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WITHDRAWN: Antibody responses 8-20 weeks after two doses of SARS-CoV-2 vaccine (CoronaVac) in hemodialysis patients: Results of a single center in northeast Turkey

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Research Article

Keywords:

Posted Date: July 13th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1622334/v1

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EDITORIAL NOTE:

The full text of this preprint has been withdrawn by the authors while they make corrections to the work. Therefore, the authors do not wish this work to be cited as a reference. Questions should be directed to the corresponding author.

Abstract

Background: The study aimed to determine the antibody responses of hemodialysis (HD) patients receiving the second dose of inactivated severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccine (CoronaVac).

Methods: Patients were divided into two groups according to the time elapsed since the second dose of SARS-CoV-2 vaccine: group 1 was 14-20 weeks after second dose of vaccine, and group 2 was 8-13 weeks. In addition, patients were divided according to their antibody (anti-spike IgG) response as inadequate < 0.2 μ g /mL and adequate response \geq 0.2 μ g /mL. Factors such as age, dialysis vintage, diabetes mellitus and Kt/V which may affect response to SARS-CoV-2 vaccine were evaluated.

Results: Out of 67 patients, according to exclusion criteria 30 patients were excluded. 52.7% and 33.3% patients had adequate response, in those groups, respectively. In the group 2, the age of those who did not have an antibody response was 65.0 ± 10.4 , while those with a response were 50.5 ± 11.0 years old (p=0.015, 95% CI).In addition, one of our two patients in the group 1, who received four doses of 40 µgr recombinant hepatitis B vaccine and did not get anti-HBs antibody response (anti-HBs <10 IU/mL) was also unresponsive to the second dose of SARS-CoV-2 vaccine. Antibody responses to the SARS-CoV-2 vaccine in both groups were not different in terms of the compared characteristics of the patients (p>0.050).

Conclusion: The second dose of SARS-CoV-2 vaccine responses in HD patients was analyzed and the positive effect of being relatively younger was determined 8-13 weeks after second dose.

Introduction

A hemodialysis (HD) patient may become infected with COVID-19 through close contact with a patient or healthcare provider with possible COVID-19. The HD patient will likely be more susceptible to COVID-19 due to having diseases such as hypertension or diabetes mellitus. In HD patients, the weakening of innate and adaptive immune systems functions due to the decrease in both skewed Th1/Th2 T-cell ratios and dendritic and T-cell cells increases the tendency to infections [1]. Therefore, end-stage renal disease (ESRD) is a risk factor for COVID-19 disease, which may result in death, and mortality is high in those who continue HD treatment [2]. In previous studies, it has been shown that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection poses high mortality risk compared to the healthy population [3]. Although isolating COVID-19 patients by taking precautions such as face mask and regular SARS-CoV-2 testing is beneficial in reducing the risk in HD patients, the mortality risk is still high in these patients.

At the same time as the start of the COVID-19 vaccination process worldwide, HD patients began to be vaccinated rapidly. With this process, it has been started to investigate how much the antibody levels obtained by vaccination in healthy or all patient groups are and how long they are in the serum. In a previous study, it was shown that T and B cell responses decreased by 17.1% four months after two

doses of SARS-CoV-2 vaccine in HD patients [4].Since SARS-CoV-2-specific IgG titer can be detected, patients can be monitored to evaluate whether additional vaccine doses are required or the selection of the vaccine effective against the common variant in that country [5].However, the response levels to the COVID-19 vaccine in HD patients and the answer to the question of how many months this response can remain after the vaccine will become clear as the data of the studies are published. Due to the immunosuppressive nature of HD patients, it seems that response levels to the COVID-19 vaccine should be monitored at certain periods.

In this study, it was tried to determine the level of antibody responses after two doses of inactivated SARS-CoV-2 vaccine in HD patients and whether there is any factor associated with these levels.

Patients And Methods

This cross-sectional study consisted of 67 patients in HD centers of Kars cities. The data of the study had been obtained by analyzing the demographic, clinical, laboratory and serological records of patients who underwent HD treatment for 4 hours 3 times a week in the centers between 1may- 1august 2021.

The information of COVID-19 vaccine:

This study to evaluate of antibody response after COVID-19 Vaccine [(Vero cell), Inactivated (CZ02 strain), each syringe contains 0.5 mL with 600SU of inactivated SARS-CoV-2 antigen, Trade Name: CoronaVac]. This vaccine is an inactivated virus COVID-19 vaccine, which was developed by Sinovac Life Sciences (Beijing, China), and received authorization for emergency use in Turkey in January 2021.

Vaccination protocol:

According to the instructions of the national health authorities, the first vaccination was given to patients aged 65 and over, and then to those under 65 years of age. Therefore, while some patients completed the two-dose vaccination protocol in march 2021, others were able to complete it in april or may. The vaccine was administered to the patients by intramuscular injection into the deltoid region of the upper arm. The first and second dose interval recommended by the manufacturer of 14–28 days for the COVID-19 vaccine.

Exclusion criteria:

Those infected with SARS-CoV-2 in the three months prior to vaccination and currently (n:16), those who were in close contact with someone who had SARS-CoV-2 infection in the last 10 days and did not have a PCR test(n:2), those who were infected with SARS-CoV-2 after the first dose (n:6), those who were infected with SARS-CoV-2 after the second dose (n:3), those who have active malignancy (n:1), those who have pregnancy (n:0), those who wasreceived any kind of immunosuppressive treatments in the previous 12 months (n:1), those who have any active infections other than COVID-19(n:1).37 of the 67 patients who participated in the study were exluded in accordance with the exclusion criteria.Finally, 37 dialysis patients were included in the study, 12 women and 25 men.

Serum samples were taken to determine the levels of SARS-CoV-2-specific IgG on august 1, 2021. Patients were divided into two different groups according to their completion of the second dose of COVID-19 vaccine.

Group 1; Blood sample collection date: August 1, 2021, the number of weeks after second dose of COVID-19 vaccine: 14–20.

Group2; Blood sample collection date: August 1, 2021, the number of weeks after second dose of COVID-19 vaccine: 8–13.

Serological assessment

The analysis was carried out by Human anti-SARS-CoV-2 (S) IgG ELISA kit (Catalogue No: EH4981, Wuhan Fine Biotech, Wuhan, China) which is a indirect enzyme-linked immune-sorbent assay (ELISA) that measures IgG antibodies to the spike protein of SARS-CoV-2. The serums were diluted by 1/50 values below 0.2µg/mL could not be determined and were considered negative [6].

Inadequate response

anti-SARS-CoV-2 (S) IgG < 0.2 µg /mL

Adequate response: anti-SARS-CoV-2 (S) $IgG \ge 0.2 \ \mu g \ /mL$ Processing of blood samples foranti-SARS-CoV-2 (S) IgG

Samples were centrifuged on a Hettich Rotanta 460r centrifuge at 3000rpm for 10 minutes, aliquoted and anonymized. They were then stored at -70° C and thawed prior to testing.

The serume samples that for variables of study were obtained pre-hemodialysis and post-hemodialysis after the blood pump was reduced to 100 ml/min for 15 seconds, before saline administration, according to the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (NKF-K/DOQI) recommendations [7]. The formulation of Daugirdas was used to determine Kt/V [Single-pool(sp) Kt/V= - Ln (R - 0.008×t) + (4-3.5×R) × UF / W] [8]. R = post-hemodialysis / pre-hemodialysis blood urea nitrogen, t (hours) = The time on HD, UF = ultrafiltration in liters and W = The post-hemodialysis body weight in kilograms. For the urea reduction rate: URR = $100 \times (1$ -postdialysis blood urea nitrogen (BUN)/predialysis BUN was used. BUN = blood urea nitrogen [9].

Statistical analysis

For statistical evaluation SPSS Statistics of Windows v.21,0 (SPSS; IBM Corporation, New York, USA) was used. Continuous parametric data were presented as average ± standard deviation and Student-t test was used for comparisons. Mann–Whitney U test was used for data that showed non-normal distribution. We applied the Chi square and Fisher's exact test in the analysis of the countable data. Results were evaluated according to a p-value of < 0.05 and confidence internal of 95%.

Results

The number of patients in the HD center was 67, and when the exclusion criteria were applied, the number of patients included in the study was 37.

The number of patients identified as anti-spikelgG Antibodie 14–20 weeks after the second dose of inactivated COVID-19 vaccine is 19, the female/male ratio is 7/12, the rate of patients with an antibody response is 52.7%, antibody response in women 42.8%, the antibody response in men was 58.3%.

When Table 1 was followed, no statistically significant difference was found between the antibody response 14-20 weeks after the second dose of COVID-19 vaccine and the parameters such as biodemographic, biochemical, hormonal, diabetes mellitus presence and dialysis adequacy of the patients. For all independent variables: p > 0.05 was found.

Table 1 Effect of independent variables on responses of inactivated SARS-CoV-2 vaccine after 14–20 weeks the second dose.

Independent variables		Dependent variable	Р		
		(anti-spike IgG Antibodies)			
		Not detectable < 0.2(µg	detectable \geq 0.2		
		/mL)	(µg /mL)		
		n(%)	n(%)		
		9(47.3)	10(52.7)		
Age	Years	9.5(mean rank)	10,4(mean rank)	0.712	
		Age Min-Max:66–75	Age Min-Max:62– 81	d	
Gender	Female	n:4	n:3	0.430 ^b	
	Male	n:5	n:7	-	
Dialysis vintage	Months	63 ± 33	67 ± 80	0.850 ^c	
		(min-max:6-120)	(min-max:12– 204)		
BMI	kg/m ²	10.6(mean rank)	9,4 (mean rank)	0.624 ^a	
		(min-max:22-38)	(min-max:23-31)		
Serum albumin	gr/dL	3.7 ± 0.3	3.8 ± 0.4	0.333 ^c	
Hemoglobin	gr/dL	11.4±1.2	11.4 ± 0.9	0.941 ^c	
CRP	range:0-5 mg/L	15.1 ± 12.0	18.5 ± 17.7	0.632 ^c	
Ferritin level	mg/dL	581 ± 494	813 ± 514	0.332 ^c	
Parathormone	pg/mL	476 ± 252	446 ± 304	0.818 ^c	
Vitamin D treatments ^k	Yes/No	4/5	4/6	1.000 ^b	
Erithropoetin used	Yes/No	7/2	8/2	1.000 ^b	
Vasculer Access	AVF/CVC	6/3	7/3	1.000 ^b	

n = number,, a = with Mann-Whitney Test, b = with Fisher's Exact Test, c = with Student's t-test, BMI = Body Mass Index, CRP = C-reactive protein, URR Urea reduction rate, AVF Arteriovenous fistulae, CVC = Central Venous Catheter(cuffed),d = statistical analysis was not performed as all patients were negative

Independent variables		Dependent variable	Р	
		(anti-spike IgG Antibodies)		
		Not detectable < 0.2(µg /mL)	detectable \geq 0.2	
			(µg /mL)	
		n(%)	n(%)	
		9(47.3)	10(52.7)	
KT/V	Daugirdas formula	1.58 ± 0.30	1.49 ± 0.20	0.454 ^c
URR	%	73 ± 7	72 ± 5	0.598 ^c
Diabetes Mellitus	Yes/No	2/7(n)	2/8(n)	1.000 ^b
Anti-HCVPositive ^d	Yes/No	0/9(n)	0/10(n)	-
HBsAg Positive ^d	Yes/No	0/9(n)	0/10(n)	-
Anti-HBstiter	< 10 IU/mL	1(n)	1(n)	1.000 ^b
	\geq 10 IU/mL	8(n)	9(n)	
n = number,, a = with Mann-Whitney Test, b = with Fisher's Exact Test, c = with Student's t-test, BMI = Body Mass Index, CRP = C-reactive protein, URR Urea reduction rate, AVF Arteriovenous fistulae, CVC = Central Venous Catheter(cuffed),d = statistical analysis was not performed as all patients were negative				

The number of patients who were determined to have anti-spikelgG antibodies 8–13 weeks after the second dose of COVID-19 vaccine was 18, female/male ratio 5/13, The rate of patients with adequate antibody response after the second dose of COVID-19 vaccine was 33.3%, While the antibody response was 20% in women, it was 38.4% in men.

In addition, one of our two patients in the first group who were negative for HBsAg and Anti-HBs and who received Four doses of 40 µgr recombinant hepatitis B vaccine and did not get anti-HBs antibody response was also unresponsive to the second dose of COVID-19 vaccine (anti-HBs < 10 IU/mL).

When Table 2 was followed, a statistically significant difference was found between the antibody response and the age of the patients 8-13 weeks after the second dose of COVID-19 vaccine. While the mean age of those who did not form an antibody response was 65.0 ± 10.4 , the mean age of responders was 50.5 ± 11.0 (p = 0.015, 95% Cl). On the other hand, no statistically significant difference was found between the parameters such as biodemographic, biochemical, hormonal, diabetes mellitus and dialysis adequacy of the patients and the Inactivated COVID-19 vaccine response (p > 0.05).

Table 2 Effect of independent variables on responses of inactivated SARS-CoV-2 vaccine after 8–13 weeks the second dose.

Independent variables		Dependent variable	Р	
		(anti-spikelgG Antibo	dies)	
		Not detectable <0.2	detectable \geq 0.2	
		(µg /mL)	(µg /mL)	
		n(%)	n(%)	
		12(66.6)	6(33.3)	
Age	Years	65.0 ± 10.4	50.5 ± 11.0	0.015 ^c
Gender	Female	n:4	n:1	0,615 ^b
	Male	n:8	n:5	
Dialysis vintage	months	8,25 (mean rank)	12,00 (mean rank)	0.156 ^a
		min-max: 6–84	min-max: 12-168	
BMI	kg/m ²	27,3 ± 6,2	22,9 ± 5,6	0.164 ^c
Serum albumin	gr/dL	3.9 ± 0.4	4.0 ± 0.2	0.433 ^c
Hemoglobin	gr/dL	12,1 ± 0,9	11,1 ± 1,9	0,123 ^c
CRP	range:0-5 mg/L	12,2 ± 13,4	6,7 ± 7,2	0,366 ^c
Ferritin level	mg/dL	573 ± 304	816 ± 422	0,179 ^c
Parathormone	pg/mL	506 ± 468	471 ± 425	0.879 ^c
Vitamin D treatments ^k	Yes/No	7/5	2/4	0.620 ^b
Erithropoetin used	Yes/No	8/4(n)	4/2(n)	1,000 ^b
Vasculer Access ^c	AVF/CVC/(Greft) ^d	9/3/0(n)	5/0/1 (n)	0,515 ^b
KT/V	Daugirdas formula	1,56 ± 0,24	1,63 ± 026	0,562 ^c
URR	(%)	72,7 ± 5,4	74,2 ± 7,2	0,631 ^c

n = number, a = with Mann-Whitney Test, b = with Fisher's Exact Test, c = with Student's t-test, BMI = Body Mass Index, CRP = C-reactive protein, k = Active Vitamin D or analog or calcimimetic, URR Urea reduction rate, AVF Arteriovenous fistulae, CVC = Central Venous Catheter(cuffed),d = not tested as there is only one person with a graft, k = Active Vitamin D or analog or calcimimetic, e = statistical analysis was not performed as all patients were negative, f = statistical analysis was not performed as all patients were Anti-HBs titer \geq 10 IU/mL.

Independent variables		Dependent variable	Р	
		(anti-spikelgG Antiboo		
		Not detectable <0.2	detectable \geq 0.2	
		(µg /mL)	(µg /mL)	
		n(%)	n(%)	
		12(66.6)	6(33.3)	
Diabetes Mellitus	Yes/No	6/6(n)	2/4(n)	0,638 ^b
Anti-HCVPositive ^e	Yes/No	0/12(n)	0/6(n)	-
HBsAg Positive ^e	Yes/No	0/12(n)	0/6(n)	-
Anti-HBstiter ^f	<10 IU/mL	0(n)	0(n)	-
	\geq 10 IU/mL	12(n)	6(n)	
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n = number,, a = with Mann-Whitney Test, b = with Fisher's Exact Test, c = with Student's t-test, BMI = Body Mass Index, CRP = C-reactive protein, k = Active Vitamin D or analog or calcimimetic, URR Urea reduction rate, AVF Arteriovenous fistulae, CVC = Central Venous Catheter(cuffed),d = not tested as there is only one person with a graft, k = Active Vitamin D or analog or calcimimetic, e = statistical analysis was not performed as all patients were negative, f = statistical analysis was not performed as all patients were Anti-HBs titer \geq 10 IU/mL.

In Table 3, SARS-CoV-2 vaccine responses are presented according to the etiological causes of both groups. Statistical comparison was not performed due to the small number of cases. In two patients with Hypertension and Coronary artery disease, antibodies were tested 14–20 weeks after the second dose of SARS-CoV-2 vaccine and no antibody response was found. In addition, two patients with renal cell carcinoma had hypertension or diabetes mellitus and they had no response 8–13 weeks after the second dose of SARS-CoV-2 vaccine.

Table 3 End-stage renal disease etiologies and SARS-CoV-2 vaccine responses of patients.

End-stage renal disease etiologies	Female/ Male(n) (Total)	Level of anti-spikelgG				
		Patients with antibodies tested that 14–20 weeks after the second dose vaccine		Patients with antibodies tested that 8–13 weeks after the second dose vaccine		
		< 0.2 µg /mL	≥ 0.2 µg /mL	< 0.2 µg /mL	≥ 0.2 µg /mL	
		(n)	(n)	(n)	(n)	
DM	5/6(11)	2	2	5	2	
HT	1/7(8)	2	3	2	1	
HT + Hypothyroidism	1/0(1)	-	1	-	-	
HT + CAD	0/2(2)	2	-	-	-	
Urolithiasis	1/3(4)	1	1	2	-	
Polycystic renal disease	1/2(3)	1	1	1	-	
Renal cell carcinoma	0/2(2)	1	1			
Renal cell carcinoma + HT	1/0(1)			1		
Renal cell carcinoma + DM	0/1(1)			1		
Chronic pyelonephritis	1/0(1)	-	1	-	-	
SLE	0/1(1)	-	-	-	1	
Unknown	1/1(2)	-	-	-	2	
Totale(n)	12/25(37)	9	10	12	6	
DM = Diabetes mellitus, HT = Hypertension, CAD = Coronary artery disease, SLE = Systemic Lupus Erythematosus						

Discussion

Previous studies have shown that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections have higher risk in HD patients compared to the general population. Especially since it was shown that antibody levels after natural COVID-19 infection seem to decline in HD patients over time. It has been started to investigate how much the antibody levels obtained by vaccinationCOVID-19 in

healthy or all patient groups are and how long they are in the serum. In HD patients, the weakening of innate and adaptive immune systems functions due to the decrease in both skewed Th1/Th2 T-cell ratios and dendritic and T-cell cells increase the tendency to infections. Therefore, it is important to determine the periodic intervals of additional doses by determining the antibody levels of these patients during the ongoing pandemic process [3, 10, 11].In recent studies in HD patients, the antibody level was 80% after two doses of SARS-CoV-2 inactivated vaccine, while the Serologic response in HD patients with mRNA vaccine was approximate90% [12, 13].These results are one month after the second dose of vaccine. Presumably, these levels may decrease as the antibody levels are checked again in the following weeks.

In one study, antibody levels were highest three months after two doses of inactivated SARS cov-2 vaccines, and decreased at six months. Therefore, we are in the process of administering additional doses of SARS-CoV-2 vaccine under pandemic conditions, regardless of the antibody levels of the patients [14].

The inactivated vaccine CoronaVac® was found effective in a Phase 3 trial on a group of volunteers aged 18–59 years old [15]. However, in some previous studies, antibody responses after the second dose of both inactivated SARS-CoV-2 and mRNA BNT162b2 vaccine were found to be lower in kidney transplant recipients and HDpatients [16, 17]. In recent studies, it has been shown that seroresponse rates increase after the third dose of SARS-CoV-2 mRNA vaccinein HD patients [18].

In our study, these levels were found to be lower both in the group in which antibodies were tested 2–3 months after the second dose and that of in the group after 4–5 months. Due to the gradual decreasing in the number of healthy people who are not infected with COVID-19 as a result of the rapid spread of the pandemic, only the antibody results of HD patients were examined in our study. In our study of humoral response to two doses of SARS-CoV-2 inactivated vaccine, we observed a low seroconversion rate of 52.7% and 33.3% in the results of two different groups after 16–20 and 8–13 week using the manufacturers' recommended. To our knowledge, this is one of the first studies on the effectiveness of inactivated SARS-CoV-2 vaccine in HD patients of northeast Turkey.

In the study, besides the biodemographic characteristics of the patients, some biochemical, hormonal, Kt/V and URR values and antibody levels for hepatitis B and C were also evaluated. HD patients are known to generate reduced immunity to the vaccines, hepatitis B vaccine being the most widely studied.

All patients in our study were negative for HBsAg and anti-HCV. Anti-HBs levels were insufficient in two patients (2/37) among all patients [19]. While one of these patients had anti-spike protein antibodies, the other did not, who is 14–20 weeks after the second dose of SARS-CoV-2 inactivated vaccine. This patient, with anti-HBs titration < 10 IU/mL, was a 72-year-old male. He was diabetic and also had heart failure, and his Kt/V and URR values were 1.85% and 81% respectively. That is, he was a patient who received adequate HD [9]. This patient received four doses of 40 µgr recombinant hepatitis B vaccine and the last HBV vaccine dose was on April 30, 2021. The second dose of the SARS-cov-2 vaccine was administered on April 4, 2021. This poor response to the HBV vaccine has been emphasized in previous studies as a potential indicator of the response to the SARS-CoV-2 vaccine [20].

As a result, it was determined that 8–13 weeks after the second dose of SARS-CoV-2 vaccine, those who responded to the vaccine were relatively younger than those who did not respond. The results of this study require cautious interpretation, since the number of patients evaluated was small. However, our study can contribute to meta-analysis studies.

Limitation

Small sample size is one of the limitations of the study. Additionally, our test system only tested humoral, but no cellular immune response. The cellular part of the adaptive immune system probably plays a role in protection from COVID-19. Another limitation is SARS-CoV-2 antibodies were not screened at baseline for all patients to exclude possible asymptomatic infections.

Declarations

Acknowledgements:

Funding: This work was supported by the Caucasian University of the Republic of Turkey, **Project Code**: 2021-TS-58

Author Contribution HIE conceived and designed the experiments. HIE, EA, IK, SE and RK collected the data. HIE, IK, EA and TK interpreted the data. HIE wrote the manuscript. HIE, IK, SE and RK revised the manuscript critically. All authors read and approved the manuscript.

Data Availability The datasets used and/or analyzed in the current study are available from the corresponding author on reasonable request.

Code Availability: Not applicable.

Ethical approval: The study protocol was approved by the Ethics Committee for Clinical Research, Faculty of Medicine, Kafkas University, Kars, Turkey. The study was conducted according to the declaration of Helsinki. Informed consent was obtained from all individual participants included in the study (Meeting decision number and date: 80576354-050-99/89 and 26.05.2021 respectively).

Consent for publication: Not applicable

Consent to Participate: Written informed consent was obtained from all participants.

Conflict of interest: The authors declare no competing interests.

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