

Original Article

FREQUENCY OF VALPROATE INDUCED THROMBOCYTOPENIA IN EPILEPTIC CHILDREN

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Objective: To determine the frequency of valproate induced thrombocytopenia in children with epilepsy.

Methods: This observational case series descriptive study was conducted at Services Hospital Lahore during December 2016 to June 2017. A total of 160 children were enrolled in this study after taking ethical approval letter from the hospital. An informed consent was also taken from the parents/guardian of the children for this study. After fulfilling the inclusion criteria the children were recorded by entering his/her demographic profile. Demographic include, name, age, gender, weight, height. Later on patients were subscribed for valproate for 30 days and asked to come for follow-up visit after 30 days. Blood sample was drawn after 30 day of treatment with valproate and sent to the laboratory. Children were assessed for the presence thrombocytopenia.

Results: In this study, out of 160 cases, 71.25%(n=114) were between 5-9 years of age whereas 28.75%(n=46) were between 10-12 years of age, mean+SD was calculated as 8.53+1.80 years, 53.75%(n=86) were male and 46.25%(n=74) were females. Mean platelet count (per mcL) was calculated as 161028.125+15127.99 per mcL. Frequency of valproate induced thrombocytopenia in children with epilepsy was recorded as 24.37%(n=39).

Conclusions: We estimated a considerable frequency of valproate induced thrombocytopenia in children with epilepsy, which necessitates that the platelet count should be monitored for children receiving valproic acid especially on higher doses. Children using higher doses of valproate may have a higher risk of developing thrombocytopenia.

Keywords: epileptic children, valproate induced thrombocytopenia, platelet count.

Introduction

Epilepsy is the commonest neurological condition affecting people of all ages, race and social class. There are an estimated 50 million people with epilepsy in the world, of whom up to 75% live in resource-poor countries with little to or no access to medical services or treatment.¹

There is scarcity of epidemiological data, required to plan services in resource constrained developing nations. The prevalence rate for epilepsy was 6.24/1000 population. Febrile seizures are reported to be one of the most common causes of symptomatic seizures in childhood.²

The incidence of epilepsy in children ranges from 41-187/100,000. Higher incidence is reported from underdeveloped countries, particularly from rural areas. The incidence is consistently reported to be highest in the first year of life and declines to adult levels by the end of the first decade. The prevalence of epilepsy in children is consistently higher than the incidence and ranges from 3.2-5.5/1,000 in developed countries and 3.6-44/1,000 in underdeveloped countries. Prevalence also seems highest in rural areas. The incidence and prevalence

of specific seizure types and epilepsy syndromes is less well documented.³

Major forms of therapy in epilepsy are the antiepileptic drugs. In children the choice of antiepileptic drugs depends upon the age at presentation, seizure types and the findings of electroencephalography and neuroimaging.⁵ Valproate is a widely used antiepileptic drug with a broad spectrum. Valproate acts by increasing the synaptic GABA concentration through the inhibition of GABA transaminases. It is used in idiopathic generalized epilepsy, absence seizures, juvenile myoclonic epilepsy and in epilepsy syndromes like Lennox Gastaut syndrome.^{5,6} Thrombocytopenia is the most common hematological side effect of valproate treatment.^{7,8} Thrombocytopenia is a known side effect associated with valproate use.⁹ In the study done by Nasreddine W and Beydoun A 6 in Beirut, Lebanon, 17.7% patients experienced thrombocytopenia in an average of 82 days after the exposure to valproate. Thrombocytopenia has been reported in 6% 33% of patients with epilepsy taking valproate.⁷ Thrombocytopenia associated with valproate therapy has been reported to resolve without interruption of

valproate treatment^{10,11} and has also been reported to endure over time or to have an erratic course.^{12,13} This study was undertaken to determine the frequency of valproate induced thrombocytopenia in children with epilepsy.^{14,15}

Methods

This descriptive study has been done in pediatric department of Services Hospital, Lahore and duration of study was six months from December 2016 to June 2017. One hundred and sixty children of aged between 5 to 12 years having clinical diagnosis of epilepsy with were included in this study. Thrombocytopenia was diagnosed by complete blood count with platelets count less than $150 \times 10^9/L$ in patients taking valproate as monotherapy⁶. Exclusion criteria include patients with epilepsy using either combination therapy with valproate or other antiepileptic drugs, receiving anticoagulants/antiplatelet drugs like Aspirin, warfarin, heparin, other NSAIDs etc. and patients with diagnosed hematopoietic diseases like congenital anemia, congenital or acquired platelet diseases, malignancy etc. The patients fulfilling the inclusion criteria after complete history, examination was included in study from Pediatric department, services Hospital Lahore.

Demographic include, name, age, gender, weight, height. Later on, patients were subscribed for valproate for 30 days and asked to come for follow-up visit after 30 days. Blood sample was drawn after 30 days of treatment with valproate and sent to the laboratory. Children were assessed for the presence of thrombocytopenia. The data was entered by SPSS version 19 Quantitative. Variables/numerical variables such as age, platelet count after treatment was presented as mean \pm standard deviation. Qualitative variables/ categorical variables such as gender, thrombocytopenia was presented as frequencies and percentages. The data was stratified for age, gender and BMI to deal with effect modifiers. Post stratification chi-square test was applied taking p-value ≤ 0.05 as significant.

Results

A total of 160 cases fulfilling the inclusion /exclusion criteria were enrolled to determine the frequency of valproate induced thrombocytopenia in children with epilepsy. Age distribution of the patients was done, it shows that 71.25% (n=114) were between 5-9 years of age whereas

Table-1: Age distribution.

Age (in years)	No. of Pts.	Percentage
5-9	114	71.25
10-12	46	28.75
Total	160	100
Mean \pm SD	8.53 \pm 1.80	

Table-2: Gender distribution.

Age (in years)	No. of Pts.	Percentage
Male	86	53.75
Female	74	46.25
Total	160	100

Table-3: Platelet count after treatment

Platelet count (permCL)	Mean \pm SD	Percentage
	161028.128 \pm 15127.99	53.75

Table-4: Frequency of valproate induced thrombocytopenia in children with epilepsy.

Valproate induced thrombocytopenia	No. of Pts.	Percentage
Yes	39	24.37
No	121	75.63
Total	160	100

Table-5: Frequency of valproate induced thrombocytopenia in children.

Age (in years)	Valproate induced thrombocytopenia		P-value
	Yes	No	
5-9	26	88	0.46
10-12	13	33	

Table-6: Frequency of valproate induced thrombocytopenia in children.

Gender	Valproate induced thrombocytopenia		P-value
	Yes	No	
Male	20	66	0.72
Female	19	55	

Table-7: Frequency of valproate induced thrombocytopenia in children.

BMI	Valproate induced thrombocytopenia		P-value
	Yes	No	
<30	26	73	0.47
≥ 30	13	48	

28.75%(n=46) were between 10-12 years of age, Mean \pm SD was calculated as 8.53 ± 1.80 years. **(Table-1)** Gender distribution of the patients was done, it shows that 53.75%(n=86) were male and 46.25%(n=74) were females. **(Table-2)** Mean platelet count (per mL) was calculated as 161028.125 ± 15127.99 per mL. **(Table-3)** Frequency of valproate induced thrombocytopenia in children with epilepsy was recorded as 24.37%(n=39) whereas 75.63%(n=121) had no findings of the morbidity. **(Table-4)** The data was stratified for age, gender and BMI to deal with effect modifiers. Post stratification chi-square test was applied taking p-value ≤ 0.05 as significant. **(Table-5-7)**

Discussion

Valproic acid (VPA) has been used with increasing frequency for the treatment of many psychiatric conditions, in patients. There have been wide-ranging reports of thrombocytopenia and other forms of platelet dysfunction as side effects of valproate therapy, but the exact incidence is not known clear yet. As there lies variation among results that are being published in local and international literature, due to absence of any consensus, the need was felt to conduct a study so that a decision could be made whether a patient should be prescribed for valproate or not. In this study, out of 160 cases, 71.25%(n=114) were between 5-9 years of age whereas 28.75%(n=46) were between 10-12 years of age, mean \pm sd was calculated as 8.53 ± 1.80 years, 53.75%(n=86) were male and 46.25%(n=74) were females. Mean platelet count (per mL) was calculated as 161028.125 ± 15127.99 /mL.

Frequency of valproate induced thrombocytopenia in children with epilepsy was recorded as 24.37%(n=39). We compared our results with a study where the frequency of thrombocytopenia induced due to valproate was 17% among epileptic children.¹⁶ Our findings are close to this study, but another study revealed that the valproate induced thrombocytopenia was noted in 2(7.69%) children out of total 26 children that gives some different

results as published earlier,¹⁷ which is lower than recorded in our study.

Some other studies reveal that thrombocytopenia is one of the most common side effects associated with VPA therapy, with incidences ranging from 1% to 30%.⁶ Thrombocytopenias has been reported in 6% - 33% of adult patient with epilepsy taking valproate, but a lowering of platelet count was seen in almost all patients and appeared to be dose related.^{18,19} Tahir Mehmood and others⁴ evaluated the frequency of thrombocytopenia in epileptic children receiving valproate as monotherapy for more than 6 months, in POF Hospital, Wah Cantt and recorded the frequency of thrombocytopenia in patients taking valproic acid as monotherapy was 19.3% and the children using higher doses of valproate were at higher risk of developing thrombocytopenia, they concluded that about one fifth of the children taking valproate as monotherapy for more than 6 months in a dose of 30mg/kg or more had thrombocytopenia.² The platelet count should be monitored for children receiving valproic acid especially on higher doses. Children using higher doses of valproate are at higher risk of developing thrombocytopenia.¹³ Our findings are in agreement with this study. Platelet counts should probably be monitored more carefully in patients known to have higher drug levels and who are also receiving drugs that would affect homeostasis, or who are undergoing surgical procedures. However, a limitation of our study was that we did not record platelet count before treatment, which may be done in coming trials.

Conclusion

We estimated a considerable frequency of valproate induced thrombocytopenia in children with epilepsy, which necessitates that the platelet count should be monitored for children receiving valproic acid especially on higher doses. Children using higher doses of valproate may have a higher risk of developing thrombocytopenia.

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