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COMPARISON OF EFFICACY OF LEVETIRACETAM AND PHENYTOIN IN GENERALIZED STATUS EPILEPTICUS IN CHILDREN FROM AGE 6 MONTHS TO 5 YEARS

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Abstract

Background: *Status epilepticus is a critical neurological emergency in children requiring urgent treatment. Traditionally managed with phenytoin, recent studies show levetiracetam offers safer, easier use, though efficacy comparisons remain controversial, prompting this study to clarify outcomes and improve clinical decision-making.*

Objectives: *To compare efficacy of levetiracetam and phenytoin in generalized status epilepticus in children from age 6 months to 5 years.*

Duration: *Six months w.e.f 03-10-2024.*

Methodology: *After approval from the Hospital's Ethical Review Board, 60 children who did not respond to two doses of midazolam were enrolled from the pediatric emergency unit at Ghurki Trust Teaching Hospital, Lahore. They were randomly divided into two groups: Group A received IV levetiracetam with a loading dose of 20 mg/kg and maintenance dosing, while Group B received IV phenytoin with a similar dosing protocol. All patients were managed by the same medical team, and data was recorded by a resident.*

Results: *The study involved 60 children (mean age 31.72±14.18 months) evenly split into two age groups. Baseline characteristics were similar between Group A (levetiracetam) and Group B (phenytoin). Group A showed significantly higher seizure control at 24 hours (93.3% vs. 66.7%, p=0.010), with subgroup differences not statistically significant due to small sample sizes.*

Conclusion: *Levetiracetam showed significantly higher efficacy in preventing seizure recurrence within 24 hours compared to phenytoin in children aged 6 months to 5 years. Although subgroup differences were not statistically significant, levetiracetam appears to be a more effective treatment option.*

INTRODUCTION

Status epilepticus (SE) is a common neurological emergency that requires immediate intervention to prevent permanent brain injury.[1] The prevalence of convulsive status epilepticus (CSE) is estimated at 14.5 per 100,000 per year in developed countries. Despite advances in treatment protocols over the last decade, SE is still associated with significant morbidity, ranging from 28% to 34%, and mortality rates between 7% and 22%.[2] The incidence,

morbidity, and mortality rates are highest among children under five years of age.[3] In Pakistan, epidemiological data estimate epilepsy prevalence at around 1%, aligning with global figures that suggest epilepsy accounts for 1% of the total disease burden, with 80% of cases occurring in developing countries.[4]

According to the International League Against Epilepsy, seizures are classified based on clinical presentation into generalized convulsive, non-convulsive, or focal seizures. Generalized seizures arise when abnormal electrical activity affects both cerebral hemispheres, involving most or all brain areas. These include various types such as atonic, tonic, clonic, absence, myoclonic, and tonic-clonic seizures, the latter being the most severe due to whole-body involvement.[5]

Standard treatment for pediatric SE begins with benzodiazepines, followed by long-acting antiepileptic drugs like phenytoin or levetiracetam. Phenytoin remains the most commonly used long-acting agent for seizure prevention in children, although newer drugs such as valproic acid and levetiracetam have recently been introduced.[6] Levetiracetam (LEV), a novel antiepileptic drug, was approved in the US in 1999 as adjunctive therapy for adults with focal epilepsy and, since 2006, licensed in Europe as monotherapy for adults and adolescents over 16 years with newly diagnosed focal-onset seizures, with or without secondary generalization.[7]

Wani et al. in India reported significantly higher seizure control rates with levetiracetam compared to phenytoin (96.0% vs. 59.6%; p=0.00001).[8] Similarly, Noureen et al. from Multan, Pakistan, found levetiracetam to be more effective than phenytoin in controlling seizures (92.7% vs. 83.2%; p=0.013).[9] These findings suggest that levetiracetam is a promising alternative to phenytoin, potentially allowing clinicians to avoid the adverse effects commonly associated with phenytoin use.[8,9] However, some studies have reported contrasting results. Nazir et al.[10] and Singh et al.[11] in India observed slightly lower but statistically insignificant seizure control rates with levetiracetam compared to phenytoin (76.0% vs. 88.0% and 94.0% vs. 96.0%, respectively; p>0.05). Likewise, Appleton et al. in the UK reported a nonsignificant trend favoring levetiracetam (70% vs. 64.0%; p>0.05).[12] Collectively, these data reveal ongoing controversy regarding the comparative efficacy of levetiracetam and phenytoin in generalized status epilepticus. Hence, this study aims to replicate and expand upon previous trials to provide clearer evidence that will guide optimal treatment choices for controlling generalized status epilepticus in children.

METHODOLOGY

This randomized controlled trial was conducted over six months in the Department of Pediatrics at Ghurki Trust Teaching Hospital, Lahore, to compare the efficacy of levetiracetam and phenytoin in children aged 6 months to 5 years with generalized status epilepticus. A total of 60 patients were enrolled using consecutive non-probability sampling, with 30 patients in each group, based on a sample size calculation with 80% power and 5% significance level, anticipating efficacies of 96.0% for levetiracetam and 59.6% for phenytoin. Generalized status epilepticus was defined as convulsions lasting over five minutes with unconsciousness or repeated seizures without regaining consciousness, and efficacy was defined as non-recurrence of seizures within 24 hours after drug administration. Inclusion criteria were children of both genders aged 6 months to 5 years meeting the definition of generalized status epilepticus, while exclusion criteria included prior antiepileptic use, meningitis, head trauma, hypersensitivity to study drugs, assisted ventilation, hypotension, and cerebral palsy. After ethical approval and informed consent, children unresponsive to two doses of midazolam (0.2 mg/kg, max 10 mg, 5 minutes apart) were randomized by lottery into Group A (levetiracetam) receiving an IV loading dose of 20 mg/kg at 3 mg/kg/min followed by maintenance of 20 mg/kg/day in two doses, or Group B (phenytoin) receiving an IV loading dose of 20 mg/kg diluted in normal saline at <1 mg/kg/min followed by maintenance of 5 mg/kg/day in two doses. All patients were managed by the same

staff with findings recorded by the resident and supervised by a senior consultant to minimize bias; confounders were controlled through exclusion. Data were analyzed using SPSS version 26; numerical variables such as age and weight were presented as mean ± SD, and categorical variables like gender and treatment efficacy as frequency and percentage. Chi-square tests assessed efficacy differences between groups, with significance set at $p \leq 0.05$, including stratified analyses for age, weight, and gender to address effect modifiers.

RESULTS

The study included a total of 60 children with a mean age of 31.72 ± 14.18 months. The participants were evenly distributed between two age groups, with 30 children (50.0%) aged 6 to 30 months and 30 children (50.0%) aged 31 to 60 months. Regarding gender, 36 children (60.0%) were boys and 24 children (40.0%) were girls. The mean weight of the participants was 13.74 ± 3.05 kg. Of these, 23 children (38.3%) weighed less than 13 kg, while 37 children (61.7%) weighed 13 kg or more. Data is given in Table 1. Table 2 compares baseline characteristics of Group A (n=30) and Group B (n=30). Mean age was similar (30.93±15.86 vs. 32.50±12.50 months, p=0.672). Age distribution (6–30 months and 31–60 months), gender, and weight (mean and categories <13 kg/≥13 kg) showed no significant differences between groups (all p>0.05). Table 3 compares treatment efficacy between Group A and Group B. Non-recurrence of seizures within 24 hours occurred in 93.3% of Group A and 66.7% of Group B, showing a statistically significant difference (p = 0.010). Efficacy analysis showed higher seizure non-recurrence rates in Group A compared to Group B across all subgroups, though differences were not statistically significant. For ages 6–30 months, 93.8% in Group A versus 71.4% in Group B (p=0.102); ages 31–60 months, 92.9% vs. 62.5% (p=0.086). Among boys, efficacy was 94.1% vs. 68.4% (p=0.052); among girls, 92.3% vs. 63.6% (p=0.142). For weight <13 kg, 92.3% vs. 60.0% (p=0.063); for ≥13 kg, 94.1% vs. 70.0% (p=0.097). The lack of statistical significance in subgroup comparisons, despite higher efficacy in Group A, is likely due to the small sample sizes, limiting the study's power to detect true differences.

Table 1: Demographic Characteristics of Children with Status Epilepticus

Characteristics	Total (60)
Age (months)	31.72±14.18
• 6-30 months	30 (50.0%)
• 31-60 months	30 (50.0%)
Gender	
• Boy	36 (60.0%)
• Girl	24 (40.0%)
Weight (kg)	13.74±3.05
• <13 kg	23 (38.3%)
• ≥13 kg	37 (61.7%)

Table 2: Comparison of Groups for Baseline Characteristics

Characteristics	Group A (n=30)	Group B (n=30)	p-value
Age (months)	30.93±15.86	32.50±12.50	0.672
• 6-30 months	16 (53.3%)	14 (46.7%)	0.606
• 31-60 months	14 (46.7%)	16 (53.3%)	

Gender			
• Boy	17 (56.7%)	19 (63.3%)	0.598
• Girl	13 (43.3%)	11 (36.7%)	
Weight (kg)	13.61±3.37	13.88±2.74	0.735
• <13 kg	13 (43.3%)	10 (33.3%)	0.426
• ≥13 kg	17 (56.7%)	20 (66.7%)	

Chi Square test/ Independent sample t test, taking p-value≤0.05 as significant.

Table 3: Comparison of Efficacy of Treatment between the Groups

Characteristics	**Group A (n=30)**	**Group B (n=30)**	**p-value**
Efficacy (Non recurrence of seizures till 24 hrs after administration of allocated drug)			
• Yes	28 (93.3%)	20 (66.7%)	0.010
• No	2 (6.7%)	10 (33.3%)	

Chi-Square test taking p-value≤0.05 as significant.

Table 4: Stratification of Efficacy between the Groups on the Basis of Sub Grousp

Efficacy	**Group A (n=30)**	**Group B (n=30)**	**p-value**
Age (months)			
• 6-30 months	15/16 (93.8%)	10/14 (71.4%)	0.102
• 31-60 months	13/14 (92.9%)	10/16 (62.5%)	0.086
Gender			
• Boy	16/17 (94.1%)	13/19 (68.4%)	0.052
• Girl	12/13 (92.3%)	7/11 (63.6%)	0.142
Weight (kg)			
• <13 kg	12/13 (92.3%)	6/10 (60.0%)	0.063
• ≥13 kg	16/17 (94.1%)	14/20 (70.0%)	0.097

Chi-Square test / Fisher's Exact test, taking p-value≤0.05 as significant.

DISCUSSION

Status epilepticus is a serious neurological emergency in children, characterized by prolonged or repeated seizures, which can lead to significant morbidity and mortality if not promptly controlled.[13,14] Traditionally, phenytoin has been the standard second-line treatment after benzodiazepines for managing generalized status epilepticus. However, phenytoin is associated with several adverse effects and variable efficacy. Recently, levetiracetam has emerged as a newer antiepileptic drug with a favorable safety profile and easier administration.[8,9] Existing literature shows controversy regarding the comparative efficacy of levetiracetam versus phenytoin.[8-12] Therefore, this study was planned to compare their effectiveness in this population.

The findings of this study align with and contribute to the ongoing debate regarding the efficacy of levetiracetam versus phenytoin in controlling generalized status epilepticus in

children. Our study demonstrated a significantly higher seizure control rate within 24 hours in the levetiracetam group (93.3%) compared to the phenytoin group (66.7%), indicating superior efficacy of levetiracetam.

Similar results were reported by Noureen et al. in Pakistan, who found levetiracetam to be significantly more effective than phenytoin (92.7% vs. 83.3%, p=0.012), supporting levetiracetam's efficacy.[9] Likewise, Wani et al. in India observed significantly higher seizure control with levetiracetam (96.0%) than phenytoin (59.6%, p=0.00001).[8] These studies bolster the view that levetiracetam is a promising alternative for status epilepticus management.[8,9]

Conversely, some studies report no significant difference between the two drugs. Nakamura et al. in Japan found comparable control rates (85.1% vs. 81.0%, p=0.69) and noted fewer adverse events with levetiracetam.[15] Mohammadi et al. in Iran also observed similar efficacy (86.7% vs. 83.3%, p=1.000) and adverse effect profiles between the drugs.[16] Chakrawati et al. in India reported equivalent seizure control rates and clinical outcomes, concluding levetiracetam as an effective alternative.[17]

Other studies such as those by Nazir et al.[10] from India and Singh et al.[11] from India reported slightly lower but statistically insignificant seizure control with levetiracetam compared to phenytoin, whereas Appleton et al.[12] from the UK observed a non-significant trend favoring levetiracetam. The variability in findings across studies may be attributed to differences in sample sizes, patient populations, dosing protocols, and study designs. Our study's significant results favoring levetiracetam may reflect its pharmacokinetic advantages and ease of use.

CONCLUSION

Levetiracetam showed significantly higher efficacy in preventing seizure recurrence within 24 hours compared to phenytoin in children aged 6 months to 5 years. Although subgroup differences were not statistically significant, levetiracetam appears to be a more effective treatment option.

LIMITATIONS & RECOMMENDATIONS

This study's strength lies in its focus on children aged 6 months to 5 years with well-matched baseline characteristics, allowing clear comparison of levetiracetam and phenytoin efficacy. However, the relatively small sample size limits statistical power for subgroup analyses. Future larger, multicenter trials are needed to confirm these findings, assess long-term outcomes, and evaluate optimal dosing and cost-effectiveness of levetiracetam in pediatric status epilepticus management.

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Authors Contribution

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Substantial contributions to study design, synopsis write up, acquisition of data

Analysis & Interpretation of Data, Manuscript writing

Has given final approval of the version to be published

Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

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