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# **Research Paper** Side Effects of First and Second Doses of Inactivated **COVID-19 Vaccine in Multiple Sclerosis**



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Received: 12 Mar 2022 Accepted: 13 Jun 2022 Published: 01 Jan 2023 Highlights

- The prevalence of side effects of the Sinopharm vaccine in dose1 was higher than in dose 2.
- Most common side effects in both doses were fatigue, myalgia, fever, and headache.
- Most side effects were moderate in severity and resolved in less than 48 h.

## Introduction

o reduce the severity and spread of COV-ID-19, vaccination is one of the most important health strategies [1]. There have been many attempts to find a cure and vaccine since the epidemic began. As one

of the inactivated COVID-19 virus vaccines developed by Sinopharm, the BBIBP-CorV vaccine is also referred to as the Sinopharm COVID-19 vaccine. At the end of December 2020, more than 60,000 people participated in phase 3 trials in Argentina, Bahrain, Egypt, Morocco, Pakistan, Peru, and the United Arab Emirates [2]. People with COVID-19 who suffer from chronic diseases deserve special attention [3]. Multiple sclerosis (MS) is a chronic disease of the central nervous system characterized by decreased motor and sensory function as a result of inflammation caused by the immune system and demyelination which is the most common cause of disability among young adults [4]. Immunosuppressive/immunomodulatory disease-modifying therapies are generally at increased risk of infections raising concerns related to different risks or outcomes in case of infection with COVID-19 [5]. As a result of the Coronavirus epidemic, several national and international associations have recommended the vaccination of people with MS (PwMS) [6]. In contrast, it is unclear what are the immunization effects of SARS CoV-2 on MS patients, and vaccination may cause an immune reaction that can activate MS [7].

During the clinical trial stages of existing vaccines, the safety of existing vaccines has been assessed in populations with general health, not in people with deviated or suppressed immune systems [8, 9]. As vaccination programs are developed, reviews of side effects are particularly important for subpopulations that have not been represented in early trials (such as MS) [10]. Vaccination should be considered carefully concerning risks and benefits for MS patients. There is an urgent need for more research on vaccination in MS patients to aid in making evidence-based decisions [11]. Several COVID-19 vaccines are currently available in various countries, including Iran. Some of these vaccines are available in Iran for target groups and groups

of specific patients, such as MS. As of May 2021, a Sinopharm vaccine is being administered to PwMS in Kermanshah (in the western provinces of Iran). In this study, side effects of the first and second doses of the Sinopharm vaccine were investigated and compared in PwMS in Kermanshah.

## **Materials and Methods**

#### Study design and research community

This descriptive-analytical follow-up study was conducted between May and August 2021. Sampling was conducted using available methods based on the national MS registry of Iran (NMSRI) [12]. All PwMS in Kermanshah province who received both doses of the Sinopharm vaccine participated in the study. The inclusion criteria included a confirmed diagnosis of age over 18 years and injection of both doses of the Sinopharm vaccine. Also, the exclusion criteria included dissatisfaction with study participation and not answering phone calls.

#### Data collection tools

A researcher-made questionnaire was used to collect demographic, clinical, and information related to COVID-19 infection and side effects of the Sinopharm vaccine. The questionnaire consisted of three parts. The first part of the survey asked for demographic and clinical information including gender, age, marital status, age of diagnosis, type of MS, and current MS medication [12]. In the second part, they discussed COVID-19 infection before vaccination and the MS medication they were taking at that time. In the third part of the questionnaire, the side effects of the vaccine were separately assessed for the 1st and 2nd doses. PwMS were asked about the type of side effects, the interval between vaccination and onset of the side effects, the duration of the side effects, the use of painkillers, and the degree of severity of the side effects. Side effects were classified as mild, moderate, or severe according to their annoying nature and interference with daily activities. The condition was classified as severe if a doctor was required. In the five to fourteen days following the vaccination, telephone contacts were made with people to collect information.



## **Ethical considerations**

The above-mentioned sampling protocols were approved by the Research Ethics Committee of Kermanshah University of Medical Sciences. Informed consent to participate in the study was obtained from PwMS after clear explanations of its objectives and the preservation of their information. They were assured that the data collected would be kept confidential and used for this research. Each participant was assigned a code that was used in all forms and questions provided.

#### Data analysis

After collecting the data, it was entered into SPSS software version 25 and according to the project objectives, related analyses were performed. Descriptive statistics such as mean, frequency, and percentage were used. After examining the normality of the data by the Kolmogorov-Smirnov test, the Wilcoxon test was used to compare the before and after means of abnormal variables. To compare the before and after conditions for class variables, the McNemar test was used. To examine the relationship between class variables, the chi-square test was used.

#### Results

The questionnaire was completed by 188 of the PwMS vaccinated as of August 2021. The Meadian age of the participants was 42.66(11.1) years (range of 23-79 years) and the Meadian of the duration of disease was 9.57(7.0) years (range of 1-36 years). Table 1 shows demographic and clinical information on all participants

In the first dose of the vaccine, 58.5% of people with MS experienced side effects, whereas, in the second dose, 47.0% of people had side effects, which was significantly higher in the first dose (P=0.012).

The vaccine side effects began on 13.80 (22.2)h after the first dose and 17.42(24.6) h after the second dose. The time interval between vaccination and onset of side effects was longer on average in the second dose, but no significant difference was observed between the first and second doses (P=0.268). In both doses, side effects resolved within 48 h on average, and there was no significant difference in side effect duration between the two doses (P=0.911). While more people used painkillers in their first dosage than in their second, there was no significant difference between them (P=0.263). Fatigue (30.1%), myalgia (29.8%), fever (25.0%), and headache (22.3%) were the most common side effects in the first dose. In the second dose, fatigue (27.1%), headache (18.6%), myalgia (17.5%), and fever (14.9%) were the most common side effects. Myalgia and fever were significantly more prevalent in the first dose than in the second (P<0.05). Three people reported that their MS symptoms became more severe after receiving the first dose, and three people reported the same after receiving the second dose (Table 2).

COVID-19 was present in 51 of the PwMS (27.3%) before vaccination. Of these, 40(78.4%) were female and 11(21.6%) were male. Among the PwMS who had COVID-19 before vaccination, as well as in the overall population of this study, fatigue, myalgia, fever, and headache were the most common Sinopharm side effects. Among patients with MS who had COVID-19 before vaccination, 33(64.7%) experienced side effects in the first dose and 28(57.1%) in the second dose. There was no significant difference in either the first or second doses in terms of the existence of side effects between people who had COVID-19 before vaccination and those who did not (P=0.276 and P=0.094, respectively) (Table 3).

For PwMS who had COVID-19 before vaccination, similar to those who did not, more than 50% had moderate severity from both vaccine doses. Both in the first and second doses, there was no significant difference in terms of the severity of side effects between people who had a COVID-19 vaccination before and those who did not (P>0.05) (Table 3).

A 46-year-old man with MS for 14 years developed severe symptoms of COVID-19 two days after receiving the Sinopharm vaccine and his COVID-19 test was positive. After being hospitalized for a week, he was released. The second dose of the vaccine was given 52 days after the first dose and he did not experience any side effects.

One woman with RRMS developed sensory, motor, and cerebellar symptoms five days after the first dose. After the second dose, 3 women with RRMS developed relapses of MS (the first after 2 days with pyramidal pathway involvement, sensory, and motor symptoms, the second after 14 days with pyramidal pathway involvement and motor symptoms, and the third after 14 days with brainstem and optic nerve symptoms).



Veriables	No. (%)	
Variables	Median (IQR)	
Age (y)	-	41.5(15)
Duration of disease (y)	-	8(10)
EDSS	-	2(2)
Condex (n. 199)	Female	148(78.7)
Gender (n=188)	Male	40 (21.3)
Marital status (n=188)	Single	46(24.6)
	Married	141(75.4)
	Primary	21(11.3)
	Middle	22(11.8)
Education (n=186)	Diploma	57(30.6)
	College level	86(46.2)
	RR	135(73)
	PP	20(10.8)
Type of Mis (n=185)	SP	21(11.4)
	RP	9(4.9)
History of infection with COVID 10 (n. 197)	Yes	51(27.3)
history of infection with COVID-19 (n=187)	No	136(72.7)

Table 1. Demographic and clinical information of MS patients vaccinated with sinopharm vaccine

Variables		No. (%)	
		MS medicine	
Oral therapy	Oral therapy	49(29.5)	
	Fingolimod	28(16.9)	
	Triflunomide	4(2.4)	
	Dimethyl fumarate	17(10)	
Injectable therapy	Injectable therapy	62(37.3)	
	Interferon beta 1a	29(17.5)	
	Interferon beta 1b	24(14.5)	
	Glatiramer acetate	9(5.4)	
Infusion therapy	Rituximab	31(18.7)	
	Ocrelizumab	2(1.2)	
Other		22(13.2)	
Total		166(100)	

IQR: interquartile range; EDSS: expanded disability status scale; RR: relapsing-remitting; PP: primary progressive; SP: secondary progressive; RP: relapsing progressive; MS: multiple sclerosis.

## Table 2. Side effects of Sinopharm vaccine by the first and second doses in people with MS

		No. (%)			
Variables		Median (IQR)		Р	
		Dose 1	Dose 2		
Injection interval to the onset of side effects (h)		6.0(9.1)	7.5(19.5)	0.268*	
Duration of side effects (h)		15.5(43.6)	24.0(46.2)	0.911*	
Existence of side effects	Yes	110(58.5)	85(47.0)	0 04 2 * *	
	No	78(41.5)	96(53.0)	0.012***	
Taking painkillers after injection	Yes	68(41.2)	34 (31.8)		
	No	97(58.8)	73(68.2)	0.263**	
	Fatigue	58(30.1)	51(27.1)	0.440**	
	Myalgia	56(29.8)	33(17.5)	0.012**	
	Fever	47(25.0)	28(14.9)	0.007**	
	Headache	42(22.3)	35(18.6)	0.360**	
	Restlessness	20(10.6)	19(10.1)	0.541**	
	Chills	22(11.7)	12(6.4)	0.078**	
	Anorexia	17(9.0)	12(6.4)	0.188**	
	Loss of consciousness	11(5.8)	15(8.0)	0.167**	
	Shortness of breath	15(8.0)	16(8.5)	0.687**	
	Flashing	6(3.2)	6(3.2)	1.000**	
Side effects	Cough	8(4.2)	7(3.7)	1.000**	
	Vomit	4(2.1)	6(3.2)	1.000**	
	Vertigo	2(1.1)	3(1.6)	1.000**	
	Low blood pressure	5(2.6)	4(2.1)	1.000**	
	Diarrhea	5(2.6)	3(1.6)	0.687**	
	Joint's pain	6(3.2)	3(1.6)	1.000**	
	Wheezing	2(1.1)	3(1.6)	1.000**	
	Skin urticaria	3(1.6)	2(1.1)	1.000**	
	Exacerbation of MS symptoms	3(1.6)	3(1.6)	1.000**	
	Heartbeat	0(0.0)	1(0.5)	1.000**	
	Redness and or swelling at the injection site	1(0.5)	2-(1.1)	1.000**	

\* Test: Wilcoxon; \*\* Test: Mc-Nemar; IQR: interquartile range; h: hours.

	_	No. (%)				
Variables		Dose 1		Do	Dose 2	
		Infected	Uninfected	Infected	Uninfected	
Existence of side effects	Yes	33(64.7)	76(55.9)	28(57.1)	57(43.2)	
	No	18(35.3)	60(44.1)	21(42.9)	75(56.8)	
	Р	0	.276	0.0	)94	
Severity of side effects	Mild	33(29.2)	48(27.7)	35(37.2)	36(29.7)	
	Moderate	74(65.5)	112(64.7)	52(55.3)	71(58.8)	
	Severe	6(5.3)	13(7.5)	7(7.4)	14(11.6)	
	Р	0	.757	0.3	<sup>383</sup> © CJNS	

Table 3. Comparison of side effects between people with MS with and without COVID-19 before vaccination

\* Test: Chi-square

#### Discussion

Our study evaluated the side effects of the Sinopharm vaccine after the first and second doses of PwMS. The first dose side effects were significantly higher than the second dose side effects. Both doses had side effects that lasted less than two days on average. In both doses, fatigue, myalgia, fever, and headache were the most common side effects, with the first dose having a higher prevalence.

Side effects after vaccination in the general population have been investigated in other studies. In August 2020, trials 1 and 2 of the Sinopharm vaccine were completed in the general population, showing that the vaccine elicited a COVID-19-neutralizing antibody response and had few side effects. The most common side effects were injection site pain and fever, but all were mild and did not require treatment [13]. The study of the general population conducted between January and April 2021 in the UAE found that doses 1 and 2 had mild side effects after vaccination and there were no hospitalizations [10]. Pain at the injection site (42.2%), fatigue (12.2%), headache (9.6%), and lethargy (9.3%) were the most common side effects. A study was conducted by Mani et al. on the safety and effectiveness of vaccination in 590655 people in the general population of the British community. After the first dose of AstraZeneca, systemic side effects were reported in 33.7% of subjects and local side effects in 58.7% of subjects. The most common side effects were headache (22.8%), fatigue (21.1%), chills and shiver (14.7%), arthralgia (11.5%), and fever (8.2%). In a study by Jayadevan et al. [14] conducting an online survey of 5396 in the general population in India from January to February 2021, 65.9% of respondents reported post-vaccination side effects. Tiredness (45%), myalgia (44%), fever (34%), headache (28%), and local pain at the injection site (27%) were the most common side effects. Comparing the results of the mentioned studies with those of the present study reveals that the side effects after injection of the Sinopharm vaccine in PwMS are similar to those of the general population.

Side effects after vaccination in PwMS have been investigated in other studies. A study by Allen-Philbey et al. [15] was conducted on PwMS and the first experience after vaccination in PwMS was reported. In this study, 33 people received the AstraZeneca vaccine, four people received the BioNTech/Pfizer vaccine, and all but two people (94%) reported symptoms, including sore in the injection site (70%), flu-like symptoms (64%), fever (21%), fatigue (27%), and headache (21%). Over two-thirds of people reported side effects lasting less than 48h at both doses. Similar to the results of Allen's study in PwMS, in our study in the first dose, fatigue, fever, and headache had a similar frequency in Allen's study, and side effects at both doses lasted less than 48h on average.

Kavosh et al. [16] conducted a study on 1538 PwMS who received two doses of the Sinopharm vaccine and evaluated the safety of the vaccine; 54.2% (833 patients) reported at least one adverse event after the first dose of vaccine and 46.8% (720 patients) after the second dose. The most prevalent adverse events after both doses were injection site pain, headache, myalgia, fever, and fatigue, in both cases going away in a few days. Sahraian et al. conducted a study on the side effects of vaccination in PwMS [17]. Of 583 patients

vaccinated with the Sinopharm vaccine, 350 (60%) reported at least one side effect and symptom (malaise, fatigue, fever, shivering, and generalized body pain) (51%) and headache (9%) as the most common side effects of PwMS. In Sahraian's [17] study, no serious side effects occurred but in the present study, one case of COVID-19 (positive test) occurred 2 days after receiving the 1<sup>st</sup> dose of the vaccine. This PwMS was probably vaccinated during the incubation period.

This study had two limitations: first, there was no complete list of PwMS in Kermanshah province who received the vaccine, and second, since the information was collected by phone calls and some people did not answer the phone, it was not possible to have a larger sample. PwMS vaccinations should be recorded at specialized centers so that a fuller list of PwMS can be compiled.

## Conclusion

In our study, the frequency of side effects of the Sinopharm vaccine in PwMS was significantly higher in the first dose than in the second dose. In both doses of the Sinopharm vaccine, fatigue, myalgia, fever, and headache were the most common side effects. Side effects of the vaccine began on average in the first dose after 13.80 h and in the second dose after 17.42 h, and in both doses, they resolved on average within 48 h. Before vaccination, 27.3% of people had COVID-19. Neither in the first nor the second dose, there was a significant difference in the presence and severity of side effects between PwMS who had previously taken COVID-19 and those who had not.

## **Ethical Considerations**

#### Compliance with ethical guidelines

All study procedures are in compliance with the ethical guidelines of the Declaration of Helsinki 2013. The ethics committee of Kermanshah University of Medical Sciences approved this study with the code IR.KUMS. MED.REC.1400.087.

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## Authors' contributions

Conceptualization and Administration: Nazanin Razazian, Mohammad Ali Sahraian, Sharareh Eskandarieh; Methodology: Nazanin Razazian, Mansour Rezaei; Formal analysis: Nazanin Razazian, Mansour Rezaei, Negin Fakhri; Visit patients: Nazanin Razazian, Seyedeh Elham Mousavi, Negin Fakhri; Data collection, formal analysis, software and writing the original draft: Negin Fakhri; Questionnaire completion and writing and reviewing: Seyede-Elham Mousavi; Editing: Nazanin Razazian, Mohammad-Ali Sahraian, Mansour Rezaei, Sharareh Eskandarieh.

## **Conflict of interest**

The authors declared no competing interests.

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