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# Unveiling Thrombocytopenia Trends In Pediatric Epilepsy: The Valproate Connection

*Kiran Nayab[1], Qurrat Ul Ain[2], Ayesha Tariq[3], Israr Liaqat[4], Samra Javed[5], Nadia Mumtaz[6]*

## Abstract

**Objective:** To determine the frequency and association of thrombocytopenia in patients on valproate therapy in the Pediatrics department of Pakistan Atomic Energy Hospital, Islamabad.

**Methods:** A descriptive cross-sectional study, conducted in the department of Paediatrics, PAEC General Hospital, Islamabad from 06-June-2022 to 05-December-2022. A total of 125 diagnosed cases of epilepsy and valproic acid therapy were included. After written informed consent from parents/guardians, demographic details were noted, and patients underwent testing for platelet count and thrombocytopenia was labelled as a platelet count of <150000/µL.

**Results:** The mean age of patients included in this study was 8.13±2.80 years. The mean duration of epilepsy was 3.44±1.56 years. Thrombocytopenia was observed in 31 (24.80%) patients on valproic acid therapy and a strong association between higher dosage of valproic acid and thrombocytopenia was observed (p <0.001).

**Conclusion:** An increased risk of thrombocytopenia is observed when valproic acid is used as a monotherapy or a part of polytherapy. Mostly this thrombocytopenia is not life-threatening but the importance of serial monitoring of platelet count during prolonged valproic acid use cannot be ignored due to the associated risk of bleeding, as children on higher doses of valproate are at greater risk of thrombocytopenia.

**Keywords:** Epilepsy, Valproic Acid, Thrombocytopenia.

[1] Trainee Paediatrics, PAEC Hospital, Islamabad; [2,3,4,5,6] Senior Registrar Paediatrics, Holy Family Hospital, Rawalpindi.

**Correspondence:** Dr. Qurat Ul Ain, Senior Registrar Paediatrics, Holy Family Hospital, Rawalpindi. **Email:** drainykhalid@gmail.com

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## 1. Introduction

Epilepsy is one of the most common neurologic disorders among the paediatric age group.[1] Epilepsy is characterised by recurrent seizures, often but not always accompanied by tongue bite and bed wetting.[2] The reported global incidence of epilepsy is 50-60 cases per 1 lac children per year,[3] and this incidence is supposed to increase in upcoming years, particularly in developing and underdeveloped countries, as they share 80% of the burden of epilepsy.[4] In Pakistan, it is reported that 9.9/1000 children suffer from epilepsy each year,[5] with the highest chances during the first year after birth.[6]

Valproic acid (VPA) is one of the commonest anti-epileptic drugs (AED) prescribed so far, because of its efficacy in controlling epileptic and non-epileptic seizures in children and adults.[7] Among various proposed mechanisms of action of VPA, augmentation of inhibitory neuronal activity by GABA is the primary focus[8,9] Along with modulation of glutamate excitatory activity.[10] Despite the global use of VPA for managing epileptic seizures, it brings negative consequences as well, in the form of side effects.[11] Thrombocytopenia is a well-known side effect of recurrent use of VPA in children,[12] But its characteristics and incidence are different from one population to another,[13] Some studies have shown that it is dose-dependent and persistent, while others have reported it to be a transient effect, irrespective of the dose.[6,7] Mehmood et al reported thrombocytopenia in 19.3% of the patients taking valproic acid as monotherapy,[8] while Kanwal et al showed that 24% of patients on valproate therapy developed thrombocytopenia.[9] These figures were much lower than those reported by Kim et al, who reported a frequency of 36.7 %.[10]

Despite the emerging era of medicine, few cases among many become resistant to epileptic drugs and pose a serious burden on physical, social and cognitive well-being.[14] Extensive use of VPA, its association with thrombocytopenia and increasing number of epileptic cases marks the need for further investigation. The literature available on the subject shows a widely variable incidence of thrombocytopenia, possibly indicating variability across different populations.[15]

The present study aims to determine the frequency of thrombocytopenia associated with VPA treatment in the paediatric age group. This may provide a basis for the establishment of a departmental protocol for the surveillance and management of thrombocytopenia in

these patients, to help reduce morbidity, mortality, and financial costs.

## 2. Materials & Methods

After approval from the Institutional Ethical Committee of PGHI (RCD-06-062), a descriptive cross-sectional study was conducted at the Department of Paediatrics, PAEC General Hospital, Islamabad, Pakistan. The duration of the study was 06-June-2022 to 05-December-2023 and included 125 patients fulfilling the following inclusion criteria. Diagnosed cases of epilepsy, who were on VPA therapy and aged between 2 and 16 years were included in the study. Patients with a history of drug intake that can interfere with the normal platelet count or had thrombocytopenia before VPA therapy were excluded. Patients having an active source of infection vitamin B12, or folic acid deficiency were also excluded. The main aim of the study was to determine the frequency and association of thrombocytopenia in patients on valproate therapy in the Pediatrics department of Pakistan Atomic Energy Hospital, Islamabad.

After written informed consent from a parent or a Guardian, a clinical history (including duration of epilepsy, type of epilepsy, duration of valproate therapy, dose of valproate therapy), and a General physical examination, followed by demographic characteristics were noted on a study designed questionnaire. Height and weight were measured using a wall-mounted stadiometer and a control-tested Medica Plus DT-916 Weighing Scale, respectively. A 1 ml sample of venous blood was taken and immediately transferred to an EDTA tube. A calibrated and control-tested Microlab-300 Haematology Analyser was used to measure platelet count, and reports were verified by a consultant pathologist.

The latest version of SPSS was used for data analysis. Descriptive statistics and other qualitative variables (gender, type of epilepsy and whether thrombocytopenia was present or not) were expressed as frequency and percentages. Quantitative variables specifically age, height, weight, duration of epilepsy, duration of valproate therapy, dose of valproate therapy and platelet count were expressed by mean±S.D. Confounders specifically age, gender, height, weight, duration of epilepsy, type of epilepsy, duration of valproate therapy and dose of valproate therapy were controlled by stratification. Post-stratification Chi-square test was applied and *p-value* $\leq 0.05$ was considered significant.

## 3. Results

Our study included 125 children with epilepsy, who were in VPA therapy. Demographics of the study population are in Table 1.

**Table 1: Demographic characteristics of the study population**

| Variable (n=125) | Mean ±Standard Deviation | Range |
|---|---|---|
| Age (years) | 8.13±2.80 | 2-16 |
| Height (cm) | 125.20±14.53 | 85-148 |
| Weight (kg) | 16.87±4.22 | 9-30 |

The majority of patients in the study population were males(n=68) Fig 1. Frequency of thrombocytopenia was reported in 31 subjects (fig 2) and generalized epilepsy was found to be common among study populations. (fig3)

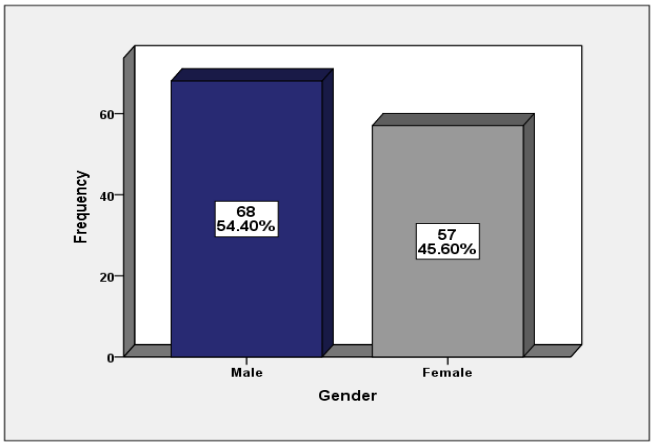


**Figure 1: frequency distribution of gender**

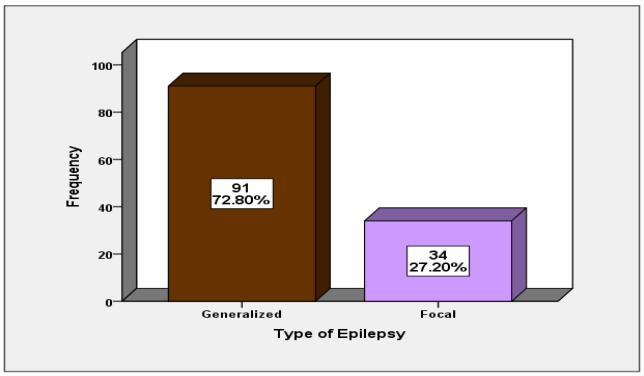


**Figure 2: frequency distribution of type of epilepsy**

Qualitative data was expressed in terms of descriptive variables (Table 2). Studies showed that most of the patients visiting the hospital reported in earlier years of

epilepsy which can in other ways indicate poor control of epileptic seizures. The average duration of valproate therapy in the study population was around 10 months, suggesting either late presentation of the patient for epileptic seizures or earlier management with other drugs but poor disease control.

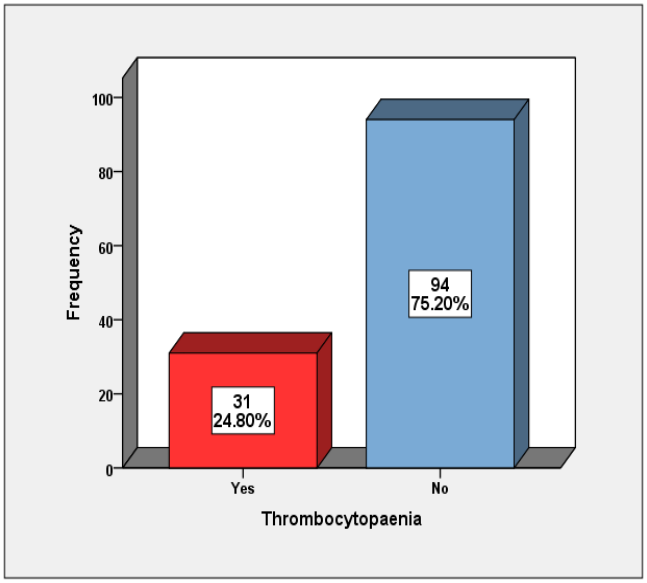


**Figure 3: frequency distribution of presence or absence of thrombocytopenia in children receiving valproate.**

To deal with confounders, the Stratification of demographic data was done, and chi-square was applied. Post-stratification of data revealed that the majority of patients with thrombocytopaenia were young males having a height between 85-127cm, and a weight between 18-30Kg but results were insignificant (p=0.949). (Table 3)

**Table 2: Descriptive statistics of the study population**

| Variable (n=125) | Mean ±SD | Range |
|---|---|---|
| **Duration of epilepsy (years)** | 3.44±1.56 | 1.00-10.00 |
| **Duration of valproate therapy (months)** | 8.39±2.71 | 2.00-15.00 |
| **Dosage of valproate (mg/kg/day)** | 37.09±5.02 | 30.00-50.00 |
| **Platelet count** | 178000±2940 | 50000-243000 |

*SD= Standard Deviation*

.On stratification of other variables, thrombocytopenia was found in 16(21.1%) patients having a duration of epilepsy of 1-3 months, and generalized epilepsy was prevalent in our study population, but the association was non-significant (p=0.227, p=0.84). On stratification of the duration of valproate therapy, thrombocytopaenia was found in 16 (22.9%) patients having a duration of valproate therapy of 2-8 months while it was found in 15 (27.3%) patients having a duration of valproate therapy 9-15 months with p-value 0f 0.227. On stratification of the dose of valproate therapy, a strong association of thrombocytopenia was found with p-value 0f <0.001. (Table 3)

**Table 3: Association of study variables and thrombocytopenia**

| Variable | Presence of Thrombocytopenia | | | | P-value |
|---|---|---|---|---|---|
| | yes | | No | | |
| **Age Group:** | | | | | |
| **2-8 Years** | 19 (25.0%) | | 57 (75.0%) | | 0.949 |
| **9-16 Years** | 12 (24.5%) | | 37 (75.5%) | | |
| **Gender:** | 17 (25.0%) | | 51 (75.0%) | | 0.955 |
| **Male** | 14 (24.6%) | | 43 (75.4%) | | |
| **Female** | | | | | |
| **Height:** | 18 (29.0%) | | 13 (20.6%) | | 0.277 |
| **85-127 cm** | 44 (71.0%) | | 50 (79.4%) | | |
| **128-148 cm** | | | | | |
| **Weight:** | 14 (21.5%) | | 17 (28.3%) | | 0.37 |
| **9-17 Kg** | 51 (78.5%) | | 43 (71.7%) | | |
| **18-30 Kg** | | | | | |
| **Duration of Epilepsy:** | 16 (21.1%) | 60 (78.9%) | 15 (30.6%) | 34 (69.4%) | 0.227 |
| **1-3 Months** | | | | | |
| **4-10 Months** | | | | | |
| **Type of Epilepsy** | 23 (25.3%) | 68 (74.7%) | 08 (23.5%) | 26 (76.5%) | 0.84 |
| **Generalized** | | | | | |
| **Focal** | | | | | |
| **Duration of valproate therapy** | | | | | 0.227 |
| **2-8 Months** | | | | | |
| **9-15 Months** | 16 (22.9%) | 54 (77.1%) | 15 (27.3%) | 40 (72.7%) | |
| **Dose of Valproate (per day)** | 11 (11.5%) | 85 (88.5%) | 20 (69.0%) | 09 (31.0%) | <0.001* |
| **30-40 mg/kg/day** | | | | | |
| **41-50 mg/kg/day** | | | | | |

## 4. Discussion

Our study found a significant association of thrombocytopenia with increasing dosage of valproic acid (VPA), while the previous studies found an association and correlation between thrombocytopenia and duration of VPA treatment. A recent study reported a 10-20% prevalence of thrombocytopenia with oral VPA in adult patients.[16]

Sahu and colleagues observed that about 12.5% of children with epilepsy who were taking valproic acid experienced thrombocytopenia. [17] On the other hand, Delgado and his team found that 21% of epileptic children on valproate developed thrombocytopenia.[18] This suggests that rather than completely stopping the medication, reducing the dosage might be a safer option for most patients with thrombocytopenia. It's advisable to closely monitor platelet counts, especially in patients with higher drug levels.

Similarly, Nasreddine and Beydoun conducted a study to explore the connection between VPA platelet counts and found that around 17.7% of patients experienced at least one episode of thrombocytopenia (platelet count < 100,000/μl) after being exposed to divalproex sodium.[19] This incidence rate closely aligns with the 19.3% observed in their study. They found a significant negative correlation between VPA levels and platelet counts, like our findings. The likelihood of developing thrombocytopenia significantly rose with trough VPA levels exceeding 100 μg/ml in females and 130 μg/ml in males.

A retrospective examination of almost 1500 patients on anticonvulsants, other than VPA, found no discrepancy in the platelet counts between individuals with and without epilepsy, however, the patients with epilepsy receiving valproic acid had notably lower platelet counts compared to those on different medications.[20] we also discovered that thrombocytopenia, although prevalent, is consistently temporary and self-limiting even with continued valproic acid use. This aligns with our clinical experience, where thrombocytopenia typically resolves without interrupting valproic acid treatment. Additionally, the severity of thrombocytopenia is generally not concerning for haemorrhagic tendencies, as we did not encounter any cases of bleeding diathesis in our study. Another study showed that 17.7% of patients in the treatment group experienced thrombocytopenia, in contrast to 4.2% in the comparison group ($P<0.05$).[18] Platelet count was inversely associated with serum valproic acid level and age, and positively correlated with polytherapy. In most cases, thrombocytopenia was mild and transient, resolving spontaneously upon dosage adjustment or discontinuation of the drug.[21, 22].

## 5. Conclusion

Thrombocytopenia caused by valproic acid, as shown in our study, is consistent with international data. However pediatric experience with valproic acid is generally increasing. The complex nature of convulsive disorders in the Pediatric age group requiring polytherapy is a major reason for limited data in this age group. Still, current data suggests increased thrombocytopenia when valproic acid is used as a monotherapy or a part of polytherapy. Mostly this thrombocytopenia is not life-threatening but cannot be ignored. Monitoring of Platelet count in children who are on valproic acid treatment should be done as children on higher dosages of valproic acid are at greater risk of thrombocytopenia.

**CONFLICTS OF INTEREST**- None

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**Contributions:**
K.N, Q.U.A, A.T, S.J - Conception of study
- Experimentation/Study Conduction
K.N, I.L, N.M - Analysis/Interpretation/Discussion
K.N, A.T, S.J - Manuscript Writing
K.N, Q.U.A, I.L, N.M - Critical Review

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