Effect of Levetiracetam on Juvenile Myoclonic Epilepsy Related Quality of Life

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Abstract: **Juvenile myoclonic epilepsy constitutes 5-10% of idiopathic generalized epileptic syndromes. This study was aimed at the efficacy and tolerability of levetiracetam and its effect on the quality of life of juvenile myoclonic epilepsy. This study includes a total of 17 patients with juvenile myoclonic epilepsy who were under levetiracetam treatment. Levetiracetam showed a significant reduction in seizure frequency at the review (after three months) from baseline (p=0.002). And the tolerability was assessed from the occurrence of adverse drug reactions. Headache, somnolence, dizziness, weight gain were found to be the most common side effects of levetiracetam therapy. Since the quality of life is an important treatment outcome indicator in epilepsy, the disease-specific quality of life was measured using the QOLIE-31 (18 years or older) and QOLIE-AD-48 (11 to 17 years old). The study results also showed a greater benefit with the introduction of levetiracetam as there were marked improvements in each dimension of the quality of life and also the total score.**

Keywords: **Juvenile myoclonic epilepsy, levetiracetam, HRQOL, QOLIE-31, QOLIE-AD-48**

I. INTRODUCTION

Epileptic seizures and epileptic syndromes should have been high prevalence and incidence rates affecting all ages and both sexes of all races. They constitute an important part of the everyday clinical practice of general and specialist health care (Panayiotopoulos, 2007).

Epilepsy refers to a clinical phenomenon rather than a single disease entity since there are many forms and causes of epilepsy. However, among the many causes of epilepsy, there are various epilepsy syndromes. The three important epileptic syndromes are Juvenile myoclonic epilepsy, Lennox-Gestaut syndrome, Mesial temporal lobe epilepsy (Lowenstein, 2001)

Juvenile myoclonic epilepsy is idiopathic generalized epilepsy. The mean onset is around 15 years of age but may vary between 8 and 26 years. Juvenile myoclonic epilepsy is characterized by myoclonic jerks, predominantly in the arms. Many patients also have generalized tonic-clonic seizures, and some have absence. Juvenile myoclonic epilepsy accounts for 5-11% of the adult population (Kleveland, *et al*,. 1998)

Juvenile myoclonic epilepsy affects both male and female patients equally, although a female predominance has been described. Juvenile myoclonic epilepsy etiology stems from genetics (Alfradique, 2007). A correct diagnosis of juvenile myoclonic epilepsy has an important impact on the treatment and outcome of patients. Juvenile myoclonic epilepsy diagnosis is based on clinical criteria and typical electroencephalogram findings. The clinical presentation is quite characteristic but misdiagnosis and the corresponding treatment delay are frequent. The primary clinical factor is the failure to elicit myoclonic jerks (Alfradique, 2007).

Sleep deprivation, fatigue, photic stimuli (television/videogames), menstruation, concentration, stress, expectation, emotions are the most common precipitating factor of juvenile myoclonic epilepsy (Panayiototopoulos, 1994). Juvenile myoclonic epilepsy patient exhibits specific cognitive deficits affected by age at seizure onset and duration of disease (Kim, *et al.*, 2007).

As juvenile myoclonic epilepsy is a lifelong disorder, its treatment should be continued indefinitely, and otherwise, recurrences are rather frequent, occurring within a variable period of months to years after antiepileptic drug discontinuation. Valproic acid was established as the first choice of drug (Alfradique, 2007). Valproic acid therapy is often limited by adverse effects or by drug interactions.

The 2004 NICE guidelines suggest lamotrigine as a substitute for valproic acid when patients fail to respond. The guidelines suggest the second choice of Levetiracetam is a novel antiepileptic drug because its mechanism of action appears to be different from that of the others. It acts through binding to the synaptic vesicle protein SV2A. Levetiracetam also reverses the inhibition of neuronal GABA and glycine-gated currents by the negative allosteric modulators and partial depression of the N calcium current (Khalil, 2008).

Levetiracetam is a good alternative also because of its efficacy against all three types of juvenile myoclonic epilepsy seizures and photosensitivity. The pharmacokinetic profile of levetiracetam makes it a good option for the treatment of pediatric patients (Verotti, 2008).

Like in all chronic disorders, the overall quality of life is worsened in patients with epilepsy. The quality of life of patients with epilepsy may be improved depending upon the effectiveness of antiepileptic activity and disease duration. The frequency of seizures seems to be one of the relevant determinants of poor quality of life scores (Guekht, 2007)

A full assessment of the health-related quality of life in adolescents (aged 11-17 years) is complex because of the wide range of maturity within this group (Cramer, *et al.*, 1999). Moreover, epilepsies in the 8-26 years age group tend

to restrict an individual's activities in a very productive and growing period of life. Hence the importance of proper therapeutic management, which will enable the adolescent to overcome his handicap and lead us normally as possible life (Cramer, *et al.,* 1999).

Levetiracetam with its low toxicity and effective pharmacokinetic characteristics in the target population makes it a good choice for patients of juvenile myoclonic epilepsy (Cramer, *et al.,* 2000). The present study was undertaken to study the efficacy of levetiracetam in juvenile myoclonic epilepsy patients considering both the therapeutics as well as the quality of life angles.

II. MATERIALS AND METHODS

The study was conducted in the department of neurology in a multispecialty hospital, Tamil Nadu. A total of 17 objects were included in this study and were conducted over six months from June 2009 to December 2009. The study was aimed to determine the efficacy and tolerability of levetiracetam and its effect on the quality of life of juvenile myoclonic epilepsy.

Study criteria

Inclusion criteria

i. Patients of age group 11 to 28 years old with juvenile myoclonic epilepsy under treatment on levetiracetam.
ii. No evidence of neurological or intellectual deficit.
iii. Unequivocal clinical evidence of generalized seizures with myoclonic jerks mainly on awakening.

Exclusion criteria

i. Clinical and/or EEG evidence of myoclonic jerks secondary to brain hypoxia, metabolic diseases, or other structural brain abnormalities.
ii. Other epileptic syndromes such as eyelid myoclonia with absence seizures, pure forms of photosensitive epilepsy, or self-induced epilepsy.
iii. EEG abnormalities but no clinical evidence of any type of seizure.

Study protocol

The patients who met the study criteria were included in the study. The study was explained to the patients and their relatives and their oral consent was taken. The levetiracetam was administered to the study population and was stabilized for one month. The patients who are above 18 years old received 1500 mg of levetiracetam and patients who are below 18 years old received two doses of levetiracetam i.e., 750 mg and 1000 mg. Then on each visit patient's demographics including the number of seizures per month and incidence of adverse reaction were collected through patient interviews. The other necessary findings like present medication history, type of seizures, and the dose of levetiracetam were collected from the patient's case reports. The review was taken after 3 months from the baseline. The efficacy of levetiracetam was calculated by the reduction in seizure frequency at the review from baseline. Seizure frequencies reported on baseline and reviews (after three months from baseline) were compared and the reduction in seizure frequency was expressed in percentages. The response to levetiracetam treatment was classified as seizure-free (100% seizure control), responders (> 50% reduction), or marginal effect (< 50% reduction). Detailed questionnaires were used to assess the quality of life of patients (QOLIE-31 for 18 years or older and QOLIE-AD-48 for 11 to 17 years old) and distributed to the patients in their two visits i.e. baseline and review and filled questionnaires were collected for further evaluation.

HRQOL Assessment

HRQOL was assessed with the administration of QOLIE-31 and QOLIE-AD-48 at the end of baseline and review. The QOLIE-31 is a self-administered questionnaire designed for completion by patients alone. QOLIE-31 consists of 31 questions divided into 7 subscales. Subscales assessed such items as seizure worry, overall quality of life, emotional well-being, energy and fatigue, cognitive function, medication effects, and social functioning. It was derived from the longer QOLIE-89, an instrument with 17 subscales, including generic and epilepsy-specific issues and a separate item on health status (not scored). Responses can be scored to provide subscale scores and a Total Score. Higher scores represent a better function.

QOLIE-AD-48 is divided into two sections; in the first section, the topics include overall health perception, physical activities, and impact of physical or emotional problems, mood, concentration, memory, cognitive skills, and social support. In section 2 topics include the impact of epilepsy and antiepileptic medications on activities, fear about seizures, perceived severity of seizures, adverse mental and physical effects of medication, and role limiting including driving. Empiric analyses provide strong evidence that the QOLIE-AD-48 is both a reliable and valid measure for adolescents with epilepsy (Cramer A *et al.,* 1999).

Statistical analysis

Reduction in seizure frequency at a review from baseline was expressed in percentages and was assessed by using paired t-test. The significance of the difference between the subscale scores of the questionnaires at the review from baseline was also assessed by using paired t-test. Spearman correlation coefficient was used to assess the correlation between the seizure frequency and quality of life scores. $P \leq 0.05$ was taken to be significant.

III. RESULTS

Efficacy and Safety

The primary efficacy criteria for estimating the safety and therapeutic efficacy of levetiracetam are the reductions in seizure frequency. In our study population, there was more than a 50% reduction in seizure frequency for 7 of 17 patients

(responders). Eight patients were identified to be completely seizure-free after the treatment. And two patients showed only a less than 50% decrease in seizure frequency (non-responder) (Verotti, 2008) (Figure 1). And the reduction in seizure frequency was found to be significant according to the paired t-test (p=0.02).

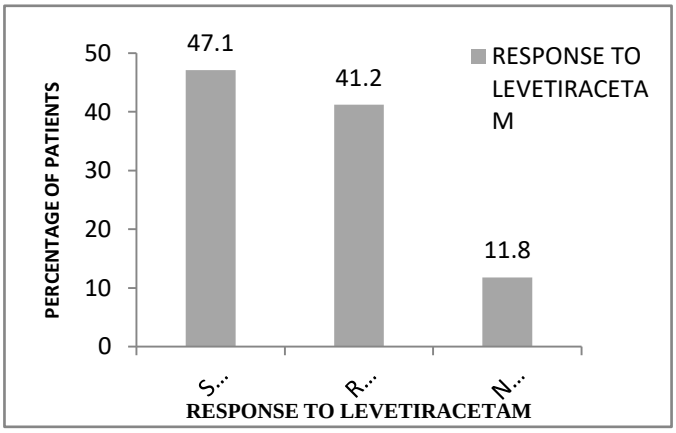

Figure 1: Percentage of patients who responded to levetiracetam therapy

Studies on the tolerability of levetiracetam show that somnolence and asthenia are the most common side effects. Other frequently reported side effects were accidental injury, weight gain, tiredness, infection, nausea, dizziness, and urinary tract infection (Betts, *et al*., 2000; Yarrow, *et al*., 2003). In our study headache, somnolence, dizziness, weight gain were found to be as most common side effects of levetiracetam therapy. Six of 17 patients (35%) had experienced headache, 1 had somnolence (5.88%), 3 had dizziness (17.64%), and the only one reported weight gain (5.88%) (Figure 2)

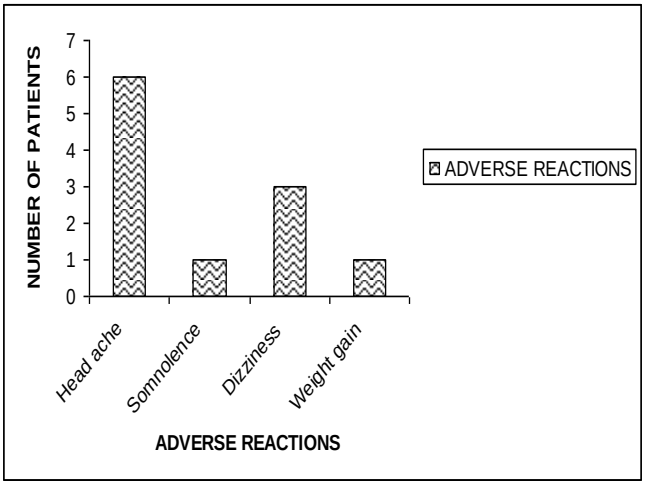

Figure 2: Various side effects identified in the study population after the levetiracetam treatement

Health-related Quality of Life

Quality of life is an important treatment outcome indicator in epilepsy. Several instruments are available to assess the quality of life in epilepsy, among which QOLIE-31(18 years and older) and QOLIE-AD-48 (11-17 years of age) are two. QOLIE-31 has seven subdivisions and QOLIE-AD-48 has eight subdivisions that are related to different aspects of life and drugs. The final score in each dimension of the questionnaire ranges from 0 to 100 on a linear scale, in which zero is worst and 100 is the best quality of life.

The mean scores for the different subscales of QOLIE-31 at baseline and review show an increase (Table 1). An overview of the table indicates a significant improvement in seizure worry, overall quality of life, energy/fatigue, cognitive, social function (p=0.029, p=0.041, p=0.003, p=0.005) in the review from baseline respectively. The total score also shows a significant improvement in review from baseline (p=0). There was good improvement in other dimensions even though it was not significant.

Table 1: Mean scores of the different subscales in the QOLIE-31 questionnaire at baseline and review in the study population;*p≤0.05, **p≤0.001

SI. NO	SUBSCALES	B.L Mean score(S.D)	REVIEW Mean score(S.D)
1.	Seizure worry	41.9(27.21)	56.43(22.02)*
2.	Overall QOL	62.75(15.29)	71.9(7.83)*
3.	Emotional well being	70.8(21)	79.6(11.7)
4.	Energy/fatigue	60(24.04)	71.5(21.22)*
5.	Cognitive	70.33(22.47)	75.08(20.43)*
6.	Medication effects	61.67(29.10)	67.22(30)
7.	Social function	73.22(16.85)	84.3(10.29)*
8.	Total score	66.7(13.56)	75.09(10.44)**

The QOLIE-AD-48 patients were divided into two groups according to levetiracetam dosage (levetiracetam 500 mg and levetiracetam 750 mg). The mean scores of different subscales in each group showed an increase (Table 2). In the levetiracetam 500mg group, there is a significant improvement in the total score (p=0.043). In the levetiracetam 750 mg group, significant improvements were noted in the epilepsy impact subscale and the total score (p=0.001, p=0.049) in review from baseline respectively.

Table 2: Mean scores of the different subscales in the QOLIE-AD-48 questionnaire at baseline and review in the study population;*p≤0.05, **p≤0.001

SI.NO	SUBSCALES	Levetiracetam 500 mg group(N=4)		Levetiracetam 750 mg group(N=3)	
		B.L Mean score(S.D)	REVIEW Mean Score(S.D)	B.L Mean score(S.D)	REVIEW Mean Score(S.D)
1.	Epilepsy impact	53.22(29.54)	62.92(22.63)	61.11(2.41)	77.33(2.13)**
2.	Memory/concentration	71.25(28.47)	75.42(22.47)	66.66(25.16)	80(15)

3.	Attitude	44.27(21.68)	41.67(24.24)	39.58(16.54)	47.91(19.09)
4.	Physical function	70(12.25)	61.25(25.62)	61.67(36.86)	58.33(27.54)
5.	Stigma	70.28(35.87)	78.89(24.45)	58.32(13.64)	67.21(18.28)
6.	Social support	65.62(32.47)	79.68(20.65)	77.08(25.26)	71.67(27.42)
7.	Social behavior	65.63(18.75)	71.87(27.24)	60.42(30.83)	83.33(3.61)
8.	Health perception	43.75(10.48)	52.08(17.18)	61.11(9.62)	77.78(20.97)
9.	Total score	58.53(15.88)	64(18.11)*	59.47(2.86)	71.64(3.86)*

Seizure outcome and HRQOL

Seizure frequency is the main factor that affects the quality of life in epilepsy patients. The relation between the seizure frequency and the quality of life was assessed by correlating the subscale scores of each questionnaire with seizure frequency at review using the Spearman correlation coefficient. QOLIE-31 subscales showed a negative correlation with seizure frequency even though it was not significant (Table 3). A significant correlation with seizure frequency was found in stigma, social behavior, and total score of QOLIE-AD-48 (P=0.01, P=0.03, P=0.01 respectively). All other dimensions showed a negative correlation with seizure frequency even though those were not significant (Table 4).

Table 3: Correlation between subscale scores in the QOLIE-31 questionnaire with seizure frequency at review

SI. NO	SUBSCALES	r VALUE	P VALUE
1.	Seizure frequency	-0.280	0.43
2.	Overall QOL	-0.4274	0.35
3.	Emotional well-being	-0.3153	0.37
4.	Energy/fatigue	-0.3493	0.32
5.	Cognitive	-0.2447	0.49
6.	Medication effects	-0.6185	0.06
7.	Social function	-0.0692	0.85
8.	Total score	-0.0878	0.81

Table 4: Correlation between subscales scores in the QOLIE-AD-48 questionnaire with seizure frequency at review;*p≤0.05

SI. NO.	SUBSCALES	r value	P value
1.	Epilepsy impact	-0.7356	0.07
2.	Memory/concentration	-0.0197	0.96
3.	Attitude	-0.4274	0.35
4.	Physical function	-0.5714	0.20
5.	Stigma	-0.8748	0.01*
6.	Social support	-0.5317	0.24
7.	Social behavior	-0.8300	0.03*
8.	Health perception	-0.6922	0.08
9.	Total score	-0.8669	0.01*

Table 4: Correlation between subscales scores in the QOLIE-AD-48 questionnaire with seizure frequency at review;*p≤0.05

IV. DISCUSSION

Juvenile myoclonic epilepsy is idiopathic generalized epilepsy, characterized by irregular myoclonic jerks, tonic-clonic seizures, and sometimes typical absence seizures (Verrotti, 2008). Juvenile myoclonic epilepsy makes its clinical appearance between 6 and 22 years of age, but 50% of cases present at ages 13 to 16 years (Arzimanoglou, 2004).

Levetiracetam is a new antiepileptic drug that has proved to be effective both as monotherapy and as adjunctive therapy in the treatment of generalized epilepsy. Recent studies report the efficacy of levetiracetam in the treatment of myoclonus and progressive myoclonic epilepsies, showing levetiracetam is very well tolerated in adults and children at high doses (Labate, 2006). One study evaluated the efficacy and tolerability of levetiracetam in 32 patients with juvenile myoclonic epilepsy. They compared the frequency and severity of baseline seizures, the response of levetiracetam treatment was classified as seizure-free (100% seizure control), responders (>50% reduction), or marginal effects (< 50% reduction) in monthly seizure frequency. The efficacy of levetiracetam therapy was calculated by counting mean seizure frequency /month. At the 6th month evaluation, out of 32 juvenile myoclonic epilepsy patients, 15 were seizure-free and 14 were responders. Marginal effects were observed in 3 patients (Verotti, 2008). In our study also the seizure frequency/month at baseline was compared with seizure frequency at review, there was more than a 50% reduction in seizure frequency at the review for 8 of 17 patients (responders). Eight patients were identified to be completely seizure-free after the treatment of 3 months (100% seizure control). And only one patient showed less than a 50% reduction in seizure frequency (marginal effects).

Studies on the tolerability of levetiracetam show that somnolence and asthenia are the most common side effects. Other frequently reported side effects were accidental injury, weight gain, tiredness, infection, nausea, dizziness, and urinary tract infection (Betts, *et al.*, 2000; Yarrow, *et al.*, 2003). In our study headache, somnolence, dizziness, weight gain were found to be as most common side effects of levetiracetam therapy. Six of 17 patients (35%) had experienced headache, 1 had somnolence (5.88%), 3 had dizziness (17.64%), and the only one reported weight gain (5.88%).

Seizure severity is an important aspect of epilepsy. Some studies assessed the relationship between seizure severity and

quality of life. The results indicate that severe and potentially injurious seizure behaviors contribute to anxiety and socially avoidant behaviors for persons with epilepsy (Thomas, *et al.*, 2005; Guekht, 2007; Harden, *et al.*, 2007). In our study, the relationship between seizure frequency and quality of life in 17 juvenile myoclonic epilepsy patients was also found to be significant (P=0.03).

One study has proved the effect of levetiracetam in the quality of life of epilepsy patients by using the QOLIE-31 questionnaire as an evaluative instrument to measure change under conditions. Statistically significant improvements were found in three of seven subscales of QOLIE-31 i.e., in seizure worry, overall quality of life, cognitive functioning. The total score also showed a significant improvement (Cramer, *et al.*, 2000). Our study population also shows a significant improvement in five of seven subscales i.e. in seizure worry, overall quality of life, cognitive, social function, and energy/fatigue, and total score improvement is also found to be significant.

V. CONCLUSION

Juvenile myoclonic epilepsy (JME) is the most common and well-delineated idiopathic generalized epilepsy, with distinctive clinical features, and is recognized worldwide. Juvenile myoclonic epilepsy is a common yet under diagnosed epileptic syndrome. Levetiracetam is probably the best new antiepileptic drug in the treatment of juvenile myoclonic epilepsy and may replace valproate for the treatment of the disorder because of high and sustained efficacy, fast action, and an excellent safety profile. More than 60% of patients with intractable JME became seizure-free with levetiracetam monotherapy or polytherapy. Our study was focused to assess the efficacy and tolerability of levetiracetam and determine its effect on the quality of life of juvenile myoclonic epileptic patients. Levetiracetam showed a significant reduction in the seizure frequency at the review (after three months) from baseline (p=0.02). And the tolerability was assessed from the occurrence of adverse reactions. Results showed only some common side effects for central nervous system drugs, reported by eleven of 17 patients. The addition of levetiracetam to the standard therapy not only decreases the seizure frequency but also enhances the HRQOL. Since the quality of life is an important treatment outcome indicator in epilepsy, the disease-specific quality of life was measured using the QOLIE-31(18 years or older) and QOLIE-AD-48(11 to 17 years old). The seizure frequency at review and each subscale score in the quality of life questionnaires showed a negative correlation even though it was not significant, which indicates that a reduction in seizure frequency has been improved the quality of life in the study population. This study result shows that adjunctive therapy of levetiracetam in JME patients not only effectively reduces the seizure frequency while maintaining a favorable safety profile but also possibly improves cognitive functions, social functions, seizure worry, energy/fatigue, and overall quality of life of juvenile myoclonic epileptic patients.

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