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Original Research Article

A comparative study of the safety, efficacy, quality of life and pharmacoeconomics of levetiracetam with controlled-release carbamazepine in patients of new onset focal seizures: A randomized controlled academic trial

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ABSTRACT

Background: Carbamazepine is used widely in focal seizures but has the disadvantage of frequent drug interactions. Levetiracetam is a novel antiseizure drug with better pharmacokinetic profile with less drug interactions and having broader therapeutic range.
Aims: The aim of our study was to generate more evidence for better management of focal seizures with available anti-seizure monotherapy.
Materials and Methods: It was a randomized, prospective, open label, comparative interventional study, conducted at Dr. R.P.G.M.C, Kangra at Tanda. 38 participants received tablet levetiracetam (LEV) 1000 mg/day and 36 participants received tablet controlled-release carbamazepine (CBZ-CR) 600 mg/day.
Results: CBZ-CR group had significantly higher CNS depression as compared to LEV (p=0.027). Hematological adverse effects with CBZ-CR were reversible. Both the drugs were safe on kidney and liver. 22 (66.7%) patients in LEV group and 26 (78.8%) in CBZ-CR group remained seizure free. QOL: Both the drugs significantly improved QOL. Pharmacoeconomics: CBZ-CR costed significantly lower than LEV (p<0.0001).
Conclusion: Both the drugs are well tolerated and equally efficacious in controlling focal seizures. Quality-of-life has improved significantly in both the groups. CBZ-CR is pharmacoeconomically better than LEV for treatment of new onset focal seizures in adult patients.

1. Introduction

A 'seizure' is brief alteration of behavior due to disordered, synchronous and rhythmic firing of brain neurons.[1] Epilepsy denotes the occurrence of recurrent, unprovoked seizures.[2] Epilepsy is diagnosed when there are recurrent seizures (defined as 2 or more unprovoked seizures occurring at least 24 hours apart) due to a chronic underlying process.[3] Focal seizure is caused by initial activation of part of one cerebral hemisphere.[2]

Nearly 1% of the world's population has epilepsy and it is the fourth most common neurological disorder after migraine, stroke and Alzheimer's disease. Several cases of epilepsy occur as a result of damage to the brain, brain tumor or developmental lesion such as a cortical or vascular malformation; these epilepsies are referred to as "symptomatic".[4] Neuro-infections, neurocysticercosis and neurotrauma along with birth injuries have emerged as major risk factors for secondary epilepsy.[5] In other cases, genetic factors are believed to be the root cause.[4]

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1.1. Incidence and prevalence

India has nearly one-sixth of the global epilepsy burden. In India the overall prevalence is 3.0 - 11.9 and incidence is 0.2 – 0.6 per 1000 population per year.[5]

Frequent seizures and polytherapy are associated with lower quality-of-life.[6]

Hence, the therapeutic goal is complete cessation of seizures, without side effects, using monotherapy and a convenient dosing schedule.

Carbamazepine was approved by the USFDA as anticonvulsant on 15 July 1974 under the brand name 'Tegretol'.[7] It is a prototype anti-seizure drug used in the treatment of focal onset seizures also.[4] It is an iminostilbene (dibenzazepine) derivative having a carbamyl group at the 5^{th} position; this provides potent anti-seizure activity.[1] It is a sodium channel-blocking drug. Its target therapeutic plasma concentration is between 6-12 microgram/ml and CNS side effects are frequently seen with plasma concentration above 9 microgram/ml. Adverse effects are drowsiness, vertigo, diplopia, blurred vision, increased seizure frequency, nausea, vomiting, aplastic anemia, agranulocytosis and hypersensitivity reactions. Late complication is retention of water, with decreased osmolality and concentration of sodium in plasma.[1]

In adults, daily maintenance dose is 800-1200 mg/day. Initial $t_{1/2}$ of 36 hours decreases to 8-12 hours due to its hepatic enzyme autoinduction.[4] Disadvantages are frequent dosing, dose related ADRs and drug interactions.[8,9]

Levetiracetam is newer anti-seizure drug with better pharmacokinetic profile, lesser drug interactions and wide therapeutic range.[8,9] Levetiracetam was approved as anticonvulsant for focal seizure in patients of 16 years or older age by the USFDA on 30 November 1999 under brand name 'Keppra'.[10]

It is the S-enantiomer of α-ethyl-2-oxo-1-pyrrolidine acetamide, and has novel mode of action by binding to synaptic vesicle protein 2A (SV2A).[10] It inhibits N-type calcium (ca^{2+}) channels and calcium release from intracellular stores. $t_{1/2}$ is 6-8 hours and adult dosing is initiated at 500-1000 mg/day. The dose may be increased every 2-4 weeks by 1000 mg to a maximum dose of 3000 mg per day based on seizure control. Adverse effects are somnolence, asthenia, ataxia, dizziness and less commonly behavioral and mood changes.[1]

2. Material and Methods

2.1. Study design and setting

The study was randomized, prospective, open label, comparative, parallel group interventional study.

The study was conducted in the Department of Neurology and Pharmacology at Dr. R.P.G.M.C, Kangra at Tanda, Himachal Pradesh, India which is a 700 bedded multispeciality tertiary health-care centre.

PRC approval vide letter no. D.No. HFW-H (DRPGMC)/Protocol/2018/45 Dated: 01/12/2018.

IEC approval vide letter no. IEC (2020)-44 Dated: 09/01/2019.

CTRI registration no. CTRI/2019/05/018990 [Registered on 08/05/2019].

Trial completed on 14/09/2020.

2.2. Study population

Adult (>18 Years old) patients of focal seizures, selected on an outpatient department basis.

2.3. Inclusion criteria

Newly diagnosed consenting adult patients of focal seizures without any other co-morbidities.

2.4. Exclusion criteria

Patients not willing to give written informed consent.

Pregnant females.

Patients already on treatment with the study drugs.

Patients of seizures others than focal seizures.

Patients of head trauma within past one month.

Patients with known contraindication or refractoriness to study drugs.

2.4.1. Study duration

11 months for the enrollment, and follow-up was done at the end of first, third and sixth month after initiating the treatment, making the total duration of study to one year and five months.

2.4.2. Study intervention

Detailed history of the patients, clinical examination and biochemical and/or radiological investigations were carried. Computerized tomography (CT) scan was obtained from 16 slice multidetector machine, model BR-16, 2007 of Philips brand. Magnetic resonance imaging (MRI) was obtained from General electric (GE) healthcare MRI machine of 1.5 Tesla strength, model Signa Excite, 2007.

The patients were informed about the study through the patient information sheet in their own language. After written informed consent, the participants were assigned to either group A or group B, based on computer generated random numbers.

Urine pregnancy test was done in women of reproductive age group to rule out the pregnancy.

Group A participants were prescribed tablet levetiracetam (LEV) 1000 mg/day per oral and group B participants received tablet controlled-release carbamazepine (CBZ-CR) 600 mg/day per oral. The dosage of drugs was titrated based upon the seizure control; LEV maximum 3000 mg/day and group B maximum CBZ-CR

1200 mg/day. The drugs in each group were given twice-daily, half-hour after the food with water.

Following baseline blood biochemical parameters were analyzed, before initiating the treatment:

1. Hemogram: Hb, TLC
2. RBS
3. Liver function tests: SGOT, SGPT, ALP
4. Renal function tests: S. creatinine
5. Serum electrolytes: S. Na+

These were repeated on follow-ups at the end of first, third and sixth month.

Patients were contacted telephonically on the next day of initiating the therapy and were enquired for any discomfort and adverse effects. Patients were counseled accordingly and were told to continue the treatment as advised and report in case of any adverse effects or breakthrough seizures.

If deemed necessary the medication was changed appropriately.

1. Safety: Adverse effects and blood biochemical parameters were considered.
2. Efficacy: Seizure freedom during six months of therapy.
3. Quality-of-life outcome: QOLIE-10-P questionnaire was used twice; at one month and at six months after initiating the treatment.
4. Pharmacoeconomics: Generic medicine price provided by "Amrit pharmacy"- a Union government of India undertaking, was considered. LEV 500 mg was available at a price of ₹87 per 10 tablets, under the brand name "Medicetam-500 MG" provided by 'EcoMed' a unit of XLRS and Ventures LLP. CBZ-CR 300 mg was available at a price of ₹18.67 per 10 tablets, under the brand name "Mazetol SR 300" provided by 'Abbott Healthcare Private Limited'.

2.5. Ethics

The investigators and supervisors are well aware of the guidelines for ethics in biomedical research by Indian council of medical research of 1994, Helsinki declaration (modified in the year 2000) and the policy of institutional ethics committee of Dr. R.P.G.M.C, Kangra at Tanda.

2.6. Statistics

The data was entered in Microsoft excel spreadsheet. Statistical analysis was done using Microsoft excel and online 'social science statistics' software.

Kolmogorov-Smirnov test of normality was used to verify normal distribution of data. Non-normally distributed data was converted to normal distribution using log10 scale and then appropriate test was used.

The quantitative data was analyzed and expressed as mean±SD and percentages.

Student's t-test was used for comparing continuous variables between the two groups.

Chi-square and Fisher's exact test was used for comparing the categorical data between the two groups.

For statistical significance p-value of less than 0.05 was taken as the criteria.

3. Results

3.1. Sociodemographic characteristics

Mean age of the patients in group A was (39.0±20.0) and in group B (32.4±12.3). 13 (39%) patients in group A and 18 (55%) patients in group B were males. 20 (61%) patients in group A and 15 (45%) in group B were females. Mean BMI in 2 groups was comparable. In group A 14 (42.4%) and in group B 12 (36.4%) patients were skilled workers. Both the groups were homogenous.

3.2. Adverse events

Treatment emergent adverse events were experienced by all the patients in both the groups at some point during the study period.

There was decrease in Hb count in CBZ-CR group at 1-month (p=0.003) as compared to that at baseline. This decrease was transient and Hb levels recovered at 3-months follow-up on continuing the treatment.

In CBZ-CR group 4 patients developed leukopenia, which was transient and reversed on continuing the treatment.[11] Table 1 shows the TLC levels observed in two groups.

1 patient developed central hypothyroidism 3-months after initiating treatment with CBZ-CR and was discontinued from the study due to change in therapy.[12]

In LEV group 1 patient was discontinued from the study due to drug-induced urticaria after 3^{rd} dose of LEV[13] and 1 due to altered behavior and agitation secondary to LEV.[14]

Random blood sugar, serum electrolytes, liver and kidney function tests remained within normal limits.

CNS depression effects like dizziness, drowsiness and somnolence were more frequent in group B (p=0.0268).

3.3. Breakthrough seizures

A total of 11 (33.3%) patients (5 males & 6 females) in group A and 7 (21.2%) patients (5 males & 2 females) in group B had breakthrough seizures during 6-months of therapy. Over 6-months of treatment, 22 (66.7%) patients in group A and 26 (78.8%) in group B remained seizure free.

3.4. Quality-of-life (QOL)

QOL has improved significantly at 6-months in comparison to that at 1-month in both the groups (p=0.0001) as depicted in Figure 1. There was no significant difference on

intergroup comparison. Lower score corresponds to better QOL.

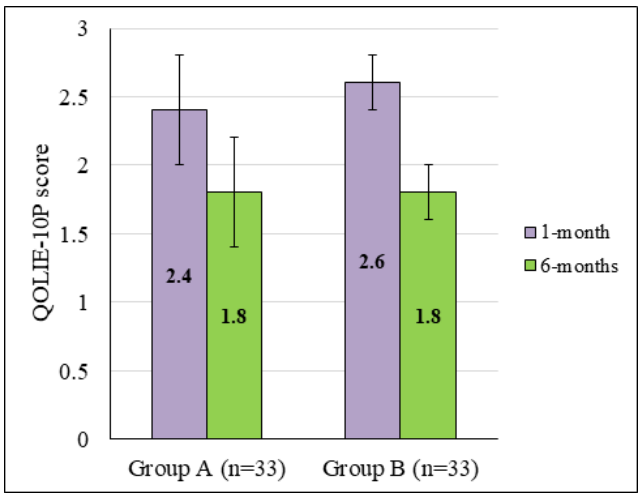

Fig. 1: Comparison of quality-of-life between two groups

3.5. Pharmacoeconomics

Over 6-months of treatment, the total cost of drug acquisition was significantly lower in group B in comparison to that in group A ($p<0.0001$) as shown in Table 2.

4. Discussion

In the present study primary objective was to compare the safety and efficacy of levetiracetam with controlled-release carbamazepine in patients of new onset focal seizures of age 18 years or above. Secondary objective was to compare quality-of-life and pharmacoeconomics between two groups.

4.1. Safety

Both the drugs are safe for liver and kidney. Hematological adverse effects with CBZ-CR were reversible.

4.2. CNS depressive effects

We found that central nervous system depressive effects such as drowsiness/dizziness/somnolence were more frequent in CBZ-CR group in 32 (97%) patients as compared to LEV group 25 (76%). This was statistically significant with p=0.0268.

Similar results were reported in studies by Pohlmann-Eden B. et al.,[15] Perry S. et al.,[16] Trinka E. et al.,[17] Consoli D. et al.,[18] Suresh SH. et al.,[19] Sharma DS. et al.[20] and Akhondian J. et al.[21]

In contrast, Brodie MJ. et al.[22] found that depression and insomnia were significantly higher in LEV group as compared to CBZ-CR group.

4.3. Headache

We reported headache in 12 (36.36%) patients in LEV group and 15 (45.45%) in CBZ-CR group. Similar results are there in studies by Brodie MJ. et al.[22] and Trinka E. et al.[17] But, Pohlmann-Eden B. et al.[8] and Consoli D. et al.[18] found that headache was more frequent in LEV treated patients.

4.4. Behavioral adverse effects

In LEV group, behavioral side effects like irritability, anxiety and agitation were found in 5 (15%) patients. 1 patient had to be discontinued from the study due to drug-induced altered behavior and agitation.[14]

Similar results were found by Brodie MJ. et al.,[22] Trinka E. et al.,[17] Suresh SH. et al.[19] and Sharma DS. et al.[20] Perry S. et al.[16] and Akhondian J. et al.,[21] reported similar results in children less than 16 years of age.

4.5. Asthenia/Easy fatiguability

We observed asthenia/easy fatiguability in 3 (9%) in LEV group only.

Studies by Pohlmann-Eden B. et al.,[8] Brodie MJ. et al.[22] and Trinka E. et al.[17] reported fatigue in patients in both the treatment groups.

4.6. Blurred vision

We found blurring of vision in 1 (3%) patient in CBZ-CR group. Similar findings were there in study by Consoli D. et al.[18]

4.7. Vertigo

Vertigo was found in 1 (3%) patient in CBZ-CR group only. Trinka E. et al.,[17] found vertigo in 16 (3.3%) patients in LEV and 25 (5%) in CBZ-CR group.

4.8. Gastrointestinal discomfort

Nausea, vomiting and epigastric pain were present in both the groups. Similar reports were found in studies by Brodie MJ. et al.,[22] Pohlmann-Eden B. et al.,[8] Trinka E. et al.,[14] Consoli D. et al.[18] and Sharma DS. et al.[20] Akhondian J. et al.,[21] reported three times transient increase in liver enzymes in 1 (4%) patient in CBZ treated children.

4.9. Skin rash

Skin rash/dermatitis was observed in 2 (6%) patients in CBZ-CR group.

One patient in LEV group developed urticarial rash after the third dose. So, LEV was discontinued and patient was dropped from the study due to change in intervention.[13]

Table 1: Comparison of total leukocyte count levels between two groups

TLC (Cells/mm^3)	LEV group (n=33)	CBZ-CR group (n=33)	p-value #
Baseline	7454.8±2219.6	7327.3±3069.1	0.847
1-month	7020.9±2357.8	5892.1±2140.5^	0.046*
3-months	6823.0±1529.0	6367.3±1390.6^	0.21
6-months	6957.6±1116.6	6500.6±1172.5	0.11
p-value# Baseline vs 1-month, 3-months, 6-months	0.262, 0.124, 0.205	0.0002, 0.022, 0.053	

#Student's t-test
^p-value=0.0002 & 0.022 on intragroup comparison in group B, baseline vs 1-month & baseline vs 3-months respectively.
*p-value=0.046 on intergroup comparison

Table 2: Comparison of cost of drug acquisition between two groups

	LEV g roup	CBZ-CR group	p-value #
Average cost of drug acquisition per patient (In ₹) during 6-months	3433.6±589.8	693.2±45.8	<0.0001

#Student's t-test

Table 3: Improvement in BMI in two groups

	Group A (n=33)	Group B (n=33)	p-value #
Baseline	22.6±4.4	21.1±4.2	0.170
1-month	22.8±4.3*	21.4±4.2^	0.184
3-months	22.8±4.4*	21.5±4.3^	0.223
6-months	22.9±4.3*	21.7±4.4^	0.263
p-value# Baseline vs 1-month, 3-months, 6-months	0.018, 0.01, 0.002	0.002, 0.0003, 0.0006	

Data expressed as mean±SD
#Student t-test
* p-value=0.018 (baseline vs 1-month), p-value=0.01 (baseline vs 3-months) and p-value=0.002 (baseline vs 6-months) on intragroup comparison in group A.
^ p-value=0.002 (baseline vs 1-month), p-value=0.0003 (baseline vs 3-months) and p-value=0.0006 (baseline vs 6-months) on intragroup comparison in group B.

Similar spectrum of skin problems was reported by Brodie MJ. et al.,[22] Pohlmann-Eden B. et al.,[8] Trinka E. et al.[17] and Consoli D. et al.[18] Akhondian J. et al.,[21] reported similar results in children less than 16 years of age.

In contrast Perry S. et al.,[16] reported rash in 1 (1.5%) patient in LEV group and no case of rash was observed in CBZ treated patients of less than 16 years of age.

4.10. Hematological side effects

We observed a decrease in Hb count in CBZ-CR group at 1-month (p=0.003) as compared to that at baseline. This decrease was transient and Hb levels recovered at 3-months follow-up on continuing the treatment. Hb levels reversed to normal with dietary interventions only.

There was a significant decrease in TLC levels in CBZ-CR group at 1-month (p=0.0002) and 3-months (p=0.022) as compared to those at baseline. Four patients in CBZ-CR group developed leukopenia within 1-month of treatment with TLC less than 4000 per mm.[3] However, the decrease in TLC was transient and this recovered gradually at 3-months follow-up on continuing the treatment.[11]

Study by Consoli D. et al.,[18] reported that 1 out of 54 patients in CBZ group developed leukopenia.

4.11. Blood biochemistry:

A patient developed central hypothyroidism 3-months after initiating treatment with CBZ-CR and was discontinued from the study due to change in therapy.[12]

Both the drugs were found safe with regard to random blood sugar, serum electrolytes, liver and kidney function tests.

This was in concurrence with the studies done by Pohlmann-Eden B. et al.,[8] Brodie MJ. et al.,[22] Perry S. et al.,[16] Trinka E. et al.[17], Consoli D. et al.,[18] Suresh SH. et al.,[19] Sharma DS. et al.[20] andAkhondian J. et al.[21]

4.12. Efficacy

During 6-months follow-up 22 (66.7%) patients in group A and 26 (78.8%) in group B were seizure free. Efficacy was comparable in the two groups.

Similar results were found by Brodie MJ. et al.[22] and Trinka E. et al.[17]using CBZ-CR and LEV.

Pohlmann-Eden B. et al.,[8] Perry S. et al., Consoli D. et al.,[18] Suresh SH. et al.[19] and Sharma DS. et al.[20] found similar results using LEV and CBZ standard preparation.

Akhondian J. et al.[21] found LEV better than CBZ standard preparation in treating focal seizures in children less than 16 years of age.

Powell G. et al.[23] (2016) in their review article concluded that only 1 of 10 studies found that slow-release preparation is significantly better than standard/immediate release preparation in controlling the number of seizures experienced. Although, in most studies slow-release carbamazepine tended to be clinically superior to standard/fast-release drug. Patients taking slow-release carbamazepine tended to experience fewer side effects.

4.13. Quality-of-Life (QOL)

4.13.1. BMI

We observed a statistically significant increase in BMI in both the groups at 1-month, 3-months and 6-months as compared to that of baseline. This increase may be attributed to improvement in QOL subsequent to drug monotherapy. Table 3 shows BMI levels in two groups.

Similarly, studies by Pohlmann-Eden B. et al.,[8] Trinka E. et al.[17] and Sharma DS. et al.[19] reported weight gain in both the treatment groups.

In contrast Brodie MJ. et al.,[22] reported that more patients gained weight in CBZ-CR group compared to LEV group ($p<0.038$) whereas, in study done by Suresh SH. et al.,[19] 2 patients in LEV group gained weight.

4.13.2. QOLIE-10P score

Mean QOL at 1-month after initiating treatment was 2.4±0.4 and 2.6±0.4 in group A and group B respectively. The QOL improved significantly to 1.8±0.2 in both the groups at 6-months ($p=0.0001$).

In KOMET trial QOL was compared using QOLIE-31 scale and no difference were found between LEV and CBZ.[17]

Suresh SH. et al.[19] and Sharma DS. et al.,[20] reported that LEV demonstrated significantly better QOL as compared to that in CBZ group.

Thomas SV. et al.,[7] in their study reported that patients on monotherapy have a significant better QOL as compared to those receiving polytherapy for seizure prophylaxis.[7]

4.13.3. Pharmacoeconomics

Over the period of 6-months treatment, 11 patients in group A and 7 in group B had one or more breakthrough seizures for which the dose was escalated for seizure control and prophylaxis. Total cost of the generic medicines procured in both the groups during 6-months period was considered. It was found that therapy to group A patient costed ₹3433.6±589.8 and in group B ₹693.2±45.8 ($p<0.0001$).

Assuming both the treatments pharmacologically equivalent, LEV costed ₹90427 more than CBZ-CR for 6-months therapy in 33 patients in each treatment arm.

No other studies compared cost of these two anti-epileptic drugs.

5. Conclusion

Cautious monitoring and patient education regarding adverse events are of paramount importance, after starting therapy with any drug. Keeping in mind the possibility of drug induced leukopenia, it is imperative to investigate complete blood counts before initiating CBZ therapy and follow-up regularly. Patients with pre-existing leukopenia should not be treated with CBZ.

6. Financial Disclosure

No Funding.

7. Conflict of Interest

No conflict of interest pertaining to any part of the study.

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