Research Article (Araştırma Makalesi)

Adverse Events After Receipt of an Inactive Coronavirus Disease-19 Vaccine in Healthcare Professionals: A Cross-Sectional Study

Sağlık Çalışanlarında İnaktif Bir Koronavirüs-19 Aşısının Alınmasından Sonra Advers Olaylar: Kesitsel Bir Çalışma

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Özet

Amaç: Sinovac tarafından üretilen aşı Türkiye'de acil kullanım onayı programına göre ruhsatlandırılmıştır. Doğal olarak bu ürünün güvenlik sorunlarıyla ilgili birçok eksikliği vardır. Amaç aşının potansiyel yan etkilerini araştırmaktı.

Gereç ve Yöntemler: Kendi kendine uygulanan 24 maddelik bir anket aracılığıyla sağlık çalışanları üzerinde retrospektif kesitsel bir çalışma yapıldı.

Bulgular: Yüz otuz üç kişiden 51'i (%38) aşının ilk dozundan sonra yan etkiler yaşadı. En yaygın yan etkiler yorgunluk, baş ağrısı, ishal ve ateşti. Deneklerin yüzde doksan beşi (n=126) ikinci aşı dozunu aldı ve sadece 43 denek (%26) advers olaylar tanımladı. Bu olaylar, ilk dozdan sonra görülenlere benzerdi. Bir kişide, akut hipertansiyon yükselmesi ciddi bir yan etki olarak kabul edildi. Yan etkilerin sıklığına ilişkin bir kadın baskınlığı, yalnızca ilk doz uygulamasından sonra tespit edildi.

Sonuç: Aşıya yanıt olarak önemli miktarda yan etki olmasına rağmen, bunlar ciddi olaylar olarak tanımlanamaz. Bu nedenle, bu aşı 2019 koronavirüs hastalığı tehdidi altındakiler için yeterince güvenli görünüyor.

Anahtar kelimeler: Advers ilaç olayı, COVID-19 aşısı, Güvenlik, SARS-CoV-2 virüsü

Abstract

Objective: The vaccine manufactured by Sinovac has been licensed according to the emergency use authorization program in Turkey. Inherently, this product has many shortcomings regarding safety issues. The aim was to explore the potential adverse reactions of the vaccine.

Materials and Methods: A retrospective cross-sectional study via a 24-item self-administered questionnaire was conducted among healthcare professionals.

Results: Of 133 persons, 51 subjects (38%) experienced adverse events after the first dose of the vaccine. The most common adverse events were fatigue, headache, diarrhea, and fever. Ninety five percent of the subjects (n=126) had the second dose of the vaccine and only 43 subjects (26%) described adverse events. These events were similar to those seen after the first dose. In one person, acute hypertension elevation was considered to be a serious adverse event. A female dominance regarding the frequency of adverse events was, solely, detected after the first dose administration.

Conclusion: Although there is a significant amount of adverse events in response to the vaccine, these cannot be identified as serious events. Therefore, this vaccine seems to be safe enough for those under the threat of the coronavirus disease 2019.

Keywords: Adverse drug event, COVID-19 vaccine, Safety, SARS-CoV-2 virus

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INTRODUCTION

In December 2019, unexplained cases of pneumonia were reported in Wuhan, Hubei province, China (1). The isolated virus was temporarily named 2019 new coronavirus (2019-nCoV) by the World Health Organization (WHO) in January 2020 (2). Then, in February 2020, WHO named the disease caused by this virus as coronavirus disease 2019 (COVID-19) (2). The name of the virus was simultaneously updated as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by the "International Virus Taxonomy Committee" (2). Thereafter, the virus has quickly spread outside of China and unfortunately led to a pandemic. As a result, COVID-19 has become a threat to all human beings. In parallel with this evolvement, many studies have been initiated in order to find novel treatment options for COVID-19. In the meantime, physicians have administered a few drugs to their patients under the name of "off-label use or emergency use authorization". On the other hand, efforts on developing vaccines to stop the pandemic have begun immediately. Some of these studies had yielded affirmative results towards the end of 2020, and regulatory authorities began granting "license and marketing authorization" or "emergency use authorization" to various vaccines.

The first vaccine registered under the name of "emergency use authorization" in Turkey was the inactivated one manufactured by Sinovac and vaccination program was brought into action in healthcare professionals and hospital staff in January 2021. Although phase 1/2 clinical trials regarding safety, tolerability, and immunogenicity of this vaccine in healthy adults was published in February, 2021 (3), phase 3 clinical trial was absent at that point.

Even if phase 3 trials are over, efficacy and safety data should be added to those obtained in pre-marketing clinical studies through post-marketing surveillance studies. In addition, spontaneous reporting of adverse drug reactions, which has a central role within the pharmacovigilance system, may contribute to the safety data of any vaccine. In this regard, the World Health Organization (WHO) defines pharmacovigilance as "the activities and scientific studies carried out to detect, evaluate, understand and prevent adverse events and other potential drug-related problems" (4). However, the performance of Turkish healthcare professionals in terms of spontaneous reporting is very low as shown in a previous study (5). Thus, it would be unrealistic to expect acquiring adequate data regarding adverse events of the vaccine from the hospital staff by this mechanism. Instead, collecting data by directly contacting with the related staff could be more rational to achieve the objectives. Hence, the aim of the present study was (i) to determine the prevalence of adverse events in the first one week post-vaccine period, (ii) to identify the profile of these adverse events, (iii) to determine the proportion of serious events among all adverse events.

MATERIALS AND METHODS

Study Design and Participants

This was an observational, retrospective, cross-sectional and questionnaire-based study conducted in a University Hospital in Turkey. After obtaining preliminary permission from COVID-19 Scientific Research Review Board of Turkish Ministry of Health, the Ethics Committee for Scientific Investigations on Human Subjects approved the study protocol (Approval number: 2021/68) and the study was carried out in accordance with the Declaration of Helsinki (Fortaleza, Brazil, October 2013). The research population consisted of those who were working in the hospital (n=1652) and got vaccinated with CoronaVac (Sinovac Life Sciences, Beijing, China). In order to reach all the hospital staff, electronic contact details were obtained from the administration office of the hospital. Thereafter, the internet link of the questionnaire was sent to the whole staff via e-mail or mobile phone message. Those who filled and sent back the electronic questionnaires were accepted to give consent to participate in the study (n=133).

Questionnaire

The questionnaire was technically prepared by means of the internet resources and roughly consisted of four sections with 24 questions. We collected information regarding demographics (age, gender, profession) in the first section, individual history (habits, chronic disease, drugs, drug allergy, vaccine allergy, food allergy) in the second section, first vaccination (adverse event, serious adverse event) in the third section, and second vaccination (adverse event, serious adverse event) in the fourth section. Fourteen questions were designed as open-ended, five as "yes or no", and five as multiple-choice. Regarding adverse events, solicited adverse events including fatigue, headache, diarrhea, fever >38°C, arthritis, COVID-19 infection, serious local reaction, vomiting, lymphadenopathy/lymphadenitis, neuropathy, loss of taste (ageusia), loss of smell (anosmia), acute allergic reaction, abscess, bell's paralysis, and region paralysis were included in the related question in order to prevent under-estimation of the rate of adverse events. In addition, other adverse events option was added within the same question to help subjects define unsolicited events. Similarly, anaphylaxis, sepsis, and toxic shock syndrome

were the items placed within the serious adverse event question, wherein other events option was also present. These solicited items were selected from the official informative document of the Turkish Ministry of Health prepared for healthcare professionals.

Statistical Analysis

For categorical data, which were presented as numbers and percentage, the Pearson χ^2 test was performed for the comparisons between groups. All statistical analyses were done using SPSS 17.0 statistical package. P values less than 0.05 were accepted to be significant.

RESULTS

Table 1 shows the demographic and other characteristics of the subjects. With regard to the first aim of the present study, 51 subjects declared that they had experienced at least one adverse event after the first dose of the vaccine within the first one week period and the total prevalence of these reactions was 38%. The frequencies of the specific adverse events are presented in **Table 2** in accordance with the second aim of the study. The most common adverse events were fatigue, headache, diarrhea, and fever. In addition, other adverse events including myalgia, dizziness, etc. were also described (see **Table 2**). After the first dose of vaccination, there were no serious adverse events seen within the first week period at all.

Table 1. Demographic and other characteristics of subjects

Age (mean±SEM)	36±0.78
Gender (number (percentage))	
Male	56 (42)
Female	77 (58)
Professions (number (percentage))	
Doctor	96 (72)
Nurse	11 (8.0)
Other healthcare professionals	26 (20)
Habits (number (percentage))	
Cigarette	11 (18)
Alcohol	3 (5)
Coffee	44 (73)
Tea	2 (4)
Total	60 (100)

SEM: Standart error of means

Ninety five percent of the subjects (n=126) had the second dose of the vaccine within the recommended schedule. Two out of the seven subjects who didn't get the second dose didn't give any reasons for their non-adherence to the vaccination. The remainders' reasons were (i) steroid administration, (ii) long-lasting adverse events due to the first dose, (iii) individual decision that there is no need for a second dose, (iv) forgetting the second dose, (v) becoming Polymerase Chain Reaction (PCR) positive after the first dose. Only thirty three subjects (26%) described adverse events after the second dose and the prevalence was statistically significantly less than that of the first dose (X2=4.363, p=0.037). These reactions were similar to those seen after the first dose (given in order of frequency): headache (n=17), fatigue (n=10), diarrhea (n=2), fever (n=1), hypertension (n=1), blurred vision (n=1), flu-like symptoms (n=1), triceps tenosynovitis (n=1), and mild acneiform lesions (n=1). In one person, acute hypertension elevation was considered to be a serious adverse event after the second dose.

To discover the potential effects of gender and presence of chronic disease on adverse events further analysis was performed (**Table 3**). A female dominance regarding the frequency of adverse events was, solely, detected after the first dose administration. On the other hand, presence of any chronic disease didn't show any contribution to the frequency of adverse events (**Table 3**). The chronic diseases stated by 35 participants out of 133 were as follows: hay fever, Hashimoto's Disease, Sjögren syndrome, coronary heart disease, peptic ulcer, hypertension, bronchitis, insulin resistance, asthma, varicose veins, epilepsy, metabolic syndrome, polycystic over syndrome, rheumatoid arthritis, diabetes mellitus, systemic lupus erythematous, hypothyroidism, migraine, anxiety disorder, glaucoma, aortic failure, psoriasis, allergic rhinitis, and rectum cancer. The frequencies regarding drug, vaccine and food allergies were 4.5%, 0.0% and 3%, respectively. However, these potential covariates couldn't be analyzed for their relationship with adverse events due to the very limited number of data.

DISCUSSION

The present study showed that 38% and 26% of the participants described at least one adverse event after the first and second dose of the inactivated vaccine manufactured by Sinovac, respectively. Considering the non-serious profile of the adverse events identified, the vaccine seems to be safe enough to accept the product as a feasible weapon against the pandemic.

Table 2. Frequencies of adverse events after the first dose of the vaccine*

Adverse event	First Dose (n=133)	Second Dose (n=126)
	n (%)	n (%)
Fatigue	18 (14)	10 (8)
Headache	18 (14)	17 (13)
Diarrhea	4 (3)	2 (1.6)
Fever >38°C	2 (1.5)	1 (0.8)
Arthritis	1 (0.75)	0 (0)
COVID-19 infection	1 (0.75)	0 (0)
Serious local reaction	0 (0)	0 (0)
Vomiting	0 (0)	0 (0)
Lymphadenopathy/Lymphadenitis	0 (0)	0 (0)
Neuropathy	0 (0)	0 (0)
Ageusia	0 (0)	0 (0)
Anosmia	0 (0)	0 (0)
Acute allergic reaction	0 (0)	0 (0)
Abscess	0 (0)	0 (0)
Bell's paralysis	0 (0)	0 (0)
Region paralysis	0 (0)	0 (0)
Other adverse events**	0 (0)	0 (0)
Myalgia	3 (2.2)	0 (0)
Dizziness	2 (1.5)	0 (0)
Weakness	2 (1.5)	0 (0)
Ventricular extrasystole	1 (0.75)	0 (0)
Angina pectoris like pain	1 (0.75)	0 (0)
Arm pain and numbness	1 (0.75)	0 (0)
Hypertension	1 (0.75)	1 (0.8)
Triceps tenosynovitis	1 (0.75)	1 (0.8)
Arthralgia	1 (0.75)	0 (0)
Emesis	1 (0.75)	0 (0)
Blurred vision	0 (0)	1 (0.8)
Flu-like symptoms	0 (0)	1 (0.8)
Mild acneiform lesions	0 (0)	1 (0.8)
TOTAL	51 (38)	33 (26)

*These adverse events were identified in the official leaflet of Turkish Ministry of Health.
**Not identified in the official leaflet of Turkish Ministry of Health.

In the phase 1 trial of the vaccine CoronaVac, the overall incidences of adverse events were 29%, 38%, and 8% in the 3 μg, 6 μg, and placebo groups in the days 0 and 14 vaccination cohort whereas those of 0 and 28 vaccination cohort were 13%, 17%, and 13%, with no statistical significant difference seen among the three groups for both vaccination schedules (3). In the phase 2 trial of the same study, the overall incidences of adverse events of the 3 μg, 6 μg, and placebo groups were 33%, 35%, and 22% for the days 0 and 14, respectively (3). These values regarding the days 0 and 28 vaccination cohort were reported to be 19% in the 3 μg group, 19% in the 6 μg group, and 18% in placebo group, with no significant difference between the three groups for both schedules (3). Although the authors of the phase 1/2 study stated that the calculated p values presented in that study couldn't support any powerful statistical conclusions and should be interpreted with caution

Table 3. Further analyses of adverse events in relation with distinct parameters

After the first dose of vaccine			
Man	**Woman**	X^2	**p**
16 out of 56 (29%)	35 out of 77 (45%)	3.909	0.048
Chronic disease (+)	**Chronic disease (-)**	X^2	**p**
16 out of 35 (46%)	35 out of 98 (36%)	1.091	0.296
After the Second Dose of Vaccine			
Man	**Woman**	X^2	**p**
10 out of 55 (18%)	23 out of 71 (32%)	3.238	0.072
Chronic disease (+)	**Chronic disease (-)**	X^2	**p**
11 out of 34 (32%)	22 out of 92 (24%)	0.19	0.890

(3), non-significance from the placebo group may be explained by the fact that the placebo just contains the aluminium hydroxide diluent solution with no virus and this ingredient may be the major reason for the adverse events outlined. However, evidence on the safety profile of aluminium salts is not sufficient, in spite of their extensive and long-standing use as adjuvants (6). Nevertheless, no association with severe adverse events in young children or with induration in older children was found and any association with chronic outcomes seems to be unlikely (6). In addition, no evidence that aluminium salts cause any serious or long-lasting adverse events has been demonstrated (6).

Although the time period (28 days) selected to collect adverse events in phase 1/2 trial was quite longer than our one week period, which could lead to detect more adverse events, the frequency obtained in our study, i.e., 32% (calculated as the mean of the frequencies of the first and second doses), seem to be slightly higher than that obtained in the study mentioned above (25%: calculated as the mean of all sub-groups with any dose of vaccination). Similarly, the incidence of total adverse events in phase 3 trial conducted in Turkey was 18.9% (7). The higher frequency seen in our study in comparison with those studies could be explained by several ways. First, as we performed an observational, cross-sectional and questionnaire-based study on the subjects, the data were collected retrospectively and mainly depended on the memories of the participants. Such dependence may be associated with re-call bias, which may in turn lead to over-reporting of adverse events due to the tendency of people to more easily remember afflicting events that they have experienced. Second, very low participation of the hospital staff to the study (133 out of 1652) makes it probable that those who did not participate may have experienced much less and annoying adverse events. As a result, such a participation bias may cause an over-estimation of the frequency of the adverse events. In contrast, the investigators of phase 1/2 and phase 3 studies performed an interventional study wherein the data were acquired prospectively and causality analysis was performed by the researchers (3,7). Thus, the lack of re-call bias and particularly of participation bias of these studies seems to be an advantage for the accurate detection of adverse events while artificial setting of interventional studies partially prevents the generalization of the data to the daily clinical routine facts. In this regard, the huge amount of exclusion criteria in the study protocol clenches the artificial atmosphere of the trial that lowers the credit of the safety data. Therefore, even after phase 3 trials post-marketing surveillance studies such as phase 4 and observational studies are still essential means to understand the real safety and efficacy profile of a given medicinal product. Without any exclusion criteria, all of the participants of the present study had chronic diseases, drug or food allergies etc. which would interfere with adverse events of the vaccine. Twenty six percent of them stated that they had at least one chronic disease before the start of the vaccination period. However, there was no statistical difference between those with and without a chronic disease regarding the frequencies of adverse events, weakening the hypothesis that those with chronic disease would be more vulnerable to adverse events. On the other hand, because of the small size of the data regarding each disease item, we couldn't analyze the potential effect of a given condition on the adverse events, leaving this mission to large-scale studies that might be conducted in the future.

The frequency of the adverse events after the second dose, i.e., 26%, was statistically significantly less than that of the first dose (38%) in the present study. In this regard, the frequencies of fatigue, diarrhea, and fever

were attenuated whereas arthritis, myalgia, dizziness, weakness, ventricular extrasystole, angina pectoris like pain, arm pain and numbness, arthralgia, and emesis totally disappeared. On the other hand, some subjects described new adverse events such as blurred vision, flu-like symptoms, and mild acneiform lesions which were lacking after the first dose. In one person, acute hypertension elevation was considered to be a serious adverse event after the second dose. However, we couldn't obtain the detailed information to understand if it was a real serious adverse event. In fact, the severity of adverse events is graded according to the Common Terminology Criteria for Adverse Events (CTCA) from grade 1 to 5 (8). Briefly, severe or medically significant but not immediately life-threatening adverse events refer to as grade 3 whereas those accompanied with life-threatening consequences and/or indication for urgent intervention to as grade 4 (8). The worst is obviously grade 5 where the patient is lost (8). From a pharmacovigilance standpoint, serious adverse event is defined as "an adverse event or reaction that results in death, requires hospitalization or extension of hospital stay, results in persistent or significant disability or incapacity or is life-threatening", which greatly matches with grade 3-5 outlined above (8, 9). As for hypertension, systolic blood pressure equal or above 160 mm Hg or diastolic blood pressure equal or above 100 mm Hg indicate grade 3 adverse event while grade 4 accounts for life-threatening consequences and/or urgent intervention (8).

After the first step of the vaccination schedule, the most common adverse events identified by 51 subjects were fatigue, headache, diarrhea, and fever. These were already identified in the official informative document of the Turkish Ministry of Health prepared for healthcare professionals and therefore could be accepted as anticipated adverse events. Although the most common adverse event in phase 1/2 trial was injection site pain, similar reactions including fatigue, diarrhea, fever etc. were identified as well (3). On the other hand, other adverse events including dizziness, weakness, ventricular extrasystole, angina pectoris like pain, arm pain and numbness, hypertension, and triceps tenosynovitis weren't defined in the document of the Turkish Ministry of Health, phase 1/2 trial, and phase 3 trial (3,7). In this regard, these could be accepted as early signals that would evolve to unanticipated adverse events. Fortunately, there were no serious adverse events seen within the first week period, an almost similar profile with that of phase1/2 trial (Only one case of acute hypersensitivity that was successfully treated was detected in the latter study.) (3). Similar to our results (14% and 8% after the first and second doses of CoronoVac), the most common systemic adverse event seen in the vaccine group was fatigue (8.2%) in the phase 3 Turkish trial of the vaccine and this was, in contrast to the phase 1/2 trial mentioned above, statistically significantly different from that observed in the placebo group (7%) (7).

Almost all subjects preferred to get the second dose of the vaccine which may show a positive attitude of the subjects towards the necessity, efficacy and safety of the product. In contrast, only seven of the participants rejected to utilize the second dose. Among the reasons expressed, steroid administration and long-lasting adverse events due to the first dose seem to be reasonable. The idea that steroid administration could halt the immunization achieved by the vaccine might be the reason for that individual to stop getting the second dose. Accordingly, immunosuppressive therapy (including steroids) within the past 6 months was one of the excluding criteria of participants enrolled in the phase 3 clinical trial of an inactivated whole-virion SARS-CoV-2 vaccine (CoronaVac) (7). The official package insert of the Turkish Ministry of Health regarding CoronoVac has stated that corticosteroids could prohibit the immune response to the vaccine and that postponing the administration of vaccine until the end of immunosuppressive therapy would be feasible. As for the latter reason, it is quite fair to one to abstain from the administration of a second dose and we can assume that the subject, as a nurse, may have done a rational judgment before deciding not to get the second dose. Becoming PCR positive after the first dose was another understandable reason for the avoidance of the second dose.

Since the adverse drug events experience in women has been found to be greater than men (10), we wondered if there was a difference between genders regarding the frequencies of adverse events. Analyzing the data after the first dose, a female dominance over males was determined which disappeared after the second dose. In fact, the difference between the genders regarding adverse drug reactions was attributed to the distinct pharmacokinetic profile of women when compared to that of men (10). However, the impact of the components of the pharmacokinetics on drugs cannot be transcribed to inactive vaccines as they are not subject to the standard procedures of pharmacokinetics. The role of biological mechanisms responsible for the sex differences regarding the responses to drugs and vaccines need to be investigated particularly in clinical research studies. The greater adverse events seen in the present study may simply be related to a higher propensity of the female subjects to report adverse events as it has been shown that women report more adverse drug reactions than men (11).

On the contrary, subjects with any chronic disease didn't show an increased frequency in comparison with those without any chronic disease after the both doses. In general, elderly people with chronic diseases are accepted to be more vulnerable to the adverse effects of medicinal products (12). This vulnerability especially results from multi-morbidity which can be defined as the co-occurrence of two or more medical or psychiatric condition in a given patient (12). Disease-related risk factors regarding adverse drug reaction in the elderly were as follows in a previous study: cardiovascular disease, diabetes mellitus, cancer, depression, impaired renal function, dementia, hyperlipidemia, elevated white blood cell count, and liver disease (13). Some of them (cardiovascular disease, diabetes mellitus, cancer, and hyperlipidemia) were present to some extent in our study population but it is not possible to figure out their impact on the adverse events occurred in response to vaccination because of the small size of the data regarding each disease item. As COVID-19 has been considered to be a systematic disease with plenty of unknown underlying pathophysiological mechanisms, special populations with distinct co-morbidities that would be more susceptible to the adverse reactions of different types of vaccines should be identified in delicately designed observational or interventional studies.

In conclusion, the inactivated vaccine administered to Turkish healthcare professionals seems to be safe enough in real-life conditions, advocating its favorable position in the battle against the pandemic. The very limited participation ratio of the hospital staff to the study shows that Turkish healthcare professionals of this hospital lack the vigilance capacity to comprehend the importance of the issue.

Ethics Committee Approval: The study was conducted in accordance with the Helsinki Declaration and the study protocol was approved by the local ethics committee (Approval Date:2021/68).

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