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Original Article

The Effect of Adding Selenium to the Treatment Regimen on Outcomes of Patients with COVID-19: A Randomized Clinical Trial

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Abstract

Background: Some studies indicate that selenium is essential in the host's response to viral infections. This study aimed to investigate the effect of selenium administration on clinical outcomes in hospitalized patients with COVID-19.

Methods: This clinical trial was conducted in Sabzevar in 2020–2021 (registration code: IRCT20160706028815N5) on hospitalized patients with COVID-19. Demographic data, clinical symptoms, and CT scan findings were recorded. The participants were randomly divided into two groups. The control group received standard care based on the latest national treatment protocols for COVID-19. The intervention group received selenium in addition to routine treatment. Clinical outcomes were compared between the two groups using SPSS statistics software. A significance level of 0.05 was considered.

Results: Fifty-four patients were randomly assigned to the intervention ($n=29$) and control ($n=25$) groups. Twenty-nine men (53.7%) and 25 women (46.3%) were included in the study. The mean and SD of age and body mass index of participants were 58.3 ± 16.8 and 25.8 ± 3.3, respectively. The groups were similar in terms of gender, addiction, smoking, commodities, symptoms, amount of pulmonary parenchyma involvement in the lung CT scan, age, and body mass index. The duration of admission was significantly shorter in the intervention group ($P=0.03$). There was no significant difference in terms of ICU admission, mechanical ventilation, and 30- and 90-day mortality rates.

Conclusion: The present study showed that the administration of selenium can reduce the duration of the disease. Other clinical outcomes did not show significant differences between the two groups.

Keywords: COVID-19, Selenium, Treatment outcome

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Introduction

At the end of 2019, an infectious disease involving several organs, mainly the lungs, was reported in China, which quickly became a global pandemic with high mortality. The cause of the pandemic was called COVID-19, and the risk factors for the occurrence and progression of the disease in people were studied from different points of view (1). Early studies clearly showed the role of the immune system in the clinical course of the disease (2,3). Also, the role of nutrition, vitamins, and minerals was investigated (4).

Selenium (Se) has been considered and studied as an effective factor in the functioning of the human immune system. Studies indicate that blood selenium level is an important factor in the response of the body to viral infections (4,5). The majority of selenium's biological functions are carried out via its inclusion in the rare amino acid called selenocysteine within the crucial group of selenoproteins. A lack of selenium, which is the primary factor influencing the expression of selenoproteins, has been linked to the disease-causing potential of various viruses (6,7). Previous laboratory studies on bronchial epithelial cells have shown that Se supplementation reduces the rate of apoptotic cell death after infection with the influenza virus (8,9). In another study on mice, Yu demonstrated that providing Selenium led to elevated plasma levels of TNF-α and IFN-γ in mice infected with the influenza virus (10). Mice lacking selenium experienced more severe lung damage from influenza virus infection compared to those with adequate selenium levels. Studies have demonstrated that particular nutritional deficiencies can significantly

influence the genome of RNA viruses (11).

Kieliszek and her colleagues reported that sodium selenite reduces the pathogenicity of some viruses by preventing them from entering healthy cells (12).

Bermano and colleagues recommended the implementation of suitable indicators to evaluate the selenium (Se) levels in COVID-19 patients and potential supplements to mitigate the intensity of symptoms, particularly in nations where selenium levels are considered inadequate. They also suggested studies to evaluate the relationship between the initial selenium levels and the effect of selenium administration on the severity of the disease (13).

Beck et al demonstrated that there were six nucleotide differences between the virulent virus obtained from the selenium-deficient host and the virulent input virus. This finding strengthens other study results about the correlation of selenium deficiency and the progression of viral infections (14).

This study aimed to investigate the effect of selenium administration on the course of the disease in hospitalized patients with COVID-19.

Methods

This clinical trial was conducted in 2020–21 in Vasei Medical Training Center, Sabzevar. The research project was approved by the Ethics Committee of Mashhad University of Medical Sciences (IR.MEDSAB.REC.1399.017). The IRCT code for the research project is IRCT20160706028815N5. The study population consisted of hospitalized patients diagnosed with COVID-19, confirmed by PCR testing of pharyngeal mucus or by characteristic findings on chest CT, including glass opacities (GGOs) and consolidation with bilateral and peripheral distribution. The inclusion criteria were adult patients with COVID-19 who were hospitalized for more than 24 hours. Exclusion criteria were pregnancy or a history of allergy to drugs. After obtaining informed consent from the patient, a checklist was completed for each participant. Demographic data (age, gender, BMI, smoking, and past medical history), clinical symptoms (fever and respiratory and gastrointestinal symptoms), and CT scan findings were recorded. The severity of the disease at the time of admission was described as mild to moderate, severe, or critical, based on the simplified Infectious Diseases Society of America (IDSA) classification (15). Participants were randomly assigned to either the control group or the intervention group. The control group received standard treatment according to the most recent national guidelines for COVID-19, which included antiviral therapy and antibiotic treatment if necessary. The intervention group received selenium in addition to routine treatment. Selenium was injected at a dose of 1000 micrograms every 12 hours during the first day, and then 500 micrograms every 12 hours from the second day onward.

At the end of the study, the outcome variables, including the need for hospitalization in the intensive care unit, need for mechanical ventilation, duration of hospitalization, and outcome of treatment (death/discharge), were compared in the two groups. Participants were followed for 3 months, and 30-day and 90-day mortality was assessed in two groups.

The data were analyzed using SPSS statistics software. A significance level of 0.05 was considered.

Results

Fifty-four patients were randomly assigned to the intervention ($n=29$) or control ($n=25$) groups. The mean and SD of age and body mass index of the participants were 58.3 ± 16.8 and 25.8 ± 3.3, respectively. Twenty-nine men (53.7%) and 25 women (46.3%) were included in the study. The groups were similar in terms of gender, addiction, smoking, commodities, symptoms, and amount of pulmonary parenchyma involvement in the lung CT scan at presentation, as shown in Table 1. In addition, there was no notable distinction regarding age and body mass index. Between the two groups. ($P=0.41$ and $P=0.65$, respectively). Table 1 demonstrates the demographic and clinical features of the two groups. As shown, there was no significant difference in the independent variables between the two groups. There were more severe cases in the control group compared to the intervention group (65% vs 48%). The consequences and course of the disease were assessed based on its severity at the time of patient admission, which is summarized in Table 2.

Based on the study results, the duration of admission was significantly shorter in the intervention group (9 ± 6 days vs 7.4 ± 4.8 days, $P=0.03$). Table 2 shows other outcome variables in the two study groups. As presented, there was no significant difference in terms of ICU admission, mechanical ventilation, and 30- and 90-day mortality rates (Table 3)

Discussion

In this clinical trial, the clinical results of selenium administration in patients with COVID-19 were investigated. None of the participants required mechanical ventilation or readmission. The present study showed that the administration of selenium can reduce the duration of the disease ($P=0.03$). As there was no significant difference between the background variables in the intervention and control groups, the reduction in the duration of the disease in the intervention group can be related to the administration of selenium.

The need for ICU care was also less in the intervention group, although there was no significant difference. 30- and 90-day mortality was higher in the intervention group although no significant difference was observed. Comparison of the mortality rate in different severities of

Table 1. Demographic and clinical characteristics of the two study groups. The chi-square statistical test was used, and a significance level of 0.05 was considered.

			Groups		*P* value
			Control	Intervention	
Gender	Male	Count	18	11	0.231
		% within Group	72.0%	37.9%	
	Female	Count	7	18	
		% within group	28.0%	62.1%	
Addiction	No	Count	19	25	0.336
		% within group	76.0%	86.2%	
	Yes	Count	6	4	
		% within group	24.0%	13.8%	
Smoking	No	Count	23	28	0.467
		% within group	92.0%	96.6%	
	Yes	Count	2	1	
		% within group	8.0%	3.4%	
Commodities	No	Count	12	8	0.282
		% within group	48.0%	27.6%	
	Yes	Count	13	21	
		% within group	52.0%	72.4%	
Fever	No	Count	17	17	0.362
		% within group	68.0%	58.6%	
	Yes	Count	8	12	
		% within group	32.0%	41.4%	
Cough	No	Count	13	12	0.435
		% within group	52.0%	41.4%	
	Yes	Count	12	17	
		% within group	48.0%	58.6%	
Dyspnea	No	Count	2	9	0.061
		% within group	8.0%	31.0%	
	Yes	Count	23	20	
		% within group	92.0%	69.0%	
Diarrhea	No	Count	25	28	0.349
		% within group	100.0%	96.6%	
	Yes	Count	0	1	
		% within group	0.0%	3.4%	
CT scan	Consolidation	Count	2	1	0.505
		% within group	8.0%	3.4%	
	GGO	Count	23	27	
		% within group	92.0%	93.1%	
	Mix	Count	0	1	
		% within group	0.0%	3.4%	
Severity	Mild to Moderate	Count	7	12	0.029
		% within group	35%	52.2%	
	Severe	Count	13	11	
		% within group	65%	47.8%	

the disease showed that, unlike the length of hospitalization and the need for admission to the ICU, the mortality rate was not related to the severity of the disease. Comparing the results of the mortality rate in the two groups also shows that the present intervention does not reduce the mortality rate in patients with different severities of the

Table 2. Association of outcome variables with disease severity. The chi-square statistical test was used, and a significance level of 0.05 was considered.

		Group		*P* value
		Mild to Moderate	Severe	
ICU admission *n* (%)	No	18 (94.7%)	21 (60%)	0.006
	Yes	1 (5.3%)	14 (40%)	
Mortality *n* (%)	30-day mortality	1 (100%)	8 (80%)	0.27
	90-day mortality	0	2 (20%)	
Duration of admission (mean ± SD)		5.8 ± 1.5	9.6 ± 6.4	0.01

Table 3. Comparison of outcome variables of the two study groups. The chi-square statistical test and the compare means test were used, and a significance level of 0.05 was considered.

			Group		Total	*P* value
			Control	Intervention		
ICU admission	No	Count	16	23	39	0.210
		% within group	64.0%	79.3%	72.2%	
	Yes	Count	9	6	15	
		% within group	36.0%	20.7%	27.8%	
Mechanical ventilation	No	Count	25	29	54	-
		% within group	100.0%	100.0%	100.0%	
	Yes	Count	0	0	0	
		% within group	0	0	0	
Readmission	No	Count	25	29	54	-
		% within group	100.0%	100.0%	100.0%	
	Yes	Count	0	0	0	
		% within group	0	0	0	
30-day mortality	No	Count	22	24	46	0.589
		% within group	88.0%	82.8%	85.2%	
	Yes	Count	3	5	8	
		% within group	12.0%	17.2%	14.8%	
90-day mortality	No	Count	22	21	43	0.156
		% within group	88.0%	72.4%	79.6%	
	Yes	Count	3	8	11	
		% within group	12.0%	27.6%	20.4%	
Duration of admission (mean ± SD)			9 ± 6	7.4 ± 4.8		0.03

disease. Despite the intervention group having a higher mortality rate, there was no significant difference found between the two groups. Thus, it appears that other recognized factors play a more substantial role in the 30- and 90-day mortality rates of patients.

A review of various studies on the therapeutic effects of selenium in COVID-19 shows that in some patients, the administration of this substance can improve the course of the disease. Some studies have reported that the patient's initial selenium level is an important intervening factor regarding this relationship. In addition, the therapeutic window of this micronutrient needs careful investigation. (16)

Zhang et al reviewed 14,045 deaths from COVID-19 in different cities in China. Also, the amount of selenium in various food products in these cities was investigated. The results showed that after removing other variables affecting the overall mortality rate, geographical areas with a lower amount of selenium in the agricultural products used had higher coronavirus-related mortality rates. Researchers recommended conducting more detailed studies among patients (17).

In a study, Razeghi Jahormi et al investigated the amount of selenium and zinc in patients with the disease and showed that after adjusting for other variables, the severity of the disease was not related to the amount of these substances. In the present study, the need for intensive care unit admission and mechanical ventilation in the control group was not significantly different from that of the intervention group. In both studies, the diagnosis of COVID was based on laboratory and imaging criteria, and the initial blood selenium level was not evaluated (18).

Sobczyk et al evaluated the micronutrient levels, clinical outcomes, and disease course in patients with COVID-19. The results showed that the need for ICU admission, the lethality of the disease, and the severity of the disease were not related to the amount of micronutrients in the blood of the patients. Although this study employed a different methodology, its findings are consistent with ours (19).

Balboni et al conducted a systematic review of clinical trials using zinc or selenium supplementation to treat or prevent COVID-19, including studies published or in press in PubMed, Scopus, and ClinicalTrials.gov. They reported that there have been no studies examining the impact of selenium supplementation on COVID-19 so far, and the limited research available on zinc supplementation did not establish its effectiveness. Consequently, using zinc or selenium supplementation as preventive or treatment measures for COVID-19 is not warranted at this time and requires additional clinical trials (20). In a meta-analysis comparing the effects on safety-related outcomes between selenium-receiving groups versus control groups, Filippini et al reviewed published and unpublished studies in databases such as PubMed/MEDLINE, Embase, and clinicaltrials.gov up to late 2022. The results of the trials seem to be variable and diverse because of variations in trial length and interventions, along with indications of neutral or even harmful effects. In summary, the evidence collected from the literature in this systematic review does not justify the necessity of selenium supplementation beyond the recommended dietary levels to achieve positive effects on immune function (21).

There were not many clinical trials on selenium administration in COVID-19 patients to compare the results with.

The results of our study are partly consistent with descriptive and review articles about the epidemiologic findings (4-8). The methods and population in the related articles are very different. Moreover, different doses of selenium have been prescribed in trials.

A noteworthy finding in our study is the 90-day mortality rate in intervention group patients. This finding is incompatible with the theoretical hypotheses of selenium's effect on the blood levels of inflammatory factors to some extent. (22-27). At the same time, it seems that the administration of selenium in large epidemics can be helpful by reducing the time spent in the hospital and the relative reduction in the need for hospitalization in the ICU.

This study was one of the few clinical trials that examined selenium administration (at a high dose) in patients with COVID-19 and assessed one- and three-month mortality rates in COVID-19 patients.

One of the limitations of the study was not measuring the initial blood levels of selenium in the patients. In addition, other background variables such as genetics, which have an effect on the course of the disease, were not measured in this study. In addition, the exact time of onset of symptoms and the amount of virus load could not be measured in this study.

Conclusion

Administration of selenium in patients with COVID-19 can reduce the length of hospitalization, although it does not reduce the one and three-month mortality rates. Larger studies measuring various variables involved in the mortality rate of COVID-19 patients are required to confirm these findings.

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Authors' Contribution

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Competing Interests

The authors declare that they do not have any conflict of interest.

Data Availability

Data are available from Tahoura Afshari Saleh with the permission of Sabzevar University of Medical Sciences.

Ethical Approval

The research project was approved by the Ethics Committee of Mashhad University of Medical Sciences (IR.MEDSAB.REC.1399.017). The IRCT code for the research project is IRCT20160706028815N5.

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