



# Treatment with High-Dose Prednisolone in Vigabatrin-Refractory Infantile Spasms

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**ABSTRACT:** *Objectives:* This research aimed to study the short-term seizure outcomes following treatment with 8 mg/kg/day prednisolone in children with infantile spasms (IS) refractory to vigabatrin. We hypothesized that high-dose prednisolone may result in similar rates of electroclinical remission when compared to published ACTH rates. *Methods:* All consecutive children with hypsarrhythmia or hypsarrhythmia variant on EEG with/without IS, who had been treated with vigabatrin as first-line anti-seizure medication (ASM) followed by high-dose oral prednisolone (8 mg/kg/day; maximum 60 mg/day) in cases who did not respond to vigabatrin, were included. Clinical and electroclinical response (ECR) at 2 weeks following initiation of treatment and adverse effects were assessed. *Results:* Sixty-five children were included. A genetic etiology was seen in 38.5% cases. Complete ECR was seen in 30.8% (20/65) of the patients 2 weeks after vigabatrin. Complete ECR was noted in 77.8% (35/45) of the patients, 2 weeks after prednisolone initiation in children who failed vigabatrin, and this was sustained at 6 weeks in 66.7% (30/45) patients. Prednisolone was generally well tolerated. *Conclusions:* High-dose (8 mg/kg/day) oral prednisolone resulted in sustained complete ECR (at 6 weeks) in two-thirds of the children with hypsarrhythmia or hypsarrhythmia variant on EEG with/without parentally reported IS. It was generally well tolerated and found to be safe.

**RÉSUMÉ :** **Prednisolone à forte dose – Traitement des spasmes infantiles réfractaires à la vigabatrine.** *Objectif :* L'étude visait à évaluer les effets antiépileptiques à court terme du traitement par la prednisolone administrée à raison de 8 mg/kg/jour, sur les spasmes infantiles réfractaires à la vigabatrine. Selon l'hypothèse émise, la prednisolone à forte dose permettrait un taux de rémission électroclinique comparable aux taux publiés de rémission, liés à l'hormone adrénocorticotrope (ACTH). *Méthode :* Ont été retenus tous les enfants consécutifs, présentant de l'hypsarythmie ou une forme d'hypsarythmie à l'EEG, accompagnée ou non de spasmes infantiles, et ayant reçu de la vigabatrine comme anticonvulsivant de première intention, après quoi ceux qui se sont montrés réfractaires à la vigabatrine ont reçu de la prednisolone orale à forte dose (8 mg/kg/jour; maximum : 60 mg/jour). Les réactions cliniques et électrocliniques (EC) ainsi que les effets indésirables ont fait l'objet d'évaluation 2 semaines après l'instauration du traitement. *Résultats :* Au total, 65 enfants ont participé à l'étude. Une cause génétique a été décelée dans 38,5 % des cas. Une réaction EC complète (rémission) a été observée chez 30,8 % (20/65) des enfants, 2 semaines après le début de la vigabatrine; il en a été de même chez 77,8 % (35/45) des enfants réfractaires à la vigabatrine, 2 semaines après le début de la prednisolone, rémission encore présente au bout de 6 semaines chez 66,7 % (30/45) d'entre eux. En général, la prednisolone a été bien tolérée. *Conclusion :* La prednisolone orale à forte dose (8 mg/kg/jour) a permis une rémission (au bout de 6 semaines) chez deux tiers des enfants présentant de l'hypsarythmie ou une forme d'hypsarythmie à l'EEG, accompagnée ou non de spasmes infantiles selon les parents. Le médicament s'est montré sûr et a été bien toléré en général.

**Keywords:** Infantile spasms, Genetic epilepsy, Epileptic encephalopathy, Steroids, Hormonal, Prednisolone, Hemispherectomy, Epilepsy surgery, Ketogenic diet, KCNQ2

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## INTRODUCTION

Infantile spasm (IS) syndrome is a severe epileptic encephalopathy caused by multiple etiologies. Early and appropriate intervention is critical for better seizure and neurodevelopmental outcomes.<sup>1</sup> Hormonal therapies (adrenocorticotrophic hormone [ACTH] or prednisolone) and vigabatrin are the commonly used first-line therapies.<sup>2</sup> The published experience with high-dose (8 mg/kg/day) prednisolone is limited.<sup>3,4</sup> This study aimed to study the short-term seizure outcomes following treatment with 8 mg/kg/day prednisolone in children with IS refractory to vigabatrin. We hypothesized that high-dose prednisolone may result

in comparable electroclinical remission rates in children with IS when compared to published ACTH rates.

## METHODS

This retrospective study recruited children seen in the IS clinic at a tertiary-level teaching pediatric hospital between July 2019 and January 2021. All consecutive children with hypsarrhythmia or hypsarrhythmia variant on EEG with/without parentally reported IS, who had been treated with vigabatrin as first-line anti-seizure medication (ASM) followed by high-dose oral prednisolone in cases who did not respond to vigabatrin, were

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included. The study was approved by the Institutional Ethics Board (ref number 1000072786).

### Institutional Infantile Spasm protocol

All children with suspected IS got an urgent 1-hour EEG (with bilateral deltoid EMG) including one sleep–wake cycle. If hypsarrhythmia or hypsarrhythmia variant was detected on EEG, patients were started on vigabatrin and then were referred to the IS clinic. Detailed physical examination coupled with urgent neuroimaging (MRI brain) was done (if already not done). A targeted genetic testing was done in a suggestive phenotype. The children with unexplained etiology underwent extensive metabolic testing and microarray. If these were negative, an infantile epileptic encephalopathy gene panel was sent. The need for whole-exome sequencing was then individualized.

Vigabatrin was started at 50 mg/kg/day and rapidly titrated up (Day 1: 50 mg/kg/day BID; Day 2: 100 mg/kg/day BID; Day 3: 125 mg/kg/day BID; Day 4 and afterward: 150 mg/kg/day BID). If the patient had a partial or complete electroclinical response (ECR) to vigabatrin at 2 weeks, it was continued for 6 months. If no response was noted or the child had intolerable side effects, it was rapidly weaned off in 1 week.

If patients failed vigabatrin therapy, oral prednisolone was started at 8 mg/kg/day (maximum 60 mg/day). The ECR was assessed after 2 weeks. If the patient responded well, it was weaned off over the next 2 weeks. If no response, it was weaned off in 5 days. Blood pressure and urine glucose were monitored weekly and blood work was done every 2 weeks while on prednisolone. A complete ECR was defined as complete cessation of IS as per parental report and resolution of hypsarrhythmia on EEG.

The therapy in children who failed prednisolone was often individualized by the treating neurologist and frequently included topiramate, clobazam, and ketogenic diet. Cases that were amenable to surgery were urgently referred to the epilepsy surgery program.

### Objectives

The primary objective was to study the proportion of children with IS, who had failed vigabatrin, and then who achieved ECR (cessation of clinical spasms and resolution of hypsarrhythmia) at 2 weeks and whom this was sustained at 6 weeks (*sustained ECR*) after the start of oral prednisolone. Other objectives included proportion of children with IS who relapsed after initial response to oral prednisolone, tolerability of high-dose prednisolone, proportion of children with clinical and ECR (cessation of clinical spasms and resolution of hypsarrhythmia) at 2 weeks after the start of vigabatrin, and proportion of children who achieved *sustained ECR* (cessation of clinical spasms for at least 28 d and resolution of hypsarrhythmia) at 6 weeks after the start of vigabatrin.

### Data Extraction

The electronic records of all the consecutive cases seen in the IS clinic who fulfilled the inclusion criteria were studied. Study data were collected, stored, and managed using the Research Electronic Data Capture (REDCap) secure electronic data capture tool.<sup>5,6</sup> Variable collected included age, gestation/birth weight,

details of the antenatal period, presence/absence of perinatal HIE, age at onset of spasms, lead time from apparent onset of spasms to treatment, developmental status at the onset of spasms (normal, delayed, regression), family history, details of EEG at time of diagnosis, at 2 weeks, at 4 weeks, at 6 weeks, and at later time points (hypsarrhythmia, hypsarrhythmia variant, normal, focal interictal epileptiform discharges [IEDs], others), treatment response to vigabatrin and oral prednisolone, other therapies used afterward (topiramate, ketogenic diet, epilepsy surgery), details of MRI brain, and genetic testing.

### Statistics

Descriptive statistics were used to describe various study variables. A logistic regression model was used to examine the effect of variables (age at spasm onset, delay from spasm onset to initiation of treatment, sex, normal, or abnormal development at spasm onset, structural or nonstructural etiology) on ECR at 2 weeks after vigabatrin and prednisolone.

### RESULTS

Seventy-three cases were identified in the IS database during the study period. Eight children were excluded – 2 children with trisomy 21 received prednisolone as first line (both had incomplete ECR on prednisolone and responded to vigabatrin); 3 children (1 – Krabbe's disease, 1 – *ECHS1*-related, 1 – unknown etiology) – prednisolone could not be given (after vigabatrin failure) due to active infection; two patients proceeded to surgery after vigabatrin failure (1 – left parieto-occipital polymicrogyria, 1 – perinatal stroke/COL4A1); parent of 1 child with bilateral periventricular leukomalacia (prematurity) refused prednisolone due to ongoing COVID-19 pandemic. Thus, 65 cases were included. The baseline characteristics are summarized in Table 1. Twenty-three patients (35.4%) were on at least one ASM before starting vigabatrin.

Two children (1 – neonatal hypoglycemia, 1 – methylmalonic acidemia) had no IS; vigabatrin was initiated after the detection of hypsarrhythmia on EEG.

### Etiology

Most common etiology was genetic in 25 cases (38.5%): Chromosomal [6 trisomy 21, one each of dup (2) (q11.2q22.1) and 16p13.11 del], single-gene disorders [3 *TSC2*, 3 *KCNQ2*, 1 each of others (*TSC1*, *TUBA1A*, *TUBB2B*, *SLC35A2*, *PRUNE1*, *GRIN2A*, *TBCK*, *GMPPB*, *STXBPI*, *CASK*, *DNMI*)]. Structural causes were seen in 16 cases (24.6%): 5 perinatal strokes, 3 perinatal hypoxic-ischemic encephalopathy (HIE), 2 polymicrogyria (one had *ARX* gene mutations), 1 lissencephaly [del (17) (p13.2p13.3)], 1 neonatal hypoglycemia sequelae, 1 periventricular leukomalacia (prematurity), 1 hemimegalencephaly, 1 temporo-occipital cortical dysplasia, and 1 Aicardi syndrome. Two cases (3.1%) had metabolic (1 – Zellweger syndrome, 1 – methylmalonic acidemia) etiology. Rest (22, 33.8%) had unknown etiology.

### Vigabatrin

Vigabatrin was started in 65 children: 63 with clinical spasms and EEG showing hypsarrhythmia, or hypsarrhythmia variant; 2 children (1 – neonatal hypoglycemia sequelae, 1 – methylmalonic acidemia) had hypsarrhythmia on EEG and no clinical

**Table 1: Salient baseline characteristics of the study participants**

N = 65	
Mean age at onset of spasms (months), SD	6.3, 4.2 (Median 5, IQR 4,8)
Median estimated delay from onset to treatment (days), (IQR)	11, (5,30) (Mean 27.5, SD 37.4)
Males n, %	32 (49.2)
Weight of the patient at the time of starting prednisolone in kilograms (n = 45)*	
≥ 7.5 kg	32
< 7.5 kg	13
Etiology, n (%)	
Structural	16 (24.6)
Genetic	25 (38.5)
Metabolic	2 (3.1)
Unknown	22 (33.8)
Developmental status at the time of onset of spasms, n (%)	
Global developmental delay	41 (63.1)
Isolated speech delay	1 (1.5)
Isolated motor delay	1 (1.5)
Normal	22 (33.8)
Regression with spasms	24 (36.9)
Gestation age, n (%)	
Term	56 (86.2)
Preterm	9 (13.8)

IQR = Inter-quartile range; SD = Standard deviation

\*The dose of prednisolone for a child with a weight of 7.5 kg (at 8 mg/kg/day) would be 60 mg (highest daily dose used in this study). Children > 7.5 kg would have received < 8 mg/kg/day daily prednisolone

spasms. At 2 weeks after starting vigabatrin, 23/63 (36.5%) had complete clinical response; however, ECR was seen in 20/65 (30.8%; 95% confidence interval [CI]: 20.9%, 42.8%) patients. This response was persistent at 6 weeks with no subsequent relapses. Both children with hypsarrhythmia but no clinical spasms did not show resolution of hypsarrhythmia on vigabatrin.

The logistic regression model showed that only normal development at spasm onset was associated with an ECR with vigabatrin at 2 weeks ( $\beta = 1.29$ ,  $p = 0.04$ ; adjusted OR = 3.66) (Table 2).

### High-dose Prednisolone

High-dose prednisolone was used in 45 children with spasms who failed (absent or incomplete ECR) vigabatrin. The mean daily dose was 56.4 mg/day (range: 45–60 mg); 32 children received 60 mg/day of prednisolone. At 2 weeks, 37/45 (82.2%) had a complete clinical response. ECR was seen in 35 children (77.8%; 95%CI: 63.7%, 87.5%). This was sustained at 6 weeks in 30 patients (66.7%). Five children (5/35, 14.3%) had a relapse of IS during/after weaning prednisolone. Two children were again started on high-dose prednisolone; one responded well and the other remained refractory. Other three

**Table 2: Multivariable logistic regression model evaluating the relationships between salient patient variables and 2-week electroclinical response to vigabatrin (A) or prednisolone (B)**

Independent variable	$\beta$ -coefficient	Adjusted odds ratio	95% CI	P-value
A. Electroclinical response 2 weeks after vigabatrin (n = 65) $R^2 = 10.6\%$				
Age at spasm onset in months	0.10	1.11	0.93, 1.31	0.25
Estimated delay from spasm onset to initiation of treatment in months	-0.001	0.99	0.98, 1.01	0.87
Sex	0.04	1.04	0.34, 3.26	0.94
Normal or abnormal development at spasm onset	1.29	3.66	1.08, 12.45	<b>0.04</b>
Structural or nonstructural etiology	-0.07	0.93	0.27, 3.16	0.91
B. Electroclinical response 2 weeks after prednisolone (n = 45) $R^2 = 31.6\%$				
Age at spasm onset in months	0.16	1.17	0.81, 1.69	0.39
Estimated delay from spasm onset to initiation of treatment in months	-0.03	0.97	0.95, 0.99	<b>0.02</b>
Sex	-0.634	0.53	0.09, 3.27	0.49
Normal or abnormal development at spasm onset	2.06	7.85	0.59, 102.77	0.12
Structural or nonstructural etiology	0.70	2.02	0.31, 13.17	0.46

Coding: Development (0 – Abnormal, 1 – normal), Etiology (0 – structural, 1 – nonstructural), Sex (0 – female, 1 – male)

children were switched to topiramate. One of the two children with hypsarrhythmia but no clinical spasms showed resolution of hypsarrhythmia on prednisolone.

It was generally well tolerated. The common adverse effects reported were irritability (15/45, 33.3%), weight gain (10/45, 22.2%), sleep disturbances (6/45, 13.3%), and hypertension requiring transient amlodipine treatment (2/45, 4.4%). Two patients were hospitalized during the weaning period: one child with *GMPPB* mutation presented with apneas and electrographic seizures (died after 1 month due to multiple organ dysfunction) and one child with *STXBPI*-related disorder with frequent dystonic episodes. One child with trisomy 21 was hospitalized within 1 week of stopping steroids due to dehydration and hypoglycemia.

The logistic regression model showed that only lesser delay from spasm onset to treatment initiation was associated with an

ECR with prednisolone at 2 weeks ( $\beta = -0.03$ ,  $p = 0.02$ ; adjusted OR = 0.97) (Table 2).

### Other Therapies

The mean follow-up duration was 13.6 months (standard deviation [SD] 6.6 months). The median number of ASMs at the last follow-up was 1 (inter-quartile range [IQR]:1,2).

Topiramate was used in 25 children. Three children were already on topiramate at the time of starting vigabatrin. In the rest, it was initiated at a mean age of 9.3 months (SD 4.1). Fifteen (15/22) had previous incomplete ECR to or relapse on prednisolone; it was started for new seizure types in the rest. Six (6/22, 27.3%) had complete seizure cessation with topiramate.

### Ketogenic Diet

In this cohort, eight patients were started on a classical ketogenic diet at a mean age of 13.3 months (SD 4.7 months). All of them (8/8) had failed vigabatrin. Five out of eight patients had also failed prednisolone in the past. Out of the three prednisolone responders, one relapsed, one evolved into other seizure types, and one presented with electrographic status epilepticus. Six patients had ongoing epileptic spasms at the time of diet initiation; 5/6 had other ongoing seizure types as well.

Six patients were still on diet at the last follow-up. One patient stopped diet after 17 months due to feeding intolerance and irritability. One child died after 1 month of starting the diet. The median follow-up available was 5 months (IQR: 3.8, 9). Six (6/8, 75%) patients had <50% seizure reduction. Only one patient had >90% seizure reduction (trisomy 21). Two out of six patients with ongoing spasms had >50% seizure reduction (patients 1 and 8 in Table 3). Two patients are awaiting initiation of the classical diet (1 – TUBA1A, 1 – HIE). Details are summarized in Table 3.

### Epilepsy Surgery

Three patients had subsequent epilepsy surgery; all seizure free at the last follow-up (Table 4). Four patients are awaiting surgery (three perinatal strokes, one extensive left temporo-occipital polymicrogyria).

## DISCUSSION

### Summary of Results

Short-term seizure outcomes following treatment were studied in our cohort of IS. Nearly one-third of patients (38.5%) had genetic etiology. Complete ECR was seen in 30.8% of patients 2 weeks after vigabatrin. This was 77.8% 2 weeks after prednisolone initiation in children who failed vigabatrin. ECR was sustained at 6 weeks after prednisolone in 66.7% cases. Prednisolone was generally well tolerated.

### High-dose Prednisolone

Few studies have reported seizure outcomes after the use of 8 mg/kg/day oral prednisolone. Eliyan et al.<sup>3</sup> treated 102 children with 8 mg/kg/day of prednisolone as first-line treatment; complete ECR was seen in 59% cases. Among the prednisolone nonresponders, 33% of children responded to ACTH. The significant adverse effects noted with prednisolone were

hypertension requiring anti-hypertensives (3), hospitalization due to known or suspected infections, (4) and hyperglycemia (1). In a smaller retrospective cohort<sup>4</sup>, complete ECR was seen in 63% (17/27) following prednisolone as first-line therapy.

One prospective study from South Korea<sup>7</sup> reported ECR in 59.1% cases following 40–60 mg/day of prednisolone in cases who had failed vigabatrin. The adverse effects were common but did not warrant discontinuation of therapy. ECR was seen in one out of five cases (20%) following 4–6 mg/kg/day of prednisolone (after vigabatrin failure) in another smaller study.<sup>8</sup> In our study, the ECR occurred in 77.8% cases after prednisolone in cases who had failed vigabatrin. Lesser delay from spasm onset to treatment initiation predicted better response to prednisolone. The rate of ECR is much higher than the reported rates in the sparse literature. We also found adverse effects commonly, but none warranted cessation of therapy. Other studies reporting on outcomes with high-dose prednisolone (> 2mg/kg/day) are summarized in Table 5.

Further, Chellamuthu et al.<sup>13</sup> showed that high-dose prednisolone (4 mg/kg/day) achieved higher clinical remission in significantly more patients when compared to low-dose (2 mg/kg/day) prednisolone (51.6% vs. 25%,  $p = 0.03$ ) though electroclinical remission was similar (38.7% vs. 21.9%,  $p = 0.15$ ).

### Prednisolone versus ACTH

Few randomized controlled trials have compared higher doses of prednisolone with ACTH. One trial<sup>11</sup> showed that prednisolone (40–60 mg/day) was superior to ACTH; other two trials showed similar efficacy.<sup>10,12</sup> ECR to prednisolone was seen in 26.7%<sup>12</sup>–71.4%<sup>10</sup> patients in these trials. Besides these, the International Collaborative Infantile Spasm study (ICISS),<sup>18</sup> which explored the effectiveness of hormonal therapy and hormonal therapy/vigabatrin combination for IS, did randomize patients into high-dose prednisolone and ACTH. However, the published data did not report effectiveness outcomes separately for ACTH and prednisolone. Further, a recent systematic review and meta-analysis (six trials)<sup>19</sup> showed that prednisolone/prednisone (all doses) elicits similar ECR as ACTH. Compared with prednisolone/prednisone, ACTH/tetracosactide was not superior in terms of cessation of spasms at day 14 (relative risk 1.19, 95% CI 0.74–1.92), day 42 (relative risk 1.02, 95% CI 0.63–1.65), and resolution of hypsarrhythmia on electroencephalogram (relative risk 1.14, 95% CI 0.71–1.81). This was further supported by another systematic review and meta-analysis which included both randomized and non-randomized studies.<sup>20</sup> Thus, oral prednisolone (especially high dose) may be a reasonable alternative to ACTH, given the ease of administration and lower cost coupled with similar effectiveness/adverse effect profile. In a recent cost-effectiveness study, prednisolone at 4–8 mg/kg/day was found to be more cost-effective than ACTH.<sup>20</sup>

### Other Therapies

Vigabatrin resulted in clinical spasm remission in 36.5% cases and ECR in 30.8% cases in this study. Data from past randomized controlled trials is variable; ECR rates have varied from 15.9% to 55.6%.<sup>10,21–24</sup>

Ketogenic diet was tried in eight patients in our cohort; six had ongoing spasms at the time of diet initiation. Overall, only 2/8 had >50% seizure reduction at the last follow-up. Two recent

**Table 3: Characteristics of study participants who received classical ketogenic diet**

ID	Age at onset of KD (months)	Etiology	Seizure types at onset of KD	EEG at time of diet initiation	ASMs at start of diet	Duration of follow-up (months)	Seizure response at the last FUP	ASMs at the last FUP	Continued or stopped at the last follow-up
1	6	Aicardi syndrome	Spasms, FIAS	Hypsarrhythmia	VGB, TPA, PHB, LEV, B6	17	>50%	PHB, LEV, TPA, CBD	Stopped after 17 months due to irritability and feeding intolerance
2	18	Neonatal hypoglycemia sequelae	Spasms, tonic	MISF	VGB, PHB, CBD	8	<50%	TPA, PHB	Continued
3	10	dup (2) (q11.2q22.1)	Spasms, FIAS	MISF	VGB, TPA	12	<50%	TPA	Continued
4	17	GRIN2A	Myoclonic, FIAS, absence	MISF	LEV, VPA, CBD	5	<50%	VPA, LEV	Continued
5	13	TSC2	Spasms, FIAS	Abundant right hemispheric discharges	VGB, cloba, CBD, CBZ	5	<50%	VGB, Cloba, CBD, RUF, LEV	Continued
6	17	Trisomy 21	Spasms	Hypsarrhythmia variant	VGB, TPA	4	<50%	VGB, TPA, Cloba, LEV	Continued
7	8	GMPPB	Electrographic SE	Left temporal electrographic seizures	VGB	1	<50%	VGB	Yes, died due to MODS (unrelated to vigabatrin or prednisolone)
8	17	Trisomy 21	Spasms, FIAS	Modified Hypsarrhythmia	VGB, TPA	3	>90%	TPA	Continued

ASMs = Anti-seizure medications; B6 = Pyridoxine; CBD = Cannibidiol; CBZ = Carbamazepine; cloba = clobazam; FIAS = Focal impaired awareness seizures; KD = Ketogenic diet; LEV = levetiracetam; MISF = Multiple independent spike foci; MODS = Multiorgan dysfunction syndrome; PHB = Phenobarbital; RUF = Rufinamide; SE = Status epilepticus; TPA = Topiramate; VGB = vigabatrin; VPA = Valproate

**Table 4: Characteristics of study participants who underwent epilepsy surgery**

	Age at spasm onset	Etiology	Response to vigabatrin or oral prednisolone	Epilepsy surgery/age at surgery	Seizure outcome at the last follow-up
1	1 month	Right temporo-occipital cortical dysplasia	Failed vigabatrin and prednisolone	R FH at 6 months of age	Seizure free after 12 months
2	10	Perinatal left MCA stroke	Responded to vigabatrin	L FH at 17 months of age	Seizure free after 9 months
3	2	Left hemimegalencephaly	Failed vigabatrin and prednisolone	L FH at 3 months of age	Seizure free after 8 months

FH = functional hemispherectomy; MCA = Middle cerebral artery

**Table 5: Summary of studies using high-dose oral prednisolone/prednisone in children with infantile spasms**

Study	Country	Study design	Number of participants	Dose of oral prednisolone	First line or second line	Electro-clinical response (ECR) at 2 weeks	Clinical response at 2 weeks
<b>Randomized controlled trials</b>							
Yi 2019 <sup>9</sup>	China	RCT	39	40–60 mg	First line	21/39 (53.9%)	28/39 (71.8%)
Lux 2004 <sup>10</sup>	UK	RCT	30	40–60 mg	First line	20/25 (80%)*	21/30 (70%)
Wanasinghe 2015 <sup>11</sup>	Srilanka	RCT	48	40–60 mg	First line	21/48 (43.8%)	28/48 (58.3%)
Gowda 2019 <sup>12</sup>	India	RCT	15	4 mg/kg/day	First Line	NR	5/15 (33.3%)
Chellamuthu 2014 <sup>13</sup>	India	RCT	31	4 mg/kg/day	First Line	12/31 (38.7%)	16/31 (51.6%)
Kunnanayaka 2018 <sup>14</sup>	India	RCT	32	4 mg/kg/day	First Line	9/32 (28.1%)	12/32 (37.5%)
<b>Observational studies</b>							
Eliyan 2019 <sup>3</sup>	USA	Retrospective	102	8 mg/kg/day	Mostly first line**	60 (59%)	NR
Hussain 2014 <sup>4</sup>	USA	Retrospective	27	8 mg/kg/day	First line	17/27 (63%)*	NR
Gonzalez-Giraldo 2018 <sup>15</sup>	USA	Retrospective	87	40–60 mg	Mostly first line <sup>#</sup>	56/87 (64.4%)	62/87 (71.3%)
Ko 2018 <sup>7</sup>	South Korea	Prospective	44	40–60 mg	Second line after vigabatrin	26/44 (59.1%) <sup>###</sup>	NR
Yi 2015 <sup>16</sup>	China	Retrospective	20	40 mg Prednisone	First line	12/20 (60%)	16/20 (80%)
Jones 2015 <sup>5</sup>	Canada	Retrospective	5	4–6 mg/kg/day	Second line after vigabatrin	1/5 (20%) <sup>§</sup>	NR
Kossoff 2009 <sup>17</sup>	USA	Retrospective	15	40–60 mg	8 as first line; 7 after failed therapies (LEV, TPA, KD)	7/15 (46.7%)	10/15 (66.7%)

KD = Ketogenic diet; LEV = levetiracetam; NR = Not reported; RCT = Randomized controlled Trial; TPA = Topiramate

\*Repeat EEG are not done in five children

\*\*Prior exposure to hormonal therapy and vigabatrin was observed among 12% and 35% of patients, respectively

<sup>†</sup>Subsequently, 40% (4/10) of prednisolone nonresponders exhibited a complete response after an additional 2-week course with ACTH

<sup>‡</sup>Eleven had a previous ketogenic diet

<sup>§</sup>22/66 (33.3%) had ECR with VGB

<sup>¶</sup>37/57 (64.9%) had ECR with VGB

controlled trials show that 54.1%<sup>25</sup> and 65.2%<sup>26</sup> children showed >50% spasm reduction with ketogenic diet and modified Atkins diet, respectively, in children with epileptic spasms refractory to hormonal therapy.

Epilepsy surgery was done in three cases (two malformations of cortical development, one perinatal stroke) in our cohort; all had excellent short-term seizure outcomes. Similar favorable

seizure and neurodevelopmental outcomes have been reported in select cases of drug-resistant IS.<sup>27,28</sup>

### Strengths and Limitations

Our study reported the short-term seizure outcomes in a cohort of IS treated at our institution in a protocolized fashion. Although

the data collection was retrospective, detailed electronic records were maintained prospectively in the IS clinic. The sample size was relatively small. This study was also limited by the short follow-up period and absence of serial structured neurodevelopmental assessments.

## Conclusions

High-dose (8 mg/kg/day) oral prednisolone resulted in complete ECR (at 2 weeks) in more than three-fourth of children with hypsarrhythmia or hypsarrhythmia variant on EEG with/without parentally reported IS who had failed vigabatrin. This was sustained at 6 weeks in two-thirds of the children. It was generally well tolerated and found to be safe. It may be a reasonable and more feasible alternative to ACTH for the treatment of IS. Further trials exploring the comparative effectiveness of 8 mg/kg/day prednisolone with ACTH, dose–response relationship with prednisolone, and exploring various drug combination therapies to improve efficacy are warranted.

## CONFLICTS OF INTEREST

None.

## ETHICS

The study was approved by the Institutional Ethics Board (ref number 1000072786).

## STATEMENT OF AUTHORSHIP

All authors provided clinical care to the study participants. WAS collected the data. PJ analyzed the results. WAS and PJ wrote the first draft of manuscript which was then reviewed and approved by all the authors.

## REFERENCES

- Pavone P, Polizzi A, Marino SD, et al. West syndrome: a comprehensive review. *Neurol Sci.* 2020;41:3547–62. doi: [10.1007/s10072-020-04600-5](https://doi.org/10.1007/s10072-020-04600-5)
- Go CY, Mackay MT, Weiss SK, et al. Evidence-based guideline update: medical treatment of infantile spasms. Report of the Guideline Development Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. *Neurology.* 2012;78:1974–80. doi: [10.1212/WNL.0b013e318259e2cf](https://doi.org/10.1212/WNL.0b013e318259e2cf)
- Eliyan Y, Heesch J, Alayari A, et al. Very-High-Dose Prednisolone Before ACTH for Treatment of Infantile Spasms: Evaluation of a Standardized Protocol. *Pediatr Neurol.* 2019;99:16–22. doi: [10.1016/j.pediatrneurol.2019.06.012](https://doi.org/10.1016/j.pediatrneurol.2019.06.012)
- Hussain SA, Shinnar S, Kwong G, et al. Treatment of infantile spasms with very high dose prednisolone before high dose adrenocorticotropic hormone. *Epilepsia.* 2014;55:103–7. doi: [10.1111/epi.12460](https://doi.org/10.1111/epi.12460)
- Harris PA, Taylor R, Minor BL, et al. The REDCap consortium: Building an international community of software platform partners. *J Biomed Inform.* 2019;95:103208. doi: [10.1016/j.jbi.2019.103208](https://doi.org/10.1016/j.jbi.2019.103208)
- Harris PA, Taylor R, Thielke R, et al. Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform.* 2009;42:377–81. doi: [10.1016/j.jbi.2008.08.010](https://doi.org/10.1016/j.jbi.2008.08.010)
- Ko A, Youn SE, Chung HJ, et al. Vigabatrin and high-dose prednisolone therapy for patients with West syndrome. *Epilepsy Res.* 2018;145:127–33. doi: [10.1016/j.eplepsyres.2018.06.013](https://doi.org/10.1016/j.eplepsyres.2018.06.013)
- Jones K, Snead OC, 3rd, Boyd J, et al. Adrenocorticotropic hormone versus prednisolone in the treatment of infantile spasms post vigabatrin failure. *J Child Neurol.* 2015;30:595–600. doi: [10.1177/0883073814533148](https://doi.org/10.1177/0883073814533148)
- Yi Z, Wu H, Yu X, et al. High-dose prednisone therapy for infantile spasms and late-onset epileptic spasms in China: The addition of topiramate provides no benefit. *Seizure.* 2019;71:174–78. doi: [10.1016/j.seizure.2019.07.016](https://doi.org/10.1016/j.seizure.2019.07.016)
- Lux AL, Edwards SW, Hancock E, et al. The United Kingdom Infantile Spasms Study comparing vigabatrin with prednisolone or tetracosactide at 14 days: a multicentre, randomised controlled trial. *Lancet.* 2004;364:1773–8. doi: [10.1016/s0140-6736\(04\)17400-x](https://doi.org/10.1016/s0140-6736(04)17400-x)
- Wanigasinghe J, Arambepola C, Sri Ranganathan S, et al. Randomized, Single-Blind, Parallel Clinical Trial on Efficacy of Oral Prednisolone Versus Intramuscular Corticotropin on Immediate and Continued Spasm Control in West Syndrome. *Pediatr Neurol.* 2015;53:193–9. doi: [10.1016/j.pediatrneurol.2015.05.004](https://doi.org/10.1016/j.pediatrneurol.2015.05.004)
- Gowda VK, Narayanaswamy V, Shivappa SK, et al. Corticotrophin-ACTH in Comparison to Prednisolone in West Syndrome - A Randomized Study. *Indian J Pediatr.* 2019;86:165–70. doi: [10.1007/s12098-018-2782-1](https://doi.org/10.1007/s12098-018-2782-1)
- Chellamuthu P, Sharma S, Jain P, et al. High dose (4 mg/kg/day) versus usual dose (2 mg/kg/day) oral prednisolone for treatment of infantile spasms: an open-label, randomized controlled trial. *Epilepsy Res.* 2014;108:1378–84. doi: [10.1016/j.eplepsyres.2014.06.019](https://doi.org/10.1016/j.eplepsyres.2014.06.019)
- Kunnanayaka V, Jain P, Sharma S, et al. Addition of pyridoxine to prednisolone in the treatment of infantile spasms: a pilot, randomized controlled trial. *Neurol India.* 2018;66:385–90. doi: [10.4103/0028-3886.227281](https://doi.org/10.4103/0028-3886.227281)
- Gonzalez-Giraldo E, Stafstrom CE, Stanfield AC, et al. Treating Infantile Spasms with High-Dose Oral Corticosteroids: A Retrospective Review of 87 Children. *Pediatr Neurol.* 2018;87:30–35. doi: [10.1016/j.pediatrneurol.2018.06.011](https://doi.org/10.1016/j.pediatrneurol.2018.06.011)
- Yi ZS, Wu HP, Yu XY, et al. Efficacy and tolerability of high-dose prednisone in Chinese children with infantile spasms. *Brain Dev.* 2015;37:23–8. doi: [10.1016/j.braindev.2014.02.005](https://doi.org/10.1016/j.braindev.2014.02.005)
- Kossoff EH, Hartman AL, Rubenstein JE, et al. High-dose oral prednisolone for infantile spasms: an effective and less expensive alternative to ACTH. *Epilepsy Behav.* 2009;14:674–6. doi: [10.1016/j.yebeh.2009.01.023](https://doi.org/10.1016/j.yebeh.2009.01.023)
- O'Callaghan FJ, Edwards SW, Alber FD, et al. Safety and effectiveness of hormonal treatment versus hormonal treatment with vigabatrin for infantile spasms (ICISS): a randomised, multicentre, open-label trial. *Lancet Neurol.* 2017;16:33–42. doi: [10.1016/s1474-4422\(16\)30294-0](https://doi.org/10.1016/s1474-4422(16)30294-0)
- Li S, Zhong X, Hong S, et al. Prednisolone/prednisone as adrenocorticotropic hormone alternative for infantile spasms: a meta-analysis of randomized controlled trials. *Dev Med Child Neurol.* 2020;62:575–80. doi: [10.1111/dmcn.14452](https://doi.org/10.1111/dmcn.14452)
- Sánchez Fernández I, Amengual-Gual M, Gaínza-Lein M, et al. Cost-effectiveness of adrenocorticotropic hormone versus oral steroids for infantile spasms. *Epilepsia.* 2021;62:347–57. doi: [10.1111/epi.16799](https://doi.org/10.1111/epi.16799)
- Appleton RE, Peters AC, Mumford JP, et al. Randomised, placebo-controlled study of vigabatrin as first-line treatment of infantile spasms. *Epilepsia.* 1999;40:1627–33. doi: [10.1111/j.1528-1157.1999.tb02049.x](https://doi.org/10.1111/j.1528-1157.1999.tb02049.x)
- Askalan R, Mackay M, Brian J, et al. Prospective preliminary analysis of the development of autism and epilepsy in children with infantile spasms. *J Child Neurol.* 2003;18:165–70. doi: [10.1177/08830738030180030801](https://doi.org/10.1177/08830738030180030801)
- Elterman RD, Shields WD, Bittman RM, et al. Vigabatrin for the treatment of infantile spasms: final report of a randomized trial. *J Child Neurol.* 2010;25:1340–7. doi: [10.1177/0883073810365103](https://doi.org/10.1177/0883073810365103)
- Vigevano F, Cilio MR. Vigabatrin versus ACTH as first-line treatment for infantile spasms: a randomized, prospective study.

- Epilepsia. 1997;38:1270–4. doi: [10.1111/j.1528-1157.1997.tb00063.x](https://doi.org/10.1111/j.1528-1157.1997.tb00063.x)
25. Zhang J, Chen G, Wang J, et al. Efficacy of the ketogenic diet on ACTH- or corticosteroid-resistant infantile spasm: a multicentre prospective control study. *Epileptic Disord*. 2021 doi: [10.1684/epd.2021.1256](https://doi.org/10.1684/epd.2021.1256)
26. Sharma S, Goel S, Kapoor D, et al. Evaluation of the Modified Atkins Diet for the Treatment of Epileptic Spasms Refractory to Hormonal Therapy: A Randomized Controlled Trial. *J Child Neurol*. 2021;8830738211004747. doi: [10.1177/08830738211004747](https://doi.org/10.1177/08830738211004747)
27. Iwatani Y, Kagitani-Shimono K, Tominaga K, et al. Long-term developmental outcome in patients with West syndrome after epilepsy surgery. *Brain Dev*. 2012;34:731–8. doi: [10.1016/j.braindev.2012.01.008](https://doi.org/10.1016/j.braindev.2012.01.008)
28. Loddenkemper T, Holland KD, Stanford LD, et al. Developmental outcome after epilepsy surgery in infancy. *Pediatrics*. 2007; 119:930–5. doi: [10.1542/peds.2006-2530](https://doi.org/10.1542/peds.2006-2530)