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KEPPRA (Levetiracetum) VS EPIVAL (Sodium Valporate) to control generalized tonic clonic seizures.

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ABSTRACT… Objective: This present study is design to assess the efficacy and frequency of side effects with a newer anti-epileptic agent levertiracetum while comparing an older anti-epileptic, Sodium Valproate, in the patients with generalized tonic colonic epilepsy. **Material & Methods:** Patients with GTC epilepsy had been allocated in two groups, A and B, Group A was given Sodium valproate while group B was given levertiracetum. **Study Design:** Randomized Control Trial. **Setting:** Fatima Memorial Hospital, Lahore and Allied Hospital, Faisalabad. **Period:** December, 2017 to December, 2018. **Results:** Seventy five subjects were taking levertiracetum from three months out of which 56(74.7%)were seizures free, 15(20%) were seizure free on higher dose,6(8%) were with dizziness ,vertigo and 9(12%) were with somnolence. Fifty-four individuals were seizures free with normal dose of sodium valproate from last 3 months, and 16(21%) were seizures free on higher doses among which 53(70%) were with side effects of weight gain and 69(92%) were with hand tremors and this was the most prominent side effects among individuals who were taking sodium valproate. **Conclusion:** Generalized tonic colonic epilepsy is one of the most common forms of epilepsy and with the advent of newer anti-epileptic drugs like levertiracetum, such seizures can be controlled in with lesser side effects as compared to older antiepileptic agent Sodium Valproate.

Key words: Alopecia, Dyspepsia, Seizures, Levertiracetum, Sodium Valproate, Somnolence, Tremors, Weight Gain.

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INTRODUCTION

Despite the emerging newer anti-epileptic drugs (AEDs) lamotrigine and levertiracetum (LEV) older drugs, carbamazepine (CBZ) and sodium valproate still remained widely used in the clinical practice. A comparative analysis of these agents in terms of tolerability and effectiveness is important to guide the clinicians to prescribes drugs with longer times to withdrawal and lower rates of epilepsy episodes. Epilepsy is one of most frequently presented disease in Neurology OPD. It has been estimated that 50 million around the globe suffers from Epilepsy.[1] Seventy five percent of these people suffering from epilepsy have been documented to be living in developing countries.[2] From findings of some studies it was estimated that 1.38 million peoples are suffering from epilepsy in Pakistan which makes it one neurologist available for every 46200 sufferers of epilepsy.[3] clinical trials have been conducted to assess the comparative effectiveness of novel AEDs such as LEV and older agents such as VPA and CBZ as monotherapy for epileptic patients. Fewer studies have been carried out to statistically record the side-effect incidence of these agents. KOMET study was first published in August, 2016, which concluded that time to withdrawal to LEV was longer as compared to other AEDs. Another study was carried out at Iran University of Medical Sciences, Iran published in April, 2014 which assessed the effectiveness of LEV in comparison with VPA in controlling seizures in patients with Juvenile Myoclonic Epilepsy. The outcome of this study showed lack of meaningful differences between two drugs in controlling seizures and myoclonus at the end of study. This study is conducted to compare the efficacy and side effects of LEV with old antiepileptic drugs

MATERIAL & METHODS

This is a randomized control trial in which 150 patients, who presented in neurology OPD at Fatima Memorial Hospital and Medical OPD department at Allied hospital Faisalabad, with the complaints of more than two episodes of generalized tonic colonic se based on clinical evidence (including videos recorded on the phone of patients) supported with the EEG, were allocated in groups, A and B (based on software generated numbers) Group A was given Sodium Valproate and group B was given levertiracetum. Both the groups were then followed with 2 weekly follow up to look for control of seizures and incidence of side effects. This study was done using a questionnaire having questions related to success rate of the two drugs in controlling the seizures and incidence of different side effects with both the drugs. The individuals were included and excluded from the study on the basis of criteria given below. In inclusions of this study includes, individuals with generalized tonic colonic epilepsy, individuals with normal neurological examination, individuals with normal brain-imagining, more than two episodes of generalized tonic colonic seizers. Individuals having no provoking factors metabolic encephalopathy or electrolyte imbalance. Informed consent was taken after enrolling of all study subjects. Data was analyzed using the Statistical Package for Social Sciences, version 16 (SPSS Inc.; Chicago, IL, USA). Frequency and percentage values were calculated for variables such as Age gender, numbers of seizures despite taking sodium valproate and levertiracetum. Chi-square test was used for categorical variables like age of patients compared with side effect profile of sodium valproate and levertiracetum, similarly comparison of gender with side effects profile of sodium valproate and levertiracetum. P-value of less than 0.05 was considered as statistically significant.

RESULTS

32(42.7%) of individuals was on levertiracetum between age group of 15-20 years. 45(60%) were with male gender ,56(74.7%) individuals were seizures free with normal doses ,56(74%) were seizure free with higher doses. 6(8%) patients were with dizziness and vertigo. similarly, 9(12%) were with over somnolence. As details related to this side effects profiles in mentioned in below Table-I

There was significant association among the patients age and seizures free rate who were taking levertiracetum from last 3 months. individuals between age of 15-20 years were free from seizures with normal dose 23(30%) and among higher doses this rate was in same age group 7(9.3%). With (P-value$<$0.05). Side effects was varying according to the age of the individual's highest rate of dizziness and vertigo were found among the age of 15-20 years 30(40%) followed by 18(24%), similarly age in headache was highest among the age group of 15-20 years 5(6.7%) as details are mentioned in Table-II. Results of the genders in comparison of treatment (levertiracetum) to treat epilepsy from last 3 months. seizures free rate among male patents was significantly higher with normal dose 36(48%) as compared to higher doses. Side effects profile was shows there was significant association among males and all the associated side effects by taking levertiracetum as details related to this results are mentioned in Table-II.

In next phase the details related to results of sodium valproate in treatment of epilepsy are mentioned, females 38(50.7%)were in greater numbers as compared to male37(49%).overall 54(72%) individuals were seizures free with normal dose of sodium valproate , among side effects weight gain was 53(70%) and hand tremors was 69(92%) this was the most prominent side effects among individuals wo were taking sodium valproate as details are mentioned in Table-III.

Results of our study shows that there was an association among the age of the subjects and number of seizures despite taking sodium valproate age group between 15-20 years shows high rate of seizures free 20(26.7%). there was significant association among the age of subjects and GI disturbance among the participant who were taking sodium valporate 3(4%). Weight gain was one of the major contributing factors among the subjects taking sodium valproate

14(18%). There was association among seizures free rate by taking sodium volparerte and gender. seizures free rate among male with normal dose was higher 28(37%) as compared with female 26(34%). There was also significant association between gender and side effect profile, hair loss was higher among females 10(13.3%) as compared with male 4(5.3%) with (P-value0.05) as details are mentioned in Table-IV.

	Categories	(n)	Percentages
Age	15-20	32	42.7%
	21-25	19	25.3%
	26-30	17	22.6%
	31-40	7	9.4%
Gender	Male	45	60%
	Female	30	40%
No of seizures despite taking in the levertiracetum **last 3 months**	Seizures free	56	74.7%
	Seizure free in higher doses	15	20%
	Noncompliance	1	1.3%
	Need of second AED	3	4%
Dizziness and Vertigo	Yes	6	8%
	No	69	92%
Over somnolence	Yes	9	12%
	No	66	88%
Deranged LFTs	Yes	3	4%
	No	72	96%
Headache	Yes	10	13.3%
	No	65	86.7%
GI Disturbance	Yes	o	0%
	No	75	100%

Table-I. Socio demographic and side effects of patients

DISCUSSION

Despite the availability of newer antiepileptic in Pakistan the trend of classic agents was still dominated in pharmacotherapy of epileptic seizure the present study reports that the subjects who were taking levertiracetum to treat the epilepsy includes majority of male gender 45(60%)and 32 (40%) were female which is refer to study conducted by Artemios K[5] Finding from our study shows that 56(74.7%) of the individuals were seizures free with normal doses and only 15(20%) need higher doses to treat the epilepsy among the study subjects. Which clarify that with normal doses of levertiracetum patients shows improvement which is refer to study conducted by M Motamedi and Dk Ngyyen their finding shows that more than 50% of their study subjects were seizures free with normal dose[6] Most common side effect in both genders and within each age group includes Headache 10(13.3%). which is refer to study conducted by Roy G Beran and Paul j spire which was conducted at Griffith university and Liverpool Hospital Australia findings of their study shows that those patients who were taking levertiracetum had more complained of headache as compared to patients who were not taking levertiracetum[7] similarly results of our study shows that There was significant association among age and seizures free rate with normal dose, age group between 15-20 years were seizures free with normal dose 23(30.7%) with (P-value<0.05) which is refer to study conducted by[7] Results of our study shows among male subjects seizures free rate was 36(48%) it shows that gender difference can also associated with the prognosis of patients.

Levels	Percentages				P- Value
Age in comparison with NO. of seizures despite taking levertiracetum	**Seizures free**	**Seizure free in higher doses**	**Non-compliance**	**Need of second AED**	
(15-20)	23(30.7%)	7(9.3%)	0 (0%)	2 (2.7%)	0.03
(21-25)	17 (22.7%)	2 (13.3%)	0 (0%)	0(0%)	
(26-30)	11 (14.7%)	5(6.7%)	1(1.3%)	0 (0%)	
(31-40)	5 (6.7%)	0(0%)	0(0%)	0(0%)	
Age in comparison with Dizziness and Vertigo	**Yes**	**No**			
(15-20)	2(2.7%)	30 (40%)			0.7
(21-25)	1(1.3%)	18 (24.0%)			
(26-30)	29 (2.7%)	15 (20%)			
(31-40)	1(1.3%)	4(5.3%)			
Age in comparison with Over somnolence	**Yes**	**No**			
(15-20)	5(6.7%)	27 (36%)			0.27
(21-25)	1(1.3%)	18 (24.0%)			
(26-30)	1 (1.3%)	16 (21 %)			
(31-40)	2 (2.7%)	3(4.%)			
Age in comparison with Headache	**Yes**	**No**			
(15-20)	5(6.7%)	27(36.%)			0.6
(21-25)	3(4%)	16(21%)			
(26-30)	2(2.7%)	15(20%)			
(31-40)	0(%)	5(6.7%)			
Age on comparison with Deranged LFTs	**Yes**	**No**			0.07
15-20)	1(1.3%)	31 (41.3%)			
(21-25)	0(0%)	19(25.3%)			
(26-30)	0(0%)	17 (22.7%)%)			
(31-40)	1 (1.3%)	4(5.3%)			
Age in comparison with GI Disturbance	**Yes**	**No**			
(15-20)	0 (0%)	32 (88.3%)			GI disturbance is a constant
(21-25)	0 (0%)	19 (100%)			
(26-30)	0 (0%)	17 (100%)			
(31-40)	0 (0%)	5 (100%)			
Levels	Percentages				P-Value
Gender in comparison with NO. of seizures despite taking levertiracetum	**Seizures free**	**Seizure free in higher doses**	**Non-compliance**	**Need of second AED**	
Male	36(48.0.0%)	6 (8%)	1 (1.3%)	2 (2.7%)	0.2
Female	20 (26.7%)	9 (12%)	0 (0%)	1(1.3%)	
Gender in comparison with Dizziness and vertigo	**Yes**		**No**		
Male	42 (56.0%)		3(4%)		0.6
Female	27(36%)		3 (4%)		
Gender in comparison with Over Somnolence	**Yes**		**No**		
Male	40 (53%)		5 (6.7%)		0.7
Female	26(34%)		4 (5.3%)		
Gender in comparison with Headache	**Yes**		**No**		
Male	40(53..3%)		5(6.7%)		0.4
Female	25(33.3%)		5 (6.7%)		
Gender in comparison with Deranged LFTs	**Yes**		**No**		
Male	3(4%)		42(56%)		2
Female	0(0%)		30 (40%)		
Gender in comparison with GI Disturbance	**Yes**		**No**		
Male	0 (0%)		30 (40%)		GI disturbance is a constant
Female	0 (0%)		45 (60%)		

Table-II

	Levels	(n)	Percentages
	15-20	25	33%
Age	21-25	21	28%
	26-30	21	28%
	31-40	8	10%
Gender	Male	37	49.3%
	Female	38	50.7%
No of seizures despite taking sodium valproate in the last 3 months	Seizures free	54	72%
	Seizure free in higher doses	16	21.3%
	Noncompliance	3	4%
	Need of second AED	2	2.7%
Weight gain	Yes	53	70.7%
	No	22	29.3%
Hand	Yes	69	92.3%
tremors	No	5	6.7%
Deranged LFTs	Yes	12	16%
	No	63	84%
Hair loss	Yes	14	18.7%
	No	61	81.3%
GI Disturbance	Yes	3	4%
	No	72	96%

Table-III

On other hand among side effects profile Over somnolence was in association with male patient 40(53%) as compare to female patients which is refer to study conducted by Gerhard Luef at department of Neurology at medical university Innsbruck Anichstrasse findings of their study shows that there was significant association among seizures free rate with respect to Gender[8] Among the male participants headache observed very commonly 40(53%) which shows that gender difference was also in association with side effects of treatment.which is refer to on the study conducted by[9] Overall severity of side effects by taking levertiracetum was much more among the male subjects as compared to females which is refer to study conducted by Sigrid svalheim and Erik.[10]

Patients who were taking sodium valproate includes 37(49.3%) males and 38(50%) of participants were females with common age groups includes 15-20 years old individuals 25(33%), seizures free with normal dose included 54(72%) of the participants and side effects profile shows that weight gain was among 53(70%) and hand tremors was among 69 (92%) in all subjects who were taking sodium valproate .which is refer to study conducted by Eugen trinka and Julia hofles findings of their studies shows that over all side effect's including weight gain tremor and some others among adults was 70.9%(601/848;95% confidence interval [CI] 67.8-73.9). Seizures free response rate was good among the children's as compared to the adults.[11] Similarly There was an association among the subjects taking sodium valproate and age of the study participants age group between 15-20 years shows good rate of seizers free 20(26%) as compared to other age groups participants which is refer to study conducted by Charles L Bowden findings of this study shows that 25 % of the patients between the teen ages were free from seizers with normal dose.[12]

Levels	Percentages				P-Value
Age in comparison with No. of seizures despite taking sodium valproate	**Seizures free**	**Seizure free in higher doses**	**Noncompliance**	**Need of second AED**	
(15-20)	20(26.7%)	3(4%)	2 (2.7%)	0 (0%)	0.12
(21-25)	12 (16%)	7 (9.3%)	0 (0%)	2 (2.7%)	
(26-30)	17 (22.7%)	4(5.3%)	0	0	
(31-40)	5 (6.7%)	2 (2.7%)	1.3	0	
Age in comparison with Hand tremors	**Yes**	**No**			
(15-20)	23 (30%)	2 (2.7%)			0.6
(21-25)	19 (25.3%)	2 (2.7%)			
(26-30)	19 (25.3%)	2 (2.7%)			
(31-40)	8 (10%)	0 (0%)			
Age in comparison with Hair loss	**Yes**	**No**			
(15-20)	5 (6.7%)	20 (26.7%)			0.97
(21-25)	4(5.3%)	17 (22.7%)			
(26-30)	4 (5.3%)	17 (22.7%)			
(31-40)	1 (1.3%)	7 (9.3%)			
Age in comparison with weight gain	**Yes**	**No**			
(15-20)	14 (18.7%)	11 (14.7%)			0.06
(21-25)	14 (18.7%)	7 (9.3%)			
(26-30)	17 (22.7%)	4 (5.3%)			
(31-40)	8 (10.7%)	0 (0%)			
Age on comparison with Deranged LFTs	**Yes**	**No**			
15-20)	5 (6.7%)	20 (26.7%)			0.16
(21-25)	3 (4%)	18(24%)			
(26-30)	1 (1.3%)	20 (26.7%)			
(31-40)	3 (4%)	5 (6.7%)			
Age in comparison with GI Disturbance	**Yes**	**No**			
(15-20)	3 (4%)	22 (29.3%)			0.07
(21-25)	0 (0%)	21 (28%)			
(26-30)	0 (0%)	21 (28%)			
(31-40)	0 (0%)	8 (10.7%)			
Gender in comparison with NO. of seizures despite taking sodium valproate	**Seizures free**	**Seizure free in higher doses**	**Noncompliance**	**Need of second AED**	
Male	28(37%)	7(9.3%)	2(2.7%)	1(1.3%)	0.8
Female	26(34%)	9(12%)	1(1.3%)	1(1.3%)	
Gender in comparison with Hand tremors	**Yes**		**No**		
Male	36(48%)		2(2.7%)		0.37
Female	33(44%)		4(5.3%)		
Gender in comparison with Hair loss	**Yes**		**No**		
Male	4(5.3%)		34(45%)		0.06
Female	10(13.3%)		27(36%)		
Gender in comparison with weight gain	**Yes**		**No**		
Male	28(37.3%)		10(13%)		0.5
Female	25(33.3%)		12(16%)		
Gender in comparison with Deranged LFTs	**Yes**		**No**		
Male	7(9.3%)		31(41%)		0.5
Female	5(6.7%)		32(42.7%)		
Gender in comparison with GI Disturbance	**Yes**		**No**		
Male	2(2.7%)		36(48%)		0.5
Female	1(1.3%)		36(48%)		

Table-IV

Weight gain was significantly associated with every age group among study participants (P-<0.05) which is refer tis study conducted by C.L Bowden V. Singh findings of their studies shows that sodium valproate is associated with gain of weight, sedation reduction in platelets counts[13] one of another side effects due sodium valproate in study subjects was GI disturbance in age groups between 15- 20 years old with (P-<0.05). which is refer to study conducted by R M pinder their findings shows was similar to findings of our study results, most common side effects in their study includes Nausea, vomiting abdominal cramp, Diarrhea, which was 9 to 16% in adults and 25% in children's[14] our study results shows that hair loss among females 10(13.3%) subjects who were taking sodium corporate was greater as compared to male subjects (p-value<0.05) which is in similarity with one the study conducted by Hosseini Ebahimi findings of their study shows 3.5% of females reported hair loss and curly hair, due sodium valproate in duration of 3 months[15] By taking the sodium valproate deranged LFTs among male study participants 7(9.3%) was in greater as compared to female with (P-value 0.05) this finding is refer to some the study conducted by Marwick, Katie F.M MBCh Taylor findings includes abnormal LFTS(32 %) with the range of 5% to 78% transaminase were most commonly elevated enzymes among these enzymes[16] As before no as such details study conducted before so over all it is suggested that levertiracetum is a safe side of treatment with leaser side effects as compared to sodium valproate for epilepsy

CONCLUSION

In this study it was identified that levertiracetum is safe side of medicine to treat the epilepsy as it has good result in relates with the treatment of epilepsy .sodium valproate is safe side of drug for treatment of epilepsy. but based on the results of this study levertiracetum is more safe as compared to sodium valproate.

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AUTHORSHIP AND CONTRIBUTION DECLARATION

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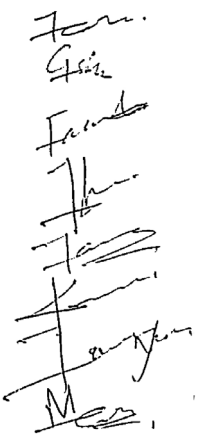
1	Fahad Farooq	Research conception/Design.	
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