COMPARATIVE STUDY OF CORTICOTRHIN VS VIGABATRIN THERAPY IN INFANTILE SPASM

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ABSTRACT

Twenty six patients were diagnosed as infantile spasm, on the basis of fixed criteria and they were divided into symptomatic (17 patients) and cryptogenic (9 patients) groups according to history, presentation and investigations. Corticotrophin as Tetracosactrin was given to eleven patients and fifteen patients received Vigabatrim (VGB). The response to VGB was significant (73%) compared to steroids (63%), irrespective of the etiology, thus emphasizing that VGB could be considered as the first line therapy for infantile spasm.

KEY WORDS: Infantile spasm (IS), Adrenocorticotrophin (ACTH), Tetracosactrin, Vigabatrin (VGB), Electroencephalography (EEG).

INTRODUCTION

Infantile Spasm (IS) is an unique age specific epileptic encephalopathy of infancy leading to uncontrolled seizures and mental retardation. First described by West in 1841, the detailed clinical aspects were fully analyzed later by many authors. The recent classification of Epilepsy and Epileptic syndrome of the International League against Epilepsy (ILAE) defines IS as spasms, arrest of psycho motor development and a hypersarrhythmnic pattern in EEG. IS was classified as symptomatic when a known underlying etiology is present and cryptogenic when identifiable cause is absent.

Adrenocorticotropic hormones or its derivatives are considered as mainstay in the treatment of IS; however its side effects limit its wide acceptance. Recently, a new synthetic polypeptide of corticotrophin, Tetracosactrin, has also been also found to be useful. Other anti epileptic drugs namely, sodium valporate, benzodiazepines, phenobarbitone have uncertain efficacy in the management of IS. Pyridoxine has been reported to be effective for IS in Japan but no randomized controlled trials proved its real efficacy. Similarly, newer novel therapies such as zonisamide, topiramate, IV immunoglobulins (IVIG), ketogenic diet, thyrotrophin releasing hormone (TRH) have been tried in IS with no significant benefit. Vigabatrin (VGB), a suicidal inhibitor of GABA transaminase, was first introduced in IS with tuberous sclerosis (TS) and found to be very effective in the control of spasms. We conducted a comparative study with a first line monotherapy with a synthetic cortiotrophin, Tetracosactrin, in one group of patients with IS and compared the efficacy with Vigabatrin, in another group of patients. The aim of the study was to evaluate the efficacy and safety of two drugs in both symptomatic and cryptogenic forms of IS.

METHODS

Twenty six patients, seventeen males and nine females were diagnosed as IS as per the
Riaz Ahmed

ILAE criteria and were included in the study between February 2001 and April 2006. The onset of symptoms of characteristic spasms were between two months to 10 ½ months. All the patients were admitted; clinical, wood’s lamp examination and metabolic work-up, were done in all. CT brain and EEG were also performed. Twelve patients were classified as of symptomatic etiology and 14 were of secondary IS. The treatment was divided into two groups: Eleven patients received daily injection of Tetracosactrin in the dose of 0.03mg/kg to a maximum of 125 microgram for a period of two weeks and depending upon the response the dose was tapered to twice a week injections and stopped in a week. No further injections were given after that and the dose remained the same for all patients. Tetracosatrin is a polypeptide synthetic derivative which has similar properties of corticotrophin which has been used in many conditions where systemic administration is indicated. Vigabatrin (VGB) was given orally as 100 mg/kg/day in two divided doses for 15 patients. The dose of VGB was increased to 125mg/kg within two weeks to a maximum of 150mg/kg, when the control of spasms was inadequate. Clinical and EEG response were evaluated weekly and noted. Ophthalmologic evaluation was done in only seven VGB treated children in follow up. Response outcome was measured by 1) complete cessation of spasms 2) normalization of EEG 3) relapse rate.

RESULTS

In the first group, of the 11 patients who received steroids, five were of symptomatic etiology; three with perinatal hypoxic insult, one each with tuberous sclerosis and neonatal transient lactic acidaemia. The rest, six patients were of cryptogenic type. The spasms were controlled in seven patients successfully with Tetracosactrin of which four were of cryptogenic etiology and three with symptomatic; one with severe perinatal hypoxia died in two weeks. The rest of the three non responders were later given VGB as per the request of parents. The duration of treatment to control spasms was three weeks in four patients and two weeks in one.

Among the second group of 15 patients, seven belonged to symptomatic group; three wit tuberous sclerosis, one cortical dyspalsia (microlissencephaly), one perinatal hypoxia, and two porencephaly and 8 patients were of cryptogenic type. VGB was given orally in a dose of 100 mg/kg/day in two divided doses, to start with, and then gradually increased to 125mg/kg/day after 4 - 7 days, not exceeding 150 mg/kg/day. The average time for the response was 13-22 days and the cryptogenic group responded to treatment earlier (22days) than the symptomatic group (25-35days). The number of responders was significant in this group compared to former group (11 cases) although the response was delayed. Seven cases of cryptogenic group and four cases of symptomatic group showed good response to VGB. All cases of tuberous sclerosis responded well to VGB. The long-term outcome measures could not be done due to poor follow-up status.

Comparing the two groups, the response to VGB was significant (73%) compared to steroid treatment (63%). Tetracosactrin group showed earlier response to treatment (8-16days), than VGB group (22 days). EEG recovery was also analyzed in two groups and found to be earlier and better in the former group- 56% vs 38%, although clinical response was better in VGB treatment group. Three patients (27%) developed steroid induced side effects; two had severe cushingoid features and one had hypertension. No significant side effects were noted in VGB group and retinal examination was found to be normal also in follow up. The hospital stay was prolonged for Tetracosactrin treated group (26 days) compared to VGB group (64 days). The follow was possible in only 12 patients (five in group one and seven in group two) and subsequent cognitive delay and incidence epilepsy were equal in both groups (37.5%) although it may not give the true incidence.


**DISCUSSION**

Corticotrophin and its derivatives were introduced for the treatment of infantile spasm (IS) in 1958 on suspicion of neuro-allergic encephalitis as an underlying pathogenesis. Since then, they are regarded as the standard treatment for this condition; however, frequent severe side effects such as infection, hypertension, hypertrophic cardiomyopathy, electrolyte disturbances and adrenocortical dysfunction occur during therapy. There is no uniformity in the dosage schedule of corticotrophins in IS and even the current practice parameters, recommended by American Academy of Neurology 2005 did not specify optimum dosage to be used in this condition. It was further proved in many studies, that there was no advantage with higher doses of corticotrophins; instead hypertension and “cerebral shrinkage” were more common with large dose.

Natural ACTH is still widely used in Europe and United States as the reported side effects with synthetic ACTH are much more severe in them. We used tetracosactrin, a synthetic derivative of corticotrophin at a low dose of 0.03-0.04mg/KG (not more than 125 microgram) with good efficacy. The incidence of side effects we encountered, viz. cushingoid features, transient hypertension, in our series was much lower (27%) compared to other series. We speculated natural ACTH may not be effective in lower doses and so side effects were unavoidable when used in higher doses. Overall cessation of spasm was seen in 91% of IS with Tuberous sclerosis (TS) had been reported. The total control of seizures in our patients with TS in group II with VGB is comparable to all other studies. There were many randomized placebo trials which confirmed efficacy of VGB in IS even with other etiology. The overall response of spasms to VGB in both cryptogenic and symptomatic etiology, was better (73%) in our patients, compared to corticotrophin usage (63%). The success rate is better than all other series reported; 68% response in Aicardi et al and 48% response in Vigveno et al, in symptomatic group. Thus we showed that VGB treatment showed good response in spasms with TS and porencephaly while corticotropin controlled spasms better in IS with perinatal hypoxic insults, as seen in other series. Drug induced side effects were minimal in VGB treated group because of slow escalation of dosage whereas adverse effects (28%) were unavoidable in corticotrophin group.

Interestingly, control of spasms, both clinical and EEG response, with corticotrophin usage was seen earlier (9-13 days) compared to VGB (12-22 days). This was in contrast to the study by Vignevedo et al, who showed earlier clinical but late EEG response with VGB. We presume this late response in our series may be due to slow escalation of dosage of VGB. However, the response was consistent in VGB treated group, with disappearance of hypsarrythmic pattern with no recurrence of spasms. Early recurrence was noted in two patients of corticotrophin group, on tapering, and needed further modification of treatment.

It thus confirms in our study that (a) low dose corticotrophin was much efficacious than high dose and (b) although VGB showed delayed response, it was consistent without recurrence of spasm and without major side effects.

**CONCLUSION**

This study clearly shows the efficacy and safety of Vigabatrin over Costicotrophins, for the management of infantile spasms, irrespective of the etiology as monotherapy, although the sample size is small. Synthetic corticotrophin is equally effective even with low doses for the control of seizures in IS but the side effects could not be avoided.

VGB usage indeed avoids this potential steroid induced toxicity, which is a major concern among physicians and parents. This study also emphasizes that VGB must be considered as the first-line monotherapy for infantile spasm.
REFERENCES