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Intermittent fasting: A "new" historical strategy for controlling seizures?

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Summary

In antiquity, fasting was a treatment for epilepsy and a rationale for the ketogenic diet (KD). Preclinical data indicate the KD and intermittent fasting do not share identical anticonvulsant mechanisms. We implemented an intermittent fasting regimen in six children with an incomplete response to a KD. Three patients adhered to the combined intermittent fasting/KD regimen for 2 months and four had transient improvement in seizure control, albeit with some hunger-related adverse reactions.

Keywords

Intermittent fasting; Ketogenic diet; Medically intractable epilepsy; Children

Introduction

Anticonvulsant medication is the first line of treatment for epilepsy but only two-thirds of patients respond to one of the first two medications tried (Kwan and Brodie, 2000). This leaves a significant number of patients who need additional treatment. In patients who do not have a lesion that can be resected surgically, one underutilized (but widely recognized) option is the ketogenic diet (KD) (Kossoff and Hartman, 2012). The KD was designed to mimic the beneficial effects of fasting on seizures, a phenomenon that was recognized in the time of Hippocrates (Bailey et al., 2005). The KD has been shown in case series and randomized controlled clinical trials to be effective in controlling seizures in a substantial number of patients who did not respond to medications (Freeman et al., 2007; Neal et al., 2008).

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Similar to medications, some patients have seizures that are not fully controlled by the KD. This raises the possibility that other diet-based treatments may provide additional benefit for some patients. Fasting was considered a treatment for epilepsy in the 1920s but we are unaware of published clinical trials using this type of intervention in the last 80 years (Conklin, 1922; Geyelin, 1921). Anecdotal reports in our clinic indicate that seizure frequency improves in some patients when they fast during illnesses. An initial fast also appears to shorten the time to first reported seizure reduction compared to a non-fasting approach, although long-term outcomes on the ketogenic diet are not influenced by an initial fast (Bergqvist et al., 2005; Kossoff et al., 2008).

Preclinical tests based on those used to screen candidate anticonvulsant medication have shown that the KD and intermittent fasting do not share identical anticonvulsant mechanisms (Hartman et al., 2010). Based on preclinical data and anecdotal reports of improvement in seizure control with fasting, we sought to determine whether an intermittent fasting regimen in children might prove beneficial. We first attempted to answer this question in children already receiving the KD (who had experience fasting at diet initiation) with incomplete seizure control. This report describes preliminary data that were collected in preparation for a future trial of intermittent fasting as a de novo therapy for children with epilepsy.

Methods

This was a retrospective analysis of intermittent fasting, which was offered to children undergoing treatment with the KD at Johns Hopkins Hospital if the family's goal for seizure control had not been met (in some instances, this was seizure freedom but in most, it was >50% improvement in seizure control). The intermittent fasting goal regimen was to skip two consecutive meals (typically breakfast and lunch) on two nonconsecutive days per week (i.e., Mondays and Thursdays). "Zero calorie" foods (e.g., lettuce) were not permitted but fluids were unlimited during this fast. During intermittent fasting, no changes were made to the ketogenic ratio, multivitamins, or oral citrates. Medications were adjusted in two patients because of a partial but incomplete response to intermittent fasting (patients 3 and 4) and in another patient, medium chain triglyceride (MCT) oil was added at the same time that intermittent fasting was initiated (patient 6).

The primary outcome measure was self-reported ability to adhere to the intermittent fasting regimen for 2 months. The 2-month time point was extrapolated from a prior study examining time to improvement of seizure outcomes during the KD (Kossoff et al., 2008) and in turn, the relationship between perceived KD effectiveness and the amount of time families continue using it (Hemingway et al., 2001). The secondary outcome measure was seizure frequency and severity. Data on seizures were maintained in diaries for the duration of the KD and intermittent fasting periods. Because this was a pilot study and the number of patients was small, formal statistical analyses were not performed. This study was approved by the Johns Hopkins University School of Medicine Institutional Review Board.

Results

Data on patient demographics, seizure histories, and seizure frequencies are detailed in Table 1. Six children attempted intermittent fasting and ranged in age from 2 to 7 years. All families offered the approach of intermittent fasting agreed to the attempt; therefore all patients were included in this series. Diagnoses included Lennox—Gastaut syndrome (two patients), Doose syndrome (two patients), and one child each with idiopathic generalized epilepsy and multifocal epilepsy. All patients except one were on a 4:1 ketogenic ratio and all were on the KD for at least 4 months, which is sufficient time to determine whether the

KD has worked as the sole dietary treatment for seizures (Kossoff et al., 2008). Interestingly, all children who had a positive response to the intermittent fasting regimen had atonic seizures as part of their semiology. Only two children (patients 2 and 6) had no improvement in seizures with the KD at the time of intermittent fasting. The other children had some level of seizure improvement, but not to the level of seizure freedom.

For the primary outcome (duration of adherence), three of the six patients were able to adhere to the combined intermittent fasting/ketogenic diet regimen for 2 months or longer, with a range of 3 weeks to 6 months. All of these patients adhered to the regimen as described (i.e., 2 meals each on 2 days/week). For the secondary outcome (seizures), seizure improvement (universally in the range of a 50—99% reduction) was noted by four families. One patient's seizures improved only on fast days (patient 4). One patient's family modified the intermittent fasting schedule to occur for 24 h once per month, which led to a further decrease in seizure frequency (patient 3) (Table 1). After an initial improvement, three patients had a recurrence of seizures during the intermittent fasting/ketogenic diet regimen. In terms of tolerability, the two patients who did best in terms of seizure control reported no adverse effects. However, the other patients reported varying levels of difficulty in implementing the intermittent fasting regimen, especially due to hunger. One patient lost 1 kg during the combined regimen.

Discussion

An intermittent fasting regimen in combination with the KD can be implemented successfully in pediatric patients. Half of the patients in this series were able to continue the regimen for at least 2 months, with evidence of modest or transient improvements in seizure control in four of six patients. Although somewhat difficult in terms of adherence, it was tolerable. In patients where the regime improved seizure control, families reported the additional benefit was worth pursuing intermittent fasting. With time, however, adherence became more of a challenge, as reflected in the retention rate. This study is one of relatively few to our knowledge to attempt to determine if the KD can be adjusted to improve seizure control, with previous attempts looking at amino acid supplementation (Evangeliou et al., 2003), ratio change (Seo et al., 2007), and achieving ideal body weight (Hamdy et al., 2007). It also represents a translational collaboration between basic and clinical science for the KD, in a manner similar to anticonvulsants.

The transient improvement in seizure control supports the hypothesis that intermittent fasting and the KD do not share identical anticonvulsant mechanisms. An alternative explanation is that intermittent fasting simply amplified the antiseizure effects of the KD. However, preclinical data support the former explanation. In juvenile NIH Swiss male mice, the KD elevates seizure threshold (i.e., is protective) in the 6 Hz electroshock test but has no effect in the kainic acid test (Hartman et al., 2010). Conversely, intermittent fasting (with normal rodent chow) protects against kainic acid-induced seizures and lowers seizure threshold (i.e., is deleterious) in the 6 Hz electroshock test. Also supporting this hypothesis, there are differences between the KD and calorie restriction in an in vitro test of seizure threshold, the maximal dentate activation test in rats (Bough et al., 2003). Although not specifically studied here, one reason for the transient nature of improvement may include a systemic metabolic adaptation to the fasted state, similar to one murine model of the ketogenic diet (Todorova et al., 2000).

The exact mechanism through which intermittent fasting exerts antiseizure effects has not been determined but preclinical data support the hypothesis that this regimen is neuroprotective. For example, intermittent fasting in adult rats for periods of 7 weeks to 6 months protects neurons after intrahippocampal kainic acid injection (Bruce-Keller et al.,

1999), anterior hippocampus GABAergic neurons after peripheral kainic acid injection (Contestabile and Ciani, 2004), and neuronal electrophysiological integrity, reflected by long-term potentiation (Youssef et al., 2008). The molecular mechanism for this protection may be due to increased expression of the neuroprotective proteins brain-derived neurotrophic factor (Duan et al., 2001) or HSP70 (Sharma and Kaur, 2005).

There are potential weaknesses in the current study. The series was retrospective. Because of the recognition that intermittent fasting combined with a KD could have adverse effects on behavior in this age group, families were given latitude to change the implementation of the fasting schedule, although in the end, only one family did so (interestingly, with significant benefit in seizure control, patient 3). Other intermittent fasting regimes, such as that implemented by the family of patient 3, may be more efficacious than the one used here. Furthermore, reintroduction of an intermittent fasting regime (at a later date) may be useful in the patients who had a response. Recall bias also may influence data on tolerability and seizure characteristics (including frequency and severity).

In summary, this case series describes the reconsideration and updating of treatments described since antiquity. Intermittent fasting combined with a KD can be implemented in pediatric patients but the optimal schedule for fasting remains to be determined. Patients and their families were able to tolerate the fasting periods but further encouragement may be needed to prolong the treatment period and perhaps improve the generally short-term benefits. Future prospective studies of intermittent fasting for children with epilepsy with a regular diet appear warranted.

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Table 1

Results of intermittent fasting/ketogenic diet.

Patient ID	Age	Diagnosis	Seizure type	Frequency pre-KD/per week	EEG	Meds pre-KD	Diet ratio	Meds during IF/KD	Time on KD at IF attempt (months)	Duration of IF/KD (months)	Response	Parent-reported adverse effects
1	4 years	LGS	Atonic, myoclonic, tonic	200	Slow spike wave	4	3:1	PB, CZP, LTG	6	1	Transient benefit for the first 2 weeks (only rare subtle single drops), then back to baseline	Difficulty with restrictiveness on fasting days
2	2 years	Multifocal epilepsy, idiopathic	Complex partial	10	Right and left posterior sharps	3	4:1	OXC, TPM	9	2	No change	Hunger
3	5 years	Doose syndrome	Absence, atonic	160	Spike-wave with normal background	3	4:1	LTG	18	6	50—90% better, changed to a monthly 24-h fast protocol	None
4	7 years	Idiopathic generalized, no classic syndrome	Atonic	100	Spike-wave bursts, slight right asymmetry	2	4:1	LEV	5	1	Good response on fasting days but no change on other days	Difficulty with restrictiveness on fasting days
5	6 years	Doose syndrome	Absence, atonic	150	Spike-wave with normal background	6	4:1	VPA, ESM, CLB	18	5	First 6 weeks: 90—99% reduction, then back to baseline	None
6	7 years	LGS, Group B strep meningitis	GTC, myoclonic	50	Slow spike wave	10	4:1	LEV, TPM	4	.0.8	No change	Hunger and fatigue during fasting

CZP: clonazepam; IF/KD: combined ketogenic diet and intermittent fasting; KD: ketogenic diet; GTC: generalized tonic clonic seizure; LEV: levetiracetam; LGS: Lennox—Gastaut syndrome; LTG: lamotrigine; OXC: oxcarbazepine; PB: Phenobarbital; TPM: topiramate.