

## Clinical Trial of Vigabatrin as Adjunctive Therapy in Children with Refractory Epilepsy

Mohammad-Mahdi Taghdiri<sup>1</sup>, MD; Mahmoud-Reza Ashrafi<sup>2,3</sup>, MD; Mohammad-Kazem Bakhshandeh-Bali<sup>4</sup>, MD;  
Seyedeh-Mohadeseh Taheri-Otaghsara<sup>5</sup>, MD; Mohammad-Mahdi Nasehi<sup>4</sup>, MD; Mohammad-Ghofrani<sup>4</sup>, MD

1. Department of Pediatrics, Shahid Beheshti University of Medical Sciences, Tehran, Iran
2. Growth and Development Research Center, Tehran University of Medical Sciences, Tehran, Iran
3. Department of Pediatrics, Tehran University of Medical Sciences, Tehran, Iran
4. Pediatric Neurology Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran
5. Brain and Spinal Injury Research Center, Neuroscience Institute, Tehran University of Medical Sciences, Tehran, Iran

Received: Apr 13, 2013; Accepted: Oct 22, 2013; First Online Available: Nov 22, 2013

### Abstract

**Objective:** Approximately one-third of all children with epilepsy do not achieve complete seizure improvement. This study evaluated the efficacy of Vigabatrin in children with intractable epilepsy.

**Methods:** From November 2011 to October 2012, 73 children with refractory epilepsy (failure of seizure control with the use of two or more anticonvulsant drugs) who were referred to the Children's Medical Center and Mofid Children's Hospital were included in the study. The patients were treated with Vigabatrin in addition to their previous medication, and followed-up after three to four weeks to determine the daily frequency, severity, and duration of seizures in addition to any reported side effects.

**Findings:** Of the 67 children, 41 (61.2%) were males and 26 (38.8%) females, their age ranging from three months to 13 years with an average of 3.1 [standard deviation (SD), 2.6] years. The mean daily frequency of seizures at baseline was 6.61 (SD, 5.9) seizures per day. Vigabatrin reduced the seizure frequency  $\leq 2.9$  (SD, 5.2) (56% decline) and 3.0 (SD, 5.3) (54.5% decline) per day after three and six months of treatment, respectively. A significant difference was observed between seizure frequencies at three ( $P < 0.001$ ) and six months ( $P < 0.001$ ) after Vigabatrin initiation compared with the baseline. Somnolence [3 (4.5%)], horse laugh [1 (1.5%)], urinary stones [1 (1.5%)], increased appetite [1 (1.5%)], and abnormal electroretinographic pattern [3 (4.5%)] were the most common side effects in our patients.

**Conclusion:** This study confirms the short-term efficacy and safety of Vigabatrin in children with refractory epilepsies.

*Iranian Journal of Pediatrics, Volume 23 (Number 6), December 2013, Pages: 653-658*

**Key Words:** Intractable Epilepsy; Antiepileptic Drugs; Vigabatrin; Add-on Therapy

### Introduction

Epilepsy is one of the most prevalent neurological diseases, and it affects approximately 0.5%-0.8% of children<sup>[1]</sup>. Despite the prescription of appropriate antiepileptic medication,

approximately 10%-30% of children with epilepsy do not respond to treatment<sup>[2]</sup>. Refractory epilepsy is defined as the failure to control seizures with the use of two or more anticonvulsant drugs<sup>[3]</sup>. An acceptable approach for patients with intractable seizures is multiple antiepileptic drug therapy

\* Corresponding Author;

Address: Division of Pediatric Neurology, Children's Medical Center, Pediatric Center of Excellence, No 62, Dr. Gharib St., Tehran, Iran

E-mail: mr\_ashrafi@yahoo.com

© 2013 by Pediatrics Center of Excellence, Children's Medical Center, Tehran University of Medical Sciences, All rights reserved.

rather than monotherapy<sup>[4]</sup>. The outcome of seizures in children with refractory epilepsy has been improved by new-generation antiepileptic drugs<sup>[5]</sup>.

Vigabatrin was formulated in 1975 by a purposeful effort to create a substance that can increase the levels of gamma-aminobutyric acid (GABA), an inhibitory neurotransmitter<sup>[6]</sup>. Vigabatrin destroys GABA transaminase (GABA-T) irreversibly inhibiting the activity of the enzyme in the nervous system tissue and cerebrospinal fluid (CSF) as well as enhancing presynaptic GABA, which leads to seizure improvement<sup>[7,8]</sup>. The structure of Vigabatrin is similar to that of GABA, so it can selectively interfere with GABA-T activity and prevent GABA decomposition<sup>[9]</sup>. Oral Vigabatrin is absorbed quickly and almost completely; it has a linear pharmacokinetic profile with a maximum concentration achieved within 2 h after administration<sup>[10]</sup>.

Vigabatrin has been used as a first-line treatment of children with infantile spasms aged between one month and 2 years and as an add-on therapy for adolescents with intractable complex partial epilepsy in over 50 countries<sup>[11,12]</sup>. Long-term Vigabatrin therapy is considered to be safe and well tolerated; the most common side effects are a self-limiting headache, somnolence, weight gain and visual field defects<sup>[13,14]</sup>.

There have been no detailed investigations on the efficacy of Vigabatrin in Iranian children with various seizure types. This study was designed to determine the efficacy of Vigabatrin in Iranian children with intractable epilepsy and its adverse effects.

## Subjects and Methods

From November 2011 to October 2012, 73 children with refractory epilepsy who visited the pediatric neurology clinics of the Children's Medical Center or Mofid Children's Hospital were enrolled in this study.

Children aged below 18 years with epilepsy refractory to previous AEDs (>2 conventional and new AEDs) were included in the study. Children with neurodegenerative diseases or hypersensitivity to anticonvulsants were excluded from

the study. After receiving written consent from the patients, initial assessments such as disease history (type, onset, etiology, and the frequency of seizures; previous treatment period; and type of AED used), physical examination (general and neurological), electroencephalography (EEG), and magnetic resonance imaging (MRI) were conducted. Seizures were confirmed and quantified monthly based on reports from parents, observing videos taken by parents, and direct observation at the hospital before and after treatment. EEG was performed on all patients. Diffuse and continuous paroxysmal epileptic discharges were considered severely abnormal when they accounted for >50% of the EEG readings and were considered mildly or moderately abnormal when they accounted for >25% of the EEG readings. Next, the children were administered an initial oral dose of Vigabatrin (40–50 mg/kg/day) that was divided into 2 or 3 doses; Vigabatrin was administered in addition to their previous medication (>2 new, conventional, or concurrent AEDs). The time required to achieve an appropriate dose of the drug was 2–3 weeks. Seizure periodicity and severity were evaluated within 3–4 weeks after Vigabatrin initiation. Vigabatrin doses were adjusted to a maximum dose of 100 mg/kg/day based on the level of seizure response. During the follow-up period, a response was defined as a stable seizure frequency or severity or a >50% reduction in seizure frequency. The primary and secondary outcomes of the study were defined as the efficacy of Vigabatrin, three and six months after initiation. The study was approved by the Ethics Committee of Shahid Beheshti University of Medical Sciences, and was registered in the Iranian registry of clinical trials (IRCT number: IRCT201209121050-8N3). Data were analyzed using SPSS 15 (SPSS Inc., Chicago, Illinois). *P*-values <0.05 were considered statistically significant.

## Findings

A total of 73 patients were enrolled in the study, but only 67 children reached the final stage. Details of the patient characteristics are listed in Table 1. Of these last patients, 41 (61.2%) were

**Table 1:** Patient characteristics in children with refractory epilepsy

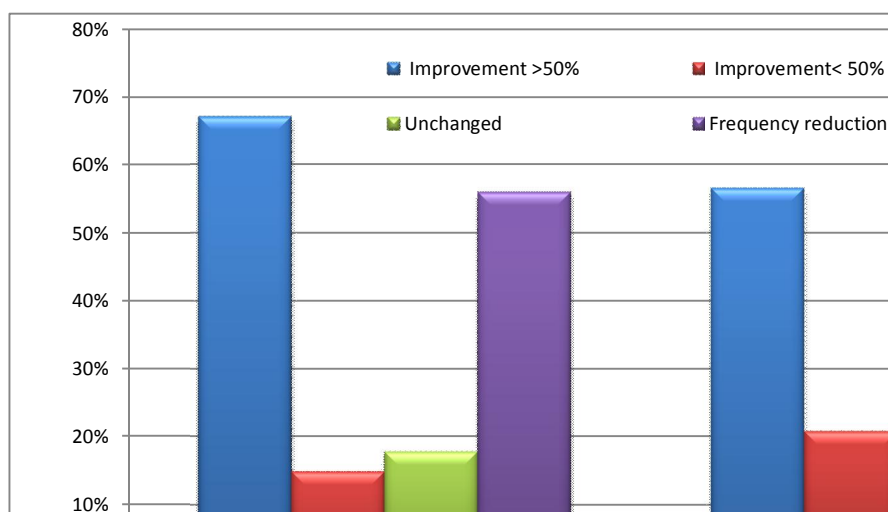
Variable	Characteristics	n (%)
<b>Gender</b>	Male	41 (61.2)
	Female	26 (38.8)
<b>Age</b>	Mean (SD)	3.1 (2.6) Y
<b>Seizure type</b>	Tonic clonic	17 (25.4%)
	Simple partial	6 (8.9%)
	Complex partial	6 (8.9%)
	Infantile spasm	12 (17.9%)
	Myoclonic	10 (14.9%)
	Tonic	5 (7.5%)
	Atonic	1 (1.5%)
	Mixed	10 (14.9%)
<b>Electroencephalography quality</b>	Normal	7 (10.4%)
	Mild abnormal	29 (43.3%)
	Moderate abnormal	17 (25.4%)
	Severe abnormal	14 (21%)
<b>Magnetic resonance imaging</b>	Normal	17 (25.4%)
	Atrophy	24 (35.8%)
	Periventricular leukomalacia	8 (11.9%)
	Mesial. temporal sclerosis	2 (3%)
	Migrational disorder	4 (6%)
	Tuberous sclerosis	5 (7.5%)
	Cortical dysplasia	2 (3%)
	Corpus callosum dysgenesis	3 (4.5%)
	Encephalomalacia	2 (3%)
<b>Third month follow-up</b>	Unchanged	12 (17.9%)
	100% reduction	16 (23.9%)
	75-99% reduction	12 (17.9%)
	50-75% reduction	17 (25.4%)
	25-50% reduction	9 (13.4%)
	<25% reduction	1 (1.5%)
<b>Six-month follow-up</b>	Unchanged	15 (22.4%)
	100% reduction	22 (32.8%)
	75-99% reduction	7 (10.4%)
	50-75% reduction	9 (13.4%)
	25-50% reduction	8 (11.9%)
	<25% reduction	6 (9%)

male and 26 (38.8%) female. They ranged in age from three months to 13 years with an average of 3.1 [standard deviation (SD): 2.6] years. The age of seizure onset ranged from one day to five years, and the mean age at seizure onset was 8.57 (SD: 12.8) months. The daily frequency of seizures varied from one attack every three months to 29 attacks per day with an average of 6.61 (SD: 5.9) seizures per day. The patients had used a minimum of three and a maximum of 16 antiseizure medications, with an average number of 5.0 (SD: 2.89) prior to this study. Primidon, Sodium valproate, Phenobarbital, Carbamazepine, Phenytoin, and Topiramate were the most commonly used concomitant drugs. Vigabatrin

was administered at a minimum dose of 40 mg/kg/day and at a maximum dose of 100 mg/kg/day; the mean dose was 76.6 (SD: 22.6) mg/kg/day.

The primary outcome, efficacy of Vigabatrin after three months, was assessed by daily seizure frequency, which decreased by 56% to 2.9 (SD: 5.2) per day. The secondary outcome, efficacy after six months, was a 54.5% decline in daily seizure frequency to 3.0 (SD: 5.3) per day.

There was significant difference between seizure frequency three ( $P=0.001$ ) and six months ( $P=0.001$ ) after the initiation of Vigabatrin therapy compared with baseline, and there was no significant difference between the daily seizure frequency at three and six months ( $P=0.6$ ).



**Fig. 1:** Seizure reduction at the three- and six-months follow-up

Frequency Reduction: Seizure frequency decline percent toward initial frequency

Improvement: Seizure severity reduction percent toward initial severity

In terms of the primary outcome and based on the severity and duration of seizures, 45 (67.2%) patients were classified as responders with the greatest responses observed in patients with partial, infantile spasms and generalized tonic-clonic seizures. There was no significant correlation between the type of seizure and drug response at this time point ( $P=0.4$ ).

Regarding the secondary outcome, the seizure severity of 38 (56.7%) patients was reduced by >50% with the greatest reductions observed in patients with infantile, partial spasms and generalized tonic-clonic seizures. The type of seizure was significantly correlated with drug response at this time point ( $P=0.008$ ). No significant difference was observed between seizure severity and decline in seizure duration at the three- and six-month follow-up ( $P=0.39$ ). After six months of Vigabatrin therapy, minor side effects were observed in nine (13.4%) patients including somnolence [3 (4.5%)], horse laugh [1 (1.5%)], urinary stones [1 (1.5%)], increased appetite [1 (1.5%)], and abnormal electroretinographic (ERG) pattern [3 (4.5%)]. The three patients who had an abnormal ERG pattern were all taking Vigabatrin at a dose of 50–70 mg/kg; the drug was discontinued in these patients and they were examined again three months after discontinuation. At this time, two had a normal ERG pattern, but one had an abnormal ERG pattern.

## Discussion

This study proved that Vigabatrin has significant efficacy in reducing the frequency, duration, and severity of pediatric seizures. Daily seizures were reduced by  $\leq 56\%$  and 54.5% after three and six months of Vigabatrin therapy. The responder rate, which means a reduction of >50% in seizure severity and duration, was 67.2% and 56.7% at three and six months of Vigabatrin therapy, respectively.

The reported overall response rate for Vigabatrin as an adjunctive therapy in intractable epilepsy differs, and ranges from 33% to 67% for partial epilepsy and 16% to 76% for infantile spasms<sup>[10]</sup>. The findings of the current study are consistent with the above-mentioned range.

Turanli reported that Vigabatrin reduced seizure frequency by 50% in 31.2% of children with intractable seizures, which is lower than the response reported in this study. A possible explanation for this discrepancy may be the fact that the mean final follow-up in Turanli's study was approximately 23.8 months, which is much longer than the six-month period used in our study<sup>[14]</sup>. Many studies have shown that the effects of antiepileptic drugs are reduced over time because of decreased receptor sensitivity resulting in pharmacokinetic tolerance<sup>[15]</sup>.

An important finding of our study was that 80% of patients with tuberous sclerosis had complete

seizure improvement with Vigabatrin therapy. This result is in agreement with Hancock et al, who reported that Vigabatrin ceased infantile spasms in 54% of infants without tuberous sclerosis compared with 95% of infants with tuberous sclerosis<sup>[16]</sup>.

In this study, we found that partial, infantile spasms and generalized tonic-clonic seizures showed the greatest response to Vigabatrin therapy. Visudtibhan reported a similar efficacy of approximately 76% for Vigabatrin in the treatment of infantile spasms<sup>[17]</sup>.

In Turanli's study, Vigabatrin resulted in >50% reduction in 33.3% of patients with partial seizures and 30.6% of those with generalized seizures, and there was no significant difference between these seizure types<sup>[13]</sup>. In a clinical trial performed by Guberman, 58% of patients with partial seizures treated with Vigabatrin achieved a reduction of >50% in daily seizure frequency versus baseline<sup>[18]</sup>. Based on our results, we suggest that Vigabatrin therapy could be an appropriate therapy for partial epilepsies that are refractory to other treatments. Our patients who showed a >50% reduction in seizures, were administered Vigabatrin at a dose of approximately 75 mg/kg/day, whereas Turanli achieved the same effect at 61.5 mg/kg/day<sup>[14]</sup>.

After six months of Vigabatrin therapy a few minor side effects were observed in nine (13.4%) patients including somnolence, horse laugh, urinary stones, increased appetite, and an abnormal ERG pattern. All of these were eliminated by a dosage reduction or by drug discontinuation. Our adverse effect rate was lower than the 18% complication rate (increased appetite, obesity, visual field defects, alopecia, drowsiness, skin rash, behavioral changes, hirsutism, and increased liver enzymes) found among Turanli's patients<sup>[14]</sup>. Guberman reported weight gain and behavior problems in 12% of his cases<sup>[18]</sup>.

In the present study, another important finding was that two children presented with a horse laugh as a Vigabatrin effect. This complication is consistent with that reported by Amirsalari et al, who found that loud laughing was a side effect in 16% of patients undergoing Vigabatrin therapy<sup>[19]</sup>.

Based on ERG examinations, only three (4.5%) children developed visual impairment at the end of the six-month treatment. Our findings are

consistent with those of Turanli et al., who confirmed visual field defects in 3.6% of children by ERG<sup>[14]</sup>.

## Conclusion

This study confirms the short-term efficacy and safety of Vigabatrin in children with refractory epilepsies. Future investigations with a longer evaluation period are needed to study the prolonged efficacy of Vigabatrin.

## Acknowledgment

We are grateful to the Pediatric Neurology Research Center of Shahid Beheshti University of Medical Sciences for supporting this study.

**Conflict of Interest:** None

## References

1. Borowicz KK, Luszczki JJ, Sobieszek G, et al. Interactions between zonisamide and conventional antiepileptic drugs in the mouse maximal electroshock test model. *Eur Neuropsychopharmacol* 2007;17(4):265-72.
2. Kwan P, Brodie MJ. Early identification of refractory epilepsy. *N Engl J Med* 2000;342(5):314-9.
3. Berg AT, Shinnar S, Levy SR, et al. Early development of intractable epilepsy in children: a prospective study. *Neurology* 2001;56(11):1445-52.
4. Kwan P, Brodie MJ. Combination therapy in epilepsy: when and what to use. *Drugs* 2006; 66(14):1817-29.
5. Lewis H, Wallace SJ. Vigabatrin. *Dev Med Child Neurol* 2001;43(12):833-5.
6. Wheless JW, Ramsay RE, Collins SD. Vigabatrin. Neurotherapeutics: *J Amer Soc Exp Neuro Therapeutics* 2007;4(1):163-72.
7. Lerner JT, Salamon N, Sankar R. Clinical profile of vigabatrin as monotherapy for treatment of infantile spasms. *Neuropsychiatr Dis Treat* 2010;6:731-40.
8. Moskowitz A, Hansen RM, Eklund SE, et al. Electroretinographic (ERG) responses in pediatric patients using vigabatrin. *Doc Ophthalmol* 2012; 124(3):197-209.
9. Storici P, De Biase D, Bossa F, et al. Structures of gamma-aminobutyric acid (GABA) aminotrans-

- ferase, a pyridoxal 5'-phosphate, and [2Fe-2S] cluster-containing enzyme, complexed with gamma-ethynyl-GABA and with the antiepilepsy drug vigabatrin. *J Biol Chem* 2004;279(1):363-73.
10. Sheean G, Schramm T, Anderson DS, et al. Vigabatrin – plasma enantiomer concentrations and clinical effects. *Clin Exp Neurol* 1992;29:107-16.
  11. Waterhouse EJ, Mims KN, Gowda SN. Treatment of refractory complex partial seizures: role of vigabatrin. *Neuropsychiatr Dis Treat* 2009;5:505-15.
  12. Greiner HM, Lynch ER, Fordyce S, et al. Vigabatrin for childhood partial-onset epilepsies. *Pediatr Neurol* 2012;46(2):83-8.
  13. Scaioli V, Franceschetti S, Binelli S, et al. Serial electrophysiological studies of the visual pathway in patients treated with vigabatrin. *Int Congress Series* 2005;1278:41-4.
  14. Turanli G, Celebi A, Yalnizoglu D, et al. Vigabatrin in pediatric patients with refractory epilepsy. *Turk J Pediatr* 2006;48(1):25-30.
  15. Löscher W, Schmidt D. Experimental and clinical evidence for loss of effect (tolerance) during prolonged treatment with antiepileptic drugs. *Epilepsia* 2006;47(8):1253-84.
  16. Hancock E, Osborne JP. Vigabatrin in the treatment of infantile spasms in tuberous sclerosis: literature review. *J Child Neurol* 1999;14(2):71-4.
  17. Visudtibhan A, Mutharai R, Chiemchanya S, et al. Treatment of infantile spasms with vigabatrin: An 8-year experience in Thai children in a referral hospital. *Neurol Asia* 2004;9(Suppl 1):117.
  18. Guberman A, Bruni J. Long-term open multicentre, add-on trial of vigabatrin in adult resistant partial epilepsy. The Canadian Vigabatrin Study Group. *Seizure* 2000;9(2):112-8.
  19. Amirsalari S, Kavehmanesh Z, Khalili Matinzadeh Z. Treatment of infantile spasms; tetracosetide or vigabatrin? a comparative study. *Iran J Child Neurol* 2006;1(2):25-9.