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Original Article

The Efficacy of Moderate-to-High Dose Oral Prednisolone Versus Low-to-Moderate Dose Intramuscular Corticotropin for Improvement of Hypsarrhythmia in West Syndrome: A Randomized, Single-Blind, Parallel Clinical Trial

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ABSTRACT

BACKGROUND: The role of therapy on improvement of hypsarrhythmia has not been systematically assessed. This study was performed to assess the efficacy of oral prednisolone and intramuscular adrenocorticotrophin hormone in improving hypsarrhythmia in West syndrome. **METHOD:** Children (2 months-2 years), with previously untreated West syndrome, were randomized to receive 40-60 IU every other day of intramuscular adrenocorticotrophin hormone or 40-60 mg/day of oral prednisolone for 14 days. Children with tuberous sclerosis were excluded. Improvement of hypsarrhythmia was assessed blindly using a hypsarrhythmia severity scale before and after completion of therapy. Adverse effects were assessed on day 14 using symptom diary. (Clinical trial registry identifier: SLCTR/2010/010.) **RESULTS:** From 92 newly diagnosed West syndrome infants, 48 were randomized to receive prednisolone and 44 to receive adrenocorticotrophin hormone. Eighty infants completed the posttreatment evaluation according to specifications. The hypsarrhythmia severity score, significantly improved with hormonal therapy for 2 weeks (10.45 ± 2.65 vs 3.45 ± 2.67); $P < 0.01$. When individual treatment arms were compared using mean differences in the improvement of scores, improvement in prednisolone arm (7.95 ± 2.76) was significantly greater than that in the adrenocorticotrophin hormone arm (6.00 ± 2.61); $P < 0.01$. Both forms of therapy were tolerated well. Frequent crying, irritability, weight gain, increased appetite, and abdominal distension were more common (but not statistically significant) with prednisolone. **CONCLUSIONS:** Hypsarrhythmia severity score improved significantly with both hormonal therapies, but this improvement was significantly better with oral prednisolone than intramuscular adrenocorticotrophin hormone. This is the first ever documentation of a superior therapeutic role of oral steroids in West syndrome.

Keywords: West syndrome, hypsarrhythmia, prednisolone, ACTH

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Introduction

West syndrome is an epileptic encephalopathy of infancy characterized by epileptic spasms accompanied by the electroencephalographic (EEG) appearance of hypsarrhythmia.

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Hypsarrhythmia includes high voltage (generally >200 μV) slow waves with variable amplitude; spike and waves from many foci; and lack of synchrony, all of which contribute to the described "chaotic" appearance.[1] Seizure control in West syndrome is often difficult, and the resulting developmental regression may be catastrophic. The cause of this acute regression is suggested to be the combined effect of frequent spasms and hypsarrhythmia.[2] However, even in the absence of clinical spasms (i.e. during prespasm stage), hypsarrhythmia may be associated with an encephalopathic state with reduced alertness to objects, noises, and caregivers; absent or severely reduced social smiling; negative opticofacial reflex; and visual inattention.[3,4] In the past, the persistence of hypsarrhythmia, irrespective of the spasm control (clinical response), has been debated as an indication for continuation of treatment. In evaluation of therapeutic interventions for West syndrome, improvement of hypsarrhythmia (electrical response), has been considered an important primary outcome measure by the West Delphi group.[5]

Treatment of West syndrome to date remains largely empirical. This is often attributed to the poor understanding of its underlying pathophysiology. Vigabatrin, an inhibitor of γ-amino butyric acid transaminase, is favored for tuberous sclerosis. Hormonal therapies, mainly adrenocorticotrophin hormone (ACTH) and prednisolone are recommended for all other etiologies.[6-8] The mode of action of ACTH and glucocorticoids is postulated to be based on their effect on immune, inflammatory, and other derangements observed in West syndrome.[9] The response to these therapies is primarily described as clinical response, EEG response, or as electroclinical response, which is a composite incorporating seizure and EEG resolution. Most prospective clinical trials and retrospective case studies in West syndrome have described only cessation of spasms (clinical outcome) as the primary outcome measure.[10-12] Some others have described the electroclinical outcome.[13-15] No randomized clinical trial has specifically addressed the effect of therapy, especially hormonal treatments, on the resolution of hypsarrhythmia (EEG response).

We report the comparison of the efficacy of moderate-to-high dose oral prednisolone and moderate-to-low dose intramuscular ACTH administered for 2 weeks on the improvement of hypsarrhythmia (electrical response) in previously untreated West syndrome.

Methods

Selection of the sample

A single-blind, parallel, randomized controlled clinical trial was conducted at the Lady Ridgeway Children's Hospital in Sri Lanka from 2010 to 2013. This is the premier tertiary care children's hospital in the country and is said to be the world's largest children's hospital.[16] It provides specialist neurology care for inpatients and outpatients referred from all parts of the country.

Infants who were either directly admitted to the hospital or referred from other hospitals by pediatricians, with newly diagnosed infantile spasms occurring in clusters, were eligible for the study. The diagnosis of infantile spasms was confirmed based on spasms directly observed by the lead author or in videos provided by parents or clinical spasms observed on video telemetry. Of them, only those with hypsarrhythmia were included. This was identified in a 30-minute sleep EEG performed using digital EEG software (Compumedics) with concurrent video recording. To perform the records during a uniform sleep state (NREM sleep), the recordings were performed within first 30 minutes of falling asleep. This was ensured by administering sedation to the babies using chloral hydrate and observing them in the laboratory till fall asleep. At the end of 30 minutes, the babies were aroused to record 5 minutes of wakefulness. Within 24 hours of admission, EEG assessments were performed and interpreted by the lead author who was blinded to the treatment arm.

Of the infants diagnosed with West syndrome, we excluded the ones aged <2 or >30 months or with a diagnosis of tuberous sclerosis, previous treatment for West syndrome, and contraindications for use of hormonal therapies. Patients were also excluded if their parents did not provide proxy consent or seemed incapable of monitoring the response to therapy as judged by the investigator who did the recruitment. Previous prescription of other anticonvulsants for any other seizure type was permitted.

Parents of the eligible infants were explained the study in detail and invited to participate in the study by a medical officer not affiliated to the hospital (E.M.). If willing, informed written consent was obtained before recruiting their children to the study. Before treatment allocation, baseline developmental assessments were performed, using the Bayley-III infant and toddler developmental scales by one of the investigators (S.S.).

Method of randomization

All consenting and eligible infants were randomized to the two treatment groups: prednisolone and ACTH groups. The minimum sample size required to achieve an expected effect size of 25% in the improvement of electrical response in West syndrome with ACTH against prednisolone was 90 (45 in each treatment arm), based on 86.6% of infants revealing clinical and EEG improvement on day 14 of the ACTH treatment,[14] alpha error of 0.05, and power of 80%. Considering decline or subsequent ineligibility of 25%, it was decided to invite 112 infants to participate in the study. Randomization was performed independently using computer-generated random numbers by one coinvestigator (C.A.) who took no part in the recruitment or outcome assessment. Assignment to treatment arm was sequentially allocated and kept in sealed envelopes.

Allocation and monitoring of treatment

Treatment followed the guidelines of the United Kingdom Infantile Spasms Study protocol.[10] The ACTH group received synthetic depot ACTH of 40-60 IU (0.5-0.75 mg) intramuscularly every other day for 14 days. The prednisolone group received daily oral prednisolone of 40-60 mg divided into four doses per day for 14 days.[10] Patients were reassessed at 7 days, and if there was even a single spasm on that day, the dose was increased to prednisolone of 15 mg four times a day or ACTH of 60 IU every other day. At 14 days, the EEG was repeated. Thereafter, a gradual step down of medication was achieved for both groups over the next 3 weeks using prednisolone as follows: 10 mg three times daily; 10 mg twice daily; and 10 mg daily reducing every week. (If the higher dose was used, 10 mg four times a day, 10 mg twice daily, and 10 mg daily, reducing weekly.) The same generic preparations were used throughout the clinical trial.

Prednisolone was crushed and packeted in sachets and administered dissolved in breast milk. This was carried out by mothers under the supervision of nursing offices during the first 2 days of hospital stay. ACTH was administered by the nursing staff. Daily oral antacid therapy was provided to both groups during the total 5 weeks of hormonal treatment. Any other anticonvulsant commenced before the onset of spasms was continued. No alterations to the treatment protocol was made during the 14 days unless at the request of parents. Crossover of treatment arm or to another therapeutic agent was performed only at the end of taper, unless requested by the parent or decided by the lead author based on the spasm load. Protocol violations of dose were defined as deviations from the correct schedule by >24 hours or >10% of the expected dose.

The ACTH group was given the option of inpatient therapy or every other day review for administration of injections as outpatients. Those in the prednisolone group were discharged after 48 hours of treatment. Both groups of mothers were monitored via telephone conversations to ensure the treatment continuation and monitoring of adverse outcomes. The mothers were also instructed to note any adverse events using a

symptom diary. The process of enrollment, treatment allocation, and evaluation is depicted in Figure.

Outcome assessment

The primary outcome was improvement in the severity of hypsarrhythmia (electrical response). The secondary outcome was the development of adverse effects to treatment. The adverse effects were further evaluated by one investigator (E.M.) on day 14, using a preidentified comprehensive list of adverse effects reported for prednisolone and ACTH.

Hypsarrhythmia severity was quantified using a hypsarrhythmia severity scale described by Kramer et al.[17] (Table 1). Components of this scale included the EEG background organization, slow wave activity, amplitude of the spikes, and frequency of spikes. Each of these components was given a score ranging from 0 to 3. These components were evaluated by selecting a 10-second epoch of EEG in NREM sleep that was considered most severe and most representative of hypsarrhythmia. Three other features were given a score of one if present in most of the sleep record: burst suppression, electrodecremental responses, and the absence of sleep transients. Relative normalization of background and epileptic discharges in wakefulness lasting for a minimum duration of 10 seconds was scored as one and was the fourth feature. This was performed by evaluating 5 minutes of record after arousal. Altogether, they accounted for a maximum score of 16, a greater score indicating higher severity. Improvement in the severity of hypsarrhythmia was measured as a reduction in the hypsarrhythmia score, based on the pretreatment (D0) and posttreatment (D14) EEG assessments. Uniformity of the assessment of hypsarrhythmia was ensured by performing the posttreatment EEG under similar conditions as described previously to capture the same state of sleep. The EEG evaluations and hypsarrhythmia severity scoring were performed by the lead author who remained blinded to the treatment arm.

To assess the intraobserver reliability of hypsarrhythmia scores, randomly selected 40 EEGs (20 pretreatment and 20 posttreatment) were rescored by the same investigator after 2 weeks. When the level of agreement between the scores and repeat-scores was assessed using spearman correlation coefficient, all components and the total scores revealed a significantly high correlation (>0.75). In addition, the total and individual component scores did not reveal a significant difference between the first and repeat measurements ($P > 0.05$), implying high reliability.

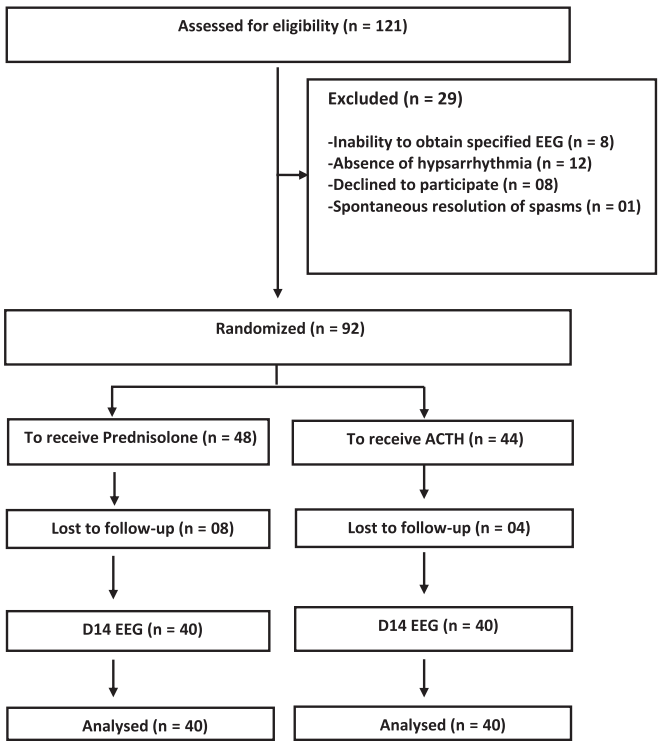

FIGURE.
The process of enrollment, treatment allocation, evaluation, and data analysis.

TABLE 1.
Hypsarrhythmia Scoring System: A Single Relatively Uniform 10-Second Segment That Contains the Most Representative and Severe Hypsarrhythmic Part of the Tracing Was Chosen for Scoring

Component	Score
Disorganization	
Good gradient and synchrony (normal for age)	0
Partially formed gradient with some synchrony	1
No gradient, some synchrony of background	2
Chaos, no synchrony, and no gradient	3
Diffuse delta activity (%)	
<50	0
≥50 but <75	1
≥75 but <100	2
100	3
Voltage (μV)	
<120	0
120-200	1
200-500	2
>500	3
Spikes and sharp waves	
No spikes or sharp waves	0
Spikes at a frequency of ≤1/5 seconds	1
Spikes at a frequency of 1/5 seconds-1 per second	2
Spikes at a frequency of ≥1 per second	3
Other items	
Electrodecremental discharges	1
Burst suppression in sleep	1
Absence of normal sleep pattern	1
Relative normalization in wakefulness	1

The maximum total score is 16 for the most severe hypsarrhythmia; minimum total score is 0 for a normal electroencephalography.
Adapted from Kramer et al.,[17] 1997.

The study was approved by the ethics review committees of the Lady Ridgeway Children's Hospital and the Faculty of Medicine, University of Colombo. It was registered in the Sri Lanka clinical trials registry before commencement (SLCTR/2010/010).

Data analysis

Data were analyzed using SPSS version 20. Descriptive statistics included mean, S.D. for quantitative data, and proportions for categorical data. Significance of the differences between the two treatment arms were assessed using chi-square test in relation to categorical baseline characteristics and posttreatment side effects and using independent *t* test in relation to quantitative baseline characteristics.

Improvement in the severity of hypsarrhythmia was assessed for each individual by calculating (pre-post) treatment scores. The significance of this improvement among all infants treated with hormonal therapy and separately in infants on prednisolone or ACTH was assessed by testing the significance of their mean (pre-post) treatment scores using paired *t* test. The same analysis was performed in the entire sample and also within each individual component of the hypsarrhythmia assessment tool. Finally, significance of the improvement in the severity of hypsarrhythmia between the two treatment groups was assessed by comparing the mean (pre-post) treatment scores between the two groups, using independent *t* test.

Results

Of the 121 eligible infants with confirmed West syndrome, 113 (93%) gave consent. Only 105 underwent EEG evaluation and of them, 12 were excluded because of the

TABLE 2.
Baseline Characteristics of the Children Treated With Prednisolone and ACTH

Baseline Characteristic	Treatment Arm				Level of Significance*
	Prednisolone, n = 48		ACTH, n = 44		
	n	%	n	%	
Sex					
Male	19	47.5	25	65.8	0.1
Female	21	52.5	13	34.2	
Ethnicity					
Sinhala	34	85.0	33	86.8	0.9
Tamil	1	2.5	01	2.6	
Muslim	5	12.5	04	10.5	
Gestation					
Preterm	4	10.3	1	2.6	0.2
Term	35	89.7	37	97.4	
Birth weight (kg)					
<2.5	13	34.2	12	31.6	0.8
>2.5	25	65.8	26	68.4	
Age of onset of spasms (mo)					
<12	38	97.4	33	86.8	0.08
>12	1	2.6	5	13.2	
Preceding and/or concurrent seizures					
Present	13	33.3	12	31.6	0.8
Absent	26	66.7	26	68.4	
Duration of treatment lag (days)					
≤28	21	55.3	16	43.2	0.3
>28	17	44.7	21	56.8	
Previous treatment with AED					
Yes	9	23.1	10	26.3	0.7
No	30	79.9	28	73.7	
Age of onset of spasms (mo)					
<12	38	97.4	33	86.8	0.08
>12	1	2.6	5	13.2	
	Mean	S.D.	Mean	S.D.	Level of Significance
Birth weight (kg)	2.61	0.5	2.67	0.5	0.6
Baseline developmental scores					
Cognitive	60.6	10.3	58.2	8.0	0.2
Language	58.6	12.8	55.9	11.7	0.3
Motor	53.5	13.4	50.9	9.1	0.3
Spasm load (clusters per day)	4.91	3.2	5.06	2.4	0.8

* *P* values obtained for assessing significant differences between the two treatment arms in relation to baseline characteristics (chi-square test used for categorical data; independent *t* test used for quantitative data).

absence of hypsarrhythmia and one because of spontaneous resolution of spasms, leaving 92 who were randomized to receive prednisolone (n = 48) and ACTH (n = 44) (Figure). The majority (71%) had an identified cause (symptomatic) for the West syndrome, although 18% had no cause evident after detailed history and examination, imaging (computed tomography or magnetic resonance imaging of brain), and metabolic screening (cryptogenic), 11% did not complete the investigations. The underlying symptomatic causes included hypoxic-ischemic injury (moderate-to-severe) in 23, neonatal seizures related to perinatal complications (excluding infection) in 10, central nervous system infection in six, congenital ischemic stroke in six, prematurity related in five, agenesis and/or dysgenesis of corpus callosum in four, trisomy 21 in two, neurofibromatosis in one, and post-status epilepticus in one. Average age of the infants in the prednisolone group was 7.5 months (S.D. = 5.2) and 10.8 months (S.D. = 9.5) in the ACTH group, with no significant difference between the two groups ($P = 0.06$). There was also no significant difference between the two groups in demographic characteristics, baseline seizure duration, and severity ($P > 0.05$) (Table 2). No significant differences were noted in those lost for follow-up and those who continued with the study ($P > 0.05$).

Of the 92 randomized infants, only 40 from each treatment group had posttreatment EEGs on day 14. This was because of deviation from protocol by one (prednisolone group), failure to return for the posttreatment EEG by eight (five in prednisolone and three in ACTH groups), and inability to obtain a sleep record in three (one in prednisolone group and two in ACTH group).

When the improvement in the severity of hypsarrhythmia of the entire sample treated with either form of hormonal therapy was considered, it revealed an average pretreatment score of 10.45 (S.D. = 2.65), improving with treatment to an average posttreatment score of 3.45 (S.D. = 2.67). The mean of (pre-post) treatment scores was 7.0 (S.D. = 2.84), which was statistically significant (paired $t = 21.72$; degrees of freedom = 78; $P < 0.01$).

When the improvement in the severity of hypsarrhythmia was assessed within each treatment arm, the

TABLE 3.
Improvement in the Severity of Hypsarrhythmia With Hormonal Therapies (n = 80)

Components in the Hypsarrhythmia Assessment Tool	Improvement in Hypsarrhythmia Scores*		Level of Significance†
	Mean	S.D.	
Background organization	1.74	1.11	<0.001
Background slowing	1.50	1.04	<0.001
Amplitude	1.12	0.82	<0.001
Spike index	1.19	0.98	<0.001
Burst suppression	0.42	0.54	<0.001
Electrodecremental pattern	0.12	0.49	0.02
Normalization in wakefulness	0.43	0.62	<0.001
Absence of sleep transients	0.43	0.59	<0.001
Overall score	7.00	2.84	<0.001

* Improvement in the severity of hypsarrhythmia was assessed by the mean (pre-post) treatment scores.
† *P* values obtained for assessing the significance of the mean of (pre-post) treatment scores using paired *t* test.

mean of (pre-post) treatment scores was significant for each treatment ($P < 0.01$) (Table 3). Furthermore, when the improvement of severity of each individual component of the hypsarrhythmia was considered, a significant improvement in all the components was revealed whether treated with either prednisolone or ACTH (Table 3). The improvement was maximal in background organization (mean = 1.74; S.D. = 1.11) followed by improvement in background slowing (mean = 1.50; S.D. = 1.04).

When the improvement in the severity of hypsarrhythmia was assessed within each treatment arm, the mean pretreatment score for prednisolone and ACTH were 10.55 (S.D.=2.51) and 10.33 (S.D.=2.82) respectively. This improved to 2.61 (S.D.= 2.31) in the prednisolone group and to 4.33 (S.D.=2.76) in the ACTH group. When the mean (pre-post) treatment scores were compared between the two groups, the prednisolone group revealed a significantly greater improvement in severity than that of the ACTH group (7.95 ± 2.76 vs 6.00 ± 2.61; $P < 0.01$) (Table 4). When the mean (pre-post) treatment score of each individual component was assessed, all components improved better with prednisolone than with ACTH. However, only in the spike index, there was a statistically significant improvement. The electrodecremental pattern was equally improved in the two groups.

Both forms of therapies were reasonably well tolerated, but weight gain, increased appetite, irritability, frequent crying spells, and abdominal distension were experienced more frequently in those treated with prednisolone (Table 5). None of these symptoms was severe enough to cause withdrawal from the study, but one child in the prednisolone group withdrew because of hypertension. During the trial period of 5 weeks, which included the treatment regimen and taper period, no deaths occurred.

Discussion

Our study is the first randomized clinical trial to reveal superiority of prednisolone over ACTH for the treatment of West syndrome from the perspective of improvement of hypsarrhythmia (EEG response). Both treatment arms were well tolerated, although frequent crying spells, weight gain, irritability, increased appetite, and abdominal distension were more common in those provided prednisolone. Contrary to expectations, this high-dose prednisolone therapy did not result in a significant risk of infective complications in our setting with a high risk of communicable diseases. The clinical outcome (sustained spasms control) is not described in the present article because assessment is still ongoing. These findings will be described in a future article after study completion.

The choice of improvement of hypsarrhythmia as our primary outcome measure is justified in part by a German study from 2008. In this study, 16 infants with an early onset cerebral insult had sequential EEGs and eventually developed West syndrome. Over a 3- to 6-week interval, there was a gradual build-up of hypsarrhythmia before the onset of spasms.[3] A gradual worsening of the EEG discharges was evident even before the onset of spasms. During this progressive, prespasm stage, the infants revealed progressive encephalopathic behavior. This indicated that in West syndrome, the chaotic EEG is also responsible for the developmental regression. Further, many have stressed that adequate therapy must abolish hypsarrhythmia early and effectively.[2,18] Other studies and guidelines have stressed

TABLE 4.
Comparison of the Improvement of Hypsarrhythmia Severity Between the Prednisolone (PNL) and Adrenocorticotrophin Hormone (ACTH) Groups

Components in the Hypsarrhythmia Scores	Improvement in the Hypsarrhythmia Severity*				Level of Significance†
	PNL Group		ACTH Group		
	Mean	S.D.	Mean	S.D.	
Organization	1.90	0.90	1.57	1.28	0.2
Background slowing	1.57	1.08	1.42	1.00	0.51
Amplitude	1.30	0.79	0.94	0.83	0.05
Spike index	1.50	0.90	0.86	0.96	0.004
Burst suppression	0.52	0.59	0.31	0.47	0.09
Electrodecremental pattern	0.12	2.76	0.13	0.57	0.95
Normalization in wakefulness	0.48	0.67	0.38	0.65	0.48
Absence of sleep transients	0.50	0.55	0.36	0.63	0.33
Overall score	7.95	2.76	6.00	2.61	0.002

Because of multiple comparisons, the level of significance was adjusted to $P < 0.05$ by Bonferroni correction: $\alpha_{adjusted} = \alpha/c$ (where α is the overall experimentwise alpha [0.05] and c is the number of comparisons made [9]).
* Improvement in the hypsarrhythmia severity was assessed by the mean of (pre-post) treatment scores.
† *P* values obtained for assessing the significant difference of the mean (pre-post) treatment scores between the two treatment groups using paired *t* test.

TABLE 5.
Comparison of Side Effects Experienced With Prednisolone and Adrenocorticotrophin Hormone (ACTH) (n = 80)

Side Effect	Prednisolone		ACTH		Level of Significance*
	n	%	n	%	
Increased appetite	25	78.5	15	42.9	0.006
Weight gain	17	51.5	10	28.6	0.05
Frequent crying spells	15	45.5	8	22.9	0.04
Drowsiness	3	9.1	6	17.1	0.32
Cushinoid features	8	24.2	5	14.3	0.29
Insomnelence	3	9.1	1	2.9	0.27
Lethargy	2	6.1	1	2.9	0.52
Reduction in social behavior	2	6.1	1	2.9	0.52
Abdominal distension	7	21.2	0	0	0.004
Hypertension	1	3.0	1	2.9	0.99
Increased susceptibility to infection	0	0	1	2.9	0.32
Irritability	8	24.2	2	5.7	0.03
Nausea	1	3.0	0	0	0.29
Vomiting	1	3.0	0	0	0.29
Diarrhea	2	6.1	1	2.9	0.52
Dyspepsia	1	3.0	1	2.9	0.96
Electrolyte imbalances	2	6.1	0	0	0.32

* Because of multiple comparisons, the level of significance was adjusted to $P < 0.00294$ by Bonferroni correction: $\alpha_{adjusted} = \alpha/c$ (where α is the overall experimentwise alpha [0.05] and c is the number of comparisons made [17]).

the importance of early treatment to allow the possibility of better developmental outcome; however, this proposal has not been definitively proven.[6,18,19] Based on current information, it appears that a therapeutic agent that reverses hypsarrhythmia promptly has some chance of improving the developmental outcome. Underlying etiology also may play a role in the improved developmental outcome. However, comparison of results separately for symptomatic and cryptogenic etiologies could not be performed adequately in this group because 11% of the infants did not complete the investigations for etiology.

Historically, the accepted therapeutic options for West syndrome have been mainly vigabatrin and hormonal therapies. Although both forms of hormonal therapies (ACTH and corticosteroids) have been used as first-line hormonal therapy for over 40 years, unlike ACTH, corticosteroids have not often been recommended as a first-line choice for short-term therapy. The reason appears to be the lack of "adequate" evidence as outlined in several evidence-based meta-analyses.[6,8,20] There are many case series and retrospective reports of successful treatment of West syndrome with oral prednisolone,[11,21,22] prednisone,[13] IV pulsatile dexamethasone,[23] and IV methyl prednisolone.[24] However, because of lack of class I or II evidence, there has been a reluctance to accept oral corticosteroids as effective.[6-8,25] Of the studies, which favored ACTH, a class II (n = 29) randomized clinical trial revealed marked superiority of high-dose ACTH (86.6%) over low-dose prednisone (28.6%); however, the doses of ACTH and prednisone were not comparable.[14] A class IV retrospective case series (n = 116) reported 100% response to ACTH vs 51% response to prednisone.[12] Other studies have reported no significant difference between ACTH and oral corticosteroids. These include a class III (n = 24) trial published in 1983[13] and a large class III (n = 55) trial in 2004 revealing equal spasm response rates of 76% (ACTH) and 70% (prednisolone).[10] This last trial was underpowered to prove a superiority of one form of hormone over the other. Lately, in a retrospective analysis of outcome with prednisolone (n = 15), which was used because of the high cost of ACTH, spasm freedom within 2 weeks was reported in 67%.[21] The systematic review by Arya et al.[20] on corticosteroids for treatment of West syndrome concluded that, based on available evidence, the effects of high-dose corticosteroids (3-4 mg/kg/day) are similar to low-dose ACTH (40-60 mg/day).

One of the crucial issues related to these trials is the absence of comparative doses of ACTH and prednisolone. A well-known study that is referenced in most meta-analyses on therapeutic outcomes used very high dose of ACTH (150 U/m^2/day) compared with a small dose of prednisone (2 mg/kg/day).[14] Although this referenced randomized clinical trial fulfills criteria for meticulous study design, the imbalance in the doses may have biased the study outcome. It is likely that such a high dose of ACTH would have a higher rate of adverse effects. The best equivalent dose for ACTH and oral corticosteroids is still unknown. It is also possible that the mechanism of action of these two treatments on altering the neurobiology in West syndrome is different.[26,27] Further, two different compounds of ACTH (natural or synthetic) have been used in trials.[28]

Apart from issues of efficacy, the greatest advantage associated with prednisolone therapy is its low cost. Completion of the treatment course in the United States with oral prednisolone typically costs less than $100 versus $70,000 for natural ACTH and $7000 for synthetic ACTH preparations.[21,24] Recent increase in the cost has worsened this situation even further. Another major advantage of oral corticosteroids is the ease of administration, which may indirectly increase the quality of holistic care to the infant.

We conclude that moderate-to-high doses of oral prednisolone appear to be more effective than low-to-moderate doses of ACTH for the initial treatment of West syndrome to reverse the hypsarrhythmia. It is hoped that this would establish recognition of oral prednisolone as a form of primary treatment option for West syndrome. Our findings should be particularly important to parts of the world where ACTH is simply not affordable or not available. On the other hand, it may also be welcomed by countries with recently escalated cost of ACTH therapy.

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