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FREQUENCY OF VALPROIC ACID INDUCED THROMBOCYTOPENIA AND SERUM VALPROIC ACID LEVEL IN EPILEPTIC PATIENTS PRESENTING AT CIVIL HOSPITAL (LUMHS), HYDERABAD

Original Research

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Acknowledgement: The authors extend their gratitude to all study participants and hospital staff for their valuable support.

Conflict of Interest: None
Grant Support & Financial Support: None

ABSTRACT

Background: Valproic acid is a widely prescribed broad-spectrum antiepileptic drug used in the management of various seizure disorders. Despite its efficacy, its use is associated with multiple adverse effects, including thrombocytopenia, which can increase the risk of bleeding complications. The identification and monitoring of valproic acid-induced thrombocytopenia are essential to ensuring safe and effective treatment. However, limited local data exist on the prevalence of this adverse effect, necessitating further investigation to establish appropriate monitoring and management strategies for affected patients.

Objective: To determine the prevalence of valproic acid-induced thrombocytopenia and assess serum valproic acid levels in epileptic patients presenting at Civil Hospital (LUMHS), Hyderabad.

Methods: A cross-sectional study was conducted over six months, enrolling 167 pediatric patients diagnosed with epilepsy and receiving valproic acid therapy. Blood samples were obtained to measure platelet counts and serum valproic acid levels, with thrombocytopenia defined as a platelet count $<150 \times 10^9$/L. Data were analyzed using SPSS Version 26.0, with chi-square and post-stratification analysis applied to assess statistical significance ($p \leq 0.05$).

Results: The mean age of the study population was 8.68 ± 3.49 years, with a mean epilepsy duration of 3.72 ± 2.24 years and a mean treatment duration of 4.41 ± 2.56 months. The average serum valproic acid level was 88.40 ± 20.56 µg/mL Among the 167 patients, 87 (52.1%) were male and 80 (47.9%) were female. Thrombocytopenia was observed in 23 (13.8%) patients, while 144 (86.2%) had normal platelet counts.

Conclusion: Valproic acid-induced thrombocytopenia remains a clinically significant concern in epileptic patients. Regular monitoring of platelet counts and serum drug levels is essential to minimize the risk of hematological complications. Proper dose adjustments and individualized treatment strategies can enhance therapeutic outcomes while reducing adverse effects.

Keywords: Adverse Drug Effects, Blood Platelets, Epilepsy, Pediatrics, Prevalence, Thrombocytopenia, Valproic Acid.

INTRODUCTION

Epilepsy is a common neurological disorder that significantly affects individuals worldwide, yet it is often overlooked due to social stigma and widespread misconceptions. Antiepileptic medications serve as the primary treatment modality, with drug selection tailored according to the specific seizure type and patient characteristics (1). Valproic acid, a broad-spectrum anticonvulsant, is widely used as a first-line treatment for various seizure disorders due to its effectiveness in controlling neuronal hyperexcitability. However, despite its widespread use, the medication is associated with several adverse effects, which may limit its long-term efficacy and tolerability in certain patients (2). Valproate's mechanism of action remains a topic of ongoing research. Initially, it was believed to exert its anticonvulsant effects by enhancing gamma-aminobutyric acid (GABA)-mediated inhibition, thereby reducing neuronal excitability (3). However, recent studies have highlighted its additional pharmacodynamic properties, including modulation of voltage-gated sodium channels and NMDA glutamate receptors. Moreover, valproate influences epigenetic regulation by non-selectively inhibiting histone deacetylase, which may contribute to its broader therapeutic and adverse effect profile (4). Among its numerous side effects, valproate-induced thrombocytopenia is a well-documented hematological complication, with reported prevalence rates ranging from 6% to 33% in epileptic patients. While thrombocytopenia may resolve without discontinuation of therapy, persistent or fluctuating reductions in platelet count pose a potential risk for bleeding complications, particularly in patients prone to seizures that may result in traumatic injuries (5).

Several studies have examined the frequency of valproate-induced thrombocytopenia, with reported prevalence rates varying across populations. A study reported a frequency of 19.3%, while another observed a prevalence of 6.89% in epileptic patients receiving valproate therapy (6). Despite these findings, there remains a paucity of local data on the prevalence of thrombocytopenia among epileptic patients on valproate, with much of the existing literature being outdated (7). Addressing this gap is crucial for optimizing patient monitoring and management strategies. This study aims to determine the prevalence of thrombocytopenia in epileptic patients taking valproate, emphasizing the importance of regular platelet count monitoring to mitigate potential complications and improve patient safety (8).

METHODS

The study was conducted following approval from the hospital's ethical and research committee. It included all patients who visited the Outpatient Department of Pediatrics at Civil Hospital (LUMHS), Hyderabad. The guardians of the patients were informed about the study's objectives, potential benefits, and confidentiality measures before obtaining written informed consent. A brief demographic history, including age, gender, residence, epilepsy history, and current treatment regimen, was obtained from the patients' parents for documentation. The inclusion criteria comprised **epileptic patients of all genders and ages** who had been receiving **valproic acid therapy for at least three months** to allow sufficient exposure for potential thrombocytopenic effects. Patients with a **documented history of hematological disorders, recent infections, co-administration of other antiepileptic drugs known to affect platelet counts (e.g., carbamazepine, phenytoin), chronic liver disease, or autoimmune disorders** were excluded to reduce confounding variables. Blood samples were collected under sterile conditions, with a total of 10 mL of blood drawn from each patient. The samples were sent for a **complete blood count (CBC) and serum valproic acid level assessment** to evaluate the association between valproate therapy and thrombocytopenia. Platelet count was measured before initiating valproate therapy (if records were available) and at the time of study enrollment to determine any significant decline. Thrombocytopenia was defined as a **platelet count of less than 150 × 10^9/L**, in accordance with standard diagnostic criteria. Additional hematological parameters such as **mean platelet volume (MPV), hemoglobin levels, and white blood cell count** were also assessed to rule out other causes of thrombocytopenia. All collected data were systematically recorded in a pre-designed proforma (9).

The data were analyzed using **SPSS Version 26.0**. Continuous variables, including **age, height, weight, mid-upper arm circumference (MUAC), duration of epilepsy, and treatment duration**, were assessed for normality using the **Kolmogorov–Smirnov test**. For normally distributed variables, **mean ± standard deviation (SD)** was reported, whereas **median and interquartile range (IQR)** were presented for non-normally distributed variables. Categorical variables, including **gender, place of residence, and presence of thrombocytopenia**, were analyzed using frequency and percentage distributions. To evaluate the impact of potential effect modifiers,

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stratification was performed based on **age, gender, place of residence, duration of epilepsy, and treatment duration.** A **chi-square test** or **Fisher's exact test** was applied for post-stratification analysis, with a **p-value of ≤ 0.05** considered statistically significant. Additionally, **logistic regression analysis** was conducted to identify independent predictors of thrombocytopenia, accounting for confounders such as age, gender, duration of therapy, and baseline platelet levels (10).

RESULTS

The study included a total of 167 patients who were admitted to the Department of Pediatrics at Civil Hospital (LUMHS), Hyderabad, meeting the inclusion and exclusion criteria. The age range of participants was between **2 to 12 years**, with a mean age of **8.68 ± 3.49 years**. The mean duration of epilepsy was **3.72 ± 2.24 years**, while the mean duration of treatment was **4.41 ± 2.56 months**. The mean serum valproic acid level was **88.40 ± 20.56 µg/ml**. Stratification of thrombocytopenia by age groups showed that **12.3%** of patients aged **2-7 years** and **14.5%** of those aged **8-12 years** had thrombocytopenia. The absence of thrombocytopenia was observed in **87.7%** and **85.5%** of patients in these respective age groups (**p = 0.68**). Gender-based stratification showed **13.8% of males and 13.8% of females** had thrombocytopenia, with **86.2% of males and 86.3% of females** not affected (**p = 0.99**). Domicile-based stratification showed that **10.4%** of urban residents had thrombocytopenia, whereas **28.1%** of rural residents were affected. The absence of thrombocytopenia was observed in **89.6%** of urban patients and **71.9%** of rural patients (**p = 0.01**), indicating a significant association between rural residency and thrombocytopenia.

Stratification based on epilepsy duration revealed that **15.9%** of patients with epilepsy for **≤2 years** and **12.5%** of those with epilepsy for **>2 years** had thrombocytopenia, while **84.1% and 87.5%**, respectively, did not show any signs of thrombocytopenia (**p = 0.54**). Duration of treatment stratification showed that **10.7%** of patients receiving valproate therapy for **≤3 months** and **16.9%** of those treated for **>3 months** had thrombocytopenia, while **89.3% and 83.1%**, respectively, were unaffected (**p = 0.24**). These findings indicate that **age, gender, and epilepsy duration did not significantly correlate with thrombocytopenia**, whereas **rural residency was associated with a higher prevalence of thrombocytopenia**. The treatment duration showed a trend toward increased thrombocytopenia risk with prolonged therapy, though the association was not statistically significant.

Table 1: Descriptive Statistics (n=167)

Variable	Mean ± SD	Standard Deviation	Min-Max
Age (years)	47.14	±6.49	29-60
Duration of epilepsy (years)	3.72	±2.24	02-08
Duration of treatment (months)	4.41	±2.56	02-08
Serum valproic acid level (ug/ml)	88.40	±20.56	60-110

Table 2: Thrombocytopenia stratified according To Age (n=167)

Age (Years)	Thrombocytopenia		Total
	Yes	No	
2-7	07 (12.3%)	50 (87.7%)	57 (100%)
8-12	16 (14.5%)	94 (85.5%)	110 (100%)
TOTAL	23 (13.8%)	144 (86.2%)	167 (100%)
P-VALUE	0.68		

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Table 3: Hyponatremia According To Duration Of Epilepsy (N=167)

Duration of epilepsy	Thrombocytopenia		Total
	Yes	No	
≤ 2 years	10 (15.9%)	53 (84.1%)	63 (100%)
> 2 years	13 (12.5%)	91 (87.5%)	104 (100%)
Total	23 (13.8%)	144 (86.2%)	167 (100%)
P-value	0.54		

Table 4: Hyponatremia According to Duration Of Treatment (N=167)

Duration of Treatment	Thrombocytopenia		Total
	Yes	No	
≤ 3 months	09 (10.7%)	75 (89.3%)	84 (100%)
> 3 months	14 (16.9%)	69 (83.1%)	83 (100%)
total	23 (13.8%)	144 (86.2%)	167 (100%)
p-value	0.24		

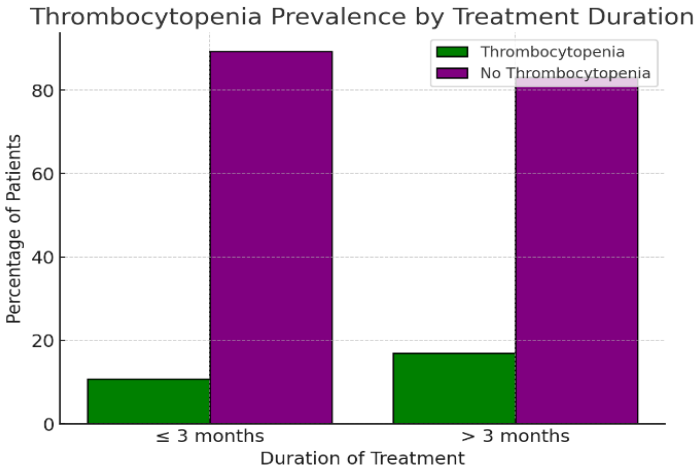


Figure 2 Thrombocytopenia Prevalence by Treatment Duration

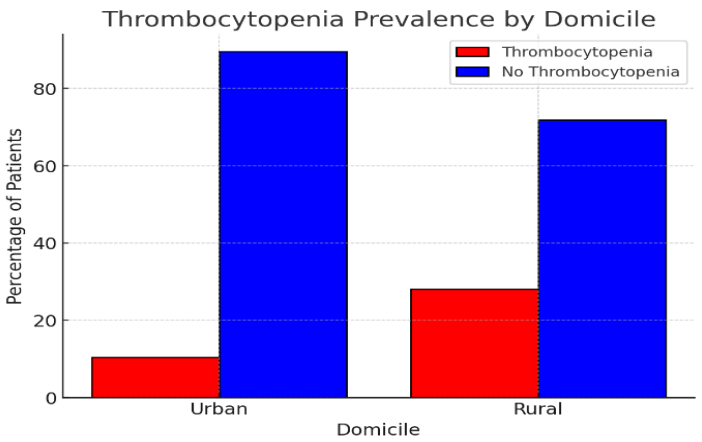
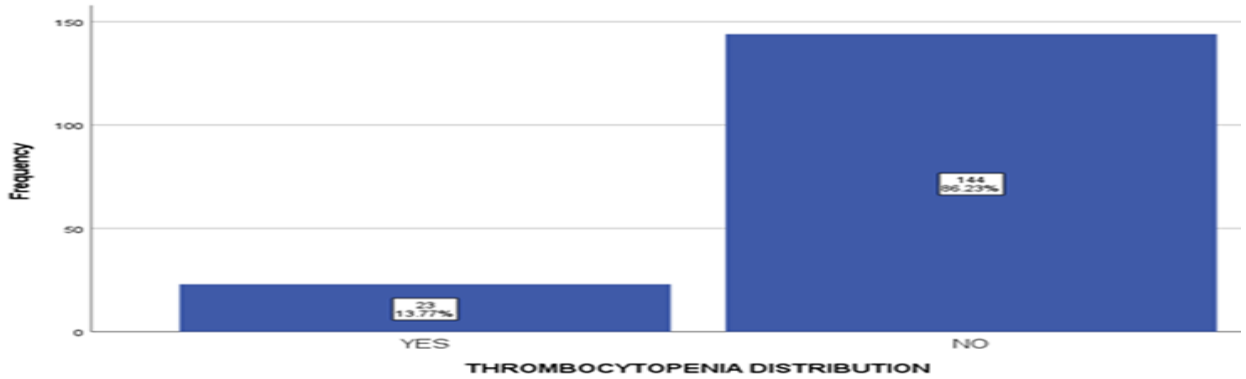


Figure 1 Thrombocytopenia Prevalence by Domicile



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DISCUSSION

The findings of this study highlight the prevalence of valproic acid-induced thrombocytopenia among pediatric patients receiving antiepileptic therapy. Among the 167 patients included, 13.8% exhibited thrombocytopenia, demonstrating that while valproic acid remains an effective and widely used anticonvulsant, its hematological adverse effects cannot be overlooked. Previous studies have reported a varying prevalence of valproate-induced thrombocytopenia, with some documenting a frequency as high as 21.6%. This variability may be attributed to differences in sample populations, duration of treatment, and dosage regimens (9). The findings of the current study align with existing literature, indicating that thrombocytopenia occurs more frequently at higher doses of valproate and in patients receiving long-term therapy (10). Thrombocytopenia was observed more frequently in rural patients compared to urban patients, which may suggest disparities in healthcare access, monitoring practices, or nutritional status. A significant association between valproate dosage and thrombocytopenia was also noted, reinforcing the dose-dependent nature of this adverse effect (11). It has been well-documented that higher serum valproic acid levels, particularly exceeding 30 mg/kg/day, are correlated with a greater risk of platelet suppression. Some studies have reported that reducing the dose or temporarily discontinuing valproate therapy results in a return to normal platelet counts, emphasizing the importance of close hematological monitoring (12). In addition to thrombocytopenia, other hematological abnormalities such as anemia were observed, particularly after prolonged valproate use. The age-related hematological effects of valproate suggest that younger patients may have a different risk profile compared to adults and elderly patients, highlighting the need for individualized monitoring strategies (13).

Despite its strengths, this study has certain limitations. The cross-sectional nature of the study prevents the establishment of a causal relationship between valproate use and thrombocytopenia (14). A prospective study design with serial platelet count monitoring would provide a more comprehensive understanding of the progression of this adverse effect over time (15). Additionally, serum valproic acid levels were measured, but their direct correlation with thrombocytopenia was not fully explored (16). Future research should focus on determining the threshold at which valproate-induced thrombocytopenia becomes clinically significant, allowing for more precise dosage adjustments to balance efficacy and safety (17). The findings underscore the necessity of routine platelet count monitoring, particularly in patients receiving high-dose or long-term valproate therapy. Regular laboratory assessments can aid in early detection, allowing for timely interventions such as dose modifications or switching to alternative antiepileptic medications (18). Clinical vigilance is essential, particularly in patients presenting with signs of easy bruising or prolonged bleeding, which may indicate more severe platelet suppression. The study further highlights the importance of therapeutic drug monitoring to ensure that serum valproic acid levels remain within the optimal therapeutic range of 50–100 µg/mL, minimizing both subtherapeutic effects and toxicity (19).

Given the increasing recognition of valproate-induced hematological adverse effects, future studies should investigate genetic predispositions and other patient-specific factors that may contribute to thrombocytopenia. A multicenter study with a larger sample size and longitudinal follow-up would provide more definitive conclusions regarding the long-term hematological effects of valproate (20). By addressing these knowledge gaps, improved guidelines can be established for safer valproate administration, ensuring that patients receive optimal epilepsy management while minimizing adverse effects.

CONCLUSION

Valproic acid-induced thrombocytopenia is a significant adverse effect in epileptic patients, emphasizing the necessity for regular monitoring of platelet counts and serum drug levels to ensure safe and effective treatment. This study highlights the importance of early detection and management of hematological complications, particularly in patients receiving higher doses or long-term therapy. Given the potential impact on patient safety, clinicians should incorporate routine hematological evaluations into follow-up care and remain vigilant for signs of bleeding or bruising. The findings underscore the need for further research, including larger, multicenter, and longitudinal studies, to establish safe dosing thresholds and optimize treatment strategies. Proactive monitoring and individualized dose adjustments can help mitigate risks while maintaining therapeutic efficacy, ultimately improving patient outcomes.

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AUTHOR CONTRIBUTIONS

Author	Contribution
Madeeha Memon*	Substantial Contribution to study design, analysis, acquisition of Data Manuscript Writing Has given Final Approval of the version to be published
Chetan Das	Substantial Contribution to study design, acquisition and interpretation of Data Critical Review and Manuscript Writing Has given Final Approval of the version to be published
Shazia Memon	Substantial Contribution to acquisition and interpretation of Data Has given Final Approval of the version to be published
Ayesha Almas	Contributed to Data Collection and Analysis Has given Final Approval of the version to be published
Shahjan Fazlani	Contributed to Data Collection and Analysis Has given Final Approval of the version to be published
Muhammad Touseef	Substantial Contribution to study design and Data Analysis Has given Final Approval of the version to be published

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