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Fasting versus Gradual Initiation of the Ketogenic Diet: A Prospective, Randomized Clinical Trial of Efficacy

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Summary: *Purpose:* The ketogenic diet (KD) is a 90% fat diet that is an effective treatment for intractable epilepsy. Rapid initiation of the KD requires hospital admission because of the complexity of the protocol and frequent mild and moderate adverse events. The purpose of the study was to compare the efficacy of a gradual KD initiation with the standard KD initiation preceded by a 24- to 48-h fast.

Methods: Children ages 1 to 14 years with intractable epilepsy were randomized to a fasting initiation (FAST-KD) or gradual initiation (GRAD-KD). Baseline seizure activity was recorded daily for 28 days before admission and continued for the 3-month duration of the study. Effectiveness was measured in two ways: (a) the proportion of subjects with >50% reduction in target seizure type from baseline to 3-month evaluation, and (b) percentage reduction in the frequency of the target seizure type from baseline to 3-month evaluation. Blood glucose was assessed q4 to 6h, and weights, electrolytes, hydration status, vomiting, acid balance, need for interventions (citric acid and sodium citrates (Bicitra) and IV fluids) were assessed daily. Fisher's exact tests were used to examine the association between protocol and occurrence of adverse events, and longitudinal mixed-effects models were used to look for trends in tolerability data over time.

Results: Forty-eight subjects, 24 in each arm, were randomized. In the FAST-KD protocol, 58% of the children had >50% reduction in the target seizure type at 3 months, and 21% were seizure free. In the GRAD-KD protocol, 67% had a >50% reduction at 3 months, and 21% were seizure free. The two protocols were equivalent in efficacy ($p = 0.033$). At 3 months, the FAST-KD median percentage seizure reduction rate was 78% (ranging from 100% reduction to 73% increase in seizures per week) and was 94% (ranging from 100% reduction to 161% increase in seizures per week) for the GRAD-KD protocol. By using a logarithmic transformed percentage reduction rate and an equivalence limit difference of 20%, the efficacy of the two protocols was equivalent ($p = 0.0002$). Children in the GRAD protocol lost significantly less weight ($p = 0.006$), and had fewer and less-severe episodes of hypoglycemia ($p < 0.001$), fewer treatments for acidosis (citric acid and sodium citrates) ($p < 0.04$) and dehydration (IV fluids) ($p < 0.04$), but no difference in vomiting was noted.

Conclusions: These data suggest that in children with intractable epilepsy, a gradual initiation results in fewer adverse events and is tolerated better overall while maintaining the efficacy of the KD. **Key Words:** Ketogenic diet—Fasting—Ketones—Children—Intractable epilepsy.

About 2.5 million people have epilepsy in the United States (1). The incidence of epilepsy in children (age 0 to 14 years) ranges from 42 to 82 per 100,000 (2,3). Seventy percent of patients attain seizure control, with the remaining refractory to standard medical treatments (4). The ketogenic diet (KD) is an effective, high-fat, low-carbohydrate and protein diet for treatment of medically refractory epilepsy. In general, 50–70% of subjects with intractable epilepsy have >50% reduction in the seizures, and ~15–20% become seizure free (5–16). Implementation and monitoring of the KD is cumbersome, time consuming, associated with adverse events, and requires both an interdisciplinary team and highly committed patients and care providers (17–19). Thus the KD is generally restricted to larger medical centers and as a result is not available to all patients who might benefit (20).

Implementation of the KD has changed little since 1921 (20). Most centers use a version of the classic KD approach with a 4:1 fat ratio, 90% fat calories, and 10% protein and carbohydrate, which results in a highly restricted diet. The KD is initiated during a hospitalization with a 24- to 48-h fast. Once a high level of ketosis is achieved, the 90% fat calorie meal plan is introduced by incremental increases in daily food intake. Hypoglycemia, acidosis, nausea, vomiting, dehydration, anorexia, and lethargy are common adverse events. A nonfasting gradual KD initiation that will result in easier implementation, shorter hospital stay,

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and reduced medical and family costs would have clinical and economic advantages (21). Some KD centers are now beginning the KD by using a gradual protocol (22,23). No randomized clinical trial has been conducted to evaluate the efficacy of the gradual protocol. The aim of this study was to compare the efficacy of a fasting and gradual initiation KD protocol in terms of seizure reduction in a randomized prospective clinical trial in children with intractable epilepsy.

METHODS

Subjects and protocol

Prepubertal children ages 1 to 14 years, having one or more seizures per 28 days, and for whom at least three appropriate antiepileptic medications (AEDs) failed were eligible. Eligibility required a normal range for serum lactate, amino acids, pyruvate, acylcarnitine esters, and urine organic acids. Steroid medication was discontinued $\geq$3 months before the admission. Children with metabolic disorders, genetic disorders known to affect growth, or known/suspected degenerative neurologic disorders were excluded. Before admission, all families attended a 4-h standardized KD education class.

Beginning 28 days before initiating the KD, caregivers kept a daily seizure activity log, recording seizure type and frequency. The daily seizure activity log was continued for the 3-month duration of the study. An average seizure count of seizures per week was calculated at each monthly follow-up visit by using the prior 28-day data. For very frequent seizure types (absence and myoclonic seizures), seizure frequency was measured over 30-min epochs at two separate times during the day, one epoch known to have increased seizure frequency and one epoch known to have decreased seizure frequency for that individual. This information was used to average the weekly seizure frequency. For children with multiple types of seizures, a target type (simple partial, complex partial, secondarily generalized, myoclonic, tonic, tonic–clonic, atonic, or absence seizure) was identified by the parents, confirmed by the neurologist with help of video-EEG, and used for the efficacy evaluation. Demographic information and information about prior and current antiepileptic drugs (AEDs) was collected. All subjects were examined by one investigator (C.B.) who determined pubertal status according to Tanner's criteria (24).

Children were randomized to begin the KD protocol (Table 1) by using either the fasting KD initiation (FAST-KD) or the nonfasting, gradual KD initiation protocol (GRAD-KD). Subjects were stratified by age (age 1 to 2, and 2 to 14 years) to ensure equal allocation to the two protocols in the two age groups, which may have different responses to the protocols. Randomization was done in permuted blocks of random size of two or four, to prevent

TABLE 1. *Initiation protocols FAST-KD versus GRAD-KD*

		Day 1	Day 2	Day 3	Day 4	Day 5	Day 6
Ratio of fat: protein+ CHO, g	FAST-KD	Regular Dinner	0	4:1	4:1	4:1	4:1
	GRAD-KD	Regular Dinner	1:1	2:1	3:1	4:1	4:1
% of calories in meal	FAST-KD	100%	0%	33%	67%	100%	Discharge
	GRAD-KD	100%	100%	100%	100%	100%	Discharge
Whole blood glucose		Q 4 hrs	Q 4 hrs	B, L, D,HS 2 AM	B, L, D 2 AM	B, L, D, 2 AM	B
Serum electrolytes, BUN, creatinine		7 AM	7 AM	7 AM	7 AM	7 AM	7 AM
Urine ketones		Every void	Every void	Every void	Every void	Every void	Every void
Serum βHB		7 AM & 7 PM	7 AM & 7 PM	7 AM & 7 PM	7 AM & 7 PM	7 AM & 7 PM	7 AM & 7 PM
Whole blood, βHB		With blood glucose	With blood glucose	With blood glucose	With blood glucose	With blood glucose	With blood glucose
Weight, kg		Daily before B	Daily before B	Daily before B	Daily before B	Daily before B	Daily before B
Total fluid Intake/Output		Q 8 hrs	Q 8 hrs	Q 8 hrs	Q 8 hrs	Q 8 hrs	Q 8 hrs

B, breakfast; L, lunch; D, dinner; Q 4 hr, every 4 hours; HS, before bedtime; % calories in meal, percent caloric intake provided; Discharge, discharged from hospital after breakfast.

any ability to guess the next assignment, because this was a single-institution study.

Subjects were admitted for the 6-day protocol. The energy-intake prescription was established by using 75–90% of RDA calories and adjusted for ideal body weight, height, and the child's physical-activity level. Nonambulatory subjects received 75% and normally physically active children received 90% of RDA calories (25). The KD was provided as three meals, with children younger than 4 years provided with one snack. Fluid intake was based on standard pediatric guidelines. The protocol was approved by The Children's Hospital of Philadelphia Institutional Review Board; informed consent was obtained from the parents; and assent was given by children cognitively able to complete the process.

Fasting and gradual KD introduction

The FAST-KD protocol began with a fast lasting $\leq$48 h. The fast was terminated when urine ketones (Urine Chemstrip UGK; Boehringer Mannheim, Indianapolis, IN, U.S.A.) were >80 mg/dl, the serum β-hydroxybutyrate (βHB) levels (Precision x-tra; Abbott Laboratories, Abbott Park, IL, U.S.A.) > 1.5 m*M*, whole blood glucose <45 mg/dl, or the subject completed the maximum 48-h fast. As shown in Table 1, the 4:1 ratio (fat:carbohydrate + protein) was then introduced, as three meals with a total of 1/3 the daily kcal on day 1, three meals with a total of 2/3 daily kcal on day 2, and finally three meals meeting the full calorie goal on day 3 after the fast.

The GRAD-KD protocol began on day 2 with a 1:1 ratio (fat:carbohydrate + protein) by weight, full-calorie-goal meals, and then daily advanced to a 2:1, 3:1, and finally to a 4:1 ratio (Table 1). The child remained on each fat/nonfat ratio for 1 day, and the 4:1 ratio meals were provided $\geq$2 days before discharge. After discharge, daily urinary ketones and fasting whole blood glucose were monitored before breakfast until the first follow-up visit.

Whole blood glucose and βHB were measured every 4 h while the child fasted (FAST-KD) or while on the 1:1 and 2:1 ratio (GRAD-KD). Once the diet was well tolerated, the frequency of glucose and βHB monitoring was reduced. During the 1/3 meal FAST-KD or 3:1 ratio GRAD-KD, whole blood glucose and βHB were measured before each meal, at bedtime, and at 0200 AM. During the 2/3 and full-meal period FAST-KD or while the child was on the 4:1 ratio GRAD-KD, whole blood glucose and βHB were measured before each meal and at 0200 AM. For all subjects, urine ketones (acetoacetic acid) were measured with each void and recorded as trace (5–14 mg/dl), small (15–39 mg/dl), moderate (40–79 mg/dl), and large (80–160 mg/dl) at the end of each 8-h shift. Serum βHB and acetoacetate levels were measured every 12 h by using spectroscopy (Sigma, St Louis, MO, and Roche Diagnostics, Indianapolis, IN, U.S.A.) and serum electrolytes were measured daily. Liquid and food intake and all output (urine, stool, vomitus) were recorded every 8 h. Fasting anthropometric measurements were obtained by the research staff on days 2 and 5.

Hypoglycemia was treated for symptomatic subjects (tremulous, tachycardic, weak, and diaphoretic) or when the serum or whole blood glucose was <45 mg/dl. Subjects who reported nausea or experienced vomiting were treated with H_2 blockers or by slowing the rate of KD-ratio advance. When vomiting persisted and subjects were at risk of dehydration, they were intravenously rehydrated with normal saline. Persistent anorexia associated with very high ketones was treated by allowing more carbohydrates in the diet. Acidosis was treated with an oral alkalinizing agent [citric acid and sodium citrates (Bicitra)] and, when severe or nonresponsive to oral treatment, medications such as topiramate and zonisamide that may worsen acidosis were discontinued. After discharge, follow-up visits were scheduled at 0.5, 1, 2, and 3 months. In general, AEDs were maintained and adjusted when required to maintain therapeutic drug levels during the study. At 3 months, children with <50% reduction in seizure frequency were considered nonresponders (26) and were carefully monitored during a gradual discontinuation of the KD over a month.

Statistical analysis

Baseline characteristics were compared between the two protocol groups to assess the comparability of the two groups. Fisher's exact test was used for dichotomous variables, and the *t* test for independent samples, or Wilcoxon matched-pairs rank-sum tests were used as appropriate for continuous variables based on skewness.

All outcome analyses were based on an intention-to-treat approach (i.e., all patients randomized were included in the analyses, wherever possible). Primary efficacy was defined based on seizure reduction after 3 months. Two outcome variables were defined: one was a dichotomous variable in which a responder was a subject whose seizures were reduced by >50%, and the other was the actual reduction in number of seizures. Because the intent of the study was to show equivalence between the two approaches, the hypothesis tested was that the outcome rates on the two protocols were no further apart than a prespecified difference (27). The difference specified for the percentage of responders was 20% (i.e., any difference in rate of response that cannot be shown to be statistically significantly larger than 20% would lead to the conclusion that the protocols are equivalent). Similarly, the equivalence limit for difference in seizure rates was set to be 20% [i.e., if the difference in average reduction in seizures (after a suitable transformation to achieve normality) is not significantly larger than 20%, the protocols will be considered equivalent].

Whole blood and serum βHB data and urine acetoacetic acid data were collected repeatedly on days 2 through 6

of the hospitalization. Whole blood βHB was measured 6 times on each of the 5 days, whereas serum βHB and urine acetoacetic acid were collected twice on each of the 5 days. Blood glucose was measured 6 times on each of the five days as well. Longitudinal mixed-effects models were used to examine the effects of Protocol, Time, and Protocol × Time interaction for each of these four outcome measurements separately. An examination of graphic displays of the various outcome variables across time indicated the potential presence of curvature in outcome across time, especially for the FAST-KD group. A time square or quadratic time component, which will indicate the extent of curvature in outcome across time (e.g., how it is leveling off or changing directions with time), was therefore added to the models. Based on these models, parameter estimates (i.e., coefficients for intercept, linear time, and quadratic time, along with their associated standard errors and p values) were produced for each of the protocols, for each outcome. The SAS proc MIXED procedure (28,29) was used.

To assess similarity between the two methods, whole blood and serum βHB measurements were compared with each other. Mean levels as measured by the two methods at 6:00 AM (time point at which both measurements were taken) were compared for each day separately by using paired *t* tests and Wilcoxon matched-pairs signed-ranks tests. In addition, Cohen's kappa was used to assess the extent of agreement between the two methods. Whole blood and serum βHB were measured repeatedly across 5 days, and the time points (hours) at which each subject reached ketosis (βHB >1.5 m*M*), as measured by both whole blood and serum βHB, were recorded. Independent samples *t* tests were used to compare the two protocols on time-point of earliest ketosis, as measured by both whole blood and serum βHB.

Fisher's exact tests were used to examine the association between protocol and proportion of children with ketosis, as indicated by whole blood βHB and as indicated by serum βHB within each day. A subject was considered to be ketotic for a particular day when the average βHB was >1.5 m*M*.

Time of the first occurrence of large urine ketones (80–160 mg/dl acetoacetic acid) was recorded for each subject. Censored cases (i.e., cases in which the subject did not experience large urine ketones by the time of discharge on day 6) were noted. The data were examined to determine which group experienced large urine ketones at an earlier time. Mean times of occurrence were calculated for each protocol, both with censored cases omitted from the analysis and also including censored cases and assigning them the maximum time point plus one. Mann–Whitney tests were used to compare protocols on time to first occurrence of large urine ketosis. In addition, Kaplan–Meier and Cox regression models were used to compare the two protocols on time to occurrence of large urine ketones. Paired *t* tests and Wilcoxon matched-pairs signed-ranks tests were used to compare time to ketosis as indicated by whole blood and by large urine ketones.

Weight and electrolyte data (Na, K, CL, HCO_3, BUN, and Cr) were measured once on each of 5 days of hospitalization. For weight, a difference score was calculated by subtracting weight at day 6 from weight at day 2, and a Mann–Whitney test was used to examine the difference between protocols on this weight-difference score. Descriptive statistics were examined for electrolyte data, and for the one electrolyte with values outside the normal range [i.e., bicarbonate (HCO_3)], a longitudinal mixed-effects model was applied. Total fluid intake and output data were measured once on each of 4 days (i.e., on days 2 through 5), and longitudinal mixed-effects models were examined.

Fisher's exact tests were used to examine the association between protocol and proportion of children with glucose levels of <45 and <60, at any time (based on the maximum possible 30 measurements) and also based on the average glucose level on any given day. Fisher's exact tests were used to examine the association between protocol and proportion of children requiring interventions/treatments (potassium citrate and citric acid to correct acidosis or IV fluids for dehydration) and experiencing vomiting.

RESULTS

The clinical characteristics of these children with intractable epilepsy are shown in Table 2. Means and standard deviations are presented for normally distributed continuous variables and medians and ranges for those variables found to be not normally distributed. Forty-eight subjects, 34 boys/14 girls, mean age 5.3 ± 2.7 years, were enrolled, and 24 were randomized to each treatment arm. These children had refractory seizures, as was evident by almost eight AEDs and concurrent treatment with three AEDs having failed at the time the KD was initiated. The percentage of subjects with partial or generalized seizure types was similar between protocol groups. No significant differences were found in the demographics and medical history of the two protocol groups. Seizure frequency varied between subjects but not significantly between the two protocol groups. In general, nonresponders (defined as $<50\%$ reduction in seizures) were weaned from the KD as per protocol. Two nonresponders (one from each protocol) were maintained on the KD by their clinician because of improved alertness.

Efficacy

Table 3 displays the proportion of subjects with $>50\%$ and $>90\%$ reduction in the target seizure frequency and with no seizure activity at each protocol evaluation. Subjects with missing seizure data (four in FAST-KD and two in GRAD-KD arms) were considered to be nonresponders

TABLE 2. *Clinical characteristics of children before KD*

Mean ± SD, Median (range) or %	All	FAST-KD	GRAD-KD
Number	48	24	24
Age, yrs	5.3 ± 2.7	5.8 ± 2.7	4.8 ± 2.7
Female/Male,%	29/71	29/71	29/71
Abnormal MRI,%	56	50	63
AED failed prior to KD	7.7 ± 2.6	7.6 ± 2.7	7.8 ± 2.6
AED used when KD initiated	2.3 ± 0.8	2.3 ± 0.8	2.4 ± 0.7
Baseline seizures/week rate	9.6 [0.2, 5206]	10.9 [0.5, 5206]	6.8 [0.2, 4116]
Age at first seizure, yr	0.9 [0, 10.0]	2.0 [0, 6.4]	0.8 [0, 10.0]
Duration seizures prior to KD, yr	2.5 [0.5, 8.7]	2.7 [0.5, 8.7]	2.5 [0.8, 7.5]
Target Seizure Type,%			
Generalized seizures,%	48	50	46
Absence	6	8	4
Atypical absence	6	4	8
Myoclonic	4	4	4
Atonic	4	8	0
Tonic/Clonic/Tonic–clonic	19	21	17
Spasms	8	4	13
Partial seizures,%	52	50	54
Simple partial	6	8	4
Complex partial	13	13	13
Secondarily generalized	33	29	38
Status Epilepticus,%	38	29	46
Epilepsy Surgery Evaluation	56	63	50
Mental Retardation,%	71	71	71
Formal IQ testing,%	21	21	21
Cerebral Palsy,%	42	38	46
Walking,%	65	71	58
Vagus Nerve Stimulator,%	6	4	8

Note: Mean ± SD presented for normally distributed continuous variables; Median [range] presented for non-normally distributed variables; p = N/S for all parameters above.

(26). Both approaches to KD initiation were effective in reducing seizure frequency. Most of the clinical impact occurred during the first month, with additional reduction in seizure frequency by the second and third months in some subjects. At the 3-month assessment, 58% of the subjects in the FAST-KD group had a >50% reduction in the target seizure, and 21% were seizure free, and in the GRAD-KD group, 67% had a >50% reduction in the target seizure and 21% were seizure free. The equivalence evaluation of the proportions of subjects with >50% reduction at 3 months showed that the two protocols were equivalent ($p = 0.03$). At 3 months, the median percentage seizure-reduction rate for the FAST-KD protocol was 78% (ranging from 100% reduction to 73% increase in seizures per week) and was 93% (ranging from 100% reduction to 161% increase in seizures per week) for the GRAD-KD protocol. The equivalence evaluation of the logarithmic transformed percentage reduction rate indicated that the two protocols were equivalent ($p = 0.0002$).

Developing Ketosis

Overall mean whole blood βHB [average of six measurements within each day) >1.5 m*M* (definition of a fasting state (30)] occurred on days 2 through 6 for the FAST-KD group and on days 4 through 6 for the GRAD-KD group. Overall mean serum βHB (average of two measurements in each day) was >1.5 m*M* on days 2 through 6 for both protocols. An examination of descriptive statistics indicates that overall mean whole blood βHB tended to be greater in the FAST-KD group on days 2 through 6, and overall mean serum βHB tended to be greater in the FAST-KD group on days 2 through 5. Change in whole blood βHB across days of hospitalization for each of the two protocols can be seen in the box plot in Fig. 1.

TABLE 3. *Proportion of subjects with >50%, >90%, or 100% reduction in seizure frequency at 1, 2 and 3 months KD treatment*

Outcome seizure reduction	Total (N = 48) %	FAST-KD (n = 24) %	GRAD-KD (n = 24) %
>50% reduction in seizure			
1 mo	52	58	46
2 mo	50	58	42
3 mo	63	58	67
>90% reduction in seizure			
1 mo	35	42	29
2 mo	31	29	33
3 mo	38	29	46
Seizure free			
1 mo	21	21	21
2 mo	17	13	21
3 mo	21	21	21

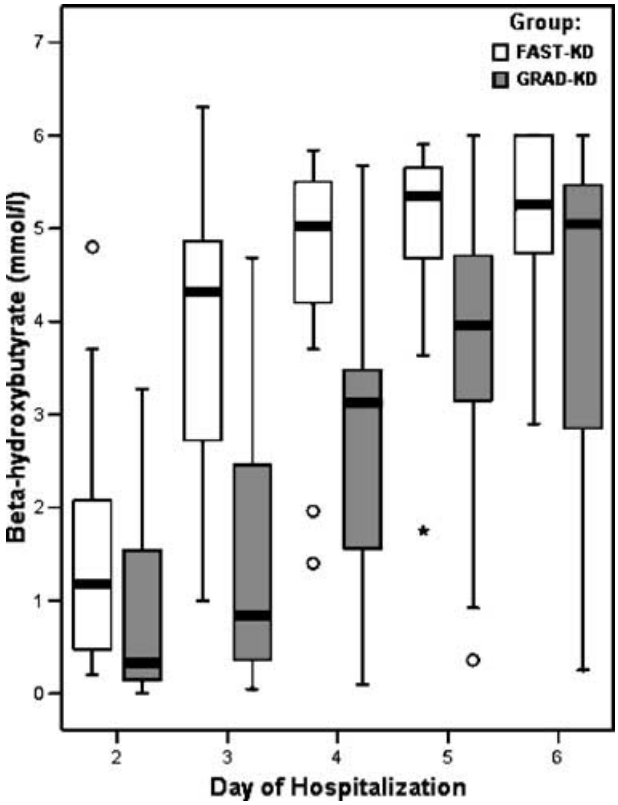

FIG. 1. Boxplot of whole blood ßHB (mmol/l) (averaged across 6 time points within each day) by FAST-KD and GRAD-KD protocol, Days 2 through 6. The box represents the interquartile range which contains the 50% of values. The whiskers are lines that extend from the box to the highest and lowest values, excluding outliers. The line across the box indicates the median. Outliers (o) are defined as cases with values between 1.5 and 3 box lengths from either end of the box. Extreme outliers (*) are cases with values greater than 3 box lengths from either end of the box.

Results from the longitudinal mixed-effects models indicate no difference between protocols in whole blood βHB ($p = 0.25$), a significant difference between protocols in serum βHB ($p = 0.008$), and a marginal difference between protocols in urine acetoacetic acid ($p = 0.065$). Whole blood βHB, serum βHB, and urine acetoacetic acid all had highly significant effects for Time (all p values <0.0001), Time squared (p values ranging from 0.018 to <0.0001), Protocol $\times$ Time interaction (all p values <0.0001), and Protocol $\times$ Time $\times$ Time interaction (all p values <0.0001). Parameter estimates (i.e., coefficients for intercept, linear time, and quadratic time, along with their associated standard errors and p values) for each of the two protocols are displayed in Table 4. For all three of these variables (whole blood βHB, serum βHB, and urine acetoacetic acid), the FAST-KD group has a stronger and statistically significant linear increase, and a significant quadratic time trend (i.e., a leveling off with time). In the GRAD-KD group, the coefficients for linear time are significant for whole blood and serum βHB, but not for urine acetoacetic acid. None of the coefficients for quadratic time effect is significant for the GRAD-KD group.

Comparing whole blood and serum βHB

The whole blood and serum βHB measurements were compared with each other. Mean levels as measured by the two methods at 6 AM were compared for each day separately by using paired *t* tests and Wilcoxon matched-pairs signed-ranks tests. Fasting levels of βHB (>1.5 m*M*) for both methods occurred on days 3 through 6, and for these days, no significant differences were found between the group means. In addition, Cohen's kappa indicated moderate to good agreement between the two methods.

Independent samples *t* tests were used to compare the two protocols on time-point of earliest ketosis (βHB >1.5 m*M*), as measured by both whole blood and serum βHB, and results indicate that the FAST-KD group achieved ketosis earlier. On average, the FAST-KD group reached ketosis $\sim$18 h earlier as measured by whole blood βHB ($p = 0.006$), and $\sim$20 h earlier as measured by serum βHB ($p = 0.002$).

Fisher's exact tests examined the association between protocol and proportion of patients with ketosis (whole blood βHB >1.5 m*M*) within each day. If the child's average βHB for any given day was >1.5 m*M*, then the subject was considered to be ketotic for that day. The FAST-KD protocol tended to have a greater proportion of subjects with ketosis than did the GRAD-KD protocol on all the days ($p = 0.18$, <0.0005, 0.093, 0.23, and 0.46, for days 2 through 6, respectively), but this association reached statistical significance only on day 3. When ketosis was determined based on average serum βHB >1.5 m*M*, the FAST-KD protocol tended to have a greater proportion of subjects with ketosis than did the GRAD-KD protocol on days 2 through 4 ($p = 0.16$, 0.002, and 0.046, for days 2 through 4, respectively), but this association reached statistical significance only on days 3 and 4. By discharge day 6, all subjects had reached ketosis based on average serum βHB >1.5 m*M*.

Urine ketones

Time of the first occurrence of large urine ketones (80–160 mg/dl acetoacetic acid) was recorded for each subject. There were 10 censored cases (i.e., two of the FAST-KD subjects and eight of the GRAD-KD subjects that had not experienced large urine ketones by time of discharge on day 6). An examination of the data indicated that the FAST-KD group was experiencing large urine ketones at an earlier time that the GRAD-KD group. With censored cases omitted, large urine ketones first occurred on average during the first of three 8-h shifts of day 3 in the FAST-KD protocol, whereas children on the GRAD-KD protocol developed large urine ketones $\sim$18 h later. Including all subjects, and using the maximum value plus one for the censored cases, large urine ketones first occurred on average during the second of 8-h shifts of day 3 in the

TABLE 4. *Parameter estimates from mixed effects models for selected outcomes: parameter estimates (coefficient, standard error, and p-value), for selected outcomes, for each protocol*

Outcome: Protocol	Intercept: Coeff, SE, p-value	Linear Time: Coeff, SE, p-value	Quadratic Time: Coeff, SE, p-value
Whole Blood ßHB:			
FAST-KD	−0.43, 0.29, 0.15	0.55, 0.03, < 0.0001	−0.013, 0.001, < 0.0001
GRAD-KD	0.06, 0.29, 0.85	0.16, 0.03, < 0.0001	0.001, 0.001, 0.65
Serum Blood ßHB:			
FAST-KD	−2.17, 0.48, < 0.0001	1.75, 0.15, < 0.0001	−0.106, 0.012, < 0.0001
GRAD-KD	−0.26, 0.49, 0.60	0.35, 0.16, 0.033	0.016, 0.013, 0.21
Urine Acetoacetic acid:			
FAST-KD	−0.24, 0.15, 0.12	0.31, 0.05, < 0.0001	−0.019, 0.004, < 0.0001
GRAD-KD	0.16, 0.15, 0.29	0.02, 0.05, 0.64	0.007, 0.004, 0.084
Whole Blood Glucose:			
FAST-KD	86.35, 2.01, < 0.0001	−3.27, 0.24, < 0.0001	0.102, 0.008, < 0.0001
GRAD-KD	92.29, 2.06, < 0.0001	−1.39, 0.26, < 0.0001	0.014, 0.009, 0.13
Serum Bicarbonate (HCO3):			
FAST-KD	31.31, 2.21, < 0.0001	−7.53, 1.17, < 0.0001	0.832, 0.146, < 0.0001
GRAD-KD	21.92, 2.22, < 0.0001	−0.73, 1.18, 0.54	−0.041, 0.148, 0.78

FAST-KD protocol, whereas children on the GRAD-KD protocol developed large urine ketones ∼35 hours later. Mann–Whitney tests indicated a statistically significant difference between the protocols in rank order of time to first occurrence of large urine ketones ($p = 0.008$ and $p = 0.001$, for the omitted censored-cases version and the censored cases–included version, respectively). Kaplan–Meier and Cox regression models also were examined. Results indicated that the two protocols differed significantly in survival distribution ($p = 0.008$), and that the FAST-KD group was more likely to experience large urine ketones ($p = 0.014$).

Comparing urine ketones and whole blood ketones

Paired *t* tests were used to compare time to ketosis as indicated by whole blood ketones and by large urine ketones. An examination of the descriptive data indicated that whole blood ketones preceded large urine ketones in both protocols. When the 10 censored urine cases were excluded, then whole blood ketones preceded large urine ketones by a statistically significant amount in the FAST-KD protocol only ($p = 0.005$ and $p = 0.223$, for FAST-KD and GRAD-KD, respectively), by an average of 11 h in the FAST-KD protocol, and by an average of 10 h in the GRAD-KD protocol. When the 10 censored urine cases were assigned the maximum value plus the value of an additional cycle, then whole blood ketones preceded large urine ketones in both protocols ($p = 0.007$ and $p = 0.003$, for FAST-KD and GRAD-KD, respectively), by an average of 18 h in the FAST-KD protocol, and by an average of 36 h in the GRAD-KD protocol.

Glucose

Results from the longitudinal model of blood glucose indicate a significant protocol effect ($p = 0.045$), in addition to highly significant effects for Time, Time squared, Protocol × Time interaction, and Protocol × Time × Time interaction (all p values <0.0001). Parameter estimates for each of the two protocols are displayed in Table 4. Blood glucose in the FAST-KD group has a stronger linear decrease and a significant quadratic time trend. In the GRAD-KD group, the coefficient for linear time is significant, but not the coefficient for quadratic time effect. Change in blood glucose across days of hospitalization for each of the two protocols can be seen in the box plot in Fig. 2.

Bicarbonate

The longitudinal model of bicarbonate indicates a significant effect for protocol ($p = 0.004$), as well as highly significant effects for Time, Time squared, Protocol × Time interaction, and Protocol × Time × Time interaction (all p values ≤0.0002). Parameter estimates for the two protocols are displayed in Table 4. In the FAST-KD group, bicarbonate has a steep and significant linear decrease and a significant change in direction over time, whereas in the GRAD-KD group, coefficients for effects of time are not statistically significant.

Adverse Events/Tolerability

During the 6-day introduction of the KD, two children dropped out. In one, pancreatitis developed (FAST-KD), and in one, a viral gastrointestinal illness developed (GRAD-KD). Neither event was related to the KD. Before the 3-month follow-up, the FAST-KD group had lost an additional three subjects from the study. In one, acute respiratory distress developed, and two dropped out because of perceived lack of efficacy. In the GRAD-KD, an additional subject withdrew before the 3-month follow-up because of perceived lack of efficacy.

Five subjects experienced serious adverse events during the first 3 months on the KD (status epilepticus, pancreatitis, extended hospital stay/admission, acidosis, dehydration, tachycardia of unknown etiology, and transient

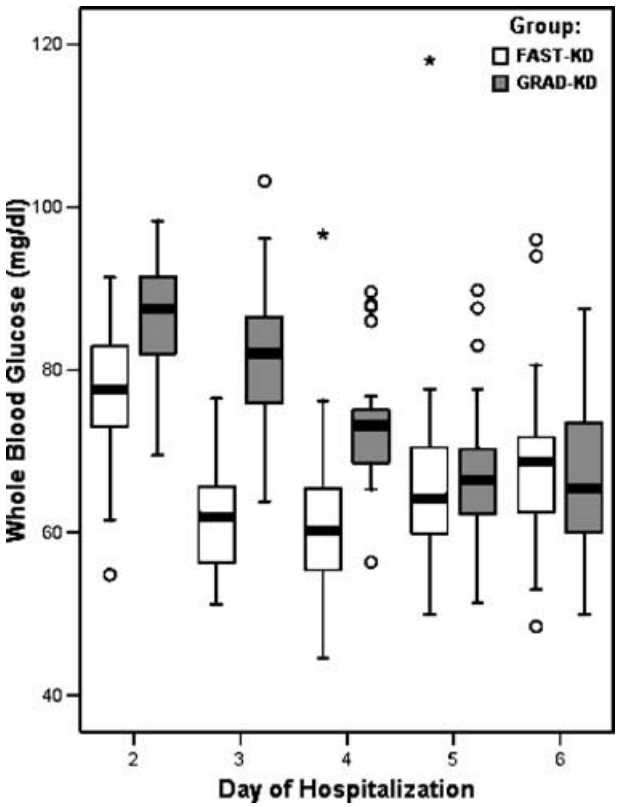

FIG. 2. Boxplot of whole blood glucose (mg/dl) (averaged across 6 time points within each day) by FAST-KD and GRAD-KD protocol, Days 2 through 6. The box represents the interquartile range which contains the 50% of values. The whiskers are lines that extend from the box to the highest and lowest values, excluding outliers. The line across the box indicates the median. Outliers (o) are defines as cases with values between 1.5 and 3 box lengths from either end of the box. Extreme outliers (∗) are cases with values greater than 3 box lengths from either end of the box.

elevation in transaminases). Four of the subjects were in the FAST-KD group.

Compared with children in the FAST-KD group, children in the GRAD-KD group lost significantly less weight from days 2 through 6 [median (range), –0.95 (–2.9, 0.6 kg) vs. –0.30 (–2.1, 1.5 kg), for FAST-KD and GRAD-KD respectively; $p = 0.006$]. Hypoglycemia (blood glucose <45 mg/dl) occurred at least once in 33% of the FAST-KD versus 4% of the GRAD-KD group ($p = 0.023$). All children in the FAST-KD had at least one glucose <60 mg/dl versus 46% in GRAD-KD group ($p < 0.0005$). A greater proportion of children in the FAST-KD versus GRAD-KD groups required citric acid and sodium citrates to correct the acidosis (63% vs. 29%; $p < 0.04$) and intravenous fluids for dehydration (63% vs. 29 %; $p < 0.04$). As a result, the FAST-KD groups' total daily intake (IV and oral fluids) was higher ($p = 0.034$). No difference was found between protocols in total fluid output. No difference was seen in the occurrence of vomiting (54% vs. 58%). With the exception if bicarbonate, no clinically important changes in electrolytes were noted for either of the protocols, as all values remained within normal ranges throughout the 5 days of hospitalization.

DISCUSSION

The use of fasting as an initiation to the KD has its root in historic tradition (31). Modern-day studies also have proven that fasting can reduce seizures (32). Brief fasting is used by some centers as a way of quickly boosting ketones and improving seizure control during breakthrough seizure clusters in children already on the KD (33). A similar boost in ketones can be obtained without fasting by briefly increasing the ratio of fat in the KD meal. Although the antiepileptic mechanism of action of the KD is unknown, maintaining a state of ketosis is essential to the success of the KD (34,35). Metabolic ketosis is achieved by consuming a very low carbohydrate diet, and induction of ketosis is accelerated by fasting. During a fast, liver and muscle glycogen is first mobilized for energy. After 2 to 3 days of fasting, glycogen stores are exhausted, blood glucose and insulin levels decrease, and lipolysis, glyconeogenesis, and ketone production begin (36). When fasting is prolonged, hypoglycemia may occur and is a higher risk for younger children who have smaller glycogen reserves. Ketone bodies are acidic and have anorexic properties (37). Very high levels of ketosis can lead to anorexia and complete food refusal (33). Increased ketone production results in an increased acid load, which may result in lethargy, sleepiness, acidosis, nausea, vomiting, and dehydration. Fasting also results in a catabolic state, protein breakdown, and loss of muscle mass (30,38,39).

All of these typical adverse events associated with a fasting initiation are unpleasant and stressful for the child and family and occasionally represent a significant health risk. A hospital admission is therefore required. Thus developing alternative, safer, yet effective approaches to initiate the KD would have many advantages. Whether a fasting initiation is necessary for the effectiveness of the KD has not been previously evaluated in a prospective randomized study.

By using retrospective data, gradual KD-initiation protocols were reviewed (22,23). Both articles were retrospective chart reviews. Wirrell et al. (22) described 14 children, 13 of whom were successfully started on the KD by using a gradual, full-calorie protocol. Five of 14 had success with the KD (defined as >50% reduction in seizures and remaining on the KD). At 19 months' follow-up, only four children remained on the KD. This was a lower success rate than generally reported with the fasting initiation KD studies, and attrition was higher than the usual 20–30% seen with a hospital-initiated fasting protocol (11). Details of the frequency and severity of the adverse events were not reported.

In a recent article, Kim et al. (23) described their clinical experience with a gradual, calorie-restricted, KD-initiation protocol. In a retrospective chart review of 41 children with intractable epilepsy, they found that 14 of 41 were seizure free at 3 months, eight of 41 had a >90% reduction in seizure frequency, and nine of 41 had a 50–90% reduction in seizure frequency. Their efficacy rates were similar to those reported by fasting initiation protocols. The gradual protocol was not free from adverse events, but in general, the adverse events were fewer or milder or both.

Our report is the first prospective, randomized study to show that a gradual initiation of the KD maintains the seizure efficacy, results in similar levels of ketosis, has a lower/milder side-effect profile, and is overall better tolerated. Randomization resulted in similar demographic characteristics of the study population including degree of intractable epilepsy. Both protocols created the desired state of ketosis. As expected, the FAST-KD group became ketotic earlier; however, by the end of the initiation phase, no difference was found in the degree of ketosis, as indicated by both whole blood and serum βHB levels between the two treatment groups. At fasting levels of βHB >1.5 mM, whole blood βHB testing with a portable bedside machine was as accurate as the gold standard serum βHB. This should be considered as an alternative for clinical decisions when serum βHB values are not readily available. Blood βHB levels were in the fasting range hours before large urine (acetoacetic acid) ketones were detected, suggesting that βHB may be a more timely and accurate reflection of metabolic changes with the KD (40). The efficacy of the KD was similar, regardless of the type of initiation, and both protocols had effectiveness outcomes similar to those previously published.

The KD remains one of the more effective treatments of intractable epilepsy. Our results show that a fasting initiation was not necessary for efficacy in children. The gradual initiation resulted in a similar high rate of seizure reduction while decreasing the expected adverse events and improving the overall tolerability. The GRAD-KD approach may simplify the KD management for the care team, thereby making the KD more available to the intractable epilepsy population in general.

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