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Original Article

Paediatrics Section

Assessment of Effectiveness of Antiepileptic Drugs under BNF Vs Regular Practice in Paediatric Age Group with Epilepsy: A Pilot Study

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ABSTRACT

Introduction: Epilepsy is considered as the most common neurological disorder.

Aim: To compare the effectiveness of Antiepileptic Drugs (AED) under British National Formula (BNF) guidelines and regular practice for different oral antiepileptic medications in enhancing and controlling the patient's disease state and tolerability.

Materials and Methods: The prospective longitudinal cohort study was conducted at Department of Paediatrics of DR. B.C. Roy Postgraduate Institute of Paediatric Sciences, Kolkata, West Bengal, between May 2018 and April 2019 where all the patients (70) were randomly divided into two groups; group I patients were on regular practice medication while group II patients followed BNF guidelines. The doses of the treatment plan was formulated and changed according to the subsequent follow-up. The formulation of doses was done by either increasing the current AED or adding a new AED to the treatment regimen. The Paediatric Quality of Life Inventory (PedsQL) was used to assess the adverse effects in epileptic patients. The data was analysed by using Microsoft Excel database and Statistical Package for the Social Sciences (SPSS) Version 21.0 was used for data computation, p-value <0.05 was considered as statistically significant.

Results: About 23.5% patients of group II had seizures whereas, 53.1% patients of group I had convulsions after six months follow-up. Patients on levetiracetam 10 mg/kg once daily then increased in steps up to 10 mg per kg twice daily (max. per dose 30 mg/kg) monotherapy were experiencing poor seizure control with a number of seizure incidence in group I patients (n=10) compared to patients (n=4) who followed the BNF guidelines. Adverse effects of AEDs such as headache, skin rash, weight loss, weight gain, diarrhoea, dizziness etc., were more in 53.12% patients of group I following regular practice medicines (n=17) compared to 23.5% patients (n=8) of group II followed BNF guidelines. In normal procedure for physical, physiological and overall functioning, there was a decrease in the PedsQL score of group I patients; while in BNF recommendation for physical, physiological and overall functioning, there was an insignificant difference in the PedsQL score of group II patients.

Conclusion: The present study concluded that unbiased individualisation of patients for the selection AEDs and its doses according to BNF guidelines has been found to be significantly effective in reducing the adverse effects as well as improved seizure control in paediatric population.

Keywords: British national formula guidelines, Paediatric population, Seizures

INTRODUCTION

Epilepsy is considered as the most common neurological disorder [1]. From early 20th century to till date, epilepsy is treated by Phenobarbital (PHB). PHB have various side effects apart from that it is considered as the gem of medicine. Much progress has been made in the area of development of AEDs, adversity with epileptic drugs prevails concurrently with the advantage of epileptic drugs [2]. Currently, AEDs which are in use mainly belong to from old generation and new generation; Carbamazepine (CBZ), Primidone (PRM), Valproate (VPA) and Phenobarbital (PHB) belong from old generation. Drugs like Clonazepam (CLNZ), Lacosamide (LAC), Lamotrigine (LMT), Oxcabazepine (OXC), Levetiracetam (LVT), Topiramate (TPM), Rufinamide (RFM) and Pregabalin (PGB) belong from new generation of AEDs [3].

Effects like dizziness, ataxia, dullness, blurred vision and drowsiness etc., are the various side effects of epileptic drugs concentration is mainly common in children; apart from this

side effects can be treated or solved by changing the dose concentration, root of administrations of the AEDs [4]. Jovanovic M et al., and Stevanovic D et al., observed that various factors like learning, psychological, sociological and behavioural disorders are linked as co-morbidities to AEDs [5,6]. The well being as well as routine functioning of the patients have been adversely affected by AEDs where time duration for use of these drugs associates the severity of the adverse effects [6,7].

In comparison to the traditional way of random prescription of drugs without individualisation, BNF guidelines help in the reduction of seizures as well as minimisation of adverse effects of the AEDs by unbiased individualisation of the patients and exact drug prescription [8].

The major concern of the paediatric population is still the lack of guidance regarding commencement and determination of dose of AED monotherapies or novel adjunctive AEDs into polytherapy regimen [9].

Hence, the main focus of this study was the comparison of the effectiveness of AEDs under BNF guidelines and the traditional way of practice for different oral antiepileptic medications in the DR. B.C. Roy Postgraduate, Institute of Paediatric Sciences, formulary (Older generation- VPA, CBZ, Phenytoin (PHT), PRM, PHB and New generation- LMT, LVT, OXC, TPM, CLNZ, VGB, PGB, RFM, LAC) in treating the patient's disease. The subsidiary result was to enhance the safety of AEDs by reducing the adverse effects with a gradual dose titration.

MATERIALS AND METHODS

A single centre prospective pilot, cohort study was undertaken at Department of Paediatrics, Dr BC Roy Postgraduate Institute of Paediatric Sciences, Kolkata, West Bengal, between May 2018 and April 2019. The study was approved by Institutional Ethical Committee (IEC) (BCH/ME/PR/2352). The type of AEDs was classified into conventional AEDs (1st generation) and newer AEDs (2nd generation). The conventional AEDs which were prescribed in the institute include: VPA, CBZ, PHT, PRM and PHB. While the newer AEDs prescribed were: LMT, LVT, OXC, TPM, CLNZ, VGB, PGB, RFM, and LAC. Types of seizures were classified based on the International League against Epilepsy classification into three main types: focal (partial) seizures, generalised seizures and undetermined whether focal or generalised seizures [10].

Study population: The population comprised of all children with epilepsy who were treated at the Neurology Outpatient Department in the hospital. A total of 70 patients were randomly divided into two groups; group I had 35 patients followed regular practice medication; while group II consisted 35 patients which were on BNF guidelines [10]. All the patients were monitored for the safety and efficacy of their AEDs at each visit.

Inclusion criteria: Paediatric patients below 14 years of age, who have been diagnosed with epilepsy.

Exclusion criteria: Patients of more than 14 years age and those on AEDs for other reasons than to control seizure were excluded from the study.

Baseline data: A case report form was filled before the patients participated in the study. The medical notes were examined to establish: weight and height, socio-economic status, seizure type were noted. Subsequent follow-up on drugs such as current anticonvulsant(s) with the doses and formulation, any changes to the treatment plan (either increasing the dose of current AED or adding a new AED to the treatment regimen) were filled.

To assess the negative effects in epileptic patients, Arabic version of The PedsQL [11,12] marker of Health Related Quality of Life (HRQoL) was used. The questionnaire was well explained to the patients and their parents before the study. HQRL was assessed twice during the follow-up; once in the beginning and once after six months.

STATISTICAL ANALYSIS

All the results were expressed in numbers and percentage. The data was analysed by using Microsoft Excel database. The data analysis focused on the presentation of descriptive statistics. SPSS Version 21.0 was manufactured by USA was used for data computation of PedsQL and categorical variables were compared using Chi-square test. Comparison of continuous variables between groups was carried out using unpaired Student's t-test, the p-value <0.05 was considered as statistically significant.

RESULTS

Present study included total 70 children suffering with epilepsy for different duration. Group I patients (35) pursued the regular practice in the titration process which did not follow any specific guideline; while group II patients (35) followed the BNF guidelines. However, three patients of group I while one patient of group II left the study due to different reasons.

Total 10,12 and 10 children of age groups up to 5 years, 6 to 10 years and 11 to 14 years respectively were on regular practice [Table/Fig-1].

Age (years)	Regular practice (n=32)		BNF guidelines (n=34)	
	Male (n=20)	Female (n=12)	Male (n=22)	Female (n=12)
<5	8	2	8	4
6-10	7	5	8	6
11-14	5	5	6	2

[Table/Fig-1]: Age, gender details of patients following regular Antiepileptic Drug (AED) therapy and BNF guidelines.

Total 24 patients of both group was on LVT among them 15 out of 32 of group I were on levetiracetam; whereas nine (9) patients were on LVT of individual AED prescription of group II [Table/Fig-2].

The most prescribed medication in group II (BNF) were LVT (n=9), CBZ (n=4), LMT (n=1), TPM (n=9), OXC (n=2), RFM (n=1) and VPA (n=5). The physician was prescribing topiramate 1 mg/kg once in a day (max. per dose 25 mg), CBZ for 1 mg/kg/day, VPA 0.2 mg per kg daily in divided dose and LVT as adjunctive therapy of 10 mg/kg once daily then increased in steps up to 10 mg per kg twice daily (max.per dose 30 mg/kg) according to BNF guideline recommendation [Table/Fig-3].

It is evident from [Table/Fig-4] that (8) 23.52% patients following BNF had seizures whereas, out of 32 patients following regular practice (17) 53.1% patients had convulsion after six months of follow-up. Patients on LVT monotherapy were experiencing poor seizure control with a number of seizure incidence in group I patients (n=10) compared to patients (n=4) who followed the BNF guidelines. In comparison the physicians use random guideline based on his or her preference; patients were experiencing fewer side effects while maintaining seizure control. The patient using a combination therapy of PHT and LVT were experiencing some behavioural disturbance and sedation effect due to the synergistic side effect of this combination [Table/Fig-3].

Baseline characteristics		Total patients n=66	LVT (n=24)	LMT (n=2)	VPA (n=8)	TPM (n=12)	CBZ (n=7)	OXC (n=4)	PHT (n=2)	PHB (n=5)	RFM (n=2)
Age	1-12 months	6	4	0	0	1	0	0	0	1	0
	1-7 years	31	12	1	4	5	2	3	2	2	0
	8-14 years	29	8	1	4	6	5	1	0	2	2
Gender	Female	24	6	1	3	5	3	1	1	3	1
	Male	42	18	1	5	7	4	3	1	2	1
Epilepsy diagnosis	Partial seizure	18	7	0	2	4	2	1	0	1	1
	Generalised seizure	20	8	2	1	- 1	3	1	1	3	0
	Other seizure type	7	2	0	1	- 2	1	0	1	0	0
	Unclassified	21	7	0	4	5	1	2	0	1	1
Treatment guidelines	Followed the BNF	34	9	1	5	9	4	2	0	3	1
	Followed the Regular practice	32	15	1	3	3	3	2	2	2	1

[Table/Fig-2]: Baseline characteristics of patients with incidence of seizure and adverse effects.
LVT: Levetiracetam; LMT: Lamotrigine; VPA: Valproate; TPM: Topiramate; CBZ: Carbamazepine; OXC: Oxcarbazepine; PHT: Phenytoin; PHB: Phenobarbital; RFM: Rufinamide

Drugs	Initial dose (mg/kg/day)	Maintenance (mg/kg/day)	Daily doses (no.)	Side effect patients (no.)	Side effects
LVT	10	20-60	2	1	Headache, anorexia, somnolence, behavioural-problems
LMT	0.5	2.0-10.0	2	0	Skin rash, somnolence, dizziness, nausea
VPA	0.2	1.0-5.0	2	0	Diarrhoea, weight gain, headache
TPM	1	6.0-9.0	2	1	Weight loss, lethargy, anorexia
CBZ	1	5.0-10.0	2	0	Dizziness, loss of appetite, ataxia, somnolence
OXC	5.0-8.0	10.0-30.0	2	1	Dizziness, ataxia, somnolence
PHT	1.5	5.0-10.0	2	0	Cardiovascular risk, dermatoxic reaction, hepatic injury
PHB	15	5.0-10.0	2	0	Dizziness, ataxia, somnolence, headache, aggression
RFM	10	1.0-5.0	1	0	CNS reaction, hypertension, multi-organ sensitivity, Leucopenia

[Table/Fig-3]: Dose information and its side effects of Antiepileptic Drugs (AED) in children according to BNF guidelines.
LVT: Levetiracetam; LMT: Lamotrigine; VPA: Valproate; TPM: Topiramate; CBZ: Carbamazepine; OXC: Oxcarbazepine; PHT: Phenytoin; PHB: Phenobarbital; RFM: Rufinamide

AEDs	Followed the regular practice (32)		Followed the BNF (34)	
	N	%	N	%
Levetiracetam	10	31.25	4	11.76
Lamotrigine	0	0	0	0
Valpeoate	2	6.25	1	2.94
Topiramate	1	3.125	1	2.94
Carbamazepine	0	0	1	2.94
Oxcarbazepine	1	3.125	0	0
Phenytoin	1	3.125	0	0
Phenobarbital	2	6.25	1	2.94
Rufinamide	0	0	0	0
Overall	17	53.12	8	23.52

[Table/Fig-4]: Patient's treatment with incidences of seizures during treatment.

[Table/Fig-5] shows that there was decrease in score of PedsQL in group I patients on routine practice for physical, psychological and overall functioning; whereas, there was an insignificant difference in PedsQLscore of group II patients in BNF guidelines physical, psychological and overall functioning.

According to the results of the previous reports of Modi AC et al., [16] and Jovanovic M et al., [5] significant effects of AEDs on PedsQLscore β=-0.37, t79=-7.16, p<0.001, 99% CI from -0.50 to -0.24 and r coefficient ranged 0.28-0.59, p-value <0.02 of epileptic children was recorded respectively. In the current study, the HRQoL level of group II patients on BNF guidelines was seen to be changed insignificantly. While the PedsQL score of group I patients was seen to be reduced significantly.

Long-term uses of AEDs in children may lead to various side effects like psychological, behavioural, educational and developmental disorder according to other studies [17]. In this study, the children on BNF guidelines found insignificant change of PedsQL score, this may be due AEDs minimal adverse effects and it has also considerable psychological effect on patients. HRQoL among epilepsy patients have not direct relation with anticonvulsion drugs with its severity and frequency [18].

Children who followed BNF guidelines and treated with small and low dose with titration of AEDs had less side effects in relation to controlling their seizures. To increase the success rate and diminish side effects titration of AEDs has been in use to treat epilepsy treatment since almost 50 years [19].

Parameters	Group I (Routine practice)			Group II (BNF)		
	Before	After	p-value	Before	After	p-value
Physical functioning	80.3±16.4	74.9±18.6	<0.05*	79.8±19.7	80.5±20.6	>0.05 NS
Psychological functioning	76.6±20.7	71.7±17.2	0.031*	76.2±18.3	77.9±16.6	>0.05 NS
Overall functioning	77.8±13.8	72.5±14.4	0.027*	78.1±14.6	79.2±15.7	>0.05 NS

[Table/Fig-5]: Paediatric Quality of Life Inventory (PedsQL) scores in both groups before and after six months.
Values expressed as Mean±SD; *p-value <0.05 Statistcaly Significant (SS) and p-value >0.05 Not Significant (NS)

DISCUSSION

The children following BNF have less chance of seizures as compared to those who were following regular practice; this observation of present study is similar to the study done by Zhuo C et al., [13]. His study showed that patient of epilepsy following individual concentration of drugs found decrease in convulsions.

Other similar studies done by Sarkis RA et al., and Kanner AM et al., observed that as compared to children following regular practice AEDs adverse effect were less found in children following BNF which is similar to present study [14,15].

To enhance the tolerability; compatibility effects of concentration of AEDs were observed by Sarkis RA et al., and Kanner AM et al., [14,15]. Both researchers found that with a purpose to enhance safety and tolerability of some AEDs, requires slow and gradual dose titration which is similar to this study, we found TPM 1 mg/kg once in a day (max. per dose 25 mg), CBZ for 1 mg/kg/day, VPA 0.2 mg per kg daily in divided dose and LVT as adjunctive therapy of 10 mg/kg once daily then increased in steps up to 10 mg per kg twice daily (max. per dose 30 mg/kg) enchanced safety and tolerability.

The old generation AEDs could not control the seizures so efficiently as the new generation AEDs. However, the balance between advantages and side effects of the both generations is still not clear [20]. The patients especially the children who are on AEDs show behavioural change as well as change in cognitive functions. The parents of such children are mostly unable to distinguish the change in the behaviour and cognitive function of the children. Nevertheless the modification and adjustments of AEDs could resolve all these side effects [21].

Limitation(s)

There is paucity of data and this study was conducted with small sample size. Hence, small sample size and frequent changes in AED dosages findings of effectiveness, management and treatments of epileptic paediatric patient's disease state and tolerability cannot be generalised. Furthermore studies with large sample size, strict observation and follow-up of paediatric epileptic patients will support this study.

CONCLUSION(S)

Paediatric patients are benefitted with reduced adverse effects and improved seizure control by the unbiased individualisation of the patients for the selection of AEDs and its doses according to BNF guidelines. To address the efficacy and tolerability of AEDs dose titration in paediatric population, multi-center efforts must be designed in large scale and in future clinically relevant randomised clinical trials must be conducted. In addition, more studies are warranted for the establishment of general guidelines for the rational use of AEDs specially children.

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