Pediatric Neurology 52 (2015) 442–445

Contents lists available at ScienceDirect

Pediatric Neurology

journal homepage: www.elsevier.com/locate/pnu

Clinical Observations

Intravenous Ketogenic Diet Therapy for Treatment of the Acute Stage of Super-Refractory Status Epilepticus in a Pediatric Patient

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ABSTRACT

BACKGROUND: A ketogenic diet has been used successfully to treat intractable epilepsy. However, the role of early intravenous initiation of ketogenic diet in the acute phase of super-refractory status epilepticus is not well-described. **METHODS:** An intravenous ketogenic diet was administered to a boy with super-refractory status epilepticus. At 24 hours after intravenous ketogenic diet, moderate ketosis appeared, and thiamylal was successfully weaned at 70 hours after admission. **RESULTS:** An intravenous ketogenic regimen led to subsequent ketosis and seizure control in a child with super-refractory status epilepticus. **CONCLUSION:** Early induction of ketosis may be a novel strategy to effectively treat super-refractory status epilepticus. Although there are few data regarding the early use of intravenous ketogenic diet in the treatment of super-refractory status epilepticus, it may be considered an alternative option.

Keywords: ketogenic diet, intravenous ketogenic diet, refractory status epilepticus, children

Pediatr Neurol 2015; 52: 442-445

Introduction

Status epilepticus is a medical emergency that must be treated immediately to prevent permanent neuronal injury and mortality. Super-refractory status epilepticus is defined as status epilepticus that continues or recurs 24 hours or more after the onset of anesthetic therapy. Included are individuals whose status epilepticus recurs upon reduction or withdrawal of anesthesia.[1] Treatment is difficult and therapeutic management is based on clinical reports and expert opinion. In recent literature reviews on the outcome of refractory and super-refractory convulsive status epilepticus, more than two of three have morbidity or mortality and less than one of three can recover to baseline.[2]

A ketogenic diet is a high-fat, low-carbohydrate, and adequate protein diet. It alters the primary cerebral energy metabolism from glucose to ketone bodies and may have multiple mechanisms of antiepileptic action, anti-epileptogenic properties, neuro-protection, antioxidant and anti-inflammatory effects, and potential disease-modifying intervention.[3] Although a ketogenic diet is typically suggested for with chronic intractable epilepsy, recent reports indicate that it can be effective as an acute treatment for refractory or nonconvulsive status epilepticus in both adults and children.[4-7]

There has been only one report of intravenous initiation of a ketogenic diet in super-refractory status epilepticus in an adult.[8] Here we describe a child with super-refractory

Article History:
Received November 1, 2014; Accepted in final form December 24, 2014
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0887-8994/$ – see front matter © 2015 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.pediatrneurol.2014.12.008

status epilepticus who developed an adverse effect from anesthesia-induced coma and became seizure-free following early intravenous initiation of ketogenic diet and maintained seizure control after transitioning to enteral ketogenic diet. This report also provides further information on intravenous ketogenic diet therapy.

Patient Description

A previously healthy boy initially presented with generalized tonic-clonic seizures at age 6 years and 3 months. He was consistently under good control with levetiracetam (40 mg/kg/day) for seven months until he developed nine seizures within a day. The seizure pattern consisted of focal twitches of the face followed by secondary generalization. There were no preceding events such as fever, upper respiratory infection, or acute gastroenteritis.

Upon admission to the hospital, he quickly became encephalopathic and developed increasingly frequent seizures progressing to status epilepticus, necessitating intubation. He was fasting with sugar-free solution because of hyperglycemia and upper gastrointestinal bleeding. Extensive investigations for bacterial, viral, autoimmune, and metabolic causes were negative, and brain computed tomography was unremarkable.

The seizures continued after the administration of diazepam, phenytoin, valproic acid, and levetiracetam. The seizures were also not controlled with midazolam (20 mcg/kg/minute). Finally, thiamylal (5 mg/kg/hour) anesthesia was established 16 hours after admission. However, profound hypotension after thiamylal occurred at 30 hours after admission, necessitating aggressive vasopressor and inotropic support. Each attempt to decrease thiamylal was followed by nearly continuous electrographic seizures arising from the left parietotemporal region. Because the patient could not tolerate tube feeding upon infusion of thiamylal, intravenous administration of ketogenic diet was initiated 40 hours after admission.

At 24 hours after initiating the intravenous ketogenic regimen, moderate ketosis appeared (serum beta-hydroxybutyrate 1.4 mmol/L, normal range <0.6 mmol/L) and thiamylal was successfully weaned at 70 hours after admission, without the recurrence of electroclinical seizures. Subsequent electroencephalographic recordings improved. Brain magnetic resonance imaging studies on day 7 after admission showed scattered areas of T2 hyperintensity in the bilateral putamen. The patient was switched to enteral ketogenic diet with medium-chain triglyceride oil via nasoduodenal tube on day 8.

On day 28, the patient was extubated because his regimen had been gradually reduced to maintenance treatment consisting of oxcarbazepine, levetiracetam, clonazepam, topiramate, and a ketogenic diet. Two months later, he was weaned from the ketogenic diet because of side effects, including weight loss and intermittent diarrhea. Cognition and learning ability improved gradually. He was discharged after 6 months of neurorehabilitation. On follow-up at 9 months, he still experienced one to three self-limited breakthrough seizures per month, mild cognitive difficulty, and mild expressive aphasia, and required minimal assistance with activities of daily living.

Intravenous initiation and maintenance of ketogenic nutrition

The previous reported method was modified to match the energy supply with physiologic needs.[8,9] The intravenous ketogenic diet protocol is summarized in Table 1. The ketogenic diet was infused continuously over 16 hours and stopped for 8 hours at nighttime. Glucose-free solutions such as saline were also given as required. The ketogenic diet had a 4:1 ketogenic ratio and was composed of commercially available fat emulsion with medium-chain triglycerides (20% SMOF lipid emulsion, Fresenius Kabi Austria GmbH, Graz, Austria), amino acid (Aminosteril Infant 10%, Fresenius Kabi Austria GmbH), and carbohydrate (Glucose 50%, Y F Chemical Corp., Taiwan) solutions for intravenous application. Amino acid was mixed with dextrose and electrolytes as parenteral nutrition and amino acids in 4% concentration together with dextrose in 5% concentration were suitable for pediatric ketogenic diet.

Serum beta-hydroxybutyrate was detected 24 hours after intravenous ketogenic diet and persisted at high concentrations since then (Table 2). There was no hypoglycemia or severe acidosis (HCO_3 <17 mmol/L) at the start of the ketogenic diet. Intravenous administration of the ketogenic diet was continued for 5 days and then switched to an enteral preparation administered via a nasoduodenal tube. The enteral ketogenic diet with medium-chain triglyceride oil was given five times per day, resulting in a total daily intake of 1500 kcal. The biochemistry data in the acute stage of intravenous ketogenic diet are summarized on Table 2.

TABLE 1.
Intravenous Ketogenic Diet Protocol*

	Solution	Total Volume	Infusion Rate	Weight	Calories
†**Day 1-2 KD: 440 kcal/d (1/3 of the estimated 70% diet energy needs)**					
Fat	20% SMOF lipid emulsion	220 mL	13.8 mL/hour	44 g fat	396 kcal
Amino acids	4% Aminosteril Infant	275 mL	17.2 mL/hour	11 g amino acids	44 Kcal
Carbohydrates	0% dextrose water			0 g carbohydrates	0 Kcal
	Total	495 mL		55 g	440 Kcal
‡**Day 3-4 KD: 880 kcal/d (2/3 of the estimated 70% diet energy needs)**					
Fat	20% SMOF lipid emulsion	440 mL	27.5 mL/hour	88 g fat	792 kcal
Amino acids	4% Aminosteril Infant	275 mL	17.2 mL/hour	11 g amino acids	44 Kcal
Carbohydrates	5% dextrose water			11 g carbohydrates	44 Kcal
	Total	715 mL		110 g	880 Kcal
§**After day 5 KD: 1320 kcal/d (3/3 of the estimated 70% diet energy needs)**					
Fat	20% SMOF lipid emulsion	660 mL	41.3 mL/hour	132 g fat	1188 kcal
Amino acids	4% Aminosteril Infant	412.5 mL	25.8 mL/hour	16.5 g amino acids	66 Kcal
Carbohydrates	5% Dextrose water			16.5 g carbohydrates	66 Kcal
	Total	1072.5 mL		165 g	1320 Kcal

Abbreviation:
KD = Ketogenic diet
The table is modified from Strzelczyk [8] and Jung.[9]
The intravenous ketogenic diet included 20% SMOF (250 mL/bottle) and 4% Aminosteril Infant plus 5% dextrose water (500 mL/bag) and was infused continuously over 16 h and then interrupted for 8 h during the night with glucose-free solution such as half saline.
* Example: 70% energy needs is 1330 Kcal/day of a 40-kg patient with classic 4:1 parenteral ketogenic diet.
† Days 1-2: sugar-free solution.
‡ After day 3, if sugar >150 or ketone body disappeared, change 5% dextrose water to sugar-free solution.
§ After day 5: Transitioning to the enteral ketogenic diet as tolerance.