

## A PROSPECTIVE STUDY TO ASSESS THE QUALITY OF LIFE AMONG THE PATIENTS OF GENERALIZED TONIC-CLONIC SEIZURE RECEIVING TREATMENT PHENYTOIN PLUS CLOBAZAM VERSUS SODIUM VALPROATE PLUS CLOBAZAM THERAPY

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### ABSTRACT

**Objectives:** The objective of the study was to compare effect of phenytoin plus clobazam (Group 1) and sodium valproate plus clobazam therapy (Group 2) on quality of life among generalized tonic-clonic seizures (GTCS) patients attending neurology out-patient department at the tertiary care center in Gwalior district.

**Methods:** The present study was a prospective study conducted between period of February 2019 and January 2020 on 45–45 patients each receiving either phenytoin plus clobazam or sodium valproate plus clobazam dual therapy for the treatment of patients with GTCS. Frequency, percentage, mean, standard deviation, independent student t-test, Chi-square test, and one-way repeated measures of ANOVA were applied, and Bonferroni adjustment was calculated using SPSS version 20 software.  $P < 0.05$  was considered to be statistically significant.

**Results:** For question 1, in Group 1, mean score was  $3.29 \pm 0.45$  at 0 month (baseline), which reduced to  $2.51 \pm 0.50$  and  $2.11 \pm 0.48$  at 3 and 6 months, respectively. In Group 2, mean score was  $3.31 \pm 0.46$  at 0 month, which reduced to  $2.35 \pm 0.48$  and  $1.95 \pm 0.29$  at 3 and 6 months. For question 2, in Group 1, mean score was  $3.44 \pm 0.54$  at 0 month (baseline), which reduced to  $2.55 \pm 0.54$  and  $2.22 \pm 0.51$  at 3 and 6 months, respectively. In Group 2, mean score was  $3.64 \pm 0.48$  at 0 month, which reduced to  $2.77 \pm 0.55$  and  $2.44 \pm 0.54$  at 3 and 6 months, respectively. There was statistically significant improvement seen within the group at 3 and 6 months as compared to baseline in both groups for question 1, question 2, question 3, question 4;  $p < 0.01$ .

**Conclusion:** It can be concluded that both combinations of our study groups have a better impact on quality of life from baseline till the end of the study. However, on comparison between them, we have not found a statistically significant difference.

**Keywords:** Anti-epileptic drugs, Epilepsy, Generalized tonic-clonic seizures, Seizure.

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### INTRODUCTION

Epilepsy is a serious chronic disorder of the brain and a common neurological abnormality affecting about more than 50 million of the world's population [1]. The factors influencing the quality of life among patients with generalized seizures include seizure severity, unpredictability, stigma, fear, anxiety, and cognitive and psychiatric problems [2]. Therefore, it is often recommended to begin treatment of epilepsy with antiepileptic drugs (AEDs) as soon as the patient has reported more than one documented or witnessed seizure bearing in mind that the goal of treatment should be to maintain normal a lifestyle through complete seizure control with no or minimal side effects [3]. The chronic nature of this disease significantly affects the quality of life of epileptic patients [4].

Phenytoin has been the standard drug for generalized tonic-clonic seizure (GTCS) and partial seizures, but now, it is used when better tolerated newer drugs cannot be used while sodium valproate is a broad spectrum anticonvulsant drug and one of the first-line drugs for partial seizures and GTCS because of good tolerability. Clobazam is less sedative and long-acting among benzodiazepines and is active against partial and generalized seizures in patients of all ages but is usually indicated as adjuvant therapy with other AEDs when monotherapy is not adequate [5].

Literature revealed very little or no scientific comparative study of clobazam as a combination with two commonly prescribed first-line

AEDs, that is, phenytoin and sodium valproate in GTCS patients are available; therefore, the present study was conducted to compare, the dual therapy which we had used in our study (phenytoin plus clobazam and sodium valproate plus clobazam) to compare, how they can improve quality of life of epileptic patients.

### Aims and objectives

This study was to compare the effect of phenytoin plus clobazam and sodium valproate plus clobazam therapy on the quality of life among GTCS patients attending neurology outpatient departments at a tertiary care center in Gwalior district.

### METHODS

The present prospective comparative study was conducted in the Department of Pharmacology and Department of Neurology at J.A. Group of Hospital and Gajra Raja Medical College, Gwalior (M.P.) for a duration of 12 months from February 2019 to January 2020.

### Sample size

The present study was conducted between 45 and 45 patients receiving either phenytoin plus clobazam or sodium valproate plus clobazam dual therapy for the treatment of having complaints of GTCS. The total sample size of the study was 90 patients. The follow-up had been done at 3 months and 6 months from the first visit.

### Inclusion and exclusion criteria

All medically stable patients of more than 14 years of age group and determined to have had at least two episodes of GTCS by epilepsy specialist or to have had a single episode of seizure with abnormal electroencephalogram (EEG) and those patients who were signed written informed consent and willing to participate in the study were included in the study. While patients with clinical suspicion of non-epileptic psychogenic seizure and pregnant mothers, breastfeeding mothers, childbearing age mothers using contraception, and patient with serious co-morbidity, diabetes, hepatic insufficiency, blood pressure instability: Pulse <50 or >100, and SBP <50 or >180 were excluded from the study.

### Screening visit

Before being included in the study, a screening was done. In this study, the outpatients from neurology were taken. During the screening visit, the subjects diagnosed as patients of GTCS by a neurologist on the basis of clinical findings and EEG reports and who had been given clobazam as adjuvant therapy either with phenytoin or with sodium valproate were included in the study.

### Follow-up

Follow-up assessment of all the patients was done after 3<sup>rd</sup> and 6<sup>th</sup> month.

### Ethical approval

The study was ethically approved by the Institutional Ethics Committee G.R.M.C. Gwalior.

### Evaluation of quality of life

Assessment of quality of life was done using epilepsy surgery inventory (ESI) – 55 scales [6,7].

### Statistical analysis

All the data analysis of this comparative study was performed by suitable statistical methods using SPSS ver.20 software. Quantitative variables were expressed as the mean and standard deviation. Categorical data were expressed in actual numbers and percentages. Chi-square test, independent t-test, one-way repeated measures ANOVA followed by Bonferroni adjustment for multiple comparisons were calculated and  $p < 0.05$  was considered to be statistically significant.

## RESULTS

For this study, 45 patients in Group 1 were taking phenytoin plus clobazam therapy and 45 patients in Group 2 were taking sodium valproate plus clobazam therapy as prescribed by a neurologist for GTCS. They were assessed for quality of life at baseline, at the 3<sup>rd</sup> month,

and 6<sup>th</sup> month on four questions of ESI-55 questionnaires for quality of life assessment.

The age of patients in our study ranged from 14 to 50 years with a mean age of  $26.83 \pm 11.37$  years. The most common age group involved was 14–20 years. Average age of participants in Group 1 (phenytoin+clobazam) was  $28.84 \pm 12.76$  years while the average age of participants in Group 2 (Sodium valproate + clobazam Group) was  $24.82 \pm 9.52$  years. There were 31 females and 59 males were participated in the study. Fifteen females were in Group 1 and 16 females were in Group 2.

Table 1 shows that 59 (65.55%) were male and 31 (34.45%) were female patients. This table shows that out of a total of 90 patients, the majority of patients, that is, 45 (50%) were primarily educated and 25 (27.8%) patients were illiterate. In this study, 49 (54.45%) patients were from rural backgrounds and 41 (45.55%) were from urban areas. There was no significant difference observed between Group 1 and Group 2 for age, sex, education, and area of residence ( $p > 0.05$ ) (Table 1).

For question 1, in the phenytoin plus clobazam group, mean score was  $3.29 \pm 0.45$  at 0 month (baseline), which reduced to  $2.51 \pm 0.50$  and  $2.11 \pm 0.48$  at 3 and 6 months. In the sodium valproate plus clobazam group, mean score was  $3.31 \pm 0.46$  at 0 month, which reduced to  $2.35 \pm 0.48$  and  $1.95 \pm 0.29$  at 3 and 6 months (statistically significant improvement was seen within the group at 3 and 6 months as compared to baseline in both groups,  $p < 0.01$ ). For question 2, in the phenytoin plus clobazam group, mean score was  $3.44 \pm 0.54$  at 0 month (baseline), which reduced to  $2.55 \pm 0.54$  and  $2.22 \pm 0.51$  at 3 and 6 months. In sodium valproate, the plus clobazam group, mean score was  $3.64 \pm 0.48$  at 0 month, which reduced to  $2.77 \pm 0.55$  and  $2.44 \pm 0.54$  at 3 and 6 months (statistically significant improvement was seen within the group at 3 and 6 months as compared to baseline in both groups,  $p < 0.01$ ). For question 3, in the phenytoin plus clobazam group, mean score was  $3.13 \pm 0.34$  at 0 month (baseline), which reduced to  $2.37 \pm 0.57$  and  $1.95 \pm 0.29$  at 3 and 6 months, in sodium valproate plus clobazam group mean score was  $3.44 \pm 0.50$  at 0 month, which reduced to  $2.42 \pm 0.49$  and  $2.08 \pm 0.28$  at 3 and 6 months (statistically significant improvement was seen within the group at 3 and 6 months as compared to baseline in both groups,  $p < 0.01$ ). For question 4, in the phenytoin plus clobazam group, mean score was  $3.42 \pm 0.58$  at 0 month (baseline), which reduced to  $2.6 \pm 0.53$  and  $2.35 \pm 0.48$  at 3 and 6 months. In sodium valproate plus clobazam group, mean score was  $3.51 \pm 0.54$  at 0 month, which reduced to  $2.71 \pm 0.50$  and  $2.17 \pm 0.38$  at 3 and 6 months (Table 2). While on comparison between the two groups, a statistically significant difference was not seen at baseline, 3 months, and 6 months except for question 3 regarding the difficulty in performing work or other activity where the sodium valproate+clobazam group showed significant improvement at 6 months ( $p = 0.03$ ) (Table 2).

Table 1: Baseline characteristics of the participants

Baseline characteristics	Phenytoin+clobazam group (n=45)	Sodium valproate+clobazam group (n=45)	Total (n=90)	Chi-square	p-value
Age group (years)					
14–20 years	17 (37.8)	22 (48.9)	39 (43.3)	4.52	0.21
21–30 years	10 (22.2)	11 (24.4)	21 (23.3)		
31–40 years	8 (17.8)	9 (20.0)	17 (18.9)		
41–50 years	10 (22.2)	3 (6.7)	13 (14.4)		
Gender				0.049	0.82
Female	15 (33.3)	16 (35.6)	31 (34.4)		
Male	30 (66.7)	29 (64.4)	59 (65.6)		
Education status				6.61	0.09
Illiterate	10 (22.2)	15 (33.3)	25 (27.8)		
Primary	25 (55.6)	20 (44.4)	45 (50.0)		
Upto intermediate	3 (6.7)	8 (17.8)	11 (12.2)		
Graduate and above	7 (15.6)	4 (4.4)	9 (10.0)		
Area of residence				2.19	0.14
Rural	21 (46.7)	28 (62.2)	49 (54.4)		
Urban	24 (53.3)	17 (37.8)	51 (56.6)		

Multiple comparisons are to compare each pair, that is, changes from baseline to 3 months, baseline to 6 months, 3 months–6 months in both the group separately; there was statistically significant improvement seen within the groups ( $p < 0.01$ ) (Table 3).

## DISCUSSION

It is well known that epilepsy is a chronic illness and long duration of epilepsy is a predictor of poor quality of life. Monotherapy is always preferred over polytherapy for the treatment of an epileptic patient and the second drug is considered only when the patient does not respond well with first-line AEDs. Sodium valproate and phenytoin are the two most commonly established first-line anti-epileptic drugs for the treatment of GTCS patients. That's why we planned to take the patients in whom clobazam was given as adjuvant to either phenytoin or sodium valproate and were compared both for quality of life. In short, the results of this comparative evaluation after the collection of data and its analysis show an impact on the quality of life between our study groups. As we all know epilepsy adversely affects the quality of life of the patients so we assessed this parameter to evaluate the impact of our studied drugs as a whole.

The present study was a prospective, comparative study aimed to compare the effect on the quality of life in phenytoin plus clobazam versus sodium valproate plus clobazam treated GTCS patients. Clobazam is an effective adjuvant drug that is used in combination with

other first-line AEDs when seizures are not controlled. No scientific studies are available about the comparative study of the combination of clobazam with phenytoin and sodium valproate in GTCS patients, therefore, we planned to conduct this study.

For this study, 45 patients in Group 1 were taking phenytoin plus clobazam therapy and 45 patients in Group 2 were taking sodium valproate plus clobazam therapy as prescribed by a neurologist for GTCS. They were assessed for ESI-55 questionnaires for quality of life assessment.

The age of patients with epilepsy in our study ranged from 14 to 50 years with a mean age of 26.83 years. The most common age group involved was 14–20 years (43%) which included 26 (44.06%) males and 13 (41.93%) females. Our study results were comparable to Krishn Veni Avvaru according to which the median age was 19.5 years and the majority of cases (49%) were in the age group of 11–30 years [8]. Similar findings [9] were reported by Khan *et al.*

In our study, 59 (65.55%) were male patients and 31 (34.45%) were female patients. Thus male patients predominated in epilepsy with a male-to-female ratio of 1.9:1. Our study results were comparable to Ahangar *et al.*, whose study results also showed similar findings, and a male: female was ratio of 1.9:1 [10]. Kotsopoulos *et al.*, the study confirmed that males had a slightly higher incidence of epilepsy with a median of 50.7/100,000 than did female median of 46.2/100000 using

**Table 2: Comparison of quality of life for two groups**

Questions	Groups	Quality of life assessment at different time interval (mean score±standard deviation)			f value <sup>s</sup> (df=2.88)	p-value <sup>s</sup>
		At 0 month	At 3 month	At 6 month		
Compared to a few months ago, how would you rate your health in general now?	Phenytoin+clobazam group	3.29±0.45	2.51±0.50	2.11±0.48	63.452	<0.001*
	Sodium valproate+clobazam group	3.31±0.46	2.35±0.48	1.95±0.29	213.270	<0.001*
Have you worried about having another seizure?	Phenytoin+clobazam group	3.44±0.54	2.55±0.54	2.22±0.51	84.348	<0.001*
	Sodium valproate+clobazam group	3.64±0.48	2.77±0.55	2.44±0.54	140.691	<0.0018*
Had difficulty to performing work or other activity?	Phenytoin+clobazam group	3.13±0.34	2.37±0.57	1.95±0.29	141.625	<0.001*
	Sodium valproate+clobazam group	3.44±0.50	2.42±0.49	2.08±0.28	202.373	<0.001*
Were you discouraged by your health problem?	Phenytoin+clobazam group	3.42±0.58	2.6±0.53	2.35±0.48	88.985	<0.001*
	Sodium valproate+clobazam group	3.51±0.54	2.71±0.50	2.17±0.38	188.394	<0.001*

#: Independent t test was applied; \$: One-way repeated measure of ANOVA was applied. \*: The difference is significant at the 0.05 level

**Table 3: Pairwise comparison (adjustment for multiple comparisons: Bonferroni) of quality of life assessment at different time intervals**

Questions	Groups	Pairwise comparison of quality of life assessment at different time intervals					
		At 0 month vs. 3 month		At 0 month vs. 6 month		At 3 months vs. 6 month	
		Mean difference	p-value	Mean difference	p-value	Mean difference	p-value
Compared to a few months ago, how would you rate your health in general now?	Phenytoin+clobazam group	0.778	<0.05*	1.178	<0.05*	0.400	<0.05*
	Sodium valproate+clobazam group	0.956	<0.05*	1.356	<0.05*	0.400	<0.05*
Have you worried about having another seizure?	Phenytoin+clobazam group	0.889	<0.05*	1.222	<0.05*	0.333	<0.05*
	Sodium valproate+clobazam group	0.867	<0.05*	1.200	<0.05*	0.333	<0.05*
Had difficulty performing work or other activities?	Phenytoin+clobazam group	0.756	<0.05*	1.178	<0.05*	0.422	<0.05*
	Sodium valproate+clobazam group	1.022	<0.05*	1.356	<0.05*	0.333	<0.05*
Were you discouraged by your health problem?	Phenytoin+clobazam group	0.822	<0.05*	1.067	<0.05*	0.244	<0.05*
	Sodium valproate+clobazam group	0.800	<0.05*	1.333	<0.05*	0.533	<0.05*

\*The mean difference is significant at the 0.05 level

systemic review and meta-analysis of incidence studies of epilepsy and unprovoked seizures [11]. Pal *et al.* in neuroepidemiology of epilepsy in Northwest India also reported that males were found to have a higher risk of epilepsy than females [12].

In our study, majority of patients, that is, 45 (50%) did not qualify for the 12<sup>th</sup> standard, 20 patients (22.23%) qualify the 12<sup>th</sup> standard or above, and 25 (27.77%) were illiterate. Hence, the majority of patients were of primary school education. Our study findings are consistent with Krishna Veni Avvaru according to which out of 100 patients 45 had primary education, 29 had secondary education, while 19 were illiterate [8].

In our study, distribution of epileptic patients according to locality, the majority of patients 49 (54.45%) belong to rural areas while 41 (45.55%) belong to urban areas. Our study findings are comparable to Ahangar *et al.*, whose study results showed that 37.3% of patients were from urban areas and 62.7% of patients belonged to rural areas [10]. According to Santhosh *et al.*, our Indian data show a prevalence rate of 5.11 and 5.47/1000 in urban and rural areas, respectively [13].

For assessment of quality of life, questions were asked about health in general, worries about another seizure, difficulty in performing the work, and discouragement due to health problems. The scores ranged from 5 to 1; the lesser the score better the performance and the scores for both the groups were compared at 0 and 6 months. For assessing improvement in general health, the mean score was 3.29 and 3.31 for the phenytoin plus clobazam group and sodium valproate plus clobazam group at 0 month which improved to 2.11 and 1.95 in the respected group at 6 months so we found 35.87% improvement in phenytoin plus clobazam group and 41.09% improvement in sodium valproate plus clobazam at the end of 6 month follow-up period, so better improvement was shown by sodium valproate plus clobazam group but the difference was not found statistically significant.

When the patients were asked about worries about another seizure, the mean score was 3.44 and 3.64 for the phenytoin plus clobazam group and sodium valproate plus clobazam group at 0 month which improved to 2.22 and 2.44 in the respected group at 6 months so we found 35.47% improvement in phenytoin plus clobazam group and 32.97% improvement in sodium valproate plus clobazam at the end of 6 months follow-up period, here better improvement was shown by phenytoin plus clobazam group but the difference was not found statistically significant.

Work performance and other activity difficulty mean score ranged between 3.13 and 3.44 in the phenytoin plus clobazam group and sodium valproate plus clobazam group in initial month which improved to 1.95 and 2.08 in the respected group at 6 months so we found 37.7% and 39.54% improvement in respected groups at the end of 6 month follow-up period, so better improvement was shown by sodium valproate plus clobazam group and difference was also found statistically significant (p=0.03).

Discouragement score due to health problem was 3.42 and 3.51 in the phenytoin plus clobazam group and sodium valproate plus clobazam group in the initial month which improved to 2.35 and 2.17 in the respected group at 6 months so we found 31.29% and 38.18% improvement in respected groups at the end of 6-month follow-up period, so better improvement was shown by sodium valproate plus clobazam group but the difference was not found statistically significant.

According to previous study by Weinstock *et al.*, positive well-being was seen in patients with clobazam as adjuvant therapy for Lennox-

Gastaut syndrome in children where patients showed improvement in quality of life indices including 62.5% in physical activity, 37.5% in well-being, 87.5% in cognition, 37.5% in social activities, and 50% in general health [14].

## CONCLUSION

After evaluation, we concluded that phenytoin plus clobazam helped the patients to cope better with their worries to have another seizure while sodium valproate plus clobazam was found better for work performance and improvement in health and courage. We concluded that both combinations of our study groups have a better impact on quality of life but on comparison between them, we have not found a statistically significant difference. There was a significant improvement in quality of life questionnaires seen in each question in both the groups (within a group) from baseline till the end of the study.

## CONFLICT OF INTEREST

Nil.

## SOURCE OF FUNDING

Nil.

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