

ORIGINAL RESEARCH

Evaluation of the clinical efficacy of phenytoin plus clobazam in the treatment of generalized tonic-clonic seizure patients

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ABSTRACT

Objectives: To evaluate the effect of phenytoin plus clobazam among generalized tonic-clonic seizure (GTCS) patients attending neurology out-patient department at tertiary care center in Gwalior district. **Methods:** Present study was prospective study conducted between period of February 2019 to January 2020 on 45 patients receiving phenytoin plus clobazam for the treatment of patients with Generalized tonic clonic seizures. Mean, standard deviation, one-way repeated measures of ANOVA were applied and Bonferroni Adjustment calculated. P value <0.05 was considered to be statistically significant. **Results:** Average age of participants was 28.84±12.76 years with male to female ratio as 1:2. The mean of seizure frequency in the first visit, second visit and third visit was 3.38±0.96, 1.53±0.63 and 0.73±0.65 per month respectively. Significant reduction was seen within the group as compared to baseline to 3rd month and 6th month visits (P <0.01). **Conclusion:** It can be concluded that phenytoin plus clobazam for the treatment of generalized tonic-clonic seizure (GTCS) patients is effective.

Key Words: Anti-epileptic drugs, Epilepsy, Seizure.

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INTRODUCTION

Epilepsy is a serious and commonest neurological abnormality affecting a large population.[1] In general, a seizure means paroxysmal abnormal discharge at high frequency from an aggregate of large number of neurons in cerebral cortex, while epilepsy is a condition characterized by recurrent, unpredictable, unprovoked episodes of such seizures.[2] Epilepsy is not a disease, but it is a syndrome of various CNS disorders. According to the International League Against Epilepsy (ILAE), epilepsy is defined as 2 or more unprovoked (or reflex) seizures occurring at least > 24 h apart.[3] Generalized seizures are characterized by involvement of whole cerebral hemisphere from the onset. Generalized seizures are further subdivided into tonic clonic, absence, myoclonic, atonic and clonic seizures according to presentation. [4] The factors influencing the treatment are seizure severity, unpredictability, stigma, fear, anxiety, cognitive and psychiatric problems. [5]

Phenytoin has been the standard drug for GTCS and partial seizures, but now it is used when better tolerated newer drugs cannot be used. Clobazam is in use for almost four decades since its introduction in 1975. It is less sedative and long acting among Benzodiazepines and is active against partial and generalized seizure in patient of all ages but is usually indicated as adjuvant therapy with other antiepileptic drugs (AEDs) when monotherapy is not adequate.[2] This drug is also not very expensive as compare to other newer anti-epileptic drugs. In India, per day cost of therapy with clobazam is one third of topiramate, half of lamotrigine and approx. similar as that of valproate and carbamazepine therapy.[6]

OBJECTIVES

To evaluate the clinical efficacy of phenytoin plus clobazam in GTCS patients attending neurology out patient department (OPD) at Gajra Raja Medical College, Gwalior in Madhya Pradesh

MATERIALS AND METHODS

Present Prospective 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 duration of 12 months from February 2019 to January 2020.

SAMPLE SIZE

Present study was conducted for 45 patients receiving phenytoin plus clobazam therapy for the treatment of having complaints of Generalized tonic clonic seizures. The follow-up had been done at 3 month and 6 months from the first visit (baseline).

INCLUSION AND EXCLUSION CRITERIA

All medically stable patients of more than 14 year 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 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, breast feeding mothers, child bearing age mothers using contraception and Patient with serious co-morbidity, diabetes, hepatic insufficiency, BP instability: pulse <50 or >100, SBP<50 or >180 were excluded from the study.

ETHICAL APPROVAL

Study was ethically approved by institutional ethics committee (IEC) of Gajra Raja Medical College, Gwalior.

STATISTICAL ANALYSIS

All the data analysis of this study was performed by suitable statistical methods by using SPSS ver.22 software. Quantitative variables were expressed as the mean and standard deviation. One-way repeated measures ANOVA followed by Bonferroni Adjustment for multiple comparisons were calculated and P value <0.05 was considered to be statistically significant.

RESULTS

For this study, 45 patients were taking Phenytoin plus clobazam therapy as prescribed by neurologist for GTCS. Average age of participants in group 1 (Phenytoin + clobazam) was 28.84±12.76 years. Sex Ratio (female: male) was 1: 2. In this study majority of patients i.e., 25(55.6%) were primary educated followed by 10 (22.2%) patients were illiterate. In this study, 21 (46.7%) patients were from rural background and 24 (53.3%) were from urban areas. [Table 1]

Table 1: Baseline characteristics of the participants

Baseline characteristics		Phenytoin + clobazam Group (n=45)	
		Frequency	Percentage
Age Group (in Years)	14-20 Years	17	37.8
	21-30 Years	10	22.2
	31-40 Years	8	17.8
	41-50 Years	10	22.2
Gender	Female	15	33.3
	Male	30	66.7
Education status	Illiterate	10	22.2
	Primary	25	55.6
	Intermediate	3	6.7
	Graduate and above	7	15.6
Area of residence	Rural	21	46.7
	Urban	24	53.3

The mean of seizure frequency in the first visit was 3.38±0.96 per months, which gradually decreased significantly in the second (1.53±0.63) and third visits to 0.73±0.65 with percent reduction of 54.7% from baseline at 3 month and 78.4% from baseline at 6 month. Significant reduction was seen within the group as compared to baseline at 3 and 6 months (P <0.01). [Table 2]

Table 2: Comparison of mean seizure frequency at three visits

Seizure frequency (Per month)		First Visit (At baseline)	Second Visit (At 3 month)	Third Visit (At 6 month)
Mean		3.38	1.53	0.73
Standard Deviation		0.96	0.63	0.65
Standard Error		0.14	0.09	0.09
95% Confidence Interval	Lower Bound	3.09	1.34	0.54
	Upper Bound	3.67	1.72	0.93

P Value	0.0000#
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#Repeted measure of ANOVA was applied

Pairwise comparison was done to see which pair differed statistically significant. It was found that all the three pair i.e., 1st visit vs 2nd Visit, 1st visit vs 3rd Visit and 2nd visit vs 3rd Visit was differed for the mean difference in Seizure frequency ($p < 0.01$). [Table 3]

Table 3: Pairwise Comparisons(Post Hoc comparison test):

Measures		1 st visit vs 2 nd Visit	1 st visit vs 3 rd Visit	2 nd visit vs 3 rd Visit
Mean Difference		1.84	2.64	0.80
Std Error		0.09	0.13	0.09
95% Confidence Interval for Difference	Lower Bound	1.61	2.31	0.57
	Upper Bound	2.08	2.98	1.03
P Value		0.000 *	0.000*	0.000*

*Bonferroni test was applied for pairwise comparison

DISCUSSION

The present study was conducted to evaluate the efficacy of phenytoin plus clobazam among generalized tonic-clonic seizure (GTCS) patients. Forty-five patients were analyzed. Among the participants, the majority were male and average age of participants were 28.84 ± 12.76 years. 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 primary educated followed by illiterate. In this study, 21 (46.7%) patients were from rural background and 24 (53.3%) were from urban areas.

Our study results were comparable to Avvaru K et al. [7] who reported median age as 19.5 years and majority of cases (49%) were in the age group of 11-30 years. Similar findings were reported by Khan N et al. [8].

In our study 59(65.55%) were male patients and 31(34.45%) were female patients. Thus male patients predominated in epilepsy with male to female ratio 1.9:1. Our study results were comparable to Ahangar JA et al [9] whose study results also showed similar findings, male: female was ratio 1.9:1. Kotsopoulos IA et al, [10] study confirmed that male had a slightly higher incidence of epilepsy with male median, 50.7/100,000 than did female median, 46.2/100000 by using systemic review and Meta-analysis of incidence studies of epilepsy and unprovoked seizures. Pal S et al. [11] in Neuroepidemiology of epilepsy in northwest India also reported the male were found to have higher risk of epilepsy than female.

In the present study the mean of seizure frequency in the first visit was 3.38 ± 0.96 per months, which gradually decreased significantly in the second (1.53 ± 0.63) and third visits to 0.73 ± 0.65 with percent reduction of 54.7% from baseline at 3 month and 78.4% from baseline at 6 month. Significant reduction was seen within the group as compared to baseline at 3 and 6 months ($P < 0.01$). Study conducted by Das S. [12] observed the efficacy of clobazam found that 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. Clobazam is an effective adjuvant drug is used in combination with other first line antiepileptic drugs, when seizures are not controlled.

Epilepsy is the tendency to have recurrent, unprovoked seizures. Although 70% of epileptic seizures can be controlled with monotherapy (treatment by single antiepileptic drug), a combination of two or more anti-epileptic drugs (AEDs) may be required to improve efficacy (seizure control) and tolerability. Polytherapy (treatment with two or more AEDs) can affect efficacies and side effects in additive, supra-additive (synergistic) or infra-additive fashion. The effect is considered supra-additive when the efficacy of the combination is greater than the sum of the individual drug efficacies, while it is considered infra-additive when the efficacy of the combination is less than the sum of the individual drug efficacies. Here, we have reviewed the available studies and evidences for the application of polytherapy in humans and animal models, to understand which combination of AEDs act as a synergistic polytherapy for epilepsy. Though effectiveness of this combination is supported by human data, there is the possibility of increased side effects. [13] Montenegro et al. [14] observed that out of the 62 patients newly started on Clobazam, 7 patients (11.3%) became seizure-free for at least 6 months after introduction of Clobazam. In addition to decrease in seizure frequency, clobazam improves global assessment consistent with improved cognitive and behavioral performance.

CONCLUSION

Significant reduction in the mean of seizure frequency was seen when baseline findings compared with at 3rd months (2nd visit) and 6 months (3rd visit). It can be concluded that phenytoin plus clobazam for the treatment of generalized tonic-clonic seizure (GTCS) patients is effective.

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CONFLICT OF INTEREST

Nil

SOURCE OF SUPPORT

Nil

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