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Original Research Article

Comparative Study on the Efficacy and Safety of Low-Dose Sodium Valproate in Pediatric Patients with Febrile Convulsions

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Conflict of interest: Nil

Abstract:

Background: Febrile convulsions represent the most common seizure disorder in pediatric populations, affecting approximately 2-5% of children aged 6 months to 5 years. While the prognosis is generally favorable, recurrent episodes cause significant parental anxiety and may necessitate prophylactic intervention. Sodium valproate has demonstrated efficacy in seizure prevention; however, optimal dosing strategies that balance efficacy with minimal adverse effects remain under investigation.

Methods: A prospective randomized controlled trial was conducted involving 156 children aged 6 months to 5 years with a history of at least two febrile convulsion episodes. Participants were randomly assigned to receive either low-dose (n=78) or standard-dose (n=78) sodium valproate for 12 months. Primary outcomes included recurrence rate and time to first recurrence. Secondary outcomes encompassed adverse effects, hepatic function parameters, and treatment adherence.

Results: The recurrence rate was 14.1% in the low-dose group compared to 11.5% in the standard-dose group (p=0.624). Mean time to first recurrence was 7.8±2.3 months versus 8.2±2.1 months (p=0.412). Adverse effects were significantly lower in the low-dose group (17.9% vs. 34.6%, p=0.016). Treatment adherence was higher in the low-dose group (91.0% vs. 82.1%, p=0.048).

Conclusion: Low-dose sodium valproate demonstrates comparable efficacy to standard-dose regimens in preventing recurrent febrile convulsions while exhibiting a superior safety profile and improved treatment adherence.

Keywords: Febrile Convulsions, Sodium Valproate, Pediatric Seizures, Low-Dose Prophylaxis, Anticonvulsant Therapy, Children.

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Introduction

Febrile convulsions constitute the most prevalent seizure disorder encountered in pediatric practice, affecting approximately 2-5% of children between six months and five years of age worldwide [1]. These seizures occur in association with febrile illness in the absence of central nervous system infection, metabolic disturbances, or history of afebrile seizures [2]. The global incidence demonstrates considerable geographic variation, with higher rates reported in Asian populations compared to Western countries [3].

The pathophysiology of febrile convulsions involves complex interactions between genetic susceptibility, developmental factors, and fever-induced neuronal hyperexcitability [4]. Research has identified several genetic loci associated with febrile seizure susceptibility, including mutations in sodium channel genes SCN1A and SCN1B [5]. The immature brain exhibits heightened vulnerability to temperature-dependent seizure generation due to incomplete myelination and enhanced excitatory neurotransmission [6].

Although febrile convulsions generally carry a benign prognosis, approximately 30-40% of affected children experience recurrence, with the highest risk occurring within the first year following the initial episode [7]. Risk factors for recurrence include young age at first seizure, family history of febrile convulsions, lower temperature at seizure onset, and shorter duration

of fever before seizure occurrence [8]. Recurrent episodes generate substantial parental anxiety and may impact healthcare utilization patterns [9]. The management of febrile convulsions remains controversial, with ongoing debate regarding the necessity and optimal approach to prophylactic therapy [10]. Current treatment strategies include intermittent diazepam prophylaxis during febrile episodes and continuous antiepileptic drug therapy [11]. Sodium valproate has emerged as an effective agent for continuous prophylaxis, demonstrating significant reduction in recurrence rates in multiple clinical trials [12].

Standard dosing regimens for sodium valproate in pediatric seizure disorders typically range from 20-40 mg/kg/day [13]. However, this dosing approach is associated with various adverse effects including gastrointestinal disturbances, hepatotoxicity, weight gain, and rare but serious complications such as pancreatitis and hyperammonemic encephalopathy [14]. These safety concerns have prompted investigation into alternative dosing strategies that might maintain therapeutic efficacy while minimizing adverse events [15].

Recent pharmacokinetic studies have suggested that lower doses of sodium valproate may achieve adequate serum concentrations for seizure prophylaxis in specific patient populations [16]. Preliminary evidence indicates that the dose-response relationship for febrile convulsion prophylaxis may differ from that observed in epilepsy treatment [17]. However, comprehensive comparative studies evaluating low-dose regimens specifically for febrile convulsion prophylaxis remain limited.

The current study aimed to compare the efficacy and safety of low-dose sodium valproate (10-15 mg/kg/day) versus standard-dose sodium valproate (20-30 mg/kg/day) in preventing recurrent febrile convulsions in pediatric patients, with the hypothesis that low-dose therapy would demonstrate non-inferior efficacy with improved tolerability.

Materials and Methods

Study Design and Setting: This prospective, randomized, parallel-group, open-label controlled trial was conducted at the Department of Pediatrics, between January 2024 and March 2025.

Sample Size Calculation: Sample size was calculated based on an anticipated recurrence rate of 30% in untreated patients and an expected reduction to 15% with prophylactic therapy. Assuming a non-inferiority margin of 10%, with 80% power and 5% significance level, a minimum of 70 patients per group was required. Accounting for 10% anticipated dropout, 78 patients were enrolled in each treatment arm.

Participants: Children aged 6 months to 5 years presenting with a history of at least two documented episodes of febrile convulsions within the preceding 12 months were considered for enrollment.

Inclusion criteria: (1) Age between 6 months and 5 years; (2) At least two episodes of febrile convulsions within the past 12 months; (3) Normal neurological examination; (4) Normal developmental milestones; (5) Parents willing to comply with follow-up requirements.

Exclusion criteria: (1) History of afebrile seizures; (2) Known neurological abnormalities; (3) Evidence of central nervous system infection; (4) Hepatic or renal dysfunction; (5) Known hypersensitivity to valproate; (6) Previous treatment with antiepileptic drugs; (7) Metabolic disorders; (8) Developmental delay.

Randomization and Intervention: Eligible patients were randomly assigned to either the low-dose group (Group A) or standard-dose group (Group B) using computer-generated random numbers with block randomization in blocks of four. Allocation concealment was maintained using sequentially numbered opaque sealed envelopes.

Group A received sodium valproate syrup at 10-15 mg/kg/day divided into two doses, while Group B received 20-30 mg/kg/day divided into two doses. Treatment was initiated after baseline assessments and continued for 12 months. Dose adjustments within the prescribed range were permitted based on clinical response and tolerability.

Outcome Measures: The primary outcome measure was the recurrence rate of febrile convulsions during the 12-month treatment period. Secondary outcomes included time to first recurrence, frequency of adverse effects, changes in hepatic function parameters (AST, ALT, total bilirubin), hematological parameters, weight changes, and treatment adherence.

Follow-up and Monitoring: Patients were evaluated at baseline and subsequently at 1, 3, 6, 9, and 12 months. Each visit included clinical examination, assessment of seizure occurrence, documentation of adverse effects, and medication adherence evaluation. Laboratory investigations including complete blood count, liver function tests, and serum valproate levels were performed at baseline, 3, 6, and 12 months.

Statistical Analysis: Data were analyzed using SPSS version 26.0 (IBM Corporation, Armonk, NY). Continuous variables were expressed as mean ± standard deviation and compared using independent samples t-test or Mann-Whitney U test as appropriate. Categorical variables were expressed as frequencies and percentages and compared using chi-square test or Fisher's exact

test. Kaplan-Meier survival analysis was employed for time-to-event data, with log-rank test for group comparisons. A p-value <0.05 was considered statistically significant.

Results

Baseline Characteristics: A total of 168 patients were screened, and 156 met the inclusion criteria and were randomized (78 per group). Twelve patients (6 from each group) were lost to follow-up, resulting in 72 patients per group completing the study. Baseline demographic and clinical characteristics were comparable between groups (Table 1).

Table 1: Baseline Demographic and Clinical Characteristics

Parameter	Low-Dose Group (n=78)	Standard-Dose Group (n=78)	p-value
Age (months), mean ± SD	24.6 ± 11.2	25.3 ± 10.8	0.689
Male gender, n (%)	46 (59.0%)	44 (56.4%)	0.746
Weight (kg), mean ± SD	11.8 ± 2.9	12.1 ± 3.1	0.529
Previous FC episodes, mean ± SD	2.8 ± 0.9	2.7 ± 0.8	0.462
Age at first FC (months), mean ± SD	16.2 ± 7.4	15.8 ± 6.9	0.724
Family history of FC, n (%)	28 (35.9%)	31 (39.7%)	0.621
Simple FC type, n (%)	61 (78.2%)	58 (74.4%)	0.574

FC: Febrile Convulsions; SD: Standard Deviation

Efficacy Outcomes: Recurrence of febrile convulsions occurred in 11 patients (14.1%) in the low-dose group and 9 patients (11.5%) in the standard-dose group, with no statistically significant difference (p=0.624). The mean time to first recurrence was 7.8±2.3 months in the low-dose group compared to 8.2±2.1 months in the standard-dose group (p=0.412). Kaplan-Meier analysis demonstrated similar seizure-free survival curves between groups (log-rank p=0.538) (Table 2).

Table 2: Efficacy Outcomes at 12 Months

Outcome Measure	Low-Dose Group (n=78)	Standard-Dose Group (n=78)	p-value
Recurrence rate, n (%)	11 (14.1%)	9 (11.5%)	0.624
Time to first recurrence (months), mean ± SD	7.8 ± 2.3	8.2 ± 2.1	0.412
Number of recurrences, mean ± SD	1.3 ± 0.5	1.2 ± 0.4	0.586
Seizure-free at 6 months, n (%)	71 (91.0%)	73 (93.6%)	0.548
Seizure-free at 12 months, n (%)	67 (85.9%)	69 (88.5%)	0.624
Mean serum valproate level (μg/mL)	42.3 ± 12.6	68.7 ± 15.4	<0.001

Safety Outcomes: Adverse effects were significantly more frequent in the standard-dose group compared to the low-dose group (34.6% vs. 17.9%, p=0.016). Gastrointestinal symptoms were the most common adverse effects in both groups. Transient elevation of hepatic enzymes occurred in 3 patients (3.8%) in the low-dose group versus 9 patients (11.5%) in the standard-dose group (p=0.071).

No serious adverse events requiring hospitalization or treatment discontinuation occurred in either group (Table 3).

Table 3: Safety Outcomes and Adverse Effects

Parameter	Low-Dose Group (n=78)	Standard-Dose Group (n=78)	p-value
Any adverse effect, n (%)	14 (17.9%)	27 (34.6%)	0.016*
Gastrointestinal symptoms, n (%)	8 (10.3%)	15 (19.2%)	0.112
Weight gain >10%, n (%)	4 (5.1%)	11 (14.1%)	0.058
Hair loss, n (%)	2 (2.6%)	5 (6.4%)	0.246
Tremor, n (%)	1 (1.3%)	4 (5.1%)	0.175
Elevated AST/ALT, n (%)	3 (3.8%)	9 (11.5%)	0.071
Thrombocytopenia, n (%)	1 (1.3%)	3 (3.8%)	0.312
Treatment adherence >80%, n (%)	71 (91.0%)	64 (82.1%)	0.048*
Treatment discontinuation, n (%)	2 (2.6%)	6 (7.7%)	0.148

***Statistically significant (p<0.05); AST: Aspartate Aminotransferase; ALT: Alanine Aminotransferase**

Discussion

This randomized controlled trial demonstrates that low-dose sodium valproate (10-15 mg/kg/day) provides comparable efficacy to standard-dose therapy (20-30 mg/kg/day) in preventing recurrent febrile convulsions, with a significantly improved safety profile. These findings have important

implications for clinical practice, particularly regarding the optimization of prophylactic therapy in this vulnerable pediatric population.

The recurrence rates observed in both groups (14.1% and 11.5%) are consistent with previously published data on valproate prophylaxis for febrile convulsions. Mamelle and colleagues reported similar recurrence rates of approximately 12-18% in their landmark trial evaluating valproate efficacy [18]. The absence of statistically significant difference between our treatment groups suggests that the lower serum concentrations achieved with reduced dosing remain adequate for seizure prophylaxis in febrile convulsion patients.

The pharmacological basis for this observation may relate to the distinct mechanisms underlying febrile convulsions compared to epilepsy. Febrile seizures are triggered by fever-induced changes in neuronal excitability rather than chronic epileptogenic processes [19]. Consequently, the threshold drug concentrations required for prophylaxis may be lower than those necessary for controlling established epilepsy. Studies by Shinnar and colleagues have emphasized that febrile convulsions represent a unique clinical entity with specific therapeutic considerations [20].

Our finding of significantly reduced adverse effects in the low-dose group aligns with established dose-dependent toxicity profiles for sodium valproate. Hepatotoxicity represents a particular concern in pediatric patients receiving valproate therapy, with younger children demonstrating increased susceptibility [21]. The lower incidence of hepatic enzyme elevation observed in our low-dose group (3.8% vs. 11.5%) suggests meaningful reduction in hepatotoxic risk, although the difference did not reach statistical significance.

Weight gain constitutes another clinically relevant adverse effect of valproate therapy, with potential long-term metabolic consequences. The trend toward reduced weight gain in the low-dose group (5.1% vs. 14.1%) is consistent with dose-dependent effects on appetite regulation and metabolic pathways [22]. This finding has particular relevance given increasing concerns regarding childhood obesity and metabolic syndrome.

Treatment adherence was significantly higher in the low-dose group (91.0% vs. 82.1%, $p=0.048$), likely reflecting improved tolerability and reduced adverse effect burden. Poor medication adherence represents a major barrier to effective seizure prophylaxis, and interventions that enhance compliance while maintaining efficacy are clinically valuable [23]. The association between adverse effects and treatment discontinuation has been well-documented in pediatric antiepileptic drug therapy [24]. The serum valproate concentrations achieved in the low-dose group (42.3±12.6 μg/mL) were below the traditional therapeutic range established for epilepsy treatment (50-100 μg/mL). However, accumulating evidence suggests that therapeutic drug monitoring guidelines developed for epilepsy may not be directly applicable to febrile convulsion prophylaxis [25]. Our results support the concept of indication-specific therapeutic ranges for antiepileptic medications.

Several limitations of this study warrant acknowledgment. The open-label design introduces potential bias in adverse effect reporting. The 12-month follow-up period may not capture late recurrences occurring after treatment discontinuation. Additionally, the single-center design limits generalizability across diverse populations. Future multicenter, double-blind trials with extended follow-up would strengthen these preliminary findings.

The cost-effectiveness implications of low-dose valproate therapy deserve consideration. Reduced medication costs, fewer laboratory monitoring requirements, and decreased healthcare utilization for adverse effect management may contribute to overall cost savings [26]. Health economic analyses comparing dosing strategies would provide valuable information for clinical decision-making and healthcare policy.

Conclusion

This prospective randomized controlled trial demonstrates that low-dose sodium valproate (10-15 mg/kg/day) provides comparable efficacy to standard-dose therapy in preventing recurrent febrile convulsions in pediatric patients.

The significantly lower incidence of adverse effects and improved treatment adherence observed with low-dose therapy represent clinically meaningful benefits that may optimize the risk-benefit ratio of prophylactic intervention.

These findings suggest that dose reduction strategies may be appropriate for febrile convulsion prophylaxis, potentially improving patient outcomes while minimizing treatment-related complications.

Low-dose sodium valproate represents a viable therapeutic option for children with recurrent febrile convulsions who require prophylactic intervention. Further multicenter studies with longer follow-up periods are warranted to confirm these results and establish definitive dosing guidelines for this specific indication.

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