



SEIZURE CLUSTERS: IMPACT OF PHARMACOLOGICAL MANAGEMENT IN PATIENTS WITH SEIZURE CLUSTERS: A PROSPECTIVE, COHORT STUDY

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Abstract

Background: Seizure cluster has a significant negative impact on the quality of life of patients and it can threaten patient's life if it progresses into status epilepticus. Seizure clusters are refractory in nature and as treatment modalities are very less. Therefore, we are evaluating to evaluate pharmacological management strategies in seizure cluster patients with epilepsy. **Materials and Methods:** Consenting patients attending Neurology/Epilepsy clinic at Dayanand Medical College, Ludhiana who fulfilled all the inclusion criteria were enrolled. Patients of any age group reporting > 3 seizures in a day was the main criterion. **Results:** A total of 101 patients were screened out of which 50 patients having cluster seizures were enrolled for the study. Out of them, 7 patients were lost to follow up. Therefore, data of 43 patients was analysed out of which 3 patients were on monotherapy and 40 patients were on polytherapy as pharmacological treatment modality. 26 patients out of 43 had their seizure clusters controlled. 40 patients were on polytherapy and only 3 patients were on monotherapy. Clobazam was the most common drug used. **Conclusion:** Drug optimization can help to control seizure clusters with minimum ADR's despite polytherapy. Treatment of seizure clusters reduces morbidity, cost of treatment, and improves quality of life for patients and their caregivers.

Keywords- seizure, clusters, management

Introduction

The World Health Organization (WHO) has recognized epilepsy as a major public health concern. According to the WHO, about fifty million people worldwide are affected by epilepsy, which makes it the most common neurological diseases worldwide. Epilepsy is a disorder characterized by abnormal neuronal discharges or hyperexcitability of neurons with synchrony without provocation, resulting in seizures. The condition is classified into three subgroups: acquired, idiopathic, and epilepsy with genetic or developmental origins^[1]. The imbalance between excitation and inhibition, leads to seizures^[2]. Although numerous underlying illness mechanisms can contribute to the epilepsy,

the origin of the condition is unknown in approximately half of all global cases^[3]. The risk of **premature death** in people with epilepsy is up to three times higher than for the general population (epilepsy WHO). Treatment for epilepsy in long term care facilities is also an important consideration, as seizure disorders in that setting may be associated with increased comorbidity burden and mortality^[4]

The FDA has recognized seizure clusters as an orphan indication^[5] defined as intermittent, stereotypic episodes of frequent seizure activity that are distinct from patient's usual seizure pattern^[6,7,8]

Many people with epilepsy (PWE) report seizures that occurs in close successions; which are termed as seizure clusters (SC), acute repetitive seizures (ARS), or crescendo seizures^[9]. Seizure cluster is defined as "closely grouped series of seizures". There is no definition accepted universally for a cluster of seizures in PWE and previous studies have used various definitions, including two to four seizures in upto 48h, 3 seizures per 24hrs, three times the baseline seizure frequency, etc.(ref). In our study, patients reporting >3 seizures per day were considered to be having seizure cluster and were enrolled in the study. It is difficult to accurately estimate the prevalence of seizure clusters; prevalence of seizure clusters depends on the definition used^[10]. The frequency of the cluster seizures has been reported in the range of 3% - 76% worldwide among PWE^[11]. In a study by Haut Et al 43% of patients who maintained a seizure diary met the clinical criterion of having three or more seizures in 24 hours^[10].

Seizure clusters are unpredictable, are emotionally burdensome to patients and caregivers. Results from long term clinical trials have shown that treatment for seizure clusters are effective.

Seizure clusters may last 24hr or more, a potential treatment would require an extended duration of action^[12]. We have planned this study to evaluate the pharmacological impact of various AED's on seizure clusters as these repetitive seizures are not very uncommon and place a burden on patients and their caregivers.

Methods

This prospective, observational study was conducted from 15th September 2022 - 14th September 2023 after obtaining approval from the Institutional Ethics Committee. People with epilepsy satisfying the definition of cluster seizures (>3 seizures in 24 hrs) of any age group, gender with any comorbidity were enrolled after obtaining written informed consent. Patient demographics i.e. Gender, age, family history, residential area along with clinical characteristics such as history of semiology, frequency, family history, drug treatment and other concomitant treatment were recorded. Patients on antiseizure medications were optimized for the ASM dosage and frequency according to seizure semiology in their subsequent visits during follow up period of 3 months. Patients were asked to maintain a seizure diary. According to the history narrated by the patients/attendants, seizure semiology was identified and seizure cluster frequency was noted.

STATISTICAL ANALYSIS

The obtained results were entered in Microsoft excel and analysed using descriptive statistics.

Results

One hundred and one patients were recruited with epilepsy. Out of which 50 patients had seizure clusters and 7 patients were lost to follow up in subsequent 3 months time period, therefore data of 43 patients was evaluated. Incidence of cluster seizures reported was 42.5%.

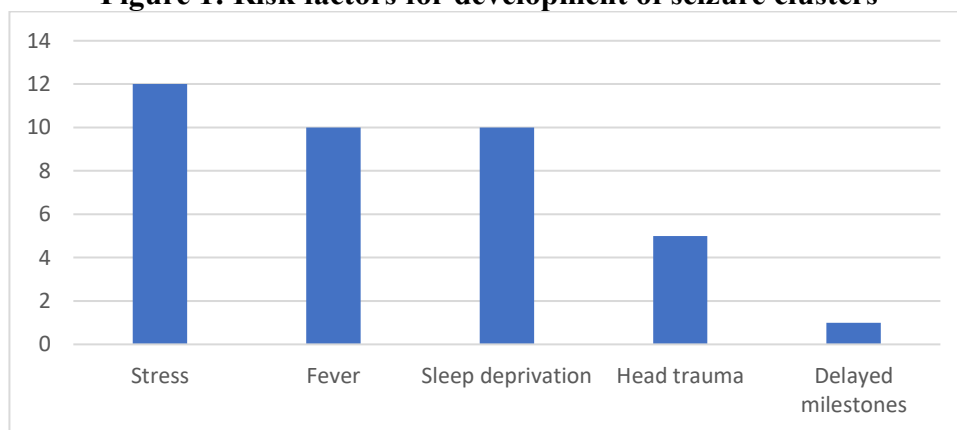
Demographic characteristics of patients have been discussed in Table 1. Majority of the patients(93%) were less than 40 years of age. There was male preponderance in our study with 55.8% of patients being males. Most of the patients belonged to rural areas(69.7%) as compared to patients in urban areas (30.2%). The association between positive family history and occurrence of seizure cluster was observed in only 27.9% of patients.

Table 1: Demographic characteristics of patients with seizure clusters

Parameter	
Age(years)	0-20 (n=20) 21-40 (n=20) 41-60 (n=3)
Gender	Male (n=24) Female (n=19)
Residential area	Rural (n=30) Urban (n=13)
Family history	Present (n=12) Absent (n=31)

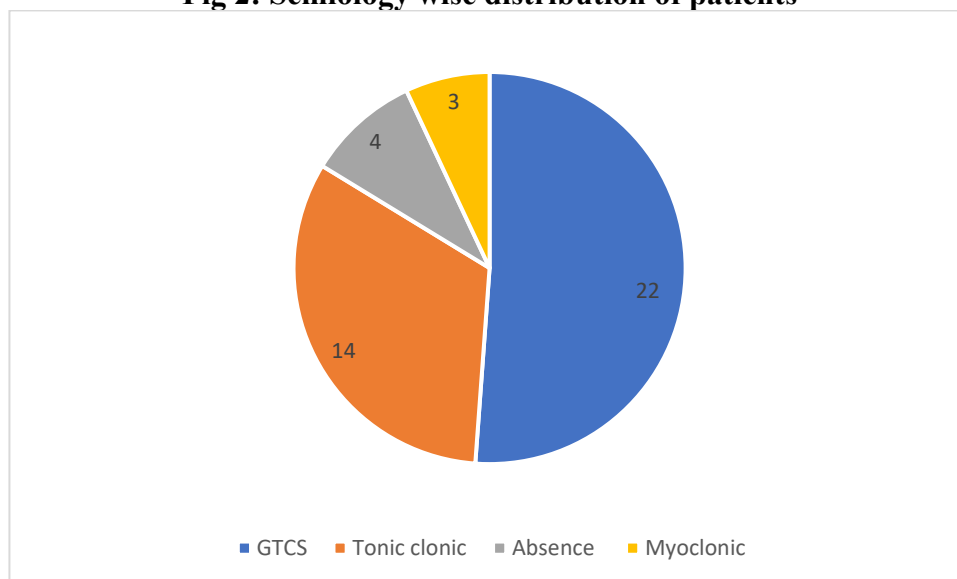
A number of risk factors associated with occurrence of seizure clusters were observed in the study(fig 1). The most common was stress (27.9%) followed by sleep deprivation(23.2%), fever(23.2%), head trauma(11.6%) and delayed milestones(2.3%).

Figure 1: Risk factors for development of seizure clusters



Most of the patients belonged to GTCS semiology(51.1%) followed by tonic clonic semiology (32.5%). Very few patients belonged to myoclonic(9.3%) and absence semiology(6.9%) as depicted in Fig 2.

Fig 2: Semiology wise distribution of patients



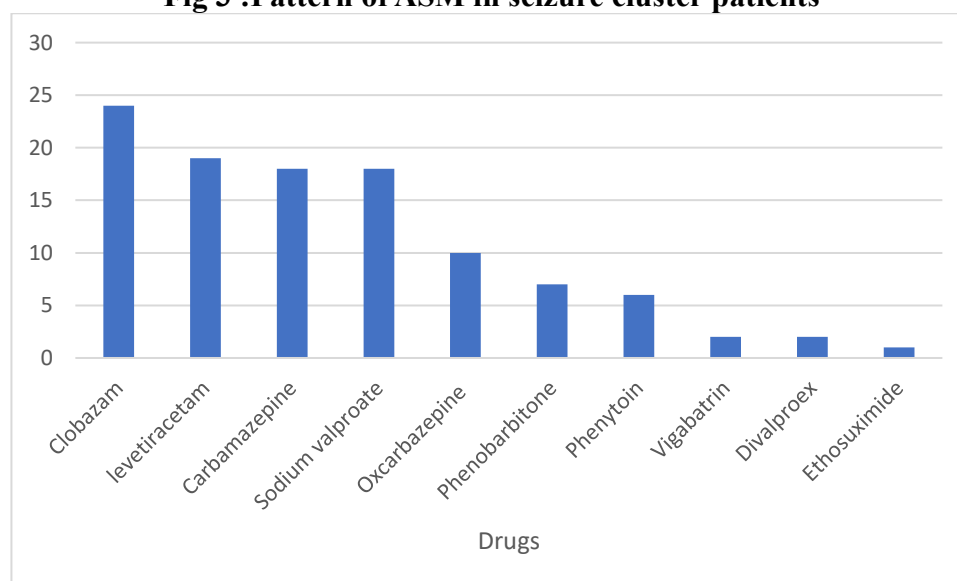
More number of patients of GTCS semiology had 4-5 seizures per day and 6 patients had frequency of 5-10 seizures. Most of the patients (92.8%) of tonic clonic semiology had 4-5 seizures and only one patient had more than five seizures in a day. All the patients of absence semiology had a frequency of 4-5 seizures in a day. Two patients of myoclonic semiology had 4-5 seizures and only 1 patient had 6-10 seizures in a day as depicted in Table 2.

Table 2: Number of seizures in different semiologies

Semiology	4-5 seizures	6-10 seizures
GTCS	16	6
Tonic clonic	13	1
Absence	4	0
Myoclonic	2	1

The most common drug prescribed in our study was clobazam (55.8%) which was primarily used as an add on drug at follow up visits in patients of all semiologies. Levetiracetam was used in 41.8% of patients belonging to various semiologies as an add on drug. However, it was used as primary drug in patients with myoclonic semiology. Carbamazepine and sodium valproate were used in equal number of patients (44.1%) each. Oxcarbazepine was the primary drug in most of tonic clonic semiology patients. Phenobarbitone, vigabatrin, divalproex and ethosuximide were most commonly used as add on drug. The pattern of use of various ASM's is depicted in Fig3.

Fig 3 :Pattern of ASM in seizure cluster patients



Three patients were on monotherapy. Each patient being prescribed sodium valproate, carbamazepine or levetiracetam. All the three patients had their seizure clusters controlled by increasing the dose of the prescribed drugs in subsequent follow ups as discussed in Table 3.

Table 3:

Drugs used in various semiologies	Seizure cluster control	
GTCS	Yes	No
Sodium valproate *+lamotrigine+ carbamazepine+clobazam #	+	
Sodium valproate+ levetiracetam+ carbamazepine* + clobazam	+	
Sodium valproate+levetiracetam*	+	
Sodium valproate* + lamotrigine	+	
Sodium valproate+lamotrigine*+ethosuximide	+	

Sodium valproate*+lamotrigine+clobazam		+
Sodium valproate+ levetiracetam* +carbamazepine +clobazam#	+	
Sodium valproate+ lacosamide* +carbamazepine +lorazepam	+	
Carbamazepine+ phenobarbitone+lamotrigine+clobazam	+	
Carbamazepine+ brivaracetam+clobazam +perampanel\$		+
Carbamazepine + levetiracetam+lacosamide*+clobazam		+
Carbamazepine*+levetiracetam+phenobarbitone		+
Carbamazepine+ levetiracetam*+divalproex+ clobazam	+	
Oxcarbazepine+ clobazam@	+	
Oxcarbazepine+ phenobarbitone*+ lamotrigine+ clobazam @		+
Oxcarbazepine+ phenobarbitone* +phenytoin + clobazam		+
Levetiracetam* +clonazepam		+
Levetiracetam+ sodium valproate*+ phenobarbitone+ clobazam	+	
Phenytoin*+ clobazam		+
Phenytoin +clobazam *	+	
Myoclonic		
Sodium valproate*+carbamazepine\$+ topiramate +clobazam		+
Sodium valproate*+clobazam		+
Levetiracetam+ sodium valproate +clobazam*	+	
Absence		
Carbamazepine*+levetiracetam	+	
Carbamazepine*+ brivaracetam+ clobazam		+
Oxcarbazepine +levetiracetam*		+
Tonic clonic		
Carbamazepine+ levetiracetam+ lacosamide @+ clobazam*	+	
Carbamazepine+ phenytoin*+phenobarbitone +clobazam#	+	
Carbamazepine*+ sodium valproate\$+ clobazam	+	
Phenobarbitone + levetiracetam + vigabatrin @+ clobazam		+
Oxcarbazepine *+ brivaracetam+ divalproex	+	
Oxcarbazepine +levetiracetam\$+ lamotrigine+ vigabatrin\$+ clobazam *		+
Oxcarbazepine+ topiramate* +clobazam		+
Oxcarbazepine +sodium valproate*+ topiramate		+
Oxcarbazepine *+sodium valproate	+	
Levetiracetam+ carbamazepine*		+
Levetiracetam +sodium valproate+ perampanel +clobazam*	+	
Levetiracetam *+phenytoin+ clobazam	+	
Levetiracetam+ sodium valproate*	+	
Levetiracetam+ sodium valproate*+carbamazepine	+	

Carbamazepine and levetiracetam were used in GTCS patients whereas sodium valproate was the drug used in absence seizure semiology.

Table 4: Seizure cluster control in patients on monotherapy

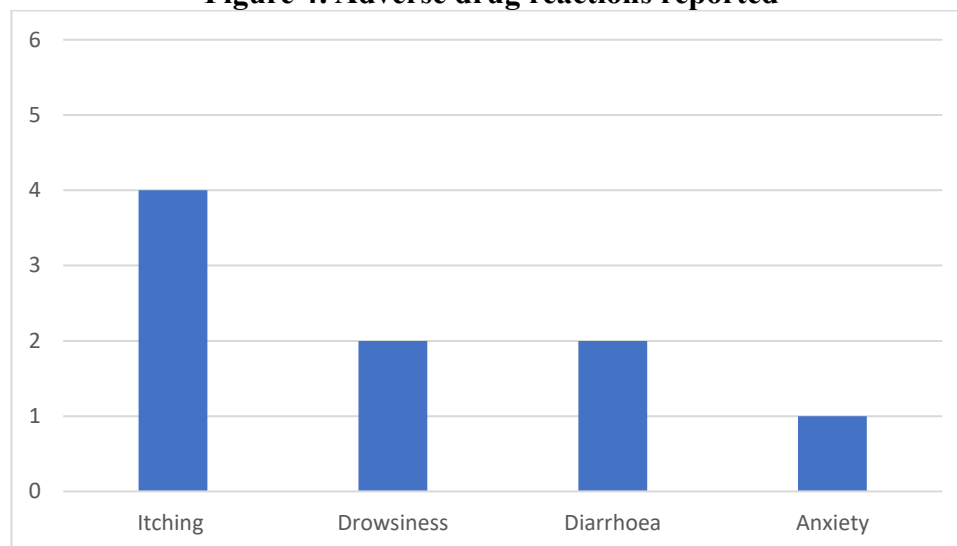
Semiology	No of patients	Drug used	Seizure cluster control	
			Yes	No
GTCS	2	- Carbamazepine - Levetiracetam	+	-
Absence	1	Sodium valproate	+	-

Forty patients were on polytherapy with number of drugs ranging from two drugs to four drugs maximum. Most common primary drug used was sodium valproate. The most common intervention used in GTCS patients was increase in dose of primary drug in subsequent visits at follow ups. Five patients out of eight had controlled seizure clusters on sodium valproate as primary drug. It was also observed that more the number of drugs used, the better it lead to control of seizure clusters. Patients of myoclonic and absence semiology had poor outcome of control of seizure clusters. All the patients of tonic clonic semiology having carbamazepine as primary drug lead to control of seizure cluster when used in combination with other drugs. Most of the patients of tonic clonic semiology had controlled cluster seizures when levetiracetam was used as primary drug in combination with sodium valproate and other add on drugs.

#addition of drug, *increase in dose, \$stop of drug, @decrease in dose

The most common adverse drug reaction(ADR) reported in patients of seizure clusters was itching(9.3%). Other ADRs were reported were drowsiness(4.6%), diarrhoea(4.6%) and anxiety (2.3%).

Figure 4: Adverse drug reactions reported



Discussion

Seizure clusters largely affects patient's quality of life.

Maximum number of patients fall in the age group of 0 to 40 years of age and least patients were found in the age group of 41 to 60 years. Similar findings were reported by other studies as well. A study by Jyoti Upadhyay which included sample size of 200 patients has analysed that 44% of patients were among the age group of 30-40 with lesser patients in younger and older age group^[13]. Another study by Getachew et al at Ethiopia reported that out of 265 patients enrolled in a tertiary care hospital, 102(38.5%) were between 21-30 year of age group and n=65 (24.5%) were between age group of 31-40^[14]

There were more number of males who reported with seizure clusters in our cohort of people with epilepsy. Similar results were observed in study by Birinus aazeala from Nigeria in which 73 adult cases with clusters had male: female ratio of 39:34^[15]. Gurumuthy et al reported similar results with males being more affected than females. In another study by Kalyani et al, 65% of enrolled patients were males and 35% were females^[16]. Pasha et al conducted an analytical, cross-sectional study at Bangalore Medical College and Research Institute, Bengaluru and he found that out of 200 patients enrolled, 105 of them (52.5%) of them were males and 95 patients (47.5%) were females^[17]. 61 males (67.8%) and 29 females (32.2%) were reported in a cross-sectional study, questionnaire based study by Chinnaiyan et al which was conducted at Sri Devaraj University Academy of higher education and Research, Kolar, Karnataka^[18]. This higher reported prevalence of epilepsy in males

could be because of the myths associated with epilepsy which make people conceal information regarding epilepsy especially for female patients as it can become a hurdle in their marriage. In addition, we live in male predominant society, so the male family member's health is the first priority in the family and any ailment is promptly reported and treated^[19]

There is heterogeneity of distribution of people with epilepsy in accordance to the area they live in. In our study, most of the patients were from rural areas (69.7%) because of social stigma among society, cultural beliefs, older treatment methods, and a shortage of health care professionals such as neurologists trained in managing epilepsy in the rural area. Besides social issues, the other possible reasons for this observed difference could be due to lack of good facilities for antenatal/postnatal care, birth injury, malnutrition, systemic and central nervous system (CNS) infections, high rates of trauma in rural settings. We have also observed the same scenario with a greater number of reported seizure clusters from rural areas (n=43,65.2%) than urban (n=23,34.8%). Other studies in concordance to our observation are the BURNs study from Bangalore which has reported a nearly twice higher prevalence of epilepsy in rural areas as compared to the urban areas^[20]. Similarly, higher rural rates have been reported for incidence of epilepsy also. An annual rate of incidence of 0.42 per 1,000 per year was reported for rural population by Mani *et al.*, as compared to 0.27 per 100,000 per year for urban population by Banerjee *et al* ^[21]. Due to better connectivity and availability options of patient outreach programs, patients from rural area were more than urban area who visited us. As our institute is a renowned and prestigious centre, the patient population visiting OPD on daily basis is very large. Epilepsy healthcare requires urgent attention in the rural areas, especially by taking into consideration the higher rates of epilepsy in these regions.

According to our study, it was found that PWE with cluster seizures had negative family history in 31 patients (72%). Our results are similar to a study conducted by Kalyani et al who also have reported that majority of patients did not have a positive family history. Out of 60 (100%) patients, 46 (77%) patients did not have family history of epilepsy and rest 14 (23%) patients had a family history of epilepsy (66). In another study conducted by Ranjan et al at IGIMS Patna from January 2017 to February 2018, it has been found that not even single patient out of 154 enrolled had positive family history^[22]. Saad et al conducted a prospective observational study at MESCO college of Pharmacy, Telangana and found that family history was present in only 19 (18.26%) out of total 104 patients enrolled^[19]. As stated by Saba jafarpur, consanguine parents of people with epilepsy are four times common factor than others for developing clusters. This has not been reported in our study as consanguinity is not a common practice in this part of world. Especially, the risk is more in patients with GTCS in whom if family history of seizure is absent, a higher caution is needed for risk of clustered seizures as observed in our study. However, seizure clusters can occur even in the absence of any risk factor^[23]. This low prevalence of family history could be due to social stigma among people with epilepsy because of which patients or their caregivers hide their family history. Based on clinical features, semiology, relevant history & investigations, familial epilepsy was not reported in any of these included subjects. This could be verified by pharmacogenomic testing for familial epilepsies in suspected patients with genetic epilepsy but is not easily available and is expensive. In our study, 63.6% of patients with GTCS semiology had seizure cluster control by dose optimization which led to patients control of seizure clusters. Most effective intervention was increasing the dose of sodium valproate in 3 patients and levetiracetam in 3 patients. The dose of carbamazepine in one patient, lamotrigine in one patient, lacosamide in one patient and clobazam was increased in one patient whereas clobazam was stopped in 2 patients and another 2 patients had addition of clobazam. Therefore, it can be interpreted that maximum effect was observed on increasing the dose of drug. Incidence of seizure cluster reported was 50% in cohort of people with epilepsy. Our findings are similar to the reported incidence of clustered seizure in the literature (13% to 76%) among outpatients^[24]. But this incidence is higher than results by Jafa mehvari & colleagues with 902 patients who also defined cluster seizure as patients self-reported with at least 3 seizures in a 24-hour and reported an incidence of 10.4%^[25].

Conclusion:

Seizure clusters are common in patients with epilepsy and can be associated with adverse outcomes. Drug optimization can help to control seizure clusters with minimum ADR's despite polytherapy. Treatment of seizure clusters reduces morbidity, cost of treatment, and improves quality of life for patients and their caregivers.

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