Factors Associated with Good Seizure Control in Patients on Valproic Acid

Mastura Ahmad[1], Ab Fatah Ab Rahman[2], Sapiah Sapuan[3]

ABSTRACT

Objective: This study aims to generate a reference range for valproic acid (VPA) in this cohort and determine the factors associated with good seizure control in patients taking this drug.

Materials and Methods: We conducted a prospective, cohort, observational study among patients with epilepsy who received VPA treatment at Hospital Kuala Lumpur. The patients were considered to have good control if they had a 50% or higher seizure reduction in the one-year study period compared with the previous year. The VPA reference range was generated from those patients who had good control and whose drug concentration values were available. Multiple logistic regression analysis with a backward likelihood ratio method was applied to assess the predicting factors for good seizure control.

Results: A total of 242 patients were recruited and followed up for one year. The VPA reference range was determined to be 40-85 mg/L. After multivariate analysis, significant predictive variables for good control were monotherapy [adjusted OR 4.74, 95% CI: 2.258, 9.947, p<0.001], non-smoking [adjusted OR 3.23, 95% CI: 1.099, 9.473, p=0.033], normal brain imaging results [adjusted OR 5.83, 95% CI: 2.507, 13.552, p<0.001], and the absence of stress [adjusted OR 19.98, 95% CI: 9.255, 42.764, p<0.001].

Conclusion: Monotherapy, non-smoking, normal brain imaging results, and the absence of stress are predictive of good seizure control in patients on VPA. However, a serum concentration of VPA in the reference range failed to predict good seizure control.

Keywords: Valproic acid, predictors, seizure

Introduction

For many years, serum drug concentration has been used to assist physicians in the management of epilepsy. However, the early enthusiasm and widespread use of drug analysis have resulted in the inappropriate use of the therapeutic drug monitoring (TDM) service, leading to wastage and increased costs [1, 2]. To provide a more rational use of TDM, several strategies have been suggested to improve its usage. It is no longer acceptable to request TDM without pharmacological justification; instead, controlled sampling with predefined indications has been put into place, which has resulted in a reduced number of requests [3-5].

A recent review found no evidence to support the routine concentration measurement of newly diagnosed patients on monotherapy [6]. Subsequent guidelines have suggested selective, rather than routine, monitoring of drug concentrations [7, 8]. When Minshall et al. [9] considered the impact of the new guidelines, they found a significant decline in the number of drug concentration requests in centers that had adhered to this new recommendation.

In Malaysia, antiepileptic drug (AED) concentrations are monitored in almost all government hospitals [10]; however, the pattern of monitoring may vary among individual hospitals. Regarding the TDM of valproic acid (VPA), the Malaysian Guidelines on the Management of Epilepsy consider monitoring VPA serum concentration to be unhelpful in the treatment of epilepsy [11]. Interestingly, our data showed an increasing utilization of VPA, but did not show a similar trend in the number of drug concentration requests. Consideration of this has provided the background for our investigation of VPA concentration, as well as other factors that could contribute to good seizure control for our patients.

Cite this article as: Ahmad M, Ab Rahman AF, Sapuan S. Factors Associated with Good Seizure Control in Patients on Valproic Acid. Eurasian J Med 2020; 52(1): 41-6.

[1]Department of Pharmacy, Hospital Tengku Ampuan Afzan, Pahang, Malaysia
[2]Universiti Sultan Zainal Abidin School of Pharmacy, Terengganu, Malaysia
[3]Department of Medical, Hospital Sungai Buloh, Jalan Hospital, Selangor, Malaysia

Received: February 12, 2019
Accepted: August 22, 2019

Correspondence to: Ab Fatah Ab Rahman
E-mail: abfatahmy@yahoo.com

DOI 10.5152/eurasianjmed.2020.19039

Materials and Methods

Patients

The present prospective, cohort study was undertaken at the Hospital Kuala Lumpur, Malaysia. Patients were recruited from the Epilepsy Clinic of this hospital. The inclusion criteria were: (i) patients aged 18 years old and above, (ii) those taking VPA (monotherapy or polytherapy) for at least 12 months before the recruitment started, and (iii) those who had given their informed consent. The exclusion criteria were: (i) the VPA dose being modified or discontinued during the study period, (ii) patients who were on any other drugs known to be enzyme-inducers or inhibitors, and (iii) patients who were taking traditional medicine.

Study protocol

For all patients who met the inclusion criteria, the following data were collected at the start of study: (i) demographic and socioeconomic information, (ii) disease and medication-related information, and (iii) the most recent EEG and brain images (i.e., CT/MRI). A seizure diary was used to record any seizure occurrences and any side effects throughout the study period. A baseline seizure frequency was retrospectively derived from the number of seizures that had occurred in the previous 12 months. A blood sample from each patient was taken on any clinic visit during the study period, for the measurement of VPA concentration All patients were followed up for one year.

The study protocol was approved by the Malaysian Research Ethical Committee (KKM/NIH-SEC/08/0804/P10-598).

Outcome of study/ Study end-point

At the end of the one-year follow-up period, the patients were categorized into good control or poor control groups. Patients were considered as good control if they had at least a 50% reduction in the number of seizures in this one-year study period compared with the previous year [12].

Statistical Analysis

Determination of the VPA reference range

Only the data of patients from the good control group were included in this analysis. Two approaches were used: the first approach was to determine the range based on mean±one standard deviation (1SD); The second approach was based on a graph that was plotted of the cumulative percentage of patients against VPA concentration to determine the lower and upper limits of the reference range [13].

Determination of predictors for good response

Data entry and analysis were carried out using Predictive Analytical Software (PASW) version 18 (IBM, USA). Descriptive statistics were applied, such as frequency (%) for the categorical data, while for the numerical data, mean and SD or median and interquartile range (IQR) were applied, depending on the distribution of the data. Simple logistic regression analysis was used to assess the significance of each variable. The crude odds ratio with its 95% confidence interval (95% CI) was calculated for each predictor variable. All the significant potential prognostic variables obtained in the simple logistic regression (p equal to or less than 0.25) that had clinical importance were selected for the preliminary final model [14, 15]. A variable selection method with a backward stepwise likelihood ratio option was applied.

All of the significant potential prognostic variables selected for the preliminary final model were further analyzed using the Enter method. A goodness-of-fit test was carried out to determine how effectively the model described the outcome variable. The model fit was tested using the Hosmer–Lemeshow test, a classification table and the area under the receiver operating characteristic (AUROC) curve. The findings from the multivariable logistic regression were expressed as adjusted OR, 95% CI, and p. The level of significance was two-tailed and set at 0.05.

Results

A total of 264 patients fulfilled the inclusion criteria and consented to being recruited in the study. However, during the study period, four patients were transferred to other health institutions, while another 18 were lost on follow up.

Patients' characteristics

Patients' ages ranged from 18-61 years. There were slightly more male patients (57.4%) than female patients (42.6%). Approximately 45% of the patients were on monotherapy with VPA, while the other 55% were on combination therapy (e.g., phenytoin, carbamazepine, phenobarbitone, clonazepam, topiramate, lamotrigine, levetiracetam). The recruited patients had no other medical problems and were not on any other drug treatment.

Out of the 242 patients, 126 patients (52.1%) were included in the good control group, and 116 patients (47.9%) were included in the poor control group. Table 1 shows the characteristics of the patients in the good control and poor control groups.

A total of 122 patients reported having various kinds of stress prior to their seizure attacks. These stressors included sleep deprivation (n=75, 61.5%), fatigue (n=21, 17.2%), loss of financial income (n=14, 11.5%) and life problems, e.g., uncomfortable living environment, lack of family support, loss of loved ones (n=12, 9.8%). There were more patients who reported experiencing stress prior to a seizure in the poor control group (81.9%) compared with the good control group (21.4%).

Determination of the VPA reference range

Data from the good control group were used to determine the VPA reference range. Serum VPA concentration data were available for only 76 of the patients in this group. The mean concentration (and SD) of VPA in these patients was 60.71 (SD 18.06) mg/L. Using this value, we determined that the concentration range within ±1 SD would be from 42.65 to 78.88 mg/L. Subsequently, of the 76 patients' VPA concentrations, we found that 52 fell within this range. For the second approach, we determined the concentration range from the plot of cumulative percentage of patients with good control against VPA concentration (Figure 1). A sharp increase

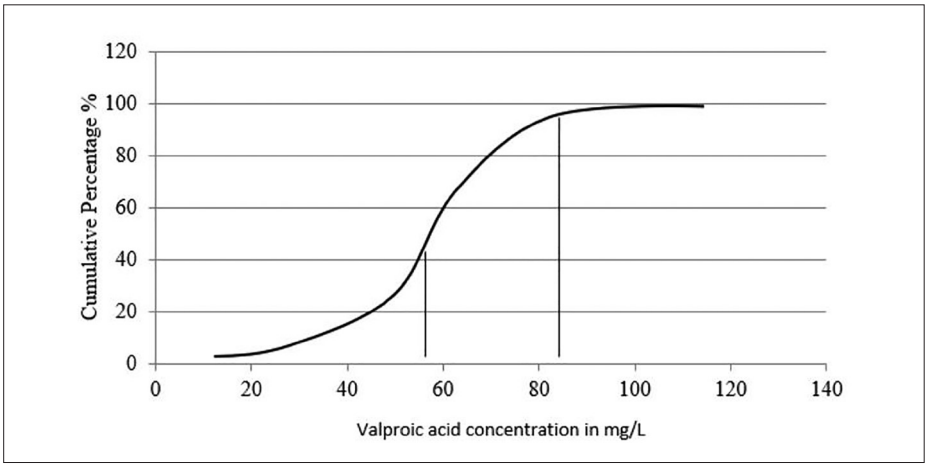

Figure 1. Cumulative percentage (%) of patients in the good control group (n=76).

Table 1. Characteristics of patients with epilepsy on valproic acid (n=242)

Characteristics	Good control (n=126)	Poor control (n=116)
Age (year), mean (SD)	33.01 (10.24)	35.92 (10.67)
Gender, n (%)		
Female	53 (42.1)	50 (43.1)
Male	73 (57.9)	66 (56.9)
Ethnicity, n (%)		
Malay	79 (62.7)	53 (45.7)
Chinese	24 (19.0)	26 (22.4)
Indian	21 (16.7)	36 (31.0)
Others	2 (1.6)	1 (0.9)
Highest level of education*, n (%)		
College/University	13 (10.3)	6 (5.2)
Secondary	98 (77.8)	89 (76.7)
Primary	15 (11.9)	21 (18.1)
Family support status, n (%)		
Yes	89 (70.6)	58 (50.0)
No	37 (29.4)	58 (50.0)
Marital status, n (%)		
Yes	23 (18.3)	27 (23.3)
No	103 (81.7)	89 (76.7)
Employment status, n (%)		
Yes	49 (38.9)	28 (24.1)
No	77 (61.1)	88 (75.9)
Active smoker, n (%)		
Yes	11 (8.7)	24 (20.7)
No	115 (91.3)	92 (79.3)
Age at diagnosis (year), mean (SD)	19.93 (8.46)	21.80 (9.75)
Seizure type, n (%)		
Generalized	103 (81.7)	37 (31.9)
Partial	14 (11.1)	43 (37.1)
Secondarily generalized	9 (7.2)	36 (31.0)
Etiology, n (%)		
Known	20 (15.9)	56 (48.3)
Unknown	57 (45.2)	28 (24.1)
Undocumented	49 (38.9)	32 (27.6)
Family history of epilepsy, n (%)		
Yes	26 (20.6)	40 (34.5)
No (65.5)	100 (79.4)	76
Age when first AED started (year), mean (SD)	20.21 (8.39)	22.34 (9.94)
Age when VPA started (year), mean (SD)	23.02 (8.65)	25.90 (9.78)
Duration on VPA (year), median (IQR)	4 (4)	4 (4)
First AED prescribed, n (%)		
VPA	85 (67.5)	37 (31.9)
PHT	24 (19.0)	42 (36.2)
CBZ	11 (8.7)	31 (26.7)
Others	6 (4.8)	6 (5.2)
Current AED regime, n (%)		
Monotherapy	78 (61.9)	32 (27.6)
Polytherapy	48 (38.1)	84 (72.4)
VPA dose (mg/day), mean (SD)	760.32 (335.64)	886.21 (349.14)
VPA concentration** (mg/L), mean (SD)	60.71 (18.06)	61.35 (26.07) †
VPA range‡, n (%)		
Not within 40–85 mg/L	13 (17.1)	14 (18.4)
Within 40–85 mg/L	63 (82.9)	62 (81.6)
EEG, n (%)		
Normal	96 (76.2)	21 (18.1)
Abnormal	30 (23.8)	95 (81.9)
Brain imaging n (%)		
Normal	109 (86.5)	68 (58.6)
Abnormal	17 (13.5)	48 (41.4)

*Secondary education is equivalent to GCE A levels, Primary education refers to elementary school up to age 12 years;
**VPA level refers to 76 patients in both groups;
† Expressed in Median (IQR);
‡Refers to predetermined reference range (40-85 mg/L).
AED: antiepileptic drug; VPA: valproic acid

in the cumulative percentage of responders occurred between 54.3 and 83.8 mg/L. Subsequently, we found that 52 out of 76 patients had VPA concentrations between this range. Based on the two ranges of values obtained above, we selected the reference range to be 40–85 mg/L, which included the lower end obtained by the first method and the upper end obtained by the second method. Given this new reference range, we found that the VPA concentrations of 63 out of the 76 patients (82.9%) were within this range.

Simple logistic regression

Table 2 shows the results of the univariate analysis by simple logistic regression. All predictors were included in the preliminary final model. Some insignificant variables with clinical importance were included despite p>0.25; these were (i) mean VPA concentration values and (ii) attainment of predetermined reference range (40-85 mg/L).

Multiple logistic regression

Preliminary final model

The preliminary final model deduced from the backward likelihood ratio method resulted in eight variables that were: age when the AED was started; monotherapy; normal brain imaging; education level; non-smoking; absence of stress; VPA concentration; and a positive family history of epilepsy. A collinearity test was performed and showed that multicollinearity did not exist. The Hosmer–Lemeshow test (p=0.113) showed that the preliminary final model fits with the overall percentage for the classification table (91.3%) at above 80%.

Final model

These eight significant variables in the preliminary final model were further analyzed using the Enter method. The test for fitness of the final model showed that the final model fit with: (i) the Hosmer–Lemeshow test (p=0.885); (ii) the overall percentage for the classification table (83.5%); and (iii) the AUROC (89.9%).

Table 3 shows the significant factors associated with good control in patients with epilepsy on VPA by multiple logistic regressions. These were: (i) age when treatment with the first AED was started; (ii) VPA monotherapy; (iii) normal brain imaging result; (iv) non-smoking; and (v) absence of perceived stress.

Discussion

VPA has an unpredictable relationship between its dose and its concentration. Therefore, there is a need to individualize and maintain therapy using TDM [7]. Although the reported range of 50 to 100 mg/L has been widely used, there are patients who achieve seizure control at lower concentrations. Patients with idiopathic generalized epilepsy have shown a good response at lower doses and concentrations [16-19]. We have attempted to develop a VPA reference range using our own patient data, based on the approach described by Eadie [13]. We plotted the drug concentrations against the cumulative proportion of patients treated whose seizures were fully controlled at these concentrations. Using this approach, approximately 83% of the patients were within the 40-85 mg/L therapeutic range. It appears that this method yielded a range of concentrations that did not differ much from the published therapeutic range for VPA. In the final model, however, we found that having a VPA concentration in the designated range of 40-85 mg/L was not a predictor of good seizure control. This confirmed the pre-

Table 2. Univariate analysis of predicting factors for good seizure control (n=242)

Variables	Crude Odds Ratio	95% CI	p*
Age (year)	0.974	0.950-0.998	0.033
Age at diagnosis (year)	0.977	0.950-1.005	0.112
Age when AED started (year)	0.975	0.948-1.002	0.073
Age when VPA started (year)	0.967	0.940-0.994	0.017
VPA dose (mg/day)	0.999	0.998-1.000	0.006
Mean VPA concentration (mg/L)	0.996	0.978-1.014	0.651
No. of side effects	0.388	0.265-0.567	<0.001
Ethnicity			
Malay	1		
Chinese	0.619	0.322-1.192	0.152
Indian	0.391	0.206-0.743	0.004
Others	1.342	0.119-15.1730.812	
Educational level			
Primary	1		
Tertiary	3.033	0.939-9.798	0.064
Secondary	1.542	0.749-3.174	0.240
Family support status			
No	1		
Yes	2.405	1.418-4.081	0.001
Employment status			
No	1		
Yes	2.000	1.147-3.487	0.015
Active smoker			
Yes	1		
No	2.727	1.270-5.858	0.010
Seizure type			
Secondarily generalized	1		
Generalized	11.135	4.898-25.317	<0.001
Partial	1.302	0.505-3.358	0.585
Etiology			
Known	1		
Unknown	5.700	2.882-11.275	<0.001
Stress preceding seizure			
Yes	1		
No	16.587	8.782-31.331	<0.001
No. of seizures before treatment initiated			
>10	1		
≤10	5.256	2.859-9.663	<0.001
Family history of epilepsy			
Yes	1		
No	2.024	1.137-3.604	0.017
History of febrile seizure			
Yes	1		
No	1.412	0.835-2.389	0.198

vious findings that treatment should not focus on achieving a concentration in the reference range. This method was implemented by the Italian TDM Study Group in Epilepsy [20], where each patient's dose was titrated to achieve concentrations within the target range. The study by this group found that this approach did not improve the overall seizure outcome.

The significant predictors to good seizure control in patients with epilepsy on VPA that were identified in our study were monotherapy, non-smoking, normal brain image (MRI or CT) results, and an absence of stress. Our study showed that patients who were on VPA monotherapy were five times more likely to have a favorable outcome. Monotherapy is more likely to be observed in newly diagnosed patients or in patients with less severe conditions [21]. In the present study, the mean age of diagnosis between the two groups was not significantly different. However, there were more patients on polytherapy in the poor control group (i.e., 72% vs. 38%). Previous studies have shown that use of a greater number of AEDs is found among patients with poor seizure control [22, 23].

Another predictive factor of seizure outcome with an obscure mechanism is non-smoking behavior. In this study, we found that patients who did not smoke were three times more likely to achieve good seizure control compared with those who smoked. Maternal cigarette smoking has previously been associated with an increased risk of seizures in children [24, 25]. Among adults, Dworetzky et al. [26] found a two-fold increase in risk of seizures in current smokers compared with non-smokers. Our findings support that cessation of smoking may be an effective means of achieving good seizure control in patients with epilepsy on VPA. In animal models, nicotine has been found to diminish the anticonvulsant activities of VPA and other AEDs [27]. Further research needs to be carried out to explore the effect of smoking cessation on seizure outcome.

We found that patients with normal brain imaging results were approximately six times more likely to achieve good seizure control. Abnormal brain image, such as MRI or CT, results have been associated with an increased risk of seizure recurrence [28]. Additionally, a higher risk of seizure recurrence has been reported in patients with intractable epilepsy [29-31]. In our study, also, abnormal findings occurred significantly more often in the poor control group of patients.

The absence of stress is associated with an approximately 20 times better chance of a favorable outcome. In this study, more than 80% of

Table 2. Univariate analysis of predicting factors for good seizure control (n=242) (continue)

Variables	Crude Odds Ratio	95% CI	p*
AED naive			
No	1		
Yes	4.426	2.580-7.594	<0.001
VPA range			
Not within range	1		
40-85 mg/L	1.094	0.476-2.515	0.832
AED regime			
Polytherapy	1		
Monotherapy	4.266	2.478-7.343	<0.001
EEG result			
Abnormal	1		
Normal	14.476	7.744-27.062	<0.001
Brain imaging result			
Abnormal	1		
Normal	4.526	2.409-8.504	<0.001

*Simple logistic regression test
AED: antiepileptic drug; VPA: valproic acid

Table 3. Multivariate analysis of predicting factors for good seizure control (n=242)

Variable	Adjusted Odds Ratio	95% CI	p
Age when AED was started (year)	0.957	0.920-0.995	0.027
On monotherapy	4.739	2.258-9.947	<0.001
Normal brain imaging	5.829	2.507-13.552	<0.001
Non-smoking	3.227	1.099-9.473	0.033
Absence of stress	19.984	9.255-42.764	<0.001

Constant: -3.373. The model fits reasonably well. There were no interaction and multicollinearity problems.
AED: antiepileptic drug

patients who reported experiencing stress had poor seizure control. Stress was reported to be as a result of sleep deprivation, fatigue, loss of financial income, and life problems. A substantial number of our patients reported that the frequency of their seizures increased when they experienced stress. Previous studies have shown that stress is among the most frequently self-reported precipitants of seizures in patients with epilepsy [32-34], which can be triggered by physical or emotional factors. Stress does not only increase the number of seizures in patients with epilepsy [35, 36], but has also been reported to induce *de novo* seizures [37].

In conclusion, we have determined VPA concentrations between 40-85 mg/L to be the reference range in our patients, but having a serum concentration in the reference range did not predict good seizure control. This study suggests that predictors of good seizure control in patients on VPA are monotherapy, non-smoking, normal brain imaging results, and the absence of stress.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Malaysian Research Ethical Committee (KKM/NIHSEC/08/0804/P10-598).

Informed Consent: Informed consent was obtained from the patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – M.A., A.F.A.R.; Design – M.A., A.F.A.R.; Supervision - A.F.A.R., S.S.; Resources – M.A., S.S.; Materials – M.A., S.S.; Data Collection and/or Processing – M.A., S.S.; Analysis and/or Interpretation – M.A., A.F.A.R., S.S.; Literature Search – M.A., A.F.A.R.; Writing Manuscript – M.A., A.F.A.R.; Critical Review – M.A., A.F.A.R., S.S.

Acknowledgements: The authors gratefully acknowledge all patients who participated in this study. We also would like to thank all medical, nursing and pharmacy staff at the Neurology Clinic for their support.

Conflict of Interest: The authors have no conflicts of interest to declare.

Financial Disclosure: This work was supported by a grant from the Malaysian Research Grant of the Ministry of Health, Malaysia MRG-2011-06.

References

1. Schoenenberger RA, Tanasijevic MJ, Jha A, Bates DW. Appropriateness of Antiepileptic Drug Level Monitoring. JAMA 1995; 274: 1622-6. [CrossRef]
2. Thapar A, Richens A, Roland M, et al. Are serum anticonvulsant levels in people with epilepsy appropriately monitored? J Eval Clin Pract 2001; 7: 335-8. [CrossRef]
3. Wing DS, Duff HJ. The impact of therapeutic drug monitoring program for phenytoin. Ther Drug Monit 1989; 11: 32-7. [CrossRef]
4. Bates DW, Soldin SJ, Rainey PM, Micelli JN. Strategies for physician education in therapeutic drug monitoring. Clin Chem 1998; 44: 401-7. [CrossRef]
5. Warner A. Setting Standards of Practice in Therapeutic Drug Monitoring and Clinical Toxicology: A North American View. Ther Drug Monit 2000; 22: 93-7. [CrossRef]
6. Tomson T, Dahl ML, Kimland E. Therapeutic monitoring of antiepileptic drugs for epilepsy. Cochrane Database Syst Rev 2007; CD002216.[CrossRef]
7. Patsalos PN, Berry DJ, Bourgeois BD, et al. Antiepileptic drugs--best practice guidelines for therapeutic drug monitoring: a position paper by the subcommission on therapeutic drug monitoring, ILAE Commission on Therapeutic Strategies. Epilepsia 2008; 49: 1239-76. [CrossRef]
8. National Institute for Health and Care Excellence. Epilepsies: Diagnosis and Management. Clinical Guideline; 2012.
9. Minshall I, Berry D, Smith D. The impact of an educational intervention, the New GP Contract and NICE guidelines on anti-epilepsy therapeutic drug monitoring. Seizure 2011; 20: 126-30. [CrossRef]
10. Ab Rahman AF, Ahmed Abdelrahim HE, Mohamed Ibrahim MI. A survey of therapeutic drug monitoring services in Malaysia. Saudi Pharm J 2013; 21: 19-24. [CrossRef]
11. Epilepsy Council. Consensus Guidelines on the Management of Epilepsy. Malaysian Society of Neurosciences, Kuala Lumpur 2010.
12. Okuma T, Kumashiro H. Natural history and prognosis of epilepsy: report of a multi-institutional study in Japan. The group for the study of prognosis of epilepsy in Japan. Epiepsia 1981; 22: 35-53. [CrossRef]
13. Eadie MJ. Plasma antiepileptic drug monitoring in a neurological practice: a 25-year experience. Ther Drug Monit 1994; 16: 458-68. [CrossRef]
14. Naing L, Than W, Rusli B. Practical issues in calculating the sample size for prevalence studies. Arch Orofacial Sci 2006; 1: 9-14.
15. Bachok N. Multivariate Analyses Regressions, School of Medical Sciences, Malaysia, 2011.
16. Karlovassitou-Koniari A, Alexiou D, Angelopoulos P, et al. Low dose sodium valproate in the treatment of juvenile myoclonic epilepsy. J Neurol 2002; 249: 396-9. [CrossRef]
17. Holland KD, Monahan S, Morita D, Vartzelis G, Glauser TA. Valproate in children with newly diagnosed idiopathic generalized epilepsy. Acta Neurol Scand 2010; 121: 149-53. [CrossRef]
18. Miro J, Aiguabella M, Veciana M, et al. Low-dose sodium valproate in the treatment of idiopathic

generalized epilepsies. Acta Neuro Scand 2014; 129: e20-3. [CrossRef]
19. Hernandez-Vanegas LE, Jara-Prado A, Ochoa A, Rodriguez NR, Duron RM, Crail-Melendez D. High-dose versus low-dose valproate for the treatment of juvenile myoclonic epilepsy: Going from low to high. Epilepsy Behav 2016; 61: 34-40. [CrossRef]
20. Jannuzzi G, Cian P, Fattore C, et al. A multicenter randomized controlled trial on the clinical impact of therapeutic drug monitoring in patients with newly diagnosed epilepsy. The Italian TDM Study Group in Epilepsy. Epilepsia 2000; 41: 222-30. [CrossRef]
21. Arts WF, Brouwer OF, Peters AC, et al. Course and prognosis of childhood epilepsy: 5-year follow-up of the Dutch study of epilepsy in childhood. Brain 2004; 127: 1774-84. [CrossRef]
22. Kharkar S, Pillai J, Rochestie D, Haneef Z. Socio-demographic influences on epilepsy outcomes in an inner-city population. Seizure 2014; 23: 290-4. [CrossRef]
23. Poudel P, Chitlangia M, Pokharel R. Predictors of Poor Seizure Control in Children Managed at a Tertiary Care Hospital of Eastern Nepal. Iran J Child Neurol 2016; 10: 48-56.
24. Cassano PA, Koepsell TD, Farwell JR. Risk of febrile seizures in childhood in relation to prenatal maternal cigarette smoking and alcohol intake. Am J Epidemiol 1990; 132: 462-73. [CrossRef]
25. Sidenvall R, Heijbel J, Blomquist HK, Nyström L, Forsgren L. An incident case-control study of first unprovoked afebrile seizures in children: a population-based study of pre- and perinatal risk factors. Epilepsia 2001; 42: 1261-5. [CrossRef]
26. Dworetzky BA, Bromfield EB, Townsend MK, Kang JH. A prospective study of smoking, caffeine, and alcohol as risk factors for seizures or epilepsy in young adult women: data from the Nurses' Health Study II. Epilepsia 2010; 51: 198-205. [CrossRef]
27. Czuczwar M, Kiś J, Czuczwar P, Wielosz M, Turski W. Nicotine diminishes anticonvulsant activity of antiepileptic drugs in mice. Pol J Pharmacol 2003; 55: 799-802.
28. Krumholz A, Shinnar S, French J, Gronseth G, Wiebe S. Evidence-based guideline: Management of an unprovoked first seizure in adults: Report of the Guideline Development Subcommittee of the American Academy of Neurology and the American Epilepsy Society. Neurology 2015; 85: 1526-7. [CrossRef]
29. Tripathi M, Padhy UP, Vibha D, et al. Predictors of refractory epilepsy in north India: a case-control study. Seizure 2011; 20: 779-83. [CrossRef]
30. Seker Yilmaz B, Okuyaz C, Komur M. Predictors of intractable childhood epilepsy. Pediatr Neurol 2013; 48: 52-5. [CrossRef]
31. Saygi S, Erol İ, Alehan F. Early clinical predictors of intractable epilepsy in childhood. Turk J Med Sci 2014; 44: 490-5. [CrossRef]
32. Frucht MM, Quigg M, Schwaner C, Fountain NB. Distribution of seizure precipitants among epilepsy syndromes. Epilepsia 2000; 41: 1534-9 [CrossRef]
33. Nakken KO, Solaas MH, Kjeldsen MJ, Friis ML, Pellock JM, Corey LA. Which seizure-precipitating factors do patients with epilepsy most frequently report? Epilepsy Behav 2005; 6: 85-9. [CrossRef]
34. Sperling MR, Schilling CA, Glosser D, Tracy JI, Asadi-Pooya AA. Self-perception of seizure precipitants and their relation to anxiety level, depression, and health locus of control in epilepsy. Seizure 2008; 17: 302-7. [CrossRef]
35. Thapar A, Kerr M, Harold G. Stress, anxiety, depression, and epilepsy: investigating the relationship between psychological factors and seizures. Epilepsy Behav 2009; 14: 134-40. [CrossRef]
36. van Campen JS, Jansen FE, Steinbusch LC, Joëls M, Braun KP. Stress sensitivity of childhood epilepsy is related to experienced negative life events. Epilepsia 2012; 53: 1554-62. [CrossRef]
37. Moshe S, Shilo M, Chodick G, et al. Occurrence of seizures in association with work-related stress in young male army recruits. Epilepsia 2008; 49: 1451-6. [CrossRef]