



**COMPARISON OF THE EFFICACY OF LEVETIRACETAM AND CLOBAZAM
INDIVIDUALLY AND IN COMBINATION IN THE MANAGEMENT OF GENERALIZED
TONIC-CLONIC SEIZURES IN ATERTIARY CARE HOSPITAL.**

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ABSTRACT

The aim of the study is to compare the efficacy of levetiracetam and clobazam individually and in combination in the management of generalised tonic-clonic seizures. An observational study was carried among patients admitted in the neurology department attending OPD of tertiary care hospital, Hyderabad. The study was carried out for a period of 6 months from September 2019 to February 2020. A total of 91 case sheets were analyzed during that period. A total of 91 case sheets were collected among which 54% were male and 46% were female. It was found that 10-20 years of age group made up the highest percentage of total population consisting upto 33% of the study population and the least populated group was 40-50 and 50-60 age group. Moreover, the results demonstrate that combination shows more efficacy than the individual drugs (levetiracetam and clobazam). This study clearly demonstrates that awareness of generalized tonic-clonic seizures in general the risk factors, signs and symptoms among hospitalized patients is inadequate. The findings of our study may also encourage health-care providers to deliver more education to patients and Patient Health Organizations about Generalized tonic-clonic seizures and their risk-factors, signs and symptoms and preventive measures.

KEYWORDS: Tonic-clonic seizures, levetiracetam, clobazam, efficacy.

INTRODUCTION

Epilepsy is a serious neurological disorder, with the prevalence of ~0.5%–1% in developed countries^[1], and it rises up to 7.4% in developing countries because of inferior health care and a higher proportion of children.^[2]
³ Epileptic seizures are manifested by an abnormal, excessive, and hypersynchronous electrical discharge of neurons in the brain.^[4] Seizures may be the presenting symptom of a brain tumor, or they may occur later during the disease. Only the recurrence of seizures justifies the diagnosis of epilepsy and the use of anticonvulsants.^[5]

A generalized tonic-clonic seizure also known as grand mal seizure is characterized by clonic or myoclonic movements evolving to tonic muscle extension of the limb and trunk muscles followed by clonic contraction.^[6] Patients are usually associated with impaired awareness or complete loss of consciousness. A

generalized tonic-clonic seizure is a motor seizure and the most common type seen in patients with epilepsy. Generalized tonic-clonic seizures arise within and rapidly involve bilateral cortical, subcortical, and brainstem networks of the brain.^[7, 8]

The etiology of most of the generalized tonic-clonic seizures is underlying epilepsy from genetic causes and can be secondary due to head injury which could trigger the brain to cause a seizure. Other factors are low levels of sodium, calcium, glucose or magnesium, brain tumor or a ruptured blood vessel in brain which could cause a stroke. Drug or alcohol abuse or withdrawal, Genetic conditions, Neurological disorders could also be a factor.^[9]

According to a study by Berkovic et al 2007, there is a definite evidence of levetiracetam efficacy as adjunctive

therapy for patients with idiopathic generalized epilepsy and uncontrolled generalized tonic-clonic seizures or generalized myoclonic seizures.^[10, 11] Levetiracetam is a novel Anti-Epileptic Drug, marketed worldwide only since 2000. It was initially only used as adjunctive therapy for partial-onset seizures. However, after recent trials, it earned its approval as adjunctive therapy for primary generalized tonic-clonic seizures and myoclonic seizures and recently earned its approval for use as initial monotherapy in the European Union.^[12] In a study by French J et al, levetiracetam has an equal efficacy compared with conventional AEDs and it is well tolerated for long-term therapy without significant effect on the immune system.^[13]

Clobazam, an older anticonvulsant, with a chemical structure quite different from that of conventional benzodiazepines, is currently utilized in the treatment of epilepsy, which has less sedative properties in terms of negative side effects.^[14] It is also better tolerated than other antiepileptic drugs, retaining similar efficacy. In epileptic patients, clobazam is effective at a minimum dose.^[15] NICE recommends clobazam as an additional treatment option for generalized tonic-clonic seizures.^[16]

Combination therapy is most often initiated due to the occurrence of adverse events or lack of seizure control on maximally tolerated doses of monotherapy. A second anti epileptic drug should be added at a low dose prior to any adjustments of the original AED and then slowly titrated up while simultaneously decreasing the dose of the original AED every 1 to 2 weeks.^[17] In a study done by Margolis JM et al which agreed that anti epileptic drug combinations with different Mechanisms of actions have greater effectiveness as measured by treatment persistence and lowers the risk for hospitalization and emergency department visits.^[18]

However, the choice of antiepileptic drug, whether substituted or added depends upon the treating physician.^[19]

MATERIALS AND METHODS

A Non-experimental (observational) study was carried out for a period of 6 months from September 2019 to February 2020 in a tertiary care hospital, Hyderabad. A total of 91 case sheets were collected of patients admitted in the neurology department attending OPD of the hospital.

Inclusion criteria

- Adults whose condition is generalised tonic-clonic seizures.
- Both the genders.
- Both outpatients and inpatients.
- All age groups.

Exclusion criteria

- Pregnant and lactating women.

- Patient refusal.
- Progressive medical or neurological disorder.
- History of chronic drug or Alcohol abuse.
- Patients with history of drug allergy.

Patient data was collected from patient case files from outpatient and inpatient, Case sheets and treatment charts. All the study specific data were collected and documented in the designed data collection form. The data collected form included the patient demographic details, IP number, admission and discharge date, current diagnosis, past medical history, co-morbidities, current medications with their dose, frequency and duration of the treatment. . The institutional ethics committee's approval was obtained prior to the study. Daily visit was made to the outpatient department to collect the data of the patients to identify the efficacy of antiepileptic drugs. Diagnosis, social history, anti-epileptic drug involved, generic names and brand names were recorded daily. Case sheets were collected from both IP and OP. The patients were followed from the day of admission till the day of discharge or death.

The data was statistically analysed using a GRAPH PAD PRISM. The data was expressed as Mean \pm SD.

RESULTS

Distribution based on demographic data Based on the Gender

This study includes 91 patients, among which 49 are males and 42 are females, out of which as shown in table 1, levetiracetam includes 16 males and 14 females; whereas clobazam include 18 males and 12 females and combination include 15 males and 16 female patients.

Table 1: Gender wise distribution of patients.

Group	Male	Female	Total
Levetiracetam	16	14	30
Clobazam	18	12	30
Combination	15	16	31
	49 (54%)	42(46%)	91

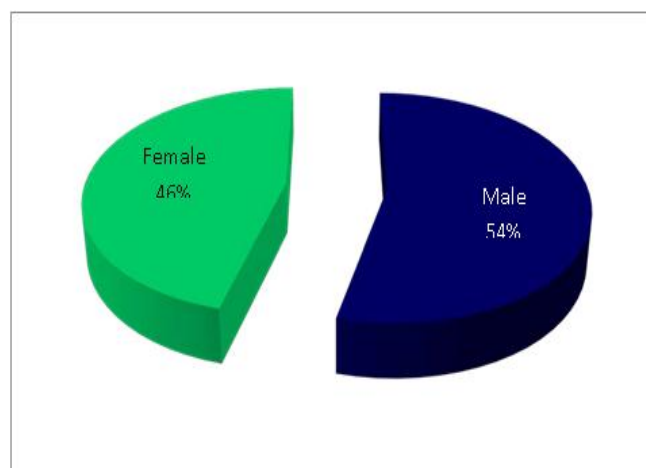


Figure 1: Gender wise distribution.

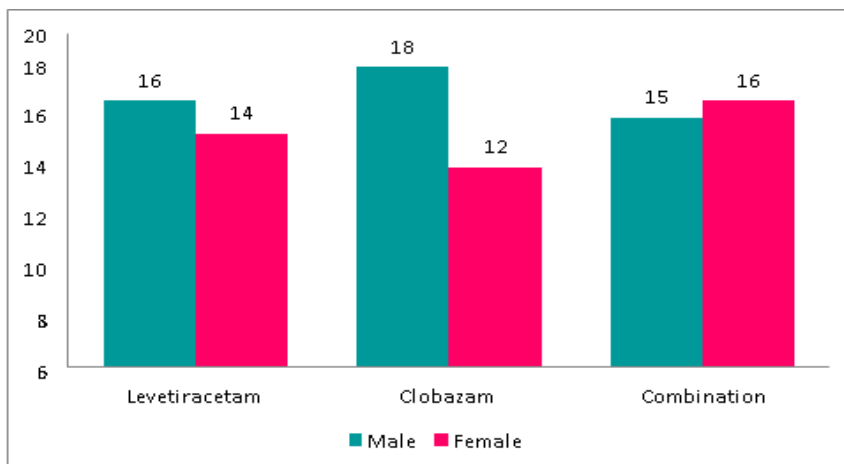


Figure 2: Gender wise distribution of patients (with drugs).

Based on the Age group

The patient distribution was done according to the age groups with 10 years of interval and it was found that 10-20 years of age group made up the highest percentage of total population consisting upto 33% of the study

population, it was followed by 20-30 age group consisting upto 30% of the study population. Whereas patients above 30 was 24% and below 10 age group was 13%. The least populated group was 40-50 and 50-60 age groups in the study population.

Table 2: Distribution of patients based on age group.

Group	<10	10-20	20-30	30-40	40-50	50-60
Levetiracetam	4	10	9	3	2	2
Clobazam	5	8	6	5	3	3
Combination	2	5	3	8	5	8
	11	23	18	16	10	13

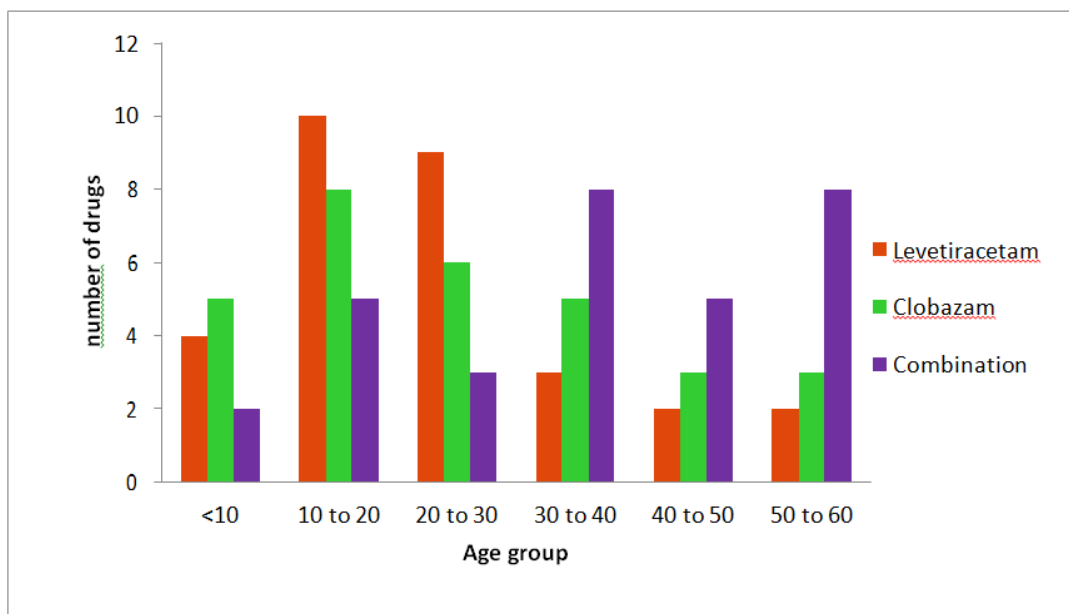


Figure 3: Distribution of patients based on age group.

The distribution of Patients based on Dietary Habits.

It was found that patients following non vegetarian diet

were 66% and the rest 25% were vegetarians.

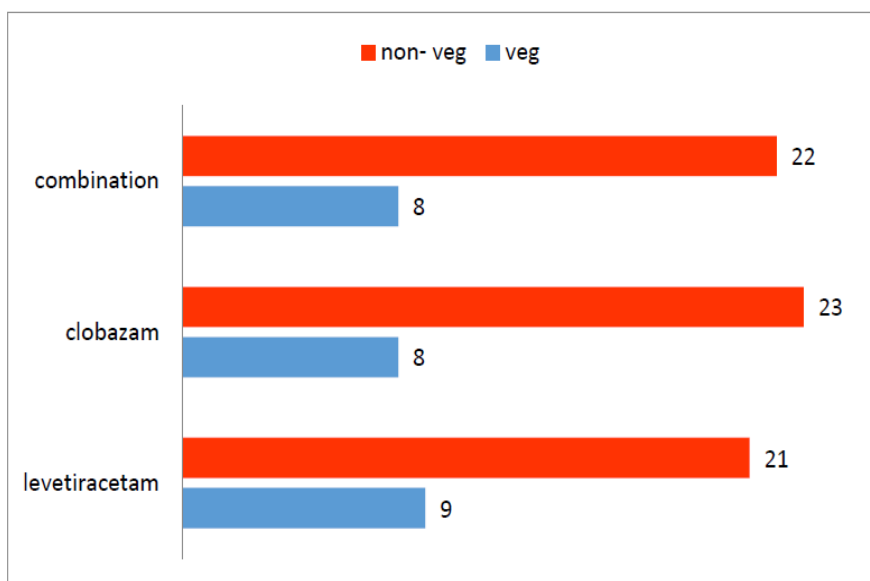


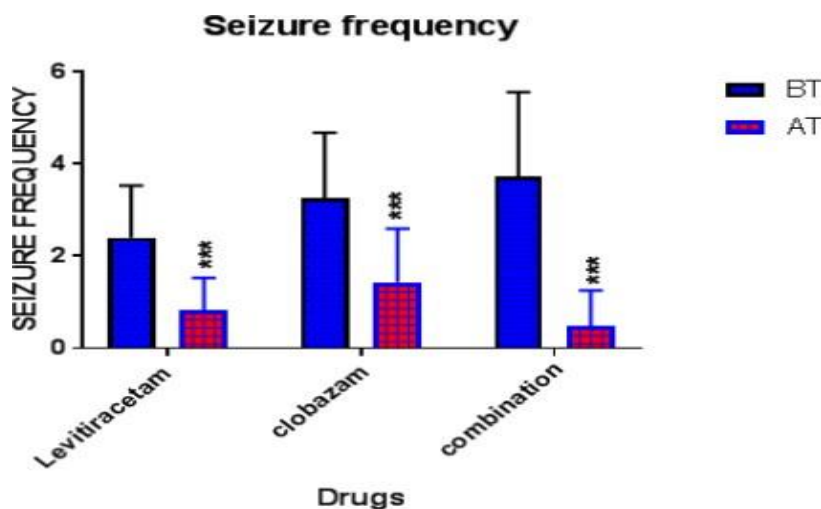
Figure 4: The distribution of Patients based on Dietary Habits.

STUDY OUTCOMES

Efficacy study

The efficacy end point of levetiracetam for treatment of generalized tonic-clonic seizures were observed as Mean(BT) -2.40 & (AT)-0.83 and SD (BT)-1.13 & (AT)-

0.70 respectively in group of patients, using clobazam were observed as Mean- (BT)-3.25, (AT)- 1.43 & SD- BT= 1.4 & (AT)-1.17. Similarly for the combination of both were observed as Mean (BT)- 3.73 & (AT)- 0.48 & for SD (BT)-1.83 & (AT)-0.77 .



Values represented as mean ±SD (n=30) p<0.01 when compared to before treatment.

Figure 5: Seizure frequency of the drugs.

	Before treatment (BT)	After treatment (AT)
Levetiracetam	2.4± 1.13	0.83± 0.70
Clobazam	3.25± 1.43	1.43± 1.17
Combination	3.73± 1.83	0.48± 0.77

***(P<0.01) Significant

ADVERSE DRUG REACTIONS

In the prospective study of generalized tonic-clonic seizures, the combination of both drugs i.e,levetiracetam and clobazam with large frequency of ADRs were reported when compared to individually given drugs.

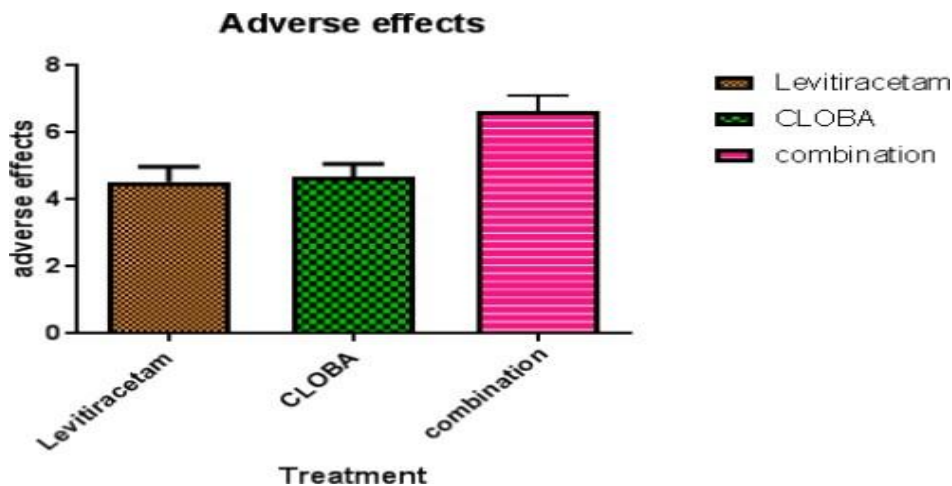


Figure 6: Adverse effects of the drugs.

SIDE EFFECTS IN CLOBAZAM MONOTHERAPY

Clobazam is generally considered safe to use, with only mild side effects when compared to other AEDs. As with any benzodiazepine, there is a risk for dependence. Data from this clinical study collected from over 30 epileptic

adult patients show that the most common side effects include fatigue was noted in 20(93%), sedation in 11(50%), ataxia in 8(40%), abnormal gait in 7(33%) and weight gain in 7 patients (33%).

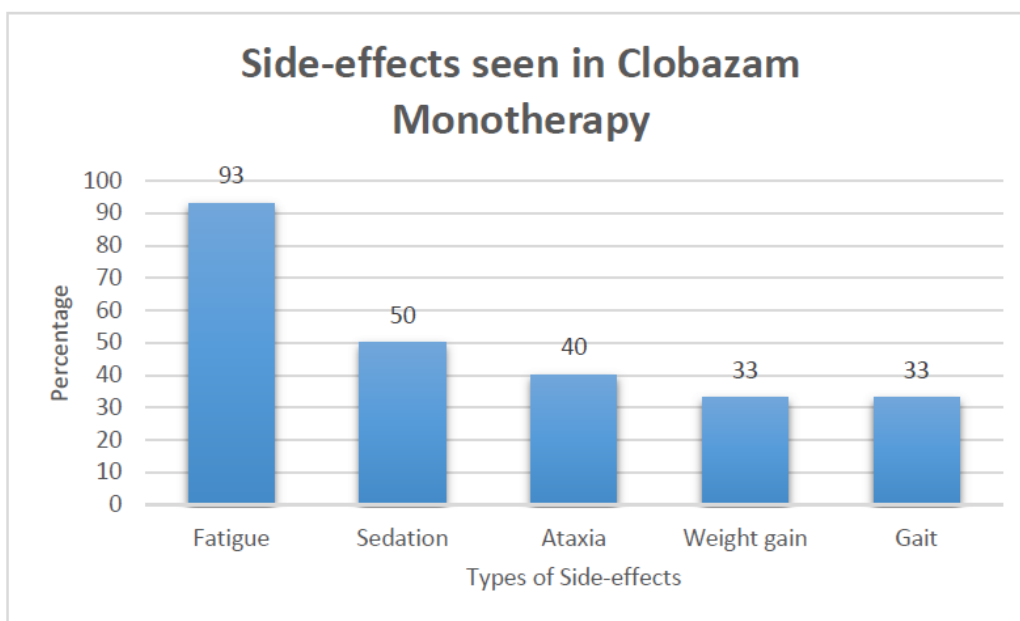


Figure 7: Side Effects seen in clobazam monotherapy.

SIDE EFFECTS IN LEVETIRACETAM MONOTHERAPY

Out of 30 patients who were given levetiracetam 20(66%) patients side effects. The most reported side effects were irritability 3(17%), somnolence 2(8%), behavioural disorders 1(5%), restlessness 1(5%), headache 2(5%).

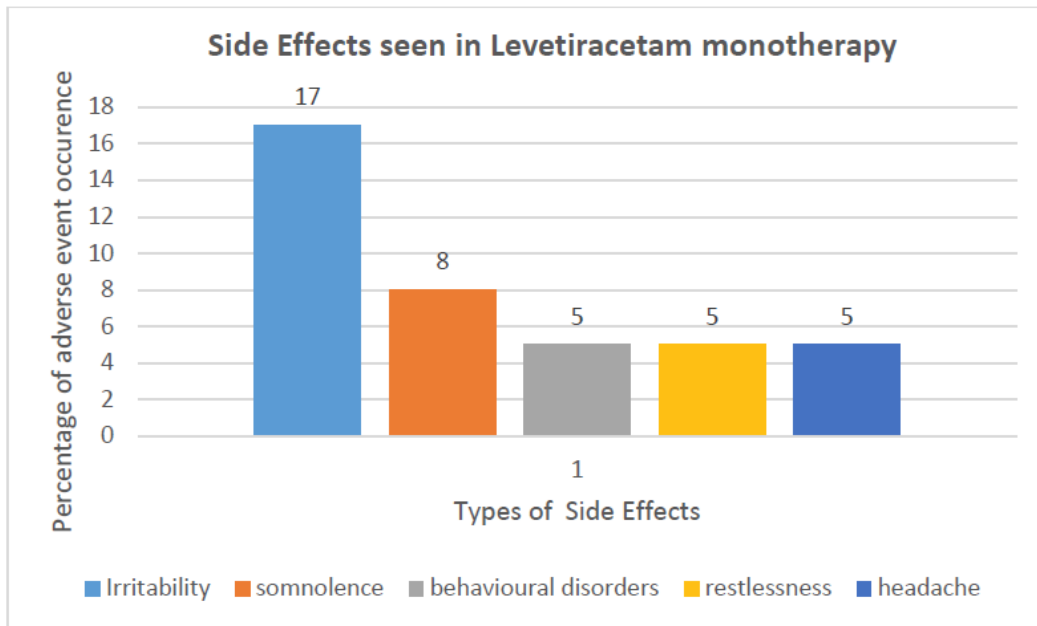


Figure 8: Side Effects Seen In Levetiracetam Monotherapy.

SIDE EFFECTS IN COMBINATION THERAPY OF CLOBAZAM AND LEVETIRACETAM

Out of 31 patients who were given levetiracetam and Clobazam 30(96.7%) patients reported side effects. The

most reported side effects were dizziness in 27(93%), drowsiness in 15(50%), difficulty in concentration 12(40%), confusion in 19(33%) respectively.

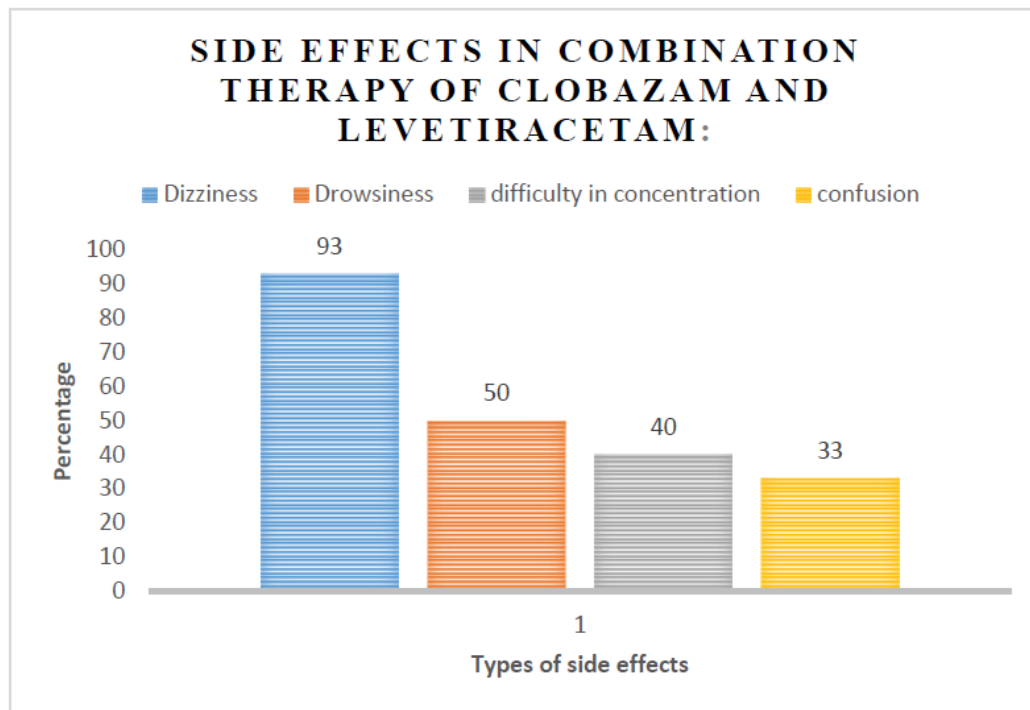


Figure 8: side effects seen in combination therapy of clobazam and levetiracetam.

DISCUSSION

In this non-experimental observational study, patients with generalized tonic-clonic seizures on a dose of Levetiracetam or Clobazam or both the drugs in their treatment regimen were included. The patient characteristics were noted from the case records. The

frequency of occurrence of seizures upon using the drugs either single or in combination were assessed. The data was analyzed using statistical calculations and tools (Graph Pad Prism). The comparison of qualitative data was done by Two-way ANOVA, tukey’s post Test within group pre and posttreatment comparisons were performed

by applying ONE WAY ANOVA. The data was expressed as mean \pm SD. A P-value <0.01 was considered statistically significant.^[20] The study results demonstrate that combination shows more efficacy than the individual drugs (levetiracetam and clobazam) which is similar to a study done by Margolis JM et al shows that anti-epileptic drug combinations with different MOAs have greater effectiveness as measured by treatment persistence and lower risks for hospitalization. Levetiracetam is quite inferior to Clobazam in efficacy but both the drugs have almost equal efficacy.^[18] According to a study by Bresnahan R et al shows that clobazam reduces the seizure frequency for people with drug-resistant focal epilepsy but there was not enough data to determine whether clobazam is as effective for generalised epilepsy.^[21] But in our study, adjuvant therapy of clobazam shows more efficacy than individual drug treatment.

CONCLUSION

A total of 91 generalized tonic-clonic seizure cases were analysed during the study period. The study reveals that majority of patient cases were in the age group of 10-20 years which shows that younger generation is the major sufferer of generalized tonic-clonic seizures. It was found that majority of the cases were male when compared to female.

The study shows predominance in patients without ADRs when compared with other patients with complaints of ADRs. The patients given with combination of both levetiracetam and clobazam drug therapy had more complaints when compared to Individual drugs. The study analysis demonstrates that the efficacy of combination of both the drugs was more when compared with Individual drug. It is interesting that majority of generalized tonic-clonic seizure patient cases were found to be moderate, neither mild nor severe. The patients were mostly treated with combination rather than Individual drugs. The therapeutic outcome of generalized tonic-clonic seizure patient cases reveals that all the cases were found to be improved with no case of death. The results suggest that combination of both the drugs levetiracetam and clobazam are effective in rapid lowering of frequency of seizures than that of individual drugs.

This study clearly demonstrates the awareness of generalized tonic-clonic seizures, the risk factors, signs and symptoms among hospitalized patients is inadequate. Thus, more emphasis should be placed on the education of at-risk patients to promote adherence to treatment which is essential for safe and high quality patient care.

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Authors contribution

All the authors have contributed equally.

Conflict of interest

The authors confirm no conflict of interest for this manuscript.

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