Article published online: 2024-08-06

COVID-19 Vaccination Status among People with Epilepsy Attending a Tertiary Care Epilepsy Clinic: A Cross-Sectional Study

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Int J Ep 2023;9:7–12.

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Abstract

Objective The vaccine is the greatest weapon in the battle against the coronavirus disease (COVID) pandemic. Even though COVID-19 vaccines are considered safe in people with epilepsy (PWE), a sizable proportion of PWE are concerned about the safety of vaccines such as precipitation of seizures. The aim of this study was to assess the frequency of COVID-19 vaccine administration, factors affecting the vaccine hesitancy, and side effects of vaccine among PWE.

Methods In this cross-sectional analytical study between December 2021 and August 2022, we included PWE > 15 years attending the epilepsy clinic irrespective of gender. We recorded the demographic and clinical details, COVID-19 vaccination status, and vaccine hesitancy. Those who had received two doses were considered as fully vaccinated.

Results We recruited 226 participants with a median age of 31.5 (15) years. Ninety-six (42.5%) PWE were women and 153 (67.7%) were of rural domicile. Only 96 (42%) had received two or more doses of any COVID-19 vaccine. After vaccination, 45 (30.8%) PWE complained of at least one general side effects and five PWE experienced seizures. Fear of precipitating the seizures was the most common reason for hesitancy in 39 (49%), whereas 26 (33%) PWE were deferred by health care workers. None of the factors such as age ($p = 0.366$), age of onset of seizures, gender ($p = 0.167$), domicile ($p = 0.090$), educational status ($p = 0.619$), and seizure characteristics ($p = 0.675$) were associated with vaccination status.

Conclusion Only 96 (42%) PWE were fully vaccinated against COVID-19 and fear of worsening of the seizure frequency was the most common reason for the vaccine hesitancy. Vaccination was associated with seizures in five PWE. A multicentric population-based study may give better information.

Keywords

- COVID-19 vaccination status
- vaccination hesitancy
- epilepsy and COVID vaccines
- PWE

article published online
August 6, 2024

DOI https://doi.org/10.1055/s-0044-1788264.
ISSN 2213-6320.

Thieme Medical and Scientific Publishers Pvt. Ltd., A-12, 2nd Floor, Sector 2, Noida-201301 UP, India

Introduction

For the last two and half years, the coronavirus disease (COVID) pandemic has been a major factor influencing human life including social, economic, and health domains. Within a few months of the pandemic, different vaccines were developed and introduced globally for emergency use.[1] The vaccine has become the greatest weapon in the battle against the COVID pandemic, preventing severe diseases, emergency, and intensive care unit admissions and thus protecting from mortality. Governments are pushing toward maximum coverage of vaccination among vulnerable populations. In India, as per the Ministry of Health and Family Welfare, 919 million people with epilepsy (PWE) above 15 years have received two doses of COVID-19 vaccine by January 2024. It has been reported that vaccination against COVID-19 is safe and well tolerated in PWE.[2] However, our personal experience is that a sizable proportion of PWE is concerned about the safety of vaccines such as precipitation of seizures. Further, a few PWE were refused COVID vaccination by some health care workers pending a certificate from the treating neurologist. This is in addition to other reasons due to which the public are hesitant to take the COVID vaccination. All these factors can affect the coverage of vaccination among PWE and, more importantly, can affect the mass vaccination strategy against the COVID pandemic.

There have been only a few publications that discuss these issues among PWE. A study conducted in the early part of the pandemic reported vaccine hesitancy in approximately 53% of the respondents in contrast to the general population of which more than 60% were willing to be vaccinated.[3] Most of the PWE were unwilling to take vaccination due to doubts about its safety and efficacy, and about one-third of them had a misconception that the vaccines are not recommended for PWE as they might increase the severity of the disease. A survey among PWE conducted in China showed that only 130 out of 557 (23%) participants attending the hospital had been vaccinated, although another 53% reported to be willing to take the vaccine in future.[4] Another report from Germany indicates that 82 out of 313 PWE attending the hospital were either vaccinated or willing for vaccination.[5] Only two of these participants had an increase in seizure frequency.

In India, since more than one vaccine is available, there are further questions about the relative safety of these vaccines. Through this study, we tried to assess the frequency of vaccine administration among PWE, factors affecting the vaccine hesitancy, and side effects (disease-specific and general) of vaccine among those who are vaccinated.

Materials and Methods

We conducted a cross-sectional analytical study among PWE and their caregivers attending our epilepsy clinic, catering to a population from five states of Southern India, from December 2021 to August 2022. The primary objective was to assess the status of COVID-19 vaccination among PWE attending the tertiary care epilepsy clinic. Our secondary objectives were to identify factors associated with hesitancy toward COVID-19 vaccine administration and the occurrence of vaccine-related side effects, both general and disease-specific side effects.

We included PWE, aged > 15 years attending the epilepsy clinic of our institute irrespective of gender and excluded those who could not give reliable history (language issues, mental subnormality, not accompanied by a reliable attendant). We consecutively recruited the participants from the epilepsy clinic after verifying inclusion and exclusion criteria (►**Fig. 1**). Recruitment was started after getting permission from the institute's ethics committee. Participants were recruited with the help of medical social workers after getting written informed consent or assent. We recorded the details by direct interview and/or from previous medical records in hospital information system.

A data collection proforma was created to document the relevant details of the study participants using the REDCap electronic data capture tools hosted at our institution's server.

In the process, we set out to identify the demographic details of the included PWE who encompassed their education level, settled in urban or rural settings, etc. We also recorded the clinical characteristics and epilepsy-related details among PWE (age of onset of seizures, type of seizures and epilepsy, frequency of seizures, antiseizure medications [ASMs], electroencephalography, and imaging findings), COVID-19 vaccination status (vaccinated or not), and hesitancy (reason for not administering vaccine) among PWE.

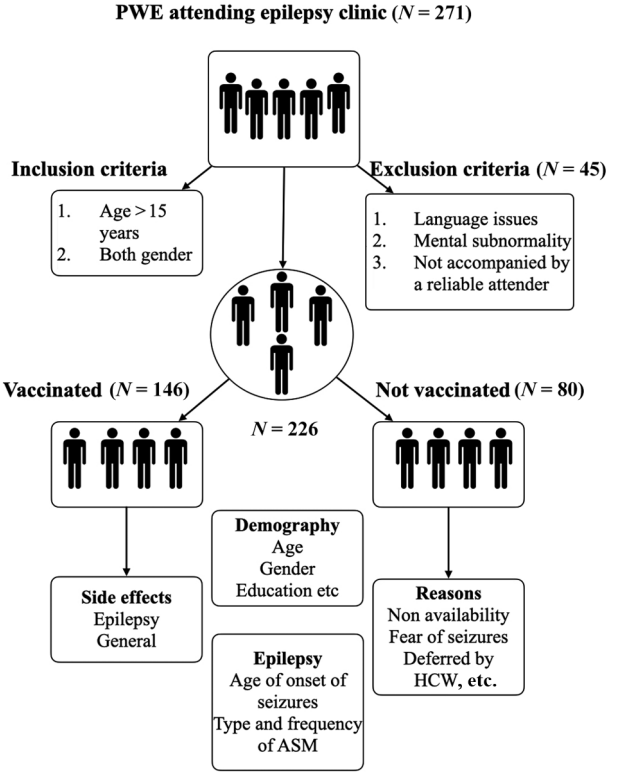

Fig. 1 Recruitment and data collection procedure for PWE presenting to our epilepsy clinic. ASM, antiseizure medication; HCW, health care worker; PWE, people with epilepsy.

We tried to collect the vaccination certificates to confirm COVID-19 vaccination status, whenever available. Those who had received one dose were considered as partially vaccinated and two doses were considered as fully vaccinated.

We recorded the reasons for the PWE who had not received their vaccination yet, such as the following: non-availability of vaccines in the locality, fear of aggravation of seizure frequency, health care workers refusing to administer without a neurologist's certificate, general hesitancy against vaccination, recent COVID infection, any other reasons, etc.

Vaccine hesitancy was defined as "delay in acceptance or refusal of vaccination despite availability of vaccination services."[6]

Among those who were already vaccinated, the date, name of the vaccine, booster dose, and occurrence of side effects, if any (general side effects such as fever, body ache, and epilepsy-specific side effects such as precipitation of seizures [if within 72 hours of vaccination]) was recorded. An event occurring within 72 hours of vaccination is commonly accepted as being associated with that vaccine; however, this does not prove causation.[7] We also educated those who are not vaccinated about the advantages and safety of COVID vaccines and urged them to get vaccinated.

Sample Size

We estimated the required sample size using the formula for estimating a single proportion. It was expected that approximately 30% of PWE attending tertiary care epilepsy clinic would be vaccinated for COVID-19 and at a 5% level of significance with 6% absolute precision. The estimated minimum sample size was finally agreed upon to be 226, and these 226 participants were recruited, as they presented to us at the hospital's epilepsy clinic.

Statistics

Continuous variables, such as age, age of onset of seizures, duration of epilepsy, frequency of seizures, are expressed as mean $\pm$ standard deviation or median with interquartile range based on the normality of data. Normality of data was assessed using the Kolmogorov–Smirnov test. Categorical variables such as gender, type of seizures, epilepsy syndrome, vaccination status, side effects, etc., are expressed as frequency/proportion.

The comparison of the continuous variables mentioned above in relation to the vaccination status was performed by using the independent Student's *t*-test or the Mann–Whitney U test. The association of different categorical variables mentioned above with vaccination status was explored by using the chi-square or the Fisher's exact test. All statistical analysis was performed at a 5% level of significance using the SPSS version 28.

Results

We screened 271 PWE, out of whom we recruited 226 participants. Ninety-six (42.5%) participants were women and 130 were men (57.5%) with a median age of 31.5 (15) years. Majority (177 [78.3%]) of the PWE belong to the neighboring state of Tamil Nadu, followed by Pondicherry (44 [19.5%]), and 153 (67.7%) participants were of rural domicile. Out of 226 PWEs, 121 (62%) had $\leq$10 years of education and 144 (63.7%) were married. Eleven (4.9%) PWE had a delayed development, and one was deaf and dumb, and five had febrile seizures. Median age of onset of seizures of the PWE was 16.0 years (16.5); median duration being 11 (16.0) years. Ninety-eight (43%) PWE experienced more than one seizure per month, whereas 48 (21%) experienced less than one seizure per year. Six PWE were not on any ASMs, and among the 220 PWE on ASMs, 98 (43.4%) were on monotherapy, 69 (30.5%) were on dual therapy, whereas the remaining 53 (23.5%) were on $\geq$3 ASMs. Majority 129 (57%) of the PWE had focal onset seizures. A few PWEs had comorbidities in the form of hypertension in 7 (3%), diabetes mellitus in 12 (5.3%), bronchial asthma in 1, and tuberculosis in 1 patient.

Vaccination Details

We found that 146 (64.6%) PWE had taken at least one dose of any COVID-19 vaccine, whereas the remaining 80 (35.4%) had not taken any vaccine. Out of these 146 PWE, 50 (22.1%) were partially vaccinated with one dose, compared with 88 (38.9%) with two doses. Only 8 patients (5.5%) had taken a booster on top of the two doses. We found that 93 (63.7%) PWE had received Covishield vaccine (ChAdOx1 nCoV-19 Corona Virus Vaccine [Recombinant]) and 29 (20%) received Covaxin, which is a whole inactivated virus-based COVID-19 vaccine, whereas in 24 (16.4%) we could not verify the name of the vaccine they had received. After vaccination, 45 (30.8%) out of the 146 PWE who had received the vaccine complained of at least one vaccine-related general adverse effect (►**Table 1**). Five PWE experienced seizure-related side effects following their vaccination. The same has been recorded with description of the event as given in ►**Table 2**. We considered the seizures associated with vaccine administration due to the close proximity of seizures with the day of vaccination (three on day 1, one each on day 2 and 3) in the absence of other precipitating factors. All those were adherent to their ASMs.

Table 1 Frequency of general side effects experienced by people with epilepsy post-COVID vaccination

Serial number	General side effects postvaccination	Frequency (%)
1	Fever	26 (17.9)
2	Muscle pain	13 (8.9)
3	Chills	1 (0.7)
4	Vomiting	2 (1.4)
5	Diarrhea	0 (0)
6	Fatigue	3 (2.0)
7	Headache	4 (2.7)
8	Pain at injection site	7 (4.7)
9	Other	4 (2.7)

Table 2 Description of seizure-related side effects experienced by people with epilepsy post-COVID vaccination

Serial number	Age/gender	Epilepsy characteristics	Event	Vaccine
1	19/M	No prior Epilepsy/seizures	One episode of TCS on the day of vaccination associated with fever	Covishield first dose
2	22/M	MTS operated (ATL + AH) in 2018 on tapering ASM. No seizures postsurgery, till vaccination	One episode of FIAS 24 h later	Second dose of Covishield
3	18/F	MTS waiting for surgery on 2 ASMs. Usual frequency is ~3 per month	Eight episodes of FIAS on the day of vaccination	Covaxin first dose
4	49/M	Posttraumatic epilepsy	One episode of TCS on the day of vaccination	Covishield first dose
5	35/F	Epilepsy with healed granuloma	One episode of TCS 48 h after vaccination	Covishield first dose

Abbreviations: AH, amygdalohippocampectomy; ASM, antiseizure medications; ATL, anterior temporal lobectomy; F, female; FIAS, focal impaired awareness seizure; M, male; MTS, mesial temporal sclerosis; TCS, tonic-clonic seizure.

We also found 80 participants (35.4%) who did not receive even one dose of COVID-19 vaccine. Although the fear of PWE of precipitating the seizures was the most common reason in 39 (49%), a sizable proportion of PWE 30 (38%) were deferred by health care workers short of recommendation from a neurologist. Reasons for the denial have been tabulated in ►**Table 3**.

None of the factors such as age (95% confidence interval: −6.23 to 2.30; $p = 0.366$), age of onset of seizures, gender ($p = 0.167$), domicile ($p = 0.090$), educational status ($p = 0.619$), and seizure characteristics ($p = 0.675$) were associated with vaccination status.

Discussion

In this cross-sectional analytical study performed at a tertiary care epilepsy clinic, we observed that only 96 (42%) PWE were fully vaccinated and 8 (5.5%) had received a booster dose. Out of 146 PWE who had received at least one dose of vaccine, 45 (30%) experienced general side effects and 5 (3.4%) PWE experienced seizure-related side effects. Fear of precipitating the seizure was the most common reason for not receiving the vaccine.

Table 3 Observed reasons and frequency of denial of COVID-19 vaccine by people with epilepsy

Serial number	Reason for denial of COVID-19 vaccine	Frequency (%)
1	Fear of aggravation of seizures	39 (48.7)
2	Worried about vaccine safety	10 (12.5)
3	Lack of vaccine knowledge	4 (5)
4	Vaccine contraindications	0 (0)
5	Pregnancy	4 (5)
6	Deferred by heath care worker	30 (37.5)
7	Others	12 (15)

We observed that even after the availability of the vaccine for more than 18 months only 96 (42%) PWE were vaccinated with two doses of COVID-19 vaccine and another 50 (22%) had received a single dose of vaccine. There are no reports of COVID vaccination status among PWE from India. A recent meta-analysis including 2,589 PWE from 10 observational studies reported that 70% PWE are yet to be vaccinated. [8] The vaccination status among PWE differs according to the country and published year. Massoud et al reported that out of 111 PWE from Kuwait, 30.5% had received two doses of Pfizer BioNTech mRNA vaccine (BNT162b2) by April 2021.[2] Qiao et al reported the observations of a cross-sectional survey conducted in 10 public hospitals in China in June 2021.[4] Only 130 (22%) out of 557 PWE were vaccinated. A more recent study from Hong Kong reported an overall uptake of 51.5% (103/200) and 43% (86/200) had completed two doses.[9] Yang X et al reported the vaccination status among BECTS (benign epilepsy with centrotemporal spike), 64% of 120 participants had received the vaccine by October 2021.[10] A multicentric observational study from Italy reported a high rate of vaccination among adults; 91% (327/358) had received full dose of vaccination.[10] Compared with the recent reports from other countries our vaccination status is low. The rate is low even in comparison with the national vaccination status among the general population. As of November 15, 2022, approximately 950 million, which is 68.8% of the total population were fully vaccinated against COVID-19 and over 74% of the total population has received at least one dose.[11] Neurologists and physicians should actively counsel PWE for vaccination.

We observed that 80 participants (35.4%) did not receive even one dose of COVID-19 vaccine. Fear of worsening of seizures by the vaccine was the most common reason among our participants. Massoud et al reported that fear of adverse effects (42.9%) and fear of epilepsy worsening (23.8%) were

the main reasons for vaccine hesitation.[2] Yang et al reported that 40% of the nonvaccinated population was worried about the worsening of seizures.[12] Qiao et al reported that most of the PWE (82.44%) were worried that COVID-19 vaccination might aggravate seizures.[4] Li et al and Hood et al also reported similar results.[13,14] The second most common reason for hesitancy in our population was the discouragement by the health care workers in the periphery. We found this as a reason for not receiving the second dose in some PWE. Qiao et al and Li et al also mentioned about a proportion of PWE being deferred by health care workers.[4,13] This indicates that we need to educate not only PWE but also health care workers in the periphery regarding the safety of the COVID-19 vaccination and the need for completing the vaccination dose.

In the meta-analysis, the factor that was associated with nonvaccination status was the active epilepsy.[10] However, we did not find any association between vaccination status and seizure frequency or any other demographic- or epilepsy-related factors. Since ours is a single-center study, the result has to be interpreted cautiously.

After the vaccination 45 (30.8%) of our participants developed one side effect. The frequency is much lower compared with the observations by Massoud et al, who reported that 66 (80.5%) out of 82 vaccinated patients developed one side effect after vaccination.[2] Similar high frequencies were observed by Hood et al and Clayton et al.[14,15] However Li et al and Lu et al observed a lower frequency of side effects, similar to our findings.[13,16] Various factors might be involved in such a higher variation including the type of vaccine.

Five of our PWE developed a seizure in close proximity with the vaccination (48 hours). One of them developed new-onset seizures, one person was seizure-free for 3 years after epilepsy surgery. All these persons had received Covishield except one. Massoud et al reported worsening of seizures in five patients and status epilepticus in one patient after vaccination.[2] However, exact timing of the seizures in relation to the vaccines was not mentioned. One of these patients who had seizures after vaccination had status epilepticus within 3 months prior to the vaccination. Chan et al reported only three (1.5%) PWE who developed seizures within 2 weeks of vaccination.[9] All three had developed after the second dose of the BioNTech vaccine. In the Italian cohort, 25 patients (7.65%) had worsening of seizures, mainly within 7 days after vaccination. None had new types of seizures or status epilepticus.[10] Yang et al reported no worsening of seizures among BECTS.[12] Clayton et al reported worsening of seizures in three (20%) PWE with Dravet syndrome.[15] There are reports of new types of seizures and status epilepticus after vaccination.[5,16] A recent retrospective observational study from Spain reported a change in seizure semiology in 5 (1%) and new-onset seizures in 15 (3.5%) patients. Many of those who had new-onset seizures/status epilepticus had comorbidities.[17]

There was another report from Northern India of new-onset focal seizures in a 68-year-old gentleman 4 days after receiving Covishield vaccine.[18] Our observations along with previous reports indicate that even though low some PWE can have seizures precipitated by vaccine or worsening of seizure control. However, this finding should not be considered as a contraindication for vaccination, rather an indication for extra caution.

Strengths and Limitations of Study

We initiated our study with the main objective to observe the vaccination status and the main reasons behind the hesitancy to get vaccinated against COVID-19 for PWE. Not only did we observe the reasons for the hesitancy in PWE, but we also made attempts to counsel them to go forward with vaccination, if deemed appropriate.

In the Indian setting, the government had already undertaken the vaccination campaign well before we started our study. This has helped the public to get sufficient time and push to go for the COVID-19 vaccination, helping us investigate the hesitancy with better accuracy. We could not find any study from India looking at this aspect. This will help the authorities to improve the vaccination drive with a special focus on chronic medical illnesses such as epilepsy.

This was a cross-sectional study with its inherent biases. We elicited the development of both general and epilepsy-related side effects through recall methods. Furthermore, all patients were not well versed with the digital certifications provided by the government, and hence, it was not feasible for us to retrieve and verify all the confirmations.

Conclusion

We observed that only 96 (42%) PWE were fully vaccinated, and fear of worsening of the seizure frequency was the most common reason for not receiving the COVID-19 vaccine. Although low, a few PWE developed seizures in association with vaccination. Educating PWE and health care workers in the periphery is important to improve the vaccination status among PWE. A multicentric population-based study may provide better information.

Funding
None.

Conflict of Interest
None declared.

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