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Local and systemic side effects of the coronanovac vaccine

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Abstract

Objective: Vaccines are biological products that provide protection against diseases by stimulating the immune system. Our aim in this study is to examine local and systemic side effects after inactivated coronavirus vaccination. In addition, when these side effects started, how long they lasted and their effect on daily life were evaluated.

Methods: 224 healthcare workers who met the study criteria and were vaccinated against coronavirus in Adana City Training and Research Hospital were included in the study. A questionnaire prepared by us was filled in for these patients in which we inquired about the local and systemic side effects of the vaccine, the onset of side effects, their duration, whether they affect daily life, the need for drug use, and some demographic data. The survey results were evaluated with the SPSS statistical program. Local and systemic side effects were evaluated according to age, gender, allergy status, onset time, duration of effect, effect on daily life, and use of medical treatment.

Results: At least one side effect was observed in 73.2% of 224 patients, while no side effects were observed in 26.8%. Being under the age of 35, being female, and being allergic increased the side effects (p:0.0027, p:0.001, p.0.031). In the logistic regression analysis, it was seen that being a woman was more effective (p.0.002). The most common local side effect was at the injection site pain was 76.2%, the most common systemic side effect was weakness 40.9%. 85.6% of local side effects and 70.4% of systemic side effects were seen in the first 24 hours. 71.3% of local side effects and 70.1% of systemic side effects lasted less than 24 hours.

Conclusion: Inactivated covid-19 vaccine causes side effects in the majority of patients.In the otorhinolaryngology outpatient clinic, attention should be paid to the side effects of the coronovac vaccine in female patients under the age of 35 who have allergies.

Keywords: Vaccine, Side Effect, Coronovac, Allergy, Pain

INTRODUCTION

A number of unexplained cases of pneumonia were reported in December 2019 in Wuhan, China. The Chinese Centers for Disease Control and Prevention (CDC) identified a new type of B-coronavirus in the sample obtained from a throat swab on January 7th, 2020 (1). This virus has been named severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) by the World Health Organization (WHO) (2). SARS-COV-2 spread to countries such as Germany, Italy, Spain, and America in February 2020, and affected the entire world over time and the WHO announced SARS-CoV2 as a pandemic on March 11th, 2020, when Turkey announced that it had its first official case of coronavirus (3,4).

Coronaviruses are positive-polar, enveloped, and single-stranded RNA viruses with rod-like protrusions on their surface. According to their genomic structures, coronaviruses are divided into alpha (α), beta (β), gamma (ɣ) and delta (δ) subgroups. SARS-CoV-1, Middle East respiratory syndrome coronavirus (MERS-CoV) and SARS-CoV-2 viruses are in the coronaviruses subgroup (I). It has four structural proteins: spike (S), envelope (E), membrane (M), and nucleocapsid (N). These proteins are very important in vaccine and drug studies in the treatment of COVID-19 (5).

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Vaccines are biologic products that protect against disease by stimulating the immune system. In vaccination, it is desired that the person's body creates immunity by encountering the agent, but not contracting the disease. The effect of the vaccine occurs when the immune system responds to the weakened or killed microorganism or parts thereof. Thus, when the person encounters the disease agent, the immune system will develop a rapid response by remembering the factor and the disease will pass before the disease occurs or with a mild picture. Vaccines are divided into two groups as live active and inactive vaccines (6). Local side effects such as pain, redness, burning, itching, rash, ulceration, abscess can be seen after vaccination, as well as systemic side effects such as fever, anaphylactic reaction, lymphadenopathy, convulsion, encephalopathy, weakness, nausea, vertigo, vomiting and thrombocytopenia. In Turkey in January 2021, inactivated Covid-19 vaccine (CoronaVac) vaccination started. First of all, healthcare workers were vaccinated (7).

Our aim in this study is to examine local and systemic side effects after inactivated coronavirus vaccination. In addition, when these side effects started, how long they lasted and their effect on daily life were evaluated.

METHODS

This study was conducted between February 1, 2021 and April 1, 2021. The study included 450 healthcare workers (doctor, nurse, assistant health personnel, technician) who were vaccinated against coronavirus at Adana City Training and Research Hospital. 125 patients who did not complete the questionnaire and 73 patients who wanted to withdraw from the study were excluded from the study. 28 patients under the age of 18 and over the age of 85 were excluded.

The questionnaire form prepared by us and containing the following questions was distributed to the patients. The patients filled out the questionnaire in the company of one of the researchers. Those who were illiterate and did not fully understand the questions in the questionnaire received support from the researchers. Volunteers completed the questionnaire containing the following information 1 week after the vaccination in the examination room.

1. Age, sex, chronic disease history, history of allergies, pregnancy status, breastfeeding, COVID-19 disease, whether antibodies were checked for COVID-19 and PCR positivity.

2. Local side effects: pain, redness, burning, stiffness, swelling, itching, bruising, rash.

3. Systemic side effects: weakness, headache, myalgia, fever, chills-chills, metallic taste in the mouth, nausea, dizziness, runny nose, numbness in legs and arms, sore throat, diarrhea, palpitations, cough, sweating, nasal congestion, chest pain, shortness of breath, blurred vision, vomiting, smell disorder, and anaphylactic shock.

4. Whether local and systemic side effects started in the first 24 hours.

5. Whether local and systemic side effects lasted longer or shorter than 24 hours.

6. Whether side effects affected daily life, if so, to what extent (such as eating, going to work, studying, doing housework, sleep patterns).

7. Whether the patient presented to the hospital due to side effects, whether they received medical treatment, the symptoms that caused a hospital visit, and symptoms requiring medical treatment.

Informed voluntary consent of all patients participating in the study was obtained.

Statistical analysis

All data were evaluated using the SPSS: 2.2 statistical program. Student's t-test, the Chi-square test, and Fisher's exact test were used for statistical analysis. Student's t test was used to evaluate whether the difference between the 2 dependent and independent groups was significant. Chi-square test was used to test the relationship between variables. In categorical data analysis, as an alternative to chi-square for small samples ($n<20$). Fisher Exact test was used to classify categorical data and examine the relationship between two types of classification.

RESULTS

A total of 224 patients were included in the study. One hundred sixty-four (73.2%) of 224 patients had at least one side effect, and 60 (26.8%) had no side effects (Figure 1).

The average age of the patients was 36.6 years.The rate of side effects was higher in those aged under 35 years compared with those aged over 35 years ($p = 0.027$). The rate of side effects was higher in women than in men ($p = 0.001$). Side effects were more common in those with allergies ($p = 0.031$) (Table 1).

Table 1: Demographic data of the patients

		Side effect (-) (n:60)		Side effect (+) (n:164)		Total (n:224)		p
Age (mean±sd) (min-max)		38.70±12.62 (23-77)		35.94±12.27 (22-84)		36.68±12.40 (22-84)		0.140[a]
		n	%	n	%	n	%	
Age n (%)	<35	20	(33.3)	82	(50)	102	(45.5)	0.027[b]
	≥35	40	(66.7)	82	(50)	122	(54.5)	
Gender n (%)	Male	25	(41.7)	33	(20.1)	58	(25.9)	0.001[b]
	Female	35	(58.3)	131	(79.9)	166	(74.1)	
Allergy n (%)	Yes	7	(11.7)	41	(25)	48	(21.4)	0.031[b]
	No	53	(88.3)	123	(75)	176	(78.6)	
Chronic disease n (%)	Yes	11	(18.3)	30	(18.3)	41	(18.3)	1.00[b]
	No	49	(81.7)	134	(81.7)	183	(81.7)	
Did you have Covid19 disease before the Covid19 vaccine? n (%)	Yes	5	(8.3)	24	(14.6)	29	(12.9)	0.214[b]
	No	55	(91.7)	140	(85.4)	195	(87.1)	
Was it PCR (+) when we had Covid 19 disease? (n:29) n (%)	Yes	5	(100)	19	(79.2)	24	(82.8)	0.358[c]
	No	0	(0)	5	(20.8)	5	(17.2)	
Have you checked antibodies for Covid19 before Covid19 vaccine? n (%)	Yes	8	(13.3)	19	(11.6)	27	(12.1)	0.722[b]
	No	52	(86.7)	145	(88.4)	197	(87.9)	
Are you breastfeeding? n (%)	Yes	1	(1.7)	2	(1.2)	3	(1.3)	1.00[c]
	No	59	(98.3)	162	(98.8)	221	(98.7)	

a: Student's t test, b: Chi-Square test, c: Fisher Exact test

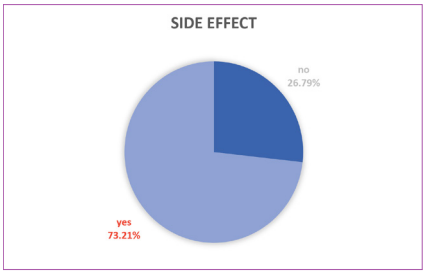

Figure 1. Incidence of side effects in patients

When age, gender and presence of allergy were evaluated together and multiple logistic regression analysis was performed, it was found that being female was 2.769 times more risky for those with side effect (odds ratio. 2.769) (Table 2).

The most common local side effect was pain at the injection site (76.2%). Other local side effects and their frequency are shown in Table 3. %64 of pain side effect started in the first 24 hours and %48.8 lasted less than 24 hours. Most of the local side effects started in the first 24 hours and lasted less than 24 hours (Table 3).

Table 2: Effect of age. gender and allergy on side effects

	Odds Ratio	95% C.I. for Odds Ratio		
		Lower	Upper	p
Age (<35)	1.891	0.999	3.581	0.050
Gender (female)	2.769	1.442	5.317	0.002
Allergy (yes)	2.324	0.955	5.657	0.063
Constant	0.890			0.704

p: Multiple Logistic Regression

Table 3: Frequency, onset time and duration of local side effects

			Time for side effects to start				Duration of Side Effects			
	Total (n:164)		First 24 hours		After 24 hours		Less than 24 hours		More than 24 hours	
	n	%	n	%	n	%	n	%	n	%
Pain	125	76.2	105	64.0	20	12.2	80	48.8	45	27.4
Redness	14	8.5	13	7.9	1	0.6	13	7.9	1	0.6
Burning	11	6.7	11	6.7	0	0.0	11	6.7	0	0.0
Stiffness	10	6.1	9	5.5	1	0.6	8	4.9	2	1.2
Swelling	6	3.7	5	3.0	1	0.6	6	3.7	0	0.0
İtching	6	3.7	4	2.4	2	1.2	4	2.4	2	1.2
Bruise	1	0.6	1	0.6	0	0.0	1	0.6	0	0.0
Rash	1	0.6	1	0.6	0	0.0	1	0.6	0	0.0

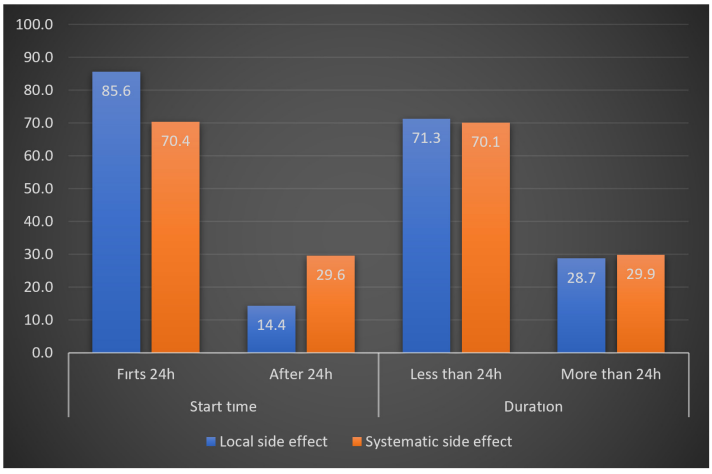

Figure 2. Onset time and duration of local and systemic side effects

The most common systemic side effect was weakness with a rate of 67 (40.9%). 55 weakness started in the first 24 hours and 38 lasted less than 24 hours. Most of the systemic side effects were seen in the first 24 hours and the symptom duration was less than 24 hours. The onset time and duration of other systemic side effects are shown in Table 4.

Anaphylactic reaction and lymphadenopathy were questioned but not observed in any patients. Other symptoms were redness in the eyes low back pain and change in the menstrual cycle in one person.

Table 4: Frequency, onset time and duration of systemic side effects

			Time for side effects to start				Duration of Side Effects			
	Total (n:164)		First 24 hours		After 24 hours		Less than 24 hours		More than 24 hours	
	n	%	n	%	n	%	n	%	n	%
Weakness	67	40.9	55	33.5	12	7.3	38	23.2	29	17.7
Headache	50	30.5	35	21.3	15	9.1	41	25.0	9	5.5
Myalgia	47	28.7	31	18.9	16	9.8	21	12.8	26	15.9
Fever	26	15.9	23	14.0	3	1.8	22	13.4	4	2.4
Chills and chills	16	9.8	12	7.3	4	2.4	12	7.3	4	2.4
Metallic taste in the mouth	14	8.5	12	7.3	2	1.2	9	5.5	5	3.0
Nausea	12	7.3	11	6.7	1	0.6	12	7.3	0	0.0
Vertigo	12	7.3	8	4.9	4	2.4	12	7.3	0	0.0
Runny nose	11	6.7	6	3.7	5	3.0	9	5.5	2	1.2
Numbness in the legs and arms	10	6.1	7	4.3	3	1.8	10	6.1	0	0.0
Sore throat	10	6.1	5	3.0	5	3.0	7	4.3	3	1.8
Diarrhea	9	5.5	5	3.0	4	2.4	5	3.0	4	2.4
Palpitation	9	5.5	5	3.0	4	2.4	8	4.9	1	0.6
Cough	9	5.5	5	3.0	4	2.4	6	3.7	3	1.8
Sweating	9	5.5	3	1.8	6	3.7	6	3.7	3	1.8
Nasal congestion	8	4.9	4	2.4	4	2.4	5	3.0	3	1.8
Chest pain	4	2.4	1	0.6	3	1.8	2	1.2	2	1.2
Shortness of breath	3	1.8	2	1.2	1	0.6	3	1.8	0	0.0
Blurred vision	3	1.8	2	1.2	1	0.6	3	1.8	0	0.0
Vomiting	1	0.6	1	0.6	0	0.0	1	0.6	0	0.0
Smell disorder	1	0.6	0	0.0	1	0.6	0	0.0	1	0.6

The majority (85.6%) of the local side effects and 70.4% of systemic side effects were seen in the first 24 hours. Most (71.3%) of local side effects and 70.1% of systemic side effects lasted 24 hours or less (Figure 2).

Pain was the most common local side effect affecting daily life ($p<0.001$).In systemic side effects, it was observed that weakness, headache, muscle pain, fever, chills-chills, metallic taste in the mouth, nausea, dizziness, runny nose, sore throat, diarrhea, palpitations, cough, nasal congestion, and chest pain affected daily life ($p<0.05$). The most affecting systemic side effect on daily life was weakness ($p<0.001$) (Table 5).

Two (1.2%) of the 164 patients who had side effects went to a hospital, and 31 (18.9%) received medical treatment. The daily life of 42.7% of the patients was not affected by these side effects (Table 6). The daily life of the patients was affected mildly at a rate of 38.4%, moderately at 16.65%, and severely at 2.4% according to the volunteers' answers (Figure 3).

Patients with pain, shortness of breath, numbness in the arms and legs, and blurred vision were admitted to the hospital.

The patients mostly received medical treatment due to pain at the injection site, headache, and weakness (Figure 4)

DISCUSSION

In our study, at least one side effect was observed in 164 (73.2%) of 224 patients. The rate of side effects was found to be significantly higher in women, those with a history of allergies, and those aged under 35 years. The most common local side effect was pain, and the most common systemic side effect was weakness. The majority (85.6%) of local side effects and 70.4% of the systemic side effects were seen in the first 24 hours. Most (71.3%) of local side effects and 70.1% of the systemic side effects lasted less than 24 hours. Of the patients with side effects, 1.2% went to the hospital, 18.9% received medical treatment due to these side effects, and the daily life of 57.3% was affected. The symptom that most affected daily life was weakness. The symptoms that caused patients to attend the hospital were usually pain, shortness of breath, numbness in the arms and legs, and blurred vision.

Against the SARS-COV-2 virus, DNA- and RNA-based formulas, viral episodes containing recombinant subunits, adenovirus-based vectors, and attenuated inactivated virus vaccines have been studied (8). Weakened inactivated virus vaccines are a traditional method used in safe and effective vaccine studies as in polio and influenza virus vaccines (9,10). A 2 µg/dose of BBIBP (Inactive SARS-Cov2 Vaccine) was used to protect against SARS-CoV-2 in mice, rats, guinea pigs, rabbits, and non-human primates. Vaccine studies using CorV (inactivated) showed that high-efficacy protection was provided and it was concluded that inactivated virus vaccines should be evaluated in further clinical studies (11).

Shengli et al. evaluated the safety and immunogenicity of the inactivated SARS-CoV-2 vaccine candidate BBIBP-CorV in humans. A randomized, double-blind, placebo-controlled, phase 1/2 trial was conducted at the CDC in Shangqiu City Liangyuan District in Henan Province, China. At least one

Table 5: The effect level of side effects on daily life

	Effect on Daily life											
	No (n:70)		Yes (n:94)			Mild (n:63)		Moderate (n:27)		Severe (n:4)		
	n	%	n	%	p	n	%	n	%	n	%	p
Pain	58	82.9	67	71.3	<0.001	46	73.0	17	63.0	4	100	0.115
redness	6	8.6	8	8.5	0.235	7	11.1	1	3.7	0	0.0	0.633
Burning	4	5.7	7	7.4	0.209*	4	6.3	3	11.1	0	0.0	0.742
Stiffness	6	8.6	4	4.3	1.000*	3	4.8	1	3.7	0	0.0	0.688
Swelling	3	4.3	3	3.2	0.697*	2	3.2	1	3.7	0	0.0	0.965
İtching	2	2.9	4	4.3	0.241*	2	3.2	2	7.4	0	0.0	0.706
Bruise	0	0.0	1	1.1	0.420*	1	1.6	0	0.0	0	0.0	0.656
Rash	0	0.0	1	1.1	0.420*	1	1.6	0	0.0	0	0.0	0.656
Weakness	9	12.9	58	61.7	<0.001	37	58.7[a]	19	70.4[a]	2	50[a]	<0.001
Headache	4	5.7	46	48.9	<0.001*	27	42.9[a]	17	63[a]	2	50[a]	<0.001
Abdominal pain	8	11.4	39	41.5	<0.001	25	39.7[a]	12	44.4[a]	2	50[a]	<0.001
Fever	4	5.7	22	23.4	<0.001*	12	19.0[a]	8	29.6[a]	2	50[a]	0.004
Chills and chills	0	0.0	16	17.0	<0.001*	8	12.7[a]	7	25.9[a]	1	25[a]	0.001
Metallic taste in the mouth	2	2.9	12	12.8	0.001*	9	14.3	3	11.1	0	0.0	0.104
Nausea	2	2.9	10	10.6	0.005*	7	11.1	3	11.1	0	0.0	0.233
Vertigo	3	4.3	9	9.6	0.031*	6	9.5	2	7.4	1	25	0.355
Runny nose	1	1.4	10	10.6	0.001*	6	9.5	3	11.1	1	25	0.075
Numbness in the legs and arms	3	4.3	7	7.4	0.099*	6	9.5	1	3.7	0	0.0	0.527
Sore throat	1	1.4	9	9.6	0.002*	4	6.3	4	14.8[a]	1	25[a]	0.033
Diarrhea	0	0.0	9	9.6	<0.001*	2	3.2	6	22.2[ab]	1	25[ab]	<0.001
Palpitation	1	1.4	8	8.5	0.005*	4	6.3	3	11.1	1	25	0.075
Cough	1	1.4	8	8.5	0.005*	3	4.8	5	18.5[ab]	0	0.0	0.010
Sweating	3	4.3	6	6.4	0.171*	1	1.6	5	18.5[ab]	0	0.0	0.011
Nasal congestion	0	0.0	8	8.5	0.001*	3	4.8	3	11.1[a]	2	50[ab]	<0.001
Chest pain	0	0.0	4	4.3	0.030*	0	0.0	2	7.4[ab]	2	50[abc]	<0.001
Shortness of breath	0	0.0	3	3.2	0.073*	3	4.8	0	0.0	0	0.0	0.179
Blurred vision	1	1.4	2	2.1	0.574*	1	1.6	0	0.0	1	25[abc]	0.006
Vomiting	0	0.0	1	1.1	0.420*	1	1.6	0	0.0	0	0.0	0.656
Smell disorder	0	0.0	1	1.1	0.420*	1	1.6	0	0.0	0	0.0	0.656

p: Chi-Square test *Fisher Exact test; represents the highest rate (a: none, b: mild, c: moderate) p<0.05

side-reaction was reported in the first 7 days of vaccination in 29% of vaccine recipients. The most common side effects were fever and pain at the injection site. All side effects were mild or moderate. No serious side-events were reported within 28 days of vaccination (12). In our study, we saw at least one side effect at a higher rate (73.2%) than Shenglis' study. The difference between the studies in terms of the frequency of side effects may be because the patients had different genetic structures in different countries, different age groups, and the humoral-cellular immune response varies between races. Similar to Shengli's study, the most common local side effect in our study was pain. We evaluated the short-term side effect results after vaccination. Different from Shengli's study, we questioned the side effects affecting daily life. It was observed that symptoms such as fever, muscle pain, diarrhea, nasal congestion, sore throat, chills-chills, chest pain, cough, headache, blurred vision, and weakness affected daily life significantly.

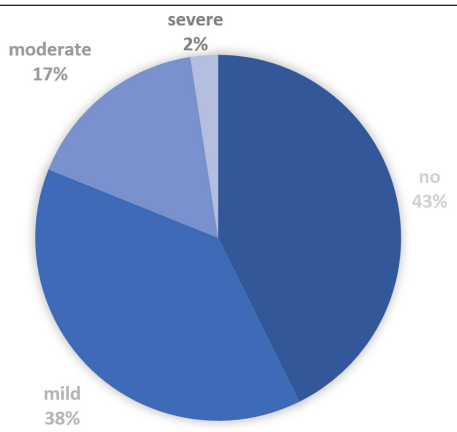

Figure 3. Affecting the daily life of the patients

Table 6: Patients with side effects. going to the hospital, receiving medical treatment and affecting their daily life

		n	%
Going to the hospital	yes	2	1.2
	no	162	98.8
Medical treatment	yes	31	18.9
	no	133	81.1
Effecting daily life	no	70	42.7
	mild	63	38.4
	moderate	27	16.5
	severe	4	2.4

As of December 23rd, 2020, the first dose of the Pfizer-BioNTech COVID-19 vaccine was administered, as reported in the United States, and 4393 (0.2%) side-events were reported after receiving the Pfizer vaccine. Ricardo et al. reported that 25 of 175 people who developed allergic reactions experienced anaphylaxis. In anaphylaxis, symptoms result in rapid onset, usually within minutes, and typically severe general itching, urticaria, angioedema, hypotension or difficulty breathing were seen. Ninety percent of anaphylactic reactions occurred in women (13). In addition to screening contraindications and precautions before administering COVID-19 vaccines, vaccination areas should have the necessary supplies to manage anaphylaxis, implement post-vaccination observation periods, and treat people experiencing signs and symptoms of anaphylaxis promptly with an intramuscular injection of adrenaline. In our hospital, a separate building was designated as a vaccination polyclinic and anesthesiologists and technicians were assigned in the vaccination areas with emergency intervention equipment due to the risk of developing anaphylactic reactions. In our study, we did not see any anaphylactic reactions in any of our patients. However, we found that the side effects were more common in women, as in Ricardo's study. Female sex

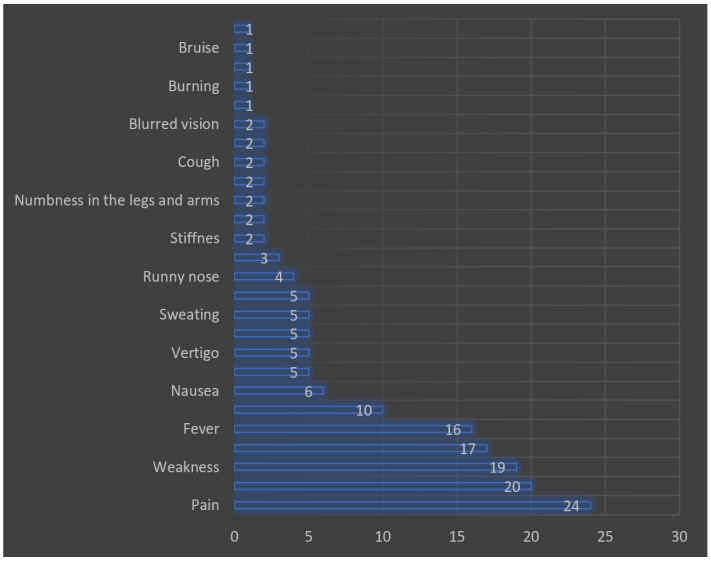

Figure 4. Side effect profiles of patients using medical treatment

significantly increases the incidence of side effects. Few studies have evaluated the effect of sex steroids on immune responses to vaccines. Studies are showing that estrogen mediates more antibody production in women (14). We think that sex hormones effecting the immune response may be important here.

Pfizer/BioNTech and Moderna vaccines are United States Food and Drug Administration (FDA)-approved vaccines that produce an immune response against SARS-COV-2, although some allergic symptoms have been reported with both vaccines. Fever, tiredness, headache, myalgia, nausea, vomiting, itching, chills and joint pain: as well as rarely anaphylactic shock, including pain, redness or swelling may be observed after the second dose (15). In our study, in the inactivated SARS-CoV-2 vaccine produced by Sinovac, similar side effects occurred with these vaccines. However, differently, in our study, we found that 1.2% of the patients with side effects went to the hospital and 18.9% received medical treatment because of these side effects. The symptoms that led the patients to go to the hospital were generally pain, shortness of breath, numbness in the arm and leg, and blurred vision. Patients should be alert to these symptoms, and perhaps medical treatment should be started earlier.

Many factors influence humoral and cellular vaccine responses in humans. These include intrinsic host factors, perinatal, and extrinsic factors. Age is very important in host factors. Many studies have stated that cellular and humoral immune response is higher in young people and decreases with age (16). In our study, we divided the age groups and we found that the side effects were significantly higher in patients aged under 35 years. We could not find a study separating vaccine side effects according to age groups in the literature. Patients aged under 35 years, in particular, should pay more attention in terms of vaccine side effects.

Some studies are reporting rare cases such as supraclavicular reactive lymphadenopathy (LAP), Bell's paralysis after the COVID-19 vaccine. It is important to question the vaccines of patients who present to the head and neck clinic with these symptoms (17,18). In our study, rare side effects such as redness of the eyes, low back pain, and a changed menstrual cycle were observed.

Limitation: We performed our study in a single center with a limited number of volunteers. In the future, multi-center prospective studies with a larger number of volunteers are needed.

CONCLUSION

Inactivated Covid-19 vaccine causes side effects in the majority of patients. In the otorhinolaryngology outpatient clinic, attention should be paid to the side effects of the CoronaVac vaccine in female patients under the age of 35 who have allergies.

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Conflict of Interest

The authors declare that they have no conflict of interests regarding content of this article..

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Ethical Declaration

Ethical approval was obtained from Adana City Training and Research Hospital Clinical Research Ethical Committee with date 13012021 and number 1257, and Helsinki Declaration rules were followed to conduct this study.

Authorship Contributions

Concept , AK, SOE, BT, Design , AK, AAÖ OG , Supervision , OG, Materials , AK, SOE, Data collection &/or processing , AK, SOE, Analysis and/or interpretation ,AK, BT, Literature search , AK, AAÖ, Writing , AK, SOE, BT, Critical review , AK, SOE, BT, OG, AAÖ

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