

Experience with very high dose (8mg/kg/day, maximum 60mg/day) prednisolone for West syndrome in a resource limited setting

*Ashok Kumar¹, Sunil Malik¹ Saurabh Chopra², Ashish Prakash¹

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Abstract

Objectives: To assess the efficacy of very high dose (8mg/kg/day, maximum 60mg/day) prednisolone in patients with West syndrome.

Method: This was an observational study conducted at a tertiary level hospital from August 2014 to August 2015. Children, aged 2 to 23 months, presenting with infantile spasms with hypsarrhythmia or its EEG variants, were enrolled. Study participants were started on very high dose prednisolone (8 mg/kg/day, maximum 60mg/day). The primary outcome measure was complete cessation of spasms and clearance of hypsarrhythmia on EEG after 2 weeks of prednisolone treatment. The study was approved by the institutional ethical committee.

Results: Forty children were started on very high dose prednisolone (8 mg/kg/day, maximum 60mg/day) of whom four did not come for the 2 week follow up and were excluded. Response rate in the remaining 36 patients was 55.6% after 2 weeks of steroid therapy Side effects seen during hormone therapy included increased appetite in 29 (80.6%) patients, irritability in 27 (75.0%) patients and weight gain in 26 (72.2%) patients.

Conclusions: Use of a very high dose prednisolone regime (8mg/kg/day, maximum 60mg/day) resulted in a complete cessation of spasms and clearance of hypsarrhythmia on EEG after 2 weeks in 55.6% of children with West syndrome in this study.

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(Keywords: Hypsarrhythmia, West syndrome, prednisolone, ACTH, response)

¹Subharti Medical College, India, ²BLK Hospital, India

*Correspondence: ashokg88@gmail.com

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Introduction

West syndrome comprises infantile spasms, a characteristic electroencephalogram (EEG) appearance (hypsarrhythmia and its variants) plus frequent neurodevelopmental delay or regression¹. Unsuccessful treatment, as well as delay in definitive treatment, results in poor neurodevelopmental outcome¹. Intramuscular (IM) adrenocorticotrophic hormone (ACTH) and oral prednisolone are commonly used in the treatment of infantile spasms²⁻⁶. There is no consensus on the role of oral steroids as first line therapy of infantile spasms⁷. Limitations like high cost, pain associated with IM injections and non-availability of skilled personnel to administer injections to young children precludes ACTH use in resource limited settings. Prednisolone is an inexpensive and easily available alternative in such settings. Recently, high dose prednisolone has been shown to be effective in infantile spasms^{8,9}.

Objectives

To assess the efficacy of very high dose (8mg/kg/day maximum 60mg/day) prednisolone in patients with West syndrome

Method

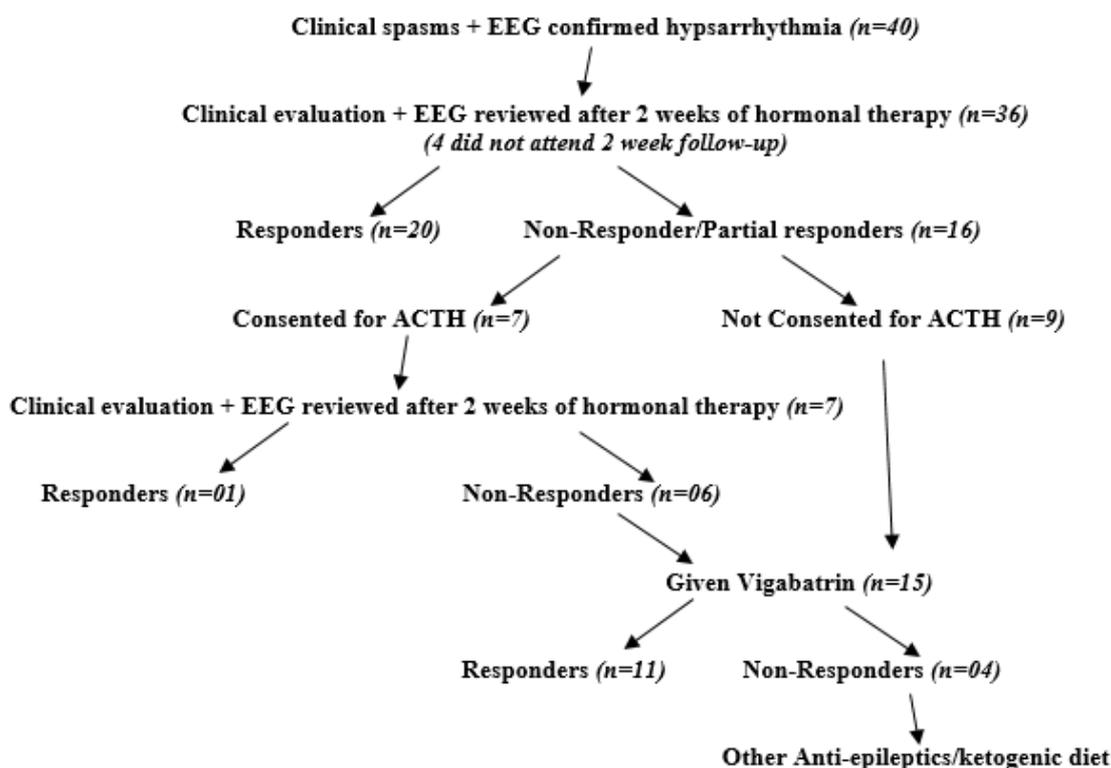
An observational study was conducted among children with poorly controlled infantile spasms referred to the pediatrics department of Subharti Hospital, Meerut, India, between August 2014 and August 2015. Ethical clearance for study was obtained from institutional ethical committee. Written informed consent was obtained from the parents. Children aged 2 to 23 months, presenting with clinical spasms and EEG evidence of hypsarrhythmia or its variants² and without history of prior hormonal treatment were included in the study. Children with systemic illness or severe acute malnutrition (presence of pedal oedema, weight for height < -3SD in WHO child growth charts), visible wasting or mid upper arm circumference <11.5cm, were excluded from the study.

A detailed history was taken and a complete examination carried out in all children. Age at onset, birth history, family history, and development status were noted in each child. Results of neuroimaging, EEG and metabolic testing were recorded. Magnetic resonance imaging (MRI) of brain was done in all patients along with

EEG as initial investigations. Children clinically suspected to have a metabolic disorder, or not having an obvious aetiology on clinical assessment and neuroimaging, were screened for inherited metabolic disorders. Based on the cause, infantile spasms were classified as symptomatic or cryptogenic.

On confirming the diagnosis, therapy with prednisolone was initiated at 8 mg/kg/day with a maximum of 60 mg/day. At the end of 2 weeks of therapy, all children clinically responding to prednisolone, according to parents and clinical examination, had the EEG repeated to confirm clearance of hypsarrhythmia. In children with complete resolution of spasms and clearance of

hypsarrhythmia, prednisolone was tapered over 2 more weeks. In children with continued spasms and/ or hypsarrhythmia on EEG, parents were advised to switch to ACTH. If the parents consented, these children were immediately given IM ACTH (Acton Prolongatum. 60IU/ml 5ml vial) 150 IU/m²/day. Simultaneously, prednisolone was tapered over 2 weeks. After 2 more weeks, all children, in whom parents reported improvement in spasms, had the EEG repeated. In those children with complete resolution, ACTH was tapered over 2 weeks. Children who failed to achieve response after hormonal treatment were given Vigabatrin in 50-150 mg/kg/day for 12 weeks. Patients who failed to respond to Vigabatrin were given other antiepileptic/ketogenic diet as shown in Figure 1.



*Response requires EEG confirmation of freedom from hypsarrhythmia and clinical spasms.
 *Two patients expired because of lower respiratory tract infection when they were in remission.

Figure 1: Flow Chart of the patients in study protocol

Results

Forty children with infantile spasms were enrolled. Four children did not come for the 2 week follow up and were excluded from the study. The

demographic and clinical characteristics of the study population are shown in Table 1.

Table 1: Demographic and clinical characteristics of the study population

a)	Total number of patients	36
b)	Gender	
	Male: No. (%)	28 (77.7)
	Female: No. (%)	08 (22.3)
c)	Age of onset of spasms in months, median (IQR)*	08 (02-22)
d)	Age at entry to protocol in months, median (IQR)	09 (02-23)
e)	Time lag from onset of spasms to initiation of treatment and response	
	i. <2 weeks, No. (%)	12 (75.0)
	ii. >2 to <4 weeks, No. (%)	10 (70.0)
	iii. >4 weeks, No. (%)	14 (28.0)
f)	Duration of follow up in months, median (IQR)	07 (1-23)
g)	Etiological classification & response	
	i. Structural West Syndrome	30 (56.6)
	ii. Cryptogenic West Syndrome	06 (50.0)

*IQR (inter quartile range)

Thirty six patients received very high dose prednisolone (8 mg/kg/day, maximum 60mg/day) for infantile spasms. Hypsarrhythmia or its variants were observed in the baseline EEG in all 36 (100%) patients. Of these, classical hypsarrhythmia was seen in 25 (69.4%), modified variants in 10 (27.8%), whilst one (2.8%) patient exhibited significant EEG abnormalities which, while not

satisfying formal criteria for hypsarrhythmia, were nevertheless compatible with a diagnosis of infantile spasms.

Twenty (55.6%) patients responded completely to prednisolone after 2 weeks. Table 2 shows the response rate of oral prednisolone in complete and partial responders.

Table 2: Response rate of oral prednisolone in complete and partial responders

Total patients	Patients with complete response No. (%)	Non-responders		Response in relapse No. (%)
		Partial response ≥ 75% reduction: No. (%)	No response < 75% reduction: No. (%)	
36	20 (55.6)	16 (44.4)	0 (0)	03 (100)

Sixteen patients who did not respond to prednisolone were advised ACTH. Of the 7 who consented for ACTH (7/16) only one (14.3%) responded. The 15 non-responders to prednisolone and ACTH were started on Vigabatrin. Of these fifteen, 11 (73.3%) showed improvement in spasms. After initially successful treatment with prednisolone, three patients had a relapse of spasms. All three patients were re-challenged with prednisolone and responded, and have remained seizure free for 3 months on follow up. None of the patients with relapse of infantile spasms had a relapse of hypsarrhythmia.

Side effects seen during hormonal therapy included increased appetite in 29 (80.6%) patients, irritability in 27 (75.0%) patients and weight gain in 26 (72.2%) patients.

Discussion

In this study response was assessed using both EEG confirmation of clearance of hypsarrhythmia and clinical cessation of spasms. Several studies utilizing video-EEG confirmation, showed that the traditional 2 mg/kg/day prednisolone is inferior to high dose ACTH^{3,4,8}. However, several studies not

utilizing video-EEG confirmation of response suggested that response to high dose prednisolone (4–8 mg/kg daily) is superior to the traditional 2 mg/kg/day prednisolone and not different from response to ACTH^{5,6}. Whilst a lack of video-EEG confirmation may inflate response rates^{7,8}, these reports nevertheless inspired this study protocol adopted at Subharti Hospital. Our 55.6% response to very high dose prednisolone is higher than the 41.9% response rate of Chellamuthu et al¹⁰ and the 31% pooled response to traditional dose prednisolone^{2,3}. Even patients who did not achieve full response to steroid showed more than 75% reduction in spasms frequency (Table 2).

Side effects related to hormonal therapy were increased appetite (81%), irritability (75%) and weight gain (72%) which were reversible. There were no treatment drop-outs and no mortality amongst the study populations.

Relapse was seen in 3 patients after initial response to hormonal therapy. All 3 (100%) patients responded to re-challenge of steroids compared to the >50% response in study by Hussain SA et al¹¹.

Conclusions

Use of a very high dose prednisolone regime (8mg/kg/day, maximum 60mg/day) resulted in a complete cessation of spasms and clearance of hypsarrhythmia on EEG after 2 weeks in 55.6% of children with West syndrome in this study.

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