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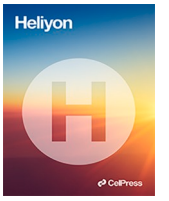

Research article

The effect of the coronavirus vaccinations on seizures in patients with epilepsy

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ABSTRACT

Purpose: Information on COVID-19 vaccine tolerance and complications in patients with epilepsy is not yet sufficient to provide a recommendation for vaccination guidelines. The aim of this study was to investigate the effect of two types of COVID vaccines currently used in Turkey (mRNA vaccine from Pfizer/BioNTech and inactivated vaccine from Sinovac) on epileptic seizures.
Methods: We included 318 patients with epilepsy who were admitted to our epilepsy outpatient clinic. Clinical characteristics such as age, gender, age at seizure onset and the duration of epilepsy were noted. Types and the numbers of the anti-seizure drugs were recorded. Patients were evaluated either by face-to-face or by teleconference interviews. The seizure frequency in the first thirty days after any dose of vaccination was questioned.
Results: A total of 318 patients (149 females, 46.8%) with a confirmed diagnosis of epilepsy were enrolled in the study. An increase in seizure frequency was reported after the COVID-19 vaccine in 19 patients. Of these 19 patients, 2 were vaccinated with Sinovac, while 17 were vaccinated with BioNTech/Pfizer mRNA vaccine. There was no significant relationship between age, age at seizure onset, duration of epilepsy, type of seizures, seizure frequency or seizure induction. Status epilepticus was not reported in any of the participants.
Conclusion: Physicians need strong scientific evidence to advocate the importance of vaccine for COVID-19, that's why accumulation of knowledge related to this issue is important not only from medical but also from medico-legal point of interest. We aimed to contribute the current literature with our study to strengthen the physicians' hand while recommending COVID vaccines to PWE. Our results show that there is no significant increase in the risk of triggering seizures with COVID-19 vaccines. These data show that vaccination against COVID-19 with both vaccine types in patients with epilepsy is safe and well tolerated.

1. Introduction

Coronavirus disease 2019 (COVID-19) is a novel infection that became a pandemic after its first appearance in Wuhan, China in November 2019 [1]. This fatal medical condition has no effective treatment yet; however, numerous types of vaccination have come

Abbreviations: PWE, Patients with epilepsy; COVID-19, Coronavirus disease.

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into prominence to end the pandemic. The WHO has authorized 6 vaccines that meet the safety and efficacy criteria including those from Moderna and Pfizer/BioNTech (mRNA based), Johnson & Johnson and Oxford/AstraZeneca (viral vector based), and Sinopharm and Sinovac (inactive virus) [2].

Vaccine welfare and safety have also emerged, particularly for certain groups with comorbid diseases, e.g., patients with epilepsy (PWE). Although some studies have shown no negative effects of COVID vaccines in PWE, epilepsy was included in the list of chronic diseases to be monitored according to the national guidelines published in the early period of vaccination in China [3,4].

Currently, epilepsy has not been prioritized for medical follow-up post-vaccination. Studies on COVID-19 vaccine tolerance and difficulties in PWE are insufficient for determining guidelines for vaccination.

The goal of this report was to determine the consequences administration of two different COVID vaccines (Pfizer/BioNTech and Sinovac) currently used in Turkey on epileptic seizures in PWE.

2. Methods

2.1. Patients and clinical evaluation

We included 318 PWE patients admitted to our epilepsy outpatient clinic between February and September 2021. Clinical characteristics such as age/age at seizure onset, gender, epilepsy duration, and number and type of anti-seizure drugs used were recorded. Patients were also subdivided according to seizure type into focal and generalized onset seizures. The baseline frequency of seizures of the patients were analyzed using the data obtained from the seizure diaries and the regular outpatient follow-ups. Seizure frequency during the previous year was categorized into three groups: Group I - once a week, Group II – twice per month, and Group III - twice per year. Patients with a frequency of seizures greater than twice per week were excluded from the study. The seizure diaries of all patients were evaluated through face-to-face or online interviews. The exact date of vaccination registered in the Turkish Ministry of Health system was used to assess the temporal relationship between seizures and vaccinations. The critical period of 72 h after vaccination was taken as the threshold value. The frequency of seizures during this period was recorded as "presence or absence of seizures", termed as vaccine-induced seizure.

The presence of fever after vaccination was also questioned and patients who described increased seizures with fever were excluded from the analysis.

2.2. Data and statistical analysis

Data were subjected to statistical analysis using SSPS v22.0. Continuous variables were noted as mean ± standard deviation, while categorical variables were given as percentages. All data were compared using the Kruskal-Wallis test, and a Mann-Whitney *U* test was used for post-hoc comparisons. For the qualitative data, a Chi-square test was used. A p-value of less than 0.05 was considered statistically significant.

Age/age at seizure onset, gender, epilepsy duration, type of seizure, and seizure frequency were the parameters considered during statistical assessment.

This study was approved by the local institutional review board committee, and informed written consent was collected from patients before the study began.

3. Results

A total of 318 patients (149 women; 46.8%) with confirmed epilepsy were recruited for the study. The mean age, age at epilepsy onset, and epilepsy duration at the time of interview were 33.79 ± 12.35, 17.53 ± 12.26 and 16.24 ± 12.09 years, respectively.

Fifty-six patients were vaccinated with the inactive vaccine (Sinovac), whereas 262 patients were vaccinated with mRNA vaccines (Pfizer/BioNTech). A total of 645 doses of vaccine were administered including the second and third doses. Five patients did not receive a second dose because of seizure induction after the first dose.

Seizures were classified as generalized onset in 55 patients and focal onset in 263 patients.

Eleven patients had fever (>37.5 °C) after vaccination. Seven of them were mRNA vaccines (Pfizer/BioNTech) whereas four of them was the inactive vaccine (Sinovac). When the seizure diaries were examined in this group, which developed fever with the vaccine, seizures that developed within 72 h were observed in 1 patient. However, this particular patient with febrile seizure was not included in the analysis of the direct effect of the vaccines.

Table 1
Number of the patients reporting increase in seizure frequency according to the type of seizures.

	Focal Onset Seizures	Generalized Onset Seizures
PWE vaccinated with S (n)	41	15
PWE reporting increase in seizure after S (n)	2	0
PWE vaccinated with B/P (n)	222	40
PWE reporting increase in seizure after B/P (n)	14	3

Abbreviations: PWE = Patient with epilepsy; B/P = Pfizer/BioNTech; and S = Sinovac.

Distribution of patients according to seizure frequency: Group I had 77 patients (24.2%), Group II had 149 patients (46.8%), and Group III had 92 patients (28.9%).

Seizure occurrence was reported following the COVID-19 vaccine in 19 PWE; two were vaccinated with Sinovac and 17 were vaccinated with the BioNTech/Pfizer. The mean time interval between the vaccination and the seizure was 14.21 ± 7.57 h. No statistically significant correlation existed between age/age at seizure onset, epilepsy duration, and seizure type, frequency, or induction following vaccination. Table-1 shows the number of patients reporting an increase in seizure frequency after vaccination according to the seizure type.

Although there was no statistically significant relationship for seizure induction and any clinical parameter of PWE, we wanted to emphasize the features of each patient with seizure induction after vaccine administration. The clinical properties of these individuals are listed in Table 2.

The distribution of seizure occurrence in all three groups was as follows: Group I 3/77 (3.9%); Group II 6/149 (4%) and Group 10/91 (11%). Vaccine induction was found to be significantly higher in Group III than Group I and Group II ($p = 0.012$ and $p = 0.010$, respectively).

An increased frequency of seizures was detected approximately two times more in those given BioNTech compared to those given Sinovac. However, there was no significant relationship between vaccine type and seizure induction after vaccination ($p = 0.748$). Status epilepticus was not reported by any participant.

4. Discussion

The COVID-19 pandemic has been more challenging and harmful to those with comorbidities compared to the general population.

Epilepsy ranks in the top for all-cause morbidity/mortality among the neurological diseases. Although some speculation has been discussed, the relationship between epilepsy and pulmonary disorders has not yet been fully elucidated [5]. PWE are more vulnerable to any other comorbidity than are other members of the community. Therefore, during the COVID-19 pandemic, these patients were considered to be at a high risk. During the first part of the COVID pandemic, a study from Spain revealed a relationship between age and epilepsy, which demonstrated increased fatalities following COVID-19 infection [6]. However, these findings were not supported by further studies with larger sample sizes [7]. Nonetheless, considering that PWE may be more vulnerable to COVID, the practice of evaluating patients with close observation was continued [8].

New intervention and its effect on seizure frequency is always a concern for PWE; hence, they may be hesitant to use a new drug or medical procedure, such as a vaccine. After the worldwide acceptance of different types of COVID vaccines, it still remains questionable whether vaccinations will cause seizures or other epilepsy-induced side effects. To our knowledge, there are only a few studies with limited number of patients that investigate the seizure related side effects in PWE [9–11]. Here, we report that 318 PWE from a specified tertiary center do not show statistically significant worsening of seizure frequency or induction of status epilepticus following vaccination.

While studies report increased seizure occurrence following COVID-19 vaccine in PWE, it is difficult to prove whether this increase is a result of the vaccination. There were no findings from our study that showed seizure exacerbation in PWE. It is not possible to establish a contributing association based on the data presented due to the lack of controls.

PWE are recommended to be vaccinated for all other infectious diseases, since the risk of increased seizures associated with the vaccine was low or moderate [12]. When the benefits of vaccines are compared with the risks, all scientific data favor vaccination

Table 2
Clinical features of patients with seizure induction after vaccine administration.

	Sex	Age	Age at seizure onset	Duration of epilepsy (years)	Type of seizures (onset)	Seizure frequency by Group	Time Interval between S–V (h)	Vaccine type
P1	F	45	28	17	Focal	II	5	B/P
P2	M	36	16	20	Focal	III	12	B/P
P3	M	38	26	12	Focal	III	6	S
P4	M	26	25	1	Focal	III	10	B/P
P5	F	36	3	33	Focal	III	18	B/P
P6	F	46	16	30	Focal	II	30	B/P
P7	F	18	1	17	Focal	II	16	B/P
P8	M	29	20	9	Focal	II	18	B/P
P9	F	34	24	10	Generalized	III	24	B/P
P10	F	55	15	40	Generalized	III	15	B/P
P11	F	34	3	31	Focal	III	14	S
P12	M	36	15	21	Focal	I	8	B/P
P13	M	19	7	12	Focal	II	12	B/P
P14	M	46	40	6	Focal	II	8	B/P
P15	F	22	1	21	Focal	I	6	B/P
P16	F	25	20	5	Generalized	III	14	B/P
P17	M	48	9	39	Focal	I	6	B/P
P18	M	27	21	6	Generalized	III	18	B/P
P19	F	34	19	15	Generalized	III	30	B/P

Abbreviations: P = patient; F = female; M = male; B/P = Pfizer/BioNTech; and S = Sinovac; S–V: Seizure and Vaccine; h: hour.

[12–14]. Most recommendations are determined from cohorts and retrospective analyses in studies performed with children which reported fever after vaccination may lead to an increase in seizures, especially in Dravet syndrome [15].

In the COVID pandemic, new types of vaccines were developed including mRNA vaccines. There is very little information on how these new procedures affect seizures. A study conducted during the early phases of COVID vaccination revealed epilepsy-related side effects in only 3 PWE (from a study of 54 patients) according to a German tertiary study [9]. They also reported no status epilepticus following vaccine administration, which is concordant with our data. Another multicenter study from China including 491 PWE reported similar results investigating the effects of inactivated vaccinations on seizures [11]. In this study, 19 PWE reported a vaccination-related increase in seizure frequency, which was similar to that in the control group. Our result was consistent with this study and demonstrated no significant increase in seizures following COVID-19 vaccination.

Another striking result of the study is that triggering seizures with vaccines was significantly higher in the group with low seizure frequency than in the group with frequent seizures. To date, there is no data reported in the literature regarding the relationship between seizure frequency and triggering seizures with vaccines. In a multicenter study reported from China, 2 of 19 patients with seizure induction were reported to be seizure-free for more than 2 years [11]. However, no sub-analysis was performed according to the frequency of seizures. This finding of our study is valuable in that it shows that although the COVID vaccine is generally safe with respect to epilepsy, it may induce a higher rate of seizures in individuals with reasonable seizure control.

Physicians need strong scientific evidence to advocate the importance of vaccine for COVID 19, that's why accumulation of knowledge related to this issue is very important not only from medical but also from medico-legal point of interest. We aimed to contribute the current literature with our study to strengthen the physicians' hand while recommending COVID vaccines to PWE.

4.1. Limitations and strengths

Our study has some limitations. First, the analysis was retrospective and cross sectional with relatively small group with 318 PWE. We did not monitor further outcome. Second, the data were obtained from a tertiary epilepsy center, which may not exemplify PWE as a whole. Third, our study did not include a control group of participants without epilepsy who were vaccinated. Another limitation was the lack of analyzes to determine whether seizure recurrence was reduced with increasing intervals between the day of vaccination and the day of relapse. However, we could not perform a statistically significant analysis on this subject, since relapses often occurred on the same day and our sample size was small. Lastly, the time window for seizure occurrence was limited by 72 h after vaccination which was decided according to our clinical observations since there is no consensus regarding this timing.

A prior study from China with more participants showed the effects of one type (whole-virus) of vaccines only. However, our study is the first which demonstrates the relationship between seizure induction in PWE and mRNA vaccines using a large sample size.

5. Conclusion

This study proved that vaccination against COVID-19 with both vaccine types is safe and well-tolerated by PWE; however, larger cohort studies are needed to understand the properties of small group of patients whose seizures may be precipitated after vaccination.

Data availability

The data that support the findings of this study are available on request from the corresponding author (BGT).

CRediT authorship contribution statement

Memet Sakir Delil: Conceptualization, Investigation. **Bengi Gul Turk:** Investigation, Writing – original draft, Writing – review & editing. **Kochan kizilkilic Esra:** Project administration. **Hikmet Abbaszade:** Investigation. **Seher Naz Yeni:** Conceptualization, Data curation, Supervision, Validation, Visualization. **Cigdem Ozkara:** Conceptualization, Data curation, Investigation, Methodology, Project administration, Supervision, Validation, Visualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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