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RESEARCH ARTICLE

COMPARATIVE STUDY ON EFFICACY AND SAFETY OF MONOTHERAPY WITH LEVETIRACETAM AND VALPROIC ACID IN EPILEPTIC PATIENTS

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ABSTRACT

Background and Objectives: A high number of populations have epileptic disorder. The choice of drug is the important factor of treatment including that for acute and chronic epileptic seizure treatment. Selecting drug depends on its safety and efficacy. Monotherapy with drug is the safest approach of treatment. Objectives include, efficacy of LEV and VPA therapy, occurrence of adverse drug reactions.

Methods: It is a prospective, observational, 9 month study in department of neurology in a 500 bedded tertiary care teaching hospital. The study population includes 90 subjects. Patient data entry form, informed consent form, Patient information sheet. The main study criteria is inpatients and out patients in the neurology department. They are selected according to specific inclusion and exclusion criteria.

Results and Discussion: LEV and VPA are equally effective in the treatment of epileptic disorder. But LEV over VPA have some advantages include, its minimal protein binding, lack of hepatic metabolism, adverse reaction of the drug is comparatively better than the older antiepileptic drugs, except the psychiatric manifestations, and no significant drug interactions. These properties also provide better quality of life in persons with epilepsy compared with VPA.

Conclusion: VPA show better efficacy than LEV in terms of seizure frequency, percentage reduction, responder rate. Safety of LEV is higher than VPA.

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INTRODUCTION

Epilepsy is the disorder of CNS associated with cerebral dysrhythmia, manifesting as seizures and convulsions, sensory or psychiatric events (Tripathi, 2010). A seizure results from an excessive discharge of neurons and is characterized by abnormalities in electrical activity (Joseph T Dipiro *et al*., 2005; Joseph T. Dipiro, 7th edition). The word epilepsy derived from the Greek work 'epilepsia' which means 'to take hold of' (Mukhopadhyay *et al*., 2012).

Etiology of epilepsy

The etiology of epilepsy is often Idiopathic (Joseph T. Dipiro, 7th edition) and also Head Injury, CNS Infections, Genetic Factors.

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Pathophysiology

Normally brain electrical activity is non synchronous. In epilepsy the resistance of excitatory neurons to fire during this period is decreased. It may occur due to changes in ion channels or inhibitory neurons not functioning properly. This then results in a specific area from which seizures may develop, known as a "seizure focus". Another mechanism of epilepsy may be the up regulation of excitatory circuits or down-regulation of inhibitory circuits following an injury to the brain (Marvin, 2010).

Clinical presentation

Staring, Eye rolling up, Repetitive blinking, Sudden loss of muscle tone, Jerking or twitching, Confusion, impairment in consciousness, Incontinence, sweating (http://www.resource center/epilepsy/about epilepsy/signs and symptoms of seizure)

Management of epilepsy

A) Nonpharmacologic therapy

Diet, Surgery, vagal nerve stimulation, Behavioral therapies

B) Pharmacologic therapy

Barbiturates (Phenobarbitone, Mephobarbitone, Primidone), Hydrantoins (Phenytoin, Mephenytoin), Iminostilbene (Carbamazepine), Oxazolidinedione (Trimethadione), Succinamide (Ethosuximide), Aliphatic carboxylic acid (Valproic acid), Benzodiazepines (Clonazepam, Diazepam), Acetyl urea (Phenacemide), newer drugs (Levetiracetam, Vigabatrin, Gabapentine, Lamotrigine, Felbamate, Topiramate), Miscellaneous (Acetazolamide).

Levetiracetam

In the 1960s, there were increased efforts to develop sedatives that were supposed to act via the inhibitory effect of the GABAergic system. For this purpose several pyrrolidone derivatives were synthesized with the rationale to design cyclic analogues of γ-aminobutyric acid (Shallcross *et al*., 2011). It binds to the synaptic vesicle protein 2A (SV2A), control of vesicle fusion and exocytosis, reduction of current through T-type Ca++ channels. LEV is rapidly and almost completely absorbed after oral administration. Peak plasma concentration is reached ~1 h after administration to fasting subjects. The half life of oral levetiracetam is 7 ± 1 h. Twice-daily dosing was established in early pharmacodynamic and phase III controlled studies. The drug is < 10% protein bound. Steady-state plasma levels are achieved after ~2 days of twice-daily dosing. (Krishna *et al*., 2011)

VALPROIC ACID

The VPA is an endogenous fatty acid, and was synthesized by Burton (1882) as an organic solvent. VPA may antagonize epileptic activity in several steps of its organization. Its pharmacological effects involve increased GABA-nergic transmission, reduced release and/or effects of excitatory amino acids, blockade of voltage gated sodium channels and modulation of dopaminergic and serotoninergic transmission. This drug may regulate the expression of neuroprotective genes and protect against excitotoxicity. It is about 90% bound to plasma proteins, and the degree of binding decreases with increasing drug concentration within the clinically occurring range. (Fagundes, 2008)

METHODOLOGY

It is a prospective observational study conducted study was conducted at the neurology department of a tertiary care teaching hospital, where an epileptic clinic is carried out on all Wednesdays. In Patients from neurology ward, included in the study population. The total study period was November 2015 to July 2016. The study population was enrolled based on Subjects those who are willing to participate in the study after signing written informed consent form, Patient consulted with focal and generalized epilepsy, Age group 0-60 years, Patient prescribed with Levetiracetam or Valproic acid, Baseline seizure frequency more than 4 per month. Some patients are excluded include Pregnant and lactating women, Patient need urgent surgery, Mentally retarded.

Study treatment

Starting doses (LEV 500 mg/day, VPA 500 mg/day, administered twice daily as equal doses) were up-titrated over 2 weeks to the initial target doses (LEV 1000 mg/day, VPA 1000 mg/day in adults and LEV 20mg/kg/day, VPA 10-15 mg/kg/day in 0 to 16 years old patient). If a seizure occurred, doses could be increased according to the clinician's judgment to a maximum of LEV 3000 mg/day and VPA 2000 mg/day in adults, LEV 40-60 mg/kg/day and VPA 60 mg/kg/day in 0 to 16 years old patient. Patients who did not tolerate higher doses could revert to lower doses, but the dose could not fall below the initial target dose. Study visits were scheduled at weeks 0, 8, 16 (evaluation visit). Patients recorded the number and type of seizures and any adverse events using daily record cards.

Materials Used

Patient data collection form, Informed consent form, Patient information sheet, Seizure severity questionnaire.

Statistics

Data collected was analyzed using Statistical Package for Social Science version 16.0 (SPSS). Descriptive statistics were given as mean and SD for continuous data or as percentage for frequency. The seizure severity by SSQ, seizure frequency before and after treatment was compared with paired t test. Independent variable t test was given as comparison of mean in two populations.

RESULTS AND DISCUSSION

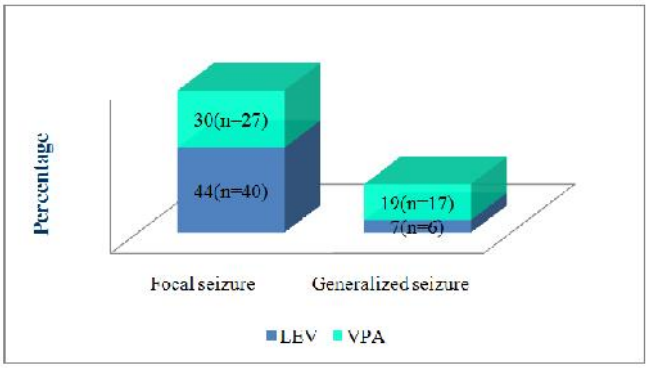
A prospective observational study was conducted to assess the efficacy and safety of monotherapy with LEV and VPA in persons with epilepsy. In this study 90 patients were selected from 303 patients from neurology department based on inclusion and exclusion criteria. 44 patients in VPA treated group and 46 patients in LEV treated group. These are results obtained from the study.

Demographic details

Table 1. Demographic details

	VPA	LEV	
Study population 90			
Total	48%	52%	
Male	31%	23%	
Female	18%	28%	
Mean age(mean±SD)	28.43±18.15		35.21±19.09
Age categorization (n=90)			
0-20	29%	20%	
21-40	7%	11%	
41-60	13%	20%	
Marital status (n=90)			
Married	17%	28%	
Unmarried	31%	22%	
Divorced	1%	1%	
Literacy (n=90)			
Literate	43%	48%	
Illiterate	3%	3%	
Occupational status (n=90)			
Working	23%	11%	
Not working	26%	40%	

Seizure type categorization



*LEV= Levetiracetam *VPA= Valproic acid

Figure 1. Comparison of study population according to drug group and seizure type

Among all this seizure types, focal seizure was found to be predominant among the study population that is 40(44%) LEV patients and 27(30%) VPA treated patients out of 90. This is followed by Generalized seizures 6 (7%) LEV and 17(19%) VPA treated patients out of 90. In all the type of epilepsies, focal seizure was found to be the predominant in this study. Camacho *et al*. (Davood *et al*., 2014) reported that majority of patients had focal seizures (74.4%). Contradictory results were found in Nabukenya *et al*. (Eugen *et al*., 2013) says that majority of the respondents were having generalized epilepsy (25.5%). In this study LEV is mostly prescribed in focal seizure and VPA mostly prescribed in generalized seizures. The similar result is obtained from study conducted by Eugen *et al*. (2013). The epilepsy mostly occurred at childhood and elderly. Because the seizure threshold increase with age, after 60 years decline the seizure threshold. Study conducted by Dutta (Nabukenya *et al*., 2014) in shows, in younger age mylenation was incomplete. So that insulating capacity of myelin sheath is less. This causes the stimulation of neighboring nerve fibers. Advancing age increases probability of degeneration also increases. Ilo (Dutta, 2007) shows, degenerative disease are one of the risk factors for generalized epilepsy. Based on gender males have higher seizure threshold than females. In younger age females are more susceptible than males, Due to the higher hormonal variation. The study conducted by Harden (Ilo *et al*., 2006) shows, perimenopausal women has a chance to depression and mood swings due to estrogen decline. In older age males are susceptible than females, due to increase risk factors include sudden switch over to sedentary life style, social habits, malignancy, decline of seizure threshold. The incidence of focal seizure and generalized seizure were independent to age and sex. That depends on the risk factors, triggers, family history, genetic susceptibility, individual variabilities.

Seizure triggers categorization

In this study identified 23(26%) of them developed seizures without any triggers. Stress as the major trigger for development of seizure in 21(23%) patients. The other common triggers found were missed dose 12(13%), sleep deprivation 4(4%), sleep deprivation+ stress 4(4%), depression 3(3%), stress+ missed dose 3(3%), alcohol 1(1%), other reasons [menstruation, fever, flickering light, smoking, caffeine] in 19(21%). The seizure episode may be triggered by several factors like sleep deprivation, missed medication, stress, alcohol, menstruation, flickering light, sadness etc. This result is supported by Nakken *et al*. (Harden *et al*., 2003). In this study stress (23%) is the major triggering factor. Jamie and Jay (Nakken *et al*., 2005) revealed that a high percentage of epilepsy patients triggered by stress. Areas of brain are important for some types of seizures. Eg: focal seizure, occur the same areas of the brain involved emotions and responding to stress. Stress can cause problems in sleeping. This is an important trigger for seizure.

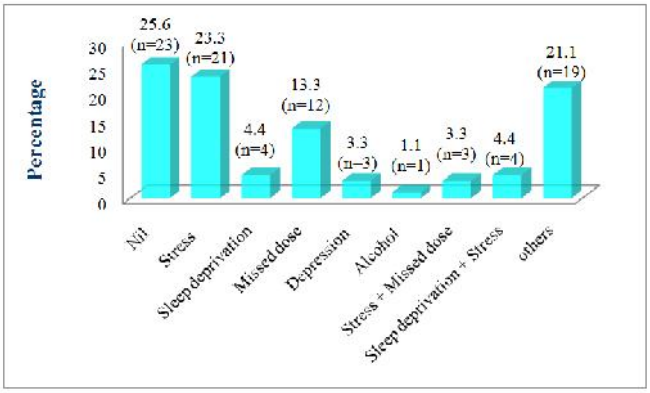
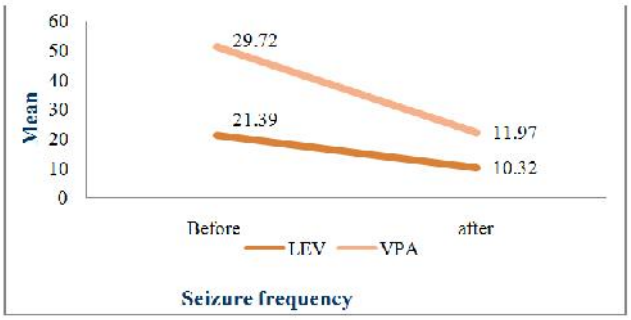


Figure 2. Comparison of study population according to Seizure triggers

Seizure frequency categorization



LEV=Levetiracetam *VPA=Valproicacid

Figure 3. Comparison of Seizure frequency of LEV and VPA arm in base line and follow up

Among this study, the LEV arm shows mean of before and after treatment seizure frequency were 21.39, 10.32 respectively. The VPA arm shows mean of before and after treatment seizure frequency were 29.72, 11.97 respectively.

Paired t test for evaluation of difference between mean of focal and generalized seizure before and after treatment in the LEV and VPA taking groups

In VPA group reduction of seizure frequency from baseline in focal seizure was 17.75 and generalized seizure was 18.46. In LEV group reduction of seizure frequency from baseline in focal seizure was 11.24 and generalized seizure was 4.32. p value is 0.000. It was statistically significant. Control of seizure frequency was the main objective in the management of epilepsy. Majority of the patients experienced greater than four seizure attack per month in the current study and maximum 140 in before treatment among study population. Seizure frequency depends upon seizure threshold and type of seizure. Seizure frequency reduced with increased seizure threshold. This study shows VPA (base line29.72±60.74, after

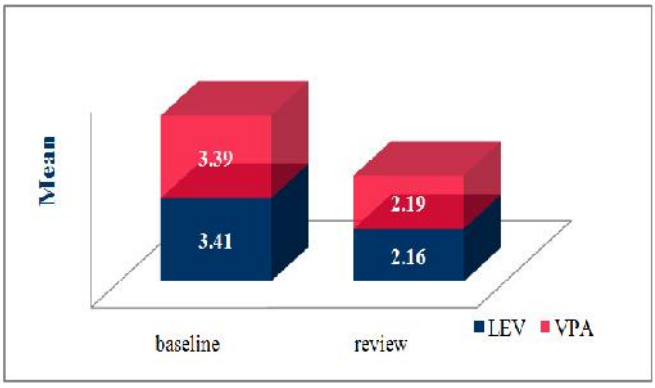
Table 2. Reduction of seizure frequency from baseline in focal and generalized seizure

Groups	Reduction of seizure frequency from baseline	Mean ± SD	P value
Valproic acid group			
Focal seizure(baseline and review)	17.75	18.10 ±	
Generalized seizure(baseline and review)	18.46	0.50	
Levetiracetam group		7.78 ± 4.8	0.000
Focal seizure(baseline and review)	11.24		
Generalized seizure(baseline and review)	4.32		

*SD= standard deviation

11.97±20.98) show better seizure frequency reduction than LEV (base line 21.39±27.83, after 10.32±12.5). VPA show better seizure frequency reduction in both focal and generalized seizure than LEV. This result was correlated with study conducted by Davood *et al*. (Jamie and Jay, 2013) VPA was highly protein bounded drug. It also increase brain levels of GABA and combating generalized as well as partial seizure than LEV. Kristin Robinson (2002) shows, VPA in pregnancy causes increase the risk of child having birth defects. Then LEV is safely used in both types of seizures during pregnancy, and females in the reproductive age group. Also LEV is more preferred in elderly, because due to the low risk of drug/drug interactions. VPA is contraindicated in hepatic impaired patients when LEV was preferred.

Seizure severity categorization



*LEV= Levetiracetam *VPA= Valproic acid

Figure 4. Seizure severity score

Base line and review seizure severity in LEV treated patient was 3.4±0.80 and 2.16 ± 0.60 respectively. Base line and review seizure severity in VPA treated patient was 3.3±0.84 and 2.19 ± 0.67 respectively. P value was 0.000. It was statistically significant.

Table 3. Over all seizure severity (n=90)

	Overall severity or bothersome score	Status
LEV	4	Improved
VPA	5	Much improved

*LEV= Levetiracetam *VPA= Valproic acid *SD=Standard deviation

Overall severity or bothersome score in LEV was 4. It means patients improved. In VPA were 5. It means patients much improved.

Responder rate

Among this study population frequency of ≥50% reduction in seizure frequency was found out.

Table 4. Responder rate in LEV and VPA

≥ 50% reduction in seizure frequency				
Drug	**Frequency**	Percentage	**Mean ±SD**	**P value**
LEV	34 out of 46	73.9	51.75±14.23	0.0347
VPA	35 out of 44	79.5	59.01±17.76	

*LEV= levetiracetam *VPA=valproic acid

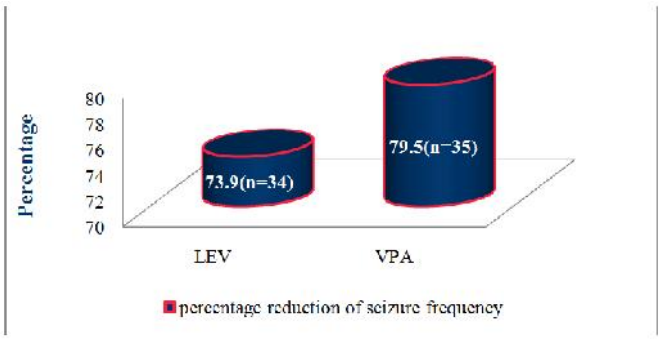
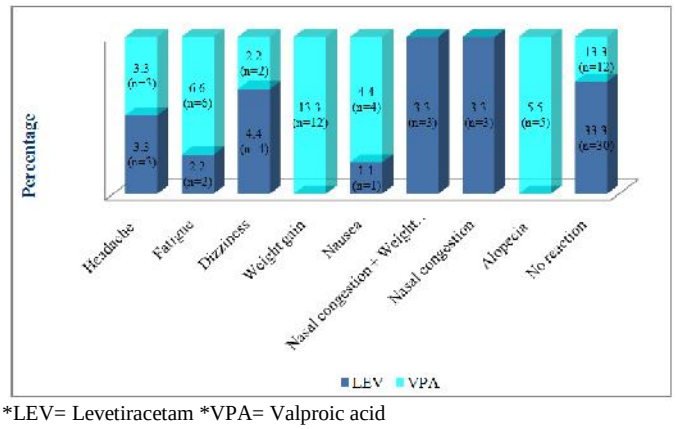


Figure 5. Responder rate in LEV and VPA

In this study 34(73.9%) patients in LEV group out of 46 and 35(79.5%) patients in VPA group out of 44 were ≥ 50% reduction in seizure frequency. P value was 0.0347. It was statistically significant. In this study VPA treated group show higher responder rate than levetiracetam treated group. This result was similar to Eugen *et al*. (Camacho *et al*., 2014)

Adverse drug reactions



*LEV= Levetiracetam *VPA= Valproic acid

Figure 6. Adverse drug reaction

In this study, LEV arm 3(7%) suffered from headache, 2(4%) suffered from fatigue, 1(2%) suffered from nausea, 4(8.6%) suffered from dizziness, 3(7%) suffered from nasal congestion, 3(7%) suffered from nasal congestion+ weight reduction out of 46 patients. VPA arm 3(7%) suffered from headache, 2(5%) suffered from dizziness, 12(27%) suffered from weight gain, 4(9%) suffered from nausea, 5(11%) suffered from alopecia out

of 44 patients. 25(54%) patients from LEV and 11(25%) patients from VPA were free from adverse events. The occurrence of adverse event in LEV was lower than VPA. Commonly occurred adverse events in LEV group were found to be somnolence, nausea, headache, nasal congestion and weight reduction, dizziness. The effect of weight reduction by LEV it is mainly used to treatment of epilepsy in obese females. The occurrence of adverse events in VPA is much high. Mainly weight gain, alopecia, nausea, headache, dizziness were occurred. Similar result shows in Eugen *et al*. (Camacho *et al*., 2014) LEV is safer than VPA. Patsalos (Patsalos, 2000) shows, LEV have minimal protein binding, lack of hepatic metabolism. ADRs of the drug are comparatively better than the older antiepileptic drugs, except the psychiatric manifestations, and no significant drug interactions. ILAE guidelines show VPA and LEV is probably effective initial monotherapy for adults with newly diagnosed or untreated partial-onset seizures, GTC seizures. VPA are possibly effective for children with GTC, absence seizures. LEV and VPA may effective for patients with newly diagnosed JME and BECTS. LEV is not superior to VPA in terms of efficacy. The overall results, associated to time to first seizure, the main efficacy outcome, show a benefit for VPA over LEV. Marson *et al*. (2007) show, VPA is mainly used as the drug of choice for difficult-to-classify seizures or generalized epilepsies. The significant proportion of the epilepsy population consist women of childbearing age. Artama (2005) shows, VPA increased teratogenicity and Bromley *et al*. (Nabukenya *et al*., 2014) shows, cognitive function impairment in children exposed in utero to VPA are the major risk factor of VPA in that population. These are the reasons for identify the effective treatments that are safer in pregnancy. Alekar *et al*. (2009) shows, a low risk of teratogenicity with LEV and Shallcross *et al*. (2011) shows, a lower risk of delayed development associated with in utero exposure to LEV over VPA. Based on these results, LEV might be a first line drug for generalized seizures, mainly for women of childbearing age. Miziak *et al*. (2014) shows, VPA affect on bone cell functions causes negative effects on skeletal system than LEV. Eugen *et al*. (Camacho *et al*., 2014) shows, time to treatment withdrawal were similar for LEV and VPA. For the comparisons by seizure type, there are no significant differences, but the trends favoring VPA in patients with primary generalized seizures, and LEV in the treatment of with focal seizures. The study shown treatment withdrawal rates of both at 6 and 12 months were similar, in patients with generalized seizures only. A similar effect has been seen when analysis included patients with only generalized seizures and with only focal seizures. But the seizure freedom rates at 6 and 12 months were higher with VPA than LEV, both for all persons with epilepsy and in those with only generalized seizures. Nicolas *et al*., (1999) shows, the drug interactions of VPA are higher than LEV. LEV, there is no significant pharmacokinetic interactions were observed between LEV and its major metabolite and adjuvant medications. Davane (2003) conducted a study on VPA shows, have drug interactions include enzyme substrate, enzyme Inducer, enzyme Inhibitor. Katherine (2011) shows, newer AED generally associated with higher drug acquisition cost than the older AEDs.

Conclusion

This study was performed to assess safety and efficacy of monotherapy with VPA and LEV. Results showed that epilepsy treated by monotherapy with LEV or VPA has better outcome. Safety of LEV is greater than VPA in terms of less adverse drug reactions and better improvement in quality of life. Efficacy of LEV and VPA is almost same. But VPA show higher efficacy than LEV in terms of seizure freedom days, seizure frequency and responder rate. This study shows VPA mainly used to treatment in generalized seizure than focal seizure and LEV is used to treat focal epilepsy than generalized seizure. Both drug shows almost similar seizure severity reduction.

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