

Role of Routine Benzodiazepin in Eliciting Classical Electroencephalogram (EEG) Response in Suspected Sub-Acute Sclerosing Panencephalitis (SSPE) Cases

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Abstract

Background: EEG could be normal or atypical in spite of suggestive clinical features and positive measles Ab of SSPE cases which could have typical EEG pattern after Benzodiazepine. **Objectives:** The purpose of the present study was to find out the necessity of administration of benzodiazepine during EEG recording of SSPE cases as well as to compare the efficacy of diazepam and midazolam in eliciting EEG pattern. **Methodology:** This double blind, parallel, single centered, non-randomized clinical trial was conducted in the Department of Pediatric Neurology at National Institute of Neurosciences, Dhaka, Bangladesh from July 2014 to June 2015 for a period of 1 (one) year. All the clinical and investigational suspected cases of sub-acute Sclerosing Panencephalitis (SSPE) children in both sexes were included as study population. Others neurodegenerative diseases including Wilson's disease were excluded from this study. Patients were divided into two groups named as group A who were given diazepam and the other group B was given midazolam in IV during EEG recording. The clinical outcomes were measured and were recorded in a pre-designed data sheet. **Result:** The characteristic typical periodic slow wave complex (PSWC) was found only in 8 (30.8%) patients among the 26 (100.0%) before intervention with benzodiazepines. The remaining 18 (69.2%) had non-typical PSWC of which 10 (38.5%) were normal, 3 (11.5%) with atypical PSWC and 5 (19.2%) were with other EEG findings. After intervention with benzodiazepines, 23 (88.5%) had shown typical PSWC and only 3 (11.5%) had non-typical PSWC. Among the typical PSWC cases after inter-

vention, 8 (30.8%) had normal EEG initially, 5 (19.2%) had other EEG finding, 2 (7.7%) had non-typical PSWC and 8 (30.8%) had typical PSWC from the beginning. Of the 3 (11.5%) of the non-typical PSWC of intervention group, 2 (7.7%) had shown no changes in EEG from the beginning and 1 (3.8%) had shown other EEG finding. The difference between before and after intervention was actually statistically extremely significant ($p < 0.0001$). Among the two study groups, 11 (84.6%) and 12 (92.3%) patients had shown typical PSWC respectively in Group A and Group B after intervention. The non-typical PSWC was seen in 2 (15.4%) of Group A and 1 (7.7%) of Group B patients. The statistical difference between the two groups was not significant ($p > 0.05$). **Conclusion:** The role of benzodiazepine is very obvious in eliciting the typical EEG pattern in SSPE patients which has shown the characteristic PSWC in EEG in most cases.

Keywords

Sub-Acute Sclerosing Panencephalitis (SSPE), EEG, Diazepam, Midazolam

1. Introduction

Subacute sclerosing panencephalitis (SSPE) is a progressive neurodegenerative disease with a high morbidity and mortality which is caused by measles virus [1]. This is characterized by cognitive and behavioral deterioration with atonic and/or myoclonic seizures; furthermore high titer of measles antibody in cerebrospinal fluid and typical periodic complexes on electroencephalogram (EEG) are the most suggestive investigational findings of SSPE [2]. The typical periodic complexes which are recorded in SSPE are composed of bilaterally symmetrical, synchronous, high voltage bursts of polyphasic, stereotyped delta waves. EEG recording is very important to diagnose as these findings are almost never seen in any other clinical condition [3]. However, EEG may not be helpful, or may be misleading, in some of the patients. Periodic complexes may not completely meet the characteristics of typical periodic complexes, which are designated as atypical periodic complexes. In addition to typical or atypical periodic paroxysms, several other EEG abnormalities may be seen [4]. Both atypical periodic complexes and the other EEG abnormalities, which are not uncommon, may result in misleading interpretations of EEG findings. EEG may be normal or only moderate, nonspecific slowing, especially in earlier clinical stages [5]. Intravenous diazepam administration during EEG recording is a procedure that helps to diagnose the patients with subacute sclerosing panencephalitis and normal EEG finding [6] [7]. Diazepam could reveal typical periodic complexes in such cases. Although diagnostic contribution of this procedure in subacute sclerosing panencephalitis has been known, it has not been well studied in the literature. Effects of diazepam on atypical EEG abnormalities have not been documented either. Furthermore, no another drug has been compared with diazepam. It is

not clear whether this effect of diazepam is drug specific or whether another drug with pharmacological or clinical advantages could be utilized in this procedure. Midazolam, as a short-acting benzodiazepine, seems to be a reasonable option for this purpose. It has a shorter half-life (0.8 - 1.8 hours) with rapid hepatorenal elimination [8]. Because midazolam may have fewer respiratory side effects compared with diazepam, it has been used more frequently in recent years, particularly in certain situations such as a prehospital setting [9]. The purpose of the present study was to find out necessity of administration of benzodiazepine during EEG recording of SSPE cases as well as to compare the efficacy of diazepam and midazolam in eliciting EEG pattern.

2. Methodology

This study was designed double blind, parallel, single centered, non-randomized clinical trial was conducted in the Department of Pediatric Neurology at National Institute of Neurosciences, Dhaka, Bangladesh from July 2014 to June 2015 for a period of 1 (one) year. All the clinical suspected cases of sub-acute Sclerosing Pan-encephalitis (SSPE) children in both sexes were included as study population. The clinical findings included deterioration of intellect, behavior and scholastic performance, myoclonic jerks, difficulty in vision, standing or walking and other pyramidal or extrapyramidal signs. Others neurodegenerative diseases including Wilson's disease were excluded from this study. Patients were divided into two groups named as group A who were given diazepam and the other group B was given midazolam in IV form during EEG recording. The dose of Diazepam and Midazolam was 0.3 mg/kg very slowly (over 30 - 60 seconds). The purposive sampling technique was used to include the patients after fulfilling the inclusion and exclusion criteria. The odd number cases were recruited in the group A and the even numbers of patients were recruited for group B. The measles IgG and IgM antibodies were detected in all patients from CSF and serum. The negative result patients were excluded from this study. The EEG patterns were recorded in a pre-designed data sheet. The bilaterally symmetrical, synchronous, high voltage bursts of polyphasic, stereotyped delta waves were designated as "typical periodic slow wave complex (PSWC)" and non-symmetrical, asynchronous with high voltage delta waves were designated as an atypical periodic slow wave complex. During analysis, the atypical PSWC were included in "non-typical PSWC" along with normal and other EEG findings. The "other" EEG finding included focal or generalized spikes, sharp waves or slow theta-delta waves not resembling periodic complex. The statistical analysis was performed by SPSS V. 20.0 (Atlanta, USA).

3. Result

Among the 26 patients, 14 were below 10 years of age and the rest 12 were 10 years or more; 16 were boys and 10 were girls. We got only 11 patients with a history of prior measles infection. Among them, 4 suffered from measles below the age of 1 year, 4 suffered from 1 - 5 years and 3 after 5 years of age (**Table 1**).

Table 1. Distribution of age and gender among the study population (n = 26).

Age group	Sex		Total
	Male	Female	
Less than 10 years	8 (50.0%)	6 (60.0%)	14 (53.8%)
More than 10 years	8 (50.0%)	4 (40.0%)	12 (46.2%)
Total	16 (100.0%)	10 (100.0%)	26 (100.0%)

*Mean \pm SD = 10.54 \pm 1.503 (Range 8 - 14 years).

The characteristic typical periodic slow wave complex (PSWC) was found only in 8 (30.8%) patients among the 26 (100.0%) before intervention with benzodiazepines. The remaining 18 (69.2%) had non-typical PSWC of which 10 (38.5%) were normal, 3 (11.5%) with atypical PSWC and 5 (19.2%) were with other EEG findings. After intervention with benzodiazepines, 23 (88.5%) had shown typical PSWC and only 3 (11.5%) had non-typical PSWC. Among the typical PSWC cases after intervention, 8 (30.8%) had normal EEG initially, 5 (19.2%) had other EEG finding, 2 (7.7%) had non-typical PSWC and 8 (30.8%) had typical PSWC from the beginning. Of the 3(11.5%) of the non-typical PSWC of intervention group, 2 (7.7%) shown no changes in EEG from the beginning and 1 (3.8%) had shown other EEG finding. The difference between before and after intervention was actually statistically extremely significant ($p < 0.0001$) (Table 2).

Among the two study groups, 11 (84.6%) and 12 (92.3%) patients had shown typical PSWC respectively in Group A and Group B after intervention. The non-typical PSWC were seen in 2 (15.4%) of Group A and 1 (7.7%) of Group B patients. The statistical difference between the two groups was not significant ($p > 0.05$) (Table 3).

4. Discussion

Although sub-acute sclerosing panencephalitis (SSPE) become extremely rare in developed countries, but the incidence is quite high in this part of the world [10]. The role of Diazepam in eliciting characteristic EEG changes of SSPE patients is not well established yet [5]. This study had shown a significant difference between the EEG finding before and after benzodiazepin (diazepam and midazolam). Although all the cases were included in this study having typical clinical features and positive measles antibody, EEG finding was really a mystery. A very few patients had shown the typical periodic slow wave complex (PSWC) in EEG before intervention. Benzodiazepine certainly played a good role in eliciting the typical periodic slow wave complex (PSWC) in these patients [2]. Both the benzodiazepines made these characteristic changes even in the initial normal EEG cases.

The atypical PSWC cases and other EEG findings also converted to typical PSWC after benzodiazepine administration. So this procedure can help us to diagnose as well as rule out subacute sclerosing panencephalitis. Diazepam and

Table 2. EEG findings before and after intervention of benzodiazepine.

EEG Findings	EEG before intervention	EEG after Benzodiazepine	Pvalue
Typical PSWC	8 (30.8%)	23 (88.5%)	
Non-typical PSWC	18 (69.2%)	3 (11.5%)	<0.0001
Total	26 (100.0%)	26 (100.0%)	

*Pearson's Chi square test has been done corrected by Fisher's exact test; *p* value is extremely statistically significant ($p < 0.0001$).

Table 3. EEG findings with diazepam and midazolam.

EEG Findings	EEG with Diazepam	EEG with Midazolam	Total	Pvalue
Typical PSWC	11 (84.6%)	12 (92.3%)	23	
Non typical PSWC	2 (15.4%)	1 (7.7%)	3	>0.05
Total	13 (100.0%)	13 (100.0%)	26	

*Pearson's Chi square test has been done corrected by Fisher's exact test; *p* value is not significant ($p > 0.05$).

midazolam on the other hand, resulted in nearly the same effects on EEG recordings in this present study. Both drugs significantly modified the EEG pattern. The normal EEG, atypical PSWC or other EEG findings were converted to typical PSWC in most cases. The difference between the two drugs was not statistically significantly different [11]. In fact, for the respiratory side effects, midazolam is preferred to diazepam in certain conditions [7]. Although the market price of midazolam is much higher than diazepam, our study found the two drugs similar in efficacy to elicit the EEG findings in SSPE patients. Considering the increased risks of diazepam for deterioration of respiration, such as pulmonary infection, respiratory difficulty, decreased consciousness, midazolam can be considered as an effective alternative. Although we had good enough samples in the particular time, larger samples could make the results different. One study administered both the drugs in same person in consecutive days [11]. It would be better if we could do so. But our ethical clearance committee did not permit to do so. As there are not many similar studies, further studies are required to make final comments.

5. Conclusion

In this unique study, the role of benzodiazepine is very obvious in eliciting the typical EEG pattern in SSPE patients. It had shown the characteristic PSWC in EEG in most cases. Regarding the two benzodiazepines, both are equal to their tasks. But due to some advantages in respiratory side effects, midazolam can be preferred over diazepam in this case. In EEG recording of the SSPE patients, it may be misleading if diazepam or midazolam is not administered.

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