Cost-effectiveness of a ketogenic diet in children with intractable epilepsy: a Dutch randomized controlled trial

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Seizures (incl subtypes)
Study type	Interventional

Summary

ID

NL-OMON34955

Source
ToetsingOnline

Brief title
Cost-effectiveness ketogenic diet/COEK study

Condition

- Seizures (incl subtypes)

Synonym
epilepsy or seizure attacks

Research involving
Human

Sponsors and support

Primary sponsor: Epilepsiecentrum Kempenhaeghe
Source(s) of monetary or material Support: Subsidie kosteneffectiviteitsonderzoek zonMw

Intervention

Keyword: children, cost-effectiveness, intractable epilepsy, ketogenic diet

Outcome measures

Primary outcome

Clinical outcome: proportion of children with a 50% or more reduction in

seizure frequency.

Economic evaluation:

• Quality of life and quality adjusted life years (QALYs).

• Societal costs

Secondary outcome

The secondary parameters are:

• Mean number of seizures as a percentage of the number of seizures during the

4-week baseline period.

• Seizure severity: National Hospital Seizure Severity Scale (NHS3).

• Side effects/complaints: Side Effects of Anti-Epileptic Drugs questionnaire

(SIDEAD).

• Psychological assessment :

o Cognition

o Behavioural and social-emotional functioning

o Psychosocial adjustment

Study description

Background summary

Up to 30 % of patients with uncontrolled seizures do not respond to drug therapy. An alternative therapy especially for children is the KD. The*re a lot of literature confirming the efficacy of the KD. Literature is nevertheless limited to class 3 and 4 data with the exception of one randomized controlled trial published in 2008. A cost effectiveness study is never performed.
The KD is used only in a minority of children who could potentially benefit from it.
In order to optimize therapy for children with uncontrolled seizures, the KD should be prescribed for more children with intractable epilepsy.
Implementation can be facilitated by a better understanding of the cost-effectiveness of this dietary treatment.
Benefit for the child is the possibility to have better seizure control with the KD.
A substantial amount of children with therapy resistant epilepsy do also have a mental disability and other handicaps as different symptoms of the underlying brain damage.
Epilepsy has been shown to have the greatest impact on quality of life when children have intractable seizures and additional disabilities (26). Groups relatedness is a fact since this are the children who can have benefit from the KD.

Study objective

Primary Objective:
To demonstrate the cost-effectiveness of treatment with a ketogenic diet compared to usual care in children with drug-resistant epilepsy who are not eligible for epilepsy surgery. Usual care is defined as: the child continuous to take his or her anti-epileptic drugs and no changes will be made to the anti-epileptic drugs treatment except when medically indicated.
Research questions are: What are the societal costs of the KD compared to usual care? What are the effects of the KD compared to usual care (changes in seizure frequency and seizure severity; side effects/complaints, psychological functioning; quality of life)? What is the incremental cost-effectiveness ratio of the KD compared to usual care (cost per QALY).
Secondary Objectives are:
In our proposed study, we will pay great attention to enhance and assess compliance for example by regular monitoring of ketone bodies with urine sticks, a standardized protocol including frequent contacts (face-to-face; telephonic; e-mail) with dietician, nurse, paediatrician and neurologist, and Internet communication (seizure and cost diaries, ketosis measurements). We also aim to improve the commitment of the child and parents by using the Internet to be in contact with them and to exchange information.

Study design

Design:

The cost-effectiveness study is designed as a randomized controlled trial (see Appendix 5 and 16). After informed consent all patients will start with a 4-week baseline period. Then, patients will be randomized to start a KD either immediately (KD group) or after a 4-month delay (control group).

Randomization - using the minimization method - will be stratified according to age (1-6 years, 7-12 years, 13-18 years) and whether the child is at the residential centre (epilepsy centre Kempenhaeghe) or not (child attends the epilepsy centre as an outpatient while s/he lives at home).
The KD group immediately starts with a KD for a 4-month study period, with a follow-up of another one year. Since a KD is a last resort treatment, the children in the control group will also receive a KD after a 4-month delay. The controls will be treated and monitored according to good clinical practice.

Neither the multidisciplinary team nor the (parents of the) children will be blinded to which group the children are randomized to. The anti-epileptic drugs the children use at the time of inclusion in the study will be continued and no changes will be made to the anti-epileptic drugs during the 4-week baseline period and the 4-month study period (except when medically indicated).

Intervention

Description of the ketogenic diet:
The ketogenic diet is introduced during a hospitalization for one week or longer if medically indicated. The diet is calculated on an individual basis by the dietitian. The intake is calculated with a computer program from a 24-hour food record. The initial calorie prescription for the ketogenic diet is based on an average between the pre-diet intake and the recommendations for energy requirements, taking into account current and previous weight and height, recommended calorific requirements and levels of physical activity. The diets begin with 25% extra fat intake, including 10 grams of MCT fat. In four days the fat-intake is built up to 100% of the calculated fat, given in LCT fat (diary cream) and a very slowly increasing amount of MCT fat, going up to a level of 60% of total dietary energy of MCT fat in the final diet. In about 3 weeks the total quantity of MCT fat is achieved and the LCT fat is left at 11% of total dietary energy. When the extra fat intake is at 100% the calculated diet is introduced. The diet then consists of protein (WHO minimum requirements for age, 10% of total dietary energy), fat (71% of total dietary energy) and carbohydrate (19% of total dietary energy). Depending on the tolerance of the MCT fat the diet may need some adjustments. The diet is fully supplemented with vitamins and minerals. Sometimes the MCT diet is not possible and the classical ketogenic diet (3:1 or 4:1 ratio) is advised. Also children with a PEG/tube feed are treated with the ketogenic diet. The diet is then adjusted to a fluid version.
Down titration of antiepileptic drugs is possible in responders from six months after initiation of the ketogenic diet. The KD is a high-fat, low carbohydrate, normocaloric diet that mimics the metabolic state of fasting. During a

prolonged fast, body energy requirements are met by lipolysis and ß-oxidation of fatty acids rather than by the breakdown of carbohydrates.
Thus, the KD maintains an anabolic nutritional state in a metabolic situation of fasting. Any diet providing nutritional fat for the generation of ketones that serve as an alternative fuel to body tissues may be called *ketogenic*. Ketones may produce an anticonvulsant effect, presumably due to changes in cerebral energy metabolism, cell properties decreasing excitability, neurotransmitter function, circulating factors acting as neuromodulators and brain extracellular milieu [20].
Most studies report the use of the classical ketogenic diet [18,19] that has been used since the 1920s and is based on a ratio of fat to carbohydrate and protein combined of 3:1 or 4:1 [33]. A modification to this diet that uses medium-chain triglycerides (MCT) as an alternative fat source was introduced in the 1970s [34]. The MCT diet yields more ketones per kilocalorie of energy provided than long-chain triglycerides (LCT) do, they are absorbed more efficiently, and are carried directly from the digestive system to the liver by the portal vein. The increased ketogenic potential of MCT means that less total fat is needed in the MCT diet, which enables the inclusion of more carbohydrate and protein [23]. In a 4:1 ratio, there are 4 grams of fat for every 1 gram of protein and carbohydrate combined. Protein is provided to meet dietary reference intake, which is approximately 1 g per kilogram of body weight. Carbohydrates complete the remaining allowance of the ratio. A medium-chain triglyceride (MCT) diet contains 70% calories from fat, using MCT as the main source
(50%) and 20% from polyunsaturated sources [35]. In a randomized controlled trial [36], 145 children were randomized to receive a classical or an MCT diet. At 3, 6 and 12 months, there were no statistically significant differences in seizure reduction between the two diet groups. There were also no significant differences in tolerability except increased reports in the classical group of lack of energy after 3 months and vomiting after 12 months.
The KD is generally used for a period of up to 3 years. Seizure control benefits are typically seen within 1-3 months of initiation of the diet. The international study group reports that the diet should be trialed for at least for 3* months before deciding to discontinue it [37]. The diet can be discontinued earlier if seizures worsen beyond expectations or adverse effects cannot be corrected [35]. Medications are tapered once efficacy of the diet has established (usually within 3-6 months of diet initiation). The diet is gradually tapered by lowering its fat content and increasing the carbohydrate and protein portion of the diet until ketosis is eliminated. Tapering starts after 2 years of treatment or in case of intolerable side effects. the Dutch guideline: *Dieetbehandelingsrichtlijn ketogeen dieet voor kinderen (0-18 jaar) met refractaire epilepsie. Evidence-based handleiding voor een multidisciplinaire behandeling* will be used.

Study burden and risks

Potential side effects of the KD are especially in the beginning of the diet

gastro-intestinal symptoms (nausea, vomiting, diarrhoea or constipation) and hypoglycaemia can occur. In a later faze there*s an elevated risk of kidney stones en growth deceleration. Growth normalises after termination of the KD. There*s a higher risk of lever dysfunction, pancreatitis, hypercholesterolemia, metabolic acidosis, hypocarnitinaemia, hypocalcaemia, hyponatriemia. In older female menstruation can become irregular. Prolonged QT time is described during treatment with the KD. Risk of the blood and urine examinations and the ECG are limited. A venapunction can cause an ecchymosis. One can have an allergic reaction on disinfectants or adhesive of ECG electrodes. There are no specific risks about neuropsychological examination. During each visit at the policlinic the children and their parents visit the neurologist, paediatrician, dietician and epilepsy nurse. These visits will be scheduled on the same day. The following assessments will take place: fysical examination with special interest to weight and length, vena puncture, urine analyses and ECG. This takes 2 to 3 hours. Neuropsychological examination consist of questionaires filled in by the parents which take maximum an hour and psychological assessment of the child. Cognitive tests will be performed as fare as the mental development of the child allows. During the testing the child wears an actimeter on his/her wrist (*bracelet* that detects movements). These testings will takes a maximum of one hour. Neuropsychologic examinations will take place during baseline, after four months and one year later for the children of the intervention group. During the baseline of four weeks all parents/patients fill in cost diaries and seizure diaries. Patients starting immediatly after randomistion with the ketogenic diet are completing the cost diaries and seizure diaries during the first sixteen months, patients of the control group during 4 months. Filling in the cost diary takes approximately 5 to 10 minutes per week. Filling in the seizure diaries takes 5 minutes per day or week depending on seizure frequency.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Children (2-11 years)
Elderly (65 years and older)

Inclusion criteria

Male and female children with uncontrolled seizures, aged between 1-18 years who are not eligible for epilepsy surgery.

Exclusion criteria

The following medical contraindications of the ketogenic diet are criteria for exclusion:
• Fatty acid oxidation disorders and related diseases
• Diabetes and hyperinsulinism
• Prolonged QT-time syndrome
• Hypercholesterolemia, hypertriglyceridemia
• Severe liver, kidney or pancreas diseases
• Renal tubular acidosis
• Treatment with topiramate or acetazolamide and a positive family history or other risk factors for kidney stones or acidosis
• Severe behavioural disorder
• Malnutrition

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	26-07-2010
Enrollment:	50
Type:	Actual

Ethics review

Approved WMO

Date:	02-07-2010
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL31155.041.10