

ORIGINAL ARTICLE

Cutaneous adverse events following 771 doses of the inactivated and mRNA COVID-19 vaccines: A survey study among health care providers

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Abstract

Introduction: As Coronavirus disease 19 (COVID-19) still continues to affect humanity worldwide, different types of COVID-19 vaccines are being administered to maintain immunization against COVID-19. As both the inactivated and mRNA vaccines are now being applied prevalently, systemic adverse events along with cutaneous side effects are frequently being reported in the literature.

Aim: In our study, we aimed to determine the cutaneous adverse effects of the inactivated (Sinovac-CoronaVac) and mRNA (Pfizer-BioNTech) vaccines in healthcare providers in a tertiary referral hospital.

Methods: A web-based survey consisting of 26 questions related to the systemic and cutaneous side effects of the inactivated and mRNA COVID-19 vaccines, was formed. The online questionnaire was spread among the healthcare professionals working in a tertiary referral hospital via common instant messaging groups and e-mail.

Findings: A total number of 234 participants were included in the study. One hundred fifty-seven were female whereas 77 were male. The mean age was 31.51 years. Eighty-nine respondents reported to have at least one cutaneous side effect after COVID-19 vaccination. Most commonly observed cutaneous side effects were local injection site reactions. Pfizer-BioNTech vaccine at the first and second doses, was shown to have statistically significantly higher rates of systemic and cutaneous adverse events compared to the Sinovac-CoronaVac vaccine.

Results: Our study shows that both inactivated and mRNA COVID-19 vaccines are associated with transient local injection site reactions, no severe systemic or cutaneous adverse events were observed in our study population.

KEYWORDS

COVID-19, skin, vaccination

1 | INTRODUCTION

Since the novel coronavirus, severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), was identified as the cause of the global pandemic Coronavirus disease 2019 (COVID-19) in December 2019,¹ different types of vaccines including messenger RNA (mRNA),

non-replicating viral vector, protein subunit, and inactivated vaccine have been developed to provide immunization against SARS-CoV-2.² In Turkey, starting from January 2021, Sinovac-CoronaVac inactivated type COVID-19 vaccine was first administered to elderly people and the healthcare providers (HCPs) working on the front lines of the fight against SARS-CoV-2. Later, as Pfizer-BioNTech

The Distribution of Covid-19 Vaccine Types According to the Dosages

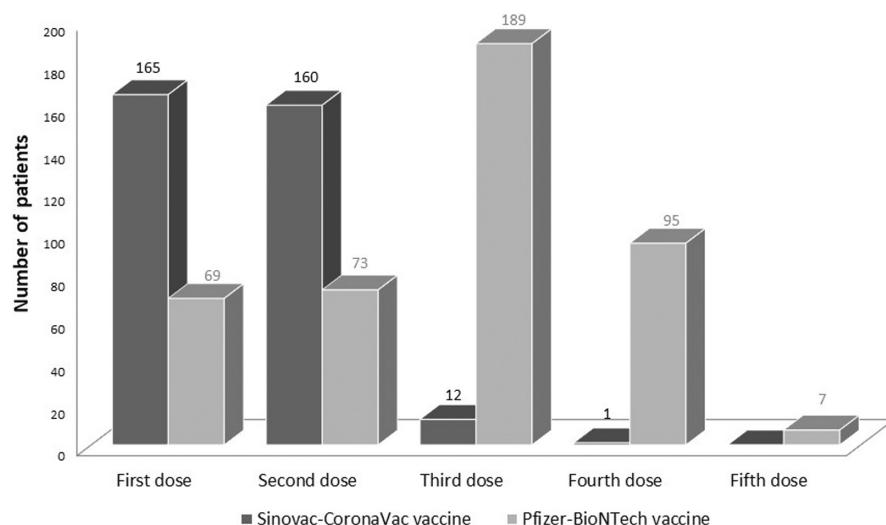


FIGURE 1 Distribution of the applied COVID-19 vaccine types according to the vaccine doses

mRNA COVID-19 vaccine along with Sinovac-CoronaVac vaccine became readily available in Turkey, the percentage of population who got vaccinated, continued to rise as a part of the national immunization program.

As variable vaccination modalities have started to become available worldwide, vaccine-related adverse events have also been frequently observed and reported.³ BNT162b2 mRNA COVID-19 vaccine was found to be most strongly associated with the elevated risks of developing myocarditis, lymphadenopathy, herpes zoster infection, and appendicitis.⁴ Besides the systemic adverse events, cutaneous skin reactions following COVID-19 vaccination have also been reported by different studies.^{5,6} Local injection site reactions, delayed-type local reactions, urticaria, and maculopapular rash have been observed as the cutaneous adverse events associated with the mRNA COVID-19 vaccine.⁶

The efficacies of variable types of COVID-19 vaccines along with their associated adverse events are among the most intriguing and investigated issues of COVID-19 era. In our study, we aimed to identify the characteristics of cutaneous adverse events associated with the application of the inactivated and mRNA COVID-19 vaccines to HCPs working in a tertiary referral hospital.

2 | METHODS

Ethical committee approval was obtained before the start of the study [Decision number: 2021/27-05 (KA-21105)]. An online questionnaire consisting of 26 questions, was formed using Google forms. The questionnaire composed of four sections: (I) personal information, (II) characteristics of COVID-19 vaccination, (III) systemic adverse events, and (IV) cutaneous adverse events observed after the vaccination parts (Appendix S1). During the questionnaire, the clinical pictures and descriptions belonging to different cutaneous adverse events were shown to make participants clearly understand and choose the correct adverse event. Informed consent was taken

from all participants before the start of the survey. The online survey was carried out among the HCPs working in a tertiary referral hospital. Instructors, specialists, research assistants, interns, medical students, nurses, medical secretaries, staff working in the administrative department, and cleaning staff who got vaccinated against COVID-19, were included in the study. The survey was spread among the HCPs via mutual instant messaging and e-mail groups. The results were collected and analyzed by the researchers at the end of the study.

IBM SPSS for Windows Version 20.0 was used for the statistical analysis of the study. Numerical variables were shown as mean \pm standard deviation (range: minimum-maximum), and categorical variables were presented as percentages and frequencies. The Kolmogorov-Smirnov test was used to determine if the numerical variables are distributed normally. For the non-normally distributed data, the Mann-Whitney U test was used to compare the median values of two independent groups. Fisher's exact test and Chi-Square test were applied for the analysis of the differences between the categorical variables. *p* values of <0.05 were considered statistically significant.

3 | RESULTS

A total number of 234 participants were included in the study. One hundred fifty-seven (67.1%) respondents were female, whereas 77 (32.9%) were male. The mean age was 31.51 ± 9.25 years (minimum: 18, maximum:55). The total number of COVID-19 vaccine (Pfizer-BioNTech mRNA and Sinovac-CoronaVac inactivated vaccines) doses was 771. The mean number of vaccine dosages was 3.29 ± 0.76 (minimum:1, maximum:5). Sixty-six (28.2%) cases had at least one accompanying systemic disease. Additionally, 74 (31.6%) had been diagnosed with one or more allergic disorder such as hay fever, food allergies, and allergic asthma, whereas 107 (45.7%) reported to have predisposition to develop acute or chronic eczema

or xerosis. Fifty (21.4%) had at least one skin disorder, most common ones being eczema ($n = 15$, 30%), seborrheic dermatitis ($n = 15$, 30%), and chronic urticaria ($n = 7$, 14%). Fifty-one (21.8%) respondents had been diagnosed with COVID-19, prior to the vaccination. Out of 234 participants, only one person (0.4%) had a single dose of COVID-19 vaccine; 32 (13.7%) had two doses, 105 (44.9%) had three doses, 89 (38%) had four doses, whereas 7 (3%) had five doses. The distribution of COVID-19 vaccine types (Pfizer-BioNTech mRNA COVID-19 vaccine vs Sinovac-CoronaVac inactivated COVID-19 vaccine) is shown in Figure 1.

One hundred eighty-eight (80.3%) respondents showed at least one systemic side effect observed after vaccination. The most common ones were fatigue ($n = 123$, 65.4%), myalgia ($n = 121$, 64.4%), headache ($n = 60$, 31.9%), fever ($n = 50$, 26.6%), arthralgia ($n = 47$, 25%), and chilling/shivering ($n = 32$, 17%). The mean time interval between the emergence of a systemic side effect and the application of the relevant COVID-19 vaccine was 13.59 ± 13.56 h (minimum: 1, maximum: 120). The distribution of COVID-19 vaccine types and doses at which systemic side effects were seen, is shown in Figure 2. Eighty-nine (38%) participants reported to have at least one cutaneous adverse event related to the vaccination, the most prevalent ones being local injection site reactions. Only one patient reported to have a flare-up of the pre-existing psoriasis and again only one participant experienced an acute urticaria episode approximately 1 day after the vaccine (Figure 3). The distribution of COVID-19 vaccine types/ doses at which cutaneous side effects were seen, is shown in Figure 4. The types of different cutaneous adverse events, their frequencies and the mean time interval between the appearance of the cutaneous adverse event and the application of the relevant vaccine, are shown in Table 1. The distribution of vaccine types at which cutaneous adverse events were observed, the number of patients with adverse events and the number of hours from vaccination until the development of cutaneous adverse events are shown in Figure 5. One hundred ninety-eight (84.6%) out of 234 participants with systemic and/or cutaneous adverse event, only 29 (14.6%) were required to use medicine for the related side effect.

We found a statistically significant relationship between developing at least one systemic adverse event after the first dose ($p < 0.001$) and the second dose ($p < 0.001$) and the type of vaccine administered. Pfizer-BioNTech vaccine was found to be associated with higher rates of systemic adverse events compared with Sinovac-CoronaVac vaccine. The systemic adverse events were not able to be compared between the two types of COVID-19 vaccine at the third, fourth, and fifth dose, due to the low numbers of patients who got vaccinated with Sinovac-CoronaVac. Additionally, we found a statistically significant relationship between developing at least one cutaneous side effect after the first vaccine dose ($p < 0.001$), after the second vaccine dose ($p < 0.001$) and the type of vaccine administered. Pfizer-BioNTech vaccine was found to be associated with higher rates of cutaneous adverse events compared with the Sinovac-CoronaVac vaccine. The comparisons of skin side effects between the two types of COVID-19 vaccine at the third, fourth, and fifth dose were not able to be performed due to the low number of participants who had the Sinovac-CoronaVac dose.

No statistically significant relationship was found between developing at least one systemic adverse event vs having any chronic disease ($p = 0.993$) and developing one or more cutaneous adverse event vs having a chronic disease ($p = 0.143$). Interestingly, female participants were found to exhibit systemic side effects compared with the male ones at a statistically significantly higher rate ($p = 0.040$). No statistically relationships were observed between the mean age ($p = 0.202$), the mean dose of vaccination ($p = 0.276$), and exhibiting at least one systemic side effect. We found no statistically significant relationship between having chronic eczema ($p = 0.534$), having at least one allergic disease ($p = 0.966$), gender ($p = 0.072$), the mean age ($p = 0.702$), the mean number of vaccine doses ($p = 0.400$), and developing at least one cutaneous side effect. Again, there was no statistically difference between having any skin disorder and developing a cutaneous side effect after COVID-19 vaccination ($p = 0.738$). Additionally, we found no statistically significant difference between being diagnosed with COVID-19 before the vaccination and developing a skin side effect ($p = 0.844$) or a systemic side effect ($p = 0.431$).

The Distribution of Covid-19 Vaccine Types and Doses in Respondents with Systemic Adverse Events

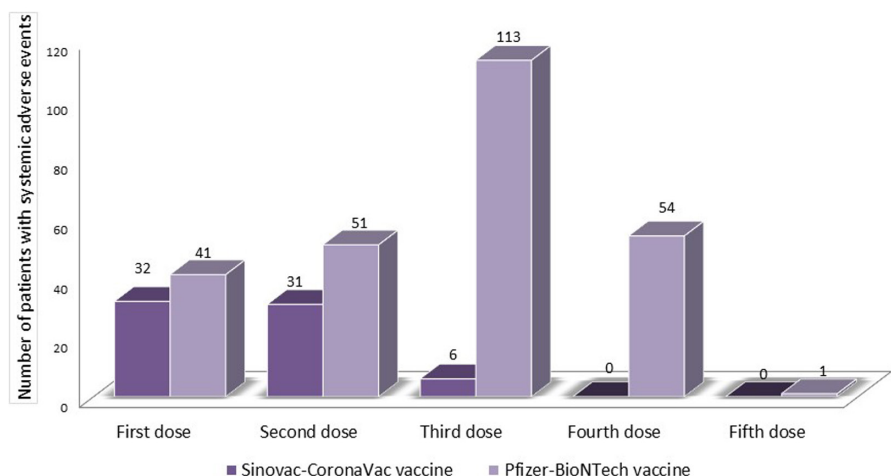


FIGURE 2 Distribution of COVID-19 vaccine types and doses at which systemic adverse events were seen

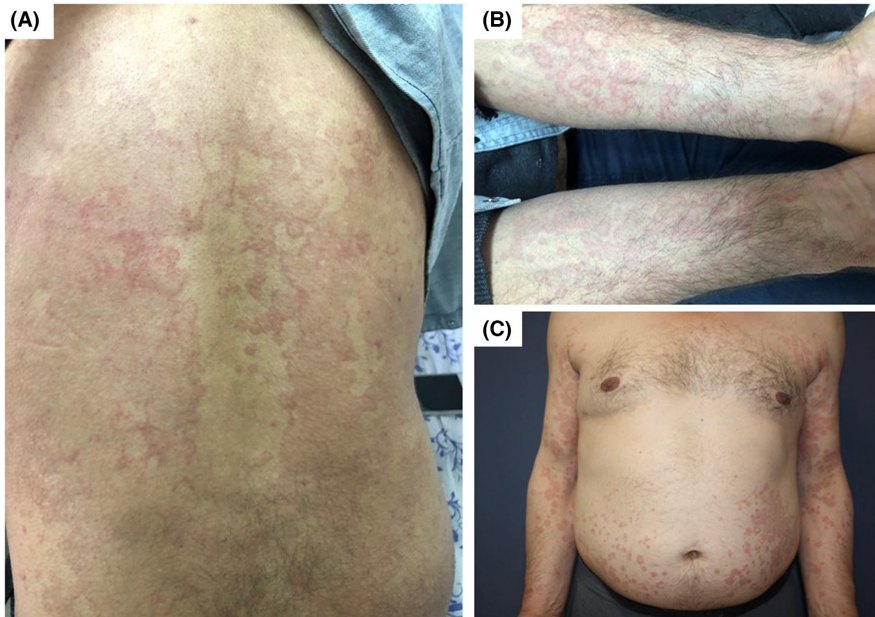


FIGURE 3 Clinical pictures of a patient who had an acute episode of urticaria 1 day after the application of mRNA COVID-19 vaccine (A and B); the clinical picture of a patient with pre-existing psoriasis who showed exacerbation after the application of mRNA COVID-19 vaccine (C)

The Distribution of Covid-19 Vaccine Types and Doses in Respondents with Cutaneous Adverse Events

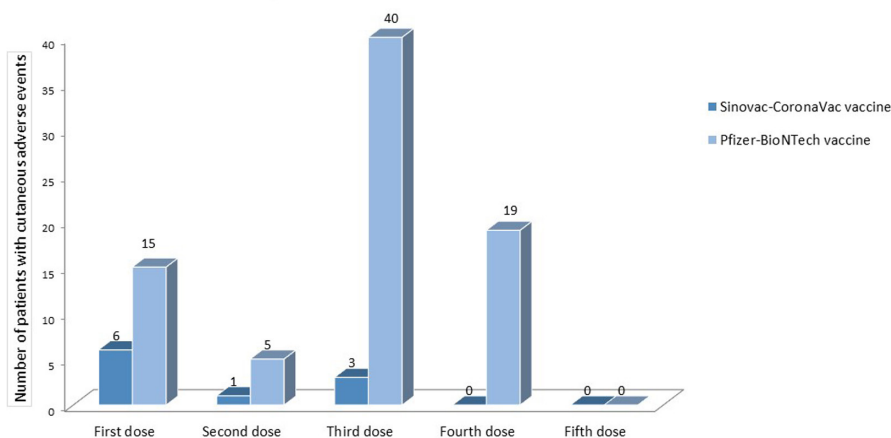


FIGURE 4 Distribution of COVID-19 vaccine types and doses at which cutaneous adverse events was seen

4 | DISCUSSION

From the start of COVID-19 outbreak in December 2019,¹ when no proven effective treatment modalities and vaccines were available, the spread of the pandemic was tried to be precluded by the enforcement of quarantine, social distancing, lockdowns, use of personal protective equipment, and maintaining personnel hygiene. When COVID-19 infection caused by SARS-CoV-2 was declared a global pandemic by World Health Organization on March 2021, international attempts for cultivating efficacious vaccines against COVID-19, accelerated worldwide. Live-attenuated, inactivated, RNA-based, protein subunit, non-replicating viral vector, replicating viral vector COVID-19 vaccines had been developed as candidate vaccines to provide immunization against SARS-CoV-2.²

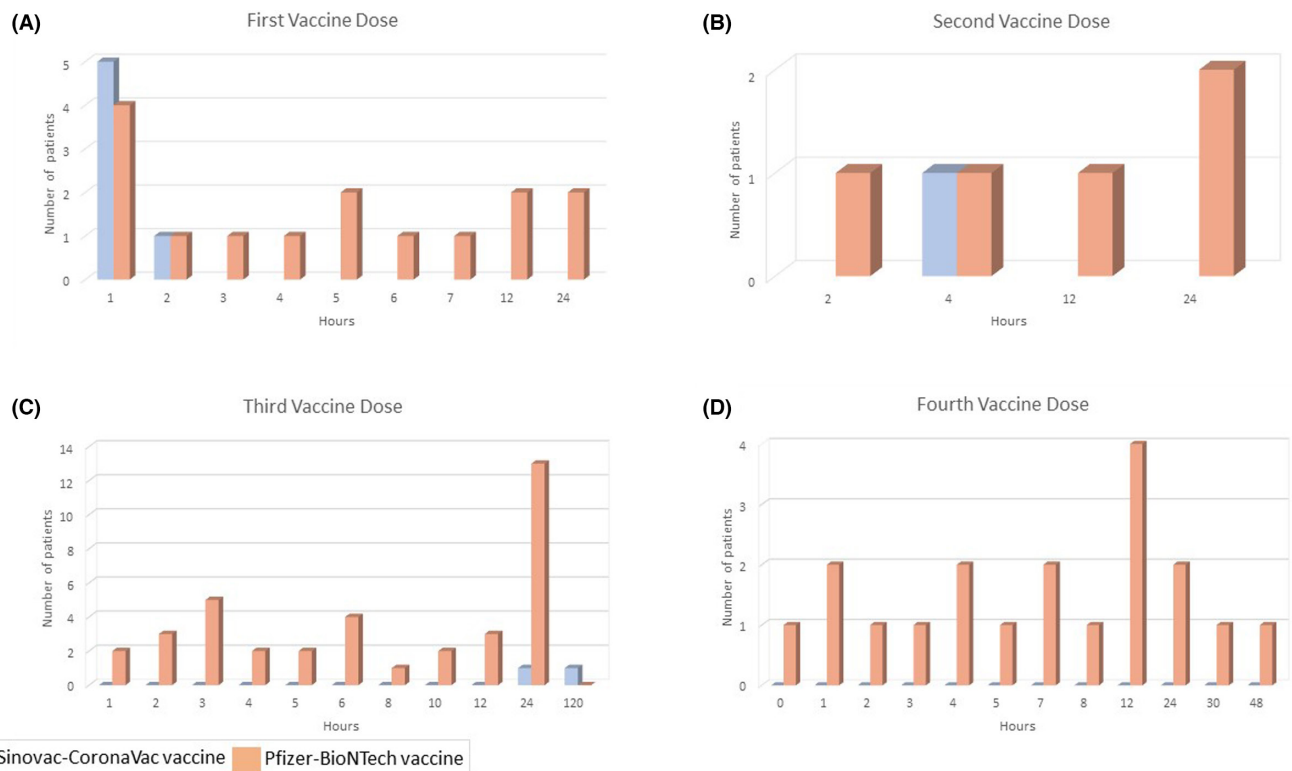
Inactivated type COVID-19 vaccine from Sinovac-CoronaVac was the first vaccine which was applied in Turkey as the part of the national immunization program against COVID-19 pandemic. Starting from January 2021, the inactivated COVID-19 vaccine was administered to the elderly people and HCPs first; as both

Pfizer-BioNTech mRNA and Sinovac-CoronaVac inactivated vaccines became accessible to everyone in Turkey, national vaccination rates gradually increased.

The efficacy as well as the safety of COVID-19 vaccines are among the mostly investigated and questioned issues during COVID-19 pandemic. In a phase 3, randomized, observed-blinded, and place-controlled trial from the United States, it was shown that both systemic and injection site-related adverse events developed more frequently in the mRNA-1273 vaccine group compared with the placebo group after the first and second doses.⁷ Additionally, the most common injection site-related adverse effect was pain at the vaccination site,⁷ which is in concordance with our results. In the same trial, delayed injection site reactions, which was defined as the formation of erythema, tenderness, or induration at the vaccination site starting on or after Day 8, were noted in 0.8% and 0.2% of the participants, at the first and second dose, respectively.⁷ In another phase 1/2, randomized, double-blind, placebo-controlled study the inactivated Sinovac vaccine, participants were divided into four groups: 1.5, 3 and 6 μ g vaccines dose receivers and the

TABLE 1 Types of different cutaneous adverse events, their frequencies, and the mean time interval between the appearance of the cutaneous adverse event and the application of the relevant vaccine

Cutaneous adverse events	Number of the observed cutaneous adverse events	Time interval (hours) between the appearance of the cutaneous adverse event and application of the relevant vaccine		
		Mean \pm standard deviation	Minimum	Maximum
Swelling at the injection site	24	14.38 \pm 23.74	1	120
Erythema at the injection site	10	22.10 \pm 35.17	4	120
Warmth at the injection site	20	15.70 \pm 25.76	1	120
Exacerbation of psoriasis	1	1.00	1	1
Itching at the injection site	6	10.67 \pm 10.50	1	24
Pain at the injection site	67	9.79 \pm 10.31	1	48
Acute urticaria	1	24	24	24

**FIGURE 5** Number of hours from vaccination (hour 0) until the emergence of a cutaneous reaction after COVID-19 vaccination. First vaccination dose (A), second vaccination dose (B), third vaccination dose (C), and fourth vaccination dose (D)

placebo group.⁸ The injections were administered to the 421 participants on Day 0 and Day 28; 21% of the all participants developed one or more adverse events within the 28 days of the vaccination but there was no statistically significant differences across groups.⁸ Supporting the findings of the above-mentioned trial and our observational study, the most common local reaction was injection-site related pain in this phase 1/2 trial.⁸

Apart from the results of the clinical phase trials; registry-based studies and prospective cohort studies have also revealed the

efficacy and safety of different COVID-19 vaccine types in the real world setting.^{5,6,9} In a registry-based study by McMahon et al.⁶ related to the cutaneous reactions observed after Moderna and Pfizer mRNA vaccines at the first and second doses, it was found that the most common cutaneous adverse events were delayed type large local reactions followed by the local injection site reactions, urticaria, morbilliform eruption, and erythromelalgia. It was also reported that <50% of the patients with cutaneous adverse events following the first dose had recurrence of the same events after the second dose.⁶

In this study, flare of the pre-existing dermatologic disease, vesicular eruption, pernio/chillblains, erythema multiforme, vasculitis, contact dermatitis, pityriasis rosea, new-onset dermatologic disorder, and filler reaction were among the heterogeneous cutaneous adverse events related to Pfizer and Moderna mRNA vaccine application.⁶ On the contrary, in our observational study, only one participant reported to experience flare-up of pre-existing psoriasis disease and again only one participant had an acute episode of urticaria approximately 1 day after the vaccine administration. Local injection site reactions constituted the majority of cutaneous adverse events in our study. Local injection site reactions were described to occur within 3 days following the first vaccination dose whereas delayed large local reactions were defined to appear ≥ 4 days after the first vaccination dose.⁶ Local injection site reactions reflect an immune response to the injected material; antigen dose, antigen features, type of adjuvants/diluents, vaccination route and site along with vaccine-associated factors are significant predictors for the development of injection site reactions.¹⁰ On the contrary, delayed type hypersensitivity reactions in association with cell-mediated immunity were thought play a role in the etiopathogenesis of the delayed large local reactions.^{11,12} Additionally, polyethylene glycol (PEG), a hydrophilic polymer ingredient of various foods, medicines, vaccines including Pfizer-BioNTech COVID-19 vaccine is also thought to play a possible role in the development of hypersensitivity reactions following COVID-19 vaccine administration.¹³

In another study from Northeast Italy in which 19485 individuals were included, only 266 adverse reactions were detected and at least one cutaneous adverse reaction was noted in 44 (0.22%) of all individuals vaccinated with the mRNA Comirnaty®-BioNTech/Pfizer COVID-19 vaccine.⁹ Urticaria, itchy erythema of the neck and hands, generalized itching, morbilliform eruption, local injection site reactions (itching, erythema, hardening of the skin, burning sensation, wheal at the inoculation site), herpes zoster, and pityriasis-rosea like eruption were among the, heterogeneous cutaneous adverse events reported to the Pharmacovigilance Service of Trieste in Italy.⁹ The time interval between the occurrence of the cutaneous adverse event and the inoculation of the vaccine ranged from 60 h to 10 days after the injection and none of the participants developed a severe reaction, the reactions were self-limited.⁹ In our web-based questionnaire, 89 (38%) respondents had at least one cutaneous reaction and a total of 129 cutaneous adverse events were reported. The time frame between the appearance of the cutaneous adverse event and the application of either the mRNA or inactivated vaccine ranged from 1 h to 5 days after the injection. Since the local site reactions which most noticeably occurs within a few days after the vaccination, were the leading adverse event in our cohort; the time interval between the cutaneous adverse event and vaccination were narrow in our study compared with the report by Farinazzo et al.⁹ Supporting the results of this report, in our study none of the participants developed any severe or life-threatening adverse event and only 29 (14.6%) out of 198 individuals with any systemic or cutaneous side effects, needed to use any kind of treatment for the vaccine-related adverse events.

In a prospective controlled study related to the cutaneous adverse events observed after Sinovac inactivated and AstraZeneca viral vector COVID-19 vaccine application, healthcare workers employed in a hospital, were included.⁵ A total dose of 29907 Sinovac vaccine and a total dose of 5322 of AstraZeneca vaccine were administered to the participants during the study period; 204 cases from Sinovac and 36 cases from AstraZeneca demonstrated cutaneous adverse events.⁵ Interestingly, urticaria, followed by eczematous reaction and angioedema were reported to be the most common cutaneous adverse events.⁵ In this study, the authors declared that skin findings were categorized by the dermatologists using available clinical images (48.01% of all cases with cutaneous adverse events)⁵; so this factor may account for the lower rate of injection site reactions in this study. In our study, only one person developed acute urticaria attack approximately 1 day after the mRNA vaccine application. PEG-2000, an ingredient of the vaccines is thought play a role in the induction of urticaria.¹⁴ Gokay et al¹⁵ reported a case of urticarial eruption occurred in a three-year-old child who was irrigated with oral PEG-3350 solution after ingesting an alkali battery. The patient developed urticarial rash at the 30th hour after the administration of PEG-3350.¹⁵ Additionally, Cox et al¹⁴ reported 6 cases who developed acute hypersensitivity to PEG-containing products which were supported by the results of the applied skin prick tests. Furthermore, Sellaturay et al.¹⁶ demonstrated that allergy to PEG, may actually cause anaphylaxis to Pfizer/BioNTech vaccine by reporting a case of vaccine-induced anaphylaxis in a patient who described a history of allergic reactions to multiple PEG-containing products.

Collectively, our data support that both systemic and cutaneous reactions from Sinovac-CoronaVac and Pfizer-BioNTech COVID-19 vaccines are self-limiting and minor reactions. In our study, none of the participants developed a serious or life-threatening systemic and skin side effects which would discourage further vaccination.

Our research has some limitations since no control group was present, and it was a single center study. Since not all cases were diagnosed by a dermatologist, the results might have been subjective. Furthermore, the questionnaire was filled by the HCPs months after the vaccination doses were applied, memory factor might have affected our results. Prospective, randomized-controlled studies with larger sample size are needed to confirm our results.

AUTHOR CONTRIBUTIONS

Ecem Bostan involved in conceptualization; visualization; data curation; analysis of the data; and writing original draft. **Beril Yel** performed conceptualization; visualization; and data curation. **Aysen Karaduman** involved in data curation and reviewing of the original draft.

ACKNOWLEDGEMENT

We would like to thank Cem Yavrum for the statistical analysis of the manuscript.

CONFLICT OF INTEREST

The authors declare that they have no competing interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author, [EB], upon reasonable request.

ETHICAL APPROVAL

The study was conducted at Hacettepe University Faculty of Medicine. Ethics committee approval was obtained for the study. Ethical committee approval decision number: 2021/27-05 (KA-21105).

INFORMED CONSENT

The authors declare that informed consent was taken from the participants before the start of the study.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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