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High-dose Corticotropin (ACTH) Versus Prednisone for Infantile Spasms: A Prospective, Randomized, Blinded Study

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Abstract

Objective—To compare the efficacy of corticotropin (ACTH) (150 U/m^2/day) and prednisone (2 mg/kg/day), given for 2 weeks, in suppressing clinical spasms and hypsarrhythmic electroencephalogram (EEG) in infantile spasms (IS). ACTH and prednisone are standard treatments for IS. ACTH at high doses causes severe dose- and duration-dependent side effects, but may be superior to prednisone, based on retrospective or uncontrolled studies. Blinded prospective studies have shown equal efficacy of prednisone and low-dose ACTH, and low versus high-dose ACTH.

Design—A prospective, randomized, single-blinded study.

Subjects and Methods—Patient population consisted of consecutive infants fulfilling entry criteria, including the presence of clinical spasms, hypsarrhythmia (or variants) during a full sleep cycle video-EEG, and no prior steroid/ACTH treatment. Response required both cessation of spasms and elimination of hypsarrhythmia by the end of the 2-week treatment period, as determined by an investigator “blinded” to treatment. Treatment of re-sponders was tapered off over 12 days; those failing one hormone were crossed-over to the other.

Results—Of 34 eligible infants, 29 were enrolled. Median age of patients was 6 months. Twenty-two infants were “symptomatic” with known or suspected cause, and seven were cryptogenic (two normal). Of 15 infants randomized to ACTH, 13 responded by both EEG and clinical criteria (86.6%); seizures stopped in an additional infant, but EEG remained hypsarrhythmic (considered a failure). Four of 14 patients given prednisone responded (28.6%, with complete clinical-EEG correlation), significantly less than with ACTH, (χ^2 test).

Conclusions—Using a prospective, randomized approach, a 2-week course of high-dose ACTH is superior to 2 weeks of prednisone for treatment of IS, as assessed by both clinical and EEG criteria.

Infantile spasms (IS) is an age-specific seizure disorder of infants.[1–6] It is relatively common (1:2000–4000 births),[7] and has distinctive clinical and electro-graphic features.[1–6] The syndrome of IS consists of myoclonic seizures accompanied by an hypsarrhythmic electroenephalogram (EEG) pattern.[8] Symptomatic IS occurs in infants with a variety of antecedent central nervous system insults (eg, malformations, infections); the cryptogenic form is found in otherwise normal infants or those with no predisposing factors.[1,6] The EEG

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pattern, response to hormonal therapy, and poor outcome distinguish IS from a variety of other myoclonic epilepsies of infancy.[1,2] The intellectual outcome of the great majority of affected infants is poor regardless of treatment, and over half develop other seizure types.[1–5,7] Therefore, IS continues to attract research concerning both pathogenesis and therapy.

IS is generally resistant to conventional anticonvulsants. However, in 1958, Sorel[9] reported on the efficacy of corticotropin (ACTH) for the seizures, and ACTH and a synthetic glucocorticoid (GC), prednisone, have become the standard therapy for IS. On a theoretical basis, ACTH, especially in high doses, may be expected to be more effective than prednisone.[5,10–12] However, a double-blinded series[13] demonstrated equal efficacy of short courses of 20 to 30 U ACTH and prednisone in the treatment of IS.

Further issues of ACTH dose and duration of treatment have not been resolved. High doses of ACTH (150 U/m^2 body surface/day) have been advocated, based on a response rate of >80% in uncontrolled trials.[10,14] Low-dose ACTH (<40 U/day) has been found effective in retrospective studies.[15,16] A recent controlled study comparing high-dose long duration ACTH to low-dose (20–30 U/day) short treatment found equal efficacy of both regimens.[17] Overall response rate (50%), however, was quite low.

We compared the efficacy of 2-week courses of high-dose ACTH and prednisone for the treatment of IS. The study was a single-blinded comparison of response, using video-EEG as the objective measure of response to treatment.

Methods

Definitions

1. IS was defined according to Jeavons.[6] Because an outcome of mental retardation could not be assessed on presentation, the criterion was not used.
2. Cryptogenic IS was defined as the absence of etiology despite a battery of tests described below. An abnormal developmental status did not preclude defining an infant as having cryptogenic IS, because drug effects or deterioration with the onset of IS could not be excluded.

Study Population

Infants with clinical IS and no previous steroid or ACTH treatment were considered for the study if parents were willing to consent to randomized treatment. All subjects underwent a 24-hour video-EEG to ascertain the presence of hypsarrhythmia or its variants,[8,18] and the presence and frequency of epileptic myoclonic events. Thirty-six consecutive infants met clinical and EEG criteria for entry. Two were ineligible for ACTH/GC treatment due to severe hypertension (1), and resolution of spasms after shunt placement (1). The remaining 34 patients were eligible for the study. Twenty-nine were entered into the study, and five were not, due to parental refusal (2), unavailability of legal guardian (2), and other issues (1).

Study Design

The study was approved by the Childrens Hospital Los Angeles Institutional Review Board.

Patients who met clinical and electrographic criteria were entered into the study subsequent to an informed consent signing by parents or legal guardians. A computer-generated random-number list determined treatment. No stratification was employed.

An evaluation for the etiology of IS was undertaken in all infants. This consisted, at a minimum, of the prenatal and postnatal history, physical and neurological exams, neuroimaging (computed tomography or magnetic resonance imaging), blood amino acids, lactate and pyruvate, and urine organic acids. Additional studies were obtained guided by clinical observations. Before beginning treatment, serum electrolytes, glucose, and blood pressure were measured.

Treatment lasted for 2 weeks (Table 1). ACTH (ACTHARGEL, Rhône-Poulenc-Rorer, Collegeville, PA; 150 U/m^2/day) was given intramuscularly in two divided doses. Prednisone (2 mg/kg/day) was given orally in two divided doses. Seizure frequency was monitored by parents who maintained seizure diaries. Side effects such as hypertension and hyperglycemia were monitored: glycosuria was checked on each specimen for the duration of treatment, and blood pressure was measured bi-weekly. Irritability and voracious appetite were the most frequent side effects, but no infant required stopping or modifying treatment.

After 2 weeks, a repeat video-EEG was performed, and clinical and EEG response assessed. Video-EEG lasted 4 to 24 hours, always including a full sleep-wake cycle. For a patient to be considered a responder to treatment, both video-EEG and clinical responses were necessary: clinical response consisted of a complete cessation of IS events. Electrographic response consisted of resolution of the hypsarrhythmic pattern on both sleep and wake EEG. The emergence of background slowing or other epileptiform patterns was considered a positive response. Video-EEG studies were interpreted by an investigator (E.J.H.) who was not informed of treatment assignment.

Infants with persistent IS or hypsarrhythmia were offered the alternative treatment. Responders were tapered off ACTH or prednisone as described in Table 1.

Statistical Considerations

Treatment groups were compared using the χ^2 test. The Mann-Whitney test was used to determine potential differences (eg, age) between treatment groups, and the effect of discrepancy in mean age among treatment groups was analyzed using the Mantel-Haenszel test.

Results

Patient characteristics are summarized in Tables 2 and 3. Ethnic background was representative of the Childrens Hospital Los Angeles patient population. There were twelve infants with Hispanic surnames (six in each treatment group). Eleven infants were white non-Hispanic (five in the ACTH group), three were Asian, and three African-American.

Twenty-two infants had “symptomatic” IS, with known or suspected cause, and seven had cryptogenic IS, but only two were entirely developmentally and neurologically normal at the time of diagnosis. Of 29 subjects, 15 were randomized to ACTH and 14 to prednisone. Mean age of the prednisone group was higher than that of the ACTH group (7.5 vs 5.1 months), but the difference did not reach statistical significance ($P = .06$ Mann-Whitney test). Cryptogenic etiology, male sex, other seizures, or duration of IS did not differ significantly between treatment groups.

Of 15 infants randomized to ACTH, 13 responded by both EEG and clinical criteria (86.6%); seizures stopped in an additional infant, but EEG remained hypsarrhythmic (considered a failure). Four of 14 patients (28.6%) given prednisone responded by both EEG and clinical criteria. No patient had clinical response only. The different response rate between treatment groups was significant: $P = .002$ χ^2 test). The difference between ACTH

and prednisone remained significant even after accounting for the potential confounding effect of age. Weighted relative response adjusted for age (Mantel-Haenszel test) was 3.94 (confidence interval 1.44 – 10.77; $P = .0026$).

The two infants who failed ACTH received prednisone for 2 weeks, and one responded by both clinical and EEG criteria. Of the 10 infants who failed prednisone, nine received ACTH (for 2 weeks), and eight responded (88%). Two of the five infants who were ineligible for the study received ACTH and responded. The remaining infants received prednisone, valproate, or clonazepam, which did not control the IS within a 2-week period.

Length of follow-up period was insufficient for comparing cognitive outcome and development of other seizures in the ACTH and prednisone-treated infants. This type of comparison was further confounded by the fact that nine infants initially randomized to prednisone went on to receive ACTH. IS recurred by clinical and EEG criteria in two infants in the ACTH group, and seven infants in each group eventually developed other seizure types (Tables 2 and 3).

Two ACTH-treated infants and one prednisone-treated infant have normal neurologic and cognitive development as of last contact (Tables 2 and 3). These include the two who were considered normal on presentation. The third is an infant with cryptogenic IS and abnormal exam on presentation who was treated with ACTH.

Discussion

In this prospective, randomized, single-blinded study, high-dose[19] ACTH was significantly superior to prednisone in terminating IS and normalizing the EEC No demographic or etiologic differences between treatment groups confounded this effect. The prednisone group was slightly older, but, when age was accounted for, the efficacy of ACTH remained significantly higher than that of prednisone (weighted relative response 3.94, Mantel-Haenszel test $P = .0026$). Moreover, younger age at onset has been associated with a worse prognosis, so that somewhat older infants (the prednisone group) would be expected to have a more favorable response.

The protocol design utilized a short-term (2-week) treatment. The rationale for this duration was based on two lines of observation: first, IS has a significant spontaneous remission rate.[20] In untreated infants, IS often evolves into a variety of other seizure types.[1-5,7,20] Thus, prolonged (3 to 10 months) therapy with a large number of agents has been reported as “effective” (reviewed in Reference 5). Further, in the majority of studies describing the time-course of treatment responses, patients who benefitted from therapy did so within the first week or two.[9,13] In the current study, median response time for ACTH was 2 days, and for prednisone, 3.5 days. No patient responded clinically more than I week after treatment began. Follow-up EEGs were obtained only at the end of treatment, precluding evaluation of the time-course of elimination of hypsarrhythmia. In a single case, ACTH treatment abolished clinical spasms in 2 days, yet video-EEG continued to show a modified hypsarrhythmia pattern on the 15th day of treatment (the patient was considered a failure). These results suggest that the short length of treatment did not bias outcome: both ACTH and prednisone exerted their therapeutic effects within days.

In a recent report, Hrachovy et al[20] compared ACTH in a regimen comparable to ours, to a low-dose (20 or 30 U/day) regimen. They found comparable efficacy of both ACTH dosage schedules, but had a low response rate (50%) overall. In a previous controlled, blinded, randomized study, the same authors described the equivalence of short-term low-dose ACTH and prednisone.[13] The response rate (33% to 42% before cross-over) was

substantially lower that obtained in other studies using high-dose ACTH, and was comparable to that obtained with prednisone in the current study.

The reasons for the different response rates are obscure. Hrachovy et al emphasized that clinical outcome measures were unreliable.[9,13,17,20] They advocated EEG response criteria, ie, the elimination of hypsarrhythmia and its variants.[9,18] The current study employed both EEG and clinical measures. Posttreatment EEGs, encompassing a minimum of a complete sleep cycle revealed persistent hypsarrhythmia during slow-wave sleep in only one patient who was free of clinical spasms.

Whether the response rate to ACTH or prednisone differs in infants with the “cryptogenic” versus the “symptomatic” form of IS is a complex issue. The definition of cryptogenic is inconsistent among investigators: some consider as cryptogenic infants with no known cause for their IS, even with an abnormal neurodevelopmental status.[1–5] With the advent of contemporary diagnostic tools, the number of infants with apparently cryptogenic IS has drastically declined. This has made comparison of results of older and more recent studies difficult. Conversely, previously normal infants may lose developmental milestones at the onset of continuous abnormal neuronal activity (hypsarrhythmia) with resulting abnormal neurological examination. In the current study, seven infants (24%) had no definite etiology for their IS. Only two (7% of total) were neurologically normal, and responded to ACTH and prednisone. Five infants had abnormal neurologic examinations (cognitive, motor, or both) in the absence of etiology for their IS. The three infants randomized to prednisone failed to respond; of the two such infants assigned to ACTH, one responded. This response pattern was not significantly different from that of infants with “symptomatic” IS.

The mechanisms by which glucocorticoids and ACTH control IS and improve or normalize the EEG remain speculative.[5,11,12,22–25] ACTH may function as a promoter of adrenal glucocorticoid secretion: high-dose ACTH may result in higher or more sustained plasma Cortisol.[10] Alternatively, ACTH may exert therapeutic effects directly on the central nervous system, in addition to or independent of Cortisol release.[11,12,22] ACTH analogues devoid of steroidogenic effects, however, are not effective for IS.[26,27] Both agents, acting via a negative feedback loop, suppress the synthesis and secretion of corticotropin-releasing hormone (CRH) (reviewed in 5). CRH is a potent convulsant in the rodent, with age-specific potency during infancy.[23,24] ACTH is more effective than prednisone in suppression of CRH gene expression, and affects cortical as well as hypothalamic CRH levels.[28] CRH excess, secondary to antecedent activation of the CRH-ACTH-cortisol stress-transduction pathway, may play a mechanistic role in IS.[5,23–25] Seizures may be “triggered” by subsequent stress-induced plasma glucocorticoid secretion, eg, with immunization.[29–30]

The minimal effective dose of ACTH remains un-clear. Ito et al[16] reported the results of retrospective analysis of patient response to graded ACTH doses. Based on nine patients, they concluded that 0.6 U/kg/day (6 units for a 10-kg infant) resulted in seizure cessation (8/9), and 0.8 U/kg/day eliminated hypsarrhythmia. Beyond that “threshold” dose, no dose effect was seen.[16] Authors in this country[10,19,21] and abroad[14] strongly advocate high-dose ACTH, based on both response and plasma hormone data.[10]

IS is a form of epilepsy that is age-specific to infancy.[31] It is triggered at a vulnerable developmental stage in the setting of a previously stressed or injured central nervous system.[5] Whether the spasms per se or the ongoing hypsarrhythmic epileptiform neuronal activity further contribute to the poor cognitive outcome is not clear.[1–5,9,11,14,21] Recently, prolonged duration of IS before treatment was correlated with graver intellectual prognosis.[32] In the current study, IS duration before treatment did not predict short-term response rate. Further studies on the relative efficacy of ACTH and prednisone on long-term

cognitive outcome of infants are needed. These require a population of neurologically normal ("cryptogenic") infants. Given the small number of such infants in clinical series, a prospective multi-center collaborative effort is indicated.

In conclusion, using a 2-week regimen, high-dose ACTH is superior to prednisone for suppression of clinical spasms and hypsarrhythmia in IS. Further studies of the mechanisms by which ACTH acts are needed.[5,31] These may point the way to the development of novel, more direct therapies for age-specific epilepsies such as IS.

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Abbreviations

IS	infantile spasms
EEG	electroencephalogram
ACTH	corticotropin
GC	glucocorticoid
CRH	corticotrop-in-releasing hormone

TABLE 1
Study Treatment Regimen for Infantile Spasms

A. Two-week treatment schedule:
ACTH: 75 U/m^2 twice a day, intramuscularly
Prednisone: 1 mg/kg twice a day, orally
Monitoring: Electrolytes, glucose at onset and end.
Glycosuria: all specimens.
Blood-pressure: twice a week.
B. Tapering schedules:
ACTH: For 3 days 30 U/M^2 in the morning.
For 3 days 15 U/m^2 in the morning.
For 3 days 10 U/m^2 in the morning.
For 6 days 10 U/m^2 every other morning.
Prednisone: For 3 days the morning dose (1 mg/kg) only.
For 6 days half the morning dose (0.5 mg/kg) only.
For 6 days 0.5 mg/kg every other morning.

TABLE 2

Characteristics of Infants Treated With ACTH

Patient Number	Age/Sex (Months)	Category	Etiology	Prior Drugs	Response (Days)	Outcome Exam/Seizures	F-U (Months)
1	5.5/F	Sympt	Agenesis CC	PBT; Carbamazepine	No	Ab/Seizures	48
2	3.0/F	Sympt	Cong CMV	PBT	Yes/5	Ab/Recurr	2
3	5.0/F	Cryp/NI			Yes/2	NL/-	12
4	3.0/F	Sympt	Cong Hydrocephalus	PBT	Yes/<7	Ab/Seizures	18
5	5.0/F	Cryp/Ab			Yes/1	NL/-	8
6	6.0/M	Sympt	CNS Bleed	PBT	Yes/1	Ab/-	37
7	4.5/M	Sympt	Down Syndrome	Valproate	Yes/<4	Ab/-	24
8	8.0/F	Sympt	IVH		Yes/2	Ab/Seizures	26
9	6.0/M	Sympt	CNS Malformation	PBT	Yes/6	Ab/IS Recurr	17
10	6.0/F	Sympt	Tuberous Sclerosis		Yes/2	NL/-	11
11	3.0/F	Sympt	Tuberous Sclerosis	PBT;	Yes/1	Ab/Seizures	8
12	3.0/F	Cryp/Ab			No*/2	Ab/-	2
13	2.0/M	Sympt	CNS Malformation	PBT; Carbamazepine	Yes/1	Ab/-	3
14	6.0/F	Sympt	CNS Malformation		Yes/2	Ab/-	2
15	10.5/F	Sympt	CNS Malformation	PBT; Clonazepam	Yes/7	Ab/Seizures	8

Abbreviations: F, female; M, Male; F-U, length of follow-up; Sympt, symptomatic; Cryp, cryptogenic; Nl, normal; Ab, abnormal; CC, corpus callosum; Cong, congenital; CMV, cytomegalovirus; CNS, central nervous system; IVH, intraventricular; PBT, phenobarbital; Recurr, recurrent; IS, infantile spasms.

TABLE 3

Characterisitcs of Infants Treated With Prednisone

Patient Number	Age/Sex (Months)	Category	Etiology	Prior Drugs	Response Days	Outcome Exam/Seizures	F-U (Months)
1	3.5/M	Cryp/Ab		PBT	No	Ab/Seizures	31
2	21/F	Sympt	Meconium Aspiration	PBT/Valproate	No	Ab/Seizures	46
3	9.0/M	Sympt	Perinatal Asphyxia(?)		No	Ab/-	28
4	7.0/F	Sympt	Chromosomal Deletion	PBT	No	Ab/Seizures	13
5	5.0/F	Sympt	Tuberous Sclerosis		No	Ab/Seizures	29
6	7.0/M	Sympt	IUGR-Malnutrition		Yes/3	Ab/-	4
7	3.0/F	Cryp/Ab			No	Ab/Seizures	34
8	10./M	Sympt	CNS Malformation	PBT	No	Ab/-	18
9	3.0/F	Cryp/Ab		PBT	No	Ab/Seizures	15
10	5.0/M	Sympt	CNS Malformation	Carbamazepine	No	Ab/Seizures	7
11	8.0/M	Sympt	Perinatal Asphyxia (?)		Yes/2	Ab/-	3
12	6.5/M	Sympt	Lactic Acidosis		Yes/4	Ab/-	3
13	9.0/M	Sympt	Tuberous Sclerosis	PBT; Carbamazepine	No	Ab/-	2
14	8.0/F	Cryp/NI			Yes/7	Nl	3

Abbreviations: M, male; F, female; Cryp, cryptogenic; Ab, abnormal; Sympt, symptom; Nl, normal; IUGR, intrauterine growth retardation; CNS, central nervous system; PBT, phenobarbital.