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EEffect of the Previous History of the SARS-CoV-2 Infections on Antibody Levels among Sputnik V Vaccinated Healthcare Workers

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ABSTRACT

Background: Measuring the level of antibodies produced post-vaccination in response to the SARS-CoV-2 spike protein is considered a strategy for estimating the effectiveness of the COVID-19 vaccines.

Objective: To examine the antibody levels among the healthcare workers in different hospitals in Mashhad, Iran after receiving the second dose of Sputnik V.

Methods: In this study, we enrolled 230 healthcare workers for evaluating the Gam-COVID-Vac or Sputnik V after the second administration in different hospitals in Mashhad. Antibody levels of spike protein were quantitatively evaluated in a sample of 230 negative RT-PCR tests for the COVID-19 individuals. The analysis has been done based on an immunological assay using enzyme-linked immunosorbent assay (ELISA). The infection history of the subjects and their families was examined through their medical records.

Results: Our results demonstrated a significant association between a higher titer of IgG and a previous history of the COVID-19 infection (P<0.001). Moreover, the chance of detecting antibodies titer more than 50 AU/ml was 16.99 in these people which was significantly higher than in people without a history of infection pre-vaccination [%95CI: (7.38,39.12), P<0.001].

Conclusion: This result demonstrates that the efficacy of antibody production is related to the previous history of the SARS-CoV-2 infections. Ongoing monitoring of the level of antibody among vaccinated populations will help evaluating the effect of vaccines on humoral immunity status.

Keywords: COVID-19, Gam-COVID-Vac, SARS-CoV-2, Sputnik V

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INTRODUCTION

This newly discovered coronavirus called COVID-19 claimed more than 4 million lives up to 28 July 2021 [1-3]. From December 2019 up to the present, researchers have made enormous efforts to propose effective therapeutic and preventive strategies to combat this new virus. With excess mortality rates of the COVID-19 around the world, it seems that efficient vaccination is the only hope for an end to this deadly pandemic.

By the end of 2020, more than 60 vaccines were launched and went through clinical trials, and at the beginning of March 2021, several highly effective vaccines were approved by the World Health Organization (WHO) for emergency use worldwide for the global control of the COVID-19 epidemic [4]. These vaccines include (i) Pfizer-BioNTech and Moderna as mRNA vaccines, (ii) AZD1222 (AstraZeneca), Ad5-nCoV(Cansino), and Sputnik V (Gamaleya) as recombinant adenovirus vectored vaccines, as well as (iii) Sinopharm and Sinovac as inactivated vaccines [5-7].

In Iran, Sputnik V was the first vaccine approved for urgent use to fight against the SARS-COV-2 pandemic [8]. The trial result of this vaccine demonstrated the robust neutralizing antibody responses to the spike protein and T-cell responses, in recipients aged 18-60 years after receiving the second dose [9, 10]. Nonetheless, with the appearance of the delta variant , a fall has been observed in antibody levels in the healthcare workers who received the Sputnik V, increasing the incidence of the SARS-CoV-2 infections. In the light of the aforementioned issues, the present study aimed to investigate the antibody levels among the healthcare workers who received Sputnik V in different hospitals in Mashhad, Iran.

MATERIALS AND METHODS

Study Population

This study was conducted on healthcare workers in the COVID-19 units in Emam Reza, Ghaem, Akbar, and Shariatee Hospitals in Mashhad, Iran. All these healthcare workers received the first dose of Gam-COVID-Vac or Sputnik V (Gamaleya National Research Center, Russia) in March 2021. A total of 230 healthcare workers were enrolled in the present study and all recived two doses of Gam-COVID-Vac or Sputnik V. The infection history of the subjects and their families was examined through their medical records. The study was approved by the Institutional Ethics Committee of Mashhad University of Medical Sciences (IR.MODARES.REC,December 2020) and all the participants gave written informed consent.

Antibody Evaluation

The present study was conducted on 230 individuals who had been vaccinated with two doses of Sputnik V to evaluate the anti-spike antibody response to vaccination in the COVID-19 healthcare workers. Quantitative evaluation of antibodies was based on immunological assay using enzyme-linked immunosorbent assay (ELISA) (COVID-19 Antibody ELISA Test Kits Manufacturers, PishtazTeb, Tehran, Iran). The test was performed according to the manufacturer's instructions. According to the manufacturer, the cutoff value for the detection of IgG is 50 AU/ml. In brief, in the first step called plate coating, a 96-well plate was coated with 100 µl/well of the antigen and incubated at 4 °C overnight. Then a blocking buffer was added to the plate. In the next step, the antibody was diluted in blocking buffer added to the wells and incubated at room temperature for 1-2 hrs. Finally, the absorbance (optical density) was read using a plate reader.

Statistical Analysis

The quantitative variables were described as the mean±SD or median (Inter-quartile Range), and the qualitative variables were described in counts and percentages. The Chi-square test was also conducted to compare gender among groups. The normality of

age and titer was assessed by one sample Kolmogorov–Smirnov test. Age and titer were similarly compared among groups using a one-way analysis of variance and the Kruskal-Wallis test, respectively. Where we needed pairwise ,the comparison was done with Bonferoni correction. Logistic regression was also employed to assess crude and adjusted odds of titer>=50 among the groups. The data were analyzed using the SPSS program, version 22.0 (IBM Corporation, Armonk, NY, USA). Significance was set at P≤0.05.

RESULTS

230 individuals with negative real-time reverse transcription-polymerase chain reaction (RT-PCR) tests for the SARS-CoV-2, including 107 (46.5) males and 123 (53.5) females, were enrolled in the present study. All these individuals have received both doses of the Sputnik V vaccine and were included in this study for the examination of antibody levels within four months after receiving the second dose. The mean±SD age of subjects was reported as 40.36±8.39 years (age range: 23-71 years). In addition to age and gender, all the participants were evaluated for the association between antibody levels and history of the COVID-19 disease before vaccination, encompassing four groups: (i) subjects without previous COVID-19 disease, (ii) participants who had the COVID-19 patients in their family but not themselves, (iii) subjects with a history of the COVID-19 disease before vaccination, as well as (iv) participants who had both a history of the COVID-19 disease in their family and themselves.

Among a total of 230 subjects, 96 (41.7%) cases had no previous COVID-19 disease. 13 (5.7%) subjects had a history of the COVID-19 disease in their family, 40(17.4%) subjects had a history of the COVID-19 disease and 81(35.2%) of participants had a history of the COVID-19 disease in their family and themselves before vaccination.

The first group consisted of 40 (42.7%) males, the second group contained 9 (69.2%) males, the third and the fourth one included 14 (35.0%) and 43 (53.1%) males, respectively. Nevertheless, the Chi-square test did not point to any significant association between gender and groups (P=0.078).

The mean±SD of age in the first, second, third , and fourth groups were 38.96±7.86, 42.46±7.37, 40.45±6.89 and 41.62±9.61, respectively. Moreover, our result demonstrated that there was not any significant association between the age and the groups (P=0.148).

The median (interquartile range) of the antibody titers in groups 1,2,3,4 were 32 (56), 34 (88.5), 101 (40), and 116 (19), respectively. The results of the Kruskal-Wallis test suggested that the antibody titers were significantly different among the four groups (P<0.001). Pairwise comparison with the Bonferoni correction shows that the antibody titers were significantly different between groups 1 and 3 (P<0.001), groups 1 and 4 (P<0.001), as well as groups 2 and 3 (P=0.001).

Among a total of 230 subjects, 96 (41.7%) cases had no previous COVID-19 disease. In this group, 64 (72.7%) cases demonstrated antibodies lower than the manufacturer's reported cutoff (50 AU/ml). Out of a total of 230 participants, 134 (58.3%) subjects had a history of the COVID-19 disease in their family or themselves before the vaccination. In this group, 24 (27.4%) participants had antibodies less than 50 AU/ml (Table 1).

The unadjusted logistic regression model indicated that there was an association between groups of subjects and antibodies of more than 50 AU/ml (P<0.001). The possibility of detecting antibody titer<=50 for the individuals who had no previous COVID-19 disease but were exposed to the COVID-19 patients in their family members was 1.714 times higher those who had no history of the COVID-19 disease [%95CI: (0.53,5.52), P=0.367]. Besides, the possibility of detecting antibody titer>=50 in individuals

Table 1. The antibody titer in different groups of participants

Groups		Antibody titer		Total
		<50	>=50	
Without history of COVID-19	Count	64	32	96
	% within Test.result50	72.7%	22.5%	41.7%
COVID-19 patients in their family	Count	7	6	13
	% within Test.result50	8.0%	4.2%	5.7%
With history of COVID-19	Count	7	33	40
	% within Test.result50	8.0%	23.2%	17.4%
Both (COVID-19 history themselves and their family)	Count	10	71	81
	% within Test.result50	11.4%	50.0%	35.2%
Total	Count	88	142	230
	% within Test.result50	100.0%	100.0%	100.0%

who had a history of the COVID-19 disease before the vaccination was 9.43 higher than the group that had no history of the COVID-19 [%95CI: (3.76,23.64), P<0.001]. In addition, the possibility of detecting antibody titer<=50 in participants who had both a history of the COVID-19 disease in their family and themselves was 14.2 higher than the group that had no history of the COVID-19 [%95CI: (6.47,31.17), P<0.001] (Figure 1).

The result of the logistic regression model adjusted by sex and age revealed a significant association between the history of infection among family members or themselves and antibodies more than 50 AU/ml (P<0.001). Our results pointed out that the possibility of detecting the antibody titer of more than 50 AU/ml was 1.90 in the group who had no previous COVID-19 disease but were exposed to the COVID-19 patients in their family members in comparison with the group who had no history of the COVID-19 themselves or in their family [%95CI: (0.57-6.32), P=0.294]. This value was reported as 10.72 among the individuals who had a history of the COVID-19 disease before the vaccination, in comparison with the group that had no history of the COVID-19 [%95CI: (4.18-27.45), P<0.001]. Furthermore, the possibility of detecting antibody titer more than 50 AU/ml was 16.99 between the participants with both a history of the SARS-CoV_2 infection in their family and themselves, in comparison with the group who had no history of the COVID-19 [%95CI: (7.38,39.12), P<0.001]. Besides, with every 10-year increase in age,

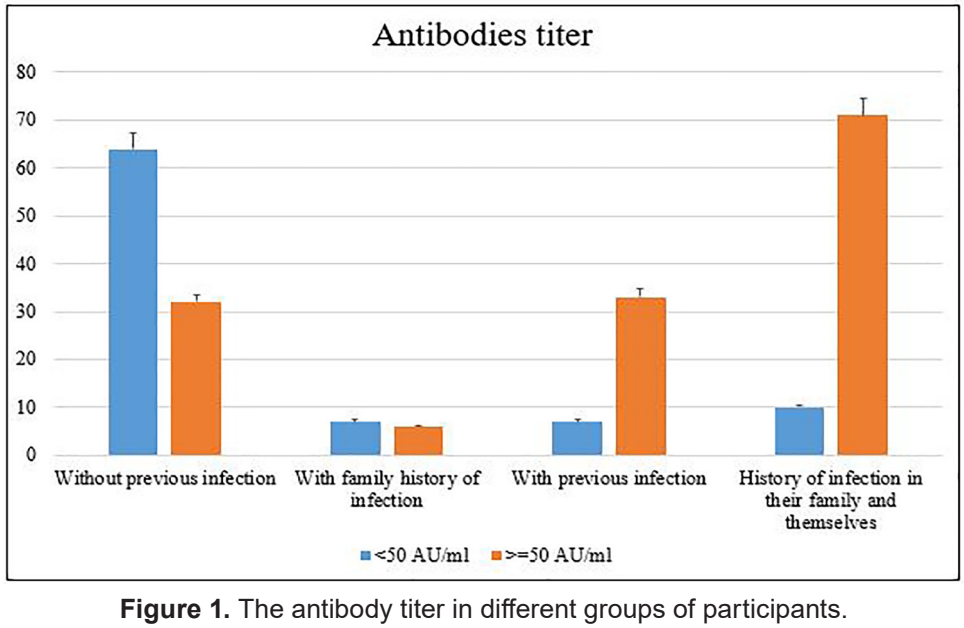

Figure 1. The antibody titer in different groups of participants.

Table 2. The crude and adjusted odds ratio (OR) by using logistic regression

Variables	Crude OR	%95 CI	P value	Adjusted OR	%95 CI	P value
Sex	-	-	-	1.280	(0.64,2.55)	0.483
Age	-	-	-	0.637	(0.424,0.966)	0.034
Groups	-	-	<0.001	-	-	<0.001
Without history of COVID-19	1[ref]	-	-	1[ref]	-	-
COVID-19 patients in their family	1.71	(0.53,5.52)	0.367	1.90	(.57,6.32)	0.294
With history of COVID-19	9.43	(3.76,23.64)	0.000	10.72	(4.18,27.45)	0.000
Both (COVID-19 history themselves and their family)	14.20	(6.47,31.17)	0.000	16.99	(7.38,39.12)	0.000

OR: Odds ratio; CI: Confidence level

the possibility of detecting antibody titer<50 was multiplied by 0.637. In other words, as age increases by 10 years, the odds of titer<=50 decrease by 36% [%95CI: (0.424,0.966), P=0.034] (Figure 1) (Table 2).

DISCUSSION

The covid-19 related mortality rate is still a major concern for different countries across the globe; moreover, the rate of potentially approved COVID-19 vaccines has markedly increased [11-13]. Considerable knowledge gained from severe acute respiratory syndrome (SARS) and the Middle East respiratory syndrome (MERS) was helpful in the selection of suitable antigenic targets and effective platforms, accelerating the SARS-CoV-2 vaccine development [14-16]. Evidence suggests the spike protein (S1 protein) of coronavirus is well known as a large type I transmembrane protein and contains a receptor-binding domain (RBD) as a key target antigen in vaccine development [6, 17-19]. The RBD of this protein is highly antigenic and is capable of stimulating both humoral and cellular immune responses, as well as neutralizing antibodies that block the attachment and infection of host cells [18, 20]. Among different vaccine candidates for protection against the SARS-CoV-2, seven vaccines were authorized by WHO for emergency use worldwide, including mRNA-based vaccines (Pfizer-BioNTech and Moderna), vaccines that mediate the viral vectors (AstraZeneca, Ad5-nCoV, and Sputnik V), and live attenuated virus-based vaccines (Sinopharm and Sinovac) [5-7, 21, 22].

Sputnik V which was the first vaccine approved for emergency use in Iran uses a heterologous recombinant adenovirus approach using adenovirus 26 (Ad26) and adenovirus 5 (Ad5) as vectors to express the spike protein of the SARS-CoV-2 [8, 23]. The trial results of this vaccine show a strong 91.6% protective effectiveness across all participant age groups 21 days after the first dose of the vaccine. These results also pointed to the reduction of disease severity in those who were infected with the SARS-CoV-2 after the vaccination [8]. Since the commencement of vaccination across the globe, the demonstration of the potential impacts of vaccines on transmission and mortality raised high hopes for an end to this pandemic. However, it seems that after the appearance of the delta variant of the SARS-CoV-2 virus, a fall has been observed in antibody levels in the healthcare workers who received the Sputnik V, increasing the incidence of the SARS-CoV-2 infections.

A cross-sectional study assessed the spike protein antibodies post-vaccination on 2,000 participants who were vaccinated with Sputnik V. To this end, 100 COVID-19 RT-PCR negative samples were collected (the first dose effect on the 21st day post-administration); thereafter, the level of antibodies was analyzed by Electro-chemiluminescence immunoassay (ECLIA). The findings of the

current study demonstrated strong positive results of antibodies<1.5 AU/ml among 85% of the participants and 34.9% of subjects with antibody titer<250 AU/ml, while most of them had a history of the SARS-CoV-2 infection. Furthermore, the present study reported that 12.7%, 9.5%, and 27% of cases had antibody titers of <100 AU/ml, <25 AU/ml, and<1.5-2.5 AU/ml, respectively. The findings of the present study pointed to the high antibody titers against the SARS-CoV-2 even before the second booster dose of the Ad5-based Sputnik V vaccine [24].

Another study that aimed to investigate the immune response to the Sputnik V vaccine among 602 healthcare personnel volunteers demonstrated a stronger immune response among those who received the vaccine and had a prior history of the COVID-19 infection [25]. In the same context, a study in the United States on 110 individuals with or without preexisting immunity ,who were vaccinated with Pfizer and Moderna vaccines, pointed out that antibody titers were 10-45 times higher in subjects with preexisting immunity, as compared with those who did not have preexisting immunity [26]. Same as the previous reports, our results also demonstrated a higher titer of anti-S-protein IgG among individuals with a history of the SARS-CoV-2 infection. Moreover, it was revealed that the chance of detecting antibodies more than 50 AU/ml was significantly higher among the cases with a previous history of the COVID-19 in their family and themselves, compared with that in subjects who did not have previous COVID-19 disease [OR: 1.90; %95CI: (0.57-6.32); P=0.294]. That signifies that individuals who received both doses of Sputnik V but did not have a history of the COVID-19 disease before the vaccination were at a higher incidence risk of the SARS-CoV-2 infections even after the vaccinations. In addition, every 10-year increase in age results in antibody production (titer<50) decreasing by 36%.

Among the notable limitations of the present study, we can refer the small sample size and lack of access to data on antibody levels after the first administration. Finally, all these findings demonstrated a high level of the SARS-CoV-2 spike antibody levels among the healthcare workers who had received both doses of Sputnik V. Moreover, the findings pointed to the low level of anti-S-protein IgG among the healthcare workers who had no previous COVID-19 disease before the vaccinations. Currently, with the emergence of different vaccines for the SARS-CoV-2, the evaluation of neutralizing antibody levels after vaccination is considered one of the effective methods for determining the humoral response and efficacy of the vaccine. These findings suggested that the booster dose (third administration) of Sputnik V may be needed in the healthcare workers who had no previous COVID-19 disease before the vaccination, and evaluating the neutralizing antibody levels can be of great help in this regard.

Conflict of Interest: None declared.

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