Vigabatrin versus ACTH in the treatment of infantile spasms

Fatma Z. Omar, FRCPE, MAAN, Nawal O. Al-AbdulWahab, MBBS, DCH, Baleegh M. Ali, MBBS, DCH, Fahd A. Karashi, MBBS, DCH, Sulaiman A. Al-Musallam, MBBS, DCH.

ABSTRACT

Objectives: To compare adrenocorticotropic hormone with vigabatrin as a single mono-therapy for infantile spasms. We studied hospitalization time, clinical response, whether complete or partial, time taken for improvement, and presence or absence of recurrence after stopping the medication. Together with improvement of electroencephalographic changes, and time taken for significant response, neurodevelopmental and cognitive responses in both groups.

Methods: Our study was conducted initially on 36 patients. They were divided randomly into 2 groups. The first group received adrenocorticotropic hormone and 2nd vigabatrin, as a single mono-therapy for infantile spasms. There was a male sex predominance of (1.25:1), with 20 males to 16 females affected. The mean age of onset was 5.2 months. Of the 36 patients, 26 patients (72.2%) were having typical hypsarrhythmia on electroencephalogram and 10 (27.8%) had burst suppression pattern. All 36 patients were having typical spasms. Four patients, all female, were excluded from the study, as their families lived outside Riyadh, and they were not regular on follow up. The remaining 32 patients continued the study. Therefore, 16 patients were put in each group randomly.

Results: In the first group (adrenocorticotropic hormone group): initial improvement was achieved in 10 infants (62.5%), with median response time of 9 days, at a dose of 20 IU intramuscular daily, in the first 10 days. In the 2nd group vigabatrin: the initial improvement was achieved at 4 days in 9 infants (56.25%) at an average dose of 87mg/ kg /day. The response was more appreciated in the secondary group infantile spasms with a known etiology. Side effects were noted in younger age group (5 months or below); 14 patients (78.5%) out of 16 suffered side effects from the adrenocorticotropic hormone group. Side effects in the vigabatrin group were much less, only 4 patients (25%) had some drowsiness, none had visual disturbances.

Conclusion: Vigabatrin is an effective therapy for infantile spasms. It has shown to be as effective as adrenocorticotropic hormone, with less hospital dependency and milder side effects. As far as this study is concerned, differences in neurodevelopmental outcome are probably due to the underlying etiology. More research may be needed to further enhance the effects on both cognitive function and vision.

Keywords: Infantile spasm, vigabatrin, adrenocorticotrophine.

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Infantile Spurs (IS) are a unique form of seizure disorder. Limited almost entirely to the infantile age group. They are refractory to conventional antiepileptic drugs and their causes are many. The clinical description includes a very specific type of seizure. Infantile spasms have a characteristic electroencephalogram (EEG) pattern, called hypsarrhythmia. These children suffer deterioration in their psychomotor development. In the recent classification of International League Against
Epilepsy (ILAE) in 1989, they were classified in the general group with myoclonic epilepsies.\textsuperscript{1,4} The name West Syndrome is used as a synonym with IS. Referring to Dr. West who described the condition in his own son. Treatment of IS is not easy. Response to conventional anti-epileptic drugs (AEDS) is not satisfactory. Adrenocorticotropic hormone (ACTH) or corticosteroids have been used, since their introduction in 1958, and have been considered the standard modality of treatment. The dose given is variable, ranging from 20-80 IU/day, depending on clinical response and side-effects. Some other preparations, like prednisolone (2-5mg/kg/day), hydrocortisone or dexamethasone have been proposed.\textsuperscript{5,6} Other AEDS like valporic acid, vitamin B6 or benzodiazepines namely clonazepam or nitrazepam, have been used, but the response is unsatisfactory. This is in addition to their own specific side effects.\textsuperscript{7,10} Vigabatrin (VGB) is a GABA aminobutyric acid (GABA) inhibitor. It is given orally, and rapidly absorbed, with no tendency to bind to plasma proteins. Half-life is 5-7 hours, and excreted mainly through the kidneys (65%). It has a limited potential to drug interaction, with the exception of phenytoin. Doses for child age group start from 40mg/kg/day up to 150 mg/kg/day in 2 divided doses. Studies have shown its efficacy as a single initial mono-therapy for IS.\textsuperscript{11-18} Side effects include somnolence, fatigue, irritability, psychological upset and finally peripheral visual field restriction due to the effect on the optic nerve. There is a lot of argument regarding this side effect but until now there is no published data in younger age groups, specifically in the first year of life.\textsuperscript{19-22}

\textbf{Methods. Patient selection.} Out of the 36 patients selected for this study, 4 were excluded due to irregularities in follow-up as their families resided far away. The children were all diagnosed clinically as having spasms based on the following: Electroencephalogram changes, 25 patients. (78.1\%) showed hypsarrhythmia and 7 patients (21.8\%) had burst suppression pattern. Clinically, 28 patients (87.5\%) showed typical flexor spasms, and 4 patients (12.5\%) showed extensor spasms. All children were between 3 and 10 months of age (mean age 5.2 months). There was a male predominance (20 males to 12 females) male to female ratio of 1.67:1. All of these patients were newly diagnosed and had not previously received treatment before.

\textbf{Patient assessment.} A complete history was taken from the mother or caregiver. Systemic examination was performed for all patients including systems review, chorionic villus sampling, respiratory, abdomen as well as general growth, and for presence or absence of dysmorphism. Skin examination by wood’s light was undertaken. Neurodevelopmental evaluation was conducted for the patients. The following evaluations were also included: (i) developmental age assessment by a pediatrician. (ii) Complete neurological examination by a pediatric neurologist. (iii) Pediatric ophthalmological assessment was carried out initially and at follow up, in the VGB group. Investigations carried out included: Routine (for admitted patients): complete blood count chemistry including blood sugar, urea, creatinine, serum sodium, potassium, calcium, magnesium, and liver functions. Non-routine: serum lactate, serum ammonia, tandem metabolic screening for aminoacidopathies, and urine gas chromatography for organic acidopathies, karyotyping if there was significant dysmorphism (2 patients) and in cryptogenic type. Radiological: computerized tomography (CT) brain was carried out for all patients and magnetic resonance imaging (MRI) brain for 18 patients only. Brain stem evoked auditory responses (BEAR) and visual evoked responses (VER) carried out by an ophthalmologist. Electroencephalogram was carried out for all patients at presentation, then at follow up after 10-14 days. A 3rd follow up EEG was carried out after 6 months to one year.

\textbf{Results.} Thirty-two patients were studied, 16 patients received ACTH and 16 received VGB for treatment of IS. Median follow up period was 6.4 months (ranging from 2 months up to one year). Data for each patient was collected and divided into 2 groups. We initially selected 36 patients for our study, but 4 patients were excluded, as the families were not easily reached when needed, and were not regular on follow-up. The remaining 32 patients were evaluated by the pediatric neurology team in Sulaimania Children Hospital. The diagnosis of IS was confirmed by clinical presentation. Twenty-eight patients (87.5\%) had typical flexor spasms, and 4 (12.5\%) had extensor spasms. Twenty-five patients (78.1\%) had hypsarrhythmia on EEG, where and 7 (21.8\%) had burst suppression pattern, before starting medications. All patients were below one year of age. Their etiological analysis is reviewed in Table 1. The seizures completely disappeared in 12 patients (75\%), and improved in 4 patients (25\%) of the ACTH group. In the VGB group, there was complete remission in 11 patients (68.7\%) and partial recovery in 5 patients (31.2\%). By partial recovery we mean improvement, but not complete disappearance of the spasms. The recurrence rate was higher in the ACTH group (25\%). Time taken for recovery was analyzed and was shorter in VGB group, median 5 days. Time taken for EEG changes to disappear was shorter in the ACTH group.

In general, the main concern regarding VGB side effects was in connection with the visual affects of VGB group.\textsuperscript{19-22} Vision was checked by an ophthalmologist before, and at 6 monthly intervals for at least one year after stopping VGB and VER.
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Table 1 - Etiological analysis of the 32 cases.

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Patients N (%)</th>
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<tbody>
<tr>
<td>Cryptogenic</td>
<td>16 (50)</td>
</tr>
<tr>
<td>Hypoxic ischemic encephalopathy at birth</td>
<td>4 (12.5)</td>
</tr>
<tr>
<td>Tubers Sclerosis</td>
<td>2 (6.25)</td>
</tr>
<tr>
<td>Cortical dysplasia</td>
<td>1 (3.125)</td>
</tr>
<tr>
<td>Prematurity</td>
<td>2 (6.25)</td>
</tr>
<tr>
<td>Metabolic</td>
<td>3 (9.375)</td>
</tr>
<tr>
<td>Others</td>
<td>4 (12.5)</td>
</tr>
</tbody>
</table>

and electroretinography (ERG) were carried out initially and after 6 months by an ophthalmologist with no significant changes. The other side effects such as weight gain, somnolence and agitation were encountered in the VGB group but they were mild and did not require stopping of medication.

Discussion. Uncontrolled studies do not usually improve the final outcome of certain studied drugs due to the lack of comparison either with the controlled group or with other drugs used previously. In this study we compared 2 drugs, the standard old treatment for IS, ACTH, and Vigabatrin, a recently used drug to some extent. The comparison touched the therapeutic effects, time needed for response, hospitalization time, and possible side effects. We came to the conclusion that both medications were effective in stopping and reducing frequency of seizures. Vigabatrin had less side effects (31.2%) in Vigabatrin and 87.5% in ACTH, and quicker response time (median response time in Vigabatrin was 5 days, and 8 days in ACTH). Reviewing visual changes, as shown in the study, it was not noted in any of our patients using Vigabatrin, this was after being evaluated by a neurologist, and ophthalmologist, though there are some publications attributing the visual changes to Vigabatrin use, but these were noted in giddiatric patients, using large doses (>300mg/kg/day), for a long time (>2 years).2-3 Reviewing other lines of treatment for IS, such as Benzodiazepine, and Valporic Acid, the therapeutic effects of these medications are less than ACTH, and Vigabatrin, and at the same time with more side effects than Vigabatrin.7-10 Other studies carried on the efficacy and outcome of Vigabatrin, also support the use of Vigabatrin as single mono-therapy for IS.11-12 We also found the same conclusion in other studies,13-15 Vigevano et al studied Vigabatrin versus ACTH in treatment of IS, and to some extent their results were similar to our study.

In conclusion, VGB is as effective as ACTH in the treatment of IS.11-18 The time taken for response (median time) is shorter, with less hospitalization time (7 days maximum) in the VGB group, and 20 days in the ACTH group. Vigabatrin was well tolerated when given to our patients, as it was with other studies.12-18 The main concern regarding asymptomatic peripheral visual field constriction with VGB was not recorded in the child age group. This may be due to difficulty of visual field assessment before 9 years of age.19,22 Our recommendation for infants on VGB group is visual check by an ophthalmologist during, and up to one year after stopping medication. Regarding neurodevelopmental outcome, it was similar in both groups. However, longer follow-up time is needed, with a larger number of patients, to compare cognitive functions in both groups.

References