Original Research Paper

Volume - 12 | Issue - 05 | May - 2022 | PRINT ISSN No. 2249 - 555X | DOI : 10.36106/ijar

Pharma

TO COMPARE EFFICACY, TOLERABILITY AND QUALITY OF LIFE WITH CONVENTIONAL AND NEWER ANTIEPILEPTIC AS MONOTHERAPY IN NEWLY DIAGNOSED PATIENTS OF EPILEPSY.

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ABSTRACT **Background:** Quality of life plays an important role in patients of epilepsy and is the most neglected part during management. The antiepileptic drugs treatment results in seizure control but adversely affect the quality of life in patients on drugs taken for the treatment of epilepsy **Methods:** An observational analytical study was conducted in the Department of pharmacology with Department of Neurology of Himalayan Institute of Medical Sciences, Dehradun over one year. Total of 120 patients fulfilling the inclusion criteria with diagnosis of epilepsy were enrolled and divided into two groups based on physicians discretion . Group A were on the conventional antiepileptic drugs , group B received the newer antiepileptic drugs and followed up for 12 weeks. Patients were evaluated for quality of life by QOLIE-10 questionnaire at baseline and 12 weeks, assessed for seizure control and drug related adverse effects. **Results:** There was significant improvement in quality of life, in both the groups as compared to baseline ($p<0.05$) at 12 weeks but there was not significant change in quality of life in conventional and newer groups. The patients who reported total seizure freedom at 6 weeks was 93% and 90% for older and newer groups respectively .Both groups achieved complete seizure control at 12 weeks. Adverse events reported in patients on conventional groups were more as compared to newer group. **Conclusions:** Quality of life improved in both group of patients on newer and conventional antiepileptic drugs, with similar seizure control but decreased number of adverse effect of newer than on conventional antiepileptic drugs .

KEYWORDS : Generalized tonic clonic seizure, partial seizure, Quality of life in epilepsy, QOLIE-10.

Introduction:

Seizure is single or paroxysmal event arising from abnormal, excessive, hyper-synchronous discharges arising from neurons in the central nervous system.[1]seizure needs to be carefully distinguished from that of epilepsy.Epilepsy is neurological disorder characterized by recurrent episodes of seizures causing neurobiological, cognitive, psychological, and social consequences .[2]The annual incidence of epilepsy in India is about 27.3 per 100,000 per year with a prevalence of 2.5 to 11.9 per 1000. [3, 4] The International league against epilepsy classifies seizures into three main types: partial, generalized, and unclassified. [1]Etiology of seizures may be idiopathic or may be related to genetic factors, brain tumour, alcoholism, stroke, heart attack etc. Multiple infectious diseases like meningitis, AIDS, viral encephalitis may lead to seizure disorders. Developmental and metabolic disorders such as cerebral palsy, neurofibromatosis hydrocephalus, autism, head injury and poisoning have also been implicated. [5] Prevention of seizures and striving toward a goal of seizure freedom remains the primary target of management of epilepsy. Many antiepileptic drugs, conventional and newer are available at present .The choices between AEDs (antiepileptic drugs) are often empirical.

Antiseizure medication can control seizures efficiently in 75-80 % of patients with epilepsy [6]. A conventional antiepileptic drug generally inhibits sodium currents (carbamazepine, phenobarbital, phenytoin, and valproate) or enhances GABA-ergic inhibition.[7] The therapeutic failure in 20-25% of patients has stimulated intensive research on novel antiepileptic drugs and many new drugs have been developed and licensed. Newer AEDs include felbamate, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, tiagabine, topiramate, vigabatrin, and zonisamide.[6] The new AEDs complement the 'conventional' AEDs, providing more options as add-on treatment of seizures with additional/novel mechanisms of action.[8]

Some of these newer antiepileptic drugs have established as monotherapy too, while others have limited evidence in this matter. Levetiracetam, oxcarbazepine, and lamotrigine are as efficacious as monotherapy in the treatment of partial-onset seizures while topiramate has been approved for monotherapy in both generalised and partial epilepsy. [9,10]

Nowadays clinicians prefer earlier use of newer AEDs as monotherapy because of better safety and tolerability in comparison to conventional drugs.[11, 12] Quality of life in epilepsy is generally impaired by occurrence of seizures. However, quality of life of an epilepsy patient not only dependent on seizure but also on adverse effects profile of AEDs. [13, 14]Therefore, other than good control of seizures, good tolerability of AED is of paramount importance to provide a seizure free time with good quality of life.

Efficacy of the conventional drugs and newer drugs as studied many a times have hardly generated any gross difference. The recent trend of choosing newer drugs is mostly due to the claim of lower incidences of adverse effects in the newer agents. The difference of tolerability and quality of life in addition to seizure free interval between the patients receiving conventional and newer drugs is therefore a matter of research. There are very few studies comparing conventional and newer antiepileptics globally. Extensive literature search yielded only a few studies comparing conventional and newer antiepileptic drugs in Indian population. However, these studies have compared few drugs only and not conventional and newer drugs as a group.

Hence, the present study was designed to compare the quality of life with conventional and newer antiepileptics in epileptic patients.

Materials & Methods:

Study design and study groups: The study was conducted on the patients visiting the outpatient department of neurology of Himalayan institute of Medical sciences, Jolly Grant Dehradun. This was a prospective observational analytical follow-up study enrolling 120 newly diagnosed patients of epilepsy. Patientswere enrolled as per the inclusion and exclusion criteria. Written informed consent was obtained from all the participating patients. Patients have undergone a thorough clinical examination including history, vital signs, systemic

examination and routine investigations were done as per clinician discretion.

Inclusion criteria:

1. Newly diagnosed Subjects with epilepsy including generalized tonic clonic seizures and partial seizures with or without secondarygeneralization as per the International league against epilepsy classification .[1]

2. Patients of both genders in the age group of 18 to 75 years.

3. Patients who have been stabilized on their respective drug dosage for more than 1.5 months or less than 4.5 months.

Exclusion criteria:

1. Subjects with progressive encephalopathy or findings consistent with progressive CNS disease or lesion (demyelination or tumor).[15]
2. Serious cardiac arrhythmia or dysfunction, congestive heart failure (CHF), recent Myocardial infarction (MI)
3. Patients with underlying neoplastic disease.
4. Known Hypersensitivity to antiseizure medication.
5.Any uncontrolled severe concurrent illness or uncontrolled diabetes.
6. Patients participating in another study within 8 weeks of the start of the Study or any time during the study.
7. Patients with known abnormal kidney function (serum creatinine> 1.5 mg/dL) or abnormal liver function (Aspartate aminotransferase [AST] and alanine aminotransferase [ALT] > 2 times the upper normal limit)
8. Pregnant and lactating mothers
9. Subjects who have experienced seizures relating to drugs, alcohol, acute medical Illness, mental retardation and psychiatric disorders.[15]

The patients will be evaluated as per the following parameters:

Primary parameter:

1. Overall quality of life after treatment was assessed by using the QOLIE- 10 questionnaire[16]

Secondary parameters:

1. Freedom from seizures: This was referred to no seizure episode up till the last follow up i.e. at 12 weeks.
2. Time to first seizure after initial dose stabilization.
3. Adverse drug reactions (ADR) as per the check list along with spontaneous reported ADRs were recorded at 0, 6, and 12 weeks and at any time during the study period.

Study groups and treatment regimen

Total of 120 newly patients diagnosed with epilepsy as per the International league against epilepsy were enrolled in the study and divided into two groups. Sample size was based on study which also compared quality of life in epilepsy patients.[17] Patients in both the groups received either a conventional or a newer antiepileptic drug as monotherapy starting at the dose decided by the treating physician based on the seizure type, drug characteristics and patient characteristics. Group A was on the conventional antiepileptic drugs (sodium valproate, carbamazepine and phenytoin) and group B received the newer antiepileptic drugs (levetiracetam, oxcarbazepine and lamotrigine). All drugs in both the groups were started as first line treatment.

Study procedure:

A general physical examination was performed, and blood pressure was recorded EEG and CT Scan/MRI head was done. Blood test (haematological and biochemistry were done before starting of the treatment.

All patients underwent complete physical examination, laboratory assessment (haematologicaland biochemical) were done. Sitting blood pressure and heart rate were measured. Pre-treatment neurological status (EEG and CT Scan/MRI head)was assessed in all patients.

After enrolment the patients were assessed for quality of life the on basis of QOLIE-10 (Quality Of Life In Epilepsy) questionnaire and were also evaluated for efficacy and safety.[6]For efficacy and safety they were assessed on each visit with the help of patient maintained seizure diary, and self reporting of adverse drug reaction.

Patients were evaluated at 0 visit (baseline) and at 12 weeks for quality of life.

The QOLIE-10 is a brief instrument for screening patients with epilepsy about the impact of the epilepsy on their lives.

QOLIE-10 evaluates patients in three areas
Epilepsy affects which assessing patients for memory, physical and mental effects.

Mental health evaluating for energy, depression and overall quality of life. Role functioning which assessing patients for seizure worry, work, driving and social limits.

QOLIE-10 score: Points are assigned from 1 to 5 based on the frequency or severity during the previous 4 weeks.
SUM (points for all 10 questions);
Common adverse events occurring due to study drugs.
Epilepsy effects = SUM (points for items 4 + 7 + 8)
Mental health = SUM (points for items 1 + 2 + 10)
Role functioning = SUM (points for items 9 + 5 + 6 + 3)

Interpretation: Score range for this questionnaire ranges from minimum of 10 to maximum of 50. Higher the score, the poorer is the expressed quality of life.

Assessment of safety of treatment: A checklist of adverse drug reaction was prepared according to the most common adverse events occurring due to study drugs.

Patient's seizure diary was used to report number and time of seizure episodes everyday up to three months. Seizure diary was also including the patient reported adverse effects. Control of seizures in terms of frequency, severity and duration was also recorded in seizure diary on each day. Patients were assessed for adverse effects at 0, 3, and 6 months and also for spontaneous reported adverse effects at any time during the study. Patients were also reassessed after three months of therapy for quality of life.

Statistical analysis:

Demographic data such as age, duration of disease and frequency of seizures were represented as mean ± SD .Data was analysed by using SPSS version 22 (SPSS South Asia Pvt. Ltd, Bengaluru, Karnataka, India).Student's *t*-test and chi-square test were applied. A p value < 0.05 was considered as statistically significant. Adverse events were interpreted and analysed using descriptive statistics.

Table 1: Basic Demographic Detail Of The Study Group.

Demography	Conventional Group A (N=63)	Newer GroupB (N=57)
Age (years, mean ± SD)	25.797.88	30.88 13.02
Sex% (n)		
Male	65.1 (41)	61.4 (35)
Female	34.9 (22)	38.6(22)
Religion		
Hindu	90.5 (57)	91.1 (52)
Muslim	7.9 (5)	7.0(4)
Christian	1.6 (1)	1.8(1)
Marital Status		
Married	49.2 (31)	54.4(31)
Unmarried	50.8 (32)	45.6 (26)
Educational Status		
Below Intermediate	63.5(40)	38.6(22)
Above Intermediate	36.5(23)	61.4 (35)
Place of Residence		
Rural	60.3 (38)	38.6 (22)
Urban	39.7 (25)	61.4(35)
Alcoholic		
Alcoholic	6.3(4)	28.1 (16)
Non-alcoholic	93.7(59)	71.9(41)
Smoking		
Smoker	7.9 (5)	35.1(20)
Non-smoker	92.1(58)	64.9(37)
Diet		
Vegetarian	54 (34)	43.9 (25)
Non-vegetarian	46 (29)	56.1 (32)

Data represented as % (frequency)

There was no significant difference between the two groups based on the baseline characteristics. The two groups differed in their personal history (education, alcoholism and smoking)

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

Parameters	Conventional AEDs(63)	NewerAEDs(57)
Family History% (frequency) Present Absent	 12.6(8) 87.3(55)	 14(8) 85.9(53)
Type of epilepsy% (frequency) Generalized Focal	 57.1(36) 42.8(27)	 84.2(48) 15.7(9)
Duration of Disease (years, mean ± SD)	5.0 2± 2.8	4.3 ± 2.4
Frequency of seizures (per month, mean ± SD)	3.10± 0.89	3.0 ± 0.92

There was no significant difference between the two groups based on the baseline characteristics.

Table 3 QUALIS -10 Score in Conventional Group(N=63)

QOLIE-10 Parameters	Base line	12 weeks	Mean change
Epilepsy effect	7.98+1.264	5.06+1.134*	2.921+1.649
Mental effects	8.56+1.446	5.00+1.205*	3.556+1.758
Role function effect	11.79+1.724.	6.13+1.171*	5.667+1.959
Total QOLIE-10 score	28.33 +2.718	16.19+1.645*	12.143+3.010

Table 4 QUALIS -10 Score in newer Group (N=57)

QOLIE-10 Parameters	Base line	12 weeks	Mean change
Epilepsy effect	8.07 + 1.223	5.37 + 1.219 *	2.702 +1.669
Mental effects	8.51+1.428	5.12 +1.310 *	3.386+1.953
Role function effect	11.72+1.770	6.21 +1.098 *	5.509+1.983
Total QOLIE-10 score	28.30+2.712	16.70+1.535 *	11.596+3.212

*P<0.05, paired sample t-test.

Table: 5 Comparison of mean change in QOLIE-10 scores between the groups at 12 weeks.

QOLIE-10 Parameters	Conventional Group. N=63	Newer Group N=57
Epilepsy effect	5.06+1.13	5.37+1.21
Mental effects	5.00+1.20	5.12+1.31
Role function effect	6.13+1.17	6.2 1+1.09
Total QOLIE-10 score	16.19+1.64	16.70+1.53

*P<0.05, as compared to conventional group values are expressed as mean± SD Independent sample t- test

Figure:1Seizure frequency at baseline,6weeks and 12 weeks in both groups

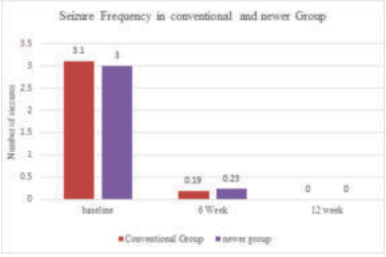

Table 6: Adverse events during the study period.

Adverse Events	Group A		Group B	
	Valproic Acid N=30	Carbamazepine N=32	Levetiracetam N=27	Oxcarbamazepine N=30
Anorexia	10% (3)	-	-	-
Drowsiness	13% (4)	3.1% (1)	11% (3)	3.3% (1)
Decreased conc	-	6.2% (2)	-	-
Dizziness	-	6.2% (2)	-	3.3% (1)
Weight Gain	10%(3)	-	-	-
Irritability	13%(4)	-	7.4 %(2)	10% (3)
Increased sleep	-	-	3.7% (1)	6.6% (2)
Decreased sleep		6.2% (2)	-	-
Headache	-	6.2% (2)	-	10 % (3)
Loose Stools	3.3% (1)	-	-	-

Adverse events presented as percentage and frequency

DISCUSSION:

Epilepsy is a chronic neurological disorder with multiple uncertainties and stigmatization which have negative impact on the QOL of patients living with epilepsy. Total freedom from seizures with minimum adverse events and an optimal quality of life is the ultimate goal of management of epilepsy. [18]Along with standard management of epilepsy, assessment of seizure frequency, adverse events monitoring and assessment the quality of life outcome need to encouraged .Hence the present study compares the quality of life with conventional and newer antiepileptics in epileptic patients.

A total of one hundred and twenty patients (120) of epilepsy irrespective of the type of epilepsy were included in the study. It was consisting of 76 men and 44 women with a higher proportion of male patients. Results were comparable to another study (53.5%).[19]

The mean age of respondents was 25.78. ± 7.9 in group A (conventional) and 30.9 ± 13.02 years in the group B (newer) .Majority of the patients in our study were below the 40 years of age While in another study the majority of the patients were younger than 30 years .[20](Table 1)

Generalized tonic-clonic seizure was the most commonly encountered seizure type in the patients in group A (57.1%) and B (84.2%).Similar results were shown in another study in India where the 59% patients had generalized seizures.[21]

Mean duration of epilepsy was 5.0 ± 2.8 in conventional group and 4.3 ± 2.4 years in newer group.The frequency of seizure was almost same in both the groups i:e 3.0± 0.89 and 3.10 ± 0.92 respectively . All the patients in our study at the time of enrolment had already completed the titration phase so no episodes of status epilepticus recorded during the study period. People with positive family history were found in both groups and were 12.63% and 14% in conventional and newer group respectively (Table 2).

An epileptic patient has not only to bear the burden of epilepsy which include physical hazards from unpredictable seizures, but also social exclusion due to negative attitudes towards people with epilepsy. Social Stigma may even prohibit adults from getting married and they are often denied employment even when seizures would not make their work unsuitable or unsafe. The quality of life in epileptic patients is generally poor than the healthy individuals. The quality of life in patients with epilepsy- as primary outcome measures was assessed by using the quality of life questionnaire (QOLIE-10), which measured three aspects of the health of the epileptic patient; mental effects, epilepsy effects and role function effect. The score corresponding to each scale as well as the QOLIE-10 total score was calculated.[16]

Baseline Total QOLIE-10 score in conventional group at the beginning of the study was 28.3±2.71which decreased to 16.19±1.64 at the end of 12 weeks (Table 3) showing a mean change of 12.14±3.0 which was statistically significant ($p<0.05$). This was supported by two different studies. SANAD trial in which VPA was compared with LTG and TPM, where VPA showed improvement in the quality of life. [22] Study done in Spanish population comparing VPA with LTG showed similar improvement in the quality of life from baseline.[17] Subgroup analysis in conventional group was also done where different aspects of QOLIE-10 scores were compared which showed significant improvement in all domains ($p<0.05$). The mean change in epilepsy effect (2.92±1.65) , mental effects (3.56±1.75) , role function effects (5.57±1.96) were observed from baseline.(Table 3).

Baseline Total QOLIE-10 score in newer group at the beginning of the study was 28.3 ± 2.71 which decreased to 16.7 ±1.53 the end of 12 weeks (Table 4) showing a mean change of 11.6 ± 3.2(Table 4) which was statistically significant ($p<0.05$). Scores in the newer group showed improvement by 40.9% from baseline. This result was supported by a study showing the percentage change 34.82 %. [23] Subgroup analysis where different aspects of QOLIE-10 scores were compared showed improvement in all spheres. The mean change in epilepsy effect 2.70±1.67 mental effects (3.48±1.95) and role function effects (5.50±1.98) were noted. Role function effect showed the maximum improvement.

Freedom from seizure is an important parameter for measurement of the efficacy of treatment in epilepsy and has positive influence on the quality of life. 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 patients reported seizure diary in our study. At the beginning of study mean seizure frequency per month was 3.03 ±0.84 and 3.07 ±0.92 in older and newer group respectively (Table 2). The frequency of seizure was less compared to other study done on epilepsy [24] but this may be due to newer patients enrolled in our study. The patients who reported total seizure freedom at 6 weeks was 93% and 90% for older and newer groups respectively and at 12 weeks both groups achieved complete seizure control (Figure 1). Increased seizure frequency had major effect on the QOL in a study done by Herodes et al. Guekht et al,[25-26] reported that patients with frequent seizures had low social contact and feelings of stigmatization. In our study all the patients were on monotherapy and various studies have proved improved QOL with monotherapy,which may be partly due to reduced adverse effects .Patients with polytherapy had poor health perception, limitation of social interaction and work, had low energy level with seizure worry, and health discouragement[27]

Adherence to therapy has an important role in the treatment of epilepsy.It can influence the recurrence of the seizure and has an impact on the quality of life. Adherence to treatment in our study was evaluated by counting pills. The adherence to AEDs in both the groups was 90% in older and 93.33% in newer group (not statistically significant) which could be caused by more adverse effects seen with older group as compared to newer group. Enhanced compliance improves quality of life.[28]

Adverse drug reaction is an important factor that can demotivate patients to continue the treatment. Adverse effect leads to reduced adherence to medication resulting in enhanced likelihood of seizure episodes resulting in lower quality of life. The adverse events recorded in the present study were based on the adverse effect check list during the entire study period.

Adverse events reported in patients on VPA group were anorexia,drowsiness,weight gain,irritabilityand loose stoolswhile adverse events reported in carbamazepine group were drowsiness, decreased concentration, dizziness and decreased sleep and headache .Among the newer drugs i:e in LEV group adverse effects reported were drowsiness and irritability ,increased sleep while in oxcarbamazipine group were headache irritability ,drowsiness, increased sleep and dizziness(table-6).Adverse effects are more in conventional than newer group of drugs. [29]

To our knowledge, this study evaluated the impact of specific pharmacotherapy characteristics on QOL in Patients living with epilepsy, as well as the tolerability profile of AED therapy in a naturalistic setting. The pattern of AED use did not show a significant difference in use between older and newer AEDs.
The major limitation of our study was a single centre study and its short duration.
In spite of this it can pave path for further studies which can compare newer AEDs with older AEDs for comparison of quality of life in epileptic patients which is mostly overlooked

Conclusions

Anti-epileptic treatment effectively controls seizure in patients living with epilepsy. Both the conventional and newer antiepileptic drugs were equal in efficacy in terms of seizure control, quality of life and lesser adverse effects in patients of epilepsy. Both the groups of drugs improved the in quality of life in terms of epilepsy effect, mental effects and role function effects in comparison to baseline findings. But there were no significant differences between conventional and newer group on the quality of life. There were no serious adverse events in this study in both groups.

ACKNOWLEDGEMENTS

Authors would like to thank Himalayan Institute of Medical Sciences, Dehradun to have provided the opportunity to conduct research work. We acknowledge the contribution of our colleagues in the department and also indebted to all patients who consented to participate in this study.

Support: Financial support from institution
Conflict of interest: There are no conflicts of interest.

Ethical approval: The study was approved by the InstitutionalEthics Committee, approval number SRHU/HIMS/ETHICS/2016/111

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