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Safety and Efficacy of Oral Brivaracetam versus Levetiracetam as Monotherapy in Children Aged 1 Month to 14 Years with Newly Diagnosed Epilepsy

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Abstract

Background: Epilepsy is one of the most common chronic neurological disorders in childhood.

Objective: To compare the safety and efficacy of oral brivaracetam, and levetiracetam as monotherapy in children with newly diagnosed epilepsy.

Methods: This randomized controlled trial was conducted at the Pediatric Neurology Department, Children Hospital Multan, Pakistan, during August 2024–February 2025. A total of 102 children aged 1 month to 14 years with newly diagnosed epilepsy, were randomized to receive oral brivaracetam or levetiracetam monotherapy. Seizure freedom at 3-month, seizure frequency reduction, time to 1st breakthrough seizure, and adverse effects were documented. Data analysis was performed using IBM-SPSS Statistics, version 26.0, taking $p<0.05$ as significant.

Results: Among 102 enrolled children, the median age was 6.3 (IQR 3.5-10.2) years, while 55 (55.9%) were males. At 3-month, 97 (95.1%) children completed follow-up, while seizure freedom was achieved in 39 (79.6%) brivaracetam-treated, and 35 (72.9%) levetiracetam-treated children ($p=0.332$). The median reduction in monthly seizure days was 4.5 (IQR 3.2–6.0) with brivaracetam, and 4.2 (IQR 3.0–6.0) with levetiracetam ($p=0.474$). The median time to 1st breakthrough seizure was 35.6 (IQR 20.2–60.4) days with brivaracetam, and 30.3 (IQR 18.0–55.5) days with levetiracetam ($p=0.563$). Adverse events occurred in 44 (45.4%) children, mainly somnolence (11.3%) and irritability (10.3%), without any significant differences ($p>0.05$)

Conclusion: Brivaracetam, and levetiracetam demonstrated comparable efficacy in achieving seizure freedom and reducing seizure frequency in children with newly diagnosed epilepsy.

Introduction

Epilepsy is estimated to affect between 0.5-1% of the pediatric population globally [1]. It is a condition of recurrent, unprovoked seizures caused by abnormal, excessive neuronal discharges, impacting neurodevelopment, cognition, psychosocial adjustment, and quality of life significantly [2]. Low and middle income countries report the highest burden of epilepsy, and these countries face diagnostic challenges and delayed initiation of therapy, along with limited access to newer antiseizure medications (ASMs), worsening the outcomes [3-5].

Concern about the commonly used ASMs in children like teratogenicity, drug interactions, and long-term neurocognitive and systemic adverse effects have stimulated the search for safer alternatives [6]. Levetiracetam has gained popularity over the last few decades as it has favorable pharmacokinetics, rapid absorption and minimal drug to drug interactions [7]. Levetiracetam has been reported to have behavioral adverse effects, including irritability, aggression, and mood disturbances, which may limit adherence and compromise long-term treatment success [8]. Brivaracetam was discovered as a novel high-affinity SV2A ligand that binds to the SV2A receptor with approximately 15-30 times more avidly than levetiracetam [9]. Brivaracetam has demonstrated effectiveness as both adjunctive and monotherapy in adults [10]. New pediatric data appear promising regarding efficacy and safety of brivaracetam but more data are required [11].

Despite increasing clinical use, comparative head-to-head data on the safety and efficacy of brivaracetam versus levetiracetam as initial monotherapy in children is lacking. Most studies have focused on adjunctive use or refractory epilepsy, with limited evidence in treatment-naïve pediatric populations. Addressing this gap is critical, as early and effective seizure control can substantially influence long-term neurodevelopmental outcomes. This study was done to compare safety and efficacy of oral brivaracetam with levetiracetam as monotherapy in children with newly diagnosed epilepsy. By evaluating seizure outcomes, tolerability, and adverse effect profiles, this study would not only furnish the local data but also provide evidence to guide clinicians in selecting the most appropriate first-line ASM for pediatric patients.

METHODS

This randomized controlled trial (NCT07163585 at https://clinicaltrials.gov) was conducted at the Pediatric Neurology Department of the Children Hospital, Multan, Pakistan, from August 2024 to February 2025, after obtaining approval from the Institutional Ethical Committee (letter number 1456). A sample size of 92 was initially calculated using the online OpenEpi sample size calculator, taking the complete treatment success after 3 months with levetiracetam as 61.3% versus 87.0% with brivaracetam, considering 95% significance level and 80% power [12]. A further 10% sample was added expecting a possible loss of follow up, so the final sample size was 102 (51 in each group). The inclusion criteria were children aged 1 month to 14 years, with a clinical diagnosis of newly diagnosed epilepsy. The exclusion criteria were history of prior use of long-term antiseizure medications. Those with evidence of progressive neurological disease, metabolic abnormalities, structural brain malformations incompatible with monotherapy, or severe systemic comorbidities were also excluded. Newly diagnosed epilepsy was defined as having ≥2 unprovoked seizures (or one with a ≥60% recurrence risk) within the past three months and no prior exposure to long-term antiseizure therapy [13]. Written informed consent was obtained from parents or legal guardians.

At enrollment, demographic and clinical information including gender, age, residential status, seizure types, and developmental status were documented. Participants were randomly assigned in a 1:1 ratio to receive either oral brivaracetam

or levetiracetam using a computer-generated randomization sequence. Allocation concealment was maintained through sequentially numbered, opaque, sealed envelopes prepared by an independent investigator. The envelopes were opened only after confirming eligibility and obtaining informed consent. Although the trial was open-label due to differences in drug formulation and dosing schedules, allocation concealment and independent sequence generation minimized the risk of selection bias. Brivaracetam was initiated at a dose of 1 mg/kg/day in 2 divided doses, titrated to a maximum of 5 mg/kg/day based on clinical response and tolerability. Levetiracetam was initiated at a dose of 20 mg/kg/day in 2 divided doses, with gradual escalation up to 60 mg/kg/day, if required. Parents/caregivers were asked to maintain seizures diaries. To enhance the reliability of seizure frequency data, caregivers were provided written and verbal instructions, along with illustrative examples to ensure uniform understanding. During each follow-up visit, the treating pediatric neurologist reviewed the diaries in detail, cross-checked them with clinic and hospital records, and clarified any inconsistencies through direct caregiver interviews. The primary outcome was a proportion of seizure-free children during the 3-month study period. Secondary outcomes included absolute reduction in number of seizure days from baseline, time to 1st breakthrough seizure, adverse effects attributable to the drug, and treatment discontinuation due to intolerance. Efficacy was primarily assessed by the proportion of children achieving seizure freedom during the 3-month follow-up after initiation of monotherapy. For secondary outcomes, caregivers maintained structured seizure diaries recording frequency, duration, and type of seizures, which were reviewed at each follow-up visit by the treating pediatric neurologist for accuracy. Safety assessment included monitoring for adverse events, tolerability, and treatment discontinuation. At each visit, caregivers were questioned about behavioral and systemic side effects

All analyses were conducted using IBM SPSS Statistics version 26.0. Quantitative variables such as age, seizure duration, and number of seizure days were summarized as mean ± standard deviation (SD) or median and interquartile range (IQR) based on the Shapiro–Wilk test of normality. Qualitative variables, including gender, seizure type, seizure freedom, and occurrence of adverse events, were presented as frequencies and percentages. Between-group comparisons for continuous variables were performed using the independent-samples t-test or Mann–Whitney U test, and categorical variables were analyzed with the chi-square or Fisher's exact test. Seizure-free survival was assessed using the Kaplan–Meier method and compared using the log-rank test. Participants lost to follow-up (two in the brivaracetam group and three in the levetiracetam group) were excluded from the final per-protocol analysis. A two-tailed p value of <0.05 was considered statistically significant.

RESULTS

In a total of 102 children the median age of the overall cohort was 6.3 (IQR 3.5–10.2) years, and 57 (55.9 %) were male. The median body weight was 21.8 (IQR 15.6–29.0) kg. Generalized seizures were reported in 65 (63.7 %) children, 19 (18.6 %) had developmental delay, and 14 (13.7 %) had a family history of epilepsy. The median seizure frequency at baseline was 5.4 days/month (IQR 3.4–7.4) (table-1).

Table-1: Baseline demographic and clinical characteristics (N=102)

Characteristics		**Brivaracetam (n=51)**	**Levetiracetam (n=51)**	**P-value**
Gender	Males	28 (54.9%)	29 (56.9%)	0.842

	Females	23 (45.1%)	22 (23.1%)	
Age (years)	1 month to 2 years	8 (15.7%)	9 (17.6%)	0.919
	>2 to 10 years	33 (64.7%)	31 (60.8%)	
	>10 to 14 years	10 (19.6%)	11 (21.6%)	
Age in years, median (IQR)		6.4 (3.6-10.1)	6.2 (3.3-10.8)	0.826
Weight in kg, median (IQR)		21.0 (15.5-28.8)	22.2 (15.8-29.5)	0.761
Residence	Rural	31 (60.8%)	34 (66.7%)	0.537
	Urban	20 (39.2)	17 (33.3)	
Seizure types	Generalized tonic-clonic	32 (62.7%)	33 (64.7%)	0.973
	Focal	13 (25.5%)	12 (23.5%)	
	Mixed	6 (11.8%)	6 (11.8%)	
Developmental delay		9 (17.6%)	10 (19.6%)	0.799
Family history of epilepsy		8 (13.7%)	6 (11.8%)	0.565
Seizure days per month		5.5 (3.1-7.0)	5.2 (3.8-7.8)	0.872

At the final 3-month evaluation, 97 (95.1%) participants completed follow up, comprising 49 (96.1%) in the brivaracetam group, and 48 (94.1%) in the levetiracetam group. Five participants (4.9 %) were lost to follow-up due to non-attendance at scheduled visits and were excluded from per-protocol analyses. None were withdrawn due to adverse events or treatment intolerance.

At three months, 39 (79.6%) children in the brivaracetam group, and 35 (72.9 %) in the levetiracetam group achieved complete seizure freedom (p=0.332). The median reduction in monthly seizure days was 4.5 (IQR 3.2–6.0) with brivaracetam, and 4.2 (IQR 3.0–6.0) with levetiracetam (p=0.474). The median time to first breakthrough seizure was 35.6 (IQR 20.2–60.4) days in the brivaracetam group, and 30.3 (IQR 18.0–55.5) days in the levetiracetam group (p=0.563) (table-2).

Table-2: Comparison of outcomes between study groups (N=102)

Characteristics	**Bivaracetam (n=49)**	**Levetiracteam (n=48)**	**P-value**
Seizure freedom at 3 months	39 (79.6%)	35 (72.9%)	0.440
Reduction in monthly seizure days from baseline, median (IQR)	4.5 (3.2-6.0)	4.2 (3.0-.6.0)	0.474
Time to first breakthrough seizure in days, median (IQR)	35.6 (20.2-60.4)	30.3 (18.0-55.5)	0.563

The Kaplan–Meier analysis demonstrated comparable seizure-free survival between the two treatment groups over the 90-day follow-up period (figure-1). The cumulative probability of remaining seizure-free was slightly higher in children receiving brivaracetam than in those receiving levetiracetam, but the difference did not reach statistical significance (p=0.560). By day 90, approximately 79.5% children treated with brivaracetam, and 72.9% with levetiracetam maintained complete seizure control.

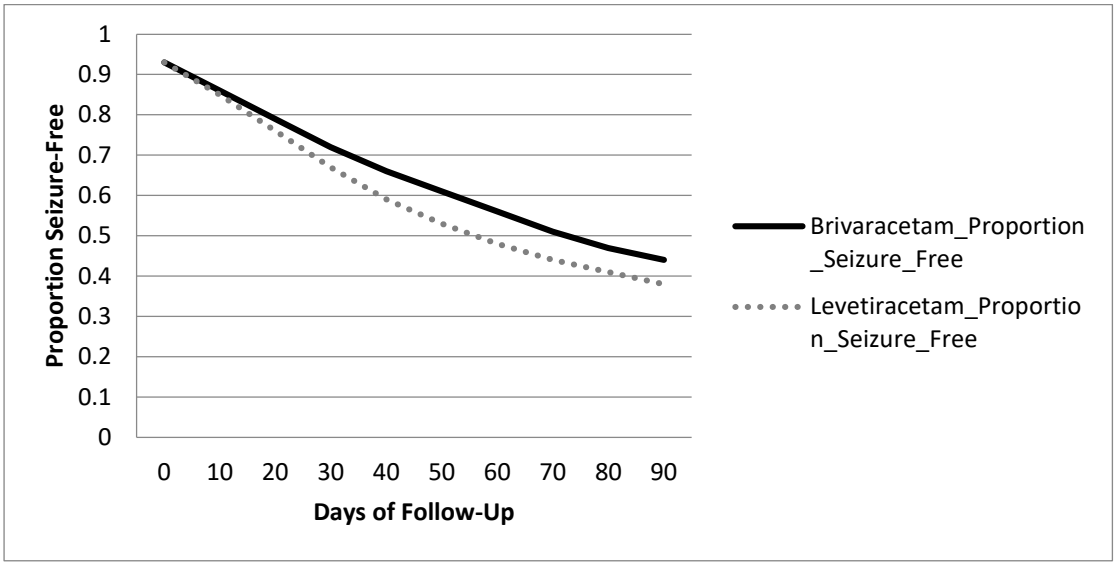

Figure-1: Time to first breakthrough seizure

Adverse events were observed in 44 (45.4%) children overall, comprising 20 (40.8%) in the brivaracetam group, and 24 (50.0%) in the levetiracetam group (p=0.417). Solmnolence or fatigue, and Irritability or aggression, were the most commonly reported adverse events, in 11 (11.3%), and 10 (10.3%) children, respectively (able-3). Adverse events were generally mild to moderate in terms of severity and resolution occurred spontaneously or following minor dose adjustment. No serious adverse events or deaths were recorded.

Table-3: Adverse events between study groups (N=102)

Characteristics	**Bivaracetam (n=49)**	**Levetiracteam (n=48)**	**P-value**
Somnolence / fitigue	5 (10.2%)	6 (12.5%)	0.758
Irritability / aggression	3 (6.1%)	7 (14.6%)	0.320
Decreased appetite	2 (4.1%)	3 (6.3%)	0.667
Psychomotor hyperactivity	1 (2.0%)	4 (8.3%)	0.208
Discontinuation due to intolerance	1 (2.0%)	2 (4.2%)	0.619
Overall adverse events	20 (40.8%)	24 (50.0%)	0.417

DISCUSSION

The primary outcome of seizure freedom at three months was achieved in 79.6% of children treated with brivaracetam and 72.9% with levetiracetam. These findings are consistent with the contemporary literature where researchers have reported relatively similar seizures control between brivaracetam, and levetiracetam [14]. The marginally higher seizure freedom observed with brivaracetam in the current study aligns with Villanueva et al., who reported a 77.8% seizure-free rate after one year of brivaracetam monotherapy across 24 hospitals in Spain [15]. Some other researchers did not observe a clear difference in seizure-free outcome between oxcarbazepine and brivaracetam in children with focal epilepsy [16]. The consistency of brivaracetam across populations in maintaining its performance was further validated by the more-than-50% seizure reduction in 56.3% of cases managed with brivaracetam as reported by a local study [17]. Survival analysis in this study confirmed that both agents maintained parallel seizure-free survival curves through the 90-day follow-up, indicating comparable seizure control. Another analysis reported a pooled seizure-freedom rate of 18% and a 35% responder rate across nine studies in children treated with brivaracetam [11].

Behavioral symptoms were most frequent side effects in this study and these findings align with Surya and colleagues who looked at 61 studies with over 15,000 patients and found that behavioral issues like irritability, mood swings, aggression, and agitation were the most frequent complaints in children and adults treated for epilepsy with brivaracetam [18]. Pooled meta-analysis have shown that around 40% of patients treated with brivaracetam have some kinds of treatment related side effect [11]. Levetiracetam is generally consider to cause more pronounced behavioral side effects, possibly because it interacts differently with synaptic vesicle proteins [14]. No serious adverse events or deaths were documented in this study, which adds to the safety track record for both drugs in children when used alone. Most of the side effects were mild and faded on their own, so both medications can be started and adjusted safely with proper supervision in a pediatric neurology setting. The pattern is similar to what Coppola and colleagues reported. For children who already have behavioral or developmental issues, brivaracetam could be easier to tolerate [19]. Clinicians can pick based on what the patient can afford and what is available. This matters a lot in low- and middle-income countries, where levetiracetam is usually the go-to SV2A drug for pediatric epilepsy [20-22]. Present results showing similar seizure control and safety of both drugs suggest brivaracetam could be a good, cost-effective alternative, especially for children who have issues with levetiracetam [23-26].

This study had some limitations. Patients were followed up only for 3 months in this study, which is not long enough to detect whether seizures return later or any late side effects surface. Single center study design, and a relatively modest sample size restricts he generalizability of the present findings. Behavioral side effects were assessed through caregiver reports and clinical observation by the treating pediatric neurologist. Although this approach ensured real-time monitoring during follow-up, the absence of a validated behavioral assessment instrument, such as the Child Behavior Checklist (CBCL) or the Neuropsychiatric Inventory–Children (NPI-C), represents a limitation.

CONCLUSION

Brivaracetam, and levetiracetam demonstrated comparable efficacy in achieving seizure freedom and reducing seizure frequency in children with newly diagnosed epilepsy. Both agents were well tolerated, with no serious adverse events.

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