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Research Article

PHARMACOLOGICAL EVALUATION OF LEVETIRACETAM AS ADD-ON DRUG TO EITHER PHENYTOIN OR SODIUM VALPROATE IN PATIENTS OF GENERALIZED ONSET TONIC-CLONIC SEIZURES HAVING BREAKTHROUGH SEIZURES: A RANDOMIZED AND COMPARATIVE STUDY

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ABSTRACT

Objective: Breakthrough seizures are sudden and unexpected seizures that occur in people with epilepsy who generally have good control over the symptoms. The present study is aimed to compare phenytoin plus levetiracetam versus sodium valproate plus levetiracetam to control breakthrough seizures.

Methods: A prospective, comparative study was carried out in Generalized onset tonic-clonic seizures (GTCS) patients with breakthrough seizures in Gajra Raja Medical College, Gwalior (M.P.) from February 2021 to August 2022. Participants were randomly allocated to 2 groups, namely phenytoin + levetiracetam (PL) (n=62) and sodium valproate + levetiracetam (SL) (n=61). Patients in group PL received phenytoin at the dose of 200 mg twice a day in adults, 5 mg/kg/day in two divided doses in children plus levetiracetam 500 mg twice a day in adults and 30 mg/kg/day in three divided doses in children. Patients in group SL received sodium valproate 600 mg 3 times a day in adults, 30 mg/kg/day in three divided doses in children plus levetiracetam 500 mg twice a day in adults and 30 mg/kg/day in three divided doses in children. The mean reduction in seizure frequency and patients response to the treatment in the last 30 days were recorded before the start of therapy and at 3 and 6 months after therapy. Adverse drug reactions were recorded during the study period. Statistical analysis was performed using (Statistical Package for the Social Sciences) software.

Results: Mean seizure frequency decreased by 59 and 85% in PL and by 59 and 91% in the SL group and is significant ($p<0.05$) from baseline value at 3 and 6 months, respectively, in both the groups. SL group showed significantly ($p<0.05$) better response, than PL group in controlling seizures at 6 months. Excellent response by patients was seen by 21% and 49% in PL and SL groups, respectively. Adverse effects noted during the study were mild, including somnolence, headache, dizziness, GIT stress, and fatigue, and responded to symptomatic treatment. Twenty-nine (29%) of PL cases and 6% of SL cases underwent fatigue as adverse drug reactions that showed better tolerability of the SL group.

Conclusion: Sodium valproate plus levetiracetam is more efficacious and safer than phenytoin plus levetiracetam in the management of breakthrough seizures in GTCS patients.

Keywords: Breakthrough seizures, Generalized onset tonic-clonic seizures, Phenytoin, Sodium valproate, Levetiracetam.

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INTRODUCTION

Epilepsy is characterized by the sudden firing of neurons followed by with or without loss of consciousness, abnormal body movements, and autonomic hyperactivity [1]. A seizure is an episode of brain dysfunction due to abnormal discharge of neurons. Two main types of seizures include generalized and partial seizures [2].

Approximately 10% of patients with epilepsy suffer from generalized onset tonic-clonic seizures (GTCS). The seizure usually begins abruptly without any warning, although some patients describe vague premonitory symptoms in previous hours, such as feelings of fear sadness, anxiety, twitching, or jerky movements leading up to the seizure [3]. Phenytoin and sodium valproate have been used as monotherapy from the old times for GTCS. These are the standard first-line drugs having good ant-seizure activity [4].

A breakthrough seizure is defined as an epileptic seizure that occurs in spite of the use of antiepileptic drugs (AEDs) that have otherwise successfully prevented seizures in the patient [5]. Breakthrough seizures might occur for a variety of reasons: Insufficient dose of AED to reduce the seizure rate to zero, missed doses of medication, or provoking factors such as emotional stress, sleep deprivation, alcohol or other recreational drugs, and television or video games [6]. For a few people, the natural history is to develop treatment refractoriness following period of remission, presumably due to ongoing epileptogenic processes [7]. Frequently, the cause of a breakthrough seizure may not be identified. Breakthrough seizures can have severe clinical consequences, like hospital admission either as a result of the seizure or due to injuries sustained during the seizure may lead to status epileptics resulting in elevated morbidity, and potentially mortality [8].

The hypothesis that a combination of drugs offers advantages over monotherapy has been illustrated in a variety of medical fields, including epilepsy therefore, patients having breakthrough seizures with a single AED, an add-on AED which is efficacious and well-tolerated is necessary to control seizures though there is the possibility of increased side effects. Thus, combinations of AEDs should be carefully selected based on the potential for synergy that is not associated with unfavorable pharmacokinetic interactions and toxicity. Levetiracetam is the newer AED that earned its approval as adjunctive therapy for primary GTCS [9]. No scientific data are available in the literature regarding the comparison of the combination of levetiracetam with either phenytoin or sodium valproate, to control breakthrough seizures; therefore, the present study was conducted to compare the safety and efficacy of phenytoin plus levetiracetam versus sodium valproate plus levetiracetam in patients of GTCS with breakthrough seizures when treated with monotherapy.

METHODS

Study design

This is a randomized, comparative, prospective, and open-label study conducted in the Department of Pharmacology and Neurology, Gajra Raja Medical College, Gwalior (M.P.) from March 2021 to February 2022. The study was approved by the Institutional Ethics Committee (Registration number is 127/IEC-GRMC/2020).

Intervention

A total of 123 patients of GTCS were enrolled and randomly divided into two groups. Group phenytoin + levetiracetam (PL) (n=62) received phenytoin at the dose of 200 mg twice a day in adults, 5 mg/kg/day in two divided doses in children plus levetiracetam 500 mg twice a day in adults, and 30 mg/kg/day in three divided doses in children.

Group sodium valproate + levetiracetam (SL) (n=61) received sodium valproate 600 mg 3 times a day in adults, 30 mg/kg/day in three divided doses in children plus levetiracetam 500 mg twice a day in adults, and 30 mg/kg/day in three divided doses in children.

Inclusion criteria

All GTCS patients who were on monotherapy with either phenytoin or sodium valproate and having breakthrough seizures were included in the study.

Exclusion criteria

The following were excluded from the study:

1. Patients who are not willing to sign informed consent
2. Clinical suspicion of non-epileptic psychogenic seizure
3. Pregnant, breastfeeding, childbearing age women using contraceptives
4. Patient with serious comorbidity, diabetes, hepatic insufficiency, pulse <50 or >100, SBP<50 or >180.

Informed consent was taken from all the study participants. A detailed medical history was taken. A general and systemic examination was done.

Evaluation of efficacy

1. Reduction in mean seizure frequency observed in the last 30 days at the end of follow-up period that is 3 months and at 6 months to assess efficacy [10]. Number of seizures per month were ascertained from the seizure diary, which the patients were asked to maintain.
2. Patient's responses observed in terms of no seizures or >50% reduction in seizure frequency or <50% reduction in frequencies and were considered as excellent response, good response, and poor response at the end of follow-up period at 3 months and 6 months [11].

Evaluation of safety

The safety of the drug combination was assessed and compared in terms of dropout rate due to adverse events and frequency of adverse events in the 3rd and 6th months.

Statistical analysis

All the data analyses of this comparative study were performed using the Statistical Package for the Social Sciences Software. Quantitative variables were expressed as the mean and standard deviation. Categorical data were expressed in actual numbers and percentages. For the intra-group (within group) comparison statistical analysis was carried out by paired "*t*" test satisfying the normality assumption using the K-S test. Intergroup comparison was done using an independent student "*t*" test satisfying the normality assumption using the K-S test. Chi-square test was used to compare the categorical data. "p"<0.05 was considered to be statistically significant.

RESULTS

The patients disposal has been depicted in the consolidated standard for reporting trials (Fig. 1).

Demographic profile

The groups were having similar characteristics at baseline concerning age and other characteristics (Table 1).

Efficacy assessment

Reduction in seizure frequency

In group PL, mean seizure frequency in the last 30 days showed a percent reduction of 59% and 85% from baseline at 3 and 6 months, respectively, and was significant (p<0.01) as compared to baseline. In group SL, mean seizure frequency in the last 30 days showed a percent reduction of 59% and 91% from baseline at 3 and 6 months, respectively, and was significant as compared to baseline (p<0.01) (Table 2). On comparison between PL and SL groups, no difference wasseen in the reduction of seizure frequency at 3 months (p=0.331) but statistically significant better reduction of seizure frequency was seen with SL group at 6 months (p=0.002).

Patient response observed at the end of follow-up period of 6 months

In the PL group, 10 (21%) patients became seizure-free, which showed an excellent response, whereas 38 (79%) patients had 50% or great reduction in seizure which showed a good response. None of the patients showed poor response. In the SL group, 23 (48%) out of 48 patients became seizure-free, which showed an excellent response, whereas 25 (52%) patients had 50% or great reduction in seizure, which showed a good response. None of the patients showed a poor response (Fig. 2) On inter-group comparison, excellent response seen in the SL group is more significant than PL group (p=0.002).

Safety assessment

In group PL, the most common adverse effect was drowsiness, which was seen in 22 (46%) patients. The next common adverse effect was somnolence and irritability in both 16 (33%) patients and fatigue/tiredness in 14 (29%), followed by headache in 13 (27%) then dizziness in 11 (23%), GI stress in 4 (8%), hypersensitivity reaction, poor memory/lack of concentration, gum hypertrophy each seen in 1 (2%) patient, respectively.

In group SL, the most common adverse effect was somnolence, which was seen in 23 (48%) patients. The next common adverse effect was dizziness in 19 (40%) and headache in 19 (40%) patients followed by irritability/aggressiveness in 18 (37%) patients, drowsiness in 13 (27%) patients, fatigue in 6 (12%) patients, GI distress in 5 (10%) and hypersensitivity and poor concentration/lack of memory each in 1 (2%) patients, respectively (Table 3).

Fatigue was seen in 14 patients of group PL and only 6 patients of group SL. A statistically significant difference between the two groups was found for fatigue/tiredness (p=0.044) at the 6th month, all other adverse effects have no statistically significant difference (p>0.05) between the two groups.

The dropout rate was equal in both groups, which included 14 patients and 13 patients in PL and SL groups, respectively. Nine and 7 patients in group PL and SL, respectively, were lost to follow-up whereas 5 and 6 patients in group PL and SL, respectively, left the study due to adverse effects.

DISCUSSION

Most people with epilepsy can achieve remission from seizures after treatment; however, 37% of these individuals develop breakthrough seizures [12]. These patients need a combination of two or more AEDs to improve the efficacy (seizure control) and tolerability of the treatment and to obtain better control of the refractory seizure when monotherapy failed [13]. The combination of AEDs having synergistic effects with no addition of adverse effects is the key to success. Levetiracetam is a second-generation AED that is chemically unrelated to other AEDs acts by a novel mechanism, is preferred nowadays owing to its better tolerance and fewer adverse effects [14].

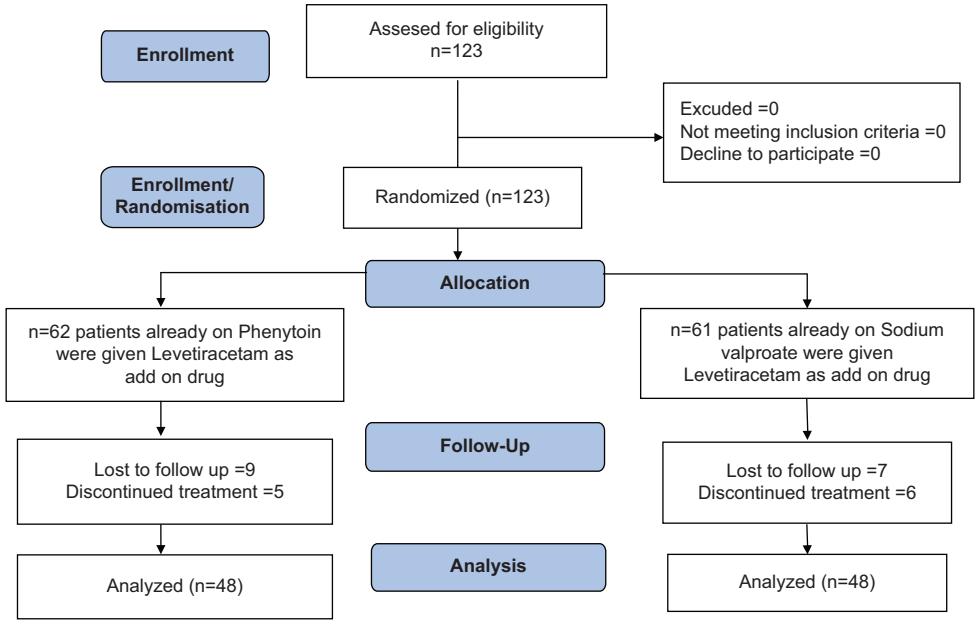

Fig. 1: CONSORT flow diagram

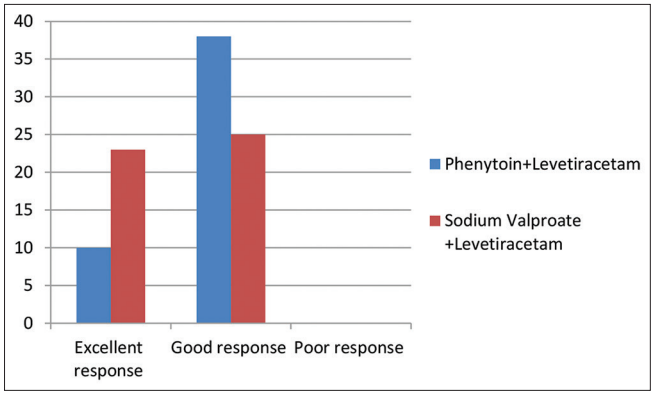

Fig. 2: Patient's responses to the treatments

Table 1: Demographic profile of patients

Demographic variable	Data	Group PL	Group SL	"p" value
Gender	Female	15	21	0.206
	Male	33	27	
Age	Mean Age	30.44	33.83	0.116
Education	Illiterate	4	5	0.726
	Literate	44	43	
Area of residence	Urban	31	26	0.299
	Rural	17	22	

Group PL (Phenytoin + levetiracetam), Group SL (Sodium valproate + levetiracetam)

Table 2: Mean seizure frequency in the last 30 days at different time intervals

Seizure frequency	Group PL Mean±sd	Group SL Mean±sd	t-value	Inter group "p" value
0 Months	102.29±45.58	94.58±43.37	0.849	0.398
3 Months	42.17±19.31	38.44±18.11	0.976	0.331
6 Months	15.48±12.25	8.00±11.02	3.145	0.002*

Group PL (phenytoin + levetiracetam), group SL (sodium valproate + levetiracetam)

Table 3: Adverse drug reactions reported by the patients at 6th month

S. No.	Adverse effects	Group PL (n=48)	Group SL (n=48)	p-value
1	Drowsiness	22	13	0.052
2	Fatigue/Tiredness	14	6	0.044*
3	Dizziness	11	19	0.078
4	Somnolence	16	23	0.146
5	Irritability/Aggressiveness	16	18	0.670
6	Headache	13	19	0.194
7	Weight gain	0	0	-
8	Gum Hypertrophy	1	0	0.315
9	Hypersensitivity reaction	1	1	1
10	Poor memory/lack of concentration	1	1	1
11	G I Distress	4	5	0.726

Group PL (Phenytoin + levetiracetam), Group SL (Sodium valproate + levetiracetam), *"p" value <0.05 considered significant.

In the present study, patients on phenytoin having breakthrough seizures when given levetiracetam showed an 85% reduction in seizure frequency after 6 months of treatment. Our results are in accordance with the earlier study, where a preclinical study showed a synergistic response between levetiracetam and phenytoin [15]. Patients on sodium valproate when given levetiracetam in the present study showed 91% reduction in seizure frequency after 6 months of treatment. Earlier studies have shown that levetiracetam acts by binding with synaptic vesicle 2A protein (SV2A) a novel and different mechanism that adds to the efficacy of both phenytoin and sodium valproate [16]. Seizure control with levetiracetam and sodium valproate is significantly better than levetiracetam plus phenytoin combination in the present study is in accordance with an earlier study suggesting strong enhancement in seizure control when levetiracetam was combined with agents either enhancing GABAergic or reducing glutamatergic neurotransmission like sodium valproate and with another study suggesting lesser enhancement of efficacy when levetiracetam is combined with drug inhibiting sodium channel like phenytoin [17]. After 6 months of the two treatments, 50% of patients were seizure-free further, the seizure-free patient number is 59% greater in the sodium valproate plus

levetiracetam group, suggesting its better efficacy than the phenytoin plus levetiracetam group.

In this comparative study, combined treatment did not show an increase in adverse effects as compared to monotherapy by phenytoin or sodium valproate or levetiracetam which shows levetiracetam does not add to the adverse effects. Earlier studies also do not show an increase of adverse effects when levetiracetam is used in combination with sodium valproate [10,18]. Only fatigue is more commonly seen in the phenytoin plus levetiracetam treated group than in the sodium valproate plus levetiracetam group, suggesting better tolerability of a combination of sodium valproate with levetiracetam. However, more studies are required to find out the cause of increased fatigue. Dizziness somnolence and headache is more in the levetiracetam plus sodium valproate treated group but on comparison between the two groups, it was statistically not significant [19]. A small number of patients and a short duration of study are the limitations of this work. Large sample size, longer follow-up and multicentric studies are needed for further evaluation of the safety and efficacy of combined use of levetiracetam with other AEDs.

CONCLUSION

Levetiracetam is a good adjuvant drug, effective in controlling breakthrough seizures in patients of GTCS on either phenytoin or sodium valproate monotherapy without an increase in adverse effects. The combination of levetiracetam with sodium valproate is more efficacious and safer than its combination with phenytoin to control breakthrough seizures in patients of GTCS.

DECLEARATION OF PATIENT CONSENT

The authors certify that they have obtained all appropriate patient consent.

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AUTHORS CONTRIBUTION

Saroj Kothari: Study design, a draft of the manuscript, revision, and finalization of the manuscript.

Vineet Chaturvedi: Concept, study design, review of literature, data collection, interpretation of results.

Ajay Gupta: Draft of manuscript, collection of data, revision of the manuscript.

Dinesh Udainiya: Collection of data, interpretation of results.

CONFLICT OF INTEREST OF AUTHORS

There are no conflicts of interest.

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REFERENCES

1. Stafstrom CE, Carmant L. Seizures and epilepsy: An overview for neuroscientists. Cold Spring Harb Perspect Med 2015;5:a022426. doi: 10.1101/cshperspect.a022426, PMID 26033084
2. Egesa IJ, Newton CR, Kariuki SM. Evaluation of the international league against epilepsy 1981, 1989, and 2017 classifications of seizure semiology and etiology in a population-based cohort of children and adults with epilepsy. Epilepsia Open 2022;7:98-109. doi: 10.1002/epi4.12562, PMID 34792291
3. Daniel HL. Seizure and epilepsy. In: Dan L, Dennis L, Kasper J, Jameson JL, Fauci AS, Stephen L, *et al*, editors. Harrison's Principles of Internal Medicine. 20th ed. New York: McGrew-Hill; 2018.
4. Tripathi KD. Essentials of Medical Pharmacology. 8th ed. New Delhi: Jaypee Publications; 2021. doi 10.5005/jp/books/12021
5. Bonnett LJ, Powell GA, Tudur SC, Marson AG. Breakthrough seizures-further analysis of the standard versus new antiepileptic drugs (SANAD) study. PLoS One 2017;12:e0190035. doi: 10.1371/journal.pone.0190035, PMID 29267375
6. Kumar S. Factors precipitating breakthrough seizures in well-controlled epilepsy. Indian Pediatr 2005;42:182-3. PMID 15767720
7. Annegers JF, Hauser WA, Elveback LR. Remission of seizures and relapse in patients with epilepsy. Epilepsia 1979;20:729-37. doi: 10.1111/j.1528-1157.1979.tb04857.x, PMID 499118
8. Cherian A, Thomas SV. Status epilepticus. Ann Indian Acad Neurol 2009;12:140-53. doi: 10.4103/0972-2327.56312, PMID 20174493
9. Abou-Khalil B. Levetiracetam in the treatment of epilepsy. Neuropsychiatr Dis Treat 2008;4:507-23. doi: 10.2147/ndt.s2937, PMID 18830435
10. Praveen AN, Panchaksharimath P, Nagaraj K. A comparative study to evaluate the efficacy and safety of levetiracetam as an add-on to carbamazepine and phenytoin in focal seizures at a tertiary care hospital. Biomed Pharmacol J 2020;13:383-90. doi: 10.13005/bpj/1898
11. Bresnahan R, Panebianco M, Marson AG. Brivaracetam add-on therapy for drug-resistant epilepsy. Cochrane Database Syst Rev 2022;3:CD011501. doi: 10.1002/14651858.CD011501.pub3, PMID 35285519
12. Cockerell OC, Johnson AL, Sander JW, Hart YM, Shorvon SD. Remission of epilepsy: Results from the national general practice study of epilepsy. Lancet 1995;346:140-4. doi: 10.1016/s0140-6736(95)91208-8, PMID 7603228.
13. Pellock JM, Dodson WE, Bourgeois BF. Pediatric Epilepsy: Diagnosis and Therapy. 3rd ed. New York: Springer Publishing Company; 2008.
14. Swaroop HS, Ananya C, Nithin K, Jayashankar CA, Babu HS, Srinivas BN. Levetiracetam: A review of its use in the treatment of epilepsy. Int J Biomed Res 2013;2:166-72. doi: 10.14194/ijmbr.232
15. Sarhan EM, Walker MC, Selai C. Evidence for efficacy of combination of antiepileptic drugs in treatment of epilepsy. J Neurol Res 2016;4:267-76. doi: org/10.14740/jnr356w
16. Rogawski MA, Bazil CW. New molecular targets for antiepileptic drugs: Alpha(2)delta, SV2A, and K(v)7/KCNQ/M potassium channels. Curr Neurol Neurosci Rep 2008;8:345-52. doi: 10.1007/s11910-008-0053-7, PMID 18590620
17. Kaminski RM, Matagne A, Patsalos PN, Klitgaard H. Benefit of combination therapy in epilepsy: A review of the preclinical evidence with levetiracetam. Epilepsia 2009;50:387-97. doi: 10.1111/j.1528-1167.2008.01713.x, PMID 18627416
18. Zhao J, Sang Y, Zhang Y, Zhang D, Chen J, Liu X. Efficacy of levetiracetam combined with sodium valproate on pediatric epilepsy and its effect on serum miR-106b in children. Exp Ther Med 2019;18:4436-42. doi: 10.3892/etm.2019.8098, PMID 31777547
19. Lambrechts DA, Sadzot B, van Paesschen W, van Leusden JA, Carpay J, Bourgeois P, *et al.* Efficacy and safety of levetiracetam in clinical practice: Results of the SKATE trial from Belgium and the Netherlands. Seizure 2006;15:434-42. doi: 10.1016/j.seizure.2006.05.013, PMID 16893660