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Original Research Article

Comparative Study of Efficacy and Safety of Levetiracetam and Carbamazepine in Partial Epilepsy

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Abstract:

Background: A more recent antiepileptic medication with a superior pharmacokinetic profile is levetiracetam (LEV). Presently, partial seizures are often treated with it. The goal of the current study was to assess the effectiveness and safety of LEV and carbamazepine (CBZ) in treating partial epilepsy.

Methods: From June 2022 to February 2023, the Department of Pharmacology in collaboration with the Neurology department at the GMCH, Purnea, Bihar, recruited volunteers who were experiencing partial seizures. Tab LEV was given to the first group (500–3000 mg/day), and Tab CBZ was given to the second group (300–600 mg/day). Efficacy and safety were the main results. Quality of Life (QOL) was the secondary result. By comparing the seizure freedom rates at the end of six months, effectiveness was evaluated. Comparing the negative effects allowed us to assess the safety profile. The QOLIE-10 scale was used to measure QOL.

Results: At the end of nine months, the overall seizure freedom rate in the CBZ group was 71.42%, compared to 78.57% in the LEV group ($p = 0.2529$). The incidence of negative reactions was similar according to LEV and CBZ. More behavioral effects, including elevated aggression and anxiety, were observed by the LEV group. Additionally, compared to the CBZ group, it displayed better QOL.

Conclusion: Both LEV and CBZ monotherapy were well tolerated and showed comparable efficacy for treating partial epilepsy.

Keywords: Antiepileptic drug, Levetiracetam, Carbamazepine, and Quality of Life (QOL).

Introduction

A chronic condition called epilepsy is defined by two or three recurring seizures with brain origin. After headache, it is the second most frequent neurological ailment. According to estimates, the average prevalence of epilepsy varies between 1.5 and 14 per 1000 people in Asia, 5.5 per 1000 people in Europe, and 6.8 per 1000 people in the United States. Based on the origin of the seizure, epilepsy is divided into partial and generalized seizures[1].

According to estimates from the World Health Organization (WHO) and International League against Epilepsy (ILAE), out of 50 million people, 34 million have epilepsy and reside in developing nations. Nearly 80% of them are not receiving treatment [2]. Out of a total population of approximately 1.23 billion, 6-10 million people in India are thought to have epilepsy. It represents over 1/5 of the burden of epilepsy worldwide [3]. Based on the origin of the episode, epilepsy is divided into partial and generalized seizures. In one hemisphere of the brain, certain, frequently tiny regions of cortex give rise to partial seizures. The majority of epilepsies that are newly diagnosed are partial or secondarily generalized. The proper classification of seizure type and epileptic syndrome determines how to treat epilepsy[4].

Pharmacological therapy using antiepileptic medications (AEDs) is the cornerstone of epilepsy treatment. The best possible care must be given to people with epilepsy because the condition is linked to higher morbidity and mortality rates as well as unexpected fatalities without obvious structural or pathological causes [5,6]. AEDs are chosen based on the patient's characteristics, the agent's efficacy and tolerability, and the type of the disease [7]. Treatment options for epilepsy include the older AEDs (carbamazepine, ethosuximide, phenytoin, phenobarbital, primidone, and valproic acid) as well as several newer drugs (Levetiracetam, felbamate, gabapentin, lacosamide, lamotrigine, oxcarbazepine, pregabalin, rufinamide, tiagabine, topiramate, vigabatrin, and zonisamide)[8]. The preferred medication for treating partial seizures is carbamazepine (CBZ), although it has drawbacks such as the need for

frequent dosages, adverse effects that are dose-related, and drug interactions. One of the newer medications that is currently most frequently prescribed for the treatment of partial seizures is levetiracetam (LEV). It has a number of benefits, including twice-daily dose, a superior safety record, fewer drug interactions, and no need for blood level monitoring. LEV is a desirable first-line or supplementary therapy for epileptic seizures as a result of its favorable pharmacologic profile[9,10]. In this study, the efficacy and safety of LEV and CBZ as monotherapies for partial epilepsy were compared.

Material and Methods

This trial involved randomized, prospective, open-label monotherapy. From June 2022 to February 2023, the study was carried out at the Govt. Medical College and Hospital, Purnea, Bihar, in the departments of pharmacology and neurology. Following the acquisition of written informed consent, the individuals were enrolled in the study. Subjects between the ages of 18 and 60 who had recently been diagnosed with focal or partial seizures with or without secondary generalization met the inclusion criteria for the study. Pregnant and nursing women, patients with nonepileptic seizures, auras, or lack of seizures, patients with acute symptomatic seizures that occurred within 14 days of an acute brain damage like a stroke, and patients with a history of psychiatric disease were excluded from the study.

Participants were drawn from the Neurology OPD who had recently been diagnosed with partial epilepsy. The patients' or their relatives' understanding of the study's goals and methods was in their native tongue. After receiving their consent to participate, the subjects were questioned and split into two groups using a coin flip. Each group gathered 30 people. Participants in group 1 were given Tab LEV, 1000–3000 mg/day orally, and those in group 2 were given Tab CBZ, 400–1200 mg/day orally. Following meals twice daily, the participants were given a low dose of 500 mg of LEV and 200 mg of CBZ. The amount was subsequently increased based on how well the subjects controlled their seizures. If seizure control was not established, the LEV dose was increased by 500 mg twice daily every two weeks, up to a maximum of 3000 mg/day. Similar to this, if seizure control was not obtained, the dose of CBZ was increased by 200 mg twice daily, up to a maximum of 1200 mg/day. According to the participant's clinical status, adjuvant therapy was used when the seizure was not controlled following drug dose titration. Additionally, the individual was dropped from the study.

Demographic, efficacy, and adverse event (AE) baseline data were analyzed using descriptive statistics and reported as mean± SD, frequencies, and percentages. The results of the QOLIE-10 were presented as mean± SD scores. The Chi-square (χ^2) test was used to compare the category variables. Unpaired Student's t-test was used to compare continuous variables between groups. The cutoff for statistical significance was $p < 0.05$.

Results

79 subjects total were screened for the study. Of these, 60 (75.6%) participants met the requirements and were randomly assigned to one of the two study groups. The outcomes of the observations are summarized below.

Thirty participants made up the CBZ group, of which 17 were male and 13 were female. Thirty individuals made up the LEV group, of which 13 were male and 17 female. Male participants' mean ages in the CBZ group were 30.70± 2.66 years and 22.62±1.152 years, respectively (p value, 0.0834). In the CBZ group, the mean age of females was 29.31± 2.44 years, whereas in the LEV group, it was 28.18± 2.553 years (p value, 0.7101). As a result, there was no discernible difference in the mean age of males and females in either group. The mean BMI for the CBZ group was 22.56±0.41 kg/m^2, while it was 21.49±0.41 kg/m^2 for the LEV group ($p = 0.0690$). Between the two groups, there was no discernible difference in BMI.

Both the CBZ group and the LEV group were randomly assigned to thirty participants. Two participants in the LEV group withdrew from the trial, one was lost to follow-up, and one person experienced acute AE. Thus, the effectiveness of LEV was evaluated in a total of 28 patients. Similar to how 2 CBZ group individuals were removed from the research owing to AE. As a result, the effectiveness of CBZ group was evaluated on a total of 28 participants.

A total of four, twelve, and twenty-six weeks after the start of monotherapy, all subjects underwent follow-up. Both groups had an equal seizure freedom rate of 85.72% at the end of the fourth follow-up week, which is not statistically significant (p value of 1.000). In comparison to the LEV group, which had 93.34% seizure freedom after 12 weeks of follow-up, the CBZ group had 89.29% of seizure freedom, which is not statistically significant (p value, 0.4595). It is not statistically significant (p value, 0.2529) that 22 (78.57%) of the LEV-taking patients and 20 (71.42%) of the CBZ-taking subjects remained seizure-free for at least six months during the monotherapy treatment.

A statistically insignificant 36.66% of participants in the CBZ group and 40% of participants in the LEV group reported having at least one adverse event (AE) (p value, 0.7714). Two patients (6.66%)

and one participant (3.33%) on LEV medication terminated the treatment because to adverse events (AE) of increased nausea and vomiting, respectively. In the LEV group, 5 participants showed signs of increased aggression, 1 showed signs of suicidal ideation, 3 showed signs of increased anxiety, 3 showed signs of increased sleep, 2 reported weight gain of about 3-5 kilograms over the course of 3 months, and 2 reported constipation. Other side effects included euphoria, disturbed sleep, nausea, itchiness, and vomiting. Six participants in the CBZ group complained of being sleepy, and four patients said they felt lightheaded. Other side effects that were mentioned were constipation, itching, poor focus, nausea, and vomiting.The QOLIE-10 score in clinical practice runs from 0 to 100. A total score range of less than 50 denotes a low quality of life, a score range of 50 to 70 denotes an ideal quality of life, and a score range of more than 70 denotes a higher quality of life. The participants in both groups underwent QOL assessments at zero weeks and 24 weeks. At 0 weeks, the mean QOL score for the CBZ group was 31.14±1.83, while it was 29.76±1.71 for the LEV group (p value, 0.5861), which is not statistically significant. The difference between the mean QOL scores at the conclusion of the 26th week for the CBZ group and the LEV group (58.41±1.89 vs. 64.58±2.02; p <0.05) was found to be statistically significant.

Table 1: Overall characteristics of patients on Levetiracetam and Carbamazepine monotherapy

Characteristics	CBZ group (n=28)	LEV group (n=28)	p-value
Male mean age	30.70±2.66 yrs	22.62±1.152 yrs	0.0834
Female mean age	29.31±2.44 yrs	28.18±2.553 yrs	0.7101
Mean BMI	22.56±0.41	21.49±0.41	0.0690
Pretreatment mean seizure frequency	2.83±0.19	4.2±0.65	0.0470
Seizure freedom at 4 weeks	85.72%	85.72%	1.0000
Seizure freedom at 12 weeks	89.29%	93.34%	0.4595
Seizure freedom at 26 weeks	96.43%	100%	0.1212
Overall seizure freedom at 6 months	71.42%	78.57%	0.2529
QOL at 0 week	31.14±1.83	29.76±1.71	0.5861
QOL at 26th weeks	58.41±1.89	64.58±2.02	0.0302

Discussion

The average age of the study sample was 27 ± 2.62 years, making it comparatively younger than average. Males in the CBZ group had a mean age of 30.70±2.66 years, whereas those in the LEV group had a mean age of 22.62±1.152 years. Females in the CBZ group had a mean age of 29.31±2.44 years, whereas those in the LEV group had a mean age of 28.18± 2.553 years. This is distinct from earlier research done in wealthy nations like the UK, USA, and Germany, where the average age ranged from 35 to 40 years. In this study, the CBZ group had 17 (56.66%) male participants and 13 (43.33%) female participants, whereas the LEV group had 13 (43.33%) male participants and 17 (56.66%) female participants. This is comparable to the research done by Brodie et al., which found that the CBZ group consisted of 58.8% men and 41.2% women, and the LEV group of 51.2% men and 48.8% women [9].

Seizure freedom rate served as the primary metric in this study to determine efficacy. A patient is deemed seizure-free after an intervention, in accordance with ILAE, whenever a time period has passed that is equal to three times the longest preintervention interseizure interval over the preceding year[12]. We measured the seizure freedom rate in this trial at 4, 12, and 26 weeks. Similar to the Amudhan trial, which evaluated seizure freedom rates at 6, 16, and 26 weeks [12], we also evaluated the overall seizure freedom rate at the end of the study first six months.

Following the start of the treatment, participants were invited for follow-up visits at 4, 12, and 26 weeks. In comparison to the CBZ group, which had a mean seizure rate of 2.83±0.19 per month, the pretreatment mean seizure rate in LEV was 4.2±0.65 per month. The seizure freedom rate was the same (85.72%) in the CBZ and LEV groups after 4 weeks of follow-up. Since the LEV group's pretreatment seizure frequency was significant, the group's seizure independence at 4 weeks was favorable. Similar to this, in the Amudhan trial, the LEV group's seizure freedom at 6 weeks was 83.6% as opposed to the Lamotrigine group's 79.8% (p = 0.47), with no statistically significant difference[12]. Despite the fact that the outcomes were not statistically significant, both groups in this study demonstrated better seizure freedom. Better medication adherence may be the cause of the greater seizure freedom.

In the LEV group, seizure freedom was 93.34% after 12 weeks of therapy, compared to 89.29% in the CBZ group (no statistical significance; p = 0.4595). In the same way, in the Amudhan trial, after 16 weeks of maintenance medication, seizure independence was 51.9% in the LEV group and 55.7% in the Lamotrigine group. Between 6 and 16

weeks, there were breakthrough seizures as well. As a result, both groups' seizure freedom rates had dramatically decreased; this could be as a result of poor medication compliance [12]. Even though the results were not statistically significant, the LEV group in this trial had a greater 12-week seizure-free rate than the CBZ group.

Seizure freedom rate at 6 months and 12 months served as the primary efficacy outcome in the majority of studies comparing LEV and CBZ. Since this was a time-limited academic study, we were unable to follow up with the cases indefinitely.

At the conclusion of six months, seizure freedom was used to evaluate the final efficacy outcome. At the end of the study six months, the CBZ group's overall seizure freedom rate was 71.42%, compared to 78.57% for the LEV group ($p = 0.2529$), which is not statistically significant. The effectiveness outcome for Kim JH trial, in which they evaluated LEV vs CBZ as a monotherapy for partial epilepsy, was seizure freedom at 6, 12, and 24 months. At the end of six months, the seizure freedom rate in the LEV group was 73% compared to 65% in the CBZ group ($p = 0.58$), showing no statistical significance similar to our study [10]. Similar to this, in the Santhosh NS study, the authors compared the seizure freedom rates of LEV and CBZ in newly diagnosed focal epilepsy. At 6 months, CBZ had a much greater seizure freedom rate than LEV, which was 57.5%. The outcomes lacked statistical significance[13]. The major effectiveness endpoint of a related research by Brodie et al. was seizure freedom rate at 6 months. The seizure freedom rate at six months was 73% in the LEV group and 72.8% in the CBZ group, practically at the same efficacy in both groups[9].

In randomized, side-by-side comparisons of newly diagnosed epilepsy patients with partial or generalized tonic-clonic seizures, no medication has demonstrated better efficacy to CBZ. Even while the majority of research state unequivocally that the efficacy of newer AEDs and older AEDs is always equivalent, no study has yet demonstrated that newer AEDs have greater efficacy than older AEDs. Similar outcomes were seen in our study as well; LEV's efficacy was close to that of CBZ, but it was not superior to CBZ.

The absence of seizures, reduced AE, and a high quality of life are the ultimate goals of epilepsy treatment. Both LEV and CBZ were well tolerated in this trial when used as a first monotherapy. Just 6.66% of CBZ patients and 3.33% of LEV patients withdrew from the study as a result of AE. In line with a prior study by Brodie et al., there were more patient withdrawals in the CBZ group. In that trial, individuals on CBZ stopped for AE at a rate of 19.2% compared to 14.4% of patients on LEV [9]. Although the difference between the LEV (40%) and CBZ (36.66%) groups in this study was not statistically significant, there were more AEs recorded from the LEV group. Similar to this, there were more significant adverse events (AE) related with LEV (13.7%) compared to the CBZ group (8.2%) in the Santhosh NS trial[13]. In contrast to these results, Kim JH et al. study found that 45% of patients on LEV and 70% of patients on CBZ both reported adverse drug reactions (ADRs)[10].

Similar to the study by Kim JH et al., where 40% of patients on CBZ reported enhanced sleep and 10% of patients reported dizziness, the participants on CBZ in this study generally experienced AEs such increased sleep (20%) and dizziness (13.33%). After the medicine was started, 2 subjects withdrew, but no patients taking CBZ reported any major adverse events.

In this study, patients who were allocated to the LEV group reported behavioral changes most frequently (17.85%), including an increase in aggression, anxiety, and suicidal ideation. Similar to this, LEV was linked to higher behavioral alterations in terms of irritation (30.5%) in the study by Kim JH et al. Numerous case studies do indicate that LEV is connected to more pronounced behavioral alterations[14,15]. LEV's package insert further states that it should not be used in people who have a history of psychiatric disease. 13.3% of patients using LEV exhibited behavioral symptoms such as agitation, hostility, aggression, anxiety, apathy, emotional instability, and depression, according to a study on the safety profile of LEV[16]. Similar to the previous study, another one on the clinical experience of LEV reports that 33.33% of patients had anxiety or irritability following the start of the medication. Additionally, 16.66% of patients stopped receiving treatment because of their irritation [8].

In this study, two individuals taking LEV reported gaining 3-5 kg of weight in just three months. There have been reports of LEV-induced weight loss up to this point. Gaining weight in this situation is associated with higher QOL. In this trial, giddiness, more sleep, itching, and nausea were all noted as AEs.

Leukopenia, hyponatremia, problems with vitamin D metabolism, agranulocytosis, and hepatitis have all been listed as long-term adverse effects of CBZ. LEV is a relatively new medication. According to trials done to date, the medication is well tolerated over the long term. There have been instances of people stopping the medication because they became irritable, although these cases were associated with prior histories of mood problems[17,18]. LEV appears to be a better long-term solution than CBZ in this aspect. Prescribers should properly assess a patient with a history of

psychiatric disorder to prevent the behavioral adverse event (AE). A relatively recent method of measuring patient-related outcomes of epilepsy therapy is the QOL evaluation.

Other studies have recently attempted to ascertain the influence of different demographic and clinical variables on the total QOL among epilepsy patients [2]. Here, we assessed QOL using the QOLIE-10 and investigated the effects of both LEV and CBZ prior to and following the start of medication.

Before the start of the therapy, the mean score in the CBZ group was 31.14±1.83 while it was 29.76±1.71 in the LEV group ($p = 0.5861$), which is statistically insignificant. The patients' low QOL is correlated with lower scores. Following the completion of the six-month therapy program, there was a statistically significant rise in the mean score for both groups.

After six months of therapy, the mean score in the CBZ group was 58.41±1.89 as opposed to 64.58± 2.02 ($p = 0.0302$, $p < 0.05$), which was statistically significant. There were no obvious differences between LEV and CBZ in terms of their effects on health-related quality of life, in contrast to the prior Santhosh NS experiment when QOL was measured using the QOLIE-31 scale[13].

LEV has been reported to improve quality of life (QOL) more than CBZ, which may be because LEV was linked to a higher seizure freedom rate than CBZ. In the CBZ group, this increased seizure frequency is associated with a lower QOL. Similar findings from another Thomas et al. study support the notion that patients receiving monotherapy have much higher QOL [2]. As a result, LEV showed improved QOL compared to CBZ after 6 months of medication.

Conclusion

LEV has been shown to be just as effective as CBZ in treating partial seizures when used alone. Compared to CBZ, LEV did not demonstrate better efficacy. When compared to pretreatment seizure frequency, both medications equally decreased the frequency of seizures. LEV and CBZ were both bearable. Equivalent incidences of AE were found in LEV and CBZ. In the safe treatment of partial epilepsy, LEV can be taken alone.

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