Original Article

Efficacy of Levetiracetam in Treatment of Childhood Stuttering

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Abstract

Background: Stuttering is a kind of speech disorder that affects about 1% of total population. As the origin of this disorder is not obviously diagnosed yet, various remedies have been practiced and among them different medicines have been studied, but unfortunately no significant effective drugs have been recognized yet. As stuttering imposes a great social and mental costs to the patients and their families, finding an effective medicine will help significantly. In this study we have focused on the effects of levetiracetam (LEV) treatment on children suffering from stuttering. **Methods:** In this clinical trial study, 30 children aged > 3 years (median 3.8 years) with stuttering and abnormal sleep electroencephalogram (EEG) were treated by LEV and followed-up for a minimum period of 6 weeks. The starting dose of 20 mg/kg/day was increased at an interval of 1 week by 20 mg/kg/day, if necessary, up to maximum dose of 60 mg/kg/day. **Results:** Overall LEV was effective in 70% of patients, decreasing stuttering to at least 50%. Three children (10%) became stuttering-free and only in one (3.3%) child an increase in stuttering was observed. There were statistically significant differences for efficacy in the presence of variables such as age groups, seizure, stuttering family history, and EEG data. **Conclusions:** LEV is an effective drug for treatment of childhood stuttering in those that have abnormal sleep EEG.

Keywords: *Child, disease management,etiracetam, stuttering, speech disorders*

Introduction

Speech production is a simple and easy activity for most children but it is so hard for other children who stutter. Stuttering is a disorder of speech motor production[1] and is identified as an interruption in normal speech fluency and temporal patterning of words. Stuttering is characterized by frequent occurrences of repetitions in sound and syllable, such as monosyllabic word repetitions, sound prolongations, interjections, and broken words.[2] Some authors refere stuttering as "emotional pain and social stigma."[2,3] This disorder may involve complex social and emotional elements.[1] Two kinds of stuttering are well known in the literature. These include developmental and acquired (or neurogenic) stuttering, which are distinguished clinically. Developmental stuttering, the more frequent type, begins in childhood or during early adolescence.[2,4,5] Acquired stuttering, on the contrary, is uncommon and may begin in adults. Acquired stuttering is usually associated with brain lesion (e.g., head trauma, stroke, centrally acting drugs) inducing gross cerebral functional impairment.[4,6] About 1% of the world population and 3–5% of preschoolers suffer from stuttering and the rate of stuttering among boys is about 3–4 times higher compared with girls.[1] Because the cause of the disorder has not been well-established until now, a wide variety of behavioral, cognitive, interpersonal, and related treatments have been attempted with different rates of success.[7] Several attempts are cited in the literature to identify the effective pharmacological therapies for this disorder, such as anticonvulsant agents, antidepressant agent, antipsychotic agents, alpha-receptor agonists, beta-receptor blockers, calcium channel blockers, dopamine antagonist, and so on.[8-11] But among those, it seems only a few anticonvulsant drugs such as levetiracetam (LEV) and divalproex sodium are effective in treating developmental and acquired stuttering.[12,13] LEV is an antiepileptic drug that has been approved in adults since 2000 and in children over the age of 4 since 2005. LEV has a highly favorable pharmacokinetic profile, including 100% bioavailability, <48 h needed for steady state, linear kinetics, twice daily

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dosing, <10% protein binding, no hepatic metabolism, and minimal blood metabolism. In addition, LEV is well-tolerated and is having a broad spectrum of efficacy. The drug is an anticonvulsant with the potential mechanism relating to the blockade of zinc and beta-carbolines from interrupting chloride influx in the GABA and glycine receptors.[5,14,15]

Recent studies have shown that although there is no significant evidence in children, LEV seems to be an effective remedy for dysfluent speech in patients with partial epilepsy[4] and developmental stuttering. In this regard, a case study has found that 12 weeks of therapy with LEV in a patient with deficits in verbal memory, oral comprehension, and verbal fluency, a complete disappearance of stuttering was observed as well as a decrease in seizure frequency.[2] Moreover, studies have shown that LEV provides betterments of Landau–Kleffner syndrome (LKS),[8] that is the inability to understand or express language,[16-18] although the symptoms of this syndrome are different to those of stuttering.

On the contrary, childhood stuttering imposes a great social and mental costs to the patients and their families, hence finding an effective medicine will help significantly. In this regard, although the efficacy of LEV on the LKS patients and stuttering disorder has been limitedly examined, in the present study we have focused on the effects of LEV treatment on children suffering from stuttering.

Methods

In this clinical trial study, 4-year-old 30 children suffered from stuttering and abnormal sleep electroencephalogram (EEG) has been subjected to this study. They have been referred to Al-Zahra Hospital, in the city of Isfahan, Iran, between June 2015 and May 2016. All research units volunteered to participate in this study. At first, the stuttering and its severity were diagnosed according to the percentage of stuttered syllabuses (%SS) by a speech-language pathologist and then LEV was prescribed. In this study, percent stuttered syllables as a measure of stuttering severity was considered,[19] and it is calculated as the number of stuttered syllables divided by the total number of syllables spoken, multiplied by 100.[20] Each child was treated with LEV and followed up for at least 6 weeks. The initial dose was determined as 20 mg/kg/day divided into two doses. If the dose was well-tolerated but stuttering was not insufficiently controlled, the dose could be increased to 20 mg/kg/day per week, and to a maximum dose of 60 mg/kg/day (two formulations were available, 250 and 500 mg tablets). If the treatment was not tolerated or the maximum dosage of 60 mg/kg/day was reached with no substantial benefits, the drug was gradually reduced to 20 mg/kg/day weekly. The trial consisted of a preselection visit, an initiation visit, and a follow-up visit after 6 weeks. In the preselection visit, the eligibility of children for the trial was checked and then they were referred to the speech-language pathologist. After the stuttering severity was diagnosed by speech-language pathologist by comparison of the percentage of stuttered syllabus with total ones, the LEV was started with advised dosage. Some data such as age, sex, previous history of seizure on the individual and his family, family history of stuttering, stuttering duration, sleep disorders were recorded through questionnaire. At the end of the sixth week, the stuttering severity of patient was studied again by the same speech-language pathologist and the same method to compare the severity before and after LEV remedy. The primary study endpoint was change in stuttering frequency and stuttering responder rates (>50% stuttering reduction) at six final-week assessments. The study was approved by the Medical Ethical Committees of our research center. All legal representative of participants received a full explanation of the nature of the study and were required to sign an agreement form. Statistical analyses were performed using SPSS-20, LEV (Levebel, Cobel Drou, Iran). Paired *t*-test and one-way analysis of variance were used to compare the decrease in means of stuttering frequencies between age group, males and females, duration of stuttering, history and family history of stuttering, types of EEG changes, and sleep disorders. *P* values <0.05 were considered significant.

Results

In this study, 30 children (18 males, 12 females) ranging in age from 4 to 6 years, with stuttering and abnormal sleep EEG were included between June 2015 and May 2016. The duration of stuttering before LEV treatment program ranged from 6 months to 3.1 years (mean 1.4 years). Of children, 9 (30%) had family history of stuttering, 7 (23.3%) had family history of seizure, 4 (13.3%) had both of them; 7 (23.3%) patients had history of partial or/and generalized seizures and 5 (16.6%) patients had sleep disorder. The rate of improvement was shown in Tables 1 and 2. An improvement over 50% was reported in a population of 21 children (70%), among them 3 children (10%) came out 100% recovered without any stuttering. In 6 (20%) and 2 (6.6%) patients, stuttering decreased to 25–50% and 10–25%, respectively. In one (3.3%) child, an increase in stuttering was observed, and showed no advantages within 6 weeks.

In this study, furthermore, 81 and 95.2% of children without family history of stuttering and seizure improved, respectively, while none of the patient with positive family history in both were improved. The results showed

Table 1: Effect of levetiracetam in treatment of childhood stuttering

Variable	Frequency	Pretest		Posttest		*t*	*P*
		Mean	SD	Mean	SD		
%SS	30	49.37	4.421	18.37	8.658	8.658	0.004

SS%: percentage of stuttered syllabuses

Table 2: Effect of different variables on LEV efficacy

Variable	Group	Frequency	Improved	Chi-square	*P**
Sex	Male	18	13 (72%)	2.207	0.23
	Female	12	8 (66%)		
Age	4–5 years	17	15 (88.2%)	7.138	0.009
	>5 years	13	6 (46.1%)		
Stuttering duration	<1 year	9	7 (77.7%)	2.874	0.16
	1–2 years	16	12 (75%)		
	>2 years	5	2 (40%)		
Sleep EEG**	Mildly abnormal	11	5 (45.4%)	7.367	0.003
	Moderately abnormal	19	16 (84.2%)		
Past history of seizure	No	23	19 (82.6%)	4.135	0.019
	Yes	7	2 (28.5%)		
Family history of seizure	No	23	20 (86.9%)	4.297	0.014
	Yes	7	1 (14.2%)		
Family history of stuttering	No	21	17 (80.9%)	6.837	0.006
	Yes	9	4 (44.4%)		
Sleep disorders	No	21	16 (76.1%)	2.675	0.32
	Yes	9	5 (55%)		

*Paired *t*-test or one-way analysis of variance test was applied.**Mildly abnormal EEG: scattered sharp or slow wave; moderately abnormal EEG: scattered spike or diffused sharp, slow or spike wave

statistically inverse correlations between positive family history and rate of improvement. In other words, only 28.6% of children with past history of seizure have been improved. According to EEG data, 84% of patients improved for moderately abnormal group, while this result for mildly abnormal group is only 45.4%. According to statistical results, in 13 patients with moderately abnormal EEG and without any history of seizure or family history of stuttering and seizure, 12 patients demonstrated more than 50% reduction in stuttering after LEV treatment. So, the probability of improvement was more than 92% in these fractions.

Discussion

Although the main causes of stuttering are actually unknown, in the present study we decided to try LEV in the treatment of stuttering because we assume stuttering is output of block or re-entry in speech neuronal pathway and LEV is able to influence the stuttering with its multipotential activity in that process. Our hypothesis in facilitation or blocking model of LEV effect in neuronal pathway can explain the decrease or increase in stuttering severity after LEV therapy. This prospective study of children with stuttering suggests LEV may be a useful treatment in this condition, although in one of the cases exacerbation of stuttering occurred. Also, during the explanation of stuttering mechanism, it has been observed that changes in the perisylvian area of stuttering affected brains which might cause abnormalities in motor speech expression. Indeed, stutterers seem to initiate the motor speech program before the preparation of articulatory code.[3,21-26]

It must be emphasized that our study population was heterogeneous in terms of age, suturing severity, presence of sleep disorder, past and family history, and disease duration, although there were statistically significant differences for efficacy in the presence of above variables. But sample sizes in different subgroups are so small to be appreciated. It should be considered that most of the patients had practiced different remedies before LEV without any improvement, while three of our patients became stuttering-free and another 18 patients (60% of all patients) demonstrated >50% reduction in stuttering severity after LEV therapy. Furthermore, no adverse side effects of the drug were observed and the drug was well-tolerated by children. In fact, this is the first structured study in which stuttering children were treated with LEV.

These findings were similar to those of previous studies of Sechi *et al.*[4] and Canevini *et al.*[2] Their results indicate that LEV may improve language abilities in patients with focal epilepsy, as well as disfluent speech irrespective of etiology, seizure frequency, EEG alterations, and localization of brain lesions. Canevini reported a 34-year-old patient suffering from intractable epilepsy and developmental stuttering who achieved a complete remission of stuttering under treatment with LEV.[2] In the study of Sechi *et al.*, LEV therapy for a few months cause seizure frequency to return to the rate before LEV in two patients, as well as the beneficial effect on verbal disfluency persisted unchanged in the same patients.[4]

In our study the probability of LEV effect on the reduction of stuttering among children showed an improvement of 60–80% based on binominal distribution.

One limitation in our study is the short follow-up duration because of time and financial restrictions of our research.

Hence the same study with more sample size and longer duration of follow-up and control group will strengthen the results.

Conclusion

LEV is an effective drug for treatment of childhood stuttering in those that have abnormal sleep EEG.

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Conflicts of interest

There are no conflicts of interest.

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