Original Research Article

Clinicopharmacological study to compare efficacy and safety of clobazam as adjunctive with phenytoin or sodium valproate in generalized tonic clonic seizure patients: A prospective study

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Abstract

Background: Epilepsy is a common neurological abnormality affecting about more than 50 million of world population. Combination therapy is used when monotherapy found insufficient to control seizure attacks. **Objective**: The present study was planned to compare the efficacy and safety of clobazam with phenytoin or sodium valproate in generalized tonic clonic seizure patients. **Methodology:** A comparative, prospective and open label study was conducted for a period of 6 months on generalized tonic clonic seizure (GTCS) patients attending neurology OPD at tertiary care hospital, Gwalior (M.P.), Patients enrolled in group 1(n=45) received phenytoin plus clobazam and group 2(n=45) received sodium valproate plus clobazam . Follow up was done at 3 and 6 months interval after initiation of study for mean seizure count, patient responses to treatment and adverse effects. **Results:** Statistically significant ($p < 0.01$) reduction was observed in mean seizure count in both groups as compared to baseline while on intergroup comparison, no statistically significant reduction was seen . 38% patients in group 1and 49% patients in group 2 were total seizure free while 58% patients in group1 and 49% patients in group 2 showed good response and 4% patients in group 1while 2% patients in group 2 showed poor responses. Statistically significant difference was observed for GI distress ($p<0.05$) and rest of the adverse effects were reported mild in both groups. **Conclusion:** Clobazam was found effective and safe adjuvant with phenytoin and sodium valproate in treating GTCS. Sodium valproate plus clobazam treated patients showed clinically better results as compared to phenytoin plus clobazam.

Key words: Clobazam, sodium valproate, phenytoin, GTCS.

Introduction

According to world health organization epilepsy accounts for 0.5% of the global burden of disease; about 80% of burden of epilepsy is in developing countries. Indian data shows general prevalence rate of 5.33 per 1000, with 5.11 and 5.47 in urban and rural areas respectively. [1]

Drug therapy is always main stay of treatment for patients with epilepsy.

Phenytoin, carbamazepine,sodium valproate, phenobarbitone and ethosuximide are generally used as first line drugs for most of seizure disorders.[2]Although drug therapy can often control the manifestation of the disease but antiepileptic drugs do not cure epilepsy. Monotherapy should remain the treatment of choice for newly diagnosed epilepsy but all seizures are not controlled by monotherapy in adequate proportion of patients [3]; may be due to lack of efficacy and failure of first line anti epileptic drugs (AEDs) .Unfortunately, approximately one-third of patients who use antiepileptic drugs (AEDs) fail to have seizures controlled for at least 1 year [4], so combination of two AEDs is considered for better seizure control.

Phenytoin has been the standard drug for GTCS and partial seizures, act by blocking voltage activated sodium channels[5] 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. [6]

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Worldwide, sodium valproate and phenytoin are commonly used antiepileptic drugs as monotherapy. It is generally believed that phenytoin is more effective for focal onset seizures, and sodium valproate is more effective for generalized onset tonic-clonic seizures (with or without other generalized seizure types). [7]

Clobazam binds allosterically to the GABAA receptor to exert its anticonvulsant and anxiolytic effects. [8] It is less sedative and long acting among other benzodiazepines and is active against partial and generalized seizure in patient of all ages but is usually indicated as adjuvant therapy with other AEDs when monotherapy is not adequate. [9] Clobazam should be considered early when first-line drugs fail to provide control or are poorly tolerated. [4]This drug is also not very expensive as compare to other newer anti epileptic drugs.

Literature survey revealed very less scientific comparative study of clobazam as add on drug with two commonly prescribed first line antiepileptic drugs i.e. Phenytoin and Sodium valproate in GTCS patients are available; therefore present study was conducted to compare safety and efficacy of phenytoin plus clobazam and sodium valproate plus clobazam combination in GTCS.

Materials and methods

This was a prospective, observational, open label, comparative and unicentre study conducted from February 2019 to January 2020 at neurology out patients department attached to J.A. Group of hospitals, Gajra Raja medical college, Gwalior (M.P.).The study was conducted after obtaining clearance and approval from the Institutional Ethics Committee (Reference number- 11/IEC-GRMC/2018). Written informed consent from each subject was obtained after the nature of the procedure explained in their vernacular language prior to enrollment in study.

Selection criteria of cases

Inclusion criteria

- Patients who were willing to sign written informed consent.
- Patients could be of either sex.
- All patients of more than 14 year of age group.
- Patients of GTCS enrolled who were receiving either phenytoin plus clobazam or sodium valproate plus clobazam dual therapy.
- Patient must be medically stable.
- Determined to have had at least two episodes of GTCS by neurologist, or to have had a single episode of seizure with abnormal EEG.

Exclusion criteria

- Patients who were not willing to sign informed consent.
- Clinical suspicion of non epileptic psychogenic seizure.
- Pregnant, breast feeding, child bearing age using contraception.
- Patient with serious co-morbidity,diabetes,hepatic insufficiency, BP instability: pulse 100, SBP180.

Study procedure

This study was carried out on out-patients who visited the neurology department of a tertiary care teaching hospital and were diagnosed as the patients of generalized tonic clonic seizure (GTCS) by neurologist on the basis of their clinical finding and EEG reports and who had given clobazam (10 mg once at night) as adjuvant therapy either with phenytoin (100 mg thrice a day) or with sodium valproate (500 mg twice a day) orally, were included. Drugs are provided to patients via government dispensary of hospital. Inclusion and exclusion criteria were followed. Total 106 patients having generalized tonic clonic seizure (GTCS) attacks given either phenytoin plus clobazam (Group 1, n=54) or sodium valproate plus clobazam (Group 2, n=52) were enrolled for the study and follow-up assessment of all the patients was done at 3rd and 6th month. Both the improvement in symptom (seizure) and presence of adverse effects were noted.

For the assessment of efficacy reduction in mean seizure count at 3 and 6 months and patient responses for treatment were observed at 6 months. Number of seizures per month was ascertained from seizure diaries maintained by all patients as these patients were on a regular follow up at 3rd and 6th month.

Patient responses were described as follows: [10]

1) Excellent response/seizure free - proportion of patients achieving cessation of seizure at the end of follow up period of 6 month.

2) Good response/>50% reduction in seizure frequency - proportion of patients with a 50% or great reduction in seizure frequency at 6 month in comparison to baseline period of study.

3) Poor response/<50% reduction in seizure frequency - proportion of patients with a less than 50% reduction in seizure frequency at 6 month in comparison to baseline period of study.

Safety of drug combination was assessed and compared in terms of dropout rate due to adverse events and frequency of adverse events at 3rd and 6th month for assessment of evaluation of safety.

Statistical analysis

All the data analysis of this comparative study was performed by suitable statistical methods by using SPSS ver.20 software.

- Quantitative variables were expressed as the mean and standard deviation.
- Categorical data was expressed in actual numbers and percentage.
- For the intra group comparison of GTCS patients receiving either phenytoin plus clobazam or sodium valproate plus clobazam , statistical analysis was carried out by one way ANOVA repeated measures while Intergroup comparison was done by using unpaired student t test.

Results

In this present study a total of 106 patients were enrolled based on inclusion and exclusion criteria but 90 patients complete the follow up study period of 6 months and 16 patients were dropout from study due to adverse effects and lost to follow up. The participant flow diagram is given in Figure 1.

The age of patients in our study ranged from 14 to 50 years with a mean age of 26.83years. Most common age group involved was 14-20 yr that included 26(44.06%) male and 13(41.93%) female. Male preponderance (65.55%) was observed in our study population.

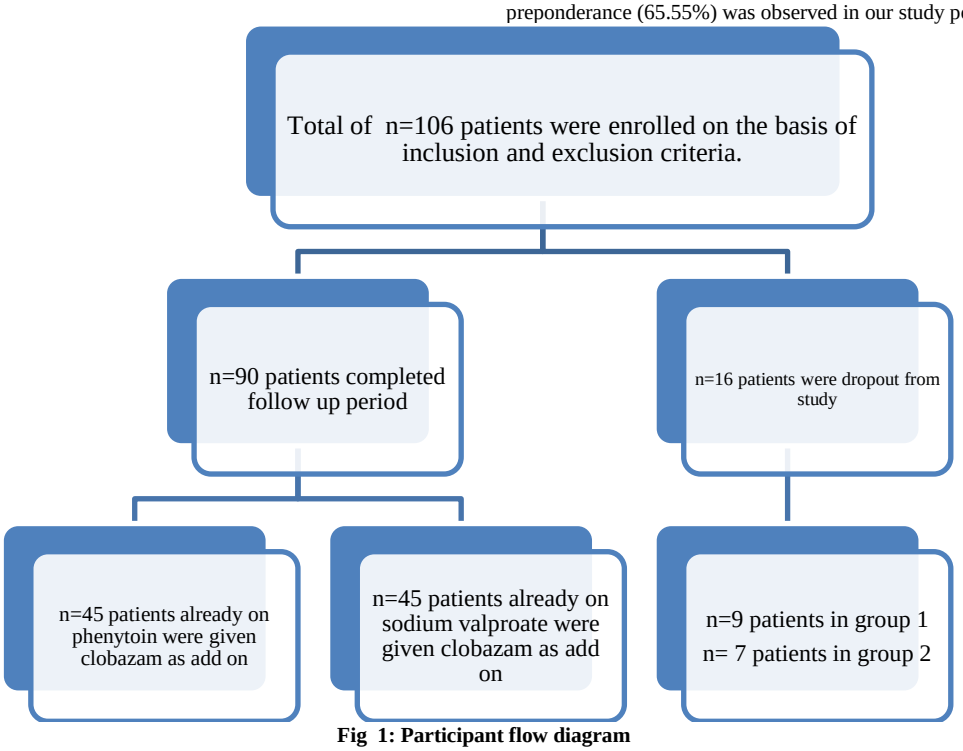

Fig 1: Participant flow diagram

Seizure count

In present study phenytoin plus clobazam group, the baseline values of mean seizure count(mean ±SD) was 3.37±.96 at 0 month, it came down to 1.53±.63, 0.73±.65 at 3 and 6 month respectively with percent reduction of 54.6% and 78.34% from baseline at 3 month and 6 month respectively. Significant reduction was seen in mean seizure count within the group as compared to baseline at 3 and 6 month (P<0.01).

In sodium valproate plus clobazam group, the baseline values of mean seizure count was 3.57±1.38 at 0 month, it came down to1.59±.65, 0.53±.54 at 3 and 6 month respectively with percent reduction of 55.47% and 85.16% from baseline at 3 month and 6month respectively. Significant reduction was seen within the group as compared to baseline at 3 and 6 month (P<0.01).

On comparison between two groups, Sodium valproate +clobazam (group 2) showed better outcome as compare to Phenytoin plus clobazam (group 1) but difference was not observed statistically significant at 3 month (P value = 0.74) and 6 months (P value =0.11) {Table 1}.

Table 1: Mean seizure count at different time interval

Groups	Mean seizure count			P value
	At baseline (Mean±SD)	At 3 mth(Mean±SD)	At 6 mth(Mean±SD)	
Phenytoin plus clobazam (n=45)	3.37±.96	1.53±.63[a]	0.73±.65[ab]	**0.01**
Sodium valproate plus Clobazam (n=45)	3.57±1.38	1.59±.65[a]	0.53±.54[ab]	**0.01**
P value	**0.43**	**0.74**	**0.11**	

Unpaired student's t test, P (<0.05) considered to be significant & ANOVA Repeated measures P [a]< 0.01considered to be significant as compared to baseline, while p [b]<0.01 considered to be significant as compared to 3rd month.

Patient responses to treatment

In this present study table 2 shows patient responses in terms of reduction in seizure count as a measure of efficacy at the end of follow up period of 6 months.In phenytoin plus clobazam group, 17 (37.8%) out of 45 patients become seizure free which showed excellent response while 26(57.7%) patients had 50% or great reduction in seizure which showed good response and 2(4.44%) patients had <50% reduction which showed poor responses.

In sodium valproate plus clobazam group, 22(48.8%) out of 45 patients become seizure free which showed excellent response while 22(48.8%) patient had 50% or great reduction in seizure which showed good response and 1(2.22%) patient had <50% reduction which showed poor response.Thus on comparison between groups, in phenytoin plus clobazam group, 43 out of 45 patients become well controlled while in sodium valproate plus clobazam group, 44 out of 45 patients become well controlled that showed improvement.{ table 2}

Table 2: Patient response to treatment observed in terms of reduction in seizure count at the end of follow up period of 6 month

Groups	Excellent response/seizure free	Good response / >50% reduction in seizure	Poor response/<50% reduction in seizure
	No. of pts (%)	No. of pts (%)	No. of pts (%)
Phenytoin plus clobazam	17(37.8%)	26(57.7%)	2(4.44%)
Sodium valproate plus clobazam	22(48.8%)	22(48.8%)	1(2.22%)

Study of safety

a. Drop out

Total 54 patients were enrolled in phenytoin plus clobazam group, out of which 45 completed the treatment during our study period with follow up. Thus total dropout rate was 16.66% (9 patients) out of which the dropout rate due to adverse effects was 7.40% (4 patients) and the dropout rate due to lost to follow up was 9.25% (5 Patients). In sodium valproate plus clobazam group, a total 52 patients were enrolled, out of which 45 completed the treatment during our study period with follow up. Thus total dropout rate was 13.46% (7 patients) out of which the dropout rate due to adverse effects was 5.76% (3 patients) and the dropout rate due to lost to follow up was 7.69% (4 Patients).{Graph 1}

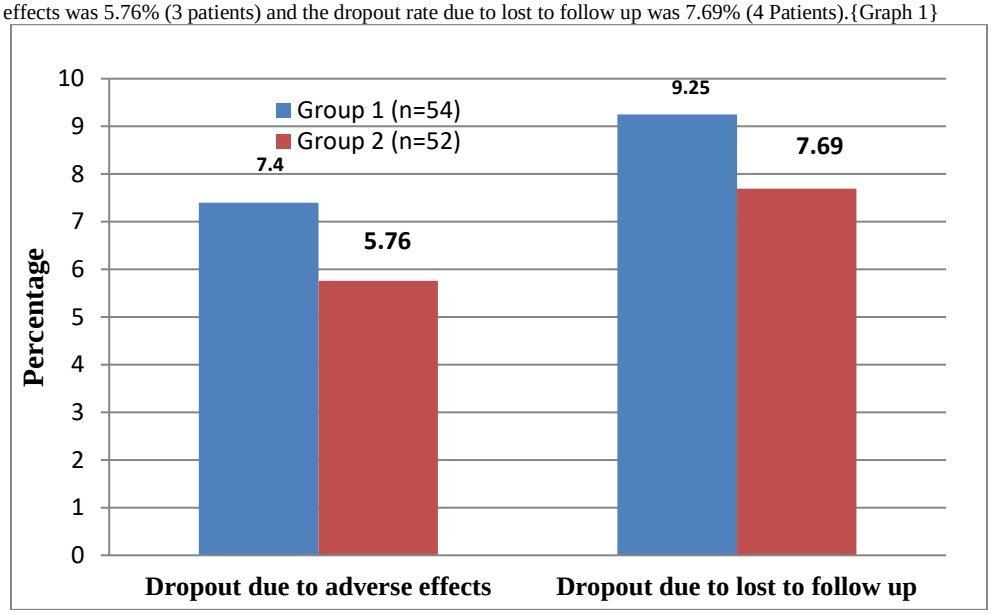

Fig 2:Comparison of dropout rates in both study groups

b. Adverse effects

In this present study on comparison of adverse effects reported by patients at the end of follow up period of 6 month, in phenytoin plus clobazam group, the most common adverse effect was somnolence, which was seen in 16 (35.55%) patients. Next common adverse effect was drowsiness in 15 (33.33%) patients and fatigue/tiredness in 15 (33.33%) followed by dizziness in 10 (22.22%) then irritability/aggressiveness, headache, poor memory/lack of concentration, GI distress, weight gain, gum hypertrophy in 9(20%),7(15.55%),6(13.33%),5(11.11%),2(4.44%),1(2.22%) patients respectively.

In sodium valproate plus clobazam group, the most common adverse effect was again somnolence, which was seen in 18(40%) patients. Next common adverse effect was drowsiness in 14(31.11%) then GI distress in 12(26.26%)patients; then followed by fatigue/tiredness, Irritability/Aggressiveness, Headache, dizziness, Poor memory/lack of concentration, weight gain, tremors in 10 (22.22%),8(17.77%), 7(15.55%), 7(15,55%), 5(11.11%), 5(11.11%), 2 (4.44%) patients respectively.

However statistically significant difference was not found between two groups except for GI distress (P<0.05) {Table 3}.

Table 3: Comparison of adverse events reported by the patients at 6th month (For safety)

S.NO.	Adverse Effects	Group 1 (Phenytoin + clobazam) n=45	Group 2 (Sodium valproate + clobazam) n=45	P value
		No. of patients (%)	No. of patients (%)	
1	Drowsiness	15 (33.33%)	14 (31.11%)	0.822
2	Fatigue/ Tiredness	15 (33.33%)	10 (22.22%)	0.239
3	Dizziness	10 (22.22%)	7 (15.55%)	0.777
4	Somnolence	16 (35.55%)	18 (40%)	0.644
5	Irritability/Aggressiveness	9 (20%)	8 (17.77%)	0.788
6	Headache	7 (15.55%)	7 (15.55%)	1.0
7	Weight gain	2 (4.44%)	5 (11.11%)	0.434
8	Gum Hypertrophy	1 (2.22%)	0 (0%)	1.0
9	Poor memory/lack of concentration	6 (13.33%)	5(11.11%)	0.748
10	G I Distress	5 (11.11%	12(26.26%)	0.04*
11	Tremors	0 (0%)	2(4.44%)	0.494

Chi square test applied to see association b/w adverse effects and groups. If expected count <5 then fisher's chi square test applied.
P value <0.05 considered to be significant (*).

Discussion

The present study showed clobazam as an effective and well tolerated adjuvant antiepileptic drug with two commonly prescribed first line AEDs. The use of a single AED at the minimally effective dose, up to the maximum tolerated dose, is the standard therapy for epilepsy. However, many patients need more than one AED to improve seizure control and clobazam was found one of the commonly used adjuvant and efficacious AED.

In this present study, clobazam was selected as adjunctive AED for patients with generalized tonic clonic epilepsy who were already on either phenytoin or sodium valproate. Patients who received sodium valproate plus clobazam group showed a reduction in seizure count by 85.16% while in phenytoin plus clobazam group where it was 78.34% as compared to baseline at 6 month follow up period but there was no statistically significant difference observed between these groups.

The overall prognosis of epilepsy is favorable in the majority of patients when measured by seizure freedom.[11] In our study we found 17 patients out of 45 (37.8%) in phenytoin plus clobazam group showed excellent response (seizure free) at 6 month while in sodium valproate plus clobazam group 22 out of 45(48.8%) showed excellent response which is comparable to study of Rupa joshi[12] who showed that when clobazam was used as add on with sodium valproate, 44.2% patients become seizure free while with phenytoin 33.3% patients become seizure free. M.M.Mehandiratta[13]found when clobazam used as monotherapy in adult patients with GTCS, 14 out of 16 patients were become well controlled at 24 weeks after initiation of therapy. So our study is comparable to this and showed better results after addition of clobazam with sodium valproate and phenytoin. In our study, in sodium valproate plus clobazam group 44 out of 45 patients were well controlled while in phenytoin with clobazam group 43 out of 45 patients were well controlled in terms of seizure frequency reduction from more than 50% to seizure free.

In our study out of 106 patients, overall 16 patients were dropout (9 in group 1 while 7 in group 2),7 patients left the study due to adverse effects (4 in group 1 while 3 in group 2) while 9 patients were lost to follow up (5 in group 1 while 4 in group 2). R E Ramsay [14] found reason for premature termination of t/t in their study due to adverse effect was 4% in valproate group and 14% in phenytoin group while 7% in valproate group and 2% in phenytoin group were lost to follow up. In this present study, at the end of follow up period, in both groups, the most common adverse effect was somnolence , next common adverse effect was drowsiness and fatigue/tiredness followed by dizziness then irritability/aggressiveness, headache, poor memory/ lack of concentration, GI distress, weight gain, gum hypertrophy, ataxia. Our study results were comparable to study conducted by Joshi [12], most common adverse effect observed in their study were somnolence followed by fatigue/tiredness, poor memory then irritability and headache. Most of them were self limiting. In present study adverse reactions were mild and self limiting and there was no statistically significant difference found in both groups except significant GI complaints were seen in patients who took valproate plus clobazam. Similar finding observed by R E Ramsay[14] , in their study most common side effect was G I complaints ,somnolence, tremor and dizziness in pts taking valproate while in phenytoin group most common side effects was somnolence ,dizziness followed by GI complaints.

Limitation of the study

Our study was conducted in limited number of patients and was for a short duration. Result of this study need to be confirmed by conducting studies on large number of patients at different centers for a long duration. This can help us to know exactly, which combination of our study is better for treatment.

Conclusion

Due to chronic nature, unpredictable pattern of this disease, the treatment is often long term, prophylactic and targeted to prevent further episodes. This calls for regular medications with minimal or

no adverse effects. We concluded that both combinations of our study groups were found effective and safe in treating GTCS but on comparison between them, we have not found statistically significant difference and sodium valproate plus clobazam group showed clinically better results as compare to phenytoin plus clobazam thus sodium valproate plus clobazam can be preferred because of better clinical outcome. Better efficacy of sodium valproate observed in this study may be due to it act through multiple mechanisms: blocks use dependent sodium channels, blocks T type Ca^{2+} Current in thalamic neurons, decrease the release of excitatory neurotransmitter glutamate in brain and GABA facilitatory mechanism.[9,15] Although the exact mechanism of this combined activity is not known. Efficacy of clobazam with its lack of significant side effects and low cost make it potentially useful adjuvant drug by physician in battle against epilepsy. We can implement this combination in those patients who are not able to afford newer costlier AED treatment.

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