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Combined Use and Side Effect Profile of Different Vaccine Models for COVID-19: Single Centre Experience

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ABSTRACT

Background Currently, the most effective method to combat the COVID-19 pandemic is vaccination. This study investigated whether the combined use of vaccines obtained by different methods affected the side-effect profile.

Methods This cross-sectional study evaluated 437 people (265 females, 172 males; mean age, 42.04±14.49 years) who applied to the emergency department due to side effects among 26,974 vaccinated people (13,460 females, 13,514 males). The complaints and outcomes of the patients who applied to the emergency department were recorded.

Results While the rate of admission to the emergency department due to post-vaccination side effects was 1.6% among all vaccinated participants, this rate was 3% in the mixed vaccination group. It was observed that hospitalisation was required in only two patients due to side effects. When vaccination methods were compared, the frequency of admission to the emergency department due to side effects was higher in the patients in the group in which the mRNA vaccine was mixed with the booster shot. However, it was not statistically significant (p=0.113).

Conclusion Different vaccine methods did not change the side effect profile, so different vaccine combinations could be used together if necessary.

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INTRODUCTION

In December 2019, cases of pneumonia of unknown aetiology were mentioned in the city of Wuhan. In January 2020, the agent was identified as a new coronavirus (2019- nCoV) that has not been detected in humans before. Later, the name of the 2019-nCoV disease was accepted as COVID-19 and the virus was named SARS-CoV-2. WHO defined COVID-19 as a pandemic on 11 March due to the emergence, spread and severity of COVID-19 cases in 113 countries outside China.[1] The COVID-19 disease had a worldwide impact, causing more than 4.5 million deaths and unleashing the most significant global health crisis since the influenza pandemic of 1918.[2] Fighting this epidemic, all countries applied methods such as masks, social distance, and quarantine. In addition, vaccine studies have started with the aim and hope of controlling the outbreak.[3] With the approval of the Food and Drug Administration (FDA), two doses of the Pfizer-BioNTech COVID-19 vaccine started to be used in December 2020.[4] The Pfizer-BioNTech COVID-19 vaccine is a messenger RNA (mRNA) vaccine and enables cells to become immune by producing antibodies after vaccination.[5] The number of people who received the first dose of the Pfizer-BioNTech COVID-19 vaccine worldwide is increasing daily. Although the frequency of side effects after vaccination is 0.2%, very few are serious side effects, such as anaphylaxis.[6] Purified inactivated viruses can induce neutralising antibody responses and have been classically used for vaccine development. CoronaVac is an inactivated COVID-19 vaccine developed by Sinovac Life Sciences (Beijing, China). It showed that CoronaVac was well tolerated and induced humoral responses against SARS-CoV-2 in those aged 18-59 who received the CoronaVac vaccine. Studies have reported that doses starting from 1.5 µg up to 6 µg for vaccination in individuals over 60 years of age are safe and well tolerated.

In our country, within the scope of combating the pandemic, two doses of COVID-19 (inactivated) Vaccine manufactured by Sinovac were used at first. Then, as the vaccine's effectiveness decreased, it was recommended to apply an additional 3rd dose of vaccine as of July 1, 2021. In this study, we aimed to compare the complaints and their differences with other types of vaccine administration in terms of side effects of patients who applied to the hospital with early-stage side effects after two doses of Sinovac-manufactured COVID-19 vaccine and one booster shot of an mRNA vaccine.

MATERIAL AND METHODS

The study protocol was approved by the Medical Ethics Committee of Karaman Training and Research Hospital (10.09.2021/32053). This was a cross-sectional retrospective study evaluating 437 people (265 females, 172 males; mean age, 42.04±14.49 years) who applied to the emergency department due to side effects among 26,974 vaccinated people (13,460 females, 13,514 males) between July 1 and August 1, 2021.

Patients aged 18-80 who received at least one dose of the COVID-19 vaccine were included in the study. The patients were divided into three groups according to vaccine dose and type. Participants in the first group received the first dose of the Pfizer BionTech COVID-19 vaccine. Participants in the second group were administered two doses of the Pfizer BionTech COVID-19 vaccine. Participants in the third group were administered two doses of the COVID-19 (inactivated) vaccine produced by Sinovac and an mRNA vaccine booster shot.

A review of medical records (including information on age, sex, and application complaint) was undertaken. In addition, the hospitalization-discharge outcomes of the patients were examined. All precautions have been taken for the confidentiality of data.

Statistical analysis

The findings of our study were evaluated using the Statistical Package for Social Sciences for Windows version 21.0 (SPSS Inc., Chicago, Illinois, USA). Descriptive statistics were given for each variable. Continuous data were expressed as mean ± standard deviation. Categorical data were expressed as frequency and percentages. Mixed ANOVA models were used to assess differences between groups in terms of continuous variables. A difference was considered statistically significant when p-value <0.05.

RESULTS

Demographic and clinical characteristics of participants were depicted in Table 1. It was observed

that 26,974 people were vaccinated in Karaman Training and Research Hospital between July 1 and August 1, 2021. All individuals had received their first Pfizer BionTech COVID-19 vaccine dose, while 17,152 (63.6%) individuals had received both doses. In addition, 3,595 (13.3%) individuals had a history of two doses of COVID-19 (inactivated) vaccine manufactured by Sinovac before the first dose of Pfizer BionTech COVID-19 vaccine.

Table 1. Demographic and clinical characteristics of participants

Parameters	Frequency n (%)
Inoculated vaccine dose	
1st dose	6,227 (23.1)
1st and 2nd dose	17,152 (63.6)
2nd sinovac plus 1st dose	3,595 (13.3)
Total	26,974 (100)
Gender (Female/Male)	
1st dose	3,305/2,922
1st and 2nd dose	8,274/8,878
2nd sinovac plus 1st dose	1,881/1,714
Total	13,460/13,514
Previous infection with SARS-CoV-2	
Infected	107 (24.5)
Non-infected	330 (75.5)
Onset of side effects	
1st dose	95 (21.7)
1st and 2nd dose	233 (53.3)
2nd sinovac plus 1st dose	109 (24.9)
Total	437 (100)

After vaccination, 437 people were admitted to our hospital due to various side effects. Among all vaccinated participants, the hospital admission rate due to side effects was 1.6%. While the rate of admission to the emergency department was 1.5% in patients vaccinated after the first dose of the Pfizer BionTech COVID-19 vaccine, this rate was 1.35% after two doses. The same rate was 3% in the mixed vaccination group. Muscle-joint pain was the most common side effect, regardless of vaccine dose and type (34.9%). Other than that, fever, malaise, nausea, headache, and flu-like symptoms were the most common side effects (18.8%, 9.2%, 10.8%, 7.1%, and 6.6%, respectively). The rarest side effects were myocarditis and seizure *(Table 2).* While hospitalisation was required for only two patients due to side effects, it was observed that all patients recovered without any sequelae.

When the mixed vaccine group was examined, the most common side effect was muscle-joint pain (25.7%). Other common reasons for admission in this group were fever, nausea, flu-like symptoms, and headache (19.3%, 15.6%, 11%, and 10.1%, respectively).

Table 2. Common side effects after getting a COVID-19 vaccine

Symptoms	Frequency n (%)
Muscle-joint pain	153 (35)
Fever	82 (18.8)
Nause	47 (10.8)
Malaise	40 (9.2)
Headache	31 (7.1)
Flu-like symptom	29 (6.6)
Injection site redness	19 (4.3)
Diarrhoea	16 (3.7)
Arm pain	13 (3.3)
Seizure	1 (0.2)
Myocarditis	1 (0.2)

We performed post hoc analysis with the Bonferroni method to compare the groups in terms of side effects. Although there was no difference in common side effects, the frequency of admission to the emergency department due to side effects was higher in patients in the group mixed with a booster shot of an mRNA vaccine. However, it was not statistically significant ($p<0.113$). We also observed that the same group was older ($p<0.05$) *(Table 3).*

DISCUSSION

This was the first study to evaluate for adverse events in patients who received two doses of Sinovac-Manufactured COVID-19 (inactive) Vaccine followed by an additional dose of Pfizer BionTech COVID-19 vaccine. The present study had two main findings. First, the frequency of admission to the emergency department for post-vaccine adverse events was higher, although not statistically significant, in people who received two doses of the COVID-19 (inactive) vaccine manufactured by Sinovac and a booster shot of an mRNA vaccine. Second, there was no difference in common side effects and side effect outcomes.

Currently, in the period following the outbreak, no specific treatment consensus has been reached for COVID-19, although various potential treatments have yielded more or less encouraging results.[7-10] Therefore, a global race has begun to develop an anti-COVID-19 vaccine in response to the COVID-19 pandemic. As of

Table 3. Comparison of the groups in terms of side effect profile

Variables	First group (n: 95)	Second group (n: 233)	Third group (n: 109)	*P*-value
Age (years)	33.86+11.97	40.86+13	51.79+14.21	<0.05
Gender (Female/Male)	63/32	141/92	61/48	0.321
Applying to the emergency room	95 (1.5)	233 (1.35)	109 (3.03)	0.113
Symptoms				
Muscle-joint pain	36 (37.9)	89 (38.2)	30 (27.5)	0.135
Fever	14 (14.7)	47 (20.2)	21 (19.3)	0.516
Nause	9 (9.5)	21 (9)	17 (15.6)	0.169
Malaise	8 (8.4)	23 (9.9)	9 (8.3)	0.857
Headache	5 (5.3)	15 (6.4)	11 (10.1)	0.348
Flu-like symptom	5 (5.3)	12 (5.2)	12 (11)	0.107
Injection site redness	7 (7.4)	9 (3.9)	3 (2.8)	0.238
Diarrhoea	6 (6.3)	8 (3.4)	2 (1.8)	0.228
Arm pain	4 (4.2)	5 (2.1)	4 (3.7)	0.540

Data were given as mean±SD or n (%).

April 19, 2021, according to the COVID-19 data of the Milken Institute, there are 252 vaccine options for use in the treatment of COVID-19 under different vaccine platforms and development stages around the world. These vaccines have been developed by different methods such as RNA-based, viral vector-mediated, virus-like particle, and inactivated virus. However, four COVID-19 vaccines specifically, BNT162, mRNA 1273, ChAdOx1 and Ad26.COV2-S have been authorised in all countries of the world. Other vaccines, such as Sputnik V, BBIBP-CorV, CoronaVac, and COVAXIN, have also completed phase III clinical trials and have been put into emergency use in many countries.[11] Many countries have developed their vaccination administration protocols. Our country used double-dose PfizerBioNTech, double-dose Sinovac plus single-dose Pfizer-BioNTech, or three-dose Sinovac vaccination protocols.[12]

In a study conducted by Hatmal *et al*.[13], 2213 participants (1,344 women and 869 men) were evaluated with a questionnaire regarding side effects after vaccination. In this study, Sinopharm 38.2% (845), AstraZeneca 31% (686), Pfizer-BioNTech 27.34% (605), and less frequently, Sputnik V, Moderna, Covaxin, and Johnson & Johnson vaccines were used for vaccination. They found that the most common side effect was pain and swelling at the injection site, and the participants who reported moderate to severe side effects were those frequently administered AstraZeneca, Pfizer-BioNTech, and Sinopharm vaccines. In addition, they also showed that the presence and number of post-vaccination side effects were significantly correlated with the number of doses received (p=0.01 and <0.001, respectively). In addition, Pormohammad *et al*.[14] showed that mRNA-based vaccines cause more side effects, and the Adenovirus vector vaccine causes more diarrhoea and arthralgia than other vaccines. The same study stated that after administering the mRNA-based vaccine, side effects such as redness, swelling, itching, general fever, chills, myalgia, joint pain, vomiting, fatigue and headache were observed in the vaccination area. In our study, while mild and moderate side effects such as muscle-joint pain, fever, nausea, weakness, headache, flu-like symptoms, rash at the injection site, diarrhoea, and arm pain were more common, in line with the literature, the most common side effect was muscle-joint pain.

Previous studies shown that the frequency of conditions that can be considered as severe side effects such as thrombocytopenia, thrombosis, anaphylaxis, myocarditis, acute myocardial infection, pulmonary embolism, deep vein thrombosis, intracranial bleeding is very low.[12-15] Barda *et al*.[16] recently demonstrated that the risk ratio of myocarditis after vaccination was 100,000/2.7, and adverse effects such as acute kidney injury, arrhythmia, deep vein thrombosis, intracranial haemorrhage, myocardial infarction, and pulmonary embolism were rare. While serious side effects were detected in only two of the participants in our study, this rate corresponded to 100,000/3.7 when considering the vaccinated ones, similar to the studies in the literature.

Due to the increase in hospitalisation rate due to COVID-19 in people who received two doses of inactive vaccine produced by Sinovac, an additional

3rd dose of vaccine was planned in our country. In our study, when the group that received two doses of COVID-19 (inactive) Vaccine produced by Sinovac and a booster shot of an mRNA vaccine, there was no significant difference in side effects when compared with the group that received only Pfizer BionTech vaccine. In addition, it was determined that the mixed-type vaccine group was older. This is because the vaccine is administered primarily to older adults in our country, and the first vaccines made in our country were produced by Sinovac since there were problems in the supply of vaccines when the pandemic first broke out. In addition, some rumours about mRNA vaccines, such as deterioration of the genetic structure and infertility, especially the religious concerns of the elderly population, may have caused the COVID-19 (inactive) vaccine produced by Sinovac to be chosen as the first choice in the elderly population.

There were several limitations in our study. First, our sample was not large enough as our study was designed as a single centre. Secondly, it should be considered that our results cannot be applied to all patients because of the differences between nationalities since almost all of the patients included in the study were Turkish. Finally, interventions and treatments for patients were not evaluated in this study.

CONCLUSIONS

In conclusion, mixed vaccination methods will be needed, especially as the pandemic progresses. In the present study, we demonstrated that although the frequency of admission to the emergency department due to post-vaccine side effects has increased in people who have received a mixed vaccine for COVID-19, the common side effects and outcomes were similar. Therefore, mixed vaccination methods can be used reliably for patients. Further randomized and controlled studies evaluating the mixed vaccination methods for COVID-19 are needed.

Conflicts of Interest

All authors declared that there was no conflict of interest in this study.

Informed Consent

Ethics committee approval was obtained from the institution for the study, and written consent was obtained from all patients.

Financial Disclosure

This study did not need financial funding.

Human Participants and/or Animal Rights

This article contains no unethical studies with human participants or animals performed by authors.

Ethical Approval

The protocol of the study was approved by the Medical Ethics Committee of Karamanoğlu Mehmetbey University, Karaman, Turkey. (Decision number: 06/02, date: 19.00.2021).

Authors' Contribution

Study Conception: AA, IB; Study Design: AA, IB, HÖ; Literature Review: MRÖ, AA, HÖ; Critical Review: İB; Data Collection and/or Processing: AA, MRS, MSY; Analysis and/or Data Interpretation: İB, HÖ; Manuscript preparing: İB, HÖ.

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