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Original Article

Immunogenicity of the Inactivated SARS-CoV-2 Vaccine (BBIBP-CorV) in Hemodialysis Patients: A Case-Control Study

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Abstract

Background: Studies have shown that immune responses to COVID-19 vaccines are impaired in dialysis patients, which may affect their immunity to vaccines. Therefore, this study aimed to evaluate SARS-COV-2 neutralizing antibodies in hemodialysis patients for 2 and 6 weeks after receiving inactivated Sinopharm vaccine.

Method: In this study, 172 people were divided into two groups. The first group included 108 hemodialysis patients, while the second group included 64 health workers as a control group. To evaluate SARS-COV-2 neutralizing antibody titers, peripheral blood samples were collected from all participants 2 and 6 weeks after receiving the second dose of the Sinopharm vaccine. Samples were centrifuged, and the neutralizing antibody against the receptor-binding domain (RBD) was determined using the indirect ELISA technique.

Results: Hemodialysis patients had lower IgG-neutralizing antibody titers than the control group (P <0.001). The titers of SARS-COV-2 neutralizing antibodies were not significantly different at two weeks compared to six weeks after vaccination (P=0.9204). Our findings showed a significant increase in titers of IgG-neutralizing antibodies after vaccination in people with a history of COVID-19 (P=0.002). The seropositivity rate for neutralizing antibodies against RBD was significantly different between seropositive (immune) and seronegative (non-immune) patients six weeks after vaccination (P=0.022).

Conclusion: The titers of neutralizing antibodies against SARS-COV-2 were lower in hemodialysis patients than in healthy individuals. This is probably due to the poor immune system. However, patients who received two doses of inactivated Sinopharm vaccine showed a higher antibody titer six weeks after vaccination.

Keywords: COVID-19 Vaccines; Hemodialysis; Neutralizing Antibody; SARS-CoV-2

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Introduction

Coronavirus Disease 2019 (COVID-19) is an emerging respiratory disease first identified in December 2019 in China. The SARS-CoV-2 causes COVID-19, and its primary clinical symptoms include fever, shortness of breath, fatigue, muscle pains, and dry cough (1). It has also been reported that 10-20% of patients with COVID-19 develop a severe stage of the disease, which will be accompanied by acute respiratory distress syn-

drome, septic shock, metabolic acidosis, coagulation disorders, and damage to the heart, kidneys, and liver. (2-4).

According to a systematic review, by February 2021, Chronic Kidney Disease (CKD) patients on dialysis are more likely to develop COVID-19 than other CKD patients (5). Dialysis patients are more at risk of COVID-19 than other people in the community due to frequent visits to health centers for dialysis (6). Also, due to the effect of uremic conditions on the immune system and the use of immunosuppressive drugs in some dialysis patients, according to a study by the European Renal Association COVID-19 Database (ERACODA), mortality from COVID-19 within 28 days of the initiation of the disease in CKD patients undergoing dialysis was estimated at 25% (6). Numerous factors such as patient's age, nutritional status, severity of disease, underlying health conditions, race, and dialysis status (type and duration of dialysis) can affect the prognosis of CKD patients infected by SARS-CoV-2 (7-9).
Along with the use of masks and social distancing, the vaccines are known as one of the most essential ways to establish a sustainable immune response and reduce the spread of the virus (10). Therefore, various studies have been performed to evaluate the efficacy of COVID-19 in healthy individuals and those with underlying diseases. Polack et al. have reported a 95% efficiency of the Pfizer-BioNTech vaccine for people over the age of 16 years in 152 regions of the world (11). Another study has reported the efficacy of the Oxford-AstraZeneca vaccine at 62.1% and 90% in people who received two standard doses and people who received a low dose followed by a standard dose, respectively. The overall efficacy of the Oxford-AstraZeneca vaccine in two groups was 70.4% (12). Moreover, the efficacy rate of Sputnik V vaccine was 91.6% for coronavirus variants (13). According to the results of phase III of clinical trials in Arab countries, the efficacy of the BBIBP-CorV vaccine was reported to be 78.1% in adults aged 18-59 years (14). The BBIBP-CorV vaccine is a passive vaccine (Vero cell) against the SARS-CoV-2 developed by the Sinopharm company. This vaccine is inactivated with 6-propiolactone and contains aluminum hydroxide as an adjuvant (14). In Iran, due to its better availability and fewer side effects, this vaccine was used to immunize people with specific and chronic diseases and the elderly. So far, there is not much evidence about the immunogenicity of this vaccine in the elderly, patients with underlying health conditions, and particular diseases (14).

Neutralizing antibodies are induced by natural or vaccine antigens to protect a cell against a pathogen or infectious particle by neutralizing all biological effects (15). Neutralizing antibodies can be used for passive immunization, especially for people who do not have an intact immune system, such as patients who receive dialysis (16). These antibodies can also be effective in vaccine production and active immunity by identifying their binding sites and structure (17). After the outbreak of COVID-19, the idea of measuring the level of neutralizing antibodies in recovered patients and vaccine recipients was introduced. A study by Khoury et al. on COVID-19 vaccines and recovered patients in 2021 found that neutralizing antibodies markedly protect against the incidence of detectable COVID-19. The study also found that the level of antibodies needed to 50% protect against severe COVID-19 was significantly lower than that of antibodies needed to 50% protect against detectable COVID-19. In addition, it was shown that after 250 days, the degree of protection against COVID-19 was significantly reduced due to a decrease in the titer of neutralizing antibodies (18). Also, several studies have suggested that people with comorbidities (e.g., diabetes mellitus and cardiovascular disease) did not develop robust immunity responses to the vaccines (19). Güzel et al. showed that people with cardiovascular diseases and diabetes mellitus had lower titers of COVID-19 IgG antibody (20). In another study, Erol et al. suggested lower seropositivity after receiving COVID-19 vaccines in solid-organ transplant recipients than in healthy adults (67.5% vs. 100%) (21).

Due to the poor immune responses in patients who receive dialysis, the efficacy of vaccines and subsequent production of protective neutralizing antibodies may be lower. It has been shown that the efficacy of antiviral vaccines, such as influenza vaccines, can be determined by the titer of the neutralizing antibodies as well as the duration of specific immunity (22). The production of neutralizing antibodies in dialysis patients after receiving a single dose of the Pfizer-BioNTech vaccine showed that only about one-third of dialysis patients developed neutralizing antibodies with a low titer after receiving a single dose of the vaccine (23).

The antibody production after receiving COVID-19 vaccines in dialysis patients is still unknown, and we do not know whether additional doses are needed or what the injection schedule should be. Virus neutralization is the gold standard method for determining antibody efficacy. Therefore, measuring the titer of neutralizing antibodies after injection of the vaccine can help determine its efficacy (23, 24). This study evaluated the efficacy of COVID-19-inactivated Sinopharm vaccines in hemodialysis patients of Birjand Special Diseases Center by examining the titers of neutralizing antibodies following vaccination.

Materials and Methods

Study population

This study included 108 dialysis patients referred to the Special Diseases Center of Birjand University of Medical Sciences in eastern Iran. Inclusion criteria included signing written informed consent to participate and completing vaccination with the Sinopharm vaccine (injected into the deltoid muscle in two doses of 0.5 ml at 21-28 days). Patients who received any immunosuppressive medications or people who received other vaccines were excluded from the study. The control group (n=64) was also selected from the Birjand University of Medical Sciences staff immunized with the Sinopharm vaccine who had no history of chronic disease or consumption of immunosuppressive medications. First, the aims of the study were complete, simple, and clearly explained to the participants, and written informed consent was obtained. This study has been approved by the Research Ethics Committee of Birjand University of Medical Sciences (Approval ID: IR.BUMS.REC.1400.344). The second dose of the vaccine was injected from 5 June 2021 to 11 June 2021. In this study, frozen serum at -20°C was obtained from 19 June 2021 to 25 June 2021 (two weeks after injection of the second dose), and fresh serum obtained from 17 July 2021 to 23 July 2021 (six weeks after injection of the second dose) were used to evaluate neutralizing antibodies. It is worth mentioning that the patients of this center are sampled monthly during dialysis sessions for biochemical tests. Therefore, in this study, routine samples were used to prevent the imposition of additional sampling on patients. The basic information of patients, including sex, age, history of COVID-19 (based on RT-PCR test), duration of dialysis, suffering from chronic diseases (cardiovascular diseases, hypertension, endocrine diseases, cancer, autoimmune diseases, immunodeficiency diseases and history of organ transplantation) and the cause of renal failure and dialysis were collected based on the Health Information System (HIS) of the center. Also, the paraclinical parameters, such as the levels of Fasting Blood Sugar (FBS), Blood Urea Nitrogen (BUN), and Complete Blood Count with Differential (CBC diff) etc., were evaluated during the study.

Assessment of neutralizing antibodies

The time interval for assessment of neutralizing antibody titers (two and six weeks after completion of the second dose vaccination) was determined based on the study of Agur et al. (25). Five milliliters of venous blood were taken from the participants and poured into tubes containing anticoagulants to obtain fresh serum. The blood was centrifuged at 3000 rpm for 10 minutes. The isolated serum was stored for 24-48 hours in a refrigerator at 2-8°C or, if necessary, at -20°C. To evaluate the level of anti-SARS-CoV-2 neutralizing antibodies, a commercial IgG antibody detection kit against the SARS-CoV-2 receptor-binding domain (RBD) (ChemoBind®, Iran) was used. This kit can detect RBD-ACE2 reaction inhibitory antibodies by indirect ELISA. Thus, the plate wells were coated with RBD antigen (spike protein). Finally, the immunological status ratio (ISR) was measured, and based on the ISR value, the samples were divided into three categories: positive (ISR ≥1.1), negative (ISR ≤0.8), and the need for retesting (0.8-1.1). According to the lab kit brochure, the specificity and sensitivity of this commercial kit were reported to be 100%.

Statistical analysis

The quantitative and qualitative variables were described by central indicators (mean ± standard deviation (SD) and frequency percentage, respectively). After checking the normality of quantitative data with the Kolmogorov-Smirnov test, non-parametric tests were used due to the ab-

normal distribution of data. Mann-Whitney and Kruskal-Wallis statistical tests were used to evaluate the significance of differences in quantitative dependent variables in two independent groups or more than two independent groups, respectively. The chi-squared test was also used to compare the two qualitative variables. Data analysis was performed using the IBM SPSS Statistics for Windows, version 23 (IBM Corp., Armonk, NY, USA). Moreover, statistical charts were drawn using Graph Pad Prism version 6.04 for Windows (Graph Pad Software, La Jolla, California, USA). The significance level was considered as P <0.05.

Results

Patients' demographic information

Table 1 shows the demographic information of participants. The mean age of individuals was 61.1 ± 16.1 and 38.9 ± 10.7 years in patients and control group, respectively. In this study, 81.2% of patients had no history of positive COVID-19 PCR tests, while 7.9% were positive after vaccination. The SARS-CoV-2 neutralizing antibodies were detected in 54.2% and 73.0% of patients and healthy individuals two weeks after vaccination, respectively.

Table 1. Comparison of demographic characteristics and neutralizing antibodies seropositivity between cases and controls

Variables	Case (n=101)	Control (n=63)	*P*-value
Age Mean ±SD	61.1 ± 16.1	38.9 ± 10.7	
Sex (%)			
Male	61 (60.4%)	15 (23.8%)	
Female	40 (39.6%)	48 (76.2%)	
Etiology of dialysis (%)			
Diabetes mellitus	38 (37.6%)	-	-
Hypertension	32 (31.7%)	-	
Others	31 (30.7%)	-	
History of COVID-19 PCR (%)			
Negative	82 (81.2%)	50 (79.4%)	
Positive, before vaccination	11 (10.9%)	13 (20.6%)	0.023**
Positive, after vaccination	8 (7.9%)	0 (0.0%)	
Antibody mean titers after two weeks (SD)	1.84 (1.69)	2.54 (1.73)	0.001*
Antibody mean titers after six weeks (SD)	1.82 (1.62)	-	-
Neutralizing antibodies after two weeks (%)			
Positive	52 (54.2%)	46 (73.0%)	0.017**
Negative	44 (45.8%)	17 (27.0%)	
Neutralizing antibodies after six weeks (%)			
Positive	42 (46.7%)	-	-
Negative	48 (53.3%)	-	

***The Mann-Whitney U test was used.**

****A chi-squared test was used.**

IgG-neutralizing antibody titer

The comparison of anti-COVID-19 IgG neutralizing antibody titers between the control group and the case group has been shown in **Figure 1** during two and six weeks after receiving the second dose of the BBIBP-CorV vaccine. The neutralizing antibody titers were significantly lower in hemodialysis patients compared to the control group (P <0.001).

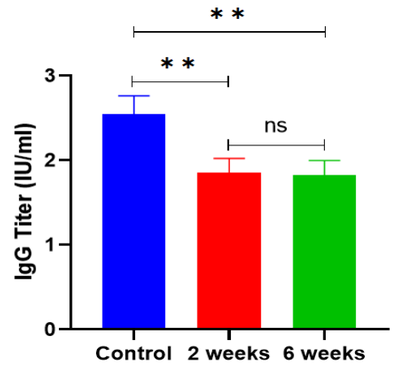

Figure 1. Comparison of anti-COVID-19 IgG neutralizing antibodies.
Hemodialysis patients had significantly lower neutralizing antibody titers than the control group (P <0.001). Data are represented as Mean ± SEM). ns, non-significant.

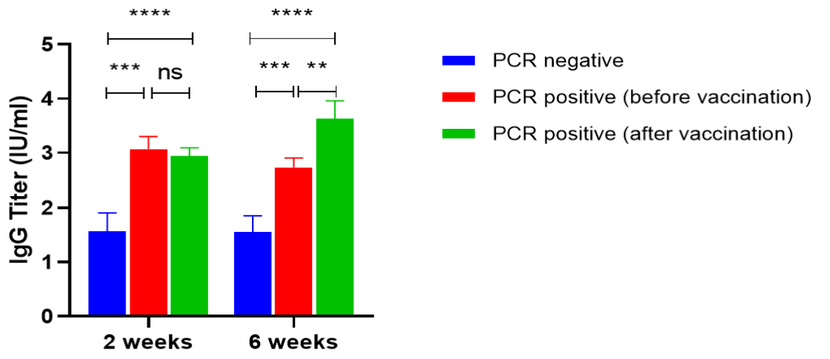

Figure 2. Titers of anti-COVID-19 IgG neutralizing antibodies before and after vaccination.
A significant difference in titers of anti-COVID-19 IgG neutralizing antibodies was seen in PCR negative compared to the PCR positive individuals (P <0.001).

However, there was no significant difference between titers of neutralizing antibodies in two weeks compared to six weeks after receiving the second dose of the BBIBP-CorV vaccine (P=0.9204).

Neutralizing antibody titers in PCR-positive and PCR-negative patients

We have also compared the IgG-neutralizing antibody titers based on the positive and negative history of COVID-19 PCR test. The titers of neutralizing antibodies were measured in patients with a history of positive PCR tests before vaccination during two and six weeks after vaccination (**Figure 2**). Data analysis showed a significant difference between the PCR-negative compared to the PCR-positive patients between two and six weeks after vaccination (P <0.001).

Seropositivity rate after vaccination

Table 2 shows the seropositivity rate in immune and non-immune individuals two and six weeks after receiving the second dose of the BBIBP-CorV vaccine. Our results suggested that the seropositivity rate in seropositive (immune) individuals was significantly higher than in seronegative (non-immune) individuals six weeks after vaccination (P=0.022).

Table 2. Comparison of the seropositivity rate for neutralizing antibodies against RBD protein on COVID-19 in two and six weeks after receiving the second dose of the BBIBP-CorV vaccine

History of COVID-19 PCR Test	After two weeks		After six weeks		Control	
	Immune	Non-immune	Immune	Non-immune	Immune	Non-immune
Negative	38 (49.3%)	39 (50.7%)	29 (39.2%)	45 (60.8%)	35 (70.0%)	15 (30.0%)
Positive, before vaccination	8 (72.7%)	3 (27.3%)	7 (70.0%)	3 (30.0%)	11 (84.6%)	2 (15.4%)
Positive, after vaccination	6 (75.0%)	2 (25.0%)	6 (100.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
***P*-value**	0.287		0.022		0.290	

Discussion

According to previous studies, dialysis patients, like other patients with chronic diseases, are more likely to be infected and die by SARS-CoV-2 (1, 7). Our results showed that the immunity developed in dialysis patients was lower than in the control group. Also, the antibody level was decreased six weeks after the second dose of the BBIBP-CorV vaccine. The low immune response to vaccines in dialysis patients may be due to the use of immunosuppressive drugs or the condition of CKD (26). In dialysis patients, due to the failure of kidney function and decreased renal clearance, a large level of inflammatory cytokines and chemokines are increased and can cause severe symptoms in these patients. Also, due to uremic conditions, epigenetic changes in hematopoietic stem cells resulted in a shift from a lymphoid cell line to a myeloid cell line (27). Therefore, B and T lymphocytes derived from the lymphoid cell line are reduced, which leads to a lower immune response to vaccines. Many studies were conducted on the immunogenicity of BNT162b2, an mRNA-based vaccine (25, 28-31), and the results were consistent with our results. However, the mean age of patients who participated in this study was relatively higher than the studies mentioned above, and this may lead to low immunogenicity after vaccination in hemodialysis patients. Also, in the present study, immunogenicity and the level of neutralizing antibodies were measured two and six weeks after the injection of the second dose, which is longer than the previous studies and makes our results valuable; this long follow-up can justify the lower immunization of the vaccine in this study.

The low immunogenicity of the inactivated vaccines such as BBIBP-CorV could be because these vaccines are not able to activate cellular immunity and T lymphocyte responses fully (32). The inactivated vaccines mostly stimulate B lymphocyte responses in order to produce neutralizing antibodies against the spike protein of SARS-CoV-2, which remain active for several months. (32). However, over time, with the disappearance of vaccine stimulation and memory B lymphocytes, the level of neutralizing antibodies decreases, and the individuals become susceptible to reinfection with SARS-CoV-2 (33)In contrast, it has been shown that mRNA-based vaccines act similarly to the SARS-CoV-2 virus and activate cellular immunity, resulting in stronger and more stable immunity. (34). Also, due to the use of aluminum hydroxide as an adjuvant in the BBIBP-CorV vaccine, the immune system tends to allergic reactions, and Th2 cells are activated more than Th1 cells. This increases the prevalence of hypersensitivity reactions and prevents the activation of cellular immunity and the production of neutralizing antibodies against SARS-CoV-2 (35).

According to our results, in both dialysis patients and the control group, a positive COVID-19 history resulted in stronger and more stable immunity. It has been shown that activation of the immune system by contact with all antigenic components of the SARS-CoV-2 leads to stronger and more stable immunity than contact with the spike protein in the inactivated vaccine (36). In the present study, there was no significant difference between the immunogenicity of the vaccine in men and women in both dialysis and control groups, which is consistent with another study performed on the BBIBP-CorV vaccine (37). Also, it is important to note that we performed biochemical tests monthly, and no significant difference was observed in the seropositivity rate of the Sinopharm vaccine based on laboratory tests. Moreover, due to the limited age range of patients in this study, no significant difference in the seropositivity rate was observed in dialysis patients based on their age. However, according to a previous study, factors such as serum albumin levels, peripheral venous iron levels, Body Mass Index (BMI) >30, and the age of patients can affect the production of neutralizing antibodies and seropositivity in dialysis patients (25).

Due to time limitations, it was impossible to lengthen the study period and further investigate the effect of time on the level of neutralizing antibodies. It is recommended that these antibodies' levels be monitored over time. Also, due to the decrease in the titers of antibodies, it is suggested to measure the titers of neutralizing antibodies three times at 0, 2, and 6 weeks after the injection of the booster dose in order to evaluate the effect of the booster dose on the immune responses to the BBIBP-CorV vaccine. Another limitation of this study was the lack of evaluation of cellular immunity in these patients. Given that many countries, especially developing countries use the Sinopharm vaccine, it seems necessary to study the immunogenicity of this vaccine in patients with other underlying diseases to better manage vaccination protocols in these patients.

Conclusions

Injecting two doses of inactivated BBIBP-CorV led to relative short-term immunogenicity in dialysis patients. Also, people with a positive history of COVID-19 showed stronger and more stable immunogenicity than those without a positive history of COVID-19. Six weeks after the injection of the second dose, the immune response quality decreased. The results showed that injecting a third or booster dose seems necessary for these patients, and it is recommended that mRNA or vector-based vaccines be used as the booster dose. These findings indicate that more long-term studies are needed to determine the immunogenicity and efficacy of the inactivated BBIBP-CorV in hemodialysis patients.

Conflict of interest

The authors have no conflicts of interest. The authors also indicate that they did not have a financial relationship with the organization that sponsored the research had full control of all primary data and agreed to allow the journal to review their data if requested.

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