Received: 25 October 2018 | Revised: 29 January 2019 | Accepted: 29 January 2019

DOI: 10.1111/epi.14679

FULL-LENGTH ORIGINAL RESEARCH

Epilepsia®

Efficacy and tolerability of the ketogenic diet versus high-dose adrenocorticotropic hormone for infantile spasms: A single-center parallel-cohort randomized controlled trial

Anastasia Dressler[1] | Franz Benninger[2] | Petra Trimmel-Schwahofer[1] | Gudrun Gröppel[1] | Barbara Porsche[1] | Klaus Abraham[1] | Angelika Mühlebner[1] | Sharon Samueli[1] | Christoph Male[1] | Martha Feucht[1]

[1]Department of Pediatrics and Adolescent Health, Medical University of Vienna, Vienna, Austria

[2]Department of Child and Adolescent Psychiatry, Medical University of Vienna, Vienna, Austria

Correspondence
Martha Feucht, MD, Department of Pediatrics, Medical University of Vienna, Vienna, Austria.
Email: martha.feucht@meduniwien.ac.at

Summary

Objective: To compare the efficacy and safety of the ketogenic diet (KD) with standard adrenocorticotropic hormone (ACTH) treatment in infants with West syndrome.

Methods: In this parallel-cohort (PC) randomized controlled trial (RCT), infants were randomly allocated to KD or high-dose ACTH. Those who could not be randomized were followed in a PC. Primary end point was electroclinical remission at day 28. Secondary end points were time to electroclinical remission, relapse after initial response, seizure freedom at last follow-up, adverse effects, and developmental progress.

Results: One hundred one infants were included: 32 in the RCT (16 KD; 16 ACTH) and 69 in the PC (37 KD; 32 ACTH). Electroclinical remission at day 28 was similar between KD and ACTH (RCT: 62% vs 69%; PC: 41% vs 38%; combined cohort: 47% vs 48%; KD vs ACTH, respectively). In the combined cohort, time to electroclinical remission was similar between both treatments (14 days for KD, 16 days for ACTH). However, relapse rates were 16% (KD) and 43% (ACTH, $P = 0.09$), and seizure freedom at last follow-up was 40% (KD) and 27% (ACTH, $P = 0.18$). Adverse effects needing acute medical intervention occurred more often with ACTH (30% with KD, 94% with ACTH, $P < 0.001$). Age-appropriate psychomotor development and adaptive behavior were similar.

Without prior vigabatrin (VGB) treatment, remission at day 28 was 47% (KD) and 80% (ACTH, $P = 0.02$); relapse rates were 29% (KD) and 56% (ACTH, $P = 0.13$). Consequently, seizure freedom at last follow-up was similar. In infants with prior VGB, seizure freedom at last follow-up was 48% (KD) and 21% (ACTH, $P = 0.05$).

Significance: The study is underpowered; therefore, its results should be interpreted with caution. KD is as effective as ACTH in the long term but is better tolerated. Without prior VGB treatment, ACTH remains the first choice to achieve short-term remission. However, with prior VGB, KD was at least as effective as ACTH in the short term and was associated with lower relapse rates in the long term; therefore, it represents an appropriate second-line treatment after VGB.

KEYWORDS
adrenocorticotropic hormone, ketogenic diet, parallel cohort, randomized controlled trial, West syndrome

1 | INTRODUCTION

West syndrome (WS)—characterized by epileptic spasms, hypsarrhythmia on the electroencephalogram (EEG), and psychomotor retardation—is the most common infantile onset epileptic encephalopathy.[1]

Medical treatment remains unsatisfactory with respect to seizure control and developmental outcomes. Although epileptic spasms and hypsarrhythmia resolve with time, many children develop other forms of drug-resistant epilepsy syndromes, and severe intellectual disabilities are shown in about 70%.[2]

Many treatment regimens have been investigated, most of them using observational or uncontrolled trials, small sample sizes, and a wide variation of treatment dosages, durations, and outcome measures. Furthermore, the investigated drugs have frequently been started long after disease onset and in combination with or after multiple other antiepileptic drugs (AEDs).[2–4]

Currently, only three treatment options showed higher than class IV evidence and are therefore recommended as standard therapies: adrenocorticotropic hormone (ACTH), vigabatrin (VGB), and oral corticosteroids.[5–7] However, only ACTH treatment has class I evidence; therefore, it is the primary treatment option.[2–4,8–11] ACTH has shown responder rates varying from 42% to 87% and cessation of spasms typically within the first 14 days.[2–4,11–13] However, ACTH is associated with high relapse rates of up to 66%[14,15] and a high potential for severe side effects including death.[3]

VGB is recommended as first-line therapy for WS associated with tuberous sclerosis, with responder rates of ≥90% reported in some studies.[16] In other patient populations, however, VGB has been reported to be less effective than ACTH, although relapse rates seem to be lower and long-term outcomes may be similar.[3,4] In addition, VGB has been reported to cause irreversible visual field defects in up to 64% of infants when used longer than 24 months.[17] Guidelines developed in 2004[3] and updated in 2012[4] stated that VGB "may be useful for the short-term treatment of [infantile spasms]," and "ACTH should be considered preferentially over VGB." A recent multicenter study showed hormonal therapy (ACTH or high-dose prednisolone) in combination with VGB to be significantly more effective at stopping infantile spasms than hormonal therapy alone.[18]

The ketogenic diet (KD) has shown efficacy in a variety of childhood onset drug-resistant epilepsy syndromes.

Key Points

- No significant differences between KD and ACTH in infants with West syndrome with respect to:
- Short-term remission at day 28 in children pretreated with VGB (whereas for infants not previously pretreated with VGB, ACTH remains the first choice)
- Time to electroclinical remission
- Relapse rates after initial response
- Long-term seizure freedom
- Less severe adverse effects needing medical intervention with KD

Three retrospective studies reported KD to also be effective and safe in WS,[19–21] as did one prospective study.[22] So far, this has not been confirmed in a head-to-head controlled study. Currently, KD is therefore considered a second-line treatment to be used when standard regimens have failed.[5]

The objective of this prospective, single-center parallel-cohort (PC) randomized controlled trial (RCT) was to assess the efficacy and safety of KD compared with standard-of-care high-dose ACTH in infants with WS.

Specific objectives were to compare:

- The incidence of electroclinical remission at day 28
- The time to electroclinical remission
- The frequency of relapse
- Sustained seizure freedom at last follow-up visit
- The frequency of serious adverse effects
- Developmental outcomes.

The hypothesis to be investigated was that KD is at least as effective and potentially better tolerated (safer) than ACTH.

2 | MATERIALS AND METHODS

2.1 | Study design

This single-center, prospective PC-RCT was performed in the Department of Pediatrics at the Medical University of

Vienna (MUW) between June 2008 and April 2017. The study protocol was approved by the ethics committee of MUW (No. 542/2007).

Consecutive infants with WS were screened at the study center. Study inclusion criteria were (1) an ascertained diagnosis of WS according to the International League Against Epilepsy,[1] based on video-EEG monitoring; and (2) written informed consent of legal guardians. Exclusion criteria were (1) contraindications for either ACTH or KD[23] and (2) previous treatment with KD and/or steroids. Concealed random allocation to either KD or ACTH was performed using a Web-based certified program of the Institute for Clinical Biometry of MUW (Randomizer 1.8.1).

Patients who fulfilled the inclusion criteria, but who could not be randomized for various reasons (see Results), were included in the PC and were treated with either KD or ACTH based on the individual's medical condition, presence of contraindications, and parents' preference, following our standard of care.

Infants included in the PC who were referred to our clinic >3 months after epilepsy onset, and without having previously received standard medication (steroids or VGB), were assigned to ACTH as first-line treatment. Treatment protocols and outcome assessments were the same for the PC and the RCT.[24,25]

KD was introduced according to the Johns Hopkins protocol without fasting and fluid restriction[26] at a 1:1 fat:nonfat ratio and individually increased to a 3:1 ratio (ratio was limited when beta-hydroxybutyrate levels reached >5 mmol L^{-1}). The amount of protein was calculated as required for age.[27] An interdisciplinary team including a pediatric epileptologist, a dietician, and a pediatric epilepsy nurse implemented the diet on an inpatient basis and performed all follow-up visits according to individual needs.[26] For safety, blood glucose and beta-hydroxybutyrate levels were measured three times per day (during the1st week). At home, urine ketone bodies were measured daily, and food diaries including recipes and data on adverse effects were kept.

High-dose synthetic ACTH was introduced with the dosage recommended by the US consensus report[5]: 150 IU/m^2 given in 2 divided doses daily for 2 weeks, then tapered gradually (total treatment duration = 28 days). Blood pressure was measured a minimum of six times per day; laboratory tests (including inflammation parameters, blood count, electrolytes, and renal and liver function parameters) were performed a minimum of three times per week.

At the baseline visit, all patients underwent complete medical and metabolic workup including neuroimaging.[13] Follow-up visits were mandatory once per week during the first month, at 3 months, and at 12 months. A final visit was scheduled at 24 months. At baseline and each follow-up visit, 24-hour video-EEGs were performed to detect spasms and/or hypsarrhythmia, and seizure diaries were collected. Hypsarrhythmia was defined according to the original description published by Gibbs and Gibbs[28] including variants.[29] Video-EEGs were assessed independently by two board-certified epileptologists (M.F., G.G.) masked to treatment allocation and outcome. In cases of disagreement, consensus was obtained by joint reevaluation. Interrater reliability was calculated prior to the study outcome. There was 100% interrater agreement for presence/absence of hypsarrhythmia. For focal discharges, there was 94% agreement (Cohen kappa = 0.87).

Thorough pediatric, nutritional, and neurological examinations were also performed at each visit. The Touwen Infant Neurological Examination was used for infants and children aged <18 months[30,31] and the Hempel neurological examination was used for children aged ≥18 months,[32] classifying results into three categories of dysfunction (age-appropriate psychomotor development, mild dysfunction, severe dysfunction).[30–32] Furthermore, the Vineland Adaptive Behavior Scales II[33] were carried out by a board-certified neuropsychologist (B.P.), masked to treatment allocation and outcome.

Adverse effects were evaluated using parental questionnaires. Laboratory findings and clinical pediatric data were collected at each follow-up visit; abdominal and cardiac ultrasounds were performed twice per year.[23]

Primary study end point was the incidence of electroclinical remission (cessation of spasms plus resolution of hypsarrhythmia) at day 28.[13] Resolution of hypsarrhythmia was defined as an EEG either completely normalized or presenting with only focal epileptiform discharges.[34]

Secondary end points were time to electroclinical remission in days, frequency of relapse after initial response until last follow-up, frequency of long-term remission at last follow-up visit to the initial treatment allocation ("long-term seizure freedom"), adverse effects, and developmental outcomes at last follow-up visit (psychomotor development, adaptive behavior level).

2.2 | Data analysis

2.2.1 | Sample size estimation

Estimates for outcome frequencies with KD and ACTH treatment, based on the existing literature when the study was planned in 2007, were quite vague. For the primary end point (electroclinical remission at 28 days), we assumed a frequency of 50% for ACTH. To detect an absolute difference of 20% between treatment arms (significance level = 0.05, power = 0.80) would have required 182 study patients in total. A noninferiority analysis was not considered for even higher sample size requirements.

Data were analyzed using the IBM Statistical Package for Social Science (SPSS Statistics version 22). The significance level was set at $P \leq 0.05$. For descriptive statistics, absolute numbers and percentages, and median, minimum, and maximum values were used. For comparisons between groups, odds ratios or absolute risk differences (when there were subgroups with 0% or 100% frequency) with 95% confidence intervals, and difference in medians with 95% confidence intervals, with corresponding P values, were calculated as appropriate. Odds ratios were adjusted for imbalances between treatment groups for relevant covariables using logistic regression. Neurological outcome was adjusted for baseline status.

For this intention-to-treat analysis, infants not responding to the initial treatment to which they had been allocated (KD or ACTH) were counted as nonresponders throughout the study. Response to successive treatments was not accounted for in this analysis.

3 | RESULTS

Figure 1 shows the study design. From June 2008 to April 2017, 130 infants with WS were screened at the study center; 29 of them did not fulfil the inclusion criteria. A total of 101 infants were enrolled; 32 were included in the RCT and 69 in the PC.

Reasons for noninclusion in the overall study and reasons for noninclusion in the RCT are listed in the legend of Figure 1. For the PC, reasons for assigning patients to KD or ACTH, respectively, are also listed in the legend of Figure 1.

Table 1 shows patients′ characteristics at baseline, separately for the RCT and the PC and for the two treatment groups. Significant differences between the RCT and PC were observed with respect to disease duration prior to enrollment in the study (ie, trial lag; median = 30 vs 230 days, $P < 0.001$), the percentage of infants with

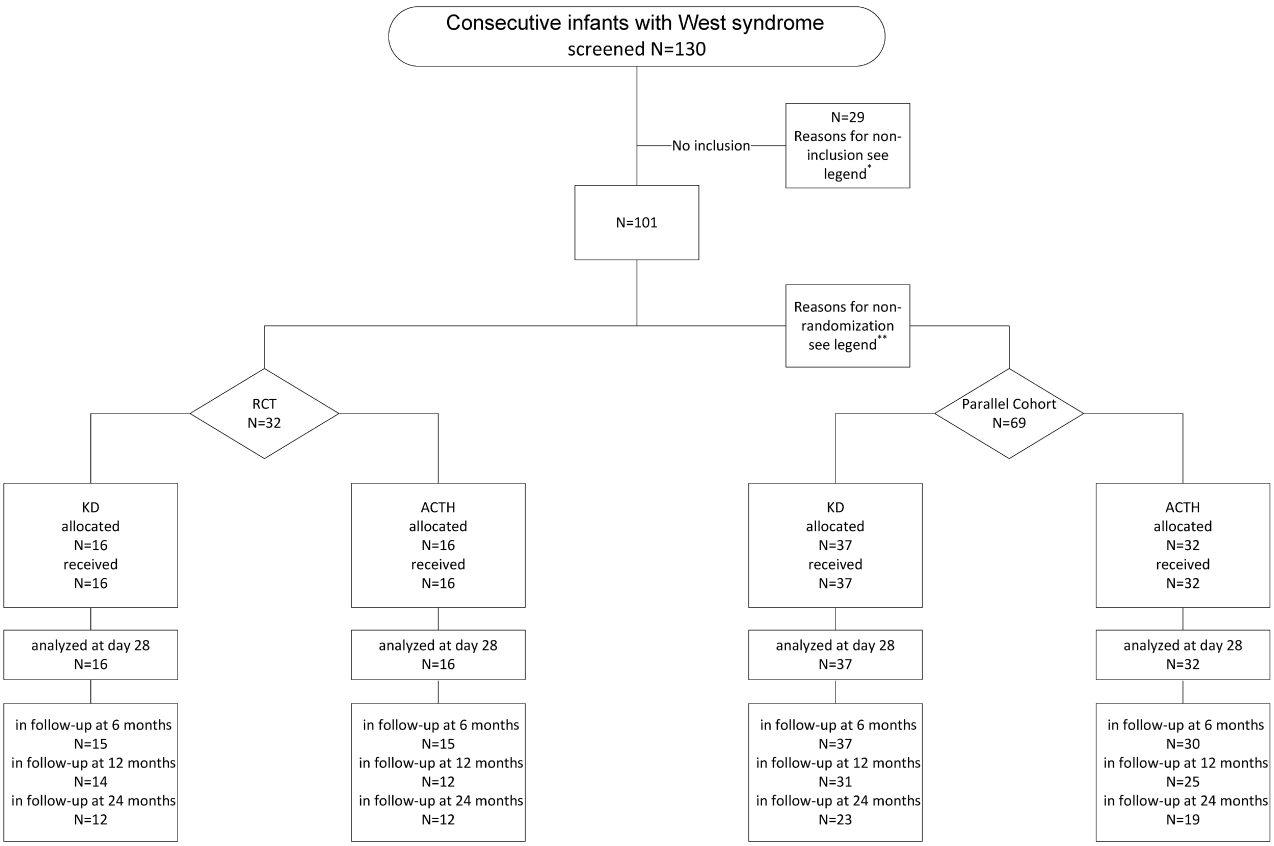

FIGURE 1 *Not enrolled in the study (n = 29). Reasons for noninclusion were: not meeting inclusion criteria (n = 2), tuberous sclerosis treated with vigabatrin and seizure-free (n = 7), treated with antiepileptic drug and seizure-free within the enrollment period (n = 11), and no consent (n = 9). **Concurrent parallel cohort (n = 69). Reasons for noninclusion in the randomized controlled trial (RCT) were as follows: for assigned to adrenocorticotropic hormone (ACTH), time to trial treatment from epilepsy onset > 3 months (n = 10), lack of initial compliance to the ketogenic diet (KD) for food preparation (n = 6), no consent to KD (n = 3), feeding difficulties (n = 11), and KD not available (n = 2); for assigned to KD, evaluation of candidacy for epilepsy surgery and no ACTH possible for not distorting neuroimaging (n = 15), infection (n = 9), no consent to ACTH (n = 4), presumed glucosetransporter-1 deficiency (n = 3), poor general condition and ventilation (n = 2), ACTH not available (n = 2), genetic hypopotassemia (n = 1), and immunosuppression (n = 1)

TABLE 1 Baseline patient characteristics

Cohort	RCT		PC	
Treatment allocation	KD, n = 16	ACTH, n = 16	KD, n = 37	ACTH, n = 32
Female[a]	10 (63%)	6 (38%)	32 (62%)	21 (66%)
Etiology known[a]	7 (44%)	11 (69%)	27 (73%)	21 (66%)
Age at epilepsy onset, mo[b]	4.9 (0-12)	5.0 (0.2-27)	3.0 (0-22)	3.3 (0-15)
Time from epilepsy onset to trial treatment, d[b]	22 (7-212)	44 (0-256)	219 (15-1085)	237 (62-504)
Drug-naive at study inclusion[a]	8 (50%)	7 (44%)	2 (5%)	1 (3%)
Number of AEDs before trial[b]	0.5 (0-3)	1 (0-5)	2 (0-10)	2 (0-7)
Vigabatrin before trial start[a]	4 (25%)	4 (25%)	19 (51%)	24 (75%)
Psychomotor development age-appropriate at baseline[a]	4 (25%)	6 (38%)	7 (19%)	1 (3%)

Data are displayed separately for patients in the RCT and PC, and by treatment groups (KD and ACTH), respectively.
ACTH, adrenocorticotropic hormone; AED, antiepileptic drug; KD, ketogenic diet; PC, parallel cohort; RCT, randomized controlled trial.
[a]n (%).
[b]Median (minimum-maximum).

concomitant VGB use (25% vs 62%, $P < 0.001$), the percentage of infants who were drug-naive (44% vs 0%, $P < 0.001$), the overall number of previously used AEDs (median 1, range 0-5 vs median 2, range 1-10, $P = 0.02$), and the percentage of infants with age-appropriate psychomotor development (31% vs 12%, $P < 0.001$).

In the RCT, there were some imbalances between the two treatment arms with respect to gender and etiology, probably resulting from the small sample size without statistical significance (Table 1). In the PC, there was a significant imbalance observed between the two treatment arms with respect to prior and concomitant VGB use (KD 51% vs ACTH 75%, $P = 0.043$).

During the first 28 days of study treatment, infants were under close follow-up, and therefore no dropouts occurred (Figure 1). Numbers of patients in follow-up at various time points are shown in Figure 1. In the RCT, dropout rates were 19% at 12 months (13% for KD, 25% for ACTH) and 25% at 24 months (25% for KD, 25% for ACTH). In the PC, dropout rates were 19% at 12 months (16% for KD, 22% for ACTH) and 39% at 24 months (38% for KD, 40% for ACTH). In the RCT, the duration of follow-up was median 3.6 years (range = 2.0 months to 8.7 years) for KD and 4.2 years (range = 1.4 months to 8.7 years) for ACTH. In the PC, the duration of follow-up was median 2.5 years (range = 5.4 months to 8.6 years) for KD and median 2.7 years (range = 1.9 months to 10.7 years) for ACTH.

3.1 | Study outcomes

3.1.1 | Comparison between KD and ACTH

Table 2 shows the primary and secondary end points, comparing KD versus ACTH, separately for the RCT and the PC. To adjust for imbalances between treatment groups, all odds ratios were adjusted for gender, time from epilepsy onset to trial treatment start, and concomitant VGB use.

Because the RCT and the PC evidently represented different subsets of the population spectrum, and comparisons between treatments were valid in both cohorts (after adjustments), we also performed an analysis in the combined cohorts for better overall representativeness. Table 3 shows primary and secondary end points comparing treatment groups in the combined cohorts of the RCT and PC, similarly adjusted for gender, time from epilepsy onset to trial treatment start, and concomitant VGB use.

3.1.2 | Primary end point: Electroclinical remission at day 28

The overall proportion of patients achieving electroclinical remission at day 28 was similar between KD and ACTH (RCT, 62% vs 69%; PC, 41% vs 38%; Table 2) as well as in the combined cohort (47% vs 48%, respectively; Table 3).

3.1.3 | Secondary end points

Time to electroclinical remission was similar between KD and ACTH in the RCT and the PC (Table 2) and in the combined cohort (Table 3).

The frequency of relapse, although similar between treatment arms in the RCT, was significantly lower for KD in the PC (KD, 0%; ACTH, 50%; $P < 0.001$; Table 2) and was 16% for KD versus 43% for ACTH in the combined cohort ($P = 0.09$; Table 3). However, dropout rates were higher in the PC, which may have induced some bias. Long-term seizure freedom at last follow-up was 34%

TABLE 2 Primary and secondary end points, comparing KD versus ACTH, separately for RCT and PC

Cohort	RCT				PC			
Treatment allocation	KD, n = 16	ACTH, n = 16	OR (95% CI)[a]	*P*	KD, n = 37	ACTH, n = 32	OR (95% CI)[a]	*P*
Primary end point								
Electroclinical remission at day 28[b]	10/16 [62%]	11/16 [69%]	0.8 (0.2-4)	0.81	15/37 [41%]	12/32 [38%]	0.8 (0.3-2)	0.67
Secondary end points								
Time to electroclinical remission, d[c]	13.5 [4-48]	10 [4-35]	3.5 (−5 to 13)[d]	0.36	15 [1-93]	21 [8-55]	−6.0 (−11 to 3)[d]	0.43
Relapse, until last follow-up[b]	4/10 [40%]	4/11 [36%]	0.8 (0.1-6)	0.86	0/15 [0%]	6/12 [50%]	−50% (−75 to −18)[e]	0.001
Seizure-free, last follow-up[b]	6/16 [38%]	7/16 [44%]	0.9 (0.2-4)	0.92	15/37 [41%]	6/32 [19%]	2.7 (0.9-9)	0.08
Adverse effects[b]	14/16 [88%]	16/16 [100%]	−12% (−36 to 9)[e]	0.13	28/37 [76%]	29/32 [91%]	0.5 (0.1-2)	0.32
Psychomotor development age-appropriate, last follow-up[b]	4/16 [25%]	5/16 [31%]	1.4 (0.1-21)	0.79	8/37 [22%]	2/32 [6%]	3.6 (0.5-28)	0.22
Adaptive level age-appropriate, last follow-up[b]	3/10 [30%]	6/11 [55%]	0.04 (0.01-3.4)	0.16	8/14 [57%]	2/6 [33%]	1.2 (0.2-16)	0.88

ACTH, adrenocorticotropic hormone; CI, confidence interval; KD, ketogenic diet; OR, odds ratio; PC, parallel cohort; RCT, randomized controlled trial.
[a]Adjusted for gender, time from epilepsy onset to trial treatment, and concomitant vigabatrin use; neurological outcome was adjusted for baseline status.
[b]n/N [%].
[c]Median [minimum-maximum].
[d]Difference in medians (95% CI).
[e]Risk difference (95% CI).

overall. Long-term seizure freedom was similar between both treatment groups in the RCT but more than twofold for KD compared with ACTH in the PC ($P = 0.08$; Table 2). In the combined cohort, long-term seizure freedom was similar between both treatments as well.

3.1.4 | Safety

The frequency of adverse effects was not different for KD and for ACTH in the RCT and in the PC (Table 2) as well as in the combined cohort (Table 3). However, medical interventions to treat adverse effects were required significantly less often during KD (30%, intravenous fluids, antibiotics, feeding via nasogastric tube) than during ACTH (94%, antihypertensive medication, intravenous potassium, antibiotics; $P < 0.001$; Table 4). During ACTH treatment, one child died of cardiomyopathy.

3.1.5 | Developmental outcomes

The proportion of patients showing age-appropriate psychomotor development at last follow-up was 23% for KD versus 15% for ACTH ($P = 0.38$; Table 3). Adaptive behavior at last observation did not differ between treatment groups. In the subset of children who were seizure-free at last observation, developmental outcomes were similar for KD and ACTH (age-appropriate psychomotor development in 52% vs 46% and age-appropriate adaptive behavior in 36% vs 29% in the KD group vs the ACTH group, respectively).

3.1.6 | Subgroup analysis of infants without and with VGB pretreatment

In infants without prior VGB treatment, electroclinical remission at day 28 was observed significantly less frequently with KD compared with ACTH (KD, 47%; ACTH, 80%; $P = 0.02$; Table 5). However, relapse rates after initial responses were 26% for KD versus 56% for ACTH ($P = 0.13$). Consequently, long-term seizure freedom at last observation was similar for both treatments. Age-appropriate psychomotor development at last follow-up was 30% for KD versus 15% for ACTH ($P = 0.30$). Adaptive levels were similar for both treatment groups.

In children with prior VGB treatment, electroclinical remission at day 28 was observed in 48% for KD versus 25% for ACTH ($P = 0.09$), and relapse rates were 0% for KD versus 14% for ACTH ($P = 0.28$). Consequently, long-term seizure freedom was significantly more frequent for KD (48% for KD, 21% for ACTH, $P = 0.05$). Psychomotor

TABLE 3 Primary and secondary end points, comparing KD versus ACTH in the combined cohorts

	Combined cohorts			
Treatment allocation	**KD, n = 53**	**ACTH, n = 48**	**OR (95% CI)[a]**	***P***
Primary end point				
Electroclinical remission at day 28[b]	25/53 [47%]	23/48 [48%]	0.8 (0.4- 2)	0.68
Secondary end points				
Time to electroclinical remission, d[c]	14 [1-93]	16 [4-55]	−2 (−8 to 6)[d]	0.87
Relapse, until last follow-up[b]	4/25 [16%]	10/23 [43%]	0.3 (0.1-1)	0.09
Seizure-free, last follow-up[b]	21/53 [40%]	13/48 [27%]	1.8 (0.8-4)	0.18
Adverse effects[b]	42/53 [79%]	45/48 [94%]	0.3 (0.1-1)	0.10
Age-appropriate psychomotor development, last follow-up[b]	12/53 [23%]	7/48 [15%]	1.9 (0.5-8)	0.38
Age-appropriate adaptive level, last follow-up[b]	11/24 [46%]	8/17 [47%]	0.5 (0.2-3)	0.45

ACTH, adrenocorticotropic hormone; CI, confidence interval; KD, ketogenic diet; OR, odds ratio.
[a]Adjusted for gender, time from epilepsy onset to trial treatment, and concomitant vigabatrin use; neurological outcome was adjusted for baseline status.
[b]n/N [%].
[c]Median [minimum-maximum].
[d]Difference in medians (95% CI).

TABLE 4 Frequencies of adverse effects during KD and ACTH treatment

KD adverse effects, n = 53	**n**	**%**	**ACTH adverse effects, n = 48**	**n**	**%**
Adverse effects overall	**42**	**79**	Adverse effects overall	**45**	**94**
Needing acute intervention	16	30	Needing acute intervention	45	94
Triglycerides high	16	30	Hypertonia	41	85
Obstipation	14	26	Potassium (intravenous)	19	40
Ketones > 5 mmol L^{-1}	13	25	Cushing syndrome	17	35
Solid food refusal	9	17	Cardiac hypertrophy	16	33
Liquids (intravenous)	7	13	Leukocytosis	16	33
Infections	6	11	Infections	14	29
Diarrhea	6	11	Hyperexcitability	12	25
High cholesterol	5	9	Acne	12	25
Growth deficit	5	9	Weight gain	11	23
Cholecystolithiasis	5	9	Drowsiness	8	17
Tiredness at start	3	6	Edema	8	17
Hypoglycemia	3	6			
Carnitine deficiency	3	6			
Weight loss	3	6			
Refusal of KD liquids	3	6			
Weight gain	1	2			

ACTH, adrenocorticotropic hormone; KD, ketogenic diet.
Bold values indicate overall adverse effects for KD and ACTH respectively (n and %)

development and adaptive levels were similar for both treatments.

3.1.7 | Comparison between RCT and PC

To assess the comparability between the RCT and PC populations, we assessed the overall frequency of outcomes between the two cohorts. The overall proportion of patients achieving electroclinical remission at day 28 was significantly different between the RCT and the PC (66% for RCT, 39% for PC, $P = 0.013$). Time to electroclinical remission was not different between the RCT and the PC. The proportion of relapse after initial response until last follow-up visit was 22% in the RCT versus 38% in the PC ($P = 0.23$). These differences may (in part) be due to the higher dropout rate in the PC. The percentage of infants with long-term seizure freedom was 41% in the RCT compared to 30% in the PC ($P = 0.31$).

The frequency of adverse effects was 94% in the RCT compared to 83% in the PC ($P = 0.132$).

The percentage of patients showing age-appropriate psychomotor development at last observation was 28% in the RCT and 15% in the PC ($P = 0.10$), consistent with the baseline differences. Adaptive behavior at last observation did not differ between the RCT and the PC.

4 | DISCUSSION

To our best knowledge, this is the first head-to-head comparison of KD versus standard-of-care high-dose ACTH for the treatment of infants with WS.

TABLE 5 Primary and secondary end points, comparing KD versus ACTH, separately for subgroups without and with pretreatment with vigabatrin

Cohort	No pretreatment with vigabatrin				Pretreatment with vigabatrin			
Treatment allocation	KD, n = 30	ACTH, n = 20	OR (95% CI)[a]	*P*	KD, n = 23	ACTH, n = 28	OR (95% CI)[a]	*P*
Primary end point								
Electroclinical remission at day 28[b]	14/30 [47%]	16/20 [80%]	0.2 (0.06-0.8)	0.02	11/23 [48%]	7/28 [25%]	2.8 (0.8-9.0)	0.09
Secondary end points								
Time to electroclinical remission, d[c]	15 [6-36]	13 [4-35]	−2 (−12 to 10)[d]	0.56	13 [1-93]	21 [9-55]	8.0 (−9 to 18)[d]	0.71
Relapse, until last follow-up[b]	4/14 [29%]	9/16 [56%]	0.3 (0.1-1.4)	0.13	0/11 [0%]	1/7 [14%]	−14 (−51 to 14)	0.28
Seizure-free, last follow-up[b]	10/30 [33%]	7/20 [35%]	0.9 (0.3-3.1)	0.90	11/23 [48%]	6/28 [21%]	3.4 (1.0-11.4)	0.05
Adverse effects[b]	22/30 [73%]	19/20 [95%]	0.1 (0.5-12.9)	0.30	20/23 [87%]	26/28 [93%]	0.5 (0.1-3.4)	0.50
Psychomotor development age-appropriate, last follow-up[b]	9/30 [30%]	3/20 [15%]	2.4 (0.5-12.9)	0.30	3/23 [13%]	4/28 [14%]	0.9 (0.2-4.5)	0.90
Adaptive level age-appropriate, last follow-up[b]	8/14 [57%]	5/8 [63%]	0.8 (0.1-4.8)	0.81	3/10 [30%]	3/9 [33%]	0.9 (0.1-5.9)	0.88

ACTH, adrenocorticotropic hormone; CI, confidence interval; KD, ketogenic diet; OR, odds ratio.
[a]Psychomotor development adjusted for baseline status.
[b]n/N [%].
[c]Median [minimum-maximum].
[d]Difference in medians (95% CI).

Results of our single-center prospective PC-RCT trial showed similar overall efficacy for both treatments but better tolerability for KD. In the subgroup analysis of infants without prior VGB treatment, ACTH was more effective in the short term, but due to higher relapse rates for ACTH, there was no difference with respect to long-term remission. In infants pretreated with VGB, KD was at least as effective as ACTH. However, due to the small sample size of the RCT and the study overall, it is underpowered, particularly for a noninferiority analysis; therefore, the results should be interpreted with caution.

Given the lack of controlled data so far, treatment of patients with WS is still empirical.[8] Evidence from controlled trials is therefore urgently needed. The gold standard is an RCT study design using an active comparator if there is an accepted standard of care. However, it is challenging to perform an RCT in this setting of severely ill infants. In our study, only one-third of the patient population could be enrolled in the RCT. Therefore, the patients in the RCT represent a selected subset of the overall population who had (1) an earlier start of study treatment, (2) less use of concomitant AEDs (in particular VGB), and (3) a better neurological status at baseline.

For comparisons between various treatment arms, the RCT provides the highest internal validity. However, because of the small sample size in this study, there were some imbalances between arms with respect to covariables, which we addressed by adjustment. Because of the small sample size, the RCT also had limited power.

An approach to maximizing the representativeness of an RCT is the PC-RCT design where patients who cannot be randomized are included in an observational PC. In the PC, patients are assigned to treatments as per standard of care and clinical circumstances but otherwise followed using the same protocol as in the RCT. Consequently, the data are representative of "real-life" clinical care.[24,25] The patients in our PC represent a complementary subset with a generally poorer previous condition and consequently with (1) longer disease duration prior to study entry, (2) more concomitant use of AEDs, and (3) a worse neurological status at baseline, which is also reflected by the overall worse outcome in the PC. For comparison between study treatment arms, the PC has a higher potential for bias and confounding, which we addressed by adjustment for relevant risk factors.

For a comprehensive analysis, representative of the total population of infants with WS, we finally compared KD and ACTH in a combined analysis of RCT and PC. Again, internal validity was improved by adjustment for relevant covariables. This combined analysis has the highest power due to the larger sample size and has the best external validity. The only potential limitations to the representativeness are that this was a single-center study at a tertiary epilepsy center with a potential selection bias toward severely affected patients.

Overall, the study showed that KD is equally effective compared with high-dose ACTH for the treatment of WS. To formally prove this would require a noninferiority

analysis, which is, however, impossible with the small sample size, even in the combined cohort. Our conclusions of similar effectiveness are, therefore, based on a descriptive comparison between the two treatment arms, which clearly has limited power. Hence, our conclusion must be considered preliminary and would require formal proof by a large-scale, multicenter RCT.

The overall remission rate (34%) observed in our trial is comparable to earlier retrospective studies (up to 50%).[22,35–41] In previous studies, however, evaluation periods were often short (eg, 1-2 months after treatment initiation) and the effects on EEG (ie, hypsarrhythmia) were not reported, although electroclinical remission is thought to be essential for favorable developmental outcomes.[36,42–44] In our study, response was therefore defined as electroclinical remission (seizure freedom plus resolution of hypsarrhythmia in the EEG).

The incidence of electroclinical remission at day 28 in this study (KD, 47%; ACTH, 48%) is comparable to previous studies (ranging from 42% to 60% for steroids[9,45] and from 14% to 65% for KD[19–21,36,40]) and was not different between KD and ACTH in the RCT, PC, or combined cohort. Similarly, time to electroclinical remission did not show significant differences between the two treatment groups. This result is in contrast to the results obtained from a retrospective chart review of infants with new onset WS (later included in Hong et al[22]) comparing 13 patients treated with KD and 20 treated with ACTH. The authors reported equal efficacy, but a significantly shorter time to electroclinical response when using ACTH.[21,22]

The overall relapse rates after initial response for KD (16%) and ACTH (44%) in our trial were comparable to reports from previous studies (KD, 16%-19%; ACTH, 41%-60%).[2,15,46] Although not different between the two treatment arms in the RCT, the frequency of relapses was significantly lower for KD in the PC. However, dropout rates were higher in the PC, which may have induced some selection bias. In the combined cohort, the incidence of relapses remained lower in infants treated with KD. In line with this, the proportion of children who showed seizure freedom in the long term was largely similar between KD and ACTH.

In our study, KD was well tolerated and showed fewer (79% in KD, 94% in ACTH) and less severe adverse effects than ACTH (needing acute intervention: 30% in KD, 94% in ACTH). This result is in line with previous retrospective studies (ranging from 30% to 56% for KD[22] and from 20% to 93% for ACTH[21,45]). Long-term psychomotor development and adaptive behavior were not different between KD and ACTH treatment arms.

Finally, 18% of the infants included in our study were drug-naive. This result is comparable to some other studies (17%).[19–22] However, most previous studies reported on children pretreated with steroids or VGB.[19,22,40] Only one study included newly diagnosed drug-naive patients.[21] To the best of our knowledge, our study is also the first to prospectively report on the initial treatment with KD of infants not pretreated with steroids. In infants not pretreated with VGB, ACTH was significantly more effective in achieving short-term remission at day 28. However, relapse rates were higher for ACTH, and hence long-term seizure freedom was similar for both treatments. In infants pretreated with VGB, KD was more effective than ACTH regarding short-term and long-term seizure freedom. Infants with prior VBG treatment had a longer duration of prior epilepsy, indicating epilepsy that was difficult to treat. As KD is highly effective in pharmacoresistant epilepsy,[26] we suppose that this is also the case in infantile spasms when pretreated with VGB.[35,40]

In conclusion, in infants without prior VGB treatment, ACTH remains the treatment of choice to achieve short-term remission. In infants with prior VGB, KD is at least as effective as ACTH for short-term remission. Overall, KD is at least as effective as ACTH in the long term, but associated with less frequent and less severe adverse effects. Because our study is underpowered, these data have to be interpreted with caution and would need to be confirmed by a large-scale, multicenter RCT.

DISCLOSURE OF CONFLICT OF INTEREST

A.D. received travel reimbursement and speaker honoraria from SHS, Nutricia, and Vitaflo; M.F. received travel reimbursement and speaker honoraria from SHS and Nutricia. P.T.-S. received travel reimbursement from SHS and Nutricia. None was related to this article. The other authors have no conflicts of interest to disclose.

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

ORCID

Anastasia Dressler http://orcid.org/0000-0002-1518-8646

REFERENCES

1. Berg AT, Berkovic SF, Brodie MJ, et al. Revised terminology and concepts for organization of seizures and epilepsies: report of the ILAE Commission on Classification and Terminology, 2005-2009. Epilepsia. 2010;51:676–85.
2. Hancock EC, Osborne JP, Edwards SW. Treatment of infantile spasms. Cochrane Database Syst Rev. 2013;6:CD001770.

3. Mackay MT, Weiss SK, Adams-Webber T, et al. Practice parameter: medical treatment of infantile spasms: report of the American Academy of Neurology and the Child Neurology Society. Neurology. 2004;62:1668–81.
4. 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.
5. Pellock JM, Hrachovy R, Shinnar S, et al. Infantile spasms: a U.S. consensus report. Epilepsia. 2010;51:2175–89.
6. 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.
7. Knupp KG, Leister E, Coryell J, et al. Response to second treatment after initial failed treatment in a multicenter prospective infantile spasms cohort. Epilepsia. 2016;57:1834–42.
8. Wilmshurst JM, Gaillard WD, Vinayan KP, et al. Summary of recommendations for the management of infantile seizures: task force report for the ILAE Commission of Pediatrics. Epilepsia. 2015;56:1185–97.
9. Hrachovy RA, Frost JD Jr, Kellaway P, et al. Double-blind study of ACTH vs prednisone therapy in infantile spasms. J Pediatr. 1983;103:641–5.
10. Snead OC III, Benton JW, Myers GJ. ACTH and prednisone in childhood seizure disorders. Neurology. 1983;33:966–70.
11. 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.
12. Baram TZ, Mitchell WG, Tournay A, et al. High-dose corticotropin (ACTH) versus prednisone for infantile spasms: a prospective, randomized, blinded study. Pediatrics. 1996;97:375–9.
13. Lux AL, Osborne JP. A proposal for case definitions and outcome measures in studies of infantile spasms and West syndrome: consensus statement of the West Delphi group. Epilepsia. 2004;45:1416–28.
14. Yamada K, Toribe Y, Kimizu T, et al. Predictive value of EEG findings at control of epileptic spasms for seizure relapse in patients with West syndrome. Seizure. 2014;23:703–7.
15. Hayashi Y, Yoshinaga H, Akiyama T, et al. Predictive factors for relapse of epileptic spasms after adrenocorticotropic hormone therapy in West syndrome. Brain Dev. 2016;38:32–9.
16. Curatolo P, Verdecchia M, Bombardieri R. Vigabatrin for tuberous sclerosis complex. Brain Dev. 2001;23:649–53.
17. Riikonen R, Rener-Primec Z, Carmant L, et al. Does vigabatrin treatment for infantile spasms cause visual field defects? An international multicentre study. Dev Med Child Neurol. 2015;57:60–7.
18. 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.
19. Eun SH, Kang HC, Kim DW, et al. Ketogenic diet for treatment of infantile spasms. Brain Dev. 2006;28:566–71.
20. Kossoff EH, Pyzik PL, McGrogan JR, et al. Efficacy of the ketogenic diet for infantile spasms. Pediatrics. 2002;109:780–3.
21. Kossoff EH, Hedderick EF, Turner Z, et al. A case-control evaluation of the ketogenic diet versus ACTH for new-onset infantile spasms. Epilepsia. 2008;49:1504–9.
22. Hong AM, Turner Z, Hamdy RF, et al. Infantile spasms treated with the ketogenic diet: prospective single-center experience in 104 consecutive infants. Epilepsia. 2010;51:1403–7.
23. Kossoff EH, Zupec-Kania BA, Amark PE, et al. Optimal clinical management of children receiving the ketogenic diet: recommendations of the International Ketogenic Diet Study Group. Epilepsia. 2009;50:304–17.
24. Goldenberg NA, Tripputi M, Crowther M, et al. The "parallel-cohort RCT": novel design aspects and application in the Kids-DOTT trial of pediatric venous thromboembolism. Contemp Clin Trials. 2010;31:131–3.
25. Hanslik A, Kitzmuller E, Tran US, et al. Monitoring unfractionated heparin in children: a parallel-cohort randomized controlled trial comparing 2 dose protocols. Blood. 2015;126:2091–7.
26. Dressler A, Stocklin B, Reithofer E, et al. Long-term outcome and tolerability of the ketogenic diet in drug-resistant childhood epilepsy—the Austrian experience. Seizure. 2010;19:404–8.
27. Deutsche Gesellschaft für Ernährung (DGE), Österreichische Gesellschaft für Ernährung (ÖGE), Schweizerische Gesellschaft für Ernährung (SGE). Referenzwerte für die Nährstoffzufuhr. Bonn, Germany: Neuer Umschau Buchverlag; 2015.
28. Gibbs FA, Gibbs EL. *Atlas of electroencephalography*. Reading, MA: Addison-Wesley; 1952.
29. Hrachovy RA, Frost JD Jr. Infantile epileptic encephalopathy with hypsarrhythmia (infantile spasms/West syndrome). J Clin Neurophysiol. 2003;20:408–25.
30. Touwen BC. Neurological examination of the young child. Ned Tijdschr Geneeskd. 1968;112:1112.
31. Hadders-Algra M, Heineman KR, Bos AF, et al. The assessment of minor neurological dysfunction in infancy using the Touwen Infant Neurological Examination: strengths and limitations. Dev Med Child Neurol. 2010;52:87–92.
32. Hempel MS. Neurological development during toddling age in normal children and children at risk of developmental disorders. Early Hum Dev. 1993;34:47–57.
33. Sparrow SS, Cicchetti DV, Balla DA. *Vineland adaptive behavior scales survey form manual.* 2nd ed. Circle Pines, MN: American Guidance Service; 2005.
34. Jozwiak S, Kotulska K, Domanska-Pakiela D, et al. Antiepileptic treatment before the onset of seizures reduces epilepsy severity and risk of mental retardation in infants with tuberous sclerosis complex. Eur J Paediatr Neurol. 2011;15:424–31.
35. Kayyali HR, Gustafson M, Myers T, et al. Ketogenic diet efficacy in the treatment of intractable epileptic spasms. Pediatr Neurol. 2014;50:224–7.
36. Dressler A, Trimmel-Schwahofer P, Reithofer E, et al. The ketogenic diet in infants—advantages of early use. Epilepsy Res. 2015;116:53–8.
37. Kang JW, Rhie SK, Yu R, et al. Seizure outcome of infantile spasms with focal cortical dysplasia. Brain Dev. 2013;35:816–20.
38. Hirano Y, Oguni H, Shiota M, et al. Ketogenic diet therapy can improve ACTH-resistant West syndrome in Japan. Brain Dev. 2015;37:18–22.
39. Numis AL, Yellen MB, Chu-Shore CJ, et al. The relationship of ketosis and growth to the efficacy of the ketogenic diet in infantile spasms. Epilepsy Res. 2011;96:172–5.

40. Pires ME, Ilea A, Bourel E, et al. Ketogenic diet for infantile spasms refractory to first-line treatments: an open prospective study. Epilepsy Res. 2013;105:189–94.
41. Lee J, Lee JH, Yu HJ, et al. Prognostic factors of infantile spasms: role of treatment options including a ketogenic diet. Brain Dev. 2013;35:821–6.
42. Darke K, Edwards SW, Hancock E, et al. Developmental and epilepsy outcomes at age 4 years in the UKISS trial comparing hormonal treatments to vigabatrin for infantile spasms: a multicentre randomised trial. Arch Dis Child. 2010;95:382–6.
43. O'Callaghan FJ, Lux AL, Darke K, et al. The effect of lead time to treatment and of age of onset on developmental outcome at 4 years in infantile spasms: evidence from the United Kingdom Infantile Spasms Study. Epilepsia. 2011;52:1359–64.
44. Payne ET, Zhao XY, Frndova H, et al. Seizure burden is independently associated with short term outcome in critically ill children. Brain. 2014;137:1429–38.
45. Shu XM, Li J, Zhang GP, et al. A comparative study of conventional dose and low dose adrenocorticotrophic hormone therapy for West syndrome. Zhongguo Dang Dai Er Ke Za Zhi. 2009;11:445–8.
46. Kang HC, Lee YJ, Lee JS, et al. Comparison of short- versus long-term ketogenic diet for intractable infantile spasms. Epilepsia. 2011;52:781–7.

How to cite this article: Dressler A, Benninger F, Trimmel-Schwahofer P, et al. Efficacy and tolerability of the ketogenic diet versus high-dose adrenocorticotropic hormone for infantile spasms: A single-center parallel-cohort randomized controlled trial. *Epilepsia*. 2019;60:441–451. https://doi.org/10.1111/epi.14679