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Cost-effectiveness of the ketogenic diet and vagus nerve stimulation for the treatment of children with intractable epilepsy

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KEYWORDS
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Summary
Purpose: The objective of this study was to estimate the expected cost-utility and cost-effectiveness of the ketogenic diet (KD), vague nerve stimulation (VNS) and care as usual (CAU), using a decision analytic model with a 5-year time horizon.

Abbreviations: KD, ketogenic diet; VNS, vague nerve stimulation; CAU, care as usual; QALY, quality adjusted life years; ICER, incremental cost-effectiveness ratio; CEAC, cost effectiveness acceptability curve; AED, antiepileptic drug; SUDEP, sudden unexpected death in epilepsy; RCT, randomized controlled trial; MCT, multi chain triglyceride.

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Intractable epilepsy;
Ketogenic diet;
Vagus nerve stimulation

Methods: A Markov decision analytical model was constructed to estimate the incremental costs, quality-adjusted life years (QALYs) and successfully treated patient (i.e. 50% or more seizure reduction) of the treatment strategies KD, VNS and CAU, from a health care perspective. The base case considered children with intractable epilepsy (i.e. two or more antiepileptic drugs had failed) aged between 1 and 18 years. Data were derived from literature and expert meetings. Deterministic and probabilistic sensitivity analyses were performed.

Results: Our results suggest that KD is more effective and less costly, and thus cost-effective compared with VNS, after 12 months. However, compared to CAU, neither KD nor VNS are cost-effective options, they are both more effective but also more expensive (€346,899 and €641,068 per QALY, respectively). At 5 years, VNS is cost-effective compared with KD and CAU (€11,378 and €68,489 per QALY, respectively) and has a 51% probability of being cost-effective at a ceiling ratio of €80,000 per QALY.

Conclusions: Our results suggest that on average the benefits of KD and VNS fail to outweigh the costs of the therapies. However, these treatment options should not be ignored in the treatment for intractable epilepsy in individual or specific groups of patients. There is a great need for high quality comparative studies with large patient samples which allow for subgroup analyses, long-term follow-up periods and outcome measures that measure effects beyond seizure frequency (e.g. quality of life). When this new evidence becomes available, reassessment of the cost-effectiveness of KD and VNS in children with intractable epilepsy should be carried out.

Introduction

Epileptic seizures are treatable with antiepileptic drugs (AEDs) in the majority of patients. About 30% of patients suffer from intractable epilepsy, indicating that their seizures are still uncontrolled after taking two or more different AEDs (Sillanpää and Schmidt, 2006). Some of these patients are eligible for resective surgery, where the area of the brain responsible for seizures is surgically removed. If resective surgery fails or is not an option, children with intractable epilepsy in particular can potentially benefit from a ketogenic diet (KD) (Kossoff et al., 2009). The KD is a high-fat, low carbohydrate diet that imitates the metabolic state of fasting while remaining normocaloric. Body energy requirements while on the KD are met by lipolysis and B-oxidation of fatty acids rather than by the breakdown of carbohydrates. Another treatment option for children with intractable epilepsy could be vague nerve stimulation (VNS). VNS is a pacemaker-like device that is implanted subcutaneously into the upper part of the chest with a connecting wire running from the stimulator to an electrode that is attached to the vagus nerve (Ben-Menachem et al., 1994). Once the stimulator is activated, electrical pulses will be generated at regular intervals depending on the anticonvulsant effect and on the patients' tolerance.

Although the exact anticonvulsant working mechanisms are still unknown (Freeman et al., 2006; Groves and Brown, 2005), the beneficial effects of both the KD and VNS are separately reported (Levy et al., 2012; Privitera et al., 2002).

Direct comparisons of the KD and VNS are, however, lacking, which makes it difficult to determine the most optimal treatment. In addition, due to scarcity of resources, it is increasingly important to examine whether benefits outweigh costs. The use of decision modeling in economic evaluation is a powerful tool for investigating this trade-off between costs and effects of comparative treatments. Modeling allows the synthesis of all available evidence from different sources. Modeling also makes it possible to include long-term costs and benefits in the analysis (Siebert et al., 2012). This is important because the impact of epilepsy (treatments) on patients' lives, seizures, and costs extends beyond the study period of most clinical studies.

The primary aim of the present study is to use a three-arm decision analytical model to evaluate the cost-effectiveness of the KD and VNS as compared to care as usual (CAU) in children aged between 1 and 18 years with intractable epilepsy.

Methods

Model description

A probabilistic Markov decision-analytical model was developed to estimate the cost-effectiveness and cost-utility of the KD, VNS and CAU as a treatment for a hypothetical cohort of children with intractable epilepsy, uncontrolled by two or more AEDs and ineligible for resective surgery. CAU means that the child continues to take his or her AEDs and no changes will be made to the AED treatment.

The model was built in Microsoft Excel 2010 following established economic evaluation state-transition modeling guidelines (Siebert et al., 2012). Costs and effects were modeled with a time horizon of 5 years.

Fig. 1 is a graphical representation of the model. In the first cycle, the hypothetical cohort started on KD, VNS or stayed on CAU. After three months, patients may have switched from KD or VNS to CAU (due to e.g. severe adverse events, difficulty of treatment or other reasons) or have died. In case of withdrawal from treatment, patients on KD would normalize their diet and VNS-treated patients would have their VNS switched off or removed surgically. After the first cycle, patients entered one of the health states: (1) seizure-free, (2) improvement (50% or more seizure reduction), and (3) no improvement (less than 50% seizure reduction). The absorbing state was 'death', either due to sudden unexpected death in epilepsy (SUDEP) or death