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Six months follow up of hemodialysis patients after SARS-CoV-2 vaccinations: Effects of the booster dose and vaccine type

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Abstract

Background: As hemodialysis patients are among the vulnerable groups for severe COVID-19, proper vaccination of these patients is quite important. However vaccine responsiveness is generally reduced in hemodialysis patients and strategies should be developed to maintain protection in the long term.

Objectives: This study aimed to analyse the changes in antibody levels of SARS-CoV-2 vaccinated hemodialysis patients after six months and to compare the effectiveness of inactivated and mRNA vaccines.

Methods: Eighty-five hemodialysis patients were followed up for six months after their initial vaccinations for SARS-CoV-2. Persistence of humoral responses were compared between patients who got inactivated or mRNA vaccines and also between patients who received a booster dose and those who didn't. SARS-CoV-2 antibody titers were measured by a commercial test that measures IgG antibodies toward the receptor-binding domain of spike protein.

Results: Seropositivity that was achieved by initial vaccination dropped abruptly by 6 months. Patients who received a booster dose had significantly higher antibody levels than those who didn't (1120,8 ± 983,3 AU/mL vs 313,3 ± 435,3 AU/mL respectively; p<0,001) and higher seropositivity as well (88% vs 65%). Seropositivity with mRNA vaccine at the end of 6th month was 81,8% while this decreased to 50% for inactivated vaccine. Patients who received mRNA vaccine initially or as the third dose could maintain 88,4% of seropositivtiy and this was higher than other patients who have just got inactivated vaccine (p=0,013).

Conclusion: Humoral immune response by SARS-CoV-2 vaccines is not very stable in hemodialysis patients and planning the booster doses should not be delayed. mRNA vaccines have better immunogenicity than inactivated vaccines.

Keywords: SARS-CoV-2, immunization, vaccines, hemodialysis, protection

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Hemodiyaliz Hastalarının SARS-CoV-2 aşılamalarının ardından 6 aylık takibi: Rapel doz ve aşı türünün etkileri

Öz

Giriş: Hemodiyaliz hastaları COVID-19'u ağır geçirmeye yatkın olduklarından, bu hastaların uygun şekilde aşılanmaları büyük önem taşımaktadır. Ne var ki, hemodiyaliz hastalarında genel olarak aşı yanıtları zayıftır ve uzun sureli koruma için stratejiler geliştirilmelidir.

Amaç: Bu çalışmada SARS-CoV-2 enfeksiyonuna karşı aşılanan hemodiyaliz hastalarındaki antikor düzeyi değişimlerinin altı aylık bir süredeki değişimlerinin analiz edilmesi ve inaktif aşı ile mRNA aşılarının etkinliklerinin karşılaştırılması amaçlanmıştır.

Yöntemler: İlk doz SARS-CoV-2 aşılamaları takiben, 85 hemodiyaliz hastası altı ay boyunca takip edilmiştir. Hümoral immün yanıtın ne kadar kalıcı olduğu inaktif veya mRNA aşısı yapılan hastalar arasında ve ayrıca rapel doz yapılan ve yaplmayan hastalar arasında karşılaştırılmıştır. SARS-CoV-2 antikor seviyeleri, virüsün spike glikoproteininin reseptör-bağlayan kısmına karşı gelişen IgG antikorlarını ölçen bir ticari kitle ölçülmüştür.

Bulgular: İlk doz aşılamalarla elden edilen seropozitifliğin 6 ay içinde ciddi bir şekilde düştüğü görülmüştür. Altıncı ayın sonunda, rapel doz yapılmış olanların yapılmamış olanlara göre hem antikor titrelerinin (sırasıyla 1120,8 ± 983,3 AU/mL vs 313,3 ± 435,3 AU/mL; p<0,001) hem de seropozitiflik oranlarının (%88 vs %65) anlamlı olarak daha yüksek olduğu saptanmıştır. mRNA aşısı olanlar için altıncı ayın sonunda %81,8 olan seropozitiflik, inaktif aşı olanlar için %50'ye kadar düşmektedir. İlk aşılama sırasında veya üçüncü doz olarak mRNA aşısı yapılanlarda %88,4'lük seropozitiflik muhafaza edilebilmiş olup, bu oran sadece inaktif aşı olanlara göre anlamlı olarak daha yüksektir. (p=0,013)

Sonuç: SARS-CoV-2 aşılarıyla elde edilen hümoral immün yanıt hemodiyaliz hastalarında kalıcı değildir ve rapel dozların planlanması geciktirilmemelidir. mRNA aşılarının immünojenitesi inaktif aşılardan daha yüksektir.

Anahtar kelimeler: SARS-CoV-2, bağışıklama, aşılama, hemodiyaliz.

INTRODUCTION

With their weakened immunity, hemodialysis patients are among the vulnerable groups for infectious diseases[1]. It's already known that COVID-19 has bad prognosis in hemodialysis patients[2,3]. That's why vaccination is great importance to halt the negative effects of the pandemic on this group. However, vaccine responsiveness is generally reduced in hemodialysis patients due to the loss of function in the cells of immune system[4]. Newly developed vaccines against SARS-CoV-2 were found to activate immune response to some extent in hemodialysis patients[5,6]. Different vaccines have been used in different settings and previous experiences showed that mRNA vaccines generated more antibodies than inactivated vaccines[7].

While initial immunologic response of hemodialysis patients to the vaccines matters, long-term protective effects of the vaccines should also be evaluated in order to integrate booster-dosing strategies in the follow up of these patients.

In this study we aimed to evaluate the persistence of antibody response to SARS-CoV-2 vaccines in hemodialysis patients. We have analyzed the effect of third doses of the vaccines on the antibody levels. In literature, longitudinal antibody analyses were previously conducted mainly for mRNA vaccines and comparison between inactivated and mRNA vaccines are lacking. With this study, we also tried to make inferences about the protective properties of different vaccines.

METHODS

Setting

Hemodialysis patients from two tertiary healthcare centers were followed up after they initially received SARS-CoV-2 vaccines. Patients

received either inactivated vaccine (CoronaVac®) or mRNA vaccine (BNT162b2) in accordance with national immunization protocols. All patients underwent hemodialysis three times weekly.

Clinical Follow up

Demographic data (age, sex), chronic kidney disease (CKD) related clinical data (etiology, duration of dialysis, dialysis adequacy, serum albumin, C-Reactive protein, parathormone and ferritin levels, complete blood count, mean arterial pressure) were evaluated. Symptom inquiries were made on monthly basis and real time polymerase chain reaction (PCR) tests were performed at each monthly visit to control any active SARS-CoV-2 infection in the follow-up.

Exclusion Criteria

Patients who had documented COVID-19, who had malignancies, and those who received immune-suppressive treatment in the previous 12 months were excluded from the study. Additionally, patients who have missed at least one of their regular monthly visits and those who have reported any upper or lower respiratory tract infections were also excluded.

The Vaccines

Patients were initially immunized either with CoronaVac®, an inactivated SARS-CoV-2 vaccine which was developed by Sinovac Life Sciences (Beijing, China) or BNT162b2, a nucleoside-modified RNA (mRNA) vaccine developed by BioNTech/Pfizer (Mainz, Germany). For initial immunization, CoronaVac® was administered intramuscularly 3 μg of two doses 28 days apart and BNT162b2 was administered intramuscularly 30-μg of two doses 28 days apart. In the follow up, patients could get an additional dose, three months after initial vaccination, with either of the vaccines (3 μg of CoronaVac or 30 μg of BNT162b2). Vaccine types and receiving the additional doses were dependent on the patients' choices.

Control group

The control group was composed of 61 healthy controls. They initially received CoronaVac® without any booster doses in the follow up. None had any documented SARS-CoV-2 infection before the initial vaccination.

Antibody Measurement

Antibody responses in the sera of vaccinated patients or controls were analyzed after the initial vaccinations and at the end of 6th month post vaccination. Initial antibody responses were controlled on 21st - 28th day following vaccinations and 6th month controls were done between 170th – 190th days. The analysis was carried out by Abbott SARS-CoV-2 IgG II Quant (Chicago, USA) which is a chemiluminescent microparticle immunoassay that measures IgG antibodies towards the spike receptor binding domain (RBD) of SARS-CoV-2. Quantitative IgG level determination was performed on Abbott ARCHITECT i1000 (Chicago, USA) equipment. All sera were diluted by 1:2 (75μL serum + 75μL diluent) and studied in full-automated mode. 50 AU (arbitrary unit) /mL was accepted as the cut-off value for positivity according to manufacturer's instructions.

Statistical Analysis

Continuous parametric data were presented as average ± standard deviation and t-test was used for comparisons. Categorical data were presented as percentages and compared by Fisher's exact or chi-square test. Correlations of continuous parameters were computed by Pearson's test. SPSS Statistics software version 22.0 (Chicago, IL) was used to carry out statistical analysis and $p < 0,05$ (two sided) was accepted as the statistical significance.

Ethics approval

The study was approved both by the institutional review board of Cerrahpasa Medical Faculty (approval nr: 09/04/2021 – A06) and by the COVID-19 research supervision

committee of Ministry of Health (approval nr: 2021-03-08T10_50_25). All patients gave informed consent to be a part of the study.

RESULTS

We recruited 85 hemodialysis patients after they received first two doses of CoronaVac® or BNT162b[2]. During six months follow-up, four patients died one of which was because of COVID-19. Three patients died of cardiovascular etiologies. Ten additional patients experienced COVID-19 infection.

Among 11 patients (12,9%) who experienced COVID-19 in the follow-up period, one patient died and she was seronegative after initial vaccination. Two of these patients were hospitalized while remaining eight could be managed as outpatients. Initial mean antibody titer generated by the vaccine in these patients was 100,9 ± 106,3 AU/mL and they were 61,3 ± 19,2 years old. 54,5% of them were seronegative after initial vaccinations.

Nineteen patients reported symptoms of upper or lower respiratory tract infection without confirmed COVID-19. Nine patients missed at least one of their regular monthly controls and two patients were diagnosed with a new malignancy in the follow-up period. SARS-CoV-2 IgG levels were measured at the end of 6th month for the remaining 41 patients. Among their chronic kidney disease (CKD) etiologies, 15 had diabetes, 10 had hypertension, 9 had glomerulonephritis, 2 had cystic kidney disease, 1 had Fabry disease and 1 had amyloidosis. CKD etiology was unknown for the remaining three patients.

Eighteen patients received a booster dose after 97,7 ± 5,0 days following the initial immunization period. 23 patients chose not to receive a booster dose. While patients with the additional dose could maintain the seropositivity rate of 88%, this fell to 65% for patients without a booster dose. Antibody titers at 6th month were significantly higher for patients with a booster dose than patients without a booster (1120,8 ± 983,3 AU/mL vs 313,3 ± 435,3 AU/mL respectively; p<0,001). Clinical comparison of patients with and without a booster dose can be found in table-I.

Table I: Clinical data, antibody levels and seropositivity of patients with and without a booster dose

	Patients with a booster döşe (n=18)	No booster dose (n=23)	p
Age	56,6 ± 16,4	63,8 ± 12,8	0,10
Male Sex (n, (%))	12 (66,6)	15 (65,2)	1,00
Dialysis Vintage (months)	40,6 ± 60,0	24,5 ± 22,8	0,24
Mean Arterial Pressure (mmHg)	100,0 ± 9,8	102,9 ± 10,2	0,36
Kt/V (Urea)	1,58 ± 0,36	1,70 ± 0,33	0,27
Albumin (g/dL)	4,0 ± 0,4	3,9 ± 0,3	0,72
CRP (mg/L)	11,3 ± 9,9	9,1 ± 10,4	0,51
Leukocytes (*10^3/μL)	6,5 ± 1,9	6,9 ± 2,3	0,54
Lymphocytes (/μL)	1577 ± 661	1856 ± 810	0,24
Hemoglobin (g/dL)	10,5 ± 1,0	10,7 ± 1,3	0,62
Parathormon (pg/mL)	533 ± 394	506 ± 462	0,84
Ferritin (ng/mL)	797 ± 357	784 ± 387	0,90
Initial antibody response (AU/mL)	541,1 ± 549,8	302,2 ± 324,1	0,09
Initial seropositivity rate (%)	88	82	0,60
6th month antibody titers (AU/mL)	1120,8 ± 983,3	313,3 ± 425,3	0,001
6th month seropositivity ratio (%)	88	65	0,07

Among patients who didn't get a booster dose, 12 patients received CoronaVac® and 11 patients got BNT162b2. Although antibody titers didn't differ at 6th month for both vaccines, seropositivity with CoronaVac decreased to 50% while it was 81,8% for BNT162b2 vaccinated patients (Table-II).

Table II: Sixth month comparison of patients who were initially immunized with different vaccines

	CoronaVac® (n=12)	BNT162b2 (n=11)	P
Age	64,0 ± 14,6	63,1 ± 11,1	0,87
Male Sex (n, (%))	6 (50)	9 (81,8)	0,12
Dialysis Vintage (months)	28,0 ± 27,2	20,7 ± 14,2	0,43
Kt/V (Urea)	1,66 ± 0,38	1,75 ± 0,28	0,54
Mean Arterial Pressure (mmHg)	105,9 ± 8,9	99,6 ± 11,0	0,14
Albumin (g/dL)	4,08 ± 0,38	3,87 ± 0,34	0,18
Leukocytes (*10^3/μL)	7,07 ± 2,67	6,83 ± 1,96	0,81
Lymphocytes (/μL)	1802 ± 926	1914 ± 702	0,74
Hemoglobin (g/dL)	10,8 ± 1,5	10,7 ± 1,1	0,92
Ferritin (ng/mL)	787,4 ± 488,3	780,6 ± 259,5	0,96
CRP (mg/L)	9,1 ± 10,7	9,2 ± 10,7	0,97
Parathormon (pg/mL)	584 ± 602	420 ± 239	0,40
SARS-CoV-2 IgG (AU/mL)	236,5 ± 397,2	397,0 ± 457,8	0,37
Seropositivity (%)	50	81,8	0,12

As initial seropositivity and persistence of the humoral response was higher with BNT162b2 vaccine, we have also compared the humoral response in patients who have received at least one dose of BNT162b2 (n=26) with those who have just got CoronaVac® (n=15). Antibody titers at 6th month were significantly higher for patients who received at least one dose of BNT162b2, when compared to others who only received CoronaVac® (921,7 ± 908,9 AU/mL vs 228,6 ± 356,9 AU/mL respectively; p=0,0075). Seropositivity could be maintained at a rate of 88,4% in patients who received BNT162b2, while it stayed around 53% for the other group (Table-III).

Table III: Comparison of patients who received at least one dose of BNT162b2 with those who has just got CoronaVac®

	At least one dose of BNT162b2 (n=26)	Pure CoronaVac® (n=15)	p
Age	59,3 ± 13,7	62,7 ± 14,2	0,49
Male Sex (n, (%))	19 (73,1)	8 (53,3)	0,19
Dialysis vintage (months)	23,7 ± 14,7	45,2 ± 67,8	0,12
Kt/V (Urea)	1,67 ± 0,33	1,61 ± 0,31	0,63
Albumin (g/dL)	3,93 ± 0,42	4,11 ± 0,36	0,17
Leukocytes (*10^3/μL)	6,75 ± 1,94	6,80± 2,50	0,94
Lymphocytes (/μL)	1759 ± 686	1689 ± 880	0,77
Hemoglobin (g/dL)	10,6 ± 0,9	10,8 ± 1,5	0,59
Ferritin (ng/mL)	775 ± 293	816 ± 485	0,73
CRP (mg/L)	10,7 ± 8,2	9,9 ± 8,9	0,77
Parathormon (pg/mL)	463,8 ± 331,6	613,2 ± 561,3	0,28
Initial antibody response (AU/mL)	505,0 ± 511,2	237 ± 240	0,07
Initial seropositivity (%)	92,3	73,3	0,16
6th month antibody titer (AU/mL)	921,7 ± 908,9	228,6 ± 356,9	0,0075
6th month seropositivity (%)	88,4	53,3	0,013

Initial antibody responses were inversely correlated with patients' age (r=-0,41, p=0,006). 6th month antibody levels were correlated with initial antibody responses (r=0,31, p=0,045). Although 6th month antibody levels were also inversely correlated with age, it didn't reach statistical significance.

Antibody titers at the end of 6th month for healthy controls (n=61, 31 males, 30 females, age: 56,5 ± 5,5) who were initially immunized by CoronaVac® were 188 ± 171 AU/mL.

Healthy subjects could maintain 88% of seropositivity without a booster dose, which was significantly higher than hemodialysis patients (p=0,002).

DISCUSSION

SARS-CoV-2 vaccines were previously shown to generate antibodies in hemodialysis patients8. While literature generally focuses on mRNA vaccines, inactivated vaccine has also been shown to generate seropositivity, albeit at a lower rate than mRNA vaccines[7].

The persistence of antibodies or protection capacities of the vaccines in the long term are not very well known yet. A report that included healthy population who were vaccinated with BNT162b2 found decreasing levels of median antibody levels towards the end of 6th month, when compared to the peak levels[9]. However, same report also found that around 80% of seropositivity could be maintained even with lower antibody levels.

Another report found that, spike antibodies decreased both for BNT162b2 and ChAdOx1 (Oxford-AstraZeneca) vaccines when 70 days pass from the 2nd dose[10]. Similarly, Collier et al. found that neutralizing capacity of BNT162b2 vaccine declined sharply by the 6th month[11].

In another study, the trend of decreasing humoral response over six months was found more profound in subjects with co-morbidities like kidney or liver diseases[12]. Increasing age was also a factor that further decreased antibody levels in that study.

B cell subpopulations, including the memory B cells are diminished in hemodialysis patients and this leads to poor humoral response[13]. Among study subjects who received CoronaVac® without any booster doses, healthy controls had significantly higher seropositivity (88%) than hemodialysis patients (50%) at 6th month. BNT162b2 seems to generate more stable humoral immune response in hemodialysis patients with 81,8% of seropositivity at the end of 6th month. Similarly, a 20% loss of seropositivity was reported for BNT162b2 vaccinated hemodialysis patients four months after initial two-dose vaccination regimen[14]. We couldn't attribute the difference to age, dialysis adequacy, inflammation, hemoglobin or lymphocyte levels, as all were similar for groups that were compared. Antibodies reaching the seropositivity threshold might provide protection from COVID-19. Eleven of our patients experienced symptomatic COVID-19 in the follow up period and 54,5% of them was seronegative after initial vaccination. It's not exactly known if there's a correlation between antibody titers and the strength of protection. However, we have found that initial antibody responses were correlated with antibody titers after 6 months. Initial antibody responses were also inversely correlated with age.

Application of booster doses is also among the areas of SARS-CoV-2 vaccine research. We have found that hemodialysis patients who received a booster dose could maintain 88% of seropositivity at the end of 6th month, while this fell to 65% in patients without the booster. Antibody levels were also significantly higher in patients who received the third dose. Such difference points out to the importance of the booster dose to maintain the protection from SARS-CoV-2. A recent report highlighted that the third BNT162b2 dose generated higher antibodies in patients older than 60 years[15]. Similarly, a third BNT162b2 dose that was applied one month after the second dose was shown to generate higher antibody levels for hemodialysis patients[16]. While exact timing of the third dose is another area for further research, our patients received the booster dose on 97,7 ± 5,0th day in average.

Current SARS-CoV-2 vaccination literature revolves around mRNA vaccines, with BNT162b2 being the most widely studied.

However, as pandemic evolves with new variants, different vaccines might be used in different resource settings. A considerable proportion of our patients chose inactivated vaccine and we had the opportunity to compare two vaccines in our patients. Results of our study suggest that BNT162b2 vaccine might have better protection in hemodialysis patients and that planning the booster dose with BNT162b2 can be a reasonable strategy for patients who didn't receive it initially.

This study has some limitations. Firstly we haven't isolated B cell subpopulations but checked the SARS-CoV-2 IgG levels as a marker of humoral immunity. Additionally, we haven't studied cellular immune response in our patients, which might have provided further information about immunogenicity of the vaccines. Antibody levels were checked twice in this study. Longitudinal analysis of antibody levels at each control might have helped us identify the kinetics of antibodies in hemodialysis patients. Also, the antibody titers are given with arbitrary units (AU). This is because of the lack of international standardization for SARS-CoV-2 antibody units that may be measured by different devices and kits. To overcome this limitation we have used the same device and kits in all phases of our study. Lastly, we didn't have a control group who were vaccinated with BNT162b2. This was mainly because earlier approval of inactivated vaccine in our country and it was the only option for healthy people when our study was designed.

In conclusion, vaccine induced humoral immunity is not very stable in hemodialysis patients and booster doses should be scheduled timely. When compared to inactivated vaccine, BNT162b2 seems to provide better protection in hemodialysis patients.

Data Availability: The dataset of this study is available from the corresponding author upon a reasonable request.

Ethics Committee Approval: The study was approved both by the institutional review board of Cerrahpasa Medical Faculty (approval nr: 09/04/2021 – A06) and by the COVID-19 research supervision committee of Ministry of Health (approval nr: 2021-03-08T10_50_25). All patients gave informed consent to be a part of the study.

Conflict of Interest: The authors declared no conflicts of interest.

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