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Efficacy of Early Addition of Vigabatrin in Non-Responder to Hormonal Treatment in a Resource Limited Cohort of Infantile West Syndrome

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Abstract: ***Objectives: This study aimed to assess the efficacy of vigabatrin as early add on therapy inpatientswho did not respond tohigh dose oral Prednisolone (8mg/kg/day)& ACTH (150IU/m^2/day). Methods: This was an observational study conducted at a tertiary-level-hospital from August-2014 to August-2015. Children aged 2-months to 23-months presenting with infantile spasms with hypsarrhythmia or its variants on EEG were enrolled. The study participants were started on high dose Prednisolone (8 mg/kg/day maximum 60mg/day). Patient who did not respond to hormonal treatment were immediately started on Vigabatrin (50-150mg/kg/day) and hormonal treatment was tapered off. The primary outcome measure was cessation of spasms and clearance of hypsarrhythmia on EEG after initiating Vigabatrin in a cohort of non responders to hormonal therapy. The study was approved by the ethical committee of the college. Results: Fifteen children were started on Vigabatrin after failure to achieve response from hormonal therapy. The response was nearly 11/15 (73.33%) which was significantly higher as compared to studies done earlier. Conclusion: Vigabatrin is good alternative when added sequentially in patients who failed hormonal therapy. Vigabatrin as add on drug resulted in better seizure control than ACTH and steroid alone.***

Keywords: responder, non-responder, hypsarrhythmia, spasms, Vigabatrin

1. Introduction

West syndrome is a rare but age specific epileptic encephalopathy. Usually provoked by many genetic/structural/metabolic or cryptogenic aetiologies. It consists of infantile spasms accompanied with characteristic EEG appearance hypsarrhythmia and its variantsplus frequent neurodevelopmental delay or regression. Unsuccessful treatment as well as delay in definitive treatment results in poor neurodevelopmental outcome[5]. Because of the poor response rate, a wide variety of drugs are used to treat Infantile Spasms the world over. However hormonal therapies such as intramuscular adrenocorticotropic hormone (ACTH) [1, 2, 7] oral steroid (prednisolone) [4, 6] and Vigabatrin [10, 11, 12] are commonly used form. There is no consensus on the role of oral steroid as the first line treatment of infantile spasms[8]. The limitations like high cost, pain associated with intramuscular injections and non availability of skilled personnel to administer injections to young children precludes the use of ACTH in children from resource limited settings. In the present study we examined a short term efficacy and safety of Vigabatrin as add on therapy in non responders to hormonal therapy for infantile spasms.

2. Methods

Many children with poorly controlled seizures are referred to the paediatric department of Subharti Hospital Meerut. Patients identified as West syndrome without history of prior hormonal therapy were recruited for the study. This observational study was conducted between August 2014 and August 2015. The ethical clearance was obtained from institutional ethical committee. A written informed consent was obtained from the parents.

3. Study Participants

Children aged 2 months to 23 months presenting with clinical spasms with EEG evidence of hypsarrhythmia or its variants so-called modified and atypical variants[1] without history of prior hormonal treatment were enrolled. Children with active/chronic systemic or severe acute malnutrition as defined by WHO criteria (presence of pedal oedema, weight for height <-3SD (WHO child growth charts), visible wasting, mid upper arm circumference <11.5cm were excluded.

4. Treatment Procedure

Each child underwent detailed history and examinations. The age at onset, birth history, family history, and the development status were noted. The results of investigations such as neuro-imaging, EEG and metabolic testing were documented. MRI scan of brain was performed in all the patients along with EEG as initial investigation. Children withclinical suspicion of a metabolic disorder (a history ofparental consanguinity, prior affected siblings, unexplainedvomiting, intermittent worsening of symptoms, recurrentepisodes of lethargy, altered sensorium, or ataxia or hepato-splenomegaly on examination) or no obvious aetiology onclinical evaluation and neuroimaging underwent screeningtests for inherited metabolic disorders. These included arterial blood gas, blood lactate, blood ammonia, urine ketones,and blood tandem mass spectrometry.

Based on the aetiology, West syndrome was classified as known aetiology orsymptomatic and no identified aetiology or cryptogenic. On the day of diagnostic confirmation, treatment with oral prednisolone was initiated at 8 mg/kg/day with a maximum of 60 mg/day. After 2 weeks, all patients with clinical response to prednisolone based on parental report & clinical examination underwent repeat

EEG to confirm clearance of hypsarrhythmia. Patients who did not respond to hormonal treatment were immediately started on Vigabatrin at 50-150 mg/kg/day. Patient who failed to achieve response to Vigabatrin were given other antiepileptic/ketogenic diet as illustrated in **Figure 1.**

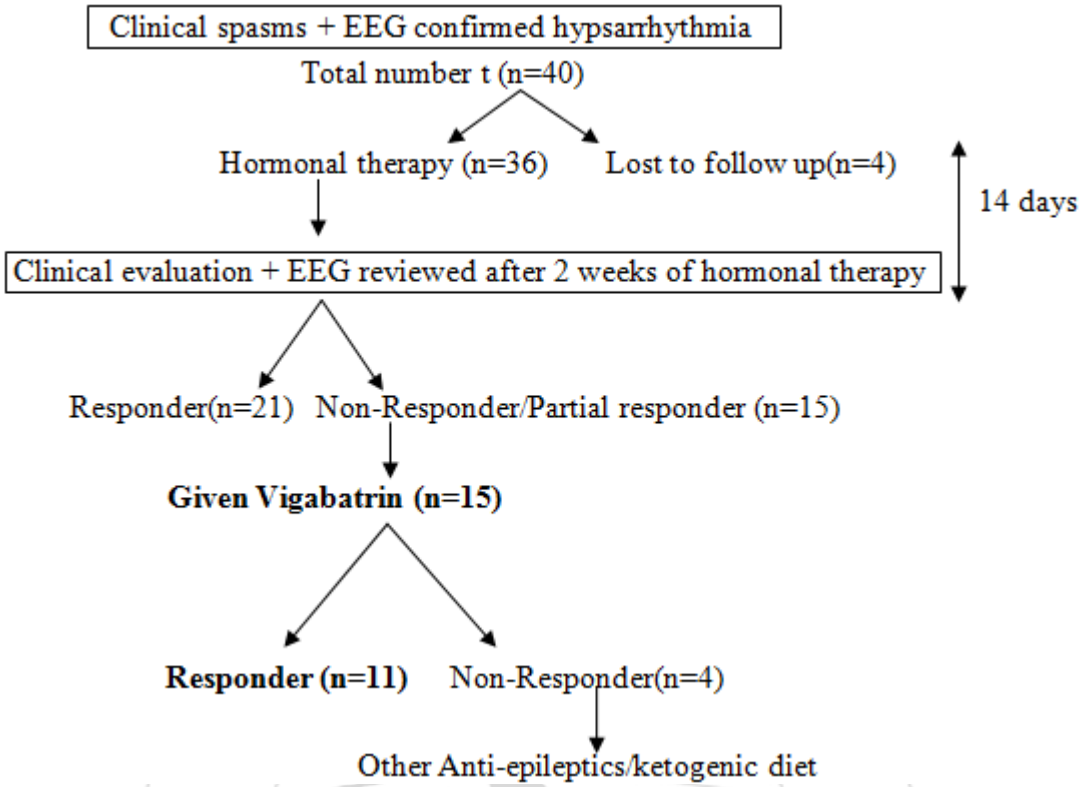


Figure 1: Flow Chart of the patients in study protocol. Response requires EEG confirmation of freedom from hypsarrhythmia and clinical spasms

5. Results

Characteristics of the study population:-

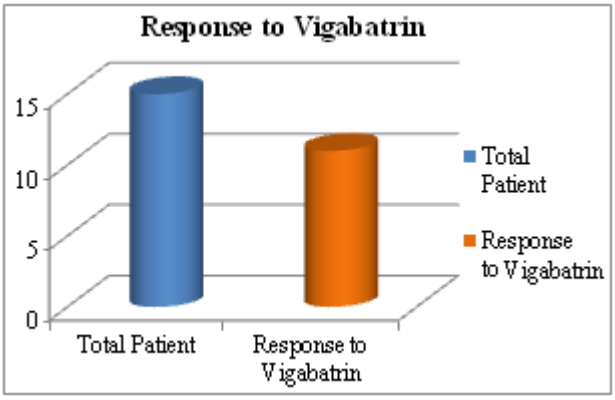
The study cohorts of 40 patients with infantile spasms were evaluated at Subharti medical college during the study period. Of these only 36 completed the study protocol.

Demographic and clinical characteristics	
a) Total Patients(n)	15
b) Sex,	
i. **male, (n) %**	12(80)
ii. **female, (n) %**	3(20)
c) Age of onset of spasms, months, median(IQR)*	7(4-22)
d) Age at entry to protocol, months, median(IQR)	10(4-23)
e) Duration of follow up, months, median(IQR)	8(1-22)
f) Aetiological classification& response	
i. **Structural West Syndrome**	12(80)
ii. **Cryptogenic West Syndrome**	3(20)
g) Improvement in development assessment, (n)%	11(73.33)
h) Response of Vigabatrin in non responder to hormonal therapy, (n)%	**11(73.33)**
*IQR(inter quartile range)	

Thirty six patients received hormonal therapy for infantile spasms according to the protocol outlined earlier. Twenty 20/36 (55.55%) patients responded completely to prednisolone after 2 weeks, 16 patients who did not respond to hormonal therapy were immediately started onVigabatrin and hormonal treatment was tapered off. This **resulted in 15/11(73.33%) reduction in infantile spasms**.

Figure 3: Response of Vigabatrin in non responder to hormonal therapy

Patient	*Response n (%)*
15	11(73.33)



6. Discussion

In this study response was assessed using both EEG clearance of hypsarrhythmia and clinical cessation of spasms. Response to Vigabatrin11/15(73.33%) is significantly higher than the 18/61(30%) response shown byJones k et al [12] &180/101 (56.9%) shown by Djuric M [11] et al in controlling spasms. In a study conducted by The International Collaborative Infantile Spasms Study (ICISS) [13] where they have used Vigabatrin in combination with steroid resulted in 133/185 (71.9%) reduction in spasms. Whereas the response of 73.33% in our study was shown by Vigabatrin when used sequentially to hormonal therapy as combined use of Vigabatrin and steroid was not feasible in resource limited study. The use of Vigabatrin along with steroid was not feasible in our resource limited study population as Vigabatrin was not easily available, and was expensive as compared to steroid. Because of the low frequency of this clinical entity historical comparators were considered. There could be demographic and aetiological variations amongst different study population reported in literature. A large-scale, multicenter, trial is required to conclusively determine whether the response rate of Vigabatrin as an add on medication after failure to hormonal therapy with good control of spasms and acceptable side effects still needs to be identified.

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