ABSTRACT

Background: CoronaVac, the first coronavirus disease 2019 vaccine administered in our country, was found safe in clinical trials.

Objective: We aimed to reveal the rate and features of CoronaVac vaccine-associated allergic reactions among vaccinated healthcare workers (HCWs) in real-life.

Methods: This study was planned as a questionnaire-based study. Participants who reported a postvaccination allergic reaction were interviewed on phone and their medical records were also checked for confirmation.

Results: A total of 2,488 HCWs took part in the study and 4,054 postvaccination complete questionnaire-responses were obtained. Twenty-one HCWs (female: male, 17:4) with a mean age of 40.95 ± 10.09 stated that they had an allergic reaction after a total of 23 vaccine injections. Accordingly, the reaction rate was 0.56% among all vaccine doses. The most common reactions were systemic skin reactions (2.7%) consisting of generalized pruritus, diffuse pruritic erythema, urticaria, and maculopapular rash. That was followed by local injection site reaction (0.12%). Anaphylaxis was reported in 4 cases (0.09%) with a mean onset time of 12 ± 6 minutes. One of them had a history of anaphylaxis with 2 drugs, another had venom and food allergy. Three of the subjects had level 2 diagnostic certainty according to the Brighton Collaboration criteria and one had level 3. All anaphylaxis cases were discharged within 24 hours and none of them required intensive care.

Conclusion: Our study demonstrated that allergic reactions to CoronaVac were rare and mostly mild. Although anaphylaxis was also rare, the importance of early intervention with close follow-up was once again emphasized.

Keywords: CoronaVac; COVID-19; Vaccine-associated allergic reactions; Anaphylaxis; Systemic skin reactions; Local injection site reaction

INTRODUCTION

Due to the serious threat of the pandemic worldwide, coronavirus disease 2019 (COVID-19) vaccines have been produced and released to the market as soon as possible by different companies as a result of intensive studies [1]. Vaccines, the first trials of which have been completed with emergency procedures, have started to be implemented in many countries.
CoronaVac (Sinovac Life Sciences, Beijing, China), an inactivated virus vaccine, is the first one to be applied as a COVID-19 vaccine in Turkey [3, 4]. The Turkish Medicines and Medical Devices Agency gave emergency use approval for the CoronaVac in January 2021 based on the efficacy and safety results of phase I/II trials and the vaccination campaign started officially across Turkey, primarily for healthcare workers (HCWs), elderly and for risky groups. The vaccination schedule was applied as a 2-dose given at least 4 weeks apart [4-6].

Following introduction of new anti-COVID-19 vaccines, undesired effects including allergic reactions were of interest. CoronaVac, contains inactivated COVID-19 viruses as the active ingredient. Aluminum hydroxide, which has been used in vaccines for many years as an adjuvant substance, is also included in CoronaVac and helps to increase the immune response. In addition, CoronaVac contains sodium chloride to adjust the density of the vaccine to suit body fluids, sodium hydroxide to adjust the pH balance necessary for long-term storage of the vaccine content, and monosodium and disodium hydrogen sulfate not to lose its antigenic properties [3]. Based on previous experience with different vaccines, aluminum salts appear to be the likely causative agent in hypersensitivity reactions to CoronaVac [7-9].

Although no serious adverse events were recorded in previous clinical trials performed by CoronaVac, real-life experience seems to be necessary as the population need to have information about safety for further vaccination schedules [10, 11]. So far, only few studies are available on the adverse events of CoronaVac, including allergic reactions [12].

We aimed to analyze the allergic reactions to the CoronaVac among the vaccinated HCWs of our tertiary care university hospital, to document the rate and characteristics of allergic reactions and the clinical features of subjects who experience them.

**MATERIALS AND METHODS**

**Study design**

The study included all HCWs in our hospital who were vaccinated with the CoronaVac. A survey was developed by study investigators for determining allergic reactions related to CoronaVac vaccination. All HCWs of the hospital were asked to fill out the survey after the first dose of vaccination. Those who agreed to fill out the questionnaire and participate in the study were asked to complete the same questionnaire after the second dose. The study protocol was approved by Ankara University Ethics Committee (Cod: İ11-692-21). The participants included in the study received sufficient information and gave their informed consent in writing to participate in that study.

The survey included questions related to demographic and disease characteristics of the subjects (age, gender, presence of any illness, past medical history) and the experience of any local and/or systemic hypersensitivity reactions after vaccination. The surveys belong to the participants who did not respond to more than 2 of the questions of the survey were considered unreliable and were excluded from the study.

The subjects who experience local or systemic hypersensitivity reactions after 1st or 2nd doses were also assessed by further questions in detail in order to clarify the reactions. In this sense, presence of signs or symptoms consistent with a local vaccine reaction, such as pain,
tenderness, redness, warmth, swelling, induration, ulceration, and the features of systemic skin reactions such as localization, time of onset, presence of itching, swelling, erythema, redness, rash, and angioedema, time of disappearance, need for treatment were assessed. The symptoms and signs of the cardiovascular, respiratory, neurological, and gastrointestinal systems were also assessed. Apart from each system’s findings, there was a separate section for the diagnosis of anaphylaxis. A telephone interview was also performed with participants who reported allergic reaction following vaccine to verify questionnaire. A photograph of local or systemic skin lesions was reviewed if available. Their medical records regarding their allergic reactions during and after vaccination were also examined.

Definition of hypersensitivity reactions

Local injection reaction
The signs or symptoms including pain, tenderness, redness, warmth, swelling, induration, ulceration at the injection site were evaluated and presence of at least one of them was considered as a local injection reaction. However, since the presence of pain alone could be subjective, existence of at least one symptom and/or finding was required to accompany pain for the definition of local injection reaction.

Urticaria/angioedema
The diagnosis of vaccine-associated urticaria was made clinically based on characteristic presentation of urticarial lesions followed the administered CoronaVac; an area of central itchy swelling of various size with surrounding erythema on skin and disappearing in 24 hours without any scar. Angioedema was diagnosed clinically based upon typical physical findings; sudden swelling of the deep dermis and mucous membranes developed within minutes to hours following vaccination.

Anaphylaxis
Diagnosis of anaphylaxis was based on patients answers, information obtained by phone calls, and medical records. The Brighton Collaboration case definition criteria were used to confirm the diagnosis of anaphylaxis and define levels of diagnostic certainty for cases reported as anaphylaxis [13]. According to that; for all levels of diagnostic certainty, the conditions of sudden onset, rapid progression of signs and symptoms, and involving multiple (≥2) organ systems were required. Diagnostic certainty was accepted as level 1, if the subjects had at least one major dermatologic and at least one major cardiovascular and/or major respiratory criterion. If the subjects met either at least one major cardiovascular and at least one major respiratory criterion; or at least one major cardiovascular or respiratory criterion and at least one minor criterion from a different system other than cardiovascular or respiratory systems, they were defined as having level 2 diagnostic certainty. Those with at least one minor cardiovascular or respiratory criterion and at least one minor criterion from each of ≥2 different systems/categories were considered to have level 3 diagnostic certainty. Brighton level 1 reflected the highest level of diagnostic certainty while levels 2 and 3 had successively lower levels of diagnostic certainty.

Statistics
Statistical analyzes were made using IBM SPSS Statistics ver. 21.0 (IBM Co., Armonk, NY, USA). Descriptive statistics for the nominal data were presented as counts and percentage, and as for quantitative data either as mean ± standard deviations or medians and minimum-maximum depending on assumptions of normality. The normality of distribution was examined by Kolmogrov-Smirnov or Shapiro-Wilk tests.
RESULTS

A total of 2,488 HCWs were included in the study and were interviewed after the first dose of inactivated COVID-19 vaccine (CoronaVac) injection. After the second dose of vaccination, 1,785 of them could be contacted and the questionnaire could be applied to them. After excluding participants whose survey responses were considered unreliable, we had postvaccination survey data of a total of 4,054 vaccine doses, 2,440 of which being the first dose and 1,614 the second dose. The mean age of 2,440 individuals who received the first dose of vaccine was 37.7 ± 10.1, and 1,504 (61.2%) were female.

An allergic reaction was reported by 15 of participants after the first dose. Four subjects had allergic reactions at the second dose whereas 2 of the cases had allergic reactions at both doses. A total of 21 HCWs (female:male, 17:4; mean age, 40.95 ± 10.09 years) reported an allergic reaction after a total of 23 vaccine injections (Table 1). Thus, the rate of allergic reactions among all vaccine doses was 0.56% in our series. More than half of these cases (n = 11, 52.4%) had allergic comorbidities and one of them had a previous history of anaphylaxis. Allergic comorbidities were asthma (n = 5, 23.8%), drug allergy (n = 4, 19%), food allergy (n = 3, 14.3%), allergic rhinitis (n = 2, 9.5%), venom allergy (n = 2, 9.5%), latex allergy (n = 1, 4.8%), and hereditary angioedema (n = 1, 4.8%). None of the subjects had a previous history of allergic reactions to any vaccine.

Characteristics of allergic reactions

Local reactions

Local injection site reactions was reported in 5 of 21 subjects (23.80%); being 0.12% of all vaccinated subjects (Fig. 1). One of the 5 participants with a local allergic reaction had swelling and redness, 1 had only redness and 3 participants had symptoms of redness and pain. Median onset time was 1 hour (range, 5–6 hours). None of these reactions required admission to a health care center or needed treatment. Three patients complained about pain at the injection site, which not considered as having local injection reactions.

Fig. 1. Types of reported allergic reactions.
Systemic reactions

Skin reactions: Ten out of 21 cases (47.6%) reported an allergic skin reaction. Skin reactions related to the vaccine were present in 2.7% of all administered vaccine doses. Four out of them had generalized pruritus and occurred after the first dose. Two cases with generalized pruritus used a dose of oral antihistamine and the others did not need treatment. Three cases suffered from diffuse pruritic erythema; one of them developed after the first dose, one of them was after the second dose, and one was after both of 2 doses. All of the diffuse pruritic erythema appeared in the 1st hour after vaccination. Only one of them received a dose of antihistamine and 40 mg methylprednisolone, the other 2 subjects did not receive any treatment. Two cases experienced generalized urticaria. In one of them, urticaria occurred 5 hours after the first dose, and spontaneous regression was observed. In the other one, it developed in an hour after both the first and second doses and regressed after a dose of antihistamine treatment (Fig. 1).

In one of the subjects who reported a systemic skin reaction, maculopapular rash developed on both arms on the eighth day after vaccination. This clinical condition was assessed by a dermatology physician and was associated with the vaccine and a urea-containing emulsion and topical steroid therapy was prescribed.

Table 1. Demographics and diseases characteristics of the cases (n = 21)

| Characteristic               | Value                      |
|-----------------------------|----------------------------|
| Female sex                  | 17 (81)                    |
| Age (yr)                    | 40.95 ± 10.09 (27–57)      |
| Profession                  |                            |
| Nurse                       | 4 (19.0)                   |
| Biologist                   | 4 (19.0)                   |
| Physician                   | 3 (14.3)                   |
| Caregiver                   | 3 (14.3)                   |
| Security guard              | 2 (9.5)                    |
| Support service worker      | 2 (9.5)                    |
| Housekeeping staff          | 1 (4.8)                    |
| Secretary                   | 1 (4.8)                    |
| Officer                     | 1 (4.8)                    |
| Education status            |                            |
| University                  | 13 (61.9)                  |
| High school                 | 4 (19.0)                   |
| Primary school              | 4 (19.0)                   |
| Allergic comorbidity        |                            |
| Absent                      | 10 (47.6)                  |
| Asthma                      | 5 (23.8)                   |
| Drug allergy                | 4 (19.0)                   |
| Food allergy                | 3 (14.3)                   |
| Allergic rhinitis           | 2 (9.5)                    |
| Venom allergy               | 2 (9.5)                    |
| Latex allergy               | 1 (4.8)                    |
| Hereditary angioedema       | 1 (4.8)                    |
| History of anaphylaxis      | 1 (4.8)                    |
| Systemic comorbidity        |                            |
| Absent                      | 16 (76.2)                  |
| Hypertension                | 1 (4.8)                    |
| Ankylosing spondylitis      | 1 (4.8)                    |
| Hypothyroidism              | 1 (4.8)                    |
| Malignancy                  | 1 (4.8)                    |
| Diabetes mellitus           | 1 (4.8)                    |

Values are presented as mean±standard deviation (range) or number (%).
**Respiratory reactions:** Difficulty in breathing after the first dose of vaccine was reported in a single case who had a diagnosis of asthma and on GINA-step-3 therapy at the time of vaccination and had no history of asthma exacerbation in the past year. The patient did not apply to any health care center for this reason and did not receive any additional treatment at home. She received the budesonide plus formoterol inhaler 160/4.5 μg twice a day as she routinely used. The patient stated recovery in symptoms spontaneously in an hour.

In a case with a diagnosis of allergic rhinitis, conjunctival itching and redness occurred at the 15th minute after the first dose of vaccine. The complaint regressed spontaneously within hours without any treatment or hospital admission.

**Anaphylaxis**
Four subjects were considered to have anaphylaxis with a rate of 0.09% among all vaccine doses administered that comprised 19% of those reporting an allergic reaction. All 4 subjects were female with a mean age of 40.75 ± 4.85 years old (Table 2). According to The Brighton Collaboration anaphylaxis case definition criteria; 3 of them had level 2 diagnostic certainty and one had level 3. Three anaphylaxis cases occurred within minutes after the first dose of the vaccine, the remaining one was after the 2nd dose. The mean interval from vaccination to symptom onset was 12 ± 6 minutes for all (range, 3–15 minutes). Shortness of breath (75%) and altered consciousness (75%) were the most common findings of anaphylaxis in our cases. Two subjects had allergic comorbidities, one of them had venom and food allergy and the other one had a history of anaphylaxis with infliximab and ferric carboxymaltose. All of the cases reported admission to a health care center and 2 of them received epinephrine, while the other 2 received other supportive treatments in addition to antihistamine and steroid treatments. All cases were discharged within 24 hours after onset of anaphylaxis and none of them required intensive care (Table 2).

**Table 2.** Characteristics of reported cases of anaphylaxis (n = 4) after receipt of inactivated COVID-19 vaccine (CoronaVac)

| Cases | Age (yr) | Sex | Allergic comorbidities | Other comorbidities | Dose of vaccine | Timing of the reactions following vaccination (min) | Signs and symptoms | Treatment | Brighton level |
|-------|----------|-----|------------------------|---------------------|----------------|-----------------------------------------------|---------------------|-----------|----------------|
| 1     | 47       | F   | Venom and food allergy | Breast cancer       | 1st            | 15                                            | Diffuse erythematos pruritic rash, Dyspnea, Tachycardia, Nausea | Epinephrine, Antihistamine and steroid | Level 2   |
| 2     | 36       | F   | Absent                 | Diabetes mellitus   | 1st            | 15                                            | Shortness of breath without wheeze, Decreased level of consciousness | Antihistamine and steroid, Level 3 |
| 3     | 42       | F   | Absent                 | Absent              | 2nd            | 15                                            | Difficulty of swallowing, The sensation of throat closure, Itching on the palate, Coldness in hands, Sweating, Headache, Shortness of breath, Hypertension, Decreased level of consciousness | Antihistamine and steroid, Level 2 |
| 4     | 38       | F   | Drug allergy/anaphylaxis (history of anaphylaxis with infliximab and ferric carboxymaltose) | Ankylosing spondylitis | 1st            | 3                                             | Shortness of breath, Nausea, Hypotension, Loss of consciousness | Epinephrine, antihistamine and steroid, Level 2 |
DISCUSSION

Our study assessed the safety of CoronaVac in the HCWs in real-life conditions in our country and showed that allergic reactions to the CoronaVac vaccine were very rare. Importantly, among 4,054 vaccinations, no fatalities or hospitalization in intensive care unit were existed. Skin reactions such as pruritis was the most common hypersensitivity reactions observed in the group which regressed without any treatment or with a single dose of antihistamine. The vast majority (80%) of participants who reported any allergic reaction were women, and half of them had at least one allergic comorbidity. Most of the allergic reactions occurred after the first dose of the vaccination. Anaphylaxis was reported to be rare and occurred in 4 women, within minutes, and was fortunately quickly dealt with. These results show CoronaVac to be a safe vaccine in terms of allergic reactions in the fight against COVID-19.

The rate of reported allergic reactions due to the vaccine was 0.08% in the phase 3 study of the whole-virion SARS-CoV-2 vaccine in Turkey [10]. Our real world data also suggested this lower rate of allergic reactions with a rate of 0.56%. The most frequent reactions to vaccine belonged to skin (2.7%) and consisted of mostly benign reactions of generalized pruritus and diffuse pruritic erythema. Urticaria, and maculopapular rash were the least reactions. A cross-sectional study from our country revealed similar findings in 780 HCWs who were vaccinated with CoronaVac [14]. In this study 2.3% of the participants had skin-related reactions, mainly skin rash in and urticaria [14]. In a report presenting the safety results from a subgroup of phase 3 study of the CoronaVac vaccine in healthy adults in Chile, the incidence of pruritus in the vaccine group was 3.7% after the first dose and 1.7% after the second dose. Exanthema was reported at the rate of 2.6% after the first dose and 1.3% after the second dose [15]. Although the rates were different in that study, the higher incidence of skin reactions after the first dose than after the second dose was similar to our study. Importantly, in our series, all of the cases with skin reactions had mild symptoms which resolved without treatment or treatment with antihistamines.

The second most common reaction was the local injection site reaction (0.12%) in the current study. In the cross-sectional study from Turkey, injection site pain was present in 41.5%, injection site swelling in 2.6%, and injection site redness was present in 1.4% of cases [14]. Thailand was one of the countries to use the CoronaVac as the first choice vaccine in the risk groups. In a study conducted there, local injection site pain was described in 52.4% of the subjects, and redness and swelling at the injection site were much less frequent [16]. In our study, the presence of pain at the injection site alone was not accepted as allergic local injection site reaction, other symptoms and findings such as redness, itching, and swelling should have been accompanied. Therefore, the rate seems to be lower than previous studies. The institution where the study was conducted was also one of the institutions that contributed to the phase study of CoronaVac. At this point, the observation of the researchers was as follows; in the phase study, single pre-filled syringes were used [10], whereas in the mass vaccination in which our study group was included, the vaccine was applied by drawing the vaccine from single-dose vials into the syringes. We think that that might be the reason for the different results mentioned.

In the current study, allergic reactions were dominated in female subjects. All of the anaphylaxis cases were female. The female predominance of postvaccine allergic reactions and side effects was reported not only after the COVID-19 vaccine but also after other viral vaccines [14, 17, 18]. It was thought that this condition might be explained by the differences in the immune response between the genders and sex-steroids [17, 18].
In our study, anaphylaxis after CoronaVac was very rare and only 4 anaphylaxis cases (3 level 2, one level 3) were reported among 4,054 vaccine doses. Although there is much more data about the safety and tolerability of m-RNA vaccines, less information is available on CoronaVac. No serious adverse events with CoronaVac were reported in phase 1/2 studies [5, 6], and, a systemic allergic reaction was reported in only one patient in the phase 3 study [10]. The data of 3 tertiary hospitals in Thailand were reviewed retrospectively in terms of cases that developed anaphylaxis after CoronaVac vaccine administration and 12 cases of anaphylaxis were presented as a case series [19]. Of the 12 cases, 10 patients had the level 2 diagnostic certainty, one patient had level 1 and the other one had level 3. In a study from Eskişehir, Turkey, the frequency of patients who developed a systemic reaction was reported as 0.12% (n = 4) for the first dose and zero after the second dose [20]. However, the authors stated that only one met the criteria of anaphylaxis [20]. Our results are in accordance with this study in terms of anaphylaxis frequency and diagnostic criteria. However, immediate treatment of anaphylaxis at the time of suspicion particularly in the tertiary hospitals may lead to the absence of some anaphylaxis symptoms, which lead incomplete anaphylaxis signs and symptoms and therefore the low level of anaphylaxis diagnostic certainty.

Unfortunately, a great number of clinicians are unaware of the administration of adrenaline as the first line of action in the treatment of anaphylaxis. Additionally, physicians tend to choose the use of steroids and antihistamines at the first step. A lot of study demonstrated that antihistamines and corticosteroids are administered more frequently than adrenaline for the acute treatment of anaphylaxis in clinical practice. Similarly, in our study, glucocorticoids and antihistamines were administered instead of adrenaline to 2 of 4 anaphylaxis cases [21-25].

It is of interest how CoronaVac causes hypersensitivity reactions. Majority of the vaccine related hypersensitivity reactions were reported to be related to adjuvants or excipients other than vaccine itself [26]. CoronaVac uses a traditional technology that is similar to the inactivated vaccines and has aluminum hydroxide as adjuvant and disodium hydrogen phosphate, monosodium hydrogen phosphate are found as excipients in the vaccine. Aluminum salts contained in the CoronaVac vaccine are included in many drugs, vaccines, immunotherapy solutions, and cosmetics [27]. Indeed, aluminum salts, which have been used as adjuvants for years [28], could be considered as the suspect content for allergic reactions associated with vaccines [8, 26]. Therefore, individuals may have been sensitized to this substance prior to vaccination. In the literature, a case was presented who experienced anaphylaxis with a tetanus vaccination and urticaria with colchicum and suggested that aluminum could be a suspicious allergen for both reactions [29]. Aluminum hydroxide has been reported to cause mast cell degranulation by activation of the complement system [30]. In our series, all 21 cases had no prior exposure to CoronaVac and showed hypersensitivity reactions at the first dose indicating a nonimmunological pathway as underlying mechanism. Previous sensitization to the excipients or adjuvant in the vaccine can explain the reactions in the first dose, direct mast cell degranulation by the activation of the complement system could also be possible. As our cases had no history of any drug allergy other than a single case, we may assume that a direct mast cell activation or previous sensitization to the other vaccine components could be responsible for hypersensitivity reactions.

One of the 4 cases who experienced anaphylaxis had venom and food allergy, and another one had a history of drug allergy. In the previously mentioned case series, 2 of the 12 cases who had anaphylaxis had shellfish allergy and 5 of them had a history of drug allergy [19].
Our study had some strengths and limitations. Although the study was based on results obtained by a self-reported questionnaire, one-to-one telephone interviews with those who stated an allergic reaction after vaccination and evaluation of medical records increased the validity of the data. Skin tests and/or graded challenges were not performed for diagnosis, and the level of tryptase was not tested in cases with anaphylaxis. The strength of the study is that it provides data on hypersensitivity vaccine reactions in a large number of cases among very few CoronaVac reaction studies.

In conclusion, our study revealed that allergic reactions to CoronaVac were rare and mostly mild. Although anaphylaxis was rare due to inactivated coronavirus vaccine CoronaVac, this study once again demonstrated the importance of early intervention of anaphylaxis with close follow-up of patients. In the light of these results, we suggest hypersensitivity reactions should not discourage vaccination but appropriate precautions should be available in vaccination areas. Much data is required about underlying mechanisms to clarify the clinical presentation.

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