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Original Research Paper

A COMPARATIVE STUDY OF EFFICACY OF COMBINATION OF VALPROIC ACID PLUS LAMOTRIGINE VERSUS CARBAMAZEPINE PLUS LAMOTRIGINE IN DIFFICULT- TO-TREAT CASES OF SECONDARILY GENERALISED TONIC-CLONIC EPILEPSY AT A TERTIARY CARE TEACHING HOSPITAL

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ABSTRACT

The epilepsies are common and frequently devastating disorders .Approximately 1% of the world population has epilepsy . Treatment part of difficult-to-cases of secondarily generalized tonic-clonic epilepsy is difficult. Our objective in this study was to assess the efficacy of combination of valproic acid plus lamotrigine v^{s} carbamazepine plus lamotrigine in secondarily generalized tonic-clonic seizure. In our study two groups of patients are recruited randomly, from the Neurology Out Patient Department (OPD), Burdwan Medical College, Burdwan, West Bengal, India. In 1st group, there was 35 patients of taking Valproic acid, and in the 2nd group 31 patients taking carbamazepine at their maximum doses. Lamotrigine was combined in both groups for one year. Efficacy was assessed in three parameters as per as guidelines laid down by Dodson,1997 , (a) percentage of seizure reduction from the base line, (b) percentage of patients rendered seizure free, meaning 100% reduction of seizure frequency, (c) 50% responder rate, meaning fraction of patients having at least 50% or greater reduction of seizure frequency from baseline. In our study , in the 1st group, 50% reduction rate was 57.14%, 14.28% of patients rendered seizure free, and among 42.86% of patients reduction of seizure frequency was less than 50%, where as in the 2nd group, 50% reduction rate was 38.709%, 12.903% of patients rendered seizure free, and among 61.290% of patients reduction of seizure frequency was less than 50%. Conclusion of this study was 1st group was more efficacious than the 2nd group regarding the treatment of such difficult-to-treat cases.

Key words: : Epilepsy, Seizure, Difficult-to-treat cases, Refractory seizure, Lamotrigine

INTRODUCTION

The epilepsies are common and frequently devastating disorders [1].Approximately 1% of the world population has epilepsy [2, 3]. Epilepsy is the second most common neurological disorder after stroke [2]. The average prevalence rate of epilepsy reported

from the epidemiological study from all over the world is 18.5 per 1000 for children and for adult 10.3 per 1000. The incidence rate is 20-70 per 100000 [5]. But prevalence and incidence rate of the developing countries are higher than those from the developed countries due to the fact that populations in the developing world are younger, have poorer medical facilities, poorer general health and lower standard of living [5]. In 65%-70% of the total cases, the age of onset of the first seizure is before the age of 20 years [6], and 2/3rd of all epileptic seizures begin in childhood [7].

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Epileptic seizure is a clinical manifestation consisting of sudden and transitory abnormal phenomena, which may include alteration of consciousness, motor, sensory, autonomic or psychic events; perceived by the patients or an observer [International League Against Epilepsy (ILAE), Commission report published in Epilepsia, 1993].

Epilepsy is treatable condition characterized by and defined as the occurrence of repeated unprovoked seizures [8]. According to ILAE, the most common one is secondarily generalized tonic-clonic seizure. Operationally, epilepsy has been considered as two or more unprovoked seizures- occurring at least 24 hours apart [ILAE Commission report published in Epilepsia 1993]. Thus, the patient who present with an isolated first unprovoked seizure or cluster of seizures within 24 hours , does not yet qualify for the diagnosis of epilepsy [8].In patients coming to medical attention with a first unprovoked seizure, the risk of recurrence has been reported to range from 23% to 71% [9] and the overall risk of recurrence after a recognized first unprovoked seizure is about 38% after 2 years [8], and after the second seizure, the risk of relapse increases to 79% -96% [10]. Berg et al, in 1996 defined " Well-Controlled-Epilepsy" as having achieved at least one seizure free year if seizure immediately ceased once treatment began and a two year seizure free period if remission did not began immediately after treatment was instituted [11].

So epilepsy treatment is an important task. Antiepileptic drugs are the primary form of treatment of seizure and epilepsy as they can suppress the occurrence of unprovoked seizure and can also abort ongoing prolonged seizure, though antiepileptic drug does not alter the long term prognosis [12].

About 70% - 80% of patients developing epilepsy may expect to be rendered seizure free with antiepileptic drugs [13]. Approximately 80% of the patients who benefit from antiepileptic drug therapy will be controlled with a single drug and 10% - 15% with a combination of two antiepileptic drugs [14, 15, 16]. So 56% to 64% of epileptic patients become easily controlled with single drug and 7% to 12% of epileptic patients become controlled with two antiepileptic drugs.

Though actually there is no uniformly accepted definition of refractory epilepsy, or intractable epilepsy or resistant epilepsy or difficult-to-treat epilepsy and the criteria for such a diagnosis vary considerably [17], but it is defined by several ways. Lowenstein in 2001 observed that approximately 1/3rd of epileptic patients do not respond to single drug and they constitute the refractory epilepsy and need combination therapy [18]. Radhakrishnan in 1999 defined "refractory epilepsy" as patients with uncontrolled seizures or those who develop intolerable side effects that interfere with their quality of life, despite maximally tolerated trials of one or more antiepileptic drugs [13]. Aicardi and Shorovon in 1997 mentioned that a strict definition of medically intractable epilepsy would imply that all therapeutic attempts with single or combined drugs have failed for a sufficient period of time [17]. But such strict numerical definition of intractable epilepsy does provide a certain logical frame work for research purposes for framing inclusion criteria, but is often of little use in the individual patient [19]. So a recent excellent suggestion is given by Shorvon in 2000 , is to define intractability by the number of ineffective drugs tried; thus second level intractability is defined as the failure of two drugs, third level intractability by the failure of three drugs and so on [20]. So from all these discussions, it becomes clear that

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intractable epilepsies have two poles – in one pole it is strictly intractable i.e. seizure remains uncontrolled for many years despite all therapeutic attempts with single or combined drugs [17, 21, 22] and in the pole seizure remains uncontrolled to treatment with one or more primary drugs at maximal clinically tolerable doses [18, 20].

Cases of these two poles are very difficult to treat or control. So difficult to treat or difficult to control cases of epilepsy includes all these patients of two poles. For this reason, the terminology of difficult to treat cases of epilepsy, intractable epilepsy and resistance epilepsy are sometimes used interchangely [17].

But according to Hauser in 1993, not more than 5% to 10% are truly strictly intractable and so a substantial portion of patients do not actually have strict intractable epilepsy.

These portions of difficult to treat epileptic patients are included in our study as they are responsive to combination of drugs [18, 23].

But in Lowenstein in 2008 stated that though there is no guideline for combination therapy , but in most cases the initial combination therapy combines 1st line drugs i.e. valproic acid, carbamazepine, phenytoin, lamotrigine.

In this scenario previous many studies on difficult to treat cases of epilepsy, shown various results [24, 25, 20] and need further study in this area, especially in this part of the world, Burdwan Medical College, Burdwan, West Bengal, India, where there is no previous such data. In this perspective we choose such study to assess the efficacy of combination of valproic acid plus lamotrigine vs carbamazepine plus lamotrigine among the difficult to treat cases of secondarily generalized tonic-clonic epileptic patients.

MATERIALS AND METHODS:

Patients: The study was conducted as out-patient basis in a tertiary care teaching medical college and hospital,Burdwan Medical College ,West Bengal, India, from February 2011 to January 2012. The study was approved by the hospital's ethical committee and written informed consent was obtained from each patient.

Inclusion Criteria: Two groups of difficult–to–treat types of secondarily generalized tonic-clonic epileptic patients are recruited those remaining uncontrolled despite taking the maximum clinically tolerated daily doses of valproic acid and in the 2nd groups of patients taking maximum tolerated doses of carbamazepine. In the 1st group total patients was 35 in number and in the 2nd group total patients was 32 in number. Patients of both sexes were included, and ages of them were between 4.4 years to 41.5 years. Efficacy was assessed in three parameters as per as guidelines laid down by Dodson,1997 [4]

Exclusion Criteria: a) patients below 2 years of age b) presence of liver disease, renal disease, progressive neurological diseases and other chronic medical disorders c) presence of pregnancy d) severe mental abnormalities e) history of alcohol or drug abuse and f) seizures related to drugs, acute medical illness, any structural C.N.S. lesion, neurocysticercosis, or encephalopathies. Before study all the patients are evaluated properly. The recruited patients were taking either valproic acid in the 1st group or taking carbamazepine in the 2nd group.

Study design: Our study was unblinded open level study to assess the efficacy of combination of valproic acid plus lamotrigine versus combination of carbamazepine plus lamotrigine.

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Drug Administration: As the principal adverse drug reaction of lamotrigine is drug rash, cautiously dose of lamotrigine was escalated as per as the following recommended schedule by Binnie and Matsuo [24, 26].

Table 1: Doses of Lamotrigine are as followed:

	Adults (mg/day)		Children(mg/day)	
	Carbamazepine only	**Valproic acid only**	**Carbamazepine only**	**Valproic acid only**
Weeks 1st and 2nd	**50**	**12.5**	**2**	**0.2**
Weeks 3rd and 4th	**100**	**25**	**5**	**0.5**
Maintenance dose:	**200-400**	**100-200**	**5-15**	**1-5**

So after combining lamotrigine the study groups of patients were 2 in number, in the 1st group valproic acid +lamotrigine and in the 2nd group carbamazepine+lamotrigine.

Follow up: The patients were followed up accordingly for the duration of one year.

Assessment of Efficacy: Efficacy was measured by the following parameters as laid down by Dodson.

(a) **Percentage of seizure reduction from the baseline period:** it is the percentage of reduction of seizure frequency from the baseline (seizure per month).It may be more than 0% but less than 100% , meaning some reduction of seizure frequency but not 100%.

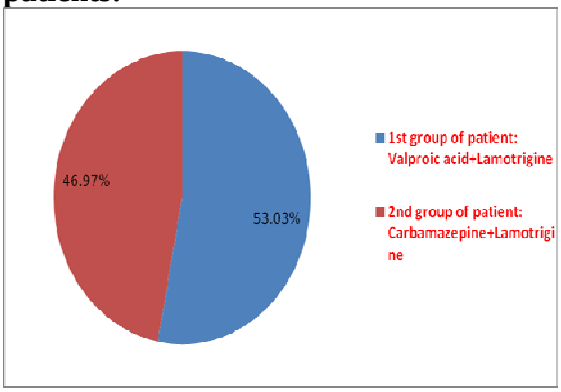
(b) **Percentage of patients rendered seizure free:** it means 100% reduction of seizure frequency.

(c) **50% Responder rate:** it means patients who had a 50% or greater reduction of seizure frequency.

RESULTS

Total number of difficult-to-treat type of secondarily generalized tonic-clonic epileptic patients selected in our study was 66, as randomly. Out of that in the 1st group it was 35 in number (53.030%) and in the 2nd group it was 31 in number (46.969%).Distribution of patients as shown in the Figure no. 1.

Figure no 1. Showing distribution of patients:



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Out of the total 66 patients, male was 36 (54.545%) and female was 30 (45.454%). Age range was 4.4 – 41.5 years (17.0± 7.13),mean±s.d.

Distribution of patients according to age of onset of epilepsy was given in table 2.

Table 2: Distribution of patients according to age of onset of epilepsy

Age of onset of seizure	Number of patients	%
Less than or = to 5 years	**23**	**34.85%**
6 - 10 years	**16**	**24.24%**
11- 15 years	**25**	**37.88%**
16 – 20 years	**2**	**3.03%**
Total	**66**	**100.00%**

Distributions of patients according to onset of seizure are shown in **Figure no 2.**

Figure 2: Distribution of patients according to age of onset of seizure.

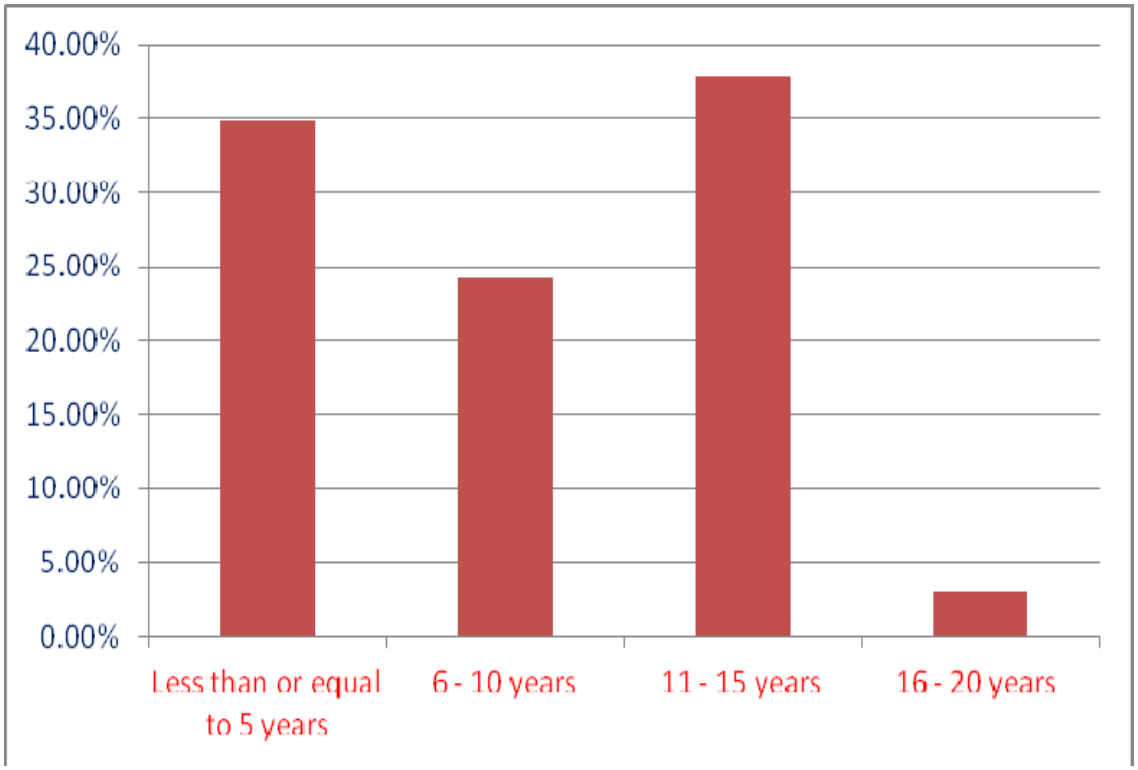

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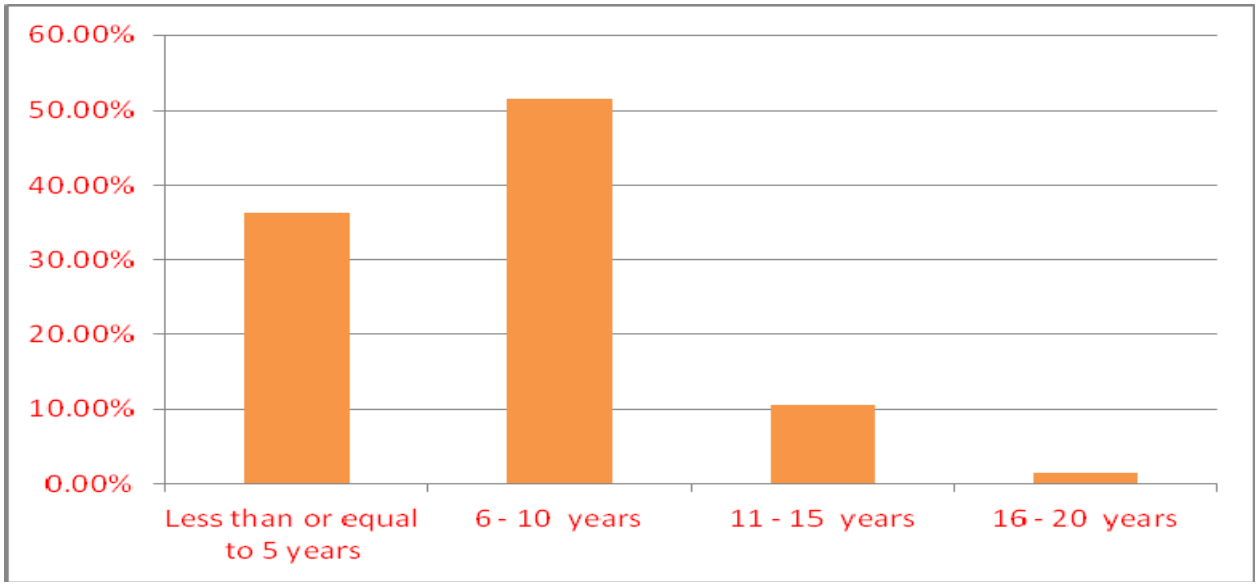
Table 3. Distributions of patients according to the duration of seizure are shown in

Duration of seizures (years)	Number of patients	%
Less than or = to 5 years	24	36.36%
6 - 10 years	34	51.52%
11- 15 years	7	10.60%
16 – 20 years	1	1.52%
Total	66	100.00%

Figure 3: showing distribution of patients according to duration of seizure.



In our study out of the 35 difficult- to - treat type of secondarily generalized tonic-clonic epileptic patients taking Valproic acid plus Lamotrigine , and categorized as Group 1. And 31 of such type of patients taking Carbamazepine plus Lamotrigine, and categorized as Group 2.

Among the Group 1 Patients , 50% responder rate was 57.14%, 14.28% of patients was rendered seizure free ,i.e. 100% reduction of seizure frequency, and the patients having more than 50% reduction but less than 100% reduction of seizure frequency was among 42.86% of patients.

Among the Group 2 Patients , 50% responder rate was 38.709%, 12.903% of patients rendered seizure free, i.e. 100% reduction of seizure frequency, and the patients having more than 50% reduction but

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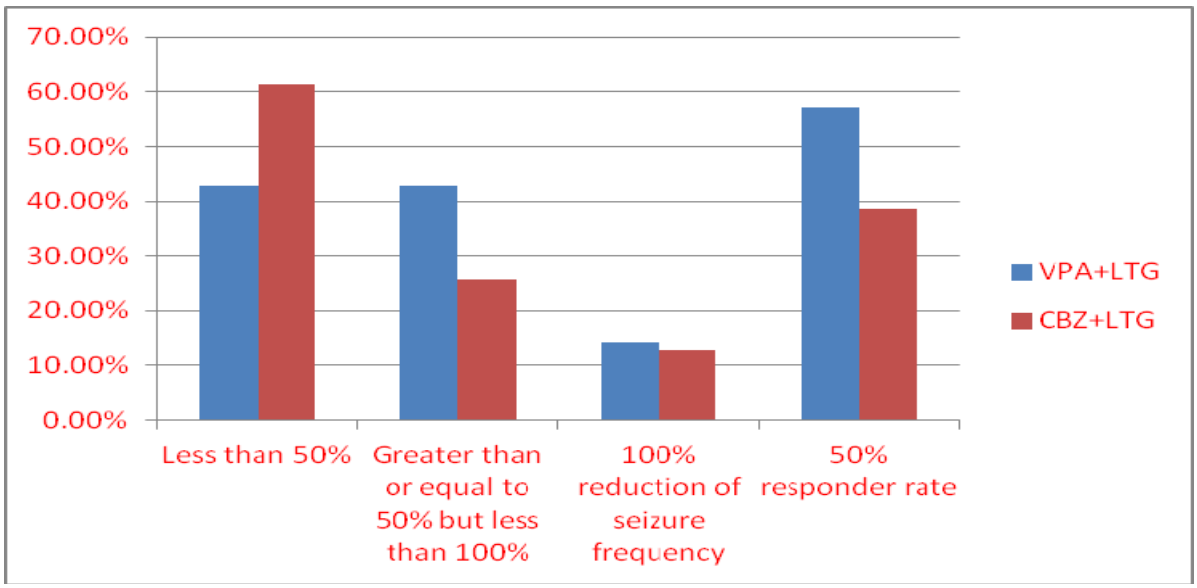
less than 100% reduction of seizure frequency was among 25.806% of patients. The response rate are of the two drug group shown in Table no.4. In 1st group= Valproic acid (VPA) +Lamotrigine (LTG), 2nd group= Carbamazepine (CBZ) +Lamotrigine (LTG).

Table 4 . Showing the distribution of response rate among the two drug groups.

Drugs groups	No of patients	% reduction of seizure frequency						50% responder rate	
		Less than 50%reduction of seizure frequency		Greater than or equal to 50% but less than 100%reduction		100% reduction of seizure frequency			
		No	%	No	%	No	%	No	%
VPA+LTG	35	15	42.86	15	42.86	5	14.28	20	57.14
CBZ+LTG	31	19	61.29	8	25.806	4	12.903	12	38.709

Figure 4. Showing the distribution of response rate among the two groups of drugs



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DISCUSSION

In our study there were total 66 patients .In the 1st group 35 patients, and in the 2nd group 31 patients. All the patients were difficult-to-treat type of secondarily generalized tonic-clonic epilepsy.

Difficult-to-treat or difficult-to-control cases of epilepsy comprise all the cases of intractable epilepsy [17]. But intractable cases of epilepsy comprise two groups of patients. In one group, it is strictly intractable, i.e. seizure remains uncontrolled for years despite all therapeutic attempt with single or combined drugs [17.21,22] and in the other group patients remained uncontrolled to treatment with one or more primary drugs at maximal clinically tolerated doses [18, 20, 27].

This last group comprises the maximum number of patients among difficult-to-treat cases. The first group of patients responsible for 5%-10% of all patients of difficult-to-treat cases of epilepsy according to Hauser [28], and they are the domain of surgical treatment [19, 20].

So we included the last group of patients in our study, as they are responsive to combination of drugs [18, 23]. Lowenstein observed that approximately 1/3rd of epileptic patients do not respond to single drug and they constitute the refractory cases and need combination therapy to control the epilepsy and he also stated that though there is no guideline, but in most cases initial combination therapy combines 1st line drugs [18]. Schmidt and Richter reported that only 30% of patients resistant to one of the 1st line antiepileptic drugs benefited from the addition of a second 1st line drug [29]. Following this guideline, we combined lamotrigine in patients taking either valproic acid or carbamazepine and remain uncontrolled for long time, to assess the efficacy.

There were varying results of so many studies with respect to 50% responder rate, percentage of reduction of seizure frequency and other efficacy measures. Shorvon has stated the results of 10 pivotal efficacy studies of lamotrigine in difficult-to-treat cases secondarily generalized tonic-clonic epilepsy. 50% responder rate was between 7% to 67% and total decrease in seizure frequency was between 17% to 59% [20]. Perucca published a pooled result of an open-level non-blined multicentric efficacy study on lamotrigine [25]. Almost similar type of study conducted by Brodie [30]. The overall 50% responder rate was 47% and 10% achieving total control of epilepsy.

In our study 50% responder rate, after combining lamotrigine to valproic acid, was 57.14% and 14.28% achieved total 100% reduction of seizure frequency. 50% responder rate, after combining lamotrigine to carbamazepine, was 38.709% and 12.903% of such patients rendered complete 100% reduction of seizure frequency.

This results tally with previous study of Brodie and Yuen [31]. They published a result of a non-randomized multicentric study in which lamotrigine was combined to treatment of resistant secondarily generalized tonic-clonic epileptic patients who were taking either valproic acid or carbamazepine. 50% responder rate was 64%, when lamotrigine was combined with valproic acid and when lamotrigine was combined with carbamazepine, 50% responder was 41%.

50% responder rate was better in the lamotrigine plus valproic acid group, even in our study. The result was interpreted to reveal synergism between lamotrigine and valproic acid, both at the pharmacodynamic and pharmacokinetic levels [26].

Our study design was uncontrolled open level. Although for evaluating the efficacy of antiepileptic drugs randomized double blined placebo controlled studies are more reliable, open level studies can also provide helpful information [4]. Moreover

several investigators performed unblined open level study to demonstrate the efficacy of combination of lamotrigine plus valproic acid and combination of lamotrigine plus carbamazepine in difficult-to-treat type of secondarily generalized tonic-clonic epilepsy [24, 25, 26, 30].

Treatment duration in our study was one year. It is a small period. But Aicardi and Shorvon in 1997, stated that the efficacy of target drugs should be assessed during a sufficient period of time and as a rule of thumb it is usual to assess the effectiveness of a drug during a period that would be expected to encompass three to five seizures or clusters of seizures or for at least two months, whichever is longer [17]. Also several investigators conducted short term period study, 8 weeks to 12 weeks [27, 29, 30]. In this perspective our study duration was not too short.

In our study patients below 2 years of age was excluded because (1) lamotrigine is not recommended for use below 2 years [24, 26], (2) Optimum time period for intractability is 2 years as per as the definition by Berge, et.al [11], (3) Well controlled epilepsy is stamped when there is seizure free period for at least 2 years [11], and in practice it is reasonable to consider epilepsy to have ceased if 2-5 years have passed since last attack, though the period of time to define intractability and well-controlled was varied in different studies [20].

CONCLUSION

From this study it is obvious that 50% responder rate was 57.14% and 14.28% of patients rendered seizure free, when lamotrigine was combined with valproic acid, and when lamotrigine was combined with carbamazepine, 50% responder rate was 38.709% and 12.903% of patients rendered seizure free. So combination of lamotrigine plus valproic acid was more efficacious than combination of carbamazepine plus lamotrigine in difficult-to-treat type of secondarily generalized tonic-clonic epilepsy, in this part of the country, Burdwan, West Bengal, India.

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