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Research Article

Levetiracetam Vs Sodium Valproate as First-Line Monotherapy in Childhood Epilepsy: An Open-Label Randomised Controlled Trial from Western India

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ABSTRACT
Background: Epilepsy affects nearly 10 million Indian children and is often treated empirically. Evidence comparing broad-spectrum agents in paediatric-onset epilepsy is limited. We compared the efficacy and tolerability of levetiracetam (LEV) versus sodium valproate (VPA) as initial monotherapy.
Methods: In this open-label parallel RCT (October 2022–March 2024, Udaipur, India) 52 drug-naïve children (1–18 y) with newly diagnosed epilepsy were randomised 1:1 to LEV (20 mg kg^{-1} day^{-1}) or VPA (20 mg kg^{-1} day^{-1}). Primary outcome was seizure-free interval over 6 months. Secondary outcomes were seizure recurrence latency, episode duration, need for rescue/adjunctive AEDs, and adverse events (AEs).
Results: Baseline characteristics were comparable (mean age 9.0 ± 4.9 y vs 9.3 ± 5.0 y; males 50 % vs 54 %; generalised-onset 62 % each). Six-month seizure freedom occurred in 77 % (LEV) vs 85 % (VPA) ($p = 0.47$). Mean time to first recurrence was shorter with LEV (39.7 ± 5.4 days) than VPA (59.4 ± 5.7 days; $p < 0.001$), yet mean repeat-episode duration favoured LEV (1.7 ± 0.6 min vs 4.0 ± 1.2 min; $p < 0.001$). No child on LEV required add-on therapy; one VPA recipient did (4 %). AEs were mild: behavioural symptoms predominated with LEV (15 % personality change, 12 % aggression) whereas metabolic/GI effects predominated with VPA (8 % weight-gain, 12 % abdominal pain). No serious or irreversible toxicity occurred.
Conclusion: Both agents provided high seizure-freedom rates. LEV shortened individual seizure duration and eliminated rescue AED need but showed earlier recurrences and more behavioural AEs. VPA achieved longer recurrence-free spans at the cost of metabolic/GI issues. Tailoring first-line therapy to individual comorbidity risk is essential.

Keywords: childhood epilepsy, levetiracetam, sodium valproate, monotherapy, randomised controlled trial, ndia.

INTRODUCTION

Epilepsy is the commonest chronic neurological illness of childhood, with an estimated global prevalence of 4–6 per 1 000 children and up to 8 per 1 000 in low- and middle-income countries (LMICs) such as India [1]. Uncontrolled seizures impede neuro-cognitive development, school performance and psychosocial functioning, and can be fatal. The overarching therapeutic goal is durable seizure freedom without troublesome adverse effects (AEs) [2].

First-generation broad-spectrum antiseizure medicines (ASMs) such as sodium valproate (VPA) remain World Health Organization essentials owing to robust efficacy against generalised and focal epilepsies and low cost. VPA increases brain γ-aminobutyric acid, modulates voltage-gated Na^+ channels and inhibits T-type Ca^{2+} currents [3]. Yet hepatotoxicity, weight gain, hair loss and teratogenicity constrain its use, particularly in adolescent females.

Levetiracetam (LEV), approved in 1999, binds synaptic vesicle protein-2A, dampening abnormal neurotransmitter release. It shows minimal drug–drug interactions and generally mild AEs, and has proven effective across seizure types in children and adults [4-6]. However, behavioural problems—irritability, aggression, mood lability—occur in up to 15 % of paediatric patients [7].

Head-to-head paediatric data are sparse. The pivotal Childhood Absence Epilepsy trial compared ethosuximide, VPA and lamotrigine, but not LEV [8]. SANAD II recently favoured VPA over LEV as first-line therapy for idiopathic generalised epilepsy in adults [9], yet its

paediatric subgroup was small and culturally heterogeneous. Indian data are limited to a small open-label study by Bhayana et al., showing similar six-month seizure control with both drugs but higher behavioural AEs with LEV [10].

Geographical pharmacogenomic variability, differential environmental comorbidities (malnutrition, neuroinfections) and drug-access disparities necessitate local evidence. We therefore undertook an open-label randomised controlled trial (RCT) at a tertiary Indian centre to compare efficacy, seizure characteristics and side-effect burden of LEV vs VPA as de-novo monotherapy in children. We hypothesised non-inferiority of LEV in seizure control with improved tolerability.

MATERIALS AND METHODS

Study Design and Setting

Single-centre, open-label, parallel RCT conducted in the Department of Paediatrics, Geetanjali Medical College & Hospital, Udaipur (tertiary-care teaching hospital) from October 2022 to March 2024. Institutional Ethics Committee approval (GU/IEC/2022/182) and CTRI registration (CTRI/2022/10/046321) preceded enrolment.

Participants

Inclusion: children 1–18 y with ≥2 unprovoked seizures >24 h apart or one unprovoked seizure with epileptiform EEG. Exclusion: prior ASM exposure, neuro-degenerative disorders, structural malformations, static encephalopathies. Written informed consent and age-appropriate assent were obtained.

Randomisation and Interventions

Block randomisation (blocks of 4) via sealed-opaque-envelope assigned participants to:

- **LEV group** – levetiracetam 20 mg kg^{-1} day^{-1} in two divided doses, titratable to 30 mg kg^{-1} if breakthrough seizures occurred.
- **VPA group** – sodium valproate 20 mg kg^{-1} day^{-1} in two divided doses, titratable to 30 mg kg^{-1}.

No other ASMs were permitted unless failure criteria (≥2 seizures in any 30-day window) were met.

Outcomes

- **Primary:** seizure-free interval (days) within 6 months.
- **Secondary:** (i) proportion seizure-free at 6 months; (ii) latency to first recurrence; (iii) duration of repeat episodes (min); (iv) need for adjunctive ASMs; (v) incidence and profile of treatment-emergent AEs (behavioural-neuropsychiatric, neuro-toxic, gastrointestinal, metabolic, dermatologic).

Follow-Up and Assessments

Visits: baseline, day 15, month 1, month 3, month 6. Seizure diaries validated at each visit. Adverse events graded per Common Terminology Criteria v5.0.

Statistical Analysis

Sample-size (26 per arm) powered (80 %, α 0.05) to detect 25 % difference in seizure-free proportion. Continuous variables analysed with unpaired t-test or Mann-Whitney; categorical with χ^2/Fisher's exact. SPSS 25 used. Two-tailed $p < 0.05$ significant.

RESULTS

Cohort Profile

All 52 randomised children completed follow-up (CONSORT flow-chart, Figure 1). Baseline features were comparable (Table 1). Generalised tonic-clonic seizures predominated (62 %).

Seizure Control

Overall 42/52 (81 %) children remained seizure-free at 6 months: 20/26 (77 %) LEV vs 22/26 (85 %) VPA ($p = 0.47$). Mean seizure-free interval did not differ (LEV 153 ± 32 days vs VPA 160 ± 27 days; $p = 0.21$). However, recurrence latency was significantly shorter on LEV (39.7 ± 5.4 days) versus VPA (59.4 ± 5.7 days; $p < 0.001$).

Repeat-seizure duration was briefer with LEV (1.7 ± 0.6 min) than VPA (4.0 ± 1.2 min; $p < 0.001$). No LEV-treated child required step-up therapy; one VPA child needed add-on clobazam. Detailed seizure outcomes are summarised in Table 2 and Kaplan-Meier curves in Figure 2.

Safety and Tolerability

Total AEs: 28 (LEV = 17; VPA = 11). Behavioural AEs were commonest with LEV—personality change (15 %), aggression (12 %), restlessness/insomnia (12 %). VPA produced more metabolic/GI issues—weight gain (8 %), abdominal pain (12 %), vomiting (8 %). Neuro-toxic effects (dizziness, tremor) were infrequent and mild in both arms. No hepatotoxicity, thrombocytopenia, hair loss > grade 1 or serious rash occurred. AE distribution shown in Table 3.

Table 1. Baseline Demographic and Clinical Characteristics

Characteristic	LEV (n = 26)	VPA (n = 26)	p-value
Age, years (mean ± SD)	9.0 ± 4.9	9.3 ± 5.0	0.85
Male sex, n (%)	13 (50)	14 (54)	0.79
Generalised-onset seizures, n (%)	16 (62)	16 (62)	1.00
Mean baseline seizure duration (min)	5.46 ± 3.81	5.61 ± 4.41	0.90

Table 2. Seizure Outcome Measures

Outcome	LEV	VPA	p-value
Seizure-free at 6 months, n (%)	20 (77)	22 (85)	0.47
Mean latency to first recurrence (days)	39.7 ± 5.4	59.4 ± 5.7	< 0.001
Mean duration of repeat episodes (min)	1.66 ± 0.60	4.00 ± 1.21	< 0.001
Rescue/adjunct ASM needed, n (%)	0	1 (4)	0.31

Table 3. Treatment-Emergent Adverse Events (≥ 5 % in Either Arm)

Adverse event	LEV % (n)	VPA % (n)	p
Personality change	15 (4)	4 (1)	0.30
Aggression	12 (3)	8 (2)	0.64
Restlessness/insomnia	12 (3)	4 (1)	0.30
Dizziness	4 (1)	12 (3)	0.61
Abdominal pain	4 (1)	12 (3)	0.30
Vomiting	0	8 (2)	0.15
Weight gain	0	8 (2)	0.15

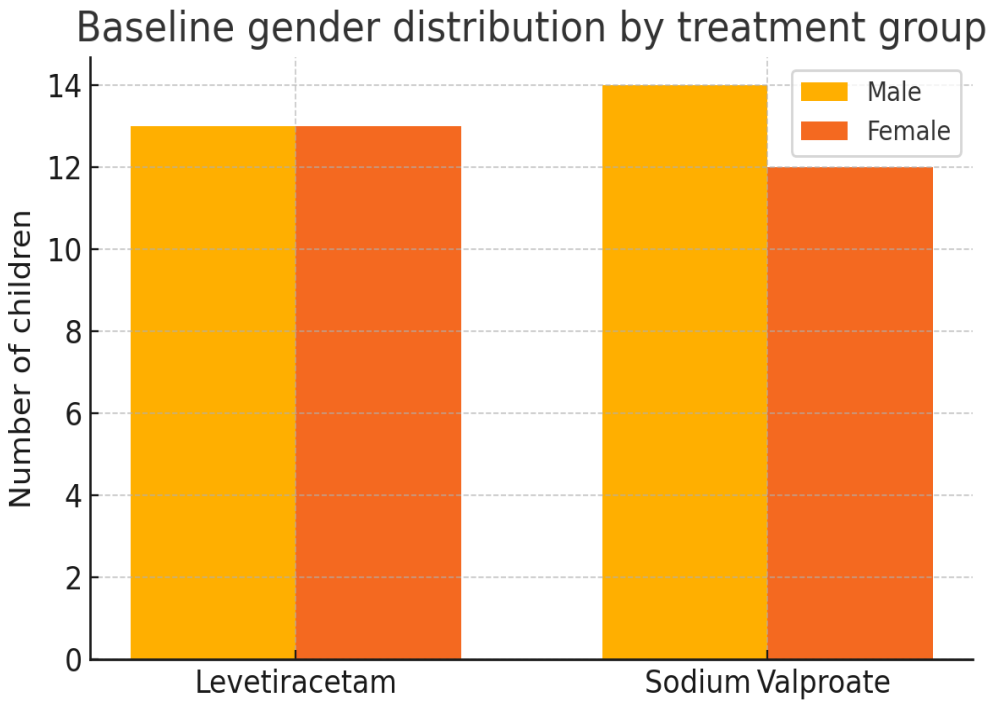

Figure 1. A Simple Grouped Bar Chart Summarising the Baseline Gender Distribution in Each Treatment Arm.

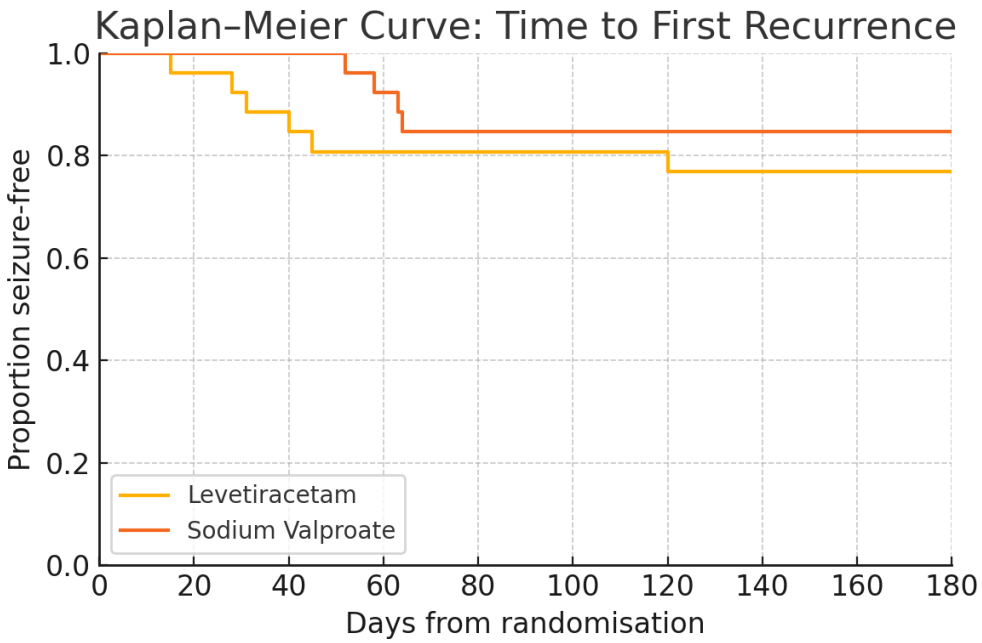

Figure 2. Kaplan-Meier Curves Depicting Time to First Seizure Recurrence for LEV Vs VPA (Log-Rank P < 0.001).

DISCUSSION

Our trial demonstrates that both levetiracetam and sodium valproate achieve high six-month seizure freedom in Indian children with newly diagnosed epilepsy, corroborating Western data [5, 9] and earlier Indian series [10, 11]. Although VPA prolonged the recurrence-free interval, LEV shortened individual seizure duration and eliminated the need for adjunct therapy. These nuanced differences provide clinicians levers for personalised selection.

The recurrence latency advantage of VPA mirrors findings from SANAD II where valproate surpassed LEV for idiopathic generalised epilepsy in adults [9]. Mechanistically VPA's broader modulation of GABAergic tone and Na^+/Ca^{2+} channels may confer more durable network stabilisation [3]. Conversely, the briefer episodes under LEV may reflect rapid SV2A-mediated truncation of ictal discharges [4].

Behavioural AEs with LEV, though expected [7], were mild and non-disabling. Aggression and personality change rates (≈ 15 %) align with multicentre paediatric reports [12]. Importantly, none required drug cessation. Weight gain and GI discomfort with VPA matched classic metabolic toxicity patterns [3, 13] and appeared even at modest doses, reaffirming vigilance in nutritionally vulnerable populations. Absence of hepatotoxicity or severe thrombocytopenia may relate to careful dose titration and short follow-up.

Our seizure-free proportion of 81 % exceeds many historical cohorts, likely owing to inclusion of both focal and generalised epilepsies, early treatment initiation, and rigorous adherence counselling. It also highlights that cost-effective generics (both study drugs are off-patent) can deliver outcomes comparable to high-income settings when treatment gaps are minimised.

Limitations include single-centre design, open-label allocation (potential expectation bias), relatively short follow-up (precluding long-term endocrine or cognitive assessment) and reliance on parental seizure diaries. We did not employ serum drug-level monitoring; nonetheless fixed weight-based dosing reflects real-world primary-care practice. Future multicentre trials with longer observation and neuropsychological endpoints are warranted.

Clinically, LEV may be preferred where behavioural tolerance is acceptable—children with obesity, hepatic risk or adolescent girls of child-bearing potential—while VPA remains valuable for frequent generalised seizures when metabolic profile is acceptable. Shared decision-making incorporating caregiver priorities and comorbidity screening is essential. Our findings support national formulary inclusion of LEV alongside VPA at primary-care level to optimise paediatric epilepsy control.

CONCLUSION

Levetiracetam and sodium valproate provided comparable overall seizure freedom as de-novo monotherapies in Indian children. Valproate yielded longer recurrence-free spans but presented metabolic/GI AEs; levetiracetam

curtailed seizure duration and negated adjunct-drug need, at the cost of mild behavioural symptoms. Tailoring first-line ASM to each child's comorbidity risk and psychosocial context can maximise benefit. Larger, longer trials should explore cognitive and quality-of-life outcomes to refine guidelines.

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