A Prospective Study on the Prescription Pattern of Anti-Epileptic Drugs in Pediatric Patients

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ABSTRACT

Background: Seizures are sudden, temporary episodes of brain activity that cause changes in behavior, sensation or consciousness and lead to uncontrollable movements. With the expanse of study on seizures, numerous therapeutic measures exist in treating this disease, it is imperative to formulate and develop a comprehensive treatment plan when encountering a patient with either seizure or epilepsy. **Materials and Methods:** This prospective, observational study was performed in a tertiary care hospital, Bengaluru in the pediatric department. The data obtained from the paediatric patients ranged from demographic data, age distribution, primary seizure or epilepsy diagnosis, number of seizure and or epileptic episodes experienced by the patients and data was documented in a standard data collection form. **Results:** The analysis population comprised 47 pediatric patients. The finding revealed a preponderance of patients <1 year were more likely affected with 36.17%. The diagnostic results state that a majority of the seizure patients presented with epilepsy (*n*=15) followed by a tie between status epilepticus (*n*=6) and febrile seizure (*n*=6). A large portion of the study population (*n*=19, 40.42%) were administered Levetiracetam as the mainstay for seizures. **Conclusion:** The conclusion of this study yields the fact that the most prescribed Antiepileptic Drug (AED) was Levetiracetam as it has proven its efficacy. The gender distribution saw a marked difference between the male and female patients, whereby, there were 32 and 15 male and female patients respectively. The distribution of seizure and epilepsy cases in the study population was 17 and 30 cases respectively.

Keywords: Anti-epileptic drugs, Epilepsy, Levetiracetam, Pediatrics, Seizure.

INTRODUCTION

A seizure is a sudden, temporary change in brain function that affects motor behavior and automatic body functions. There are different types of seizures that have been reported based on various factors of their causes and some of them are discussed here. Like epileptic seizures, which are characterized by abnormal brain activity shown on EEG tests, causing symptoms like convulsions. Non-epileptic seizures have symptoms that mimic seizures, but no abnormal EEG activity is detected. EEG Seizures show abnormal EEG readings without noticeable symptoms.[1] Neonatal seizures are a neurological phenomenon in pediatric populations globally, with the majority lasting less than 5 min. Prolonged seizures exceeding 5 min pose a greater concern, while status epilepticus-a potentially life-threatening condition-arises when seizures persist beyond 30 min or occur sequentially without interictal recovery.

Febrile Seizures (FS) are the most common seizure type in children aged 6-60 months, typically occurring in conjunction with febrile illnesses sans evidence of intracranial infection or metabolic disturbances. While the generally accepted age range is 6 months to 6 years, younger children may also experience FS if no alternative explanation exists.[2]

We have different kinds of FS which hold some specific features within and they are as, simple FS (70%): Characterized by brief duration less than 15 min, generalized seizure activity and singular occurrence during a febrile illness. Complex FS (30%): Distinguished by prolonged duration more than 15 min, focal or multifocal seizure activity and recurrent episodes within a single febrile illness, potentially accompanied by post-seizure neurological dysfunction, such as Todd's paresis. Key statistical findings indicate that approximately 5% of FS progress to febrile status epilepticus, while complex FS account for nearly one-third of all FS cases.[3]

Within the pediatric population, distinct disparities exist between older and younger children regarding epilepsy's incidence, underlying causes, frequency of pre-existing neurological abnormalities and history of unprovoked seizures. Epilepsy's disease burden is quantified through two key metrics:

incidence rate and prevalence. Prevalence represents the product of incidence and average disease duration. Notably, epilepsy incidence peaks in infancy, steadily declining throughout childhood and adolescence. It is shown as:

- Infancy (first year) exhibits the highest epilepsy incidence.

- Cumulative incidence rate by age 15: approximately 0.8%.

- Childhood absence epilepsy disproportionately affects girls.[4,5]

India bears a substantial epilepsy burden, with 12 million affected individuals. Childhood epilepsy prevalence varies significantly between rural (6.99/1,000) and urban (5.48/1,000) areas. As most epilepsy cases emerge in childhood, pediatricians play a vital role in addressing this critical health issue, particularly considering unique childhood seizure types like infantile spasms.[6]

Inborn errors of metabolism, although relatively rare, are crucial considerations in paediatric seizure evaluations, as timely diagnosis can facilitate treatable outcomes and improved seizure control.

Prompt identification of these disorders is vital, enabling:

1. Initiation of therapeutic interventions to prevent or mitigate complications.

2. Directed management plans and prognostic counselling.

3. Recurrence risk assessment and prevention strategies.[7]

Over 200 metabolic diseases are known to induce seizures, often as a primary manifestation or part of complex phenotypes encompassing neurological and metabolic abnormalities.

Metabolic disorders precipitate seizures through various mechanisms, including:

1. Accumulation of toxic metabolites (e.g., ammonia) causing neurotoxicity.

2. Hyperammonaemia, characteristic of urea cycle disorders and organic acidaemia.

3. Astrocyte swelling and brain oedema resulting from increased glutamine synthesis.[8]

There are various classifications of anti-epileptic drugs which are chosen for the treatment for the treatment of epilepsy and seizures in paediatric patients. Some are, Phenobarbital, which is an effective medication for controlling seizures, it works by enhancing the effects of GABA, a calming neurotransmitter in the brain and suppressing seizure activity. It is safe and effective for neonates thus controlling seizures in 43-85% of affected infants. Having slow oral absorption with intramuscular absorption of

2-4 hr and rapid with Intravenous (IV) administration. A loading dose is 20 mg/kg IV and the Maintenance dose: is 3-4 mg/kg orally per day with additional bolus doses of 5-10 mg/kg to 40 mg/kg may be given until seizures subside.[9]

Phenytoin serves as a viable alternative when phenobarbitone's maximal dosage of 40 mg/kg proves ineffective or elicits adverse reactions, such as respiratory depression, hypotension, or bradycardia. Its intravenous administration entails a loading dose of 20 mg/kg, infused at a carefully calibrated rate of 1 mg/kg/min or less, under rigorous cardiac monitoring.

To ensure optimal compatibility, phenytoin must be diluted in normal saline, precluding co-administration with dextrose solutions. In cases of refractory seizures, a supplementary dose of 10 mg/kg may be warranted. Maintenance therapy involves a precisely titrated dosage of 3-5 mg/kg/day (capped at 8 mg/kg/day), divided into 2-4 carefully spaced increments. Notably, oral suspension is contraindicated in neonates due to its erratic absorption profile, rendering intravenous administration the preferred modality.[1]

Diazepam is the most widely available benzodiazepine and plays a crucial role in acute seizure management. For optimal efficacy, dosing is tailored to the administration route: intravenous administration involves 0.25 mg/kg (0.05 mL/kg), while rectal administration, reserved for pre-hospital or resource-limited settings and utilizes 0.5 mg/kg (capped at 10 mg). Importantly, in cases of severe growth restriction or malnutrition, dosing should be guided by the child's physiological age rather than chronological age to ensure precise treatment.[10]

Lorazepam, when IV administration is done with the dose of (0.1 mg/kg/dose, up to 4 mg) demonstrates exceptional efficacy in seizure management, boasting swift onset, robust anticonvulsant activity and sustained duration of action. This benzodiazepine's distinct receptor-binding properties confer a marginal therapeutic advantage over diazepam, particularly in mitigating seizure recurrence and minimizing respiratory complications.[11]

Clobazam when taken orally at 0.3-1 mg/kg/day for 2 days, effectively prevents febrile seizure recurrence. However, its benefits come with considerations. The medication's sedative effects may mask early signs of meningitis, requiring vigilant monitoring. Additionally, some children may experience irritability or restlessness as adverse reactions to clobazam therapy.[12]

Levetiracetam is a novel anticonvulsant agent and has gained prominence in neonatal seizure management due to its unique mechanism of action, modulating presynaptic neurotransmitter release to mitigate seizure activity. Initiated at 10 mg/kg/day, the dosage is incrementally titrated by 10 mg/kg/day every 3 days to achieve a therapeutic threshold of 30 mg/kg/day. For refractory seizures, further escalation to 45-60 mg/kg/day can be undertaken,

leveraging levetiracetam's favourable pharmacokinetic profile and efficacy in reducing seizure frequency and severity.[13]

MATERIALS AND METHODS

Study design

This is a prospective and observational study, conducted in the inpatient department of pediatrics in a tertiary care hospital in Bangalore. A study period of 6 months was carried out on pediatric patients diagnosed with seizures. Pediatric patients below the age of <=10 years and receiving anti-epileptic drugs during hospital stay and those who were already on AEDs in their existing treatment were selected for the study. Any patients who were above the age of 10 years, under any sort of chemotherapy or radiation therapy and diagnosed with any other underlying comorbidities were not selected as samples for this study.

As for collecting the data, a standard-designed data collection form was used and an informed consent form and Patient medication history chart were considered.

During the study period, a total of 47 pediatric patients were included as the sample in this study. Detailed data collection form was framed to access the patient's demographic details, seizure type, onset and duration of each episode, years of diagnosis, all the information on treatment related to drugs, dose, duration of treatment, route of administration and other relevant data. Patients were enlisted for the study based on inclusion and exclusion criteria, those who met the required criteria were voluntarily enrolled, with documented informed consent forms signed by their respective.

RESULTS

The primary outcomes measured were to identify the distribution of age among the paediatric patient population who presented with either seizures or epilepsies. To study the type of seizure and epilepsy that were observed, record the duration of seizure episodes and lastly identify and classify the antiepileptic drugs that were being administered in mitigating these illnesses.

DISCUSSION

In this study, the aim was to discuss the distribution level of antiepileptic medications that are being prescribed in a paediatric population at a tertiary care facility. This evaluation was done by using the concise record and data collection system whereby the patient's age, type of seizure and the medication prescribed were categorically logged and recorded. This was a challenging fact as neonatal/paediatric seizure may be difficult to distinguish from non-seizure/ on-epileptic origins. An analysis was thereby carried out to find out which age group of patients were most predisposed to this illness and the percentage distribution of this has been presented in Table 1. Organizing the data, the subjects were initially grouped based on their gender, which yielded a wide margin between the male and female patients by 63.07% and 36.93% respectively distributed as shown in Table 1. According to the study conducted by Chad Carlson *et al.*, there is a significant gender difference in the occurrence of seizures where male patients are more prone than females due to, male-specific vulnerability, neuronal excitability and imbalance that can lead to hyperexcitability in the male brain, the hormonal influence of testosterone and lower seizure threshold in male.[13]

Table 1: Socio-demographic Data.

Demographic details	Categories	Sample (*n*=47)	Percentage %
Gender	Male	32	68.09%
	Female	15	31.91%
Pediatric age grouping (Age in years)	<1	17	36.17%
	2-3	6	12.77%
	4-5	6	12.77%
	6-7	10	21.28%
	8-9	6	12.77%
	>=10	2	4.26%
Types	Seizures	17	36.17%
	Epilepsy	30	63.83%
Number of episodes (during hospital stay)	1	21	44.68%
	2	13	27.66%
	3	6	12.77%
	4	4	8.51%
	5	2	4.26%
	12	1	2.13%

The assessment of all the data collected shows light on information regarded patient gender as well as age group distribution. The age groups represented in this study were group: <=1, 1-2, 3-4, 5-6, 7- 8, 9-10, <10 as presented in Table 1. As evident by the results obtained at the end of the study, the age group which saw a majority presence of seizures or epilepsies were the patients who were below 1 year (*n*=17, 36.17%). It indicates that rapid brain development causes hyperexcitability of neurons along with incomplete myelination leading to insufficient brain signalling and increased risk of electrical misfiring, vulnerability to metabolic and electrolyte imbalance initiating risk for dehydration and immature thermoregulations resulting in high fever.

In as much as the very low age group with the most occurrence of seizures therefore implying that they're the most frequently treated group with antiepileptics, followed by *n*=10 belonging to the age group of 6-7 years and least seen in the age group of 10 years *n*=2 4.26% in this study. During the study tenure, it was observed that the patients had experienced multiple episodes of seizure attacks during the hospital stay. According to illustrated in Table 1, the maximum number of patients experienced only one episode of seizure attack (*n*=21, 44.68%) and some patients were observed with 2-5 episodes of attacks and with least (*n*=1) with 12 episodes of seizures.

Table 2 describes the different types of seizures or epilepsy attacks being diagnosed within the sample population. In view of this study, *n*=15 patients were diagnosed with simple epilepsy followed by simple febrile seizures (*n*=6, 12.77%) and status epilepticus (*n*=6, 12.77%). 10.64% of patients were diagnosed with complex febrile seizures and febrile seizures. Breakthrough seizure and genetic epilepsy were found in the least number of patients i.e., (*n*= 2, 4.26%).

Table 3 describes a vast majority of the patients underwent a monotherapy treatment regime involving various antiepileptics individually. The most common antiepileptic medication that was being administered was Levetiracetam which was administered to 73.86% of the patient population. From the study conducted by Feriha Hadzagic Catibusic *et al.*, levetiracetam is an efficient antiepileptic drug for different types of epilepsies in childhood, used as mono, di or polytherapy, due to its wide spectrum of action with a favourable safety profile, lesser therapeutic drug monitoring with flexible dosing and better cognitive tolerability.[14]

In a greater number of the patient population(*n*=47), Levetiracetam was given as the first line treatment for their presenting illness which falls in line with various articles that postulate the widespread use of Levetiracetam as the primary drug of choice for seizure and/or epilepsy.[15]

1st generation class of drug including Phenobarbital *n*=2, clonazepam *n*=2, sodium valproate *n*=2, lorazepam *n*=2 was also prescribed respectively.

Table 2: Type of diagnosis.

Type of Diagnosis	Sample (*n*=47)	Percentage %
Epilepsy	15	31.91
Simple Febrile Seizure	6	12.77
Status Epilepticus	6	12.77
Complex Febrile Seizure	5	10.64
Febrile Seizure	5	10.64
Seizure	3	6.38
Viral Fever	3	6.38
Breakthrough Seizure	2	4.26
Genetic Epilepsy	2	4.26

Table 3: Prescribing Pattern of Drugs.

Generation of drugs	Drugs name	Sample (*n*=47)	Percentage %
1st generation	Phenobarbital	2	4.26%
	Phenytoin	1	2.12%
	Clonazepam	2	4.26%
	Sodium Valproate	2	4.26%
	Carbamazepine	1	2.12%
	Lorazepam	2	4.26%
	Nitrazepam	1	2.12%
2nd generation	Lamotrigine	1	2.12%
	Levetiracetam	19	40.42%
	Oxcarbazepine	2	4.26%
	Topiramate	1	2.12%
3rd generation	Lacosamide	2	4.26%
	Clobazam	7	14.89%
	Perampanel	1	2.12%

LIMITATIONS OF THE STUDY

While this study provides valuable insights, its observational nature necessitates an acknowledgement of its limitations, including:

The study's single-center design constrained the sample size, potentially limiting the generalizability of the findings.

Study duration of 6 months may not have captured the full spectrum of outcomes, potentiating introducing temporal biases.

Lack of consistent follow-up among discharged patients lacks completeness of the data.

Patient disengagement and reluctance to provide personal and past information hindered data quality and completeness.

The study evaluated a relatively small population, i.e., *n*=47.

The self-reported nature of the data introduces potential biases, as the accuracy and reliability of participant responses cannot be assured.

POTENTIAL DIRECTIONS FOR FUTURE RESEARCH

• Ongoing research into emerging AEDs.

• Exploration of novel therapeutic targets.

• Continued evaluation of treatment outcomes.

This study provides critical evidence for optimizing anti-epileptic drug therapy in pediatric patients, highlighting the importance of individualized treatment strategies. By aligning prescribing practices with these findings, healthcare providers can improve seizure control, reduce adverse effects and enhance the quality of life for pediatric patients with epilepsy.

CONCLUSION

This clinical study played a pivotal role in assessing the prevalence and treatment patterns of seizures and epilepsy among pediatric patients at a tertiary care facility. The investigation focused on evaluating the demographic distribution, specifically age, gender and treatment modalities employed. In this study it was found that male patients were more significantly prevalent to develop seizures, with the age group <1 years. The major possible reason contributing the male patients is due to neuronal excitability and imbalance, the hormonal influence of testosterone and lower seizure threshold. Potential cause of epilepsy in patients aging less than a year would be rapid brain development along with incomplete myelination leading to insufficient brain signalling, electrolyte imbalance causing dehydration and high fever.

During the study analysis different types of seizures were diagnosed among the study population, where simple epilepsy was predominant followed by simple febrile seizures and status epilepticus. The treatment regimen includes of anti-epileptic drugs either given mono or combine therapy respectively.

In monotherapy regimen Phenytoin, Carbamazepine, Nitrazepam, Topiramide were drug of choice. Through the study conducted it was observed that Levetiracetam was the most frequently prescribed drug because of its better tolerability, efficacy and safety profile.

The conclusions drawn from this study inform evidence-based prescribing practices, ensuring optimized AED selection tailored to pediatric patients' unique needs, enhanced seizure control and improved patient outcomes and informed clinical decision-making aligned with emerging research and guidelines.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ETHICAL CONSIDERATIONS

This study did not require ethical approval because it was an observational study that did not involve any intervention, treatment, or administration of medication. The research was conducted by observing and analysing existing data, without modifying any treatment plans or affecting the participants' care in any way.

ABBREVIATIONS

AED: Antiepileptic drugs; **EEG:** Electro-encephalogram; **FS:** Febrile seizure; **GABA:** Gamma-aminobutyric acid; **IV:** Intravenous.

SUMMARY

This study was a prospective observational study which was conducted in the tertiary care hospital within the duration of six months of time period. During the study period the paediatric patients were included who were diagnosed with the seizure. The patient details were collected in the specially designed data collection form. During the study period the demographics details, medical history, medications history and on-going treatment for the seizures were collected and analysed. Regarding the present treatment, all the datils about prescribed antiepileptics drugs were evaluated and recorded.

During the course of study 47 patients were included for the study and them 32 were male and 15 were female. Maximum patients were under the age of 1 year. Patients were diagnosed with different kind of seizures but most prominently fond was epileptic attack an febrile seizure. On evaluating the prescribing pattern of the antiepileptic drugs, most of the drugs were prescribed from second generation category of AED class. The most commonly prescribed drug was levetiracetam, that is 19 patients (40.42%). Other commonly used drug was clobazam that is 7 patents (14.89%). The conclusions drawn from this study was all the prescribed drugs were under evidence-based prescribing practices, ensuring optimized AED selection tailored to pediatric patients' unique needs, enhanced seizure control and improved patient outcomes and informed clinical decision-making aligned with emerging research and guidelines.

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