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Research Paper

A Comparative Study of Carbamazepine, Valproic Acid and Levetiracetam in Treatment of Patients with Generalised Tonic Clonic Seizures in Department of Neurology, Gauhati Medical College and Hospital

Pharmacy

KEYWORDS : Seizures, Carbamazepine, Valproic acid, Levetiracetam

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ABSTRACT

Objectives: To study the efficacy and safety of Levetiracetam in comparison with Carbamazepine and Valproic acid in treatment of patients with generalised tonic clonic seizures. Methodology: It was a hospital based prospective and open labelled study. Group A included 31 patients who received carbamazepine, Group B included30 patients who received valproic acid and Group C included 29 patients who received levetiracetam. Each patient was followed up for six months. Results: All three drug treated patients showed significant reduction within treatment groups in the mean seizure counts($p<0.0001$). The mean time to first seizure after initiation of treatment was less in patients receiving levetiracetam (10.55 weeks) as compared to those receiving carbamazepine (14weeks) or valproic acid (13.8 weeks). Adverse effects caused by levetiracetam were relatively lower.None of the adverse events were severe enough to demand withdrawal from treatment. Conclusion: Levetiracetam is equally effective like carbamazepine or valproic acid in generalised tonic clonic seizures with fewer adverse effects.

INTRODUCTION

A seizure is a paroxysmal event due to abnormal excessive or synchronous neuronal activity in the brain.[1] Generalized tonic clonic seizures are the main seizure type in nearly 10 % of all persons with epilepsy and are frequently encountered in many different clinical settings.[1] Approximately 1% of the world's population has epilepsy, the second most common neurological disorder after stroke.[2] In India , prevalence rate per 1000 is 4.[3]

Carbamazepine was initially approved in the U.S. for use as an antiseizure agent in 1974.[4] Carbamazepine blocks sodium channels and inhibits high frequency repetitive firing in neurons. It also acts presynaptically to decrease synaptic transmission.[2,5] It is one of the standard treatments for newly diagnosed tonic clonic seizures.[5]

Valproic acid is one of the drug of choice in primary generalized tonic clonic seizures.[6] It causes prolonged recovery of voltage activated sodium channels from inactivation.[4]

Levetiracetam is approved for adjunctive therapy for generalized tonic clonic seizures in adults and children as young as 4years old.[4] It enriches synaptic vesicles in the brain by binding with synaptic vesicle protein SV2A.[7]

It is approved as adjunctive therapy for primary generalized tonic-clonic seizures and a recent comparative monotherapy trial earned it approval for use as initial monotherapy in the European Union.[8]

The treatment of epilepsy should always begin with monotherapy. In common practice if the first drug is not tolerated or if it is totally ineffective, alternative monotherapy is the best approach.[8] Compared with the partial epilepsy, the comparative effects of antiepileptic drugs for patients with generalized onset seizures are poorly studied.[9]

With several antiepileptic drugs to choose between, it is essential to evaluate the effectiveness of these drugs against each other in the best possible way. This study is therefore, intended to compare the efficacy and safety of carbamazepine, valproic acid and levetiracetam in patients with generalised tonic, clonic seizures.

MATERIALS AND METHODS

It is a hospital based prospective and open labelled study conducted within a study period of one year. Study protocol was approved by the Institutional Ethics Committee, No. MC/108/2012/62 , dated 12-09-2012.

Informed consent was taken before enrolling the patients into the study. The patients were assigned into three groups. Patients were assessed at base line and during treatment at the end of 2 months and after 6 months of initiation of therapy. During this time, they maintained seizure diaries. Measures of efficacy were the time of the first seizure after start of treatment and proportions of patients who remained seizure free till six months of treatment.

Inclusion criteria :

- Age ≥ 15years
- History of minimum two or more generalized tonic clonic seizures.
- Patients of either sexes.

Exclusion criteria :

- Other seizure types.
- Drug or alcohol induced seizure
- Clinical or other evidence of progressive neurological disease.
- Pregnant or lactating mothers.

Study medication and treatment groups:

Group A : Carbamazepine was given orally 15 mg/kg body weight in 2-3 divided doses.

Group B : Valproic acid was given orally 15 mg/kg bodyweight per day in three divided doses.

Group C : Levetiracetam was given orally 20 mg/kg body weight per day in two divided doses.

RESULTS

The following tables illustrate the results of this study:

Table 1. Comparison of Baseline characteristics between groups

	Group A (n = 31)	GroupB (n= 30)	Group C (n = 29)	p value
Age (years) Mean ± SD	34.55±12.05	29±11.70	32.27±13.02	0.213
Median(IQR_{25-75})	35(30.12 – 38.9)	26.5 (24.6-33.4)	28 (27.3-37.2)	

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Sex Male Female	17 14	20 10	19 10	0.576
Weight (Kg) Mean ±SD Median (IQR_{25-75})	58.45±9.56 58(54.95-61.96)	57.16±9.87 58(53.48-60.85)	57.34±9.18 56(53.85-60.84)	0.850

*SD = Standard deviation; IQR = interquartile range, n = sample size. p value is obtained by intergroup comparison by ANOVA for age and weight. Chi square test followed by ANOVA was performed for sex.($p<0.05$ is considered significant)

The majority of the patients belonged to the age group of 25-44 years and were males. The male- female ratio is 1.7 : 1. The mean body weight was 58.45 kg in those who received carbamazepine, 57.16 kg in those who received valproic acid and 57.34 kg in those who received levetiracetam.

TABLE 2. Age distribution of the patients

Age	Group A	Group B	Group C	Total
16 – 24 years	8	13	11	32
25-44 years	16	12	10	38
>45 years	7	5	8	20

TABLE 3. Seizure counts at 0 month and after 6 months of initiation of therapy in Group A, Group B and Group C:

		0 month Mean ± SD	6 month Mean ± SD	p value
Group A n = 31	No. of seizures Median (IQR_{25-75})	4.77±3.17 5(3.61-5.94)	0.90±1.51	< 0.05
Group B n = 30	No. of seizures Median (IQR_{25-75})	5.77±3.66 5.5(4.39-7.13)	0.9±1.52	< 0.05
Group C n = 29	No. of seizures Median (IQR_{25-75})	5.48±3.92 4(3.99-6.97)	0.96±1.40	< 0.05

*p value was obtained by within the group comparison using Paired Student's t-test, $p < 0.05$ shows significant.

The mean seizure counts before initiation of treatment (at 0 month) were 4.77 in group A, 5.77 in group B and 5.48 in group C. At six months the mean seizure counts were 0.90 in group A, 0.90 in group B and 0.96 in group C showing that each of the drugs was efficacious in controlling the frequency of seizures.

TABLE 4. Comparison between Group A, Group B and Group C

	Group A	Group B	Group C	
No. of seizures at 0 months (Mean±SD)	4.77±3.17	5.77±3.66	5.48±3.92	p = 0.540; d,f (2, 87); F = 0.619
No. of seizures at 6 months (Mean±SD)	0.90±1.51	0.9±1.52	0.96±1.40	p = 0.982; d,f (2, 87); F = 0.018

**p* value obtained by comparing seizure numbers in the three groups by ANOVA.

There was no significant difference in decreasing the overall seizure frequency in either of the three drugs.

Table 5. Comparison of patients in the three groups at end of 6 months

	Group A	Group B	Group C	
Seizure free patients	21	20	18	p = 0.88
Patients with seizures	10	10	11	

*Chi-square test, $p > 0.05$ is considered not significant.

The number of patients who remained seizure free at six months were 21 in group A, 20 in group B and 18 in group C. On comparing the three groups there was statistically no significant difference found in the number of patients who remained seizure free (p = 0.88) .

Table 6. The time to the first seizure after initiation of treatment

Time (weeks)	Group A	Group B	Group C
Mean ± SD	14±5.07	13.8±4.37	10.55±3.7
Median (IQR_{25-75})	14(10.37-17.63)	14(10.68-16.92)	12(8.06-13.03)

*p value is obtained by intergroup comparison by ANOVA ; p = 0.144; d,f (2, 28) F = 2.074 ($p > 0.05$ is considered not significant)

TABLE 7. Table showing comparison of weights of patients at 0 months and after 6 months

	Weight (kg) at 0 months Mean±SD	Weight (kg) at 6 months Mean±SD	*p* value
Group A	58.45±9.56	58.97±8.94	0.0692
Group B	57.16±9.87	57.83±8.97	0.1247
Group C	57.34±9.18	57.65±9.27	0.4025

*p value is obtained by within the group comparison using Paired-T Test .$p > 0.05$ is considered not significant.

There was no significant difference in the weight of the patients at 0 months and after 6 months of treatment.

Table 8. Number of patients with adverse events at any time during the treatment.

	Group A	**Group B**	**Group C**
Nausea	5	2	3
Dizziness	2	1	0
Headache	6	4	4
Sleepiness	3	1	3

The most common adverse effects seen with carbamazepine were headache in 6 patients, nausea in 5 patients, sleepiness in 3 patients and dizziness in 2 patients. The adverse effects seen with valproic acid were headache in 4 patients, nausea in 2 patients, dizziness in 1 patient and sleepiness in 1 patient. The adverse effects related to levetiracetam were headache in 4 patients, nausea in 3 patients and sleepiness in 3 patients. None of the adverse effects were severe and hence treatment was continued in the patients.

DISCUSSION

In this study most of the patients were male i.e. 58 patients and the number of female patients were 34. Neligan A and Sander L[32(10)] in 2011 had also found the incidence of epilepsy to be

more in males as compared to females.

The mean age of the patients receiving carbamazepine, valproic acid and levetiracetam were 34.55 yrs, 29 yrs and 32.27 yrs ,respectively. There was statistically no significant difference in age of the patients between the three groups.

The mean weight of the patients in group A, group B and group C were 58.45 kg, 57.16 kg and 57.34 kg, respectively. There was no statistically significant difference present at the baseline demographic profile between the groups in age (p = 0.213), sex (p = 0.576) and weight (p = 0.850) parameters.

Seizure counts:

The average seizure counts at the time of enrollment were 4.77, 5.77 and 5.48 in patients receiving carbamazepine, valproic acid and levetiracetam, respectively. Whereas the average seizure counts at the end of the study period were 0.90, 0.90 and 0.96 in carbamazepine, valproic acid and levetiracetam groups, respectively.

There was statistically no significant difference in decreasing the overall seizure frequency among the three drugs. It was found that the efficacy of levetiracetam in decreasing the number of seizures was statistically similar to carbamazepine and valproic acid (p = 0.982). Mattson RH et. al. in 1992[141(11)] and Heller AJ et. al. in 1995[142(12)] in their study had found that the efficacy of carbamazepine and valproic acid are similar in controlling the number of seizures. Cosoli D et. al.[143(13)] in their study in 2012 found that levetiracetam was equally efficacious in adults in controlling seizures. The finding in our study correlates with the findings of the above mentioned studies.

At the end of six months of initiating treatment 21 patients who received carbamazepine, 20 patients who received valproic acid and 18 patients who received levetiracetam were seizure free during the entire period of study. However, there was statistically no significant difference in the number of patients who remained seizure free among the three groups (p = 0.88).

The mean time to first seizure after initiation of treatment was less in patients receiving levetiracetam (10.55 weeks) as compared to those receiving carbamazepine (14 weeks) or valproic acid (13.8 weeks). Thus, patients who were on levetiracetam treatment had earlier relapse of seizure as compared to carbamazepine or valproic acid group. However, this difference was statistically found to be insignificant (p > 0.05).

Among patients who received carbamazepine , 6 patients complained of headache , 5 patients complained of nausea, 3 patients complained of sleepiness and 2 patients complained of dizziness.

Adverse effects caused by valproic acid and levetiracetam were relatively lower than carbamazepine. With valproic acid 4 patients complained of headache, 2 patients had nausea, 1 patient complained of dizziness and 1 patient complained of sleepiness.With patients receiving levetiracetam 4 had headache, 3 had nausea and 3 had sleepiness. Callaghan N et.al. in 1978[144(14)] found drowsiness as a side effect of carbamazepine but required only reduction of its dose. The incidence of drowsiness, sedation or headache was more with carbamazepine.

Alsaadi TM et. al. in 2005[125(15)] had found that levetiracetam monotherapy was associated with fewer side effects. Privitera M[146(16)] in a review in 2001 found that levetiracetam was generally well tolerated and most common side effects associated with it were CNS disturbance such as somnolence, asthenia and dizziness.

In our study no significant increase in weight gain was observed with either carbamazepine or valproic acid, but other adverse effects were more in patients receiving carbamazepine as compared to those who received either valproic acid or levetiracetam.

Overall 12 patients who received carbamazepine, 5 who received valproic acid and 8 patients who received levetiracetam complained of adverse events. Some of the patients showed more than one adverse effect.

However, none of the adverse events were severe enough to demand withdrawal from treatment.

CONCLUSION

This study revealed that carbamazepine, valproic acid and levetiracetam were equally effective in controlling the seizures in patients with GTCS. Though adverse events were reported more in patients who received carbamazepine as compared to those who received valproic acid or levetiracetam, they were not severe in intensity and hence the treatment was continued. We have asked all the patients to continue the treatment and come for follow up at regular intervals and also to report any adverse event as soon as possible.

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