RESEARCH ARTICLE

# TREATMENT OF INFANTILE SPASMS; TETRACOSECTIDE OR VIGABATRIN? A COMPARATIVE STUDY

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Abstract:
Introduction:
Infantile spasms (IS) is an age specific epileptic syndrome. Due to poor response of IS to conventional antiepileptic drugs, scientists are always on the lookout for newer, more effective drugs to treat the condition.
Materials & Methods:
In this study, 50 infants with IS symptoms, aged between 2-24 months, were randomly divided into two equal groups, each treated either with Vigabatrin or ACTH (long acting Tetracosectide); the results for clinical efficacy of medication and drug side effects were compared.
Results:
After the sixth week of treatment, in the Vigabatrin group, 28% complete remission and 40% reduction in seizure frequencies was seen, while in the Tetracosectide group there were 40.9% complete remission and 45.5% reduction in seizure frequencies, showing no significant difference between the clinical responses found in the two groups (P = 0.44).
Conclusion:
Vigabatrin effeciacy is similar to Tetracosectide, but since it is impossible to evaluate visual field constriction, a probable irreversible side effect of Vigabatrin , It's better to use Tetracosectide for the first line in the treatment of IS .
Keywords:
Infantile spasms,Hypsarrhythmia, Vigabatrin,Tetracosectide

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## Introduction

Infantile spasms(IS), a specific kind of seizure characterized by a series of sudden muscular contractions in the neck, body and extremities, most commonly develops between the ages of 3 to 8 months; in about half the patients, we can see normal mental development up until onset of seizures but in the remainder there is a definite or a probable delay (1).Mental retardation and cerebral palsy are seen in 50% and 75% of the patients with infantile spasms respectively (2,3). Incidence of infantile spasms is between two to five in 10000 live births(4,5). Infantile spasms can be classified into three clinical (flexor type, extensor type and mixed type) and three etiologic categories (symptomatic, cryptogenic and idiopathic). Classic EEG patterns in these patients show hypsarrhythmia characterized by an irregular unorganized background and also high voltage slow waves and spikes which are asynchronous and nonrythmic with different duration and topography. It should be kept in mind that hypsarrhythmia is not a pathognomonic EEG pattern for IS; in a limited number of patients, clinical spasms are seen without hypsarrhythmia.

Infantile spasms are intractable to most conventional antiepileptic drugs. Since early treatment is necessary for remission of spasms and to prevent severe neurological complications,aggressive treatment should be started immediately following diagnosis(6).

Since 1956, ACTH gel has been successfully used in the treatment of infantile spasms, and has until now been the drug of choice; however because of multiple side effects (hypertension, hyperglycemia, susceptibility to infections, CNS hemorrhage, etc.) physicians are inclined to use newer drugs with more efficacy and fewer side effects. Vigabatrin (VGB) has rapidly gained popularity for the treatment of infantile spasms because of both its efficacy and its favorable profile. Chiron et al 1991(7) reported complete cessation of seizures in 43% of their patients of all ages afflicted with refractory epilepsy. However, superiority of VGB to steroids, withregard to efficacy and side effects has not been studied. Side effects produced by a steroid are reversible on discontinuation of the drug. Recent concerns about the seemingly permanent visual field constriction caused by VGB use makes it diffult for clinicians to decide between these two drugs. The aim of this study is to compare the efficacy and side effects of VGB and ACTH. Since ACTH gel is expensive we treated our patients with synthetic ACTH (long acting Tetracosectide).

**Materials & Methods**

In this study, we enrolled 50 children aged between 2 months and 2 years selected among patients with infantile spasms, who attended the pediatric neurology clinic of Mofid Children Hospital from Sept 1st 2000 to Sept 1st 2002. The patients were randomized into two equal groups of 25 cases each; the study group was treated with Vigabatrin and the controls were treated with synthetic ACTH (long acting Tetracosectide). In neither group had patients taken either Steroids or Vigabatrin previously; some patients had however previously taken conventional antiepileptic drugs like Phenobarbital , Nitrazepam, Clonazepam and Pyridoxine without any success. 3 patients in control group were excluded from study during the first days of study, due to severe drug side effects (2 cases due to severe hypertension and one case due to severe infection).

All patients were hospitalized for 4 days in order to carry out paraclinical studies, daily clinical evaluations, to start the treatment.and to educate family members. The controls were treated with synthetic ACTH (long - acting tetracosectide) 1 Iu/kg/day in one single intramuscular dose and the case group with oral Vigabatrin 50-100 mg/kg/day divided into two doses. In both groups, the drugs were continued for 3 weeks. If there was no appropriate response, the drug was tapered and discontinued. Following an appropriate response, in the control group, Tetracosectide was continued every other day for another 3 weeks, after which it was tapered and discontinued in 10 days, whereas in the study group, Vigabatrin was continued for about 1 year. For all patients before starting treatment, paraclinic studies consisting of EEG, brain CT-scan and laboratory studies (CBC, BS, Ca, Mg, Na, K, serum lactate, serum ammonia, blood and urine aminoacid chromatography, urine sugar chromatography, venous blood gas, TORCH study and thyroid function tests) were done.

Blood pressure was measured daily during hospitalization and twice weekly following discharge. Body weight was measured on the first day of treatment and then after the 3rd and 6th weeks. At the end of the 3rd and 6th weeks, parents were asked about probable side effects like somnolence, irritability and abnormal laughing. Patients were examined for other side effects like cushingoid appearance, hirsutism and infections.

Clinical criteria for response to treatment was complete remission of spasms or a decreasing frequency of spasms (50% reduction compared to the first day of trearment). Electroencephalogaphic criteria for response to treatment was partial improvement or complete disappearance of hypsarrhythmia. For statistical analysis, we used the Pearson chi-square for comparing qualitative data and independent sample T-test for comparing quantitative data. P-value $< 0.05$ was considered significant.

**Results**

50 patients were enrolled in the study, with 3 patients being excluded in the first few days due to severe drug side effects. Of the 47 remaining, 25 cases (53.2%) or the study group took Vigabatrin and 22 cases (46.8%) or the control group took Tetracosectide. Mean age for the Vigabatrin group was $11 \pm 5.3$ months or the Tetracosectide group was $11.5 \pm 5$, differnce not significant; 23 cases (48.9%) were male and 24 cases (51.1%) female. From the etiologic point of view, 34 cases (72.3%) had

symptomatic IS, while 13 (27.7%) had the cryptogenic kind. Clinically, 15 cases (31.9%) had the flexor type, 6 (12.8%) the extensor and 26 cases (55.3%) the mixed type of IS. Neuroimaging studies showed 33 cases (70.2%) had brain atrophy, 8 cases (17%) normal brain CT-scans and 6 cases (12.8%) revealed brain structural disorders.

In the Vigabatrin group, clinical responses to treatment after 3 weeks were 32% remission of seizures and 44% reduction in seizure frequency (50%),whereas in the Tetracosectide group it was 63.6% and 22.7%, respectively (table I ).

Table I: Clinical response to treatment after 3 weeks in the study and control groups

| Groups \ Response | | Complete remission | >50%Reduction in Seizure Frequency | <50%Reduction in Seizure Frequency | Increase in Seizure Frequency |
|---|---|---|---|---|---|
| Vigabatrin | Frequency | 8 | 11 | 6 | 0 |
| | Percent | 32 | 44 | 24 | 0 |
| Tetra-cosectide | Frequency | 14 | 5 | 3 | 0 |
| | Percent | 63.6 | 22.7 | 13.6 | 0 |

df= 2 P= 0.08 (Difference is not Significant)

Clinical response to treatment after 6 weeks in Vigabatrin group, was 28% remission of seizures and 40% reduction in seizure frequency (50%), and in Tetracosectide group it was 40.9% and 45.5%, respectively (table II).

Table II:Clinical Response to treatment after 6 weeks in study and control groups

| Groups \ Response | | Complete remission | >50% Reduction in Seizure Frequencies | <50% Reduction in Seizure Frequencies | Increase in Seizure Frequencies |
|---|---|---|---|---|---|
| Vigabatrin | Frequency | 7 | 10 | 7 | 1 |
| | Percent | 28 | 40 | 28 | 4 |
| Tetra-cosectide | Frequency | 9 | 10 | 3 | 0 |
| | Percent | 40.9 | 45.5 | 13.6 | 0 |

df= 3 P= 0.44 (Difference is not Significant)

The differences between clinical responses in the two groups after 3 and 6 weeks of treatment were not significant(P=0.08 and P=0.44, respectively). EEG results before treatrment in the Vigabatrin group showed 52% severe abnormality (hypsarrhythmia), 16% moderate abnormality and 32% mild abnormality, while in the Tetracosectide group showed 68.2%, 22.7% and 9.1%, of the abnormalities mentioned respectively (table III).

Table III: Electroencephalographic status in study and control groups before treatment

| Groups \ EEG | | Severly Abnormal (Hypsarrhythmia) | Moderatly Abnormal | mildly abnormal or normal |
|---|---|---|---|---|
| Vigabatrin | Frequency | 13 | 4 | 8 |
| | Percent | 52 | 16 | 32 |
| Tetracosectide | Frequency | 15 | 5 | 2 |
| | Percent | 68.2 | 22.7 | 9.1 |

df= 2 P= 0.15 (Difference is not Significant)

EEG results after the treatment in the Vigabatrin group showed 36% complete recovery, 44% partial improvement and 20% no improvement; in the Tetracosetide group, 40.9% showed complete recovery, 36.4% partial improvement and and in 22.7% no improvement was seen (Table IV)

Table IV: Electroencephalographic status in the study and control groups after treatment

| Groups \ EEG | | Complete Recovery | Partial Improvement | No Change |
|---|---|---|---|---|
| Vigabatrin | Frequency | 9 | 11 | 5 |
| | Percent | 36 | 44 | 20 |
| Tetracosectide | Frequency | 9 | 8 | 5 |
| | Percent | 40.9 | 36.4 | 22.7 |

df= 2 P= 0.88 (Difference is not Significant)

The differences seen in EEG improvement between the two groups is not significant(P=0.88).

A probable side effect of Vigabatrin is constriction of visual field which was not evaluated in our patients; another side effect of Vigabatrin is laud laughing (8) which was found in 16% of cases in this group. 31.8% abnormal increase in weight, 25.3% cushingoid appearance, and 18.2% hypertention were observed in the Tetracosectide group, not seen in the Vigabatrin group. The difference between these side effects in the two groups is significant. While Hirsutism was seen in 4.5% and susceptibity to infections in 4.5% of cases in the Tetracosectide group, these side effects were not seen in the Vigabatrin group(difference between side effects in the two groups not sigificant)

Overall the side effects were 16% in the Vigabatrin group and 81.8% in the Tetracosectide group, a difference which is significant ( P= 0.001) (Table V).

Table V: Drug side effects in the study and control groups

| Groups \ Side Effects | | Present | Absent |
|---|---|---|---|
| Vigabatrin | Frequency | 4 | 21 |
| | Percent | 16 | 84 |
| Tetra-cosectide | Frequency | 18 | 4 |
| | Percent | 81.8 | 18.2 |

df= 1 P= 0.001 (Difference is Significant)

**Discussion**

Different studies compared the efficacy of Vigabatrin and ACTH, and showed equal efficacy (8) or preference of ACTH usage(9). In these studies, Vigabatrin had fewer side effects and was better tolerated by patients (8,9). In a retrospective, multicenter study (10), VGB was given as the first treatment at an average dose of 99 mg/kg/day; complete cessation of spasms was seen in 131 of 192 (68%) patients, and of these 96 (50%) were seizure-free at follow-up after 0.5-28.6 months. Initial suppression of spasms was obtained in 68% of infants, and the median time before a response was 4 days. In contrast to this study, in another reseach the favorable response rate to VGB was only 26% (11). VGB was given as the first-line drug for all patients for 7-20 days; of 42 patients 11 responded to VGB. Ninety-one percent of the infants responded to a dose of 50-100 mg/kg/day, of which 82% did so within 1 week. ACTH (3-12 IU/kg) was offered in combination with VGB to 22 patients for 4-12 weeks and Valproate to four infants for whom VGB failed. Eleven of the nonresponders to VGB responded to ACTH and one to Valproate. The total response rate was 62%.

Our study shows that clinical response and EEG improvement are similar in the two groups, but as mentioned in the results, side effects in the Vigabatrin group are significantly fewer; it must be kept in mind that side-effects of ACTH are well known by physicians and are reversible by drug cessation; however we could not identify the limitation of visual field in infants taking Vigabatrin, so we recommended ACTH (long acting Tetracosectide) as the first choice of treatment for IS, and encountering severe side effect, Vigabatrin can always be used as an effective alternative therapy.

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