Original Article

# FREQUENCY OF VALPROATE INDUCED THROMBOCYTOPENIA IN EPILEPTIC CHILDREN

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**ABSTRACT:**

**BACKGROUND:**

Valproic acid (VPA) is a commonly used antiepileptic drug in children as well as adult population. It is widely used as a first-line agent for patients with partial or generalized epilepsy. Thrombocytopenia is one of the common side effects associatedwith VPA therapy.

**OBJECTIVES:**

To find out the frequency of thrombocytopenia in epileptic children receiving valproate as monotherapy for more than 6 months, in POF Hospital, Wah Cantt.

**DESIGN:**

Descriptive cross-sectional study.

**PATIENTS AND METHODS:**

This study was a carried out at Neurology clinic of paediatric OPD of POF hospital Wah Cantt from January 2011 till June 2011. Eighty eight patients, 2-12 years of age with the diagnosis of epilepsy and taking valproate as monotherapy for more than 6 months in a dose of 30mg / kg or more were included in the study. The complete blood count was done and the diagnosis of thrombocytopenia was made with the platelet count less than 150 x $10^9$/L.

**RESULTS:**

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.

**CONCLUSION**:

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. 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.

**KEY WORDS:** valproic acid, platelet count, thrombocytopenia, epilepsy

## INTRODUCTION:

Epilepsy is defined as two or more unprovoked seizures more than 24 hours apart in a child over one month of age.[1] It is not a specific disease, but rather a condition arising from a variety of pathological insults involving the cortex, such as tumors or genetic channelopathies.[2]Epilepsy is a common neurological disorder; the overall prevalence rate in the world is approximately 1%.[3] There are approximately 20-70 new cases of epilepsy per 100,000 people per year with a higher incidence in males.[4] In Pakistan

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the prevalence of epilepsy is 9.99 per 1000 population and more cases of epilepsy are seen in people younger than 30 years.

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 synaptosomal 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.

Valproate use is also associated with adverse effects like weight gain, hair thinning, tremors and thrombocytopenia.[6] Valproate can also cause decrease factor VII, factor VIII, protein C, and fibrinogen levels.[7] Thrombocytopenia is a known side effect associated with valproate use.[8] 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.[9]Thrombocytopenia associated with valproate therapy has been reported to resolve without interruption of valproate treatment[10]and has also been reported to endure over time or to have an erratic course.[11]

Valproate is a frequently prescribed antiepileptic drug. This study was conducted to identify the burden of side effect in our epileptic patients receiving valproate as monotherapy. An epileptic patient during a fit can sustain trauma, so the patients receiving valproate can be advised to look for bleeding and bruising along with regular monitoring of platelet count on follow up in the hospital.

## PATIENTS AND METHODS:

This study has been done in Neurology clinic, department of Paediatrics (OPD) POF Hospital, Wah Cantt and duration of study was six months. Eighty eight patients having clinical diagnosis of epilepsy with 2 or more unprovoked seizures 24 hours apart, between 2-12 years of age were included in this study. Thrombocytopenia was diagnosed by complete blood count with platelets count less than 150 x $10^9$/L in patients taking valproate as monotherapy for more than 6 months in the dose of 30mg/Kg (mg/Kg) or more. 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 were included in study from Neurology clinic OPD, Paediatric department, POF Hospital Wah Cantt. The complete blood count done from the laboratory and the diagnosis of thrombocytopenia was made with the platelet count less than 150,000 cmm Confounding variables were controlled by taking fresh blood samples in standard vials and immediate transfer and handing over of these samples to pathologist, under supervision of resident doctor and the reports being collected on the same day after verification by consultant pathologist.

## RESULTS:

The age of the children ranged from 2 to 12 years with a mean age of 7.28±2.46 years. The median and mode ages were 7 and 8 years respectively. 40 (45.5%) were males and 48 (54.5%) were females. The weight of the children ranged from 10 to 37 kg with a mean weight of 23.78±7.78 kg.

One (1.1%) child was taking 350 mg/day, 13 (14.8%) were taking 500 mg/ day, 19 (21.6%) were taking 750 mg/ day, 33 (37.5%) were taking 1000 mg/ day,8 (9.1%) were taking 1250 mg/ day and 14 (15.9%) were taking 1500 mg/ day. The valproate dose ranged from 350-1500 mg/day with a mean dose of 967±317.4 mg/day. The weight adjusted dose ranged from 30.3-76.9 mg/kg/day in divided doses with a mean dose of 41.86±9.37 mg/kg/day.

The platelet count of the children ranged from 34 to 350 × $10^9$/L with a mean platelet count

of 189.93±66.1 × $10^9$/L. Thrombocytopenia was defined as a platelet count <50× $10^9$/L . 17 (19.3%) children had thrombocytopenia and in 71 (80.7%) the platelet count was > 150× $10^9$/L.

The mean age of the children with thrombocytopenia was 6.35±2.5 years, whereas the mean age of the children with normal platelet count was 7.5±2.4 years; this difference in age of the two groups was not statistically significant; p= 0.083.

10 out of 40 boys (25%) had thrombocytopenia and 7 out of 48 girls (14.6%) had thrombocytopenia; this difference in gender distribution of the two groups was not statistically significant; p= 0.218.

There was a linear negative correlation (inversely proportional) between the per kg weight dose and the platelet count; Pearson Correlation coefficient = -0.346. This correlation was statistically significant (p=0.001). The mean dose of patients with thrombocytopenia was 53.9±10.9 mg/kg whereas the mean dose of children with normal platelet count was 38.98±6.22 mg/kg; this difference was statistically significant; p<0.0001. Hence children using higher doses of valproate were at higher risk of developing thrombocytopenia.

**Table 1– Pearson Correlations of platelet count and valproate dose per kg per day**

| | Platelet count | Valproate dose mg per kg per day |
|---|---|---|
| Pearson Correlation | 1 | -.346(**) |
| Sig. (2-tailed) | . | .001 |
| N | 88 | 88 |

**Correlation is significant at the 0.01 level (2-tailed).

**Table 2-Thrombocytopenia and age**

| Thrombo cytopenia | | N | Mean | Std. Deviation | P value |
|---|---|---|---|---|---|
| Age in years | Yes | 17 | 6.35 | 2.49 | 0.083 |
| | No | 71 | 7.50 | 2.42 | |

## DISCUSSION:

Valproic acid (VPA) is a commonly used antiepileptic drug. It is widely used as a first-line agent for patients with partial or generalized epilepsy. Thrombocytopenia is one of the most common side effects associated with VPA therapy, with incidences ranging from 1% to 30%.[12] 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.[13] The frequency of valproate (VPA)-induced thrombocytopenia varied widely in previous studies, due to methodological differences.

In our study age and gender were not significantly associated with thrombocytopenia; p> 0.05. However, there was a linear negative correlation (inversely proportional) between the per kg weight dose and the platelet count, hence children using higher doses of valproate were at higher risk of developing thrombocytopenia. About one fifth of the children taking valproate as monotherapy for more than 6 months in a dose of 30mg/kg ore more had thrombocytopenia. Theplatelet count should be monitored for children receiving valproic acidespecially on higher doses. Children using higher doses of valproate are at higher risk of developing thrombocytopenia.

In a similar study Nasreddine and Beydoun[6] evaluated the relationship between trough VPA plasma levels and platelet counts and assessed risk factors for the development of thrombocytopenia. A total of 851 VPA levels and concomitant platelet counts were analyzed in 265 patients. Of these, 17.7% of patients experienced at least one episode of thrombocytopenia (platelet count < 100,000/µl) after exposure to divalproex sodium. The frequency of valproate-induced thrombocytopenia was very similar to the finding of 19.3% in our study. A significant negative correlation was found between VPA levels and platelet counts. These findings were in accordance with our study. The probability of developing thrombocytopenia substantially increased at trough VPA levels above 100 µg/ml in females and above 130 µg/ml in males. These data strongly support a causal relationship between rising plasma VPA levels and reduced platelet counts, with additional risk factors including female gender and lower baseline platelet counts.

In a retrospective study of nearly 1500 samples from mentally handicapped patients, Eastham and Jancar[14] found no difference in

the platelet counts of individuals with and without epilepsy who were receiving anticonvulsants other than valproic acid, but patients with epilepsy who were receiving valproic acid had significantly lower counts than those who were being treated with other drugs. Serial, prospective sampling, as conducted in our study, showed that thrombocytopenia, while common, is always transient and self-limiting despite continuing drug administration; we had elected to pursue this policyon the basis of previous clinical experience[15] of the resolution of thrombocytopenia without interruption of treatment with valproic acid. Moreover, the degree of thrombocytopenia is such that a haemorrhagicdia thesis is predictably unlikely. We also did not encounter any patient with bleeding diathesis in our study.

To investigate the relationship between platelet count and serum valproic acid level, age, duration of valproic acid therapy, and polytherapy, and to determine the clinical significance of thrombocytopenia associated with high-dosage valproic acid therapy in paediatricout-patient clinic, Hong Kong by Ko et al[16]Ninety-six neurologically impaired children who were treated with valproic acid between 1 July 1991 and 3 June 1999. The comparison group consisted of 48 children receiving antiepileptic drugs other than valproic acid. Seventeen (17.7%) patients in the treatment group developed thrombocytopenia, compared with two (4.2%) in the comparison group($P<0.05$). The platelet count was negatively correlated to serum valproic acid level and age, and positively correlated to polytherapy. Thrombocytopenia is mild and transient in most cases and usually resolves spontaneously on dosage reduction or withdrawal of the drug.[17] The platelet count has also been shown to be inversely correlated to VPA dose and plasma VPA concentration.[18]In a retrospective study[19] of children treated with VPA as monotherapy or polytherapy, the serum VPA level and older age were shown to be the two most important independent predictors for thrombocytopenia. Previous studies adopted various definitions for thrombocytopenia, ranging from a platelet count of <75to 200 x $10^9$ /L. Peak or random serum VPA levels have also been measured, but they may be more variable and do not reflect the therapeutic range as doesthe trough level. We used the cut off value of 150x $10^9$ /L. The duration of VPA therapy may also be aconfounding factor in this apparent relationship. We recruited all patients with more than 6 months therapy to minimize the bias due to duration of therapy. Most patients in previous studies received a low to moderate dosage of VPA therapy on an out-patient basis.

At the department of neurology, University of Texas Southwestern Medical Center at Dallas the frequency of valproate-induced thrombocytopenia in children with epilepsy was reviewed.[20] Sixty-four (21%) of 306 children taking valproate developed thrombocytopenia. Thirty-two of these 64 patients had at least one platelet count lower than 100 x 10(3)/$mm^3$. Eight patients developed signs of bleeding. However, duration of valproate use was related. These data suggest that, although valproate may cause thrombocytopenia via more than one mechanism, by far the most common factor is the presence of high valproate levels. Thus, the medication can be safely lowered in most patients with thrombocytopenia rather than discontinued altogether.

Valproate has been used with increasing frequency for the treatment of many psychiatric conditions.[21] Thomas et al[22] assessed the platelet-lowering effects of valproate among psychiatric patients. More than half (53.8%) of the elderly patients but only 13.0% of the nonelderly patients had at least one episode of thrombocytopenia. This difference corresponded to a significantly greater lowering of platelet counts among elderly patients than among nonelderly patients. The high rate of thrombocytopenia in this study suggests the need for routine monitoring of platelet counts among patients taking valproate, particularly among elderly patients.[23]

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.

**CONCLUSION:**

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. An epileptic patient during a fit can sustain trauma, so the patients receiving valproate can be advised to look for bleeding and bruising along with regular monitoring of platelet count on follow up in the hospital.

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