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Coronavirus Pandemic

Efficacy and safety of Sinovac vaccine administered in patients undergoing hemodialysis

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Abstract

Introduction: COVİD-19 disease is more serious and fatal in patients on dialysis treatment due to their immunosuppressive status. In this study, we aimed to evaluate the protection and safety of Sinovac vaccine, which is an inactivated vaccine, in patients undergoing hemodialysis.

Methodology: A control group consisting of 220 hemodialysis patients (HD group) and 648 healthcare professionals who were healthy in our institution were included in the study. Quant II IgG anti-Spike antibody was measured 3 weeks after two doses of Sinovac vaccine were administered to both groups.

Results: The antibody response after two doses of Sinovac vaccine was 85.2% in the HD group and 99.8% in the control group. The mean antibody level before vaccination in the HD group was 3.5 ± 7.2 AU/mL and increased significantly 3 weeks after two doses of vaccine (mean 751 ± 1196 AU/mL). The control group's mean antibody level after vaccination was 1723 ± 1878 AU/mL. The mean antibody level after vaccination in the control group was significantly higher than the HD group ($p < 0.0001$). Despite higher levels of anti-Spike antibodies in the control group, post-vaccination antibody response was acceptable in both HD and control groups. The HD group was significantly older (mean 64 ± 12 years) than the control group (36 ± 10 years) ($p < 0.0001$).

Conclusions: Although dialysis patients are immunocompromised, and some may not develop antibodies to the virus as strongly as healthy people, this study revealed that dialysis patients developed significant amounts of antibodies. Being old or on dialysis is an independent predictor of low antibody response to the Sinovac vaccine.

Key words: COVID-19; hemodialysis; treatment; Sinovac; vaccine.

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Introduction

The World Health Organization began realizing the enormity of the 2019 coronavirus disease (COVID-19) pandemic late in the first quarter of 2020. The frightening public health implications of the pandemic for people with kidney disease have become increasingly evident since then [1,2]. The immune system is deeply affected by uremia. Severe coronavirus disease is a risk factor in patients with chronic kidney disease due to their immunosuppressive status. End-stage renal disease (ESKD) patients may be more vulnerable to infections and have a suboptimal response to vaccination. Patients with ESKD and severe acute.

Prioritizing vaccination for patients undergoing maintenance hemodialysis has been at the forefront of international SARS-CoV-2 vaccination programs [4]. Vaccine response in hemodialysis patients weakens over time, its effect decreases, and its duration of action is shortened compared to the general population, due to the accumulation of uremic toxins and the acceleration of immuno-aging caused by chronic inflammation, as demonstrated with hepatitis B virus vaccine or pneumococcal capsular polysaccharide vaccine [5-9].

Since the beginning of the epidemic, several vaccines for SARS-CoV-2 infection have been rapidly developed and approved. They have also been proven safe and effective in the general population. Both mRNA vaccines BNT162b2 (Pfizer-BioNTech) and vaccines with replication-defective viral vectors such as mRNA-1273 (Moderna) and ChAdOx1 nCoV-19 (Oxford-AstraZeneca) are considered safe for use in patients treated with maintenance HD [10]. Sinovac vaccine, which is inactivated and produced in Vero cells, is one of the vaccines approved for emergency use by WHO [11].

However, the efficacy of vaccines has not been clearly tested in patients on dialysis, meaning that vaccine efficacy or immunogenicity is not well understood [12].

We do not know whether the Sinovac vaccine achieves high antibody titers and provides protection in undergoing HD patients. In this study, we aimed to evaluate the protection and safety of the vaccine against COVID-19 disease by administering each of two doses (inactivated) of Sinovac by measuring antibodies against the receptor binding protein of the S1 subunit of SARS-COV-2 spike protein in undergoing HD patients.

Methodology

Study Design

The study included two cohorts: 220 undergoing maintenance hemodialysis patients in Denizli city (HD group) and a control group (control group) of 648 healthcare workers from our institution without renal impairment, or any immunosuppressive disease. This study was conducted according to the World Medical Association Declaration of Helsinki. All the participants were over the age of 18, had no previous COVİD-19 disease, and were not vaccinated. Following approval by the local institutional review board (Pamukkale University-Non-Invasive Clinical Research Ethics Committee, the approval number: E-60116787-020-17057), we obtained informed consent from the participants to collect 10 mL blood samples at the beginning of the dialysis session for the HD group prior to vaccination. Samples were stored at −80 °C. All participants were previously vaccinated with the Sinovac vaccine with the recommended 4-week dose interval between the first and second doses. The vaccine is manufactured by Sinovac Life Sciences (Beijing, China) and contains 3 μg/0.5 mL (equivalent to 600 SU per dose) inactivated SARS-CoV-2 virus and aluminum hydroxide as an adjuvant. Three weeks after vaccination, 10 mL blood samples were taken from the participants at the beginning of the dialysis session for the HD group and venous blood for the control group.

IgG antibody levels against SARS-CoV-2 were measured in serum from participants before and 3 weeks after vaccination. Immunogenicity assessment was determined using a method previously published by Walsh *et al.* [13]. In summary, we used a chemiluminescent microparticle immunoassay (SARS-CoV-2 IgG II Quant assay on an ARCHITECT analyzer; Abbott) to measure IgG antibodies in the patient's plasma. The test detects antibodies against the receptor binding protein of the S1 subunit of the SARS-CoV-2 spike protein. The test offers a positive predictive agreement of 99.4% (95% CI [95% CI], 96.50% to 99.97%) and a negative predictive agreement of 99.6% (95% CI, 99.15% to 99.37%), and consistent with the neutralization method (positive agreement, 100.0%; 95% CI, 95.72% to 100.00%) [13,14].

A value of ≥ 50 arbitrary units per milliliter (AU/mL) was accepted as evidence of vaccine response [14]. A high antibody response level was defined as antibody > 1000 AU/mL, while a low responder antibody level was defined as antibody < 1000 AU/mL.

Statistical Analyses

Means were expressed as mean ± standard deviations. Comparison between groups was performed by using the Student's t-test for parametric values and chi-square for categorical variables. A p value < 0.05 was considered statistically significant, and 95% confidence intervals of differences between proportions were calculated. Regression analysis to define independent predictors of high antibody response in our cohorts**.**

Results

This study included 220 HD patients and 648 healthcare workers as a control group. Pre-vaccine antibody levels of the patients were studied. Since the pre-vaccine antibody level of 31 patients was > 50 AU/mL, they were considered to have previous asymptomatic infections and were excluded from the study.

Table 1. Antibody level in HD group and control group.

Characteristics	HD Group (n = 189)	Control Group (n = 648)	*p*-value
Mean age (years)	64 ± 12	36 ± 10	< 0.0001
Sex Female (%)	35.1	66.4	< 0.0001
Weight (kg)	68 ± 15	71 ± 35	ns
BMI (kg/m2)	24 ± 5	25 ± 12	ns
Antibody level (AU/ml)	751 ± 1196	1723 ± 1878	< 0.0001
Subjects with Antibody level >50 AU/mL (%)	85.2	99.8	< 0.0001
Subjects with Antibody level >1000 AU/mL (%)	22.8	60.2	< 0.0001

HD: Hemodialysis; BMI: Body Mass Index; ns: non-significant.

HD group was significantly older (mean 64 ± 12 years) than the control group (36 ± 10 years) ($p < 0.0001$). Pre-vaccine mean antibody level was 3.5 ± 7.2 AU/mL and increased significantly 3 weeks post-vaccine (mean 751 ± 1196 AU/mL) in the HD group. Post-vaccines mean antibody level was 1723 ± 1878 AU/mL in controls. The post-vaccine mean antibody level in the control group was significantly higher than HD group ($p < 0.0001$) (Table 1).

Although it was higher in the control group, the post-vaccination antibody response was acceptable in both HD group and the control group. However, the percentage of subjects with high antibody (> 1000 AU/mL) level was significantly lower in the HD group.

We have performed regression analysis to define independent predictors of high antibody response in our cohorts. We investigated sex, age, and dialysis status as predictors in binary logistic analysis using enter method. Dialysis status ($p = 0.005$, RR = 0.464 CI: 0.27-0.79) and age ($p = 0.0001$, RR = 0.971 CI: 0.96-0.99) were independent predictors of High Antibody response after two doses Sinovac vaccine. Sex was not an independent predictor (Table 2).

In an analysis of the HD group (n = 189), 83% were on 3/wk dialysis, 13% on 2/wk dialysis, Diabetes mellitus (DM) was present in 47%, Hypertension (HT) in 46%, and Coronary Heart Disease in 26%. An antibody level < 50 AU/mL was observed in 28 of HD subjects (14.8%). The mean age of 28 people from the HD group with a negative antibody response was 73.64 ± 9.5, while the mean age of those with a positive antibody response was 62.3 ± 11.9. High antibody response was defined as antibody > 1000 AU/mL and observed in 43 subjects (22.8%) (Table 3).

All dialysis-related parameters were similar between high and low-no responders in the dialysis group. Age was the sole significant factor in our hemodialysis subgroup analysis, similar to the general population. No statistically significant adverse effects related to the vaccine were observed in either group.

Discussion

It is well known that patients on dialysis may mount less response to vaccines. Therefore, we aimed to evaluate this assumption regarding the Sinovac vaccine. Our main finding in this study is that the majority of patients on maintenance HD develop a significant antibody response following two doses of the vaccine; however, it was significantly lower when compared with a control group representative of the general population. The threshold for a positive response in our test was 50 AU/mL, and 85.2% of HD group was well above this threshold. In the group of 28 patients with a negative antibody response, we found a significant difference in age compared with the dialysis patients who developed anti-spike antibodies in response to the

Table 2. Comparison of high responders with low responders in the general group.

Characteristics	Antibody level < 1000 AU/mL (N = 407)	Antibody level > 1000 AU/mL (N = 430)	*p* value
Mean age	47 ± 17	37 ± 12	< 0.0001
Sex Female (%)	53.6	64.8	0.001
BMI (kg/m^2)	26 ± 15	25±5	ns
HD group (%)	36	10	< 0.0001

HD: Hemodialysis; BMI: Body Mass Index; ns: non-significant.

Table 3. Comparison of high responders with no-low responders in HD group.

Characteristics	Antibody level < 1000 AU/mL (N = 146)	Antibody level > 1000 AU/mL (N=43)	*p* value
Mean age	65 ± 12	59 ± 11	0.012
Sex Female %	35.2	34.9	ns
BMI kg/m^2	25 ± 5	24 ± 4	ns
HD patients 3/wk %	83	83	ns
Diabetes	47	45	ns
HT	44	54	ns
CHD	24	33	ns
Kt/V	1.62 ± 0.31	1.61 ± 0.33	ns
PTH ng/L	540 ± 508	519 ± 402	ns
Hb g/dL	10.9 ± 1.8	11.0 ± 1.7	ns
CRP mg/L	12 ± 17	12 ± 22	ns
Lymphocytes %	16.95 ± 607	16.38 ± 603	ns

HD: Hemodialysis; BMI: Body Mass Index; HT: Hypertension; CKD: Coronary heart disease; PTH: Parathyroid hormone; Hb: Hemoglobin; CRP: C-reactive protein; ns: non-significant.

vaccine. The group of 28 individuals with a negative antibody response was older, with a mean age of 73.6 years, while those with a positive antibody response had a mean age of 62.3 years.

The mean anti-spike antibody level was lower in the dialysis group compared to the control group. Advanced age in the dialysis group was associated with lower antibody levels.

Advanced age has an important role among the risk factors for unresponsiveness or low response in patients undergoing dialysis. The use of age as a risk factor for vaccine unresponsiveness was consistent with previous studies [15-18].

Although our findings require further validation, we believe these findings should be considered following further information to change the vaccine dose/vaccination schedule in patients with maintenance HD, as has been done in the past with different vaccines: for example, double-dose as four series of vaccines instead of three series of vaccines in healthy individuals, such as the hepatitis B vaccine given [19].

In addition, we found no association between the level of antibody response and body mass index, dialysis dose, dialysis vintage, sex, DM, HT, or lymphocyte counts.

Our study has several limitations: There was a significant age difference between the dialysis group and the control group due to the structure of both populations. This study was conducted before delta or omicron variants of COVID-19 became widespread in the population. Variant data not studied in the cohort, alpha variant responsible for most cases in the population. It was the absence of pre-vaccination antibody levels in healthcare workers.

Conclusions

Antibody response Sinovac vaccine is produced in 85.2% of the patients from the HD group. Although dialysis patients are immunocompromised, and some may not develop antibodies to the virus as strongly as healthy people, this study revealed that dialysis patients develop antibodies close to healthy people. However, the antibody titer is not as high as in the control group. Dialysis-related parameters seem to not be related to high antibody response in the dialysis group. Advanced age or dialysis status are independent predictors of low response to Sinovac vaccine. Therefore, the HD group may need to be followed for antibody titer, and further studies are required to define the clinical consequences of this low antibody titer.

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