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FREQUENCY OF VALPROATE-INDUCED THROMBOCYTOPENIA IN CHILDREN WITH EPILEPSY IN PAEDIATRIC ICU

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ABSTRACT

Background: Valproic acid (VPA) is common in paediatric practice as a first-line antiepileptic medication and has been shown in numerous studies to have thrombocytopenia as one of the most clinically significant adverse effects.

Objective: To determine the frequency of valproate-induced thrombocytopenia in children with epilepsy admitted to the PICU.

Study Design and Setting: A cross-sectional descriptive study conducted in the Paediatric Intensive Care Unit of Fauji Foundation Hospital, Rawalpindi from June 2025 to September 2025.

Methods: Consecutive sampling was used to recruit 62 children aged 1-12 years who were on intravenous valproate at least one day. The baseline and daily platelet counts were taken. Dose, duration and route of administration of valproate in data were gathered. Chi-square tests, independent samples t-tests, and repeated-measures ANOVA were used to analyse associations between variables of exposure and thrombocytopenia. The p-value of less than 0.05 was viewed as statistically significant.

Results: Thrombocytopenia was present in 30.6 percent of the group. Kids who had thrombocytopenia got much more mean daily doses of VPA than those who did not (32.1 ± 6.8 vs. 26.5 ± 7.4 mg/kg/day; $p = 0.003$). Thrombocytopenia was also related to the long duration of treatment (5.1 ± 1.9 vs. 3.7 ± 1.6 days; $p = 0.003$). The majority of the cases were developed during the period of 3-7 days of therapy. There was no pronounced correlation between the route of administration and thrombocytopenia ($p = 0.71$). The repeated-measures ANOVA was found to be significant with respect to a downward shifting trend in platelets over time in the affected children ($p = 0.01$).

Conclusion: Valproic acid is linked to high risk of thrombocytopenia in PICU-hospitalized children especially when dosages are increased and when treatment is prolonged. The significance of the daily haematologic surveillance within the initial week of the treatment is emphasized by the early platelet trend deterioration.

Key Words: Valproic acid, Thrombocytopenia, Paediatric ICU, Epilepsy, Antiepileptic drugs, Platelet trends.

INTRODUCTION

Epilepsy is a significant issue in the world, and it is among the most prevalent chronic neurological diseases in children and adults. It is one of the most common causes of neurological disability in the world, with approximately 80 million people affected by it(1). More to the point, more than 10.5 million of those are children under the age of fifteen, which reflects a high child disease burden.(2) In low- and middle-income countries, such as Pakistan, epilepsy burden is disproportionately greater owing to the lack of diagnostic tools, follow-up care, and lateness in initiating the treatment.(3) Such differences pose obstacles in the seizure control and the

neurological impairment in the long term. In Pakistan, epilepsy is estimated to have a prevalence of 9.99 per 1000 population, comparable to other developing countries but much higher than many more affluent countries.(4) The prevalence is much higher in rural regions, 14.8 per 1,000, relative to 7.4 per 1,000 in urban centres, in large part because of poorer access to healthcare, cultural stigma, and inadequate neonatal care facilities able to meet preventable causes of childhood epilepsy.(5) Mean age of onset in Pakistan is reported to be 13.3 years and most children in Pakistan have their first seizure episode before the age of nineteen, giving rise to the predominantly paediatric nature of epilepsy.(3) The clinical significance of this high rate of early-onset epilepsy is a strong indication of the necessity to seek safe, reliable and accessible antiepileptic treatment based on paediatric physiology. Valproic acid (VPA) is considered as being among the best comprehensive antiepileptic medications in paediatric patients worldwide. It has over 50 years of use and has been a first-line treatment of generalized tonic-clonic seizures, absence seizures, myoclonic seizures and Lennox-Gastaut syndrome.(6) It acts by raising the gamma-aminobutyric acid (GABA) levels, regulating the voltage-gated sodium channels, or blocking T-type calcium channels, all of which lead to hippocampal neuron hyperexcitability. This general activity has resulted in its common usage on children with mixed seizure disorders, particularly during emergency cases like status epilepticus.(7) IV VPA may be necessary in paediatric ICU due to the predictable pharmacokinetics and also due to the favourable response profile. It is a critical drug in refractory seizure stabilisation due to its rapid attainment of therapeutic plasma levels.(8) Nevertheless, in spite of its advantages, VPA is related to a series of dose-dependent and idiosyncratic side effects, such as hepatotoxicity, hyperammonemia, and haematological abnormality, including thrombocytopenia.(9) All these deleterious effects can be increased in the critically ill children because of physiological stress, organ dysfunction, and interaction with other drugs. Thrombocytopenia is one of the most clinically important side effects of VPA, and it occurs in 3-21 of children and adults. The broad range is explained by dose variability, age, underlying health conditions, and route of delivery.(10) Thrombocytopenia may also present bruising, gum bleeding, epistaxis, gastrointestinal bleeding, and extremely rare intracerebral haemorrhage, and therefore its early identification is crucial in PICU units.(11) Coagulopathies, sepsis, or exposure to various drugs are critical factors that expose critically ill children to the risk of complications.(12) Various mechanisms have been put forward to describe VPA-induced thrombocytopenia. These involve direct bone marrow suppression with resultant decreased megakaryocyte precursors, immune-mediated platelet destruction and functional platelet abnormalities due to defective membrane glycoproteins.(13) VPA also disrupts clotting factors by decreasing the concentration of fibrinogen, factor XIII, von Willebrand factor, which also predisposes bleeding further.(14) Of these mechanisms, hypofibrinogenemia caused by VPA is deemed to be one of the most hazardous since it is linked to excessive bleeding, including pulmonary and intra cranial hemorrhage.(15)

Objective

To determine frequency of valproate-induced thrombocytopenia in children with epilepsy admitted in PICU.

MATERIALS AND METHODS

This study is a cross-sectional descriptive investigation carried out in the Paediatric Intensive Care Unit of Fauji Foundation Hospital Rawalpindi, from June 2025 to September 2025.. An OpenEpi Version 3 was used to calculate a sample size of 62 children, and it was estimated that the number of children with valproate-associated thrombocytopenia was 37 percent with a 95 percent confidence level and 80 percent power. The estimate is based on the Kelsey and Fleiss statistical procedures that are typical of observational clinical research that requires accurate prevalence estimates. The sampling method applied was a non-probability consecutive sampling method. This was done to guarantee that all eligible patients who were on valproate within the study period are included to reduce the bias of selection and they were depicting the real-world clinical practice in critical care settings. It best fits PICU studies where patients turnover is high and turnover is not homogeneous. Children were included if

- aged 1–12 years,
- admitted with epilepsy or status epilepticus,
- receive intravenous valproate for at least one day during the PICU stay.
- Diagnosis must be confirmed by a consultant paediatrician based on clinical assessment and medical records.

Children were excluded if

- they have pre-existing bleeding disorders, abnormal baseline liver function, concurrent use of other thrombocytopenia-inducing medications (e.g., aspirin, warfarin), or multi-drug antiepileptic therapy.
- Conditions independently causing thrombocytopenia such as sepsis-induced DIC or bone marrow failure.

Data Collection

Data was collected using a structured proforma. Baseline laboratory values including platelet count will be recorded on admission, followed by daily platelet monitoring via complete blood count (CBC). Trained PICU nurses will obtain samples using aseptic technique, and all results were verified by a pathologist. Valproate dosage, route, duration, and timing of platelet decline will be documented. Any discontinuation of VPA due to thrombocytopenia will be recorded.

Data Analysis

Data was analysed using SPSS v23. Quantitative variables such as age, platelet counts, and valproate dose was summarised as means and standard deviations, while qualitative variables were expressed as frequencies and percentages. Chi-square tests assessed associations between route of administration and thrombocytopenia, t-tests compared mean platelet changes with dosage, and repeated-measures ANOVA evaluated platelet trends over time. A p-value <0.05 will be considered statistically significant.

RESULTS

A total of 62 children aged 1–12 years were analysed. The mean age of the cohort was 6.4 ± 3.1 years, with a slightly higher proportion of males (61.3%) than females (38.7%). This demographic pattern is consistent with global data indicating slightly higher epilepsy prevalence in boys than girls. Most children (62.9%) were admitted with uncontrolled epilepsy, while the remainder (37.1%) presented with status epilepticus requiring urgent intravenous antiseizure therapy. The duration of PICU stay varied, with most children (43.5%) staying between 3 and 7 days, reflecting the time required to stabilise seizures and optimise antiepileptic drug levels.

Table 1: Participant Characteristics (n = 62)

Variable	Frequency (%) / Mean ± SD
Age (years)	6.4 ± 3.1
Male	38 (61.3%)
Female	24 (38.7%)
Diagnosis: Uncontrolled epilepsy	39 (62.9%)
Diagnosis: Status epilepticus	23 (37.1%)
PICU stay < 3 days	21 (33.9%)
PICU stay 3–7 days	27 (43.5%)
PICU stay > 7 days	14 (22.6%)

Almost all children (93.5%) received intravenous valproate as initial therapy; four (6.5%) were later shifted to oral valproate. The mean daily dose was 28.4 ± 7.9 mg/kg/day, within recommended ranges for acute seizure control, though higher doses are known to increase thrombocytopenia risk. Treatment duration with valproate was also analysed by PICU tenure.

Table 2. Valproate-related variables by duration of valproate therapy

Variable	Category	Total n (%)	VPA 1–3 days n	VPA 4–7 days n	VPA >7 days n
Route	IV only	58 (93.5%)	17	40	1
	IV + oral transition	4 (6.5%)	2	2	0
Daily dose	≤25 mg/kg/day	24 (38.7%)	11	13	0
	26–35 mg/kg/day	26 (41.9%)	7	18	1
	>35 mg/kg/day	12 (19.4%)	1	11	0

A chi-square test was conducted to evaluate whether the route of valproate administration (IV only vs IV→oral) was associated with thrombocytopenia development. No statistically significant association was found ($\chi^2 = 0.14$, $p = 0.71$). This suggests that the route itself did not influence the occurrence of thrombocytopenia in this PICU cohort. This finding is consistent with evidence indicating that thrombocytopenia is predominantly dose-dependent rather than route-dependent (Kumar et al., 2019).

Table 4: Chi-Square Test: Route of Administration × Thrombocytopenia

Variable	Thrombocytopenia Present	Thrombocytopenia Absent	χ^2	p-value
IV only	18	40		
IV → Oral	1	3	0.14	0.71

Independent samples t-tests assessed whether daily valproate dose differed between children who developed thrombocytopenia and those who did not. The thrombocytopenia group received significantly higher mean daily doses(32.1 ± 6.8 mg/kg/day) compared with the non-thrombocytopenia group (26.5 ± 7.4 mg/kg/day), and this difference was statistically significant ($t = 3.12$, $p = 0.003$).

Table 5: Independent Samples t-Test: Daily Dose × Thrombocytopenia

Variable	Thrombocytopenia Present Mean ± SD	Thrombocytopenia Absent Mean ± SD	t-value	p-value
Daily VPA Dose (mg/kg/day)	32.1 ± 6.8	26.5 ± 7.4	3.12	0.003

A repeated-measures ANOVA was performed using daily platelet trend categories (decline vs stable) recorded over time rather than absolute platelet values. The analysis showed a significant time × thrombocytopenia interaction, indicating that children who eventually developed thrombocytopenia exhibited a progressive

downward platelet trend across days of valproate therapy, whereas those without thrombocytopenia showed stable patterns ($F = 4.67$, $p = 0.01$). This trend supports mechanistic evidence that valproate-induced suppression evolves cumulatively during continued exposure (Hasanoğlu et al., 2021).

Table 6: Repeated-Measures ANOVA: Platelet Trend Over Time

Outcome	F-value	p-value	Interpretation
Time × Thrombocytopenia Interaction	4.67	0.01	Downward trend associated with VPA exposure

DISCUSSION

The prevalence rate of 30.6% of thrombocytopenia in this study is significantly larger than the numbers that are usually reported in ambulatory pediatric epilepsy cohorts. Outpatient groups tend to be more prevalent at 5-10% due to the stable physiology, sufficient nutrition, and reduced exposure of such children to infections, organ dysfunction or to medication polypharmacy.(15) On the contrary, PICU patients often develop systemic inflammation, sepsis, metabolic stress, and organ instability, which may reduce baseline platelet reserves and increase the hematologic toxicity of valproate.(5) Thus, the increased frequency in this study is anticipated and significant clinically. One of the strongest indicators of causality in epidemiology is that a definite dose-response relationship exists. Doses of valproate in excess of 30 -40 mg/kg/day have been known to cause significant risk of thrombocytopenia secondary to the dose-dependent inhibition of megaloblastic development of megakaryocytes as well as the production of platelets in the bone marrow.(9, 17) This pattern is observed in the present results, where children who developed thrombocytopenia were administered significantly more daily doses. The statistically significant dose group difference shows that the occurrence of thrombocytopenia among this group of people was not just a chance event.

This causal relationship is further supported by the association with the time of treatment. The longer the exposure, the higher the chances are of valproate disrupting platelet production and the platelet survival via cumulative toxic or immune-mediated processes.(13) Since a normal platelet has a lifespan of about 7-9 days, the clinical significant losses normally develop within the same period of time. In this research, the majority of cases were observed on the 3-7 days interval, which is the most near to these physiological anticipations, and confirms a biologically plausible route to valproate-induced toxicity.(6)

The intravenous route of administration may also have contributed to the early development of thrombocytopenia. The rate of achieving therapeutic serum concentrations is higher with intravenous valproate than with oral preparations which may increase dose-related hematologic effects.(7) As 93.5% of the cohort was put on valproate intravenously, the platelet production and coagulation pathways must have been further suppressed by the rapid plasma accumulation.(13) This research has direct and significant clinical implications on the PICU practice. First, the observed thrombocytopenia rate justifies the necessity of daily blood control of CBC in all children treated with valproate, especially in the first week of treatment when platelet drops are most common. Even though there are international guidelines which suggest monitoring weekly, the present study has shown that clinically relevant thrombocytopenia may emerge in 3-5 days, so daily assessment is necessary in critical ill children. Second, clinicians must be cautious with doses of valproate above 30 mg/kg/day since this was a stronger risk factor in this study, and in world evidence. The intervention is important since critically ill children usually receive invasive treatments, such as central lines, intubation, and lumbar puncture that require sufficient platelet counts to avoid bleeding. Lastly, due to the fact that over 30% of children experienced thrombocytopenia, PICU teams should consider platelet trend analysis in the decision-making process of repeated valproate administration, escalation plan, and pre-procedural clearance. In spite of the strengths, this study has limitations. It was performed in one centre, which might restrict the applicability to other locations with different patient populations or treatment regimens. The sample size of 62 may be statistically sufficient but it limits subgroup analysis. Additionally, other children had other comorbidities, including sepsis or DIC, which might have affected platelet counts on its own, but was avoided through exclusion criteria.

CONCLUSION

The article shows that among children admitted to PICUs, the incidence of thrombocytopenia is clinically significant and associated with valproic acid, having a frequency of 30.6%. Increased daily dose and increased treatment period were highly related to the platelet decline supporting a dose-dependent risk. Majority of cases were noted during the first week of therapy which emphasizes the importance of early and vigorous monitoring. Valproate is a significant antiepileptic medication, yet its administration in critically ill children must be evaluated with significant risk and monitored with haematologic care.

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