Evaluation of the Frequency of Side Effects after Coronovirus Inactive Vero Cell Vaccine in Healthcare Workers of Gazi University Hospital

Gazi Üniversitesi Sağlık Çalışanlarında Coronavirus İnaktive Vero Hücre Aşısı Sonrası Gelişen Yan Etkilerin Sıklığının Değerlendirilmesi

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ABSTRACT

Objective: COVID-19 (Coronavirus disease 2019) is a global pandemic that affected more than 125 million people all over the world. Vaccines will play a key role in the control of this pandemic. Although inactive vaccine technologies are reliable and being used for a long time, Coronavac is a newly developed vaccine and studies on the side effects of this vaccine are limited. The aims of this study is to evaluate the frequency of possible side effects of Coronovac vaccine and to investigate whether there is a difference between the 1st and 2nd dose vaccines in terms of the frequency of side effects.

Methods: This single-center, retrospective descriptive study was carried out in health care workers (HCWs) of Gazi University Hospital who received 2 doses of Coronavac vaccine between January and March 2021. At least 14 days after 2 dose of vaccination, serious advers events, non-serious advers events and possible side effects are collected by the questionnaire forms prepared for the study by the researchers. All data were analyzed by IBM SPSS Statistics version 20.0 (IBM Corp., Armonk, N.Y., USA). The questionnaire forms, prepared for the study, were delivered to volunteer HCWs manually or online by the researchers at least 14 days after 2 dose of vaccination. The data obtained through the questionnaires were transferred to the computing environment and analyzed.

Results: 1102 HCWs were enrolled in the study and 392 (35.6 %) had at least one adverse event after the 1st or 2 nd dose Coronavac vaccine. The most common adverse events were: Headache 230 (20.9%), fatigue 225 (20.4 %) and local reactions 193 (17.5%). Serious adverse events occurred in 3 (0.3 %) patients (1 Anaphylaxis,2 Angioedema) after vaccination. The majority of adverse events associated with Coronavac vaccine occured within the first 48 hours. The incidence of adverse events after vaccination is higher in healthcare workers with a known history of vaccine and non-vaccine allergies (42.7% vs. 34.3%, $p<0.05$, Chi-square test). More frequent side effects were observed after second doses in healthcare workers who developed side effects after the 1st dose of vaccine (70.5% vs. 5.3, $p<0.01$, Chi-square test)

Conclusion: In our study, we found that short-term adverse events of Coronovac vaccine were found to be consistent with phase 1/2 studies and it was observed to be safe for clinical use. However, there is still a need for long-term follow-up in terms of monitoring side effects after administration for the safety of vaccine use.

Keywords: Coronavac, healthcare worker, side effect, vaccine

Received: 05.24.2021 **Accepted:** 09.28.2021

ÖZET

Amaç: Çalışmamızın amacı Ocak-Mart 2021 tarihleri arasında 2 doz Coronavac aşısı olan Gazi Üniversitesi Hastanesi sağlık çalışanlarında, aşılama sonrası olası yan etkilerinin sıklığını değerlendirmek ve yan etki sıklığı açısından 1. ve 2. doz aşılar arasında fark olup olmadığını araştırmaktır.

Yöntem: Çalışmamız tek merkezli, retrospektif tanımlayıcı araştırmadır. 2 doz aşılamadan en az 14 gün sonra, ciddi ve ciddi olmayan advers olaylar ile olası yan etkiler, araştırmacılar tarafından çalışma için hazırlanan anket formlarına kaydedilmiştir. Veriler elektronik ortama aktarılmış, IBM SPSS Statistics version 20.0 (IBM Corp., Armonk, N.Y., USA) paket program kullanılarak analiz edilmiş. tablolar ve grafikler ile özetlenmiştir.

Bulgular: Çalışmaya 1102 sağlık çalışanı dahil edildi ve 392'si (%35.6) 1. veya 2. doz Coronavac aşısından sonra en az bir advers olay yaşadı. En yaygın yan etkiler şunlardı: Baş ağrısı 230 (%20,9), yorgunluk 225 (%20,4) ve lokal reaksiyonlar 193 (%17,5). Aşılamadan sonra 3 (%0.3) hastada (1 anafilaksi,2 anjiyoödem) ciddi yan etkiler meydana geldi. Coronavac aşısı ile ilişkili yan etkilerin çoğu ilk 48 saat içinde meydana geldi. Bilinen aşı ve aşı dışı alerji öyküsü olan sağlık çalışanlarında aşılama sonrası yan etki insidansı daha yüksek bulundu (%42.7'ye karşı %34.3, $p<0.05$, Ki-kare testi). 1. doz aşıdan sonra yan etki gelişen sağlık çalışanlarında ikinci dozdan sonra daha sık yan etki geliştiği gözlendi (%70.5'e karşı 5.3, $p<0.01$, Ki-kare testi).

Sonuç: Çalışmamızda Coronovac aşısının kısa süreli yan etkilerinin faz 1/2 çalışmaları ile uyumlu olduğu ve klinik kullanım için güvenli olduğu sonucuna ulaştık. Ancak aşıların güvenle kullanımı açısından uygulama sonrası uzun süreli yan etki izlemi ve takibine ihtiyaç duyulmaktadır.

Anahtar Sözcükler: Coronavac, sağlık çalışanı, yan etki, Aşı

Geliş Tarihi: 24.05.2021 **Kabul Tarihi:** 28.09.2021

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doi:http://dx.doi.org/10.12996/gmj.2021.147

INTRODUCTION

COVID-19 (Coronavirus disease 2019), that causes respiratory distress and affects many organs and systems by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is a global pandemic that affected more than 125 million people and so far caused the death of nearly 3 million people worldwide (1). Vaccines will play a key role in the control of infection during the pandemic process that the whole world has been in for nearly a year (2,3). The World Health Organisation (WHO) has listed more than 200 COVID-19 vaccines so far as under development. The most commonly used vaccines in the fight against COVID-19 pandemic are those produced with mRNA technology (Moderna and Pfizer / BioNTech, USA), developed with adenovirus vector (Oxford / AstraZeneca,UK and Sputnik V, Russia) and inactive vaccines produced in Vero cells (Sinovac and Sinopharm,China) since December 2020 (4). In Turkey, 'Emergency Use Authorization' was given to Coronavac inactivated vero cell vaccine, which was manufactured by Sinovac Life Sciences (Beijing, China) and contains 3 µg/0.5 mL (equivalent to 600 SU per dose) of inactivated SARS-CoV-2 virus, and aluminium hydroxide as adjuvant (5). More than 70 million shots of Sinovac's vaccine has been given worldwide (6). Until 13 April 2020, about 19 million vaccine are known to be applied againts COVID 19 in Turkey, the majority was Coronovac inactivated vero cell vaccine (7).

Due to pandemic, the necessity of applying the vaccination processes rapidly and by generalizing them to the public increases the importance of monitoring and evaluation of vaccine-related side effects even more. Although inactive vaccine technologies are reliable technologies that have been used for a long time, the Coronavirus vaccine is a newly developed vaccine and studies on the side effects of this vaccine are limited.

This study is aimed to determine the side effects of the inactivated vaccine in healthcare-workers, who were first vaccinated in our country.

METHODS

Study Design, study population and definitions

This single-center, retrospective descriptive study was carried out in health care workers (HCWs) of Gazi University Hospital who received 2 doses of CoronaVac inactive vero cell vaccine between January and March 2021. Among these HCWs who had 2 doses of the Coronavac vaccine and agreed to participate in the study were included. HCWs who did not have the Coronavac vaccine or received a single dose of vaccine were excluded from the study.

In the study, HCW's were defined and grouped according to the definitions determined by the WHO in 2006 (8). The study was approved by the Gazi University Clinical Studies Ethical Committee (Decision number: 116 and date:17.02.2021).

The vaccine-related adverse events evaluated in the study were selected from the US Vaccine Adverse Event Reporting System (VAERS) Table of Reportable Events and a recent report from a European consortium on vaccine surveillance (ADVANCE project). In addition, side effects frequently reported during phase studies of the Coronovac vaccine were evaluated during the study period In the study, 'Known vaccine side effect after vaccination or anything thought to be due to the vaccine' described as a vaccine-related adverse event.

Serious adverse event report — These reports meet the definition of "serious" specified by the Code of Federal Regulations because one of the following is reported: death, life-threatening illness, hospitalization or prolongation of hospitalization, permanent disability, congenital anomaly, or birth defect (9).

Non-serious adverse event report — These reports do not meet the regulatory definition of a serious adverse event report (9).

Possible side effects after getting a COVID-19 vaccine be defined as local reactions (pain, redness, swelling), systemic reactions (tiredness, headache, muscle pain, chills, fever, nausea and other), by CDC (Centers for Disease Control and Prevention) (10).

Study protocol

The questionnaire forms, prepared for the study, were delivered to volunteer HCWs manually or online by the researchers at least 14 days after 2 dose of vaccination. The data obtained through the questionnaires were transferred to the computing environment and analyzed.

Statistical analysis

All data were analyzed by IBM SPSS Statistics version 20.0 (IBM Corp., Armonk, N.Y., USA). The normality of the data distribution was determined by the histogram and Q-Q plots. The categorical values of the patients were expressed as a number and a percentage and were analyzed with a Chi-square test. Continued values were presented as a mean and standard deviation (SD) or median values and an interquartile range (IQR) of 25%–75%. The non-parametric values were analyzed using the Mann–Whitney U, and the parametric ones with a Student t-test. A p-value <0.05 was considered statistically significant.

RESULTS

1102 HCWs were enrolled in the study. The baseline characteristics of all HCWs were shown in Table 1.

Table 1. The baseline characteristics of HCWs, n= 1102

Age *median (IQR 25-75%)*	38 (29-46)
Gender, n (%)	
Male	352 (31.9)
Female	750 (68.1)
Occupational distribution of HCWs	
Physician	390 (35.4)
Nurse	210(19.1)
Laboratory personnel	151 (13.7)
Cleaning staff member	87 (7.9)
Technical personnel	135 (12.3)
Others	129 (11.7)
Occupational distribution of HCWs	
Comorbid diseases, n(%)	255 (20.4)
Hypertension	48 (4.4)
Diabetes mellitus	30 (2.7)
Hypothyroidism	23 (2.1)
Rheumatologic disease	15 (1.4)
Cardiovascular disease	13(1.2)
Malignancy	6 (0.5)
Previously known allergy	150 (13.6)
Pollen and dust allergy	40 (3.6)
Antibiotic allergy	30 (2.7)
NSAI drug allergy	18 (1.6)
Others	65 (5.9)
Previously known vaccination allergy	17 (1.5)

Among the HCWs, 392 (35.6 %) had at least one adverse event after the 1st or 2nd dose Coronavac vaccine. The incidence of at least one adverse event after the 1st and 2nd doses of vaccine was 352 (31.9%) and 288 (26.1%), respectively.

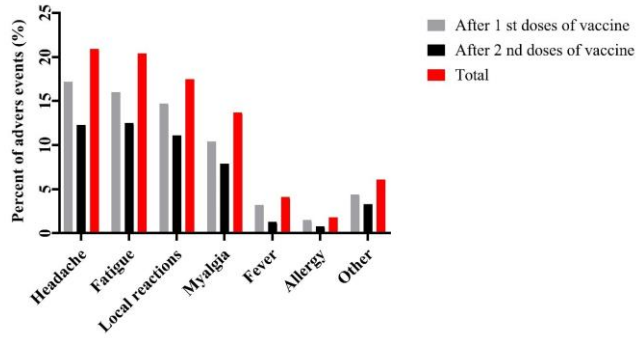
The most common adverse events after Coronavac vaccine were: Headache 230 (20.9%), fatigue 225 (20.4 %), local reactions 193 (17.5%), myalgia 151 (13.7 %), fever 45 (4.1 %), allergy 20 (1.8%), respectively (Table 2, figure 1).

Table 2. Common adverse events after Coronavac vaccine.

Adverse events	**After 1st doses of vaccine, n (%)**	**After 2nd doses of Vaccine, n (%)**	**Total, n (%)**
Non-serious adverse events	349 (31.6)	288 (26.1)	389 (35.3)
Serious adverse events	3 (0.3)	0	3 (0.3)
Distribution of adverse events			
Headache	189 (17.2)	135 (12.3)	230 (20.9)
Fatigue	176 (16.0)	138 (12.5)	225 (20.4)
Local reactions	162 (14.7)	122 (11.1)	193 (17.5)
Myalgia	115 (10.4)	87 (7.9)	151 (13.7)
Fever	35 (3.2)	14 (1.3)	45 (4.1)
Allergy	16 (1.5)	9 (0.8)	20 (1.8)
Rash	13 (1.2)	9 (0.8)	17 (1.54)
Angioedema	2 (0.2)	-	2 (0.18)
Anaphylaxis	1 (0.1)	-	1 (0.09)
Other	48 (4.4)	36 (3.3)	67 (6.1)
Hypertensive attack	3 (0.3)	1 (0.1)	4 (0.36)
Neurological manifestations*	9 (0.8)	4 (0.4)	12 (1.09)
GIS symptoms**	9 (0.8)	7 (0.6)	12 (1.09)
Numbness in the tongue And around the mouth	9 (0.8)	7 (0.6)	12 (1.09)
Chest pain-arrhythmia†	6 (0.5)	3 (0.3)	8 (0.73)
Others‡	12 (1.1)	14 (1.3)	19 (1.72)

* Numbness in the arms and legs
** Nausea, vomiting, diarrhea
† Pericarditis was diagnosed in 1 HCW 1 week after vaccination.
‡ Drowsiness, sore throat, runny nose, conjunctival bleeding, joint pain, oral aphthae

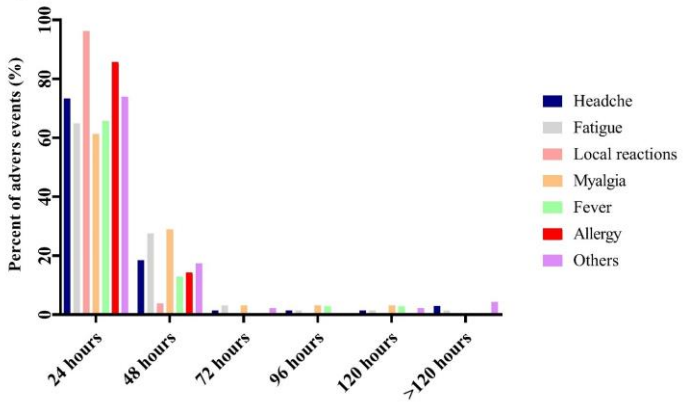
Figure 1. The Distributions Adverse events related to Coronavac Vaccine



Serious adverse events occurred in 3 (0.3 %) patients (1 Anaphylaxis,2 Angioedema) after vaccination. Clinical improvement was achieved with emergency intervention in all 3 patients. (Table 2).

The incidence of adverse events after vaccination is higher in healthcare workers with a known history of vaccine and non-vaccine allergies (42.7% vs. 34.3%, $p<0.05$, Chi-square test). More frequent side effects were observed after second doses in healthcare workers who developed side effects after the 1st dose of vaccine (70.5% vs. 5.3, $p<0.01$, Chi-square test). The majority of adverse events associated with Coronavac Vaccine occured within the first 48 hours (Figure 2).

Figure 2. Time distributions of Adverse events related to Coronavac Vaccine



DISCUSSION

In our study, it was observed that approximately one-third of HCWs developed at least one vaccine-related side effect. It was found that the majority of detected side effects were local reactions and non-serious systemic reactions. An acute allergic reaction was detected in only three per thousand patients.

In phase 1/2 studies of Coronovac vaccine between the ages of 18-59 and over 60 years, vaccines were used with different concentrations and different dose schedules, and the frequency of side effect reporting in these two studies ranged between 20-24% (3,11). The majority of reported side effects are non-serious side effects. The most common side effects are local reactions with a percentage of 13.3% and 10%, respectively (3,11). It was stated that the frequency of local reactions reaches approximately 50% in Chile, another country where the Coronovac vaccine is applied (12). Acute allergic reactions and anaphylaxis, which usually develop within the first hours after vaccination applications, are important side effects and shoud be followed up. In studies conducted with Coranavac vaccine, stated that the frequency of acute allergic reactions and anaphylaxis is 0-0.01% (3,11). However, no anaphylactic reaction was detected in the phase 3 study conducted in Chile (12). Especially, the low frequency of serious side effects and anaphylaxis reduces vaccine-related safety concerns. However, our study data include young (median 38years) and healthy population with low frequency of comorbid diseases (20%) as in phase studies.

For this reason, it should not be ignored that our results cannot be generalized for the population > 65 years of age and special groups (children, pregnant women, patients with comorbid diseases, immunosuppressive patients) where the vaccine is primarily administered in the society.

In our study, evaluation of side effects was performed approximately 42-49 days after the 1st dose and approximately 14-21 days after the 2nd dose. Therefore, it enabled the evaluation of late-period side effects as well as early period side effects after vaccination. It was observed that the majority of side effects develop within the first 48 hours (3,11,12). As seen in our study, since the incidence of side effects in the late period after vaccination was low, it is more important to monitor side effects in the early period after vaccination in the practical approach. It has been shown that vaccine-related side effects develop more frequently in HCWs, who had an allergic history before and who developed side effects after the first dose of vaccine. Due to the pandemic, the intensity of the vaccination process should not make these basic needs trivial.

There are vaccines in the world that are applied to control the COVID-19 pandemic and have already been applied to more people around the world. In 4 041 396 people using the mRNA-1273 vaccine produced by Moderna, the frequency of side effects was reported as 0.03% (13,14). In 1 893 360 people who received Pfizer-BioNTech, the frequency of side effects was 0.2% (severe allergic reactions observed in 175 patients, anaphylactic reaction in 21 patients, (11.1 cases per million vaccine doses administered) (15). Another study evaluated the side effects of two mRNA vaccines produced by Pfizer-BioNTech and Moderna, the most frequently reported side effects for both vaccines were acute allergic reactions at 1.95% and 2.20%, respectively. When compared with these two vaccines, the results we obtained in our study show that the frequency of non-serious side effects was higher with the coronovac vaccine. However, the frequency of anaphylaxis reported in both vaccines was found to be 0.027% and 0.023%, respectively (16). These results should not be considered primarily of safety concerns in determining vaccine preference among these vaccines. However, since our study was conducted in a small homogeneous cohort group, it should not be ignored that there may be misleading results in the comparison of the two data.

In concusion, in our study, we found that short-term adverse events of Coronovac vaccine were found to be consistent with phase 1/2 studies and it was observed to be safe for clinical use. However, there is still a need for long-term follow-up in terms of monitoring side effects after administration for the safety of vaccine use.

Conflict of interest

No conflict of interest was declared by the authors.

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