent plasma from apheresis donors who had symptomatic COVID-19 history and asymptomatic blood donors, i.e., whole blood donors without prior any COVID-19 positive diagnosis nor symptoms/contact history related to COVID-19.
Methods. – Observational study conducted at the Blood Centre, Tertiary Care Hospital, South India on blood donor samples during the period July–December 2020. A total of 90 samples (43 convalescent plasma donors and 47 whole blood donors) were tested for SARS-CoV-2-IgG and Neutralising antibodies.
Results. – No significant difference in neutralization capacity was observed between these symptomatic vs. asymptomatic donors. Also, inhibition % appeared similar in the two groups with respect to age, gender, blood group, donation status, or type of donation without any statistical significance. On analyzing the correlation between the SARS-CoV-2-IgG levels and neutralizing antibodies among the WBD and CCP, both the groups showed a positive correlation, while neutralizing antibodies showed a significant correlation with SARS-CoV-2-IgG levels among the whole blood donors (Pearson correlation $P = 0.000$).
Conclusion. – No significant difference in neutralizing antibody capacity was observed in asymptomatic whole blood donors and convalescent plasma donors. Therefore, donors having adequate levels of SARS-CoV-2-IgG antibody levels on screening can be considered for convalescent plasma donation irrespective of prior COVID-19 diagnosis or COVID-related symptoms.

1. Background

The COVID-19 disease symptoms are ranging from being asymptomatic, mild to moderate self-limiting respiratory tract illness to severe progressive pneumonia, multi-system involvement, multi-organ failure, and death [1]. For treatment purposes, various therapeutic agents were being explored, in addition to Convalescent Plasma Therapy, and are under evaluation for the treatment of COVID-19 [2]. COVID-Convalescent plasma therapy is the passive transfer of SARS-CoV-2 antibodies obtained from patients recovered from COVID-19 infection, who have generated antibody responses [3]. The secreted antibodies are also known as neutralizing antibodies that bind quickly and strongly to the pathogen, block cellular infiltration and replication thus providing protection against future infections [4].

Although moderate to severely ill patients are being treated using COVID Convalescent plasma across the world, there is a lack of standardization or information about the relative neutralizing capacity of antibodies from convalescent plasma donors [5]. The US Food and Drug Administration has issued a recommendation that the *titre* of neutralizing Abs should be at least 160, but 80 can also be considered in absence of eligible donors [6]. However, the guidance doesn't specify the level of virus neutralization to be achieved at these *titres* or how to measure it. Various approaches available to test neutralizing Abs include Plaque Reduction Neutralization Test

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https://doi.org/10.1016/j.tracli.2022.02.004

(PRNT), Micro neutralization test (MNT), fluorescence-based assays [7].

PRNT is a low throughput assay that takes several days to develop viral plaques, which are units of measurement, whereas MNT requires BSL3 containment for SARS-CoV-2 culture, which is a barrier [8]. Utilizing the pseudotyped viruses vs. fully infectious SARS-CoV-2 requires a higher level of expertise and is vulnerable to biological and experimental variation and the assays utilizing them can take a longer duration of time to obtain results. Thus, a simple rapid, and validated measure of neutralizing antibody responses against S protein, that could be measured in a Surrogate virus-based ELISA-type assay, can be utilized.

To screen the blood donors for convalescent plasma donation eligibility, many centers have adopted tests based on antibody levels, cut-off values, and clinical recovery time from PCR positive results. Donors with a history of COVID-19 positive results and clinical symptoms were known to have higher levels of neutralizing antibodies.

The current study aimed to estimate the neutralizing antibody levels by using the Surrogate Neutralization ELISA assay in terms of inhibition percentages and compare the neutralizing antibody inhibition% levels between COVID-19 Convalescent plasma apheresis donors who had symptomatic COVID-19 history and asymptomatic blood donors, i.e., whole blood donors without any COVID-19 positive diagnosis nor any symptoms/contacts related to COVID-19.

2. Methods

2.1. Study setting

An observational study was conducted during July–December 2020 at the Blood Centre, Tertiary Care Hospital, South India on blood donor samples. All the donors were selected following standard donor selection criteria with informed consent obtained for additional testing for SARS-CoV-2 antibodies. No additional sampling was performed. A total of 90 samples were analyzed. As vaccination was started at a later date in the country (January 2021), none of the donors were vaccinated at the time of inclusion into the study.

2.2. Study set 1

During the study period, 43 COVID-19 Convalescent plasma (CCP) donor samples were included in the study. CCP donations were obtained from the individuals recovered from COVID-19 infection. Recruitment Criteria for CCP donation included past symptomatic COVID-19 infection, with a positive reverse transcriptase-polymerase chain reaction (RTPCR) report, complete resolution of symptoms at least 14 days prior to donation, and one negative RTPCR test report for SARS-CoV-2. The donor's symptoms included fever, cold, cough, generalized weakness, dyspnoea, etc., lasting anywhere between 7–10 days. None of these donors had any history of hospitalization. All the donor samples were tested for complete blood counts, ABO and Rh D blood grouping, antibody screening, routine Transfusion Transmissible Infectious disease testing (anti-HIV I &II, HBsAg, anti-HCV, Syphilis, and Malaria), and anti-SARS-CoV-2-IgG antibodies.

2.3. Study set 2

During the same period, 200 regular whole blood donors who came for donations were included in this study after obtaining additional informed consent for testing of SARS-CoV-2 antibodies along with routine mandatory tests. The selection of whole blood donors is based on the currently existing national guidelines for blood donation. None of the blood donors were vaccinated at the time of inclusion into the study. These donors were asymptomatic and never had prior COVID-19 positive diagnosis or symptoms related to COVID-19 with no history of COVID-19 in close contacts/family members prior to donation. Whole blood was separated into components including fresh frozen plasma.

2.4. SARS-CoV-2-IgG antibodies

The whole blood donor and convalescent plasma donor samples were tested for SARS-CoV-2-IgG antibodies using Chemiluminescence assay (CLIA, Ortho Vitros, USA). CCP donor samples with a signal-to-cut-off (S/C) value of 6 or greater were qualified for COVID-19 Convalescent Plasma donations. Among 200 whole blood donor samples that were tested for SARS-CoV-2-IgG antibodies, about 98 had seropositivity for SARS-CoV-2-IgG antibodies, S/C > 1.0. Forty-seven samples among the 98 had a signal-to-cut-off (S/C) value of 6 or greater. All qualified CCP donor samples ($n = 43$) and whole blood donor samples ($n = 47$) with signal-to-cut-off (S/C) values of 6 or greater were preserved for neutralization assay.

2.5. Enzyme-linked immunosorbent assay: neutralization assay

Further, both the group samples were tested for neutralization assay. The Kit detects and measures circulating neutralizing antibodies against the SARS-CoV-2 virus. The SARS-CoV-2 Surrogate Virus Neutralization Test kit (GenScript USA) is a blocking ELISA, which mimics the virus neutralization process. The test uses HorseRadish Peroxidase HRP conjugated recombinant SARS-CoV-2 RBD fragment and human ACE2 receptor protein. The protein-protein interaction between HRP-RBD and hACE2 (human ACE2 receptors) can be blocked by neutralizing antibodies against SARS-CoV-2 RBD. The absorbance of the sample is inversely dependent on the titre of SARS-CoV-2 neutralizing antibodies. The neutralization Inhibition capacity was expressed in percentage %; manufacturer recommended cut-off of 20% reduction i.e., $\geq$ 20% inhibition was extrapolated to high *titres* of neutralizing antibodies and the mean of percentage is compared between the two groups.

Validation and evaluation: the clinical performance of the GenScript cPass SARS-CoV-2 Neutralization Antibody detection kit was validated using the Comparator Plaque Reduction Neutralization Test (PRNT) utilizing the SARS-CoV-2 virus (WA01/2020 isolate) as per manufacturer evaluation.

2.6. Data analysis

The complete data was recorded into MS Excel 2016 and SPSS 26.0 software for data analysis. Data included demographic details, blood groups, donation status, and type of donation. In the end, both the groups were compared and expressed in frequencies. A Chi^2 test was used to determine the association between the variables. *P*-value < 0.05 at CI-95% were considered significant. Bivariate Pearson correlation was used to find a correlation between variables and the test is significant at 0.01 level for a two-tailed test.

3. Results

Forty-three convalescent plasma donors and 47 whole blood donor samples, a total of 90 samples were tested for SARS-CoV-2-IgG and neutralizing antibodies.

3.1. Sociodemography

The mean age of donors was 31.53 years, (range 19–50 years, SD. ±7.127) with a significantly higher (58%) number of donors belonging to age group 30–45 years (with *P*-value < 0.05). The distribution of gender, blood groups, and donation status between the

Table 1
Summary of donor characteristics in both the groups.

Sociodemographics of study population	CCP donors ($n=43$) n (%)	WB donors ($n=47$) n (%)	Total ($n=90$) n (%)	P-value
Age groups				
18–29 years	8 (18)	26 (55)	34 (38)	0.001*
30–45 years	33 (77)	19 (40)	52 (58)	
46–60 years	2 (5)	2 (5)	4 (4)	
Gender				
Male	42 (99)	47 (100)	89 (99)	0.293
Female	1 (1)	0	1 (1)	
Blood groups				
Group A	10 (23)	9 (19)	19 (21)	0.274
Group AB	2 (5)	9 (19)	11 (12)	
Group B	10 (23)	9 (19)	19 (21)	
Group O	21 (49)	20 (43)	41 (46)	
Donation status				
First time donor	5 (12)	10 (21)	15 (17)	0.220
Repeat donation	38 (88)	37 (79)	75 (83)	
Type of donation				
Voluntary donor	43 (100)	20 (43)	63 (70)	0.000*
Replacement donor	0 (0)	27 (57)	27 (30)	

two groups of donors were similar. Almost 100% of the whole blood donors were males as compared to CCP donors including one nulliparous female donor. Convalescent plasma donors were exclusively voluntary donors as compared to whole blood donors including both voluntary and replacement donors. A detailed characteristic of donors in both groups is shown in Table 1.

3.2. Chemiluminescence assay

Among the 90 (43 CCP and 47 WBD) samples tested for SARS-CoV-2-IgG antibodies using Chemiluminescence assay, 33 donors had a mean OD S/Co value of 7.4 with a range of 6.1–11.8 and 57 donor samples had a mean OD S/Co value of 24.3 with a range of 12.1–42.

3.3. Neutralizing antibodies (NAb) assay

In total, 90 SARS-CoV-2 antibody-positive samples of both groups were tested for neutralization assay. Both the groups had neutralizing antibodies with a threshold greater than 20%. The mean inhibition percentage among the CCP donors group was found to be 77.4% while among the whole blood donors it was 75.2%. No significant difference in neutralization capacity was observed between the blood donors with prior COVID-19 symptomatic history vs. donors without prior COVID-19 symptoms/infection or any positive diagnosis. Also, inhibition % appeared similar in two groups with respect to age, gender, blood group, donation status, or type of donation without any statistical significance.

Refer to Table 2 for a detailed depiction of neutralizing assay results. On analyzing the correlation between the SARS-CoV-2-IgG levels among the WBD and CCP both, the groups showed a positive correlation of anti-SARS-CoV-2-IgG with the neutralizing antibody inhibition percentage, while the significant correlation of neutralizing antibodies with anti-SARS-CoV-2-IgG levels was noted among the whole blood donors without prior COVID-19 diagnosis or clinical symptoms (Pearson correlation $P=0.000$) (Fig. 1).

4. Summary/discussion

Convalescent plasma therapy, a form of passive immunotherapy, was successfully used in the recent past to combat various infections like H1N1 influenza, Middle East Respiratory Syndrome (MERS) CoV, SARS, Ebola with satisfactory efficacy and safety [9–11].

Currently, for SARS-CoV-2, there have been reports of compassionate use and reports of administration of high titer convalescent plasma [12]. The plasma from recovered COVID-19 patients after screening for antibodies is being collected by apheresis techniques and used for moderate to severely ill COVID-19 patients [13,14]. The US FDA guidelines recommended collection of convalescent plasma from individuals who had symptoms of COVID-19 and a positive test result or Individuals without any prior positive diagnosis and/or never had symptoms of COVID-19 with reactive and detectable SARS-CoV-2 antibodies [6].

In our study, the whole blood donors without any prior positive diagnosis and/or symptoms related to COVID-19 had SARS-CoV-2 antibodies comparable to the CCP donors with symptoms. These whole blood donors without prior COVID-19 positive diagnosis or symptomatology had detectable levels of SARS-CoV-2-IgG antibody levels. This could be due to asymptomatic infections occurring in the community. Studies showed that 30% to 45% of SARS-CoV-2 infections are asymptomatic in nature [15,16].

An increase in seroprevalence of SARS-CoV-2 antibodies in the general population was seen as quoted by various studies recently, thereby an expected increase in seroprevalence of SARS-CoV-2 antibodies in the blood donor population [17–19]. Therefore, for the purpose of selection of donor for convalescent plasma collection, testing of the presence of adequate SARS-CoV-2 antibodies during the period of convalescent may be preferred than with the history of COVID-19 RT-PCR positive diagnosis and/or symptoms.

Whole blood-derived COVID Convalescent plasma with adequate SARS-CoV-2 antibodies makes the Convalescent Plasma therapy an economical, affordable, and readily available alternative among the developing countries where facilities of apheresis technology are not widely established [20,21]. With the upcoming third wave of COVID-19, preparedness in terms of COVID-Convalescent plasma can be obtained with the addition of the SARS-CoV-2 antibody test to the whole blood donations and reserving FFP units with adequate antibody levels as CCP, possibly effective against the variants [22]. This shall reduce the cost related to plasma collection by apheresis. Moreover, the availability of plasma will increase, especially in developing countries with resource constraints.

Immunoglobulin, hyperimmune globulins manufacturing from convalescent plasma can be attempted from the whole blood-derived CCP units in similar lines to plasma fractionation and component extraction.

Also, further studies on larger sample size are required to find the seroprevalence across the general population. Clinical efficacy and outcomes of such plasma transfusions obtained from asymptomatic whole blood donors with high neutralizing antibody titres need to be assessed.

Table 2
Detailed neutralization assay results in both the groups.

2A. Comparison of chemiluminescence assay OD S/Co with neutralization inhibition percentage among two groups

	Chemiluminescence assay (CLIA)	Total $n=90$	CCP donors $n=43$	WB donors $n=47$	*P*-value
	CLIA OD S/Co 6-12 ($n=33$)		($n=28$)	($n=5$)	
	CLIA OD mean (range)	7.4 (6.1–11.8)	7.53 (6.1–11.8)	6.68 (6.1–7.3)	0.157
CLIA OD S/Co 6-12 ($n=33$)	Inhibition mean (range)	76.16 (41.1–94.6)	76.35 (41.1–94.6)	75.1 (68.8–82.8)	
	CLIA OD S/Co ≥ 12 ($n=57$)			($n=15$)	($n=42$)
CLIA OD S/Co ≥ 12 ($n=57$)	CLIA OD mean (range)	24.37 (12.1–42)	29.09 (12.1–42)	22.69 (12.1–39.9)	0.153
	Inhibition % mean (range)	76.38 (21.1–95.4)	79.37 (21.1–95.4)	75.31 (44.13–94.09)	

2B. Demographic parameters and Inhibition percentage among two groups

Demographic parameters	Number; mean inhibition % (range)			*P*-value
	Total $n=90$	CCP donors $n=43$	WB donors $n=47$	
Age groups				0.199
18–29 years	34; 76 (45.3–94.09)	8; 77.5 (45.3–92.9)	26; 75.8 (47.8–94.09)	
30–45 years	52; 76.6 (21.1–95.4)	33; 78.2 (21.1–95.4)	19; 73.9 (44.1–89.8)	
46–60 years	4; 73.4 (45.6–89.1)	2; 65.6 (45.6–85.7)	2; 81.2 (73.3–89.1)	
Gender				–
Male	89; 76.4 (21.1–95.4)	42; 77.7 (21.1–95.4)	47; 75.2 (44.1–94.0)	
Female	1; 64.7 (64.7)	1; 64.7 (64.7)	0; ()	
Blood groups				0.213
Group A	19; 77.7 (58.4–94.3)	10; 82.3 (64.7–94.3)	9; 72.5 (58.4–82.8)	
Group AB	11; 70.6 (44.1–93.3)	2; 80.4 (75–85)	9; 68.4 (44.1–93.3)	
Group B	19; 74.5 (21.1–95.4)	10; 72.9 (21.1–95.4)	9; 76.3 (50.2–90.2)	
Group O	41; 77.9 (45.3–94.6)	21; 76.8 (45.3–94.6)	20; 79.1 (48.6–94.0)	
Donation status				0.157
First time donor	15; 75.7 (50.25–94.6)	5; 83.4 (64.7–94.6)	10; 71.8 (50.2–93.4)	
Repeat donation	75; 76.4 (21.1–95.4)	38; 76.6 (21.1–95.4)	37; 76.2 (44.1–94.9)	
Type of donation				–
Voluntary donor	63; 76.6 (21.1–95.4)	43; 77.4 (21.1–95.4)	20; 75.0 (44.1–93.4)	
Replacement donor	27; 75.4 (47.7–94)	0; ()	27; 75.4 (47.7–94)	

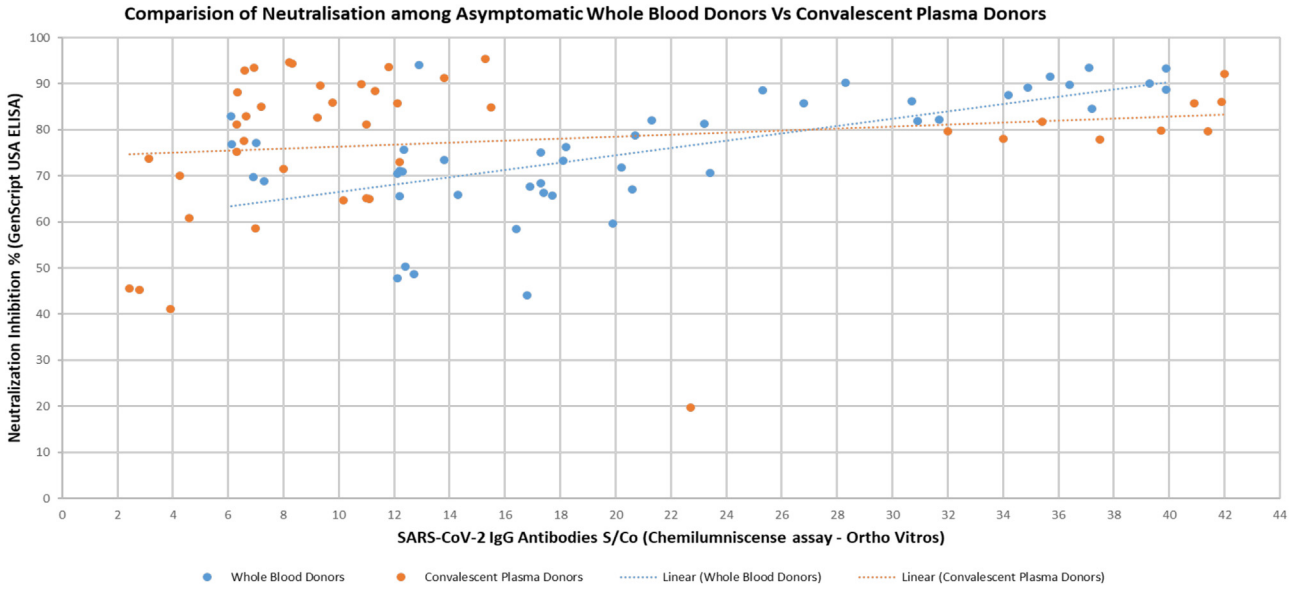

Fig. 1. Comparison of neutalization among asymptomatic whole blood donors vs. convalescent plasma donors. Bivariate Pearson correlation (2 tailed) *P*-value 0.000 among whole blood donors without prior COVID-19 symptomatic history and $P=0.402$ among the convalescent plasma donors with prior symptomatic COVID-19 history and a positive COVID-19 RTPCR diagnosis (Correlation is significant at 0.01 level for two tailed test).

5. Conclusion

No significant difference in neutralizing antibody capacity was observed in asymptomatic whole blood donors and convalescent plasma donors. Therefore, donors having adequate levels of SARS-CoV-2-IgG antibody levels on screening can be considered for convalescent plasma donation irrespective of prior COVID-19 diagnosis or COVID-related symptoms.

Statement of ethics

The study protocol was reviewed and approved by Institutional Ethics Committee, Employees State Insurance Corporation Medical College (Proposal No: ESICMC/SNR/IEC-F0266/11-2020).

Funding

No funding was received.

Disclosure of interest

The authors declare that they have no competing interests.

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