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Original Research Article

To Compare the Quality of Life in Newly Diagnosed Patient's of Epilepsy on Monotherapy with Levetiracetam and Valproic Acid

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Abstract

Background: Quality of life (QOL) is often neglected while managing epilepsy, as the main goal is to enable a person to live a seizure-free life. Epilepsy and its treatment affect the quality of life of the patient.

Methods: The present study was an observational analytical study, comparing QOL in epileptic patients receiving monotherapy with either levetiracetam or valproic acid. It was conducted in the Department of Neurology, Himalayan Institute of Medical Sciences, Dehradun. Over 12 months period, 120 patients satisfying inclusion criteria were enrolled and divided into two groups based on the treating physician's discretion. They were followed up for a period of 12 weeks. Patients were evaluated based on a QOLIE-10 self-administered questionnaire for quality of life at 0 and 12 weeks. They were also assessed for drug-related adverse effects and seizure control.

Results: Significant improvement in quality of life was seen with both drugs. Levetiracetam (18.117 ± 1.967) showed a mean change significantly greater than valproic acid (11.317 ± 2.931) ($p<0.05$). The most common adverse event in the levetiracetam group was drowsiness; in the valproic acid group, the most common were anorexia and drowsiness. Seizure control was similar in both groups at the end of 12 weeks.

Conclusions: Monotherapy with levetiracetam resulted in a better quality of life, with similar seizure control and a lesser number of adverse events as compared to valproic acid.

Keywords: Quality of Life in Epilepsy, QOLIE-10, Levetiracetam, Valproic Acid.

Introduction

Quality of life (QOL) is impaired in patients with epilepsy. Factors contributing to the poor QOL in epilepsy include worrying about seizures, functional impairment, educational handicap, difficulties with relationships, and

depression. Drug-related side effects play an important role in patients' adherence to medication, which is related to seizure control and QOL in epilepsy patients.

The prevention of seizures and striving towards the goal of seizure freedom remain the primary target for the management of epilepsy. For the most definitely diagnosed epilepsy, long-term treatment with anti-epileptic drugs (AEDs) is needed [1]. Monotherapy with AEDs is gold-standard in the treatment of epilepsy. The benefit of using one single drug or monotherapy is decreased incidence of adverse events and drug interactions which in turn increases patients' adherence to medication and better seizure control [2].

Drugs approved for use in epilepsy are divided into two generations based on the time of discovery, those approved before 1993 { Phenobarbitone (PB), Phenytoin (PHT), Carbamazepine (CBZ), Ethosuximide (ESM), Valproic acid (VAP), etc } are considered as older generation AEDs and those approved after 1993 { Lamotrigine (LTG), Levetiracetam (LEV), Vigabatrin (VGB), Tiagabine (TGB)} were labeled as newer AEDs [3]. Conventional AEDs have a proven efficacy record with around 75-80 % of patients achieving adequate seizure control. The therapeutic failure in 20-25 % of patients has stimulated intensive research on newer AEDs.

In the present study, we conceptualized comparing a broad spectrum and considered safest AEDs from the older generation which is VPA with a drug of the newer generation which is found its usage both in approved as well as off-label use in major types of seizures i.e. LEV. Even after an extensive search, there was a lack of studies that compared VPA with LEV on efficacy, safety, and QOL both in India as well as the world to date.

Subjects and Methods:

This was an observational analytical follow-up study in newly diagnosed patients with epilepsy. The study was conducted for one year from January 2016 to December 2016. The minimum sample size which was required was 120 patients, with 60 patients in each group. The sample size was based on a previous study that compared the quality of life in epilepsy patients[4]. Ethical clearance was taken from Institutional Ethical Committee. Patients were included after taking written informed consent. Patients were selected from the outpatient department of the Department of Neurology. Patients were followed up for 12 weeks. Patients satisfying below mentioned inclusion criteria were included in the study: Patients with a diagnosis of epilepsy, both sexes in the age group of 18-60 years, and patients who have been stabilized on their respective drug dosage for more than 1.5 months or less than 4.5 months [4]. Subjects excluded from the study were: patients with progressive CNS disease and lesion, any uncontrolled co-morbid condition, malignancy, hypersensitivity to the study drugs, participating in another study, subjects with deranged liver and renal functions, pregnant and lactating mothers, patients who have experienced acute onset of seizures related to drugs, alcohol, acute medical illness, patients leaving the study due to any reasons will be excluded from final analysis. Demographic profiles and detailed history were obtained from each recruited patient; this included family history, educational status, age of onset of epilepsy, duration of disease, and personal habits. Study subjects included in the study were divided into two groups of 60 each. The drugs were given to subjects based on the physician's discretion. The dose ranges of the two drugs at the start of the study were as follows Levetiracetam (LEV) 500-2000 mg/day and Valproic acid (VPA) 300-1000 mg/ day. After recruitment patients were assessed for their QOL based on the QOLIE-10 questionnaire and were also evaluated for efficacy and safety. For efficacy and safety, they were assessed on

each visit with the help of a patient-maintained seizure diary and self-reporting of adverse drug reactions. Patients were evaluated at baseline (1st visit) and 12 weeks for QOL.

Assessment of QOL in patients: The QOLIE-10 is a brief standardized instrument for screening patients with epilepsy about the impact of epilepsy on their lives [5]. QOLIE-10 evaluates patients in three domains: (i) Epilepsy effects which evaluated patients for memory, physical effects, and mental effects. (ii) Mental health assessment for energy, depression, and overall quality of life. (iii) Role functioning which evaluated patients for seizure worry, work, driving, and social limits. Scores for QOLIE- range from 1-to 5 for each question with a minimum of 10 and a maximum of 50. Higher the score poor is the expressed QOL. Assessment of the safety of treatment: A checklist of adverse drug reactions was prepared according to the most common adverse events occurring due to study drugs. Adverse drug reactions were recorded at every visit of the patient i.e. at monthly intervals. A seizure diary was used to record patients' experiences weekly and how their seizures improved or deteriorated, frequency of seizures, duration, and post-ictal confusion seizure-related injury.

Data management and analysis were done using Microsoft Excel 2007 and IBM SPSS version 20.0. Demographic data was presented as either frequency or mean ± sd. The intra-group comparison was done using Paired sample Student t-test and inter-group analysis was done using the Unpaired Student t-test. Adverse events were interpreted and analyzed using descriptive statistics and the chi-square test. [6]

Results

There was no significant difference in both groups based on baseline characteristics. The two groups differed only on the base of personal history (alcoholism and smoking). The baseline pattern in included patients for epilepsy which are included in this study were types of seizures, family history, duration of disease, and frequency of seizures, Table 2, with no underlying significant difference in duration of disease and disease frequency.

Intragroup comparison in Group A and B for QOLIE showed a significant change in score from the baseline at the end of the study. Improvement in QOILE-10 scores was seen on all parameters but it was more seen in role function, which was seen in both groups.

Intergroup comparison shows a significant difference between LEV and VPA acid groups. Total QOLIE-10 scores improved in both the groups but the increase was more in LEV (18.117 ± 1.967) than VPA (11.317 ± 2.931) and was significant ($P<0.05$). Seizure freedom was seen at 6 and 12 weeks in both groups. It was seen that patients achieved better seizure control in the LEV group than VPA group at 6 weeks which was equaled in both groups at 12 weeks. It was found to be statistically non-significant at 6 weeks ($p<0.05$, Chi-square=0.5628). Complete seizure control was achieved at 12 weeks.

The study population was evaluated for medication adherence. Out of 120 patients, adherence was seen in 83.33% patients. We also evaluated the adherence pattern based on place of residence (Urban/Rural). In Group A adherence was seen in 96% and 73.52% of the urban and rural population respectively ($p=0.0197$, chi-square=5.429). It was found to be 86.95% and 81.08% for urban and rural populations respectively in Group B ($p=0.552$, chi-square=0.352).

Patients who had seizure episodes after stabilization on their medication were 10 out of 60 in Group A and 11 out of 60 in Group B. There were no episodes of status epilepticus during the study period in any of the groups. Seizure reoccurrence was

seen in patients who were non-adherent to their medication.

Table 1: Demographic profile of patients in study Group A (LEV) & Group B (VPA).

Demography	Group A (LEV)	Group B (VPA)
Total no. of patients	60	60
Age (Years, Mean±SD)	31.13 ± 13.46	25.13 ± 7.01
Sex (Male/Female)	36 / 24	36 / 24
Religion (Hindu/Muslim/Christian/Sikh)	53/6/1/0	54/5/1/0
Smoker/Non-smoker	19/41	3/57
Alcoholic/Non-alcoholic	19/41	3/57
Diet (Vegetarian/Non-Vegetarian)	30/30	28/32
Marital status (Married/Bachelor)	35/25	28/32
Residence (Urban/ Rural)	26/34	23/37

* Student t-test, P<0.05 Values are expressed in frequency

Table: 2 Baseline characteristics of epilepsy among both the study groups

Data has been represented as frequency and Mean ± SD

Parameters	Group A (LEV)	Group B (VPA)
Type of seizure		
GTCS	41	44
Partial	19	16
Family History		
Present	5	5
Absent	55	55
Duration of Disease (Years)	4.23 ± 2.25	4.32 ± 2.34
Frequency of seizure (seizures/month)	3.26 ± 0.82	3.23 ± 0.96

***** Student t-test**,** P<0.05 was considered significant

Table: 3 Mean QOLIE-10 score comparison in both groups.

	Group A (LEV)		Group B (VPA)	
QOLIE-10 Parameters	**Baseline**	**12 weeks**	**Baseline**	**12 weeks**
Epilepsy Effects	10.27±0.972	5.13±0.999*	8.38±1.250	5.18±1.214*
Mental Effects	10.13±1.295	4.70±1.124*	8.75±1.310	5.33±1.284*
Role Function Effects	14.07±1.191	6.52±1.000*	11.77±1.566	7.07±1.364*
Total QOLIE score	34.47±1.567	16.35±1.351*	28.90±2.363	17.58±1.565*

*P<0.05, Student t-test (Values presented as Mean±SD.)

Table 4: Comparison of mean change in QOLIE-10 scores between the groups at 12 weeks.

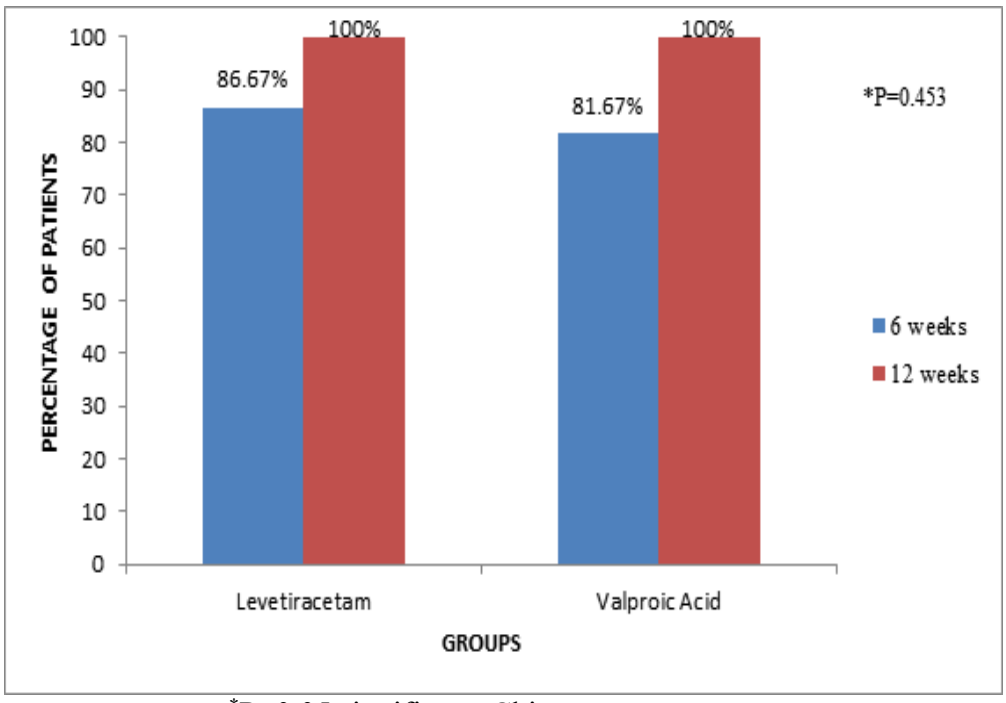
QOLIE-10 Parameters	Group A (LEV)	Group B (VPA)
Epilepsy Effects (Scores)	5.133 ± 1.282	3.2 ± 1.735*
Mental Effects (Scores)	5.433 ± 1.577	3.417 ± 1.844*
Role Function Effects (Scores)	7.550 ± 1.610	4.700 ± 2.110*
Total QOLIE score	18.117 ± 1.967	11.317 ± 2.931*

*P<0.05, Student t-test

Table 5: Adverse events during the study period.

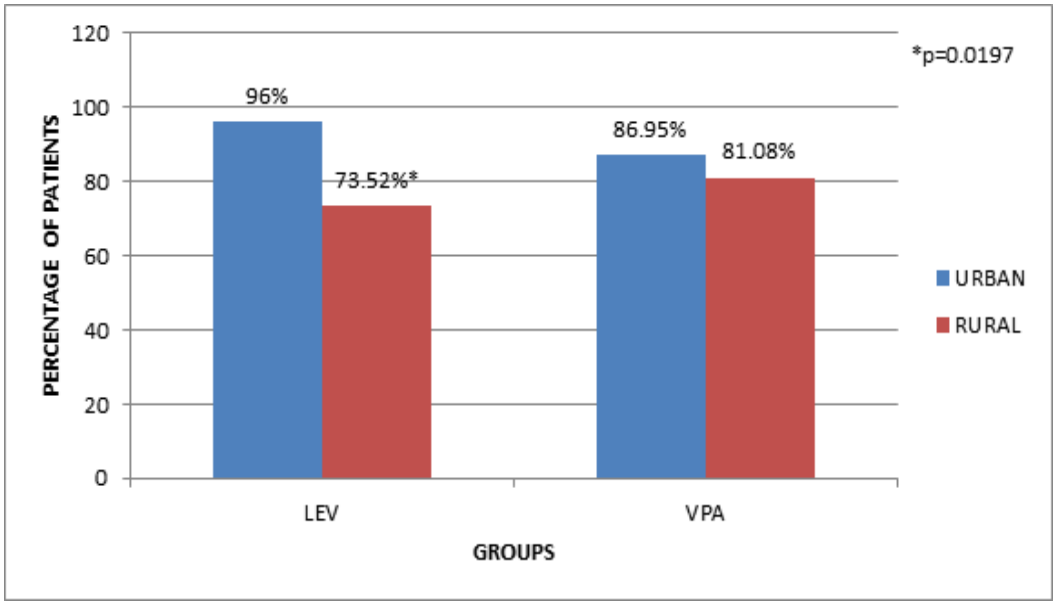
Adverse Events	Group A (n=60)	Group B (n=60)
Anorexia	0	8
Drowsiness	5	8
Weight Gain	0	5
Irritability	3	2
Increased sleep	2	0
Headache	2	0
Loose Stools	0	2
Total	12	25*

Adverse events presented as frequency, p<0.05, Chi-square



*P<0.05 significant, Chi-square test

Figure 1: Seizure freedom at 6 and 12 weeks in both groups.



*P<0.05 was significant. Chi-square test.

Figure 2: Medication adherence in both groups based on the urban and rural populations.

The adverse event in both groups was well recorded. Adverse effects recorded were 12 and 25 in Group A and B respectively. This was statistically significant (P=0.0107, chi-square=6.6037).

The cost of therapy plays an important role in adherence to medication. It becomes more important in patients who are on long-term therapy with any drug. Hence cost comparison was done to compare the monthly cost of the two groups which was INR 1063.90 ± 193.54 and INR 494 ± 82.78 for Group A and Group B respectively.

Discussion

The ultimate goal for the treatment of epilepsy is total freedom from seizures with minimum adverse events and optimal QOL. Adopting evaluation of the QOL outcomes in the standard management plan along with traditional measures of assessment of seizure frequency and adverse effects needs to be encouraged [6]. To address this objective, the present study compared the drugs Levetiracetam and Valproic acid based on the quality of life in newly diagnosed patients with epilepsy.

General baseline demographic characteristics included in our studies were age, gender, and place of residence. The mean age of the study population in the present study was 31.13 ± 13.46 years and 25.13 ± 7.01 for LEV and VPA respectively (Table 1).

The mean age of patients in our study was comparable to the study done on epileptic patients on the QOL where the mean age of the enrolled patient was 31.8 ± 11.0 [7]. In the present study male to female ratio was 60:40 (Table 1) in both groups which was slightly higher than in the above study where the ratio was 56.6:43.4 with a higher percentage of male patients [7].

Education is an important aspect of life and has a positive influence on the QOL. In our study, the number of patients who had completed their formal education up to graduation was 58.34 % in the LEV group and 51.66 % in the VPA group (Table 1). The percentage of educated patients sharply rose to 90 % in the LEV group and 95 % in the VPA group when formal education up to the matriculation was considered (Table 1). A similar trend was seen in another study done on patients with epilepsy [8]. A Higher level of literacy, in

turn, can influence patients understanding of the importance of a seizure diary and improves treatment adherence.

We in this study also observed the rural-urban divide in the patients included. In the present study number of patients from rural backgrounds was more than in the urban; LEV group (56.67 % rural and 43.33 % urban) and in the VPA group (61.67 % rural and 38.33 % urban) (Table 1). Both groups were similar in this regard.

GTCS was the most encountered seizure type in both LEV and VPA which was 68.33 % and 73.33 % (Table 2) respectively. This finding was similar to another study in India where GTCS was the most common type of seizure at 68.33 % [8]. Patients with partial seizures were 31.67 % and 26.67 % in LEV and VPA groups respectively (Table 2).

There were no absence seizures detected in our study, this may be due to the silent presentation of absence seizure [9].

The mean duration of illness was comparable in both the groups in the present study. In the LEV group, it was 4.23 ± 2.25 years and in VPA it was 4.32 ± 2.34 years (Table 2) was lower than in another study where the mean duration of the disease was found to be 6.62 ± 4.21 years[9]. The percentage of patients with post-ictal confusion was similar in both groups. There were no episodes of status epilepticus recorded in both groups during the entire duration of this study as patients at the time of enrollment had already completed the titration phase. The percentage of people with positive family history was similar in both groups at 8.33 % (Table 2). This result was similar as compared to another study [9].

Epilepsy is both a medical diagnosis and a social label because people with epilepsy face many psychosocial challenges (anxiety, social stigma, difficulty in driving, unemployment) that can negatively impact their QOL. Such growing recognition of the importance of the psychosocial effects of epilepsy has led to the need to quantify the QOL in affected individuals. Hence, appropriate AEDs use, along with monitoring of adverse effects and assessment of the QOL as an outcome measure is important in the management of epilepsy to achieve optimal seizure control [10]. The QOL in our study was assessed using a standardized QOLIE-10 questionnaire as the primary outcome measure. The questionnaire in QOLIE-10 assesses three aspects of the health of the epileptic patient; mental effects, epilepsy effects, and role function. The score corresponding to each scale as well as the QOLIE-10 total score was calculated [5].

The baseline QOLIE-10 score in the LEV group at the beginning of the study was 34.47 ± 1.567 which decreased to 16.35 ± 1.351 at the end of 12 weeks (Table 3) showing a mean change of 18.117 ± 1.967 (Table 4) which was statistically significant ($p<0.005$). Scores in the LEV group showed improvement by 36 % from baseline. This result was supported by a study done by S.S. Hassan et.al. where the percentage change is seen was 34.82 % [11]. Subgroup analysis was also done where different aspects of QOLIE-10 scores were compared which showed improvement in all spheres. The mean change in epilepsy effect (5.133 ± 1.282), mental effects (5.433 ± 1.577), and role function effects (7.550 ±1.610) (Table 4). Role function showed maximum improvement.

The baseline QOLIE-10 score in the VPA group at the beginning of the study was 28.80 ± 2.705 which decreased to 17.58 ± 2.705 at the end of 12 weeks (Table 3) showing a mean change of 11.217 ± 3.279 (Table 4) which was statistically significant ($p<0.05$). Scores in the VPA group showed an improvement of 22.43 % from the baseline. This was supported by two different studies. SANAD trial in which VPA was compared with LTG and TPM, where VPA showed improvement in the QOL [12]. A similar study was done in

the Spanish population comparing VPA with LTG and showed improvement in the quality of life from baseline [4].

Subgroup analysis was also done where different aspects of QOLIE-10 scores were compared which showed improvement in all spheres. The mean change in epilepsy effect (3.2 ± 1.735), mental effects (3.417 ± 1.844), and role function effects (4.6 ± 2.180) (Table 4). Role function showed maximum improvement.

We could not find studies where these two drugs were compared head-to-head even after an extensive literature search. Intergroup comparison between the two groups showed a statistically significant ($p<0.05$) difference in mean change in QOLIE-10 score i.e. 18.117 ± 1.967 for LEV and 11.217 ± 3.279 for VPA(Table 4).

Freedom from seizure is an important parameter for the measurement of the efficacy of treatment in epilepsy. How rapidly the seizure control is achieved as well as how good is seizure control, determines the length of treatment in epilepsy patients. Hence this was measured by the patient's reported seizure diary in our study. At the beginning of the study mean seizure frequency per month was 3.26 ± 0.82 and 3.23 ± 0.96 in LEV and VPA groups respectively (Table 1). The frequency of seizures was less than in other studies done on epilepsy [13] but this may be due to newer patients enrolled in our study. The patients who reported total seizure freedom at 6 weeks were 86.67% and 81.67% for LEV and VPA groups respectively and at 12 weeks both groups achieved complete seizure control (Figure 1).

This is per another study where the freedom from seizure did not vary between older and newer AEDs [14].

Adherence to medication plays an important role in chronic illnesses like epilepsy which can affect seizure recurrence which in turn affects the QOL. In our study adherence was measured using pill counting. Adherence at 6 weeks was poor in the VPA group (not statistically significant $p<0.05$) which may be due to more adverse effects caused by VPA in comparison to LEV (Fig.2). Improved adherence improves the QOL this was supported by findings of another study [15]. There is a lower level of adherence in the rural population as compared to the urban population in both groups which was significant in the LEV group and insignificant in the VPA group. This result was in similarity to another study [16].

Adverse drug reaction is a major factor that will either motivate or demotivate patients to continue medication. Adverse effects result in decreased medication adherence which results in increased chances of seizure episodes and more the chances of seizure episodes poorer the QOL. In the present study, the adverse events recorded were based on an adverse effect checklist during the entire period of study. A total number of adverse effects recorded in the study were 37, out of this 67.57 % of adverse events occurred with VPA and 32.43 % with LEV (Table 5). The adverse events were statistically significant between groups ($p<0.05$). As we did not find any head-to-head comparison of our study drugs we tried to correlate results with other studies which compared older versus newer AEDs. Our findings were not following other studies where it was inferred that both do not differ statistically in terms of adverse events [17]. The adverse event in group LEV group was drowsiness (41.67%), irritability (25%), increased sleep (16.67%), and headache (16.67%). In VPA adverse events were anorexia (32%), drowsiness (32%), weight gain (20%), irritability (8%), and loose stools (8%). The most common adverse effect in the LEV group was drowsiness and in the VPA group were anorexia and drowsiness (Table 5).

An important part of any study which compares two different drugs is to assess the cost-benefit ratio in terms of efficacy and safety. In the present study, we determined that the average monthly cost of therapy for LEV was INR 1063.90 ± 193.54 and for VPA was INR 494 ± 82.78. There was a significant difference in the monthly cost of the two drugs, but this did not affect the patient's adherence as is expected with costly medication. As cost is an important factor that determines the continuation of medication by patients as stated by another study [18,19].

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