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Clobazam as First Add on Therapy along with Valproic Acid in Treatment of Epilepsy: A Prospective Study in Eastern India

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ABSTRACT

Background and objectives: People with refractory epilepsy on Valproic acid monotherapy, need safer and more effective therapy. Clobazam is frequently used as a supplement to treat drug-resistant epilepsy. But data regarding efficacy and safety of Clobazam as add on therapy is scarce. The present study was conducted to estimate the efficacy of Clobazam as first add on therapy along with Valproic acid in treatment of GTCS, in the form of reduction of seizure frequency and to identify the adverse drug reactions as add-on medication for the treatment of refractory GTCS not managed with valproic acid monotherapy. **Methods**: An observational prospective study was conducted among 113 Neuromedicine OPD attendees who were aged ≥18 years, suffering from GTCS and was on Valproic acid monotherapy but not responding. Patients were recruited for 4 months with two follow ups in 3 months interval. Data related to baseline parameter, seizure frequency, blood parameter were collected in all visits using a pre-designed, pre-tested, structured interviewer-administered questionnaire. Analysis was done using statistical software SPSS 20.0. One way repeated measured analysis of variance (ANOVA) with post hoc Bonferroni, Friedman test, Cochran's Q test with post hoc McNemar was conducted. p value ≤ 0.05 was considered as significant with 95 % confidence. **Results**: Mean (±SD) age of the study participants was 37.69±11.54 years. Seizure frequency was decreased from 1st visit to 3rd visit. Body weight of the participants increased in successive visits [Wilk's Lambda =0.528, F (2, 99) =44.178, $p<0.05$, $\eta 2=0.472$]. Frequency of somnolence was increased over time (Cochran's Q=119.011, p=0.000). **Conclusion**: Clobazam is a very effective add-on drug for control of refractory GTCS patients who are on Valproic acid monotherapy. Clobazam has good safety and efficacy profile as an add-on drug.

***Keywords**: Add on therapy, Clobazam, Epilepsy, GTCS, Valproic Acid*

INTRODUCTION

Epilepsy is a severe disorder that affects about 1% of people worldwide[1]. Regretfully, about one-third of individuals taking antiepileptic medications experience uncontrollable seizures for at least a year[2,3]. For people with refractory epilepsy, safer and more effective therapies are required.

The majority of definitions of "drug-resistant" epilepsy relate to persistent seizures in spite of antiepileptic medication treatment, while there is no single, accepted description for this condition. The

definition that is most frequently used is that of seizures that persist despite constant drug adjustments. The 1,5-benzodiazepine clobazam is frequently used as a supplement to treat drug-resistant epilepsy[4].

Clobazam (CLB) binds less to subunits that underlie sedative effects than other benzodiazepines, and it allosterically activates the GABAA receptor. Because of its active metabolite, N-desmethylclobazam, it acts rapidly and has a long-lasting therapeutic impact[5].

Clobazam is absorbed quickly and completely through the mouth. One to four hours is the range for the time to peak concentration[6]. Due to its high lipophilicity, the medication is quickly absorbed by fat and grey matter in the brain. After being administered for 14 hours, it accumulates in white matter and is subsequently broadly dispersed; the volume of distribution is substantial[7,8].

Clobazam varies from traditional benzodiazepines in that it has fewer adverse effects and no significant medication interactions. Research has indicated that up to 87% of subjects exhibit tolerance[9]. This characteristic shows promise in the management of adult GTCS, particularly in patients who are not responding well to traditional antiepileptic medications.

Multiple research investigations have been conducted about the use of clobazam in the treatment of paediatric epilepsy and Lennox Gastaut syndrome[10]. Studies in Indian population have demonstrated the efficacy of CLB as monotherapy in adult patients and in refractory childhood epilepsy, though data regarding efficacy and safety of clobazam as add on therapy is scarce[11,12]. Although the usage of clobazam is widespread in Eastern India, studies showing broad information on safety and efficacy remain unanswered. With this background the present study was conducted to estimate the efficacy of Clobazam as first add on therapy along with Valproic acid in treatment of GTCS, in the form of reduction of seizure frequency and to identify the adverse drug reactions as add-on medication for the treatment of refractory GTCS not managed with valproic acid monotherapy.

Methods

An institution-based observational prospective study was conducted in Neuromedicine Out Patient Department (OPD) of a medical college in Eastern India from July 2023 to June 2024. All patients, aged ≥18 years suffering from GTCS and is on Valproic acid monotherapy but not responding even after tolerable dose of Valproic acid (i.e. either 60mg/kg/day or intolerability at a lower dose, whichever is earlier), constituted the study population. Patients with altered IQ, GTCS with concurrent diseases, Valproic acid with other concomitant antiepileptic drug before starting Clobazam, not willing to give consent for participation, with pregnancy and with severely ill were excluded from the study.

Respondents were chosen using convenient sampling method. After fulfilling inclusion and exclusion criteria and obtaining informed consent, patients were recruited for 4 months (i.e. in the months of July to October 2023, eligible & consented patients were included as study participants). Two follow ups had been done of those patients in 3 months interval post recruitment dates. A pre-designed, pre-tested, structured, interviewer-administered questionnaire was used for collecting data. On first visit socio-demographic profile, baseline parameters like body weight, respiratory rate, heart rate were recorded. Modified B. G. Prasad scale was used to determine the socio-economic class of participants[13]. To assess the efficacy and adverse effects of Clobazam data regarding seizure frequency, retention rate of Clobazam, blood parameter were gathered. Data related to baseline parameter, seizure frequency, blood parameter were taken in same manner on subsequent two visits.

Statistical Analysis

Data were entered into MS excel spread-sheet. Calculation was done with the help of MS excel and statistical software SPSS 20.0 version. Descriptive statistics were expressed by mean, SD and proportion of baseline characteristics. Normality of the data set was tested by Kolmogorov-Smirnov, Shapiro-Wilk's normality test as well as P-P plot, Q-Q plot, Box & Whisker plot etc. Oneway repeated measured analysis of variance (ANOVA) with post hoc analysis (Bonferroni) was conducted to evaluate seizure frequency and various physiological, haematological, biochemical parameters in consecutive follow-up which followed normal distribution. For non-parametric evaluation Friedman test was performed. To evaluate the relationship between somnolence and successive visits, Cochran's Q test with post hoc McNemar Test was conducted. p value ≤ 0.05 was considered as significant with 95 % confidence.

Ethical Considerations

Ethical clearance had been obtained from Institutional Ethics Committee of North Bengal Medical College (IEC/NBMC/M11/018/2023). Eligible participants were briefed about the study purpose, procedures, voluntary nature of participation, anytime withdrawal without any further adverse consequences. Informed consent was taken from all participants before beginning the study. Anonymity & confidentiality were maintained.

Results

The mean (±SD) age of the total 113 study participants was 37.69±11.54 years. The majority of them were male (67.23%), residing in rural area (64.6%), educational qualification upto middle school (28.3%), married (65.5%), daily labourer (25.3%) and belonged to class III socio economic status (50.4%) [**Table 1**].

Table 1. Distribution of study participants according to socio-demographic variables (n=113)

Variables	Frequency	Percentage
Sex		
Male	76	67.3
Female	37	32.7
Residence		
Rural	73	64.6
Urban	40	35.4
Literacy		
Illiterate	16	14.1
Primary school	18	15.9
Middle school	32	28.3
Secondary	29	25.7
Higher secondary	11	9.7
Graduation & above	7	6.3
Marital status		
Married	74	65.5
Unmarried	27	23.9
Widowed	9	8.0
Divorced	3	2.6
Occupation		
Service	10	8.8
Business	18	15.9
Unemployed	9	7.9
Home maker	27	23.9
Daily labourer	29	25.7
Others*	20	17.8
Socio Economic Status		
Class I	15	13.3
Class II	12	10.6
Class III	57	50.4
Class IV	21	18.6
Class V	8	7.1

**Others- students, drivers, electrician, private job, farmers*

Table 2. Distribution of study participants according to Seizure frequency in successive visits and their association (n=113)

Visits	Mean rank of Seizure frequency	Friedman Test, df	p value
1st visit	3.00	187.708, 2	**0.000**
2nd visit	1.76		
3rd visit	1.24		

Table 3. Distribution of study participants according to adverse drug effects related to Clobazam (n=113)

Adverse drug effects*	Frequency	Percentage
Weakness	21	18.6
Headache	14	12.4
Tremor	9	7.9
Acidity	7	6.1
Depression	6	5.3
Constipation	5	4.4
Poor memory	4	3.5
Blurred vision	2	1.7

***Multiple responses present*

Friedman test was conducted to assess effectiveness of add on therapy of Clobazam in the form of seizure frequency. Seizure frequency was decreased from 1st visit to 3rd visit, and it was statistically significant. Follow up comparison indicated a significant difference between 1st and 2nd visit (z=-7.810, p=0.000), 1st and 3rd visit (z=-9.058, p=0.000) and 2nd & 3rd visit (z=-3.507, p=0.000) (post hoc Wilcoxon signed ranks test) [**Table 2**]. Majority of patients had weakness (18.6%), headache (12.4%), tremor (7.9%), acidity (6.1%), depression (5.3%) etc. as side effects [**Table 3**].

One-way repeated measured analysis of variance (ANOVA) was conducted to evaluate body weight of patients before, during and after participation in the study. Body weight of the participants increased in successive visits [Wilk's Lambda =0.528, F (2, 99)=44.178, p<0.05, η^2=0.472]. Follow up comparison indicated that each pairwise difference was significant, p<0.05 (post hoc Bonferroni). The mean value of Platelet count (Lakh/microliter) was statistically decreased from 1st to 3rd visit (pairwise difference=0.037, p=0.001) and from 2nd to 3rd visit (pairwise difference=0.032, p=0.009) (adjustment for multiple comparison: Bonferroni). There was significant decrease in mean value of Urea (mg/dl) level over time. Follow up comparison indicated that 1st & 3rd, 2nd & 3rd pairwise differences were significant (mean difference=0.871, p=0.000), (mean difference=0.693, p=0.002) respectively (post hoc Bonferroni). The mean value of SGOT was significantly decreased in consecutive visits. Follow up comparison indicated that 1st, 2nd & 3rd pairwise differences were significant (post hoc Bonferroni). The mean value of SGPT was statistically increased from 1st visit to 3rd visit and 2nd to 3rd visit. Post hoc adjustment for multiple comparison (Bonferroni) was done and indicated that pairwise differences were significant [**Table 4**].

Frequency of somnolence was increased over time (Cochran's Q=119.011, p=0.000) (Cochran's Q test). There was significant increase in somnolence from 1st visit to 2nd visit; χ^2=59.016, p=0.000, 2nd to 3rd visit; χ^2=11.256, p=0.001, from 1st to 3rd visit; χ^2=80.105, p=0.000 (post hoc McNemar Test). Mean rank of haemoglobin level was statistically increased from 1st visit to 3rd visit (z=-2.477, p=0.013) and from 2nd to 3rd visit (z=-3.309, p=0.001) (post hoc Wilcoxon signed ranks test) [**Table 5**].

Table 4. Distribution of study participants according to various parameters in successive visits and their association (n=113)

Baseline physiological parameter					
body weight(kg)					
Visits	**Mean ± SD**	**Wilk's Lambda**	**F, df ***	**p value**	**Partial Eta Squared(η^2)**
1st visit	61.37 ±5.94	0.528	44.178,2,99	**0.000**	0.472
2nd visit	62.32±5.66				
3rd visit	62.97±5.82				
Haematological parameter					
Platelet count (Lakh/microliter)					
1st visit	1.80±0.18	0.869	7.453, 2, 99	**0.001**	0.131
2nd visit	1.80±0.18				
3rd visit	1.77±0.17				
Biochemical parameter					
Urea					
1st visit	23.94±2.97	0. 798	12.546, 2, 99	**0.000**	0.202
2nd visit	23.76±3.09				
3rd visit	23.07±3.09				
SGOT					
1st visit	30.22±3.34	0. 844	9.162, 2, 99	**0.000**	0.156
2nd visit	30.48±3.47				
3rd visit	29.59±3.34				
SGPT					
1st visit	30.23±2.70	0.761	15.582, 2, 99	**0.000**	0.239
2nd visit	30.51±2.74				
3rd visit	31.30±3.72				

Table 5. Distribution of study participants according to Somnolence and Haemoglobin level in successive visits and their association (n=113)

Visits	Somnolence			
	Present No. (%)	Absent No. (%)	Cochran's Q, df	p value
1st visit	6 (5.3.)	107 (94.7)	119.011, 2	**0.000**
2nd visit	75 (66.4)	47(33.6)		
3rd visit	101 (89.4)	12(10.6)		
Visits	**Mean rank of Haemoglobin level**		**Friedman Test, df**	**p value**
1st visit	1.92		11.450, 2	**0.003**
2nd visit	1.84			
3rd visit	2.24			

DISCUSSION

Mean (±SD) age of the patients was 37.69±11.54 years. Majority of the study participants (77.23%) were male. Male predominance was also seen in a study by Joshi R et al. where 65.7% were male participants[14]. Similar picture was depicted in the study by Alsulami A, where out of 121 epileptic participants, 73 were male[15].

The majority of present patients (18.3%) reported weakness followed by headache (12.4%), tremor (7.9%), acidity (6.1%) etc. A similar result was seen in a study by Joshi et al. where different side effects were found after use of Clobazam as an add-on therapy with other antiepileptic drug for the treatment of epilepsy[14]. Another study by Klehm J et al. in Boston found that the most common adverse effects was tiredness in 44 of 300 (14.6%)[16]. However, instead of many side effects, Clobazam was well tolerated as per opinion from present recipients, because the side effects were least bothersome in daily activity of those participants.

In the current study seizure frequency was significantly decreased from 1st visit to 3rd visit (p=0.000). A retrospective study revealed that the median decrease in the average number of monthly seizures for all patients was 30 seizures per month (p=0.0001)[14]. Klehm J et al. reported that 203 (67.7%) out of 300 patients showed a response to clobazam medication; of these, 84 (28%) stopped having seizures[16].

In very recent year, Satishchandra P et al. has found that patients had a mean (±SD) body weight of 55.2 (±16.9) kg at baseline; at the one-year follow-up, that weight had increased to 58.4 (±15.4) kg[17]. In this study also, body weight of the patients was significantly increased over time.

In the present study mean value of SGOT was significantly decreased while mean value of SGPT was statistically increased in consecutive visits. Regarding Clobazam's hepatotoxicity, very little information was made available. The simultaneous administration of valproic acid may be the cause of this alteration in liver enzymes[18]. Merely statistically significant, the changes in biochemical markers did not have a clinical impact.

In this study, haemoglobin level was statistically increased from 1st visit to 3rd visit. The seizure threshold is lowered by anaemia, which leads to an increase in seizure activity. Seizures can be brought on by anaemia in a number of ways, such as decreased levels of neurotransmitters that block gamma-aminobutyric acid, changes in neuronal metabolism, decreased levels of enzymes, and decreased energy and oxygen metabolism in the brain[19]. However, some research suggested that it was a shielding factor[20]. Joshi P et al. had found no significant difference in haemoglobin level with clobazam therapy among paediatric population (0.1g/dL, p=0.59)[21].

Even while none of the subjects reported having difficulty with their everyday tasks, there was a noticeable rise in somnolence on subsequent visits. Joshi R et al. discovered a similar outcome, with somnolence being the most common side effect among others[14]. Humayun MJ et al. in 2023 mentioned that the somnolence was the most frequent adverse medication reaction observed during the trials when compared to a placebo. These adverse effects were far less common and more tolerable as compared to other benzodiazepines (such as diazepam). With time, tolerance to these adverse effects builds[22].

CONCLUSION

Clobazam is a very effective add-on drug for control of refractory GTCS patients who are on Valproic acid monotherapy. Clobazam has good safety and efficacy profile as an add-on drug. Clobazam has beneficial effect on adult population too. More such studies with larger sample size from various clinical setup should be conducted. In the management of patients with refractory

epilepsy, Clobazam can be used clinically as add-on antiepileptic drug therapy.

Limitation

Due to small sample size and time constraint, there was no scope for assessment of withdrawal effect & long-term adverse effect of Clobazam. Concomitant therapy was not assessed that would have been impact on efficacy and safety profile of the study drugs. Plasma level of Valproic acid and Clobazam was not evaluated. The cumulative or delayed effect from concurrent anti-epileptic drugs could not be excluded.

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Conflict of interest

The author declares that there isn't any conflict of interest regarding the publication of this paper.

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