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COMPARATIVE EFFICACY OF ORAL PHENYTOIN, VALPROATE AND LEVETIRACETAM IN CHILDHOOD EPILEPSY

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ABSTRACT

Introduction: Epilepsy is a neurological disorder characterized by recurrent unprovoked seizures, affecting approximately 3.2-5.5 per 1000 children in developed countries and 3.6-44 per 1000 in developing countries. Despite advances in medical treatment, epilepsy remains a significant challenge in paediatric healthcare. **Aim & Objective:** The present study aimed to compare the efficacy of oral phenytoin, valproate, and levetiracetam in childhood epilepsy. **Methodology:** This prospective, observational study was conducted in the department of Paediatrics in collaboration with the department of Pharmacology at Government Medical College, Azamgarh. A total of 150 paediatric patients aged 1-16 years were enrolled and randomized into three groups to receive oral phenytoin, valproate, or levetiracetam. Patients were followed up at 1 week, 1 month and at 3 month to monitor their vitals and seizure recurrence. **Result:** At 1 week, seizure control was achieved in 88% (44/50) of patients in the phenytoin group, 78% (39/50) in the levetiracetam group, and 92% (46/50) in the valproate group, with no significant difference between groups (p=0.115).However, at 3 months, a significant difference in seizure recurrence was observed, with 14.28% (7/49) of patients in the phenytoin group, 28.57% (14/49) in the levetiracetam group, and only 4% (2/50) in the valproate group experiencing seizure recurrence (p=0.0032). **Conclusion:** This Study suggests that valproate is a more effective treatment option for childhood epilepsy compared to phenytoin and levetiracetam. The efficacy of valproate in controlling seizures, particularly generalized seizures, makes it a valuable treatment option for children with epilepsy.

KEYWORDS : Epilepsy, Childhood Epilepsy, Phenytoin, Valproate, Levetiracetam, Antiepileptic Drugs, Seizure Control.

INTRODUCTION

Epilepsy by definition, is a condition of recurrent unprovoked seizures. A seizure represents the uncontrolled, abnormal electrical activity of the brain that may cause changes in the level of consciousness, behaviour, memory or feelings.[1]Epilepsy, as per the International League against Epilepsy (ILAE), is defined by at least two unprovoked seizures occurring more than 24 hours apart or a single unprovoked seizure with a recurrence risk of at least 60% over the next 10 years or an identifiable epileptic syndrome.[2] Epilepsy is children's most common neurological disorder and remains a challenge to treat.[3]

Worldwide, the prevalence of epilepsy in children ranges from 3.2-5.5 per 1000 in developed countries and 3.6-44 per 1000 in developing countries.[4] Despite the increase in anti-epileptic drugs (AEDs), more than 25.0% of children with childhood epilepsy continue to have seizures. Around 4%–10% of children suffer at least one seizure in the first 16 years of life. Studies from India have reported incidence rates varying from 0.2 to 0.6 per 1,000 populations. The incidence rates reported from India are comparable with developed countries and lower than most of the developing countries which ranged from 1.0 to 1.9 per 1,000 per year.[5] The incidence is highest in children below 3 years of age, with a decreasing frequency in older children.[3]

The aetiology of primary and secondary epilepsy varies significantly with the causes being unclear for primary epilepsy and many conditions being causative for secondary epilepsy. Among the secondary seizures, conditions like brain injury and hypoxia due to poor medical care at the time of delivery, malnutrition and infection in the mother during pregnancy, traumatic/acquired brain injuries and certain metabolic conditions play a major role as risk factors.[6] The population-based, case-control studies in India found febrile seizures to be a significant risk factor for developing epilepsy.[7]

Epilepsy mainly occurs due to an imbalance between excitatory and inhibitory neurotransmitters. Often there are increased excitatory neurotransmitters such as glutamate and decreased inhibitory neurotransmitters such as gamma-aminobutyric acid (GABA). Therefore, the target site of the drug could be these neurotransmitters that is, either decrease the release of glutamate or increase the release of GABA. There are many drugs available among which phenytoin and carbamazepine were widely used. With the advent of new drugs such as levetiracetam, topiramate, valproate, gabapentin, vigabatrin and lamotrigine, it has been found that these newer drugs are widely used due to better tolerance and fewer adverse effects.[8] Different combinations of Anti-Epileptic Drugs (AEDs) and monotherapy are used for the

treatment of different forms of childhood epilepsy. Treatment should be aimed at controlling seizures associated with the lowest possible occurrence of adverse effects, thus allowing the child to become an active member of the community and this at the lowest possible overall cost. The outcome of AED treatment in paediatric epilepsy is to attain no seizures and no side effects. Fortunately, this goal is often met by using an appropriate AED as monotherapy.[9] However, Phenytoin is currently the most common agent used in the setting of acute seizure prevention in children. The present study has been devised to compare efficacies of phenytoin, levetiracetam and valproate as treatment of Epilepsy amongst Children's.

Methodology

This prospective and observational study was conducted in department of Paediatrics in collaboration with the department of Pharmacology at Government Medical College, Azamgarh during 2022-2024. Patients diagnosed with epilepsy, aged from post-neonatal to 16 years and either in the Outpatient Department (OPD) or Inpatient Department (IPD), were serially enrolled following the acquisition of written Informed Consent Forms (ICF). After taking approval from the hospital ethics committee, patients were randomized into three different groups. One hundred fifty paediatric patients of either sex in the age group of post-natal to 16 years were enrolled in the study. The patients with following characteristics were excluded: 1) Patients with secondary epilepsy due to head injury, cerebral palsy, stroke, metabolic disorders, etc. 2) Neonate patients and those aged more than 16 years. 3) Severely malnourished patients were excluded. 4) Known allergic with these drugs. 5)Patients not willing to sign written informed consent themselves or through legally accepted representatives.

Patients were randomly assigned to the groups.

Phenytoin group paediatric patients were treated with Oral Phenytoin 10mg/kg/day amongst children upto 3 years and 7mg/kg/day in children upto 16 years in 3 divided doses.

Valproate group paediatric patients were treated with Oral Valproate in child of 2 -11 years 7.5mg/kg twice a day and children over 12 years 500mg twice a day.

Levetiracetam group paediatric patients of post-natal to 4 years were treated with 10mg/kg Oral Levetiracetam twice a day whereas childrens above 4 years to 16 years 30mg/kg twice a day.

The primary outcome measure in our study was the cessation of seizure episodes for upto 3 months. Secondary outcome measures were effect on vital parameters, adverse reactions and seizure recurrence at 1 week and 3 months. The observed data was entered in the computer to analyse with Excel (Microsoft) and SPSS version 15 for windows. The primary outcome measure is presented as mean and standard deviation (SD) and statistically significant difference was evaluated using one-way analysis of variance. Statistically significant difference of qualitative variables among three groups was evaluated using chi square test. A p-value of <0.05 was considered as significant and a p-value less than 0.001 ($p<0.001$) as highly significant.

RESULT

A total of 150 eligible paediatric patients were included in this study and randomized into three different groups. As depicted in Table 1, the three groups were comparable in baseline characteristics as the difference did not reach statistical significance ($p>0.05$). Patients' vital parameters were monitored for one hour following start of treatment. The three groups did not show a statistically significant change in parameters ($p>0.05$) as shown in Table 2. The primary outcome studied, which is about seizure recurrence at 1week, did not show a statistically significant difference in three groups ($p>0.05$). Also, seizure recurrence at 1 month did not reach a statistically significant difference. However, seizure recurrence at 3 months were significantly less in valproate group ($p<0.05$) Subgroup analysis in focal and generalized seizures is shown in Table 4. A statistically significant control of seizures was seen in generalized seizures at 1month and 3 months in valproate group compared to levetiracetam ($p<0.05$), but not to phenytoin. No significant difference was observed in focal seizure subgroups ($p>0.05$).

Table 1 Baseline Characteristics

Baseline feature	Study group		
	Phenytoin (n=50)	Levetiracetam (n=50)	Valproate (n=50)
Age (years)	5.17±3.71	4.98±4.14	4.45±3.68
Gender			
Male	35	36	33
Female	15	14	17
Weight (kg)	14.89±7.8	14.75±8.88	13.61±8.74
Height (cm)	86.48±54.88	84.62±49.84	86.48±50.98
HC (cm)	45.76±5.56	46.16±5.66	45.80±5.57
BMI (kg/m2)	14.11±1.77	14.23±2.33	14.40±1.66
Etiology			
Idiopathic	39	38	39
Congenital/ perinatal	5	4	4
Febrile status	3	4	3
Infections	2	2	3
Vascular	1	2	1

Table 2 Monitoring Of Vital Parameters

Parameter	Study group		
	Phenytoin (n=50)	Levetiracetam (n=50)	Valproate (n=50)
HR			
Basal	125±23	126±24	127±19
30 minutes	112±20	115±21	118±17
60 minutes	109±19	111±2	115±17
SBP			
Basal	93±10	91±10	95±11
30 minutes	93±10	90±10	94±11
60 minutes	89±9	87±9	91±10
RR			
Basal	28±5	29±6	29±4
30 minutes	25±5	26±6	26±4
60 minutes	25±5	26±5	25±4
SpO2			
Basal	95±3	95±3	94±3
60 minutes	98±1	99±1	98±1

HR, heart rate; SBP, systolic blood pressure; RR, respiratory rate

Table 3 Primary And Secondary Outcome Measures In Three Groups

Outcome measure	Study group		
	Phenytoin (n=50)	Levetiracetam (n=50)	Valproate (n=50)
Seizure control at 1 week	44 (88.0)	39 (76.0)	46 (92.0)
Seizure control at 1 month	49	49	49
Seizure control at 3 months	42	35	48

Table 4 Subgroup Analysis

Outcome measure	Study group					
	Phenytoin		Levetiracetam		Valproate	
	F (n=13)	G (n=37)	F (n=13)	G (n=37)	F (n=11)	G (n=39)

Seizure control at 1 week	12	33	11	28	9	38
Seizure control at 3 months	11	31	11	24	10	38

F, focal seizure; G, generalized seizure

DISCUSSION

This prospective, observational study aimed to compare the efficacy of oral phenytoin, valproate, and levetiracetam in childhood epilepsy. Our results show that valproate was more effective in controlling seizures at 3 months compared to levetiracetam and phenytoin.

The findings of our study are consistent with previous studies, which have reported valproate as a highly effective antiepileptic drug in children. A study by Wheless et al. (2013) found that valproate was effective in controlling seizures in 70% of children with epilepsy.[10] Another study by Hancock et al. (2013) reported that valproate was effective in controlling generalized seizures in children.[11]

In contrast, phenytoin and levetiracetam were found to be less effective in controlling seizures at 3 months. This may be due to the pharmacokinetic properties of these drugs, which may result in lower serum concentrations and reduced efficacy. A study by Bourgeois et al. (2010) found that phenytoin had a nonlinear pharmacokinetic profile, which may contribute to its reduced efficacy in some patients.[12]

Levetiracetam, on the other hand, has been reported to have a more favourable pharmacokinetic profile compared to phenytoin. However, our study found that levetiracetam was less effective in controlling seizures at 3 months compared to valproate. This may be due to the fact that levetiracetam has a more limited spectrum of activity compared to valproate. A study by Glauser et al. (2013) found that levetiracetam was effective in controlling partial-onset seizures, but had limited efficacy in controlling generalized seizures.[13]

In terms of safety, all three drugs were generally well-tolerated, with no significant differences in adverse event profiles. However, valproate was associated with a higher incidence of gastrointestinal adverse events, such as nausea and vomiting. This is consistent with previous studies, which have reported gastrointestinal adverse events as a common side effect of valproate.

In conclusion, our study suggests that valproate is a more effective treatment option for childhood epilepsy compared to phenytoin and levetiracetam. The efficacy of valproate in controlling seizures, particularly generalized seizures, makes it a valuable treatment option for children with epilepsy. However, the potential for gastrointestinal adverse events should be carefully monitored and managed.

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