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Evaluation of efficacy and safety of clobazam as an add-on drug in the treatment of generalized tonic-clonic seizure not controlled with valproic acid monotherapy

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Abstract:

BACKGROUND: Epilepsy is one of the major neuron-damaging neurological disorders. Generalized tonic-clonic seizure (GTCS) is the commonest one. Refractory patterns cannot be controlled by simple monotherapy with antiepileptic drugs (AEDs). Valproic acid (VPA) is one of the widely prescribed AEDs but it may not control many cases up to its maximum tolerable doses. In this study, we have seen the safety and efficacy of clobazam to control seizure in the adult population as an add-on drug over valproate, in cases of valproate uncontrolled seizures.

MATERIALS AND METHODS: Patients on VPA monotherapy but not responding to it were recruited after applying inclusion and exclusion criteria and clobazam was added. There were two follow-ups at the interval of 6 months each. Seizure frequency and quality of life inventory in epilepsy-31 items (QOLIE-31) score were recorded to denote efficacy, and the occurrence of any adverse effect was also noted to elicit safety.

RESULTS: Out of 101 patients, 78 were male and 23 were female. The most common age group was 18–30 y. Seizure frequency from 2.99 ± 0.95 decreased significantly on the third visit to 0.25 ± 0.43. QOLIE-31 scores of seizure worry, overall quality, emotional well-being, and cognition improved in the second follow-up. Fatigue, somnolence, and weight gain were the major side effects.

CONCLUSION: Clobazam could be a good choice as an add-on in GTCS not controlled with VPA monotherapy. Clobazam definitely reduces seizure frequency and seizure worry and improves cognitive function and overall quality of life.

Keywords:

Clobazam, seizure frequency, somnolence, valproic acid

Introduction

The term Seizure refers to a transient alteration of behavior due to the disordered, synchronous, and rhythmic firing of populations of brain neurons,[1] and the term Epilepsy is defined as a brain disorder characterized by an enduring predisposition to generate epileptic seizures and by the neurobiological, cognitive, psychological, and social consequences of this condition.[1] Out of 70 million persons with epilepsy (PWE) worldwide, nearly 12 million PWE are Indians.[2] Epilepsy is the second most common and more frequently encountered neurological condition that forces a heavy burden on patients, relatives, families, and on health care systems. Seizures often cause transient impairment of awareness and often interfere with education and employment. Males getting

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more affected by epilepsy was reported in a study conducted in India by Bharucha *et al*.[3] Factors that influence and create treatment gaps are as follows: lack of knowledge of antiepileptic drugs (AEDs), poverty, cultural beliefs, poor health delivery infrastructure, and shortage of trained professionals.[4]

There are many anticonvulsant drugs marketed in India. First-line drugs and then add-on drugs are prescribed when primary treatments are not effective to control the seizure episode. They act by different mechanisms to suppress repetitive firing action potentials by an epileptic focus in the brain. Irrespective of the type of epilepsy, progressive neuronal damage occurs to some extent. To avoid this neuronal damage, pharmacological treatment is usually required for a long duration or often throughout the lifetime. The majority of AEDs have serious side effects, which are the greatest disadvantages for the drugs to continue for a longer duration. Among all other AEDs, the benzodiazepine group of drugs is used today as add-on therapy with other first-line AEDs to control episodes of seizures. Clobazam is an effective antiepileptic drug in case of most varieties of seizures for both short-term and long-term add-on therapy.[5] Clobazam has lesser side effects and no significant drug interactions which differs from conventional benzodiazepines. This property proves to be effective in the treatment of adult GTCS (generalized tonic-clonic seizure), especially for those who are resistant to conventional antiepileptics. There are many studies about clobazam in the treatment of epilepsy in pediatrics and also those who have Lennox Gastaut syndrome. Such an area is still unexplored in the Indian sub-continent. In Eastern India, the use of clobazam is quite common but studies depicting overall data on efficacy and safety are still a research question.

Clobazam could be tried as long-term therapy in some cases, especially can be used as add-on therapy for patients with epilepsy not controlled with valproic acid (VPA) monotherapy. This study has been done to evaluate the efficacy and safety of clobazam to treat VPA non responders to GTCS as an add-on drug in adult patients.

Aims of the study are as follows:

- To estimate the incidence of seizure episodes and the effectiveness of clobazam as an add-on therapy in the treatment of GTCS not controlled with VPA monotherapy.
- To identify the adverse drug reaction related to clobazam add-on therapy over VPA in the treatment of GTCS.
- To assess the quality of life of the participants by using a scale name – "QOLIE 31."

Materials and Methods

Study design and settings

This observational prospective study was done within a time period of 18 months from February 2018 to August 2019. It was conducted in the department of pharmacology with the collaboration of the department of neurology of a tertiary health care center.

Study participants and sampling

After proper calculation of sample size, a total of 108 patients who gave consent, suffering from GTCS which was not controlled with VPA monotherapy up to 1000 mg, of either sex, between age 18 and 60 were included. Exclusion criteria were patients not giving consent, GTCS with altered intelligent quotient, pregnant females, and VPA with other concomitant antiepileptic drug before starting clobazam.

Data collection tools and techniques

All patients signing informed consent forms and fulfilling inclusion criteria were recruited for 3 months and were followed up at the interval of 6 months. All data were noted in case record form. There were two follow-ups. On the first visit, for those patients who already achieved the maximum tolerable dose of VPA but still seizure not controlled, to them, clobazam 10 mg once daily was added. Efficacy was measured based on questions written on a form depicting seizure frequency, seizure-free period, and also retention period after the use of clobazam. For safety, adverse effects of the drug used (signs, symptoms), laboratory tests like liver function test, renal function test, and complete hemogram were done. To assess and evaluate safety, causality analysis of adverse events was done with the help of the WHO-UMC scale. To assess the quality of life, we use the "QOLIE 31" chart.[6] Tools used in this study are the informed consent form, case report form, and quality assessment scorecard (QOLIE-31 VERSION 1.0). This is the scoring scale, which is used to find out the quality of life of those who have GTCS and are taking antiepileptic medication. These types of scoring are mainly applicable above the age of 18 years. There are 31 questions present within quality of life inventory in epilepsy-31 items (QOLIE-31). The questions are divided under the headings name seizure worry, overall quality, emotional well-being, energy/fatigue, cognitive function, medication effect, and social function. The T-score of every patient at baseline and second follow-up is calculated and compared to find out whether any improvement happened or not in the quality of life of those patients. According to "QOLIE31," the T score range is from 0 to 100. A T-score towards "100" means better improvement of daily lifestyle and a T-score towards "zero" means poor quality of life. T-score was divided into three groups - <30 (poor), moderate (31-50),

and better (>50). All the data collected were then uploaded in a Microsoft Excel sheet, categorized, and statistically analyzed accordingly with appropriate tests with SPSS VERSION 16.

Ethical clearance

The commencement of the study was done after proper ethical clearance from the institutional ethics committee of the tertiary health care center.

Results

During the entire study period, a total of 119 patients were recruited, of which 11 patients did not meet the inclusion and exclusion criteria. So, 108 patients were enrolled for the study but 7 patients were lost to follow-up. The final analysis was done on 101 patients. Out of 101 patients, 78 were male and 23 were female. Maximum patients (31.68%) belonged to the age group of 18–30 y, and the minimum (17.82%) from 51 to 60 years [Figure 1]. The majority of the patients were farmers - 25.74%, followed by self-employed -17.82% (drivers, teachers, self-business, electricians), government-employed - 16.83% (employees and clerks), students -11.88%, daily wage workers -10.89% (casual worker), housewife -9.90%, and unemployed - 6.93%. At baseline, body weight (kg), respiratory rate per minute, and heart rate per minute were measured which were then compared to second and third visits. Weight gain was significant in follow-up visits whereas other physiological parameters remained unchanged [Table 1]. At baseline, hemoglobin, total leukocyte count, and platelet count were recorded which were compared to the subsequent visits depicting a significant decrease in the second and third visits. On comparison of biochemical parameters between the two visits with the baseline visit, significant changes were noted in blood urea, and SGOT (serum glutamic oxaloacetic transaminase) and SGPT (serum glutamic pyruvic transaminase) liver enzymes [Table 2]. We did not find any significant difference, when comparison of baseline serum Na+, K+, creatinine, and fasting plasma glucose (FPG) were done with subsequent visits. The mean of seizure frequency in the first visit was 2.99, which gradually decreased significantly in the second and third visits to 0.87 and 0.25, respectively [Table 3]. According to the assessment of QOLIE-31, it was found that overall patient's physical, mental, social, and emotional health improved. Most of the scores were >50 at the second follow-up when compared to baseline. All criteria such as seizure worry, overall quality, emotional well-being, cognitive function, social well-being, and medication effect were improved except the energy fatigue score, where incidences of feeling fatigued increased at the second follow-up when compared to baseline [Table 4]. Retention rate means how many patients were needed to escalate the dose of clobazam. From our study, we found that 57% of patients did not need to escalate the dose of clobazam, and the rest 43% needed dose escalation [Figure 2]. Total cases of treatment-emergent adverse events (TEAE) were

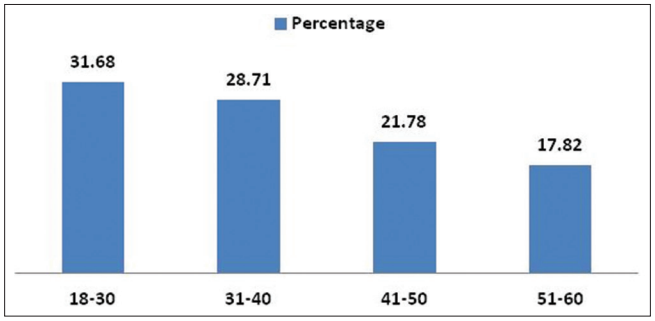

Figure 1: Percentage of age group distribution

Table 1: Comparison of physiological parameters in three visits

	First visit	Second visit	Third visit	*P*
Body weight (kg)				
Mean	61.56	62.39	63.04	<0.0001 (****)
SD	6.06	5.67	5.84	
Respiratory rate per minute				
Mean	19.32	19.47	19.23	Not significant
SD	1.36	1.55	1.33	
Heart rate per minute				
Mean	76.87	77.13	76.93	Not significant
SD	4.80	4.97	4.34	

Table 2: Comparison of biochemical parameters in three visits

	First visit	Second visit	Third visit	*P*
Na+				
Mean	137.32	137.30	137.18	Not significant
SD	1.50	1.64	1.47	
K+				
Mean	3.51	3.51	3.51	Not significant
SD	0.25	0.27	0.23	
Urea				
Mean	23.99	24.18	23.57	0.0167 (1st and 3rd visit), 0.0074 (2nd and 3rd visit)
SD	3.00	3.10	3.18	
Creatinine				
Mean	0.80	0.79	0.78	Not significant
SD	0.10	0.11	0.10	
SGOT				
Mean	29.36	29.66	28.90	0.019 (1st and 2nd), 0.0194 (1st and 3rd), 0.0017 (2nd and 3rd)
SD	3.09	3.45	3.25	
SGPT				
Mean	29.13	29.62	29.45	0.0001 (1st and 2nd)
SD	2.46	2.62	2.53	
FPG				
Mean	90.00	90.43	89.79	Not significant
SD	5.66	6.87	5.62	

calculated. Causality was assessed by the Uppsala-WHO causality assessment scale. Adverse effects come across were mainly tiredness, irritability, poor memory, and headache. All the side effects are well tolerated among the patients [Figure 3]. The majority of patients were complaining of fatigue or tiredness (16.83%). 9.9% of patients were complaining of headaches. Other side effects were poor memory, irritable behavior, abdominal pain, acidity, and depression (4.95% of individuals each). 5.94% of patients were complaining of tremors. Few patients were complaining of blurred vision (1.98%) and constipation (2.97%). There was no need to escalate the dose and all the side effects were tolerable. Among all of the side effects, somnolence (100%) and weight gain were the major complaints.

Table 3: Comparison of seizure frequency in three visits

	First visit	Second visit	Third visit	*P*
Seizure frequency				
Mean	2.99	0.87	0.25	<0.0001
SD	0.95	0.72	0.43	

Table 4: Comparison of QOLIE 31 scores between first and third visits

T-score	First visit	Third visit
Seizure Worry		
<30	64%	11%
31-50	26%	12%
>50	10%	77%
Overall quality		
<30	24%	13%
31-50	30%	21%
>50	46%	66%
Emotional well-being		
<30	39%	19%
31-50	30%	20%
>50	31%	61%
Energy/Fatigue		
<30	33%	51%
31-50	28%	23%
>50	39%	26%
Cognitive function		
<30	31%	16%
31-50	33%	20%
>50	36%	64%
Medication effect		
<30	14%	20%
31-50	17%	12%
>50	69%	68%
Social function		
<30	38%	12%
31-50	37%	21%
>50	25%	67%

Discussion

The present study was conducted to evaluate the efficacy and safety of clobazam as an add-on therapy to VPA-resistant GTCS type of epilepsy. One hundred and one patients were analyzed. Among the participants, the majority were male and most commonly from the 18 to 30 y age group. An unusual disparity was found in the male-female ratio, which is gradually widening up with increasing age reflecting the poor health awareness among females. The majority of the participants were farmers (25.74%) followed by self-employed (17.82%).

A significant increase in body weight was observed in two follow-ups with a *P* value (<0.0001) when compared to the baseline. Similarly, weight gain was also found in studies which were held on December 2007 at the epilepsy outpatient clinic of HC-UNICAMP which showed that almost 56% of patients among the participants gained weight which is one of the major adverse effects of AEDs, in monotherapy as well as polytherapy.[7,8] Changes in other baseline parameters were non-significant indicating no direct effect of clobazam on heart rate and respiratory rate.[9] Our study demonstrated a significant change in the value of hemoglobin between the second and third visits similar to the finding of a study that showed changes in hemoglobin among participants were due to the effect of the concomitant drug VPA.[10] When biochemical parameters were compared, liver enzymes like SGOT and SGPT were found to be raised significantly among

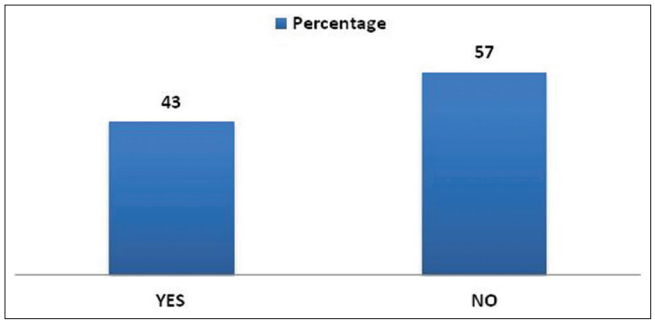

Figure 2: Percentage of dose escalation required

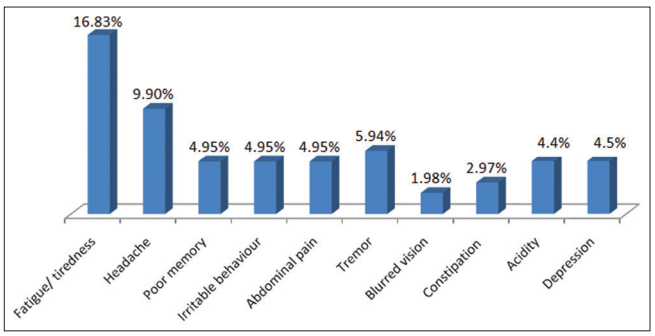

Figure 3: Percentage of occurrence of different adverse events

two follow-ups when compared to baseline. It was the same with serum urea also. Very few data are available about the hepatotoxicity of clobazam. No individual case reports of clobazam hepatotoxicity have been published till now in spite of its widespread clinical availability.[11] The change in hepatic enzymes elicited in this study may be due to the effect of the concomitant drug VPA. Retrospective studies have demonstrated a transient elevation of liver aminotransferases in up to 10-15% of patients on VPA.[12,13] In a retrospective study by Montenegro *et al*.,[14] it was found that 57 percent of 97 adult patients with refractory partial epilepsy achieved a >50 percent improvement in seizure control over a mean of 16.7 months. To assess the efficacy of clobazam, the occurrence of seizures during treatment was noted as "seizure frequency" in the last 6 months at baseline and in two follow-up visits. A highly significant *P* value for the reduction of seizure frequency in the second and third visits with respect to the baseline was observed in this study. So, from the present study, it was proved that seizure frequency significantly decreased with the add-on use of clobazam with VPA. Two retrospective studies on efficacy stated that clobazam can reduce the frequency of seizures in pediatric patients when used as add-on therapy but with other drugs.[15,16]

The participants were emotionally well after including clobazam as an add-on in the third follow-up visit. Following the use of clobazam, patients were less energetic and felt more fatigued on the third visit when compared to the baseline. There are studies stating that fatigue due to clobazam is least than other benzodiazepines.[17] The cognitive functions of participants were improved after the use of clobazam as an add-on drug with VPA at the third visit. According to "QOLIE 31," social functions of participants had improved very much on the third visit. The medication effect had no drastic change when the first and third visits were compared. Our study calculated the retention rate. It means how many patients were needed to escalate the initial dose of clobazam? The retention rate was based on the escalation of the dose of clobazam at the second follow-up visit. This study detected that majority of the patients (57%) did not need to escalate their dose and 43% needed dose escalation which is similar to Kumar *et al*.[18] Due to the small sample size and short duration of the study, there was no scope for assessment of the need for further dose escalation or withdrawal effect of clobazam.

To assess the safety of clobazam as an add-on drug to VPA, different complaints related to any kind of adverse events were noted and causality analyses were done as per WHO-UMC. All adverse events which had occurred were either from probable or from possible criteria as the effects of VPA could not be separated. Somnolence was the major complaint among all the participants in all three visits but there was no interference with daily activities. This result was similar to another study by *Weinstock et al*.[19] Other adverse effects experienced by the patients in decreasing order include fatigue/tiredness, headache, tremors, poor memory, irritable behavior, abdominal pain, acidity, depression, blurred vision, and constipation. Instead of many side effects, the drug clobazam was well tolerated among all patients because the side effects were least bothersome to them. This finding of the present study matches with the result of *Joshi et al*.[9] and Ng and Collins.[20] They had researched data from 50 clinical studies collected from over 3000 epileptic adult and pediatric patients, which showed that the most common side effects include sedation, dizziness, and ataxia.[20] These adverse effects are mainly dose-dependent and only 40% experience mild to moderate severity.[20]

Limitations

- The sample size is small.
- The present study did not assess the effects of the concomitant AED, which is VPA.
- Recommendation - If the study period is increased, the long-term effects of drugs can be inferred.

Conclusion

Clobazam could be a good choice as an add-on in GTCS not controlled with VPA monotherapy. Clobazam definitely reduces seizure frequency and seizure worry and improves cognitive function and overall quality of life. Somnolence is the major complaint along with fatigue but it does not hamper daily life functions. There may be issues of raised liver enzymes and weight gain but all of these are reversible.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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