Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Research Paper

Safety and Tolerability of COVID-19 Vaccine in Children With Epilepsy: A Prospective, Multicenter Study

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ABSTRACT

Background: We designed this study to investigate the effects of the coronavirus disease 2019 (COVID-19) vaccine on epileptic seizures, as well as its adverse effects, in children with epilepsy (<18 years).
Methods: This anonymous questionnaire study involved a multicenter prospective survey of outpatients and inpatients with epilepsy (< 18 years) registered in epilepsy clinics in eight hospitals in six cities of Shandong Province.
Results: A total of 224 children with epilepsy were included in the study. Fifty of them experienced general adverse events after vaccination. The most common local adverse events were pain or tenderness at the injection site. The most common systemic adverse effects were muscle soreness and headache. No severe adverse events were reported. There were no significant differences in the number of antiseizure medications ($P = 0.459$), gender ($P = 0.336$), etiology ($P = 0.449$), age ($P = 0.499$), duration of disease ($P = 0.546$), or seizure type ($P = 0.475$) between the patients with and without general adverse events. We found that the risk of seizure after vaccination was decreased in children who were seizure free for more than six months before vaccination. There was no significant difference in the number of seizures during the first month before vaccination, the first month after the first dose, and the first month after the second dose ($P = 0.091$).

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Author contributions: Zhihao Wang and Xiqin Fang conceptualized and designed the study, collected and organized the data, drafted the initial manuscript, and reviewed and revised the manuscript. Tao Han, Chunxiang Li, Aihua Ma, Zhaolun Jiang, Shishen Lv, Wenke Li, Wenxiu Sun, Wenying Sun, Yuxing Gao, Zaifen Gao, Yong Liu, Qiubo Li, Suli Wang, Baomin Li, and Xinjie Liu assisted in collecting data and provided important suggestions for the design of research scheme and the writing of manuscript. Xuewu Liu conceptualized and designed the study, coordinated and supervised data collection, and critically reviewed the manuscript for important intellectual content. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Conclusion: The benefits of vaccination against COVID-19 outweighed the risks of seizures/relapses and severe adverse events after vaccination for children with epilepsy.

Introduction

According to the data of the World Health Organization, there have been approximately 505 million confirmed cases of infection and 6.21 million deaths from the first discovery of the severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) in December.[1] To effectively control the epidemic, the coronavirus disease 2019 (COVID-19) vaccine has been promoted globally; 11.3 billion doses have been inoculated globally.[1]

Epilepsy, as one of the most common neurological diseases, has approximately 50 million patients globally.[2] There has been no consensus on the increase in the susceptibility of the epileptic population to COVID-19 in existing studies.[3-5] However, a meta-analysis has shown that patients with epilepsy have a higher risk of severe disease and mortality than people without epilepsy after COVID-19.[6] Another study has suggested that epilepsy may be an independent risk factor for the death of hospitalized patients with COVID-19.[5] Children infected with SARS-CoV-2 are mainly mild or asymptomatic compared with adults, but a relatively small number of children and adolescents might be at risk for severe COVID-19, especially those with underlying health comorbidities.[7-10] Studies have also found that the SARS-CoV-2 infection can lead to a serious complication called multisystem inflammatory syndrome in children, which includes myocardial dysfunction, shock, and respiratory failure requiring intensive care. Furthermore, children and adolescents can be important transmitters of SARS-CoV-2 in communities.[8,11,12] A systematic review found that 10% of children critically ill due to COVID-19 had epilepsy.[13] Given the threat of COVID-19 to children with epilepsy, vaccination against COVID-19 is critical for patients with epilepsy.

At present, 409 COVID-19 candidate vaccines have been documented: 276 vaccines are in development, 109 are now in clinical testing, and 24 are in use,[14] including protein subunit, inactivated, mRNA, and vector-based vaccines. In China, BBIBP-CorV (Beijing Institute of Biological Products, Beijing China), WIBP-CorV (Wuhan Institute of Biological Products, Wuhan China), CoronaVac (Sinovac Life Sciences, Beijing China), Ad5-nCoV (CansinoBIO, Tianjin China), and ZF2001 (Chongqing Zhifei Biological Products, Chongqing China) have been widely used. BBIBP-CorV, WIBP-CorV, and CoronaVac have been allowed for children aged three to 17 years in 2021. Small-scale clinical trials have shown that the seroconversion rates of neutralizing antibodies in children after two-dose vaccination is more than 96%.[15-17] However, there is limited information on the use of the COVID-19 vaccine for patients with chronic diseases such as epilepsy, and its safety and tolerability are of concern among patients with epilepsy.[18] Studies of other vaccines found that vaccination, except for diphtheria, tetanus, and pertussis and measles, mumps, and rubella, did not increase the risk of seizures.[19] In addition, clinical trials of COVID-19 vaccines have shown no severe neurological adverse events.[20-22] Based on available data, the International League Against Epilepsy (ILAE) has reported that there is no clear evidence that patients with epilepsy have a higher risk of side effects following COVID-19 vaccination. The ILAE specially recommends that patients with epilepsy receive vaccination for COVID-19.[23] In contrast, early national guidelines by China listed severe neurological diseases including "uncontrolled epilepsy" as contraindications.[24] At present, there is no clear definition of "uncontrolled epilepsy."

The limited large-scale studies on the safety and tolerability of COVID-19 vaccines for children with epilepsy motivated this study. We aimed to investigate the effects of COVID-19 vaccines on seizures in children (<18 years old) with epilepsy, as well as their adverse effects.

Methods

Study design

This prospective multicenter study was conducted from November 2021 to March 2022 and involved eight hospitals (Qilu Hospital of Shandong University, Shandong Provincial Hospital, Qilu Children's Hospital of Shandong University, Yantai Yuhuangding Hospital, Affiliated Hospital of Jining Medical, Weifang Maternal and Child Health Care Hospital, Tengzhou Central People's Hospital, and Liaocheng People's Hospital). Shandong Province is located in eastern China and is divided into 16 cities classified into urban and suburban districts according to population density and local economic levels. As of the 2019 census, Shandong had a population of nearly 100 million.[25] Hospitals in China are categorized into three levels, depending on the level of sophistication, equipment available, and staff or bed numbers; level 3 is the highest. Only level 2 and 3 hospitals were included in this study.[26]

Eligibility criteria

We included patients who met the following criteria: having been diagnosed with epilepsy according to the ILAE guidelines, age below 18 years, having had COVID-19 vaccination intentions, and having received at least two doses of vaccines during the follow-up period and by the time of follow-up, the second dose of vaccine had been vaccinated for one month.[27] We excluded any conditions listed as contraindications in national vaccination guidelines.[24] The zero- to two-year-old infants were also not included in this study because the guidelines for vaccination against COVID-19 issued by China did not include them.

Data extraction

All participants were provided a written description of the aims of the present study, and written consent was obtained from them and/or their legal guardians. Questionnaires were administered through face-to-face interviews by trained investigators. During the interviews, participants were asked to complete the questionnaire themselves or with the help of interviewers if they had difficulty reading or writing. Considering that some young participants (aged less than five years) could not understand the meaning of the questions, we allowed their parents to answer the questions for them.

The survey was conducted using a self-administered, anonymous questionnaire that contained questions about the demographic and clinical characteristics of the patients and information about vaccination and its general adverse events.

Seizures were classified according to ILAE Epilepsy Classification 2017 guidelines.[27]

The following information about vaccination and vaccine-related general adverse events was recorded: vaccination date, type of vaccine, and vaccine-related general adverse events after vaccination (tenderness or pain at the injection site, pruritus, mass or induration at the injection site, fever, fatigue, headache, muscle soreness, nausea, vomiting, abdominal pain, and diarrhea). The severe adverse events (such as anaphylactic shock) were also counted. Postvaccine fever was defined as body temperature of > 38.0°C within seven days after vaccination. Severe adverse events are defined by the World Health Organization as those resulting in death, hospitalization, or compelling or persistent disability.[28]

Patients were asked about their seizures at one month, three months, six months, one year, and two years before the vaccination and the type and dosage of antiseizure medications (ASMs) they were taking. The questionnaire included questions about vaccination-related general adverse events, the number of seizures within one month after the first dose, the number of seizures within one month after the second dose, and the types and dosage of ASMs after vaccination.

Ethics statement

This study was approved by the Ethics Committee of Qilu Hospital, Shandong University (2021035) and conducted according to the principles of the Declaration of Helsinki. Written informed consent was obtained from all study participants and/or their legal guardians.

Statistical analysis

The data were analyzed using SPSS version 25. Numeric variables, with a normal distribution, were summarized as means and standard deviations, and those without a normal distribution were summarized as median values. The Shapiro-Wilk test was used to test for the normality of distribution. The Student *t* test was used to compare the data with a normal distribution, and the Mann-Whitney U test was used for data without a normal distribution. The $\chi 2$ and Fisher exact tests were used to determine the differences between groups. Logistic regression analysis was used to investigate the influencing factors of binary dependent variables. The Friedman test was used to evaluate statistically significant differences between the distributions of three or more paired groups. *P* values ≤ 0.05 were considered statistically significant.

Results

Demographic and clinical characteristics

We conducted 247 interviewers from December 2021 to March 2022. In the later follow-up, 23 patients were excluded due to loss of follow-up or noncompliance with the criteria, and 224 patients were finally included in the study. All the patients were injected inactivated vaccine. Among them, 125 (55.80%) were male, 98 (43.75%) were female, and one patient (0.45%) did not want to reveal her or his gender. The median age of children with epilepsy was 8.50 (7.00, 11.00) years. The majority of children included in this study were aged three to 12 years (193 cases, 86.16%); only 13.84% (31 cases) were aged 13 to 17 years.

The median duration of epilepsy among the children was 3.0 (2.0, 4.875) years. Only one patient had a disease duration of more than 10 years. According to etiology, the patients were divided into genetic (17 cases, 7.59%), structural (10 cases, 4.46%), immune (two cases, 0.89%), infectious (four cases, 1.79%), and unknown (191 cases, 85.27%) groups. In this study, 140 (62.50%) children suffered from focal epilepsy, 59 (26.34%) suffered from generalized epilepsy, and 25 (11.16%) suffered from epilepsy of unknown origin.

The statistics of ASM prescriptions before vaccination in children with epilepsy showed that only eight (3.57%) patients did not use any ASMs, 175 (78.13%) patients received monotherapy, 36 (16.07%) patients were taking two ASMs simultaneously, and five (2.23%) patients were taking three at the same time. The types of ASM prescribed did not change after vaccination. The clinical and demographic characteristics of the patients are shown in Table 1.

General adverse events of children with epilepsy after vaccination with the COVID-19 vaccine

A total of 50 patients experienced varying degrees of general adverse events after full vaccination with the COVID-19 vaccine; these were mainly local adverse events (61.19%). It was found that 16.07% of all the patients (36 cases) had pain or tenderness at the injection site; 2.23% (five cases) had pruritus, induration, or a mass at the injection site. The number of patients with fever, fatigue, headache, muscle soreness, nausea and vomiting, and abdominal pain and diarrhea were one (0.45%), four (1.79%), five (2.23%), 10 (4.46%), five (2.23%), and one (0.45%), respectively. There were no serious adverse events such as anaphylactic shock after COVID-19 vaccination. Thirteen children had two or more different general adverse events. For detailed information on general adverse events following COVID-19 vaccination, see Table 2.

To determine the relevant factors underlying general adverse events after the vaccination against COVID-19, we analyzed the clinical and demographic characteristics of children with and without general adverse events (Table 3). The median age of patients with general adverse events was 9.0 (7.0, 11.0) years, and the median age of patients without general adverse events was 8.0 (6.50, 11.0) years. There was no significant difference between the two groups ($P = 0.499$). The median duration of epilepsy was 3.0 (1.50, 5.00) years for the patients with general adverse events and 3.0 (2.00, 4.63) years for those without general adverse events; there was no significant difference between the two groups

TABLE 1.
Demographic and Clinical Characteristics of the Study Population

Variable	Children With Epilepsy (n, %)
Median age (years, (Q1, Q3))	8.50 (7.00, 11.00)
Gender	
Male	125 (55.80%)
Female	98 (43.75%)
Unknown	1 (0.45%)
Median duration (years) (Q1, Q3)	3.0 (2.0, 4.875)
Etiology	
Genetic	17 (7.59%)
Structural	10 (4.46%)
Metabolic	0 (0.00%)
Immune	2 (0.89%)
Infectious	4 (1.79%)
Unknown	191 (85.27%)
Seizure type	
Generalized epilepsy	59 (25.34%)
Focal epilepsy	140 (62.50%)
Unknown	25 (11.16%)
Numbers of ASMs	
0	8 (3.57%)
1	175 (78.13%)
2	36 (16.07%)
3	5 (2.23%)
Vaccine type	
Inactivated vaccine	224(100%)

Abbreviation:
ASM = Antiseizure medication

TABLE 2.
Status of General Adverse Events From the First Dose of COVID-19 Vaccine to One Month After the Second Dose

General Adverse Event	Frequency of General Adverse Event (n, %)
Pain or tenderness at injection site	36 (16.07%)
Pruritus, induration or mass at injection site	5 (2.23%)
Fever	1 (0.45%)
Fatigue	4 (1.79%)
Headache	5(2.23%)
Abdominal pain and diarrhea	1 (0.45%)
Serious adverse event	0 (0.00%)

($P = 0.546$). There were no significant differences in the number of antiepileptic drugs ($P = 0.459$), gender ($P = 0.336$), etiology ($P = 0.449$), and seizure type ($P = 0.504$) between the two groups.

Seizures in children with epilepsy before and after COVID-19 vaccination

During the first month after the first and second doses of the COVID-19 vaccine, 24 (10.71%) of the 224 followed up patients had seizures, and the frequencies increased by varying degrees in 19 (8.48%). Two had a seizure relapse after being seizure free for more than two years. Only one of the 19 people had adjustment of the ASM dosage. One person did not take medications before and after vaccination, and no one changed the type of ASM. The duration in 15 patients was more than two years, and 15 had seizures within a year before vaccination. After vaccination, the seizure frequency of nine people decreased.

The seizure frequencies of the 224 patients were counted a month before vaccination and the first month after the first and second doses. The frequency of seizures was 0.183 during the first month after the first dose of the COVID-19 vaccine, 0.125 during the first month after the second dose, and 0.183 within the month before vaccination. There were no significant differences among the three ($P = 0.091$).

To explore the effect of the seizure-free duration before the COVID-19 vaccination on seizures after vaccination, we analyzed the seizure data of the patients before vaccination. Using the odds ratio (OR) results from Table 4, we can assume that the risk of seizure after vaccination was decreased in children with seizure-free time duration before vaccination of more than six months (one to two months, OR = 2.917, $P = 0.287$; two to three months, OR = 0.875, $P = 0.888$; three to six months, OR = 0.117, $P = 0.070$; six to 12 months, OR = 0.188, $P = 0.023$; one to two years, OR = 0.032, $P = 0.003$; greater than two years, OR = 0.032, $P < 0.001$).

Discussion

The study used data from several hospitals in Shandong province, China. In our patients, the average number of seizures one month before vaccination was 0.183, one-tenth the value of the same category in an Italian study.[29] This finding may be attributed to the enlistment of "uncontrolled epilepsy" as a contraindication by early Chinese vaccination guidelines. "Uncontrolled epilepsy" is not clearly defined, and this may cause some clinicians to be more cautious when vaccinating patients with epilepsy.

In our study, the COVID-19 vaccine did not affect the number of seizures per month. An Italian study arrived at the same conclusion[29]; 8.48% reported an increase in the number of seizures, and 4.02% reported a decrease in the number of seizures after vaccination. We found that the patients who reported an increased frequency of seizures after vaccination either had epilepsy for more than two years or still had seizures in the year before vaccination. Several other studies have also reported that the proportion of patients with increased seizures after vaccination against COVID-19 was no more than 10%.[29,30] In a study on adult patients with epilepsy, the common points of patients with increased seizure frequency after vaccination were as follows: (1) epilepsy duration more than 10 years; (2) treatment with multiple ASMs; and (3) developed a fever after vaccination.[29] In the study by Massoud et al., patients who had more seizures than usual after being administered the COVID vaccine received polytherapy and had had epilepsy for more than two years.[18] This observation may suggest that children with poorly controlled epilepsy are more likely to experience an increase in seizure frequency after vaccination.

We found that the risk of seizure after vaccination was decreased in children who were seizure free for more than six months before vaccination.

TABLE 3.
Clinical and Demographic Characteristics of Children With and Without Adverse Events

Variable	Children With Adverse Events (n = 50)	Children Without Adverse Events (n = 174)	*P*
Median age (years) (Q1, Q3)	9.00 (7.00, 11.00)	8.00 (6.50, 11.00)	0.499
Median duration (years) (Q1, Q3)	3.00 (1.50, 5.00)	3.00 (2.00, 4.63)	0.546
Number of ASMs			0.459
0	3	5	
1	36	139	
2	10	26	
3	1	4	
Gender			0.336
Male	28	97	
Female	21	77	
Unknown	1	0	
Etiology			0.449
Genetic	2	15	
Structural	3	7	
Immune	1	1	
Infectious	0	4	
Unknown	44	147	
Seizure type			0.504
Generalized	12	47	
Focal	30	110	
Unknown	8	17	

Abbreviation:
ASM = Antiseizure medication

TABLE 4.
Logistic Regression Analysis of Seizure-Free Time Before Vaccination and Seizure Results After Vaccination

Variable	OR	95% CI	*P*
Seizure-free time before vaccination			< 0.001
< 1 month	Reference	Reference	
1-2 months	2.917	0.407-20.899	0.287
2-3 months	0.875	0.137-5.576	0.888
3-6 months	0.117	0.011-1.195	0.070
6-12 months	0.188	0.044-0.796	0.023
1-2 years	0.032	0.003-0.313	0.003
> 2 years	0.032	0.007-0.155	< 0.001

Abbreviations:
CI = Confidence interval
OR = Odds ratio

Among our patients, 50 (22.3%) had general adverse events of varying degrees from the first dose of the COVID-19 vaccine to a month after the second dose. The local adverse events were mainly pain and tenderness at the vaccination site (36 cases, 16.07%) and pruritus, mass, or induration at the vaccination site (five cases, 2.23%). Some clinical trials have shown that headache and fatigue are the most common systemic adverse events.[20,21] A real-life study from Czechia also found fatigue and headache as the most common adverse events.[31] Headache and fatigue were also common systemic general adverse events in our study. Similar to our results, the incidence of adverse events in three small-scale clinical trials was 17%, 25.79%, and 27%, respectively.[15-17]

Clinical trials have shown that severe adverse advents are infrequent with BNT162b2 and CoronaVac.[20,21] The incidence of severe adverse events was 0.1% for both vaccines. No serious adverse events were reported in small-scale clinical trials for children.[15-17] No patient reported severe adverse events in our study.

In conclusion, on the basis of the good safety and protective efficacy exhibited by the vaccine, children with epilepsy, as a potential at-risk population, can be better protected by vaccination from the threat of COVID-19.

We explored the relationships between patient clinical and demographic characteristics and general adverse events after vaccination. No demographic and clinical characteristics, including the type of epilepsy, cause of epilepsy, patient age, duration of epilepsy, and the number of patients using ASM, were associated with vaccine-related general adverse events in our study. Von Wrede et al. indicated that having an earlier onset of epilepsy and using fewer ASMs can predict a vaccine adverse event with an accuracy of 83.3%.[32] Massoud et al. found that receiving multiple therapies was associated with a higher incidence of vaccine adverse events, whereas no association was found with the duration of epilepsy.[7] In our study, there were 191 cases of epileptic classification with unknown etiology, which may have influenced our conclusions. In addition, the few patients with immune and infectious epilepsy may also have affected our results. The differences between the findings of our study and the other studies may be attributed to the different populations.

Our study has limitations. First, the self-reported questionnaires used in this study may have led to information bias. Some patients or their families may have ignored or exaggerated some situations when answering the questions. Second, most of the child patients we recruited were aged ≤12 years, and our results may not accurately reflect the situation of adolescent patients with epilepsy. Third, we did not analyze the manufactures of different inactivated vaccine in our study, which may cause us to ignore the differences between different inactivated vaccines. Fourth, the participants of this study were mainly from east China and are not representative of the country as a whole. Fifth, we partially cited in the article studies focused on adult populations, and these conclusions may have some differences from the actual situation in children. Larger cohort studies are needed in the future to improve the understanding of the safety of vaccination in children with epilepsy.

Conclusion

Data from this study suggest that vaccination against COVID-19 is safe and well-tolerated by patients with epilepsy. The vaccine did not affect the number of seizures patients had per month. The incidence of general adverse events after vaccination was 22.32%; they were mainly local adverse reactions. No severe adverse events occurred. A few patients (8.48%) experienced an increase in seizures after vaccination; this may be due to poor epilepsy control. We found that the risk of seizure after vaccination was decreased in children who were seizure-free for more than six months before vaccination. The existing research on adults and children shows that the COVID-19 vaccine has good protective effect and low adverse reactions. Overall, we believe that the benefits of vaccination against COVID-19 outweigh the risks of seizures and relapses and severe adverse events after vaccination in children with epilepsy.

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