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Side effects and antibody response of an inactive severe acute respiratory syndrome coronavirus 2 vaccine among health care workers

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SUMMARY

OBJECTIVE: This study aims to investigate the antibody response and the side effects of the two-dose inactive SARS-CoV-2 vaccine (CoronaVac, Sinovac, China) among a health care worker population in Turkey.

METHODS: This study was a prospective, cross-sectional, single-center study conducted between December 16, 2020, and March 15, 2021. We evaluated the side effects from a questionnaire, and anti-spike immunoglobulin G response to the vaccine (0- and 28-day schedule) using an enzyme-linked immunosorbent assay.

RESULTS: A total of 94 of 184 health care workers completed this study. The percentages of participants who were seronegative at baseline and achieved to the seropositivity were 21.3 and 97.9%, respectively, on day 21 after vaccinations. The seropositivity was predominantly detected in 31–45 years of the age group (55.4%, p=0.636), normal body mass index (47.8%, p=0.999), nonsmokers (64.1%, p=0.999), those without any comorbidities (73.9%, p=0.463), and those without any side effects (70.2%, p=0.256). The frequencies of overall side effects within seven days after the first and second doses of CoronaVac were 37.2 and 28.7%, respectively. The most common side effects was localized pain at the injection site (15.7 and 11.6%, respectively).

CONCLUSIONS: We found that vaccination by two-dose CoronaVac could elicit a specific humoral response, and it was well tolerated in health care workers. The high seropositivity developed after the second dose attracted attention. Our study will be useful in terms of showing short-term immunity and side effects.

KEYWORDS: COVID-19. Pandemics. Vaccine. Adverse events. Health personnel.

INTRODUCTION

Since the development of the first vaccine for smallpox 225 years ago, vaccinations have been saving three million people every year. However, radical changes in population density, nutrition, travel habits around the world, climate change, and ecosystem degradation are leading to the emergence of old and new pathogens that pose a risk of pandemic threats. The current pandemic, the coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has led to 198.2 million laboratory-confirmed cases, with more than 4.2 million deaths[1,2]. As of August 2, 2021, in Turkey, 5.75 million people have been infected with

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SARS-CoV-2, and 51.43 of them have died[2]. At the same time period, in Brazil, 19.918 million people have been infected, and 556.37 of them have died[2]. There are currently more than 200 preclinical and clinical vaccine candidates with various antigen delivery systems such as non-replicating viral vector, protein subunit, mRNA, and inactivated virus[3]. However, a limited number of them (currently, six), which has their own advantages and disadvantages, had emergency use authorization (EUA) including CoronaVac[4]. A CoronaVac study among fully immunized people (≥14 days after receipt of the second dose) in Chile reported that the effectiveness of the vaccine was 65.9% for the prevention of COVID-19 and 87.5% for the prevention of hospitalization, 90.3% for the prevention of intensive care unit admission, and 86.3% for the prevention of COVID-19-related death. This study is invaluable as it reflects real-life data[5]. Few studies have examined antibody response for the vaccine efficacy among health care workers (HCWs)[6-9].

In this study, we investigated the anti-spike antibody response to the two-dose CoronaVac and the side effects (SEs) experienced within 7 days of each postvaccination period among an HCW population in Turkey.

METHODS

Study design and participants

This is a prospective cross-sectional study conducted between December 16, 2020, and March 15, 2021, at a 576-bed tertiary university hospital using 184 HCWs who had a negative test result before vaccinations. Of 184 HCWs, 94 who did not meet any of the exclusion criteria completed the study. Blood samples of eligible participants were collected after 20 days following each dose of vaccinations. Signed informed voluntary consent was obtained from all participants. We recorded demographic characteristics, medical history, smoking habit, whether they experienced any SEs, and needed treatment during the seven days after each dose of the vaccination by a questionnaire.

Exclusion criteria were as follows:

- COVID-19 polymerase chain reaction (PCR) test positivity or anti-SARS-CoV-2 immunoglobulin G (IgG) test result as borderline/positive at any time during the pandemic,
- Compatible COVID-19 symptoms (i.e., fever, cough, and dyspnea) in the past three months,
- Any compatible symptoms or PCR positivity after the first dose of CoronaVac,
- Changed the decision to have a second dose for whatever reason.

The classification of obesity according to body mass index (BMI) was made by the World Health Organization (WHO) classification[10].

The grading (severity) scales of SEs are Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), and Grade 4 (life-threatening)[11].

Serological test

The antibody response was tested using an enzyme-linked immunosorbent assay (Euroimmun, Medizinische Labordiagnostika, Germany), which provides semi-quantitative determination of anti-SARS-CoV-2 IgG against the S1 domain of the spike protein. Serum samples with a result of ≥1.1 were considered positive, a result of ≥0.8–<1.1 as borderline, and a result of <0.8 as negative in accordance with the manufacturer's instructions. Borderline results were considered negative for analysis.

Statistical analysis

Descriptive statistics for the categorical variables were given as frequency (n) and percentage (%). Categorical variables were compared using Fisher–Freeman–Halton test or Pearson's χ^2 test. Statistical analysis was performed using Statistical Package for the Social Sciences version 25.0 package program (SPSS, IBM, USA). A $p<0.05$ was set as statistically significant.

RESULTS

Demographic characteristics and comorbidities of HCWs

A total of 94 participants of 184 HCWs with a predominance of male (54.3%) met the necessary criteria for the study. All the participants were Turkish nationals. The age of the study group ranged from 22–54 years, with a mean of 41.03±7.74 (22–54). The demographic characteristics, comorbidities, and smoking status of participants are demonstrated in Table 1.

Antibody response

The proportion of participants who were seronegative at baseline and achieved antibody positivity on day 21 after the first dose of vaccination was 21.3%. The seropositivity rate increased from 21.3–97.9% after the second dose of vaccine. The majority of seropositivities were found in the 31–45 years of the age group after both doses of vaccine (70%, p=0.166; 55.4%, p=0.636, respectively). In a comparison of the seropositivity rates between genders, the predominance of people were women (65%) after the first dose (p=0.158) and men (53.3%) after the second dose (p=0.498). The majority of seropositivities were found in those who had normal BMI (18.5–24.9) after both doses of vaccine (50–47.8%, p=0.932; p=0.999, respectively).

The seropositivities were found predominantly in those who were not smokers after each dose of vaccine (75–64.1%, p=0.555 and p=0.999, respectively). The rates of seropositivity in HCWs without any comorbidities were higher after each of two doses (60%, p=0.142; 73.9%, p=0.463, respectively). Among the participants who did not develop any antibody response after the first dose, 9.5% had an endocrine disease (five HCWs with hypothyroidism and two HCWs with diabetes mellitus) and 8.1% had a cardiovascular disease (hypertension) (p=0.007). However, these participants developed a higher rate of antibody response after the second dose (7.5–9.4%, respectively) (p=0.015) (Table 2).

Table 1. Demographic characteristics and comorbidities of the health care workers.

Items	Results (n=94)
Age (years), mean values±SD (min–max)	41.0±7.74 (22–54)
Sex (F/M), n (%)	43/51 (45.7/54.3)
Weight (kg), mean values±SD	72.86±12.74
Height (cm), mean values (min–max)	170 (155–190)
BMI (kg/m^2), mean values±SD	24.95±3.25
BMI groups, n (%)	
18.5–24.9 (Normal)	45 (47.9)
25–29.9 (Preobesity)	42 (44.7)
30–34.9 (Obesity)	7 (7.4)
Age groups, n (%)	
18–30	11 (11.7)
31–45	53 (56.4)
45–60	30 (31.9)
Comorbidities	
None	69 (68.3)
Cardiovascular diseases	11 (10.9)
Rheumatic diseases	2 (2.0)
Endocrine diseases	9 (8.9)
Autoimmune diseases	3 (3.0)
Malignancy	3 (3.0)
Other diseases*	4 (4.0)
Smoking status, n (%)	
Non-smoker	60 (63.8)
Smoker	34 (36.2)

SD: standard deviation; F/M: female/male; BMI: body mass index. *Other diseases include uveitis, seborrheic dermatitis, endometriosis, asthma, and migraine.

Side effects

The frequencies of overall SEs within the first seven days after vaccinations were 37.2% (35/94) and 28.7% (27/94), respectively. The most common SE was localized pain at the injection site, which accounted for 15.7% and 11.6%, respectively. Headache (10.7%) was the most common systemic SE following localized pain. The distribution of multiple types of SEs after vaccinations is shown in Table 3. Nearly all the SEs were mild or moderate (Grade 1/2) in intensity. After the first dose, 5.3% (n=5) of the participants used oral acetaminophen tablets for headache. After the second dose, 7.5% (n=7) of the participants required oral therapy (six participants needed oral paracetamol for headache, one sublingual captopril for hypertension). Sixty percent of those who received treatment due to the SEs after the first dose of vaccine also required treatment after the second dose. The antibody positivity rates were higher (70.2%, p=0.256) in participants without any SEs after a second dose of CoronaVac, and their seroconversion rate was also slightly higher (66.3%, p=0.222). However, in the analysis of dependency status between antibody responses and variables (age groups, sex, BMI, smoking habits, comorbidities, and presence of SEs), a statistically significant relationship was found along with comorbidities after both doses of vaccination (p=0.007 and p=0.015, respectively) (Table 2).

DISCUSSION

Our study showed that the vaccination by two-dose CoronaVac administered 28 days apart elicits a specific humoral response, and it was well tolerated as all SEs experienced were mild and moderate in severity in agreement with the clinical phase trials[12-17].

We found that seropositivity after the first dose of vaccination (21.3%) was low, but it achieved a higher percentage of 97.9% after the second dose. This rate was slightly higher than the clinical phase trials[13,14]. In a recent study in Turkey, the seropositivity after the first dose was reported higher (77.8%) than ours, but it concurs with our finding after the second dose (99.6%). The higher rate of seropositivity after the first dose was because those who had before COVID-19 were included in their study and there was a methodological difference[6]. The high seropositivity rate we found (97.9%) is important and a promising finding; however, today, we know that in the case of some mutations in the S protein, which causes new virus variants (P.1, P.2, B.1.351, B.1.1.7, B.1.325, B1.617, etc.), the variants not only change transmissibility and clinical severity of disease but also affect the susceptibility of the virus to naturally or vaccine-induced immunity (especially E484K and

Table 2. Antibody response after each doses of CoronaVac according to the variables.

	After the first dose of vaccine				After the second dose of vaccine				Ratio of antibody index value increase		
	Negative	Borderline	Positive	p-value	Negative	Borderline	Positive	p-value	<4-fold	≥4-fold	p-value
Age groups (years), n (%)											
18–30	6 (9.0)	2 (28.6)	3 (15.0)	0.166[a]	–	–	11 (12.0)	0.636[a]	2 (11.8)	9 (11.7)	0.356[b]
31–45	36 (53.7)	3 (42.9)	14 (70.0)		–	2 (100.0)	51 (55.4)		12 (70.6)	41 (53.2)	
45–60	25 (37.3)	2 (28.6)	3 (15.0)		–	–	30 (32.6)		3 (17.6)	27 (35.1)	
Sex, n (%)											
Female	27 (40.3)	3 (42.9)	13 (65.0)	0.158[a]	–	–	43 (46.7)	0.498[a]	11 (64.7)	32 (41.6)	0.083[b]
Male	40 (59.7)	4 (57.1)	7 (35.0)		–	2 (100.0)	49 (53.3)		6 (35.3)	45 (58.4)	
BMI groups (kg/m^2), n (%)											
18.5–24.9	31 (46.3)	4 (57.1)	10 (50.0)	0.932[a]	–	1 (50.0)	44 (47.8)	0.999[a]	9 (52.9)	36 (46.8)	0.128[b]
25–29.9	30 (44.8)	3 (42.9)	9 (45.0)		–	1 (50.0)	41 (44.6)		5 (29.4)	37 (48.0)	
30–34.9	6 (8.9)	–	1 (5.0)		–	–	7 (7.6)		3 (17.6)	4 (5.2)	
Smoking status, n (%)											
Non-smoker	41 (61.2)	4 (57.1)	15 (75.0)	0.555[a]	–	1 (50.0)	59 (64.1)	0.999	13 (76.5)	47 (61.0)	0.276[b]
Smoker	26 (38.8)	3 (42.9)	5 (25.0)			1 (50.0)	33 (35.9)		4 (23.5)	30 (39.0)	
Comorbidities											
Negative	53 (79.1)	4 (57.1)	12 (60.0)	0.142[a]	–	1 (50.0)	68 (73.9)	0.463	13 (76.5)	56 (72.7)	0.752[b]
Positive	14 (20.9)	3 (42.9)	8 (40.0)		–	1 (50.0)	24 (26.1)		4 (23.5)	21 (27.3)	
Total	67 (100.0)	7 (100.0)	20 (100.0)		–	2 (100.0)	92 (100.0)		17 (100.0)	77 (100.0)	
Comorbidities*, n (%)											
Cardiovascular disease	6 (8.1)	3 (30.0)	2 (8.0)	0.007[a]	–	1 (33.3)	10 (9.4)	0.015[a]	1 (5.3)	10 (11.1)	0.680[b]
Rheumatic disease	2 (2.7)	–	–		–	–	2 (1.9)		–	2 (2.2)	
Endocrine disease	7 (9.5)	–	2 (8.0)		–	1 (33.3)	8 (7.5)		1 (5.3)	8 (8.9)	
Autoimmune disease	1 (1.4)	–	2 (8.0)		–	–	3 (2.8)		1 (5.3)	2 (2.2)	
Malignancy		–	3 (12.0)		–	–	3 (2.8)		1 (5.3)	2 (2.2)	
Other diseases**	58 (78.4)	7 (70.0)	16 (64.0)		–	1 (33.3)	80 (75.5)		15 (78.9)	66 (73.3)	
Side effects, n (%)											
None	45 (67.2)	4 (57.1)	10 (50.0)	0.381[a]	–	1 (33.3)	66 (70.2)	0.256[a]	14 (82.4)	53 (66.3)	0.222[b]
Any local SEs	12 (17.9)	2 (28.6)	6 (30.0)		–	1 (33.3)	12 (12.8)		–	13 (16.3)	
Any systemic SEs	12 (17.9)	2 (28.6)	7 (35.0)		–	1 (33.3)	16 (17.0)		3 (17.6)	14 (17.5)	

BMI: body mass index; SE: side effect. [a]Fisher–Freeman–Halton test; [b]Pearson's χ^2 test. *Multiple response variables. Among the participants, 69 had none, 18 had only one, and seven had more than one coexisting condition. **Other diseases include uveitis, seborrheic dermatitis, endometriosis, asthma, and migraine.

N501Y), as previously reported[7-9,16]. In Brazil, where the P.1 variant is widely circulated, the estimated efficacy of CoronaVac was reported to be 49.6% after at least one dose, and another phase 4 study similarly reported 50.7%[15,16]. In another study, it was also reported that antibodies from naturally infected or CoronaVac-vaccinated individuals were less effective at neutralizing P.1 isolates[8].

As previously reported, anti-spike IgG (innate immunity) maintains for at least 8 months after COVID-19[18]. However, there are still evidence gaps for the duration of vaccine-induced immunity, appropriate timing for booster shots, and interchangeability of vaccines, all of which need to be assessed in further studies.

The seropositivity was predominantly detected in 31–45 years of the age group (55.4%), normal BMI (47.8%), non-smokers (64.1%), those without any comorbidity (73.9%), and those without any SEs (70.2%). Although there are insufficient data on the relationship between antibody responses and demographic and clinical variables, it has been reported in detail that the efficacy of the vaccine in the elderly and young adults is similar, and the elderly have lower neutralizing antibody titers[6,15,19]. The real-life data in Chile also reported that the efficacy of the vaccine in fully immunized persons aged 60 years or above was 66.6% (65.9% in 16–59 years of age group) for the prevention of COVID-19, 85.3% (87.5% in 16–59 years of age group) for the prevention of hospitalization, 89.2% (90.3% in 16–59 years of age group) for the prevention of intensive care unit admission, and 86.5% (86.3% in 16–59 years of age group) for the prevention of COVID-19-related death[5]. The seropositivity among HCWs with obesity was low (7.6%), similar to a study with mRNA vaccine[20]. This lower seropositivity can be due to the fact that obesity induces defects in B cells and compromised immune system responds poorly to vaccination against influenza, rabies, tetanus, and hepatitis B[21]. Smoking is associated with numerous diseases and impacts both innate and adaptive immunity. The lower rate of antibody response in smokers (35.9%) was compatible with the data previously reported; smoking reduces avidity and/or synthesis of Ig (IgM, IgA, IgG) in B cells[20-23]. The antibody response was lower (40%) among participants with any comorbidity, similar to the efficacy report of the phase 3 clinical trial (48.9%) in Brazil[15]. As previously reported, the defects in blood glucose regulation due to diabetes can cause dysfunction in cellular and humoral immunity, thus explaining the lower seropositivity among diabetic participants[24].

In our study, the frequencies of overall SEs after vaccinations were in agreement with the phase 1/2 clinical trials in China[13] (29% and 33%, respectively) but higher than the phase 3 clinical trials in Turkey[14] (18.9%). The most common SE (local pain at the injection site), distribution (local pain at injection site, headache, fatigue, and myalgia), and severity of all SEs were similar to the findings in clinical phase trials[13-15].

Our study has some limitations: humoral immunity was tested semiquantitatively, and neutralizing activity or vaccine-induced cellular immunity was not studied. The duration

Table 3. Side effects within seven days after each dose of CoronaVac.

Side effects within seven days	After the first dose of vaccine n (%)	After the second dose of vaccine n (%)
None	59 (48.8)	67 (59.8)
Localized pain	19 (15.7)	13 (11.6)
Localized redness	–	1 (0.9)
Localized swelling	2 (1.7)	1 (0.9)
Weakness	10 (8.2)	4 (3.6)
Headache	13 (10.7)	12 (10.7)
Fever	–	1 (0.9)
Myalgia	5 (4.1)	5 (4.4)
Dyspnea	1 (0.8)	–
Nausea–vomiting	3 (2.5)	1 (0.9)
Arthralgia	3 (2.5)	3 (2.7)
Hypertension	2 (1.7)	2 (1.8)
Runny nose	2 (1.7)	1 (0.9)
Asthenia	1 (0.8)	1 (0.9)
Numbness, tingling in the left arm	1 (0.8)	–

of antibody protection and reinfection rates after vaccination remain to be identified. This study was conducted in a small group of HCWs.

CONCLUSIONS

We found that vaccination by two-dose CoronaVac elicits a specific humoral response, and it was well tolerated as all SEs experienced were mild and moderate in severity. However, studies with larger numbers of populations and longer follow-up periods will be beneficial in terms of determining the duration of immunity and late SEs. Continuously following up the current variants in circulation in both vaccinated and unvaccinated populations by genome analyzes and monitoring of vaccine-induced immunity are crucial to develop new control measures and to determine the timing of new vaccination strategies.

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AUTHORS' CONTRIBUTIONS

HHG: Conceptualization, Data curation, Formal Analysis, Methodology, Writing – review & editing. **IÖ:** Formal Analysis, Investigation, Writing – original draft. **HEA:** Formal Analysis, Writing – review & editing. **AK:** Data curation. **SK:** Data curation. **MÖ:** Writing – review & editing. **EG:** Formal Analysis.

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