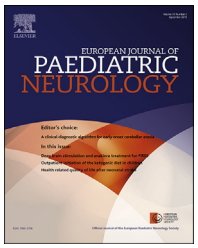
Official Journal of the European Paediatric Neurology Society



Original article

Outpatient initiation of the ketogenic diet in children with pharmacoresistant epilepsy: An effectiveness, safety and economic perspective

Elles van der Louw [a,*], *Joanne Olieman* [a], *Marten J. Poley* [b,c], *Tessa Wesstein* [d], *Florianne Vehmeijer* [d], *Coriene Catsman-Berrevoets* [d], *Rinze Neuteboom* [d]

[a] *Department of Dietetics, Erasmus MC-Sophia Children's Hospital, University Medical Center Rotterdam, Wytemaweg 80, 3015 CN, Rotterdam, the Netherlands*
[b] *Institute for Medical Technology Assessment, Erasmus University Rotterdam, Rotterdam, the Netherlands*
[c] *Intensive Care and Department of Pediatric Surgery, Erasmus MC-Sophia Children's Hospital, University Medical Center Rotterdam, Wytemaweg 80, 3015 CN, Rotterdam, the Netherlands*
[d] *Department of Pediatric Neurology, Erasmus MC- Sophia Children's Hospital, University Medical Center Rotterdam, Wytemaweg 80, 3015 CN, Rotterdam, the Netherlands*

ARTICLE INFO

Article history:
Received 24 March 2019
Received in revised form
29 May 2019
Accepted 6 June 2019

Keywords:
Refractory epilepsy
Ketogenic diet
Seizure reduction
Side effects
Costs

ABSTRACT

Background: Children with pharmacoresistant epilepsy usually receive ketogenic diet (KD) as an inpatient, which makes it an expensive treatment.
Objective: To compare the effectiveness, safety, and costs of outpatient versus inpatient initiated KD.
Design: Retrospective observational non-inferiority study.
Patients/setting: Patients (1–18 years of age) who started KD either inpatient or outpatient.
Main outcome measures: Effectiveness was defined as ≥50% seizure reduction. Safety was measured by the numbers of emergency visits and complications. Economic impact was analyzed by calculating total costs of treatment.
Statistical analyses: Non-inferiority of outpatient initiation was tested using 95% confidence intervals of the differences in effectiveness and safety endpoints between groups with non-inferiority margins of 10%. Nonparametric bootstrap techniques were used to derive a 95% confidence interval for the mean difference in total costs between the groups.
Results: Hundred and five patients started KD in the period 2001 to 2017: 43 inpatient and 62 outpatient. At three months, the KD was effective in 61% of outpatients versus 63% of inpatients. The KD was considered safe in 36% of the outpatients, as compared to 29% in the inpatients. Outpatient initiation was shown to be non-inferior to inpatient initiation in terms of safety. Total health care costs of outpatient initiation were € 2901, as compared to € 8195 of inpatient initiation per patient (mean difference € 5294, 95% CI; -€ 7653 to -€ 2935).

* *Corresponding author*. Erasmus MC-Sophia Children's Hospital, University Medical Center Rotterdam, Wytemaweg 80, 3015 CN, Rotterdam, the Netherlands. Fax: +0031 10 7035065.
E-mail address: e.vanderlouw@erasmusmc.nl (E. van der Louw).
https://doi.org/10.1016/j.ejpn.2019.06.001

Conclusions: Our study suggests that outpatient KD initiation is no worse than inpatient initiation in terms of effectiveness and safety, while carrying lower health care costs.

1. Introduction

The ketogenic diet (KD) is a therapeutic option in children with pharmacoresistant epilepsy, in children with intolerable side effects of anti-epileptic drugs (AEDs) and/or some metabolic diseases such as Glucose Transporter Deficiency type I (GLUT1 DS) and Pyruvate Dehydrogenase Complex Deficiency (PDHC). It is a high-fat, low-carbohydrate diet that mimics the metabolic state of fasting, whilst being in an anabolic state.[1] The beneficial effects of the KD on seizures were proven in several observational studies.[2–4] Seven randomized controlled trials showed that the KD induces a 50% seizure reduction in 38–72% of patients within three months of diet[5]

In practice, the children that qualify for KD treatment are the most severely affected patients. For this reason, and possibly incentivized by remuneration schemes, the KD is often initiated during a hospital stay, and patients are usually closely monitored and receive expert guidance,[6] especially in cases of infants and children with severe co-morbidities.[7,8] Management strategies are typically based on the short-term side effects during KD initiation, such as hypoglycemia, food refusal, and gastro-intestinal problems like vomiting and constipation.

Initiation of the KD in an inpatient setting is costly and often involves a considerable social and economic burden for parents and children. Given that resources are limited, the high costs of inpatient initiation cause barriers for patients to gain access to the KD.[7] It would be worthwhile, therefore, to consider outpatient initiation. However, this is not a general routine in many centers.[7,9] In fact, in the most recent consensus statement, 20 out of 25 cooperating centers (80%) confirm to admit children for diet initiation, although 92% of them believed that outpatient initiation would be possible.[6]

Little information is available supporting outpatient KD. One previous study compared inpatient KD initiation in 54 children to initiation in an outpatient setting.[10] In this study, only the effect on seizure reduction was evaluated and no significant difference was found with regard to seizure control between groups suggesting inpatient initiation was not superior. Another small-scale study, dating back to 2002, documented that in 14 children who commenced on the KD the success rate of the KD was not higher in patients admitted to hospital than in those initiated as outpatients.[11]

To our knowledge, no studies have yet evaluated the difference in economic burden between in- and outpatient initiation of the KD. Several studies focused on the economic aspects of the KD in children with pharmacoresistant epilepsy.[12–15] For example, using before-after designs, three studies found that the KD is associated with a reduction of health care costs.[13–15] However, the economic consequences of the choice between inpatient and outpatient KD are unexplored. This is a significant knowledge gap, given the importance of accountability and cost-effective health care.

In the present study, we aim to compare the effectiveness, safety, and economic impact of outpatient and inpatient KD initiation. Our hypothesis is that initiating the KD in an outpatient setting will be at least as effective and safe as inpatient initiation, while offering additional economic benefits.

2. Methods and materials

2.1. Study setting and initiation protocol

This study was performed in the Erasmus MC-Sophia Children's Hospital in Rotterdam, the Netherlands. The KD has been prescribed here since 2001 to treat pharmacoresistant epilepsy and metabolic diseases (e.g., Glucose Transporter Deficiency; GLUT1 DS). Children on KD are treated by a multidisciplinary team consisting of pediatric neurologists, pediatric dietitians, pediatricians, pharmacists and an epilepsy nurse.

Inclusion, screening, and treatment is done according to (inter)national guidelines and is practiced without fluid restriction or fasting.[6,16] Before 2008, patients were routinely hospitalized (2–10 days) for KD initiation. Because the increasing number of patients eligible for KD treatment conflicted with the resources available for hospital admissions, outpatient initiation – including one daycase admission for baseline measurements and education-was introduced in 2008, in parallel with the introduction of an updated multidisciplinary protocol. Starting in 2008, initially patients aged 2 years and older were initiated on KD as outpatient. After the outpatient protocol proved to be successful, the minimum age for outpatient initiation was gradually lowered from 2 towards 1 year. After 2008, hospitalization remained indicated for children with a severe medical condition (e.g. status refractory epilepticus, respiratory insufficiency) and for those aged below 1 year. Table 1 illustrates the protocol for outpatient and inpatient diet initiation.

2.2. Study design and subjects

In this retrospective non inferiority study we included children aged 1–18 years with pharmacoresistant epilepsy (i.e. not responding to at least two AEDs) eligible for KD treatment between January 1st, 2001 and January 1st, 2017. Infants younger than 12 months of age were excluded from the study

Table 1 – Different protocols for inpatient and outpatient Ketogenic Diet initiation[a].

	Inpatient initiation	Outpatient initiation
Pre-diet consultation	1 consultation at outpatient clinic	1 consultation at outpatient clinic
Inclusion criteria	- Infants <1 year[b] - Severe medical condition	- Children >1 year
Initiation method	Step-wise approach: 1–2 days/step	Step-wise approach: 1-week/step
Admission	2–10 days	Day-case (1 day)
Duration of initiation	2–10 days	+/– 28 days
Follow-up	1-2 outpatient consultations/month (additional visits if necessary)	1-2 outpatient consultations/month (additional visits if necessary)
Effectiveness evaluation (goal: ≥ 50% seizure reduction or more)	3 months after initiation	3 months after initiation

[a] Erasmus MC Sophia Children's Hospital protocols; before 2008 inpatient initiation was obligatory for all patients.
[b] Initially 2 years, gradually lowered towards 1 year of age.

because in our center they still are routinely admitted to the hospital for KD initiation to prevent the relatively high risk of hypoglycemia. The patients were divided into two study groups: one including patients with outpatient-initiated KD, treated since 2008 (the 'outpatient group'), and a second one including patients with inpatient-initiated KD (the 'inpatient group').

From both groups, patients with severe co-morbidities (e.g. status refractory epilepticus, respiratory insufficiency) were excluded, leaving only those patients who would have been eligible for both types of diet initiation, for group comparison reasons.

This study was reviewed by the Medical Ethics Committee of the Erasmus MC, which exempted the study from formal ethical approval (MEC-2018-1705). Anonymous patient data has been retrospectively analyzed at group level. The privacy rights of patients were observed and informed consent was not required.

2.3. *Treatment*

There are different types of KD with different nutritional composition, like the Classic Diet with long chain triglycerides (LCT), the KD with medium chain triglycerides (MCT) and a combined LCT/MCT diet which are equivalent in seizure reduction.[1,17] Every KD prescribes a ratio of ketone-producing nutrients (fat) and non-ketone producing nutrients (protein plus carbohydrates). The most strict diet is the Classic Diet that mainly consists of a 4.0:1 fat-to-protein/carbohydrate ratio, but also lower ratio's (e.g. 3.5:1 or 3.0:1) are used. In our study all types of KD were used to reach adequate ketone levels (within range 2.5–6.5 mmol/l). The diets were individualized based on ketosis and tolerance.

2.4. *Data collection*

We obtained data from medical records and recorded it using standardized case record forms. Outcome measures were scored at baseline, i.e. the date of initiation (t0), at 0–1 month (t1), 1–2 months (t2) and 2–3 months (t3) after diet initiation. The end of the follow-up period was at 3 months, or, if the patient was weaned from the KD earlier, at the day when the KD was stopped. If patients restarted the KD after a first KD treatment period, only data from the first treatment period were included.

The following data were collected: gender, date of birth, etiology of epilepsy (classified as either genetic, structural-metabolic, or unknown[18]), electro-clinical syndrome at baseline, date of onset of epilepsy, number of AEDs, date of KD initiation and duration in days, KD type at baseline, route of feeding at baseline (oral/enteral), number of drop-outs before end of study period and the reasons for quitting.

2.5. *Outcome measures*

2.5.1. *Effectiveness*

To determine effectiveness of the diet, data on seizures (i.e. frequency, all types) at baseline and after 3 months of KD treatment were collected by parental report (that is, the parents were asked to indicate the average number of all types of seizures per week of the past month to the neurologist). Seizure reduction was categorized into <50% seizure reduction and ≥50% seizure reduction from baseline at 3 months. Effectiveness was defined as the proportion of cases with a seizure reduction of at least 50%.

2.5.2. *Safety*

Safety was assessed by examining the number of emergency department visits and diagnosed complications of the KD. Three types of complications were distinguished: gastrointestinal complications, compliance complications (e.g. feeding difficulties), and metabolic complications (e.g., unstable ketosis or glucose levels). The latter complications were divided into hyperketosis (blood ketones > 6.5 mmol/l) and hypoglycemia (blood glucose < 2.5 mmol/l). For the non-inferiority analysis, a composite endpoint was constructed, consisting of at least one emergency department visit or any complication within 3 months.

2.5.3. *Economic impact*

To analyze the economic impact of the two treatments, we calculated total costs of treatment from the date of initiation of the KD until the end of the follow-up period. All costs of epilepsy treatment were included, apart from the costs of the KD itself and medication costs as these were not assumed to differ significantly between the study groups. First, we

documented resource use for the following items: length of stay of hospital admission, daycase admissions, emergency department visits, outpatient visits, and consultations with the multidisciplinary KD team (either inpatient, during day-care admission, during an outpatient visit, by e-mail, or by telephone). Then, the quantities of each resource used were multiplied by cost-prices per unit, which were calculated using economic cost prices or standard prices.[19] Finally, the total costs per patient (expressed in Euros €) were calculated.

2.6. Data analysis

First, descriptive statistics were calculated. In case of a normally distributed variable, the mean and standard deviation (SD) were shown. In case of a non-normal distributed variable, the median and inter quartile range (IQR) were shown. Valid percentages for categorical variables were presented and in case of normal distribution as mean and SD, otherwise median and IQR were given. Continuous variables were compared between the groups using either unpaired t-test (normally distributed data) or Mann–Whitney U test (non-normally distributed data). For categorical data, the Pearson's Chi-square was used and presented with a P value.

Second, effectiveness and safety of the KD were compared between the two study groups. Non-inferiority of outpatient initiation was tested using one-sided 95% confidence intervals of the differences in the effectiveness and safety endpoints between the groups. The a priori, non-inferiority margin was set to an absolute difference of −10%. By the absence of comparative studies on efficacy of inpatient and outpatient initiated KD, this margin was chosen on the basis of a conservative interpretation of ILAE guidelines, which suggested a relative non-inferiority margin of 20% for non-inferiority studies on AEDs.[20] Assuming that the proportion of patients in the inpatient group who achieved a ≥50% seizure reduction was 54%,[21] a non-inferiority margin of 10% for the absolute difference is equivalent to a relative non-inferiority margin of 18.6%. Non-inferiority of outpatient initiation, compared with inpatient initiation, was assumed if the lower bound of the 95% confidence interval was greater than the non-inferiority margin of −10%. No power analysis was performed, since this study retrospectively included all patients who received the KD over a 16-year period.

Third, total health care costs were compared between the two study groups. Since cost data per patient were highly skewed to the right, we used nonparametric bootstrap techniques (based on 10,000 bootstrap samples) to derive a 95% CI for the mean difference in total costs between the groups.

A P-value of 0.05 was considered significant. Data were analyzed using Statistical Package for the Social Sciences (SPSS Statistics version 23).

3. Results

3.1. Patient and epilepsy characteristics

Of the initial 136 patients with measurable seizures, 31 patients with a severe medical condition (e.g. status refractory epilepsy, ICU admittance and respiratory insufficiency), requiring hospitalization were excluded. Of the remaining 105 patients, 43 (41%) received inpatient initiation and 62 (59%) had outpatient initiation. Fig. 1 shows a flowchart of the patient selection.

As outlined in Table 2, the study groups were comparable in terms of sex, etiology, electro-clinical syndrome and age of seizure onset. However, patients in the inpatient group started the KD significantly sooner after seizure onset (median 2.3 (IQR 3.2) versus 4.5 (IQR 5.6) years, $p = 0.01$) and were significantly younger at KD start (median 3.8 (IQR 3.8) versus 6.0 (IQR 5.8), $p = 0.001$).

There was a significant difference in dietary treatment between both groups. More inpatients were initiated on a Classic KD ($n = 16$ versus $n = 10$) and more outpatients ($n = 42$ versus $n = 19$, $p = 0.03$) were initiated on the Combined KD.

Outpatients have used fewer different AEDs prior to diet initiation (median 2.0 (IQR 1.0) versus 3.0 (IQR 2.0), $p = 0.046$).

Because the outpatient initiation protocol prescribes a slower initiation of KD, the median diet initiation duration in the outpatient group was significantly higher (27.5 days, IQR 14) compared to the inpatient group (3 days, (IQR 4.0) p =<0.001).

3.2. Effectiveness

As shown in Table 3 the effectiveness of the diet in the outpatient group (61%) was comparable to that in the inpatient group (63%). According to the statistical analysis, the one-sided confidence interval of the difference between these proportions was -0.019 ± 0.164 (or: −0.183 to 0.145). So, non-inferiority cannot be assumed, as it cannot be concluded that outpatient initiation decreases the rate of the effectiveness endpoint by less than 10 percentage points (0.10). The dropout rate before 3 months was 12% (inpatient) versus 0% (outpatient).

Reasons for discontinuation included insufficient effect of the diet ($n = 2$), adverse effects ($n = 2$), and restrictiveness ($n = 1$).

3.3. Safety

Fig. 2 shows data on safety. Gastro intestinal complaints were seen in both groups at all three time moments: showing a decline in the inpatient group but being constant in the outpatient group. In the first month, hyperketosis or hypoglycemia was found in five patients in the inpatient group and one patient in the outpatient group. In the second month of KD, hypoglycemia ($n = 2$) and hyperketosis ($n = 2$) were found only in the outpatient group. They were either caused by an intercurrent illness ($n = 2$) or hyperkinetic movement disorder ($n = 2$). After dietary adjustments (e.g. correcting with apple juice, increasing calories) hypoglycemia did not reoccur and hospitalization was not needed in these cases. In the third month of KD hyperketosis was found in one patient in both outpatient and inpatient group due to intercurrent illness in which hospitalization was not needed. Compliance complications were increasingly seen at three months in the outpatient group (13% versus 0%, $p = 0.02$). Taken together, the mean number of all complications in the outpatient group was 0.3 (SD 0.6) during all time moments, whereas the number of

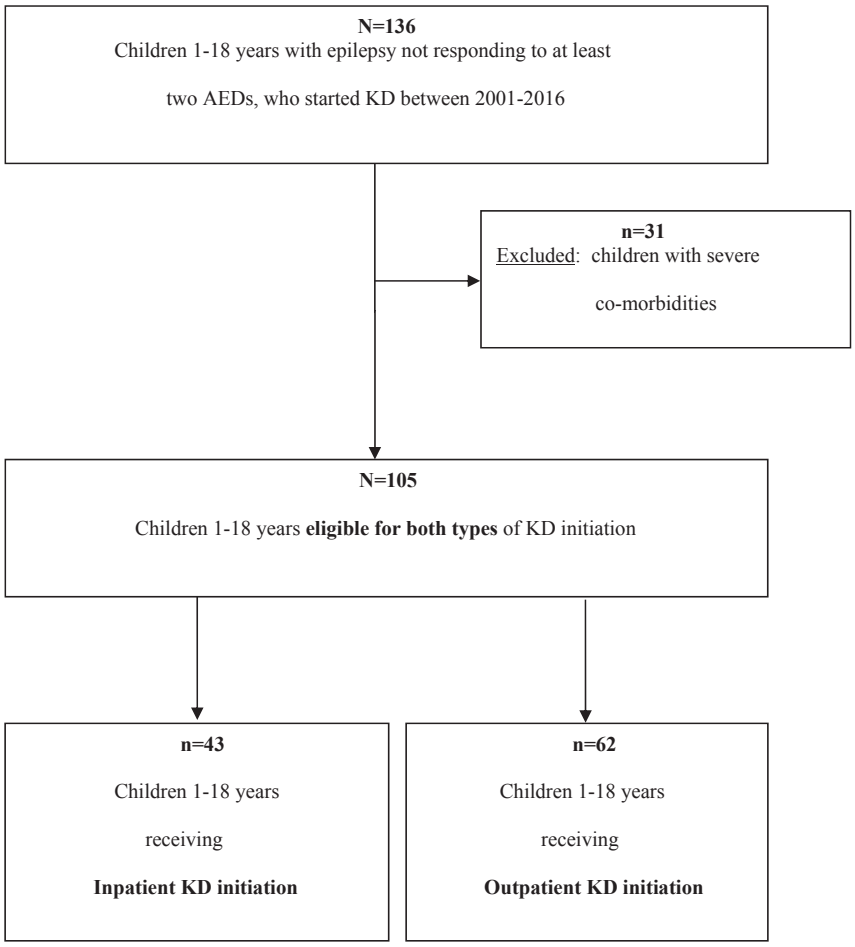


Fig. 1 – Flowchart of patient inclusion.

complications in the inpatient group declined from 0.6 (SD 0.8) at t1 to 0.1 (SD 0.3) at t3.

There was only a small difference between the study groups in the mean number of emergency visits during all study periods (0.4 (SD 0.6) inpatient versus (0.3 (SD 0.7) outpatient).

Based on the composite safety endpoint, the KD was considered safe in 36% (n = 22) of the patients in the outpatient group, as compared to 29% (n = 11) in the inpatient group. Statistical analysis revealed that the confidence interval of the difference between these proportions was 0.071 ± 0.158 (or: −0.087 to 0.229). So, outpatient initiation was non-inferior to inpatient initiation in terms of safety, as it did not decrease the rate of the composite endpoint by more than 10 percentage points.

3.4. *Economic evaluation*

As a consequence of the initiation protocol described before, inpatients were hospitalized for more days during the first month in comparison to the outpatient initiated patients (mean, 8.4 (median 8.0) versus 0.4) (Table 4). They also received more inpatient consultations by the multidisciplinary KD team in comparison to the outpatients (mean, 10.6 versus 0.5, in the first month). On the other hand, the number of day-case admissions in the first month was highest in the patients in the outpatient group (mean, 1.0 versus 0.0), as was the number of consultations by the KD team during day-case admissions (mean, 2.1 versus 0.1).

Patients from the outpatient group incurred fewer costs regarding hospital days and consultations by the interdisciplinary team, whereas costs of day-case admissions were higher in this group (Table 4).

Overall, total health care costs were € 2901 in the outpatient group, as compared to € 8195 in the inpatient group, resulting in a mean difference of € 5294 (95% confidence interval, -€ 7653 to -€ 2935; $p < 0.001$).

4. Discussion

Initiation of the KD in an inpatient setting is expensive and often involves a considerable social and economic burden for parents and children. Although almost all expert centers (92%) believe that outpatient initiation would be possible, the majority of them (20/25, 80%) does not routinely practice this.[6] The results of our study show that effectiveness and safety of the KD after outpatient initiation were similar to inpatient initiation, although the statistical analysis could only confirm non-inferiority regarding safety which might be caused by the

Table 2 – Patient characteristics (N = 105).

	Inpatients	Outpatients	P value
Number of patients	43 (41%)	62 (59%)	
Gender (male)	26 (60%)	36 (58%)	0.81
Age at start KD in years *(Median, IQR)*	3.8 (3.8)	6.0 (5.8)	0.001
Etiology of epilepsy:			0.47
Genetic:	6 (14%)	7 (11%)	
Structural/metabolic:	13 (30%)	26 (42%)	
Unknown:	24 (56%)	29 (47%)	
Electro clinical syndrome:			0.08
Non-syndromic	21 (49%)	41 (66%)	
Syndromic	22 (51%)	21 (34%)	
Age seizure onset in months *(Median, IQR)*	9.1 (23.0)	7.8 (22.8)	0.97
Number AED's at start *(Median, IQR)*	3.0 (2.0)	2.0 (1.0)	0.046
Able to change AED's during 3 months KD *(number, %)*			0.02
Yes	13 (30)	7 (11)	
No	30 (70)	55 (89)	
Time from seizure onset to KD in years *(Median IQR, range)*	2.3 (3.2) (0.22–9.4)	4.5 (5.6) (0.35–13.1)	0.01
Duration of initiation in days *(Median, IQR)*	3.0 (4)	27.5 (14)	<0.001
Type of diet at start: *(number, %)*			0.03
Classic LCT	16 (37)	10 (16)	
Ketogenic diet MCT	8 (19)	10 (16)	
Combined diets	19 (44)	42 (68)	
Way of feeding at start: *(number, %)*			0.32
Oral	28 (65)	46 (74)	
(partially) tube feeding	15 (35)	16 (26)	

Table 3 – Effectiveness of Ketogenic Diet after 3 months.

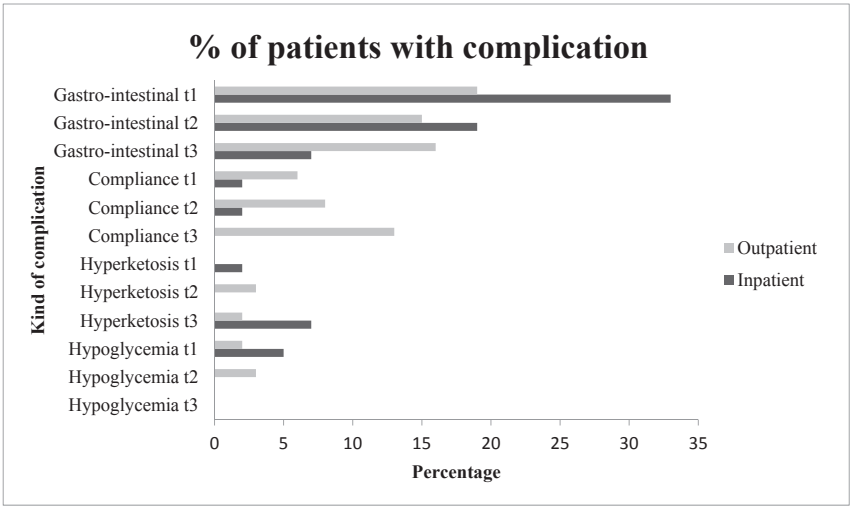
Seizure reduction (%)	Inpatients n = 43	Outpatients n = 62
≥50% seizure reduction	24 (63%)	38 (61%)
Diet ended before t3	5 (12%)	0 (0%)

sample size of our study. Importantly, based on our results, the choice for outpatient KD instead of inpatient KD may be expected to result in a statistically significant reduction of health care costs (€5294 for every patient).

To some extent, the results of our study confirm those of Vaisleib et al.,[10] who also found that the effectiveness of the KD after outpatient initiation was rather close to inpatient initiation. The overall effectiveness rate found in our study (62%, irrespective of the mode of initiation) was comparable with results in earlier studies, which were in range of 38–85%.[22]

Regarding safety, we observed that during the first month after KD initiation, inpatients more frequently experienced gastro-intestinal complications. Vaisleib et al.[10] also found a trend towards a greater frequency of adverse effects in inpatients. They ascribe this difference in complications to the more compromised medical status of patients who required inpatient initiation. In our study, this is less likely to be the cause, as the patients in compromised medical condition and the vulnerable group of infants younger than 12 months were excluded from both groups (Fig. 1), although some bias cannot be ruled out. An alternative explanation could be a difference in tolerability between the types of diet, which differed between the study groups. However, the RCT of Neal et al.[23] showed no difference concerning the incidence of side effects between either Classic KD or KD with MCT. Studies on tolerability of combined diets are lacking. It is more likely that the duration of KD initiation might have contributed to the higher incidence of gastro-intestinal complications in our inpatient group, which was much shorter than in the outpatient group (median of 3 days versus 27.5 days).

In our study, compliance complications were seen in both patient groups. Surprisingly, at three months significantly more patients from the outpatient group reported compliance complications (in terms of food refusal and compromised daily intake) caused by behavior problems (such as non-acceptance, anger, sadness) although it did not result in diet termination. The higher rate of compliance complications



Legenda: KD= Ketogenic Diet, t1 = 0-1 month after KD initiation; t2 = 1-2 months after KD initiation; t3 = 2-3 months after KD initiation.

Fig. 2 – Safety after 1, 2 and 3 months Ketogenic Diet.

Table 4 – Resource use and costs of treatment.

	Inpatients				Outpatients			
	t1 (n = 43)	t2 (n = 42)	t3 (n = 38)	Total (n = 38)	t1 (n = 62)	t2 (n = 62)	t3 (n = 62)	Total (n = 62)
Resource use								
Hospital days (ward)	8.4 (4.7)	1.3 (4.1)	0.5 (1.5)	9.8 (6.6)	0.4 (1.2)	0.8 (3.0)	1.2 (5.6)	2.4 (7.4)
Day-care admissions	0.0 (0.2)	0.1 (0.4)	0.1 (0.3)	0.3 (0.8)	1.0 (0.0)	0.0 (0.2)	0.0 (0.1)	1.0 (0.3)
Emergency department visits	0.1 (0.4)	0.1 (0.4)	0.1 (0.3)	0.4 (0.6)	0.1 (0.2)	0.1 (0.3)	0.1 (0.4)	0.3 (0.7)
Outpatient visits	0.5 (0.8)	0.6 (0.7)	0.7 (0.8)	1.8 (1.3)	0.4 (0.7)	0.4 (0.6)	0.6 (1.0)	1.4 (1.6)
Consultations by the multidisciplinary team:								
Inpatient	10.6 (5.9)	0.8 (3.0)	0.8 (2.1)	11.6 (6.8)	0.5 (1.9)	1.0 (3.7)	0.9 (4.9)	2.4 (8.2)
During day-case admission	0.1 (0.4)	0.1 (0.4)	0.1 (0.4)	0.3 (0.7)	2.1 (0.2)	0.0 (0.3)	0.0 (0.0)	2.1 (0.3)
During outpatient visit	0.6 (2.3)	0.9 (1.1)	0.7 (1.0)	2.2 (3.6)	0.5 (0.9)	0.5 (0.7)	0.7 (1.2)	1.6 (1.9)
By e-mail	0.6 (0.8)	0.9 (1.2)	0.4 (0.8)	2.0 (2.0)	0.8 (1.0)	1.2 (1.1)	0.8 (0.9)	2.8 (2.2)
By telephone	3.3 (2.2)	2.0 (1.9)	1.6 (1.4)	7.1 (3.9)	3.4 (1.7)	2.5 (1.6)	1.8 (1.7)	7.8 (3.3)
Costs								
Hospital days	€ 6104 (3397)	€ 947 (2983)	€ 383 (1107)	€ 7116 (4776)	€ 282 (907)	€ 552 (2162)	€ 850 (4043)	€ 1711 (5355)
Day-case admissions	€ 28 (127)	€ 71 (235)	€ 47 (163)	€ 157 (452)	€ 595 (0)	€ 19 (106)	€ 10 (76)	€ 624 (169)
Emergency department visits	€ 25 (62)	€ 25 (62)	€ 14 (48)	€ 66 (104)	€ 11 (43)	€ 17 (61)	€ 20 (65)	€ 49 (120)
Outpatient visits	€ 16 (27)	€ 22 (26)	€ 24 (27)	€ 62 (44)	€ 14 (25)	€ 14 (22)	€ 21 (37)	€ 49 (55)
Consultations by the multidisciplinary team	€ 586 (292)	€ 124 (167)	€ 101 (117)	€ 789 (376)	€ 222 (101)	€ 118 (203)	€ 111 (237)	€ 451 (433)
Total costs	€ 6765 (3631)	€ 1188 (3087)	€ 569 (1193)	€ 8195 (5067)	€ 1127 (1042)	€ 720 (2395)	€ 1002 (4233)	€ 2901 (5840)

Data expressed as mean (standard deviation). KD=Ketogenic Diet, t1 = 0–1 month after KD initiation; t2 = 1–2 months after KD initiation; t3 = 2–3 months after KD initiation.

may be related to autism spectrum disorders (ASD) and associated behavior problems, which seemed to be more common in the outpatient group. In the literature, it has been shown that ASD are a co-morbidity in many epilepsy syndromes and that it is difficult for patients with ASD to adhere to the diet.[24,25]

Not surprisingly, length of hospital stay was longer in the inpatient initiated group than in the outpatient group, who had only one day-case admission. The fact that the patients in the inpatient group were admitted for a median period of 8 days (exceeding the median 3 days of KD initiation which can be explained by, among other things, difficulties in managing the child's epilepsy) contributed to the higher costs in this group. Patients from the inpatient group required more consultations by the KD team during the first month of the KD treatment. One explanation could be the era in which the inpatient KD was initiated; this was in the start-up period of the multidisciplinary team. Another explanation could be that, while parents from both groups received all the necessary information and education regarding the KD during a short period of time (either during one day-case admission or during hospital admission), the inpatients' parents were allowed less time to develop the skills of preparing and calculating the diet (during hospitalization that took a median of 8 days) than the outpatients' parents (during a median period for KD initiation of 27.5 days). This may have resulted in the need for extra support by the team when they started applying this strict and complex diet at home.

The economic analysis was restricted to health care costs. However, outpatient KD initiation may also have an impact on other costs, such as costs of productivity losses. For instance, it may reduce the number of absence days from work of parents and reduce transportation costs from home to hospital and vice versa. However, outpatient treatment possibly also requires a substantial time investment (and absence from work) from parents. Furthermore, outpatient initiation may prevent the inconvenience and stress caused by hospital admission in both patients, parents and siblings, contributing to patients' and parents' satisfaction and quality of family life. This would be a fruitful avenue for future research.

One of the strengths of our study is the strictly protocolled manner of KD initiation, which resulted in uniform treatment regimens and a well-maintained database. Moreover, our study is the first to describe the cost difference between inpatient and outpatient initiation and includes a larger patient cohort than the study of Vaisleib et al.[10]

Our study also has some limitations that need to be addressed. First, the retrospective design of our study precludes drawing a strict cause-and-effect relationship, which would require a prospective RCT. There might be a period effect, in that the administration of more effective AEDs and the introduction of the evidence-based protocol in 2008 may lead to better seizure control. However, this probably did not result in systematic bias, because in both groups, seizure frequency in each patient was compared to its own baseline. Furthermore, to avoid selection bias, we tried to construct comparable groups by excluding from the earliest group those patients who would not have been eligible for outpatient initiation would it have been available at the time. The inpatient group included some children (between 1 and 2 years of age) commenced on the KD after 2007. We feel, however, that this did not bias our results, since these patients were still initiated on an inpatient basis was not because they were more severely affected but was related to the gradual implementation of outpatient initiation. The study groups were indeed comparable in certain important respects (sex, etiology, electro-clinical syndrome, age of seizure onset, and way of feeding). Yet, differences in other patient characteristics

(i.e., age and number of AEDs at start of the KD, time between epilepsy onset and start of the KD, and type of KD) did exist, which might mean that either one of the study groups included patients with less complex epilepsy. It is unknown whether the groups were similar in terms of the amount of seizures at baseline, because the amount of seizures was classified by the neurologist based on parent reports and not on exact numbers. Finally, our results represent a rather small sample from one center, so they may be limited in their generalizability.

5. Conclusions

Although firm conclusions from this study may not be reached, these results suggest that outpatient initiation of the KD is non-inferior to inpatient initiation in terms of safety. Albeit non-inferiority of outpatient initiation in terms of effectiveness could not be statistically confirmed, effectiveness rates were found to be similar. Moreover, outpatient initiation seems to reduce health care costs, mainly due to a reduction in the cost of hospital admissions. This could be especially helpful to promote access to the KD in low-resource countries. We conclude that a multidisciplinary approach of outpatient initiation of the KD is a realistic and safe option in patients over one year of age whose medical condition allows outpatient initiation. This finding supports the opinion of the majority of expert centers that outpatient initiation is possible.[6] Our study might also help to stimulate management decisions to make the KD more widely available for children in the future.

Sources of funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflict of interest

None of the authors has any conflict of interest to disclose.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejpn.2019.06.001.

REFERENCES

1. Neal EG, Cross JH. Efficacy of dietary treatments for epilepsy. *J Hum Nutr Diet* 2010 Apr;**23**(2):113–9. https://doi.org/10.1111/j.1365-277X.2010.01043.x.
2. Schwartz RH, Eaton J, Bower BD, Aynsley-Green A. Ketogenic diets in the treatment of epilepsy: short-term clinical effects. *Dev Med Child Neurol* 1989 Apr;**31**(2):145–51. https://www.ncbi.nlm.nih.gov/pubmed/2786822.
3. Freeman JM, Vining EP, Pillas DJ, Pyzik PL, Casey JC, Kelly LM. The efficacy of the ketogenic diet-1998: a prospective evaluation of intervention in 150 children. *Pediatrics* 1998 Dec;**102**(6):1358–63. https://www.ncbi.nlm.nih.gov/pubmed/9832569.
4. Hemingway C, Freeman JM, Pillas DJ, Pyzik PL. The ketogenic diet: a 3- to 6-year follow-up of 150 children enrolled prospectively. *Pediatrics* 2001 Oct;**108**(4):898–905. https://www.ncbi.nlm.nih.gov/pubmed/11581442.
5. Martin-McGill KJ, Jackson CF, Bresnahan R, Levy RG, Cooper PN. Ketogenic diets for drug-resistant epilepsy. *Cochrane Database Syst Rev* 2018 Nov 7;**11**:CD001903. https://doi.org/10.1002/14651858.CD001903.pub4.
6. Kossoff E, Zupec-Kania B, Auvin S, Ballaban-Gil K, Bergqvist A, Blackford R, et al. Optimal clinical management of children receiving dietarytherapies for epilepsy: updated recommendations of the International Ketogenic Diet Study Group. *Epilepsia Open* 2018:1–18. 10.1002.
7. Kossoff EH, Al-Macki N, Cervenka MC, Kim HD, Liao J, Megaw K, et al. What are the minimum requirements for ketogenic diet services in resource-limited regions? Recommendations from the International League Against Epilepsy Task Force for Dietary Therapy. *Epilepsia* 2015 Sep;**56**(9):1337–42. https://doi.org/10.1111/epi.13039.
8. van der Louw E, van den Hurk D, Neal E, Leiendecker B, Fitzsimmon G, Dority L, et al. Ketogenic diet guidelines for infants with refractory epilepsy. *Eur J Paediatr Neurol* 2016 Nov;**20**(6):798–809. https://doi.org/10.1016/j.ejpn.2016.07.009.
9. Kossoff EH, Zupec-Kania BA, Amark PE, Ballaban-Gil KR, Christina Bergqvist AG, Blackford R, et al. Optimal clinical management of children receiving the ketogenic diet: recommendations of the International Ketogenic Diet Study Group. *Epilepsia* 2009 Feb;**50**(2):304–17. EPI1765 [pii] 10.1111/j.1528-1167.2008.01765.x.
10. Vaisleib II , Buchhalter JR, Zupanc ML. Ketogenic diet: outpatient initiation, without fluid, or caloric restrictions. *Pediatr Neurol* 2004 Sep;**31**(3):198–202. https://doi.org/10.1016/j.pediatrneurol.2004.03.007.
11. Wirrell EC, Darwish HZ, Williams-Dyjur C, Blackman M, Lange V. Is a fast necessary when initiating the ketogenic diet? *J Child Neurol* 2002 Mar;**17**(3):179–82. 10.1177/088307380201700305.
12. de Kinderen RJ, Lambrechts DA, Wijnen BF, Postulart D, Aldenkamp AP, Majoie MH, et al. An economic evaluation of the ketogenic diet versus care as usual in children and adolescents with intractable epilepsy: an interim analysis. *Epilepsia* 2016 Jan;**57**(1):41–50. https://doi.org/10.1111/epi.13254.
13. Kayyali HR, Luniova A, Abdelmoity A. Ketogenic diet decreases emergency room visits and hospitalizations related to epilepsy. *Epilepsy Res Treat* 2016;**2016**:5873208. 10.1155/2016/5873208.
14. Mandel A, Ballew M, Pina-Garza JE, Stalmasek V, Clemens LH. Medical costs are reduced when children with intractable epilepsy are successfully treated with the ketogenic diet. *J Am Diet Assoc* 2002 Mar;**102**(3):396–8. https://www.ncbi.nlm.nih.gov/pubmed/11902372.
15. Whiting S, Donner E, RamachandranNair R, Grabowski J, Jette N, Duque DR. Decreased health care utilization and health care costs in the inpatient and emergency department setting following initiation of ketogenic diet in pediatric patients: the experience in Ontario, Canada. *Epilepsy Res* 2017 Mar;**131**:51–7. https://doi.org/10.1016/j.eplepsyres.2017.01.013.
16. Hurk vd TAM, Louw van der EJTM. *Dietary treatment guideline for the ketogenic diet for children with refractory epilepsy, Evidence based treatment for multidisciplinary treatment*. Utrecht: University Medical Center Utrecht; 2010.
17. Neal EG, Chaffe H, Schwartz RH, Lawson MS, Edwards N, Fitzsimmons G, et al. The ketogenic diet for the treatment of

childhood epilepsy: a randomised controlled trial. *Lancet Neurol* 2008 Jun;**7**(6):500–6. S1474-4422(08)70092-9 [pii] 10.1016/S1474-4422(08)70092-9.

18. Berg AT, Berkovic SF, Brodie MJ, Buchhalter J, Cross JH, van Emde Boas W, et al. Revised terminology and concepts for organization of seizures and epilepsies: report of the ILAE Commission on Classification and Terminology, 2005–2009. *Epilepsia* 2010 Apr;**51**(4):676–85. https://doi.org/10.1111/j.1528-1167.2010.02522.x.
19. Manual for costing research; methods and reference prices for economic evaluations in health care. In: Institute NHc, editor. *Updated edition 2015 ed*. Diemen: National Healt care Institute; 2015.
20. Glauser T, Ben-Menachem E, Bourgeois B, Cnaan A, Guerreiro C, Kalviainen R, et al. Updated ILAE evidence review of antiepileptic drug efficacy and effectiveness as initial monotherapy for epileptic seizures and syndromes. *Epilepsia* 2013 Mar;**54**(3):551–63. https://doi.org/10.1111/epi.12074.
21. Li HF, Zou Y, Ding G. Therapeutic success of the ketogenic diet as a treatment option for epilepsy: a meta-analysis. *Iran J Pediatr* 2013 Dec;**23**(6):613–20. https://www.ncbi.nlm.nih.gov/pubmed/24910737.
22. Martin K, Jackson CF, Levy RG, Cooper PN. Ketogenic diet and other dietary treatments for epilepsy. *Cochrane Database Syst Rev* 2016 Feb 9;**2**:CD001903. https://doi.org/10.1002/14651858.CD001903.pub3.
23. Neal EG, Chaffe H, Schwartz RH, Lawson MS, Edwards N, Fitzsimmons G, et al. A randomized trial of classical and medium-chain triglyceride ketogenic diets in the treatment of childhood epilepsy. *Epilepsia* 2009 May;**50**(5):1109–17. EPI1870 [pii] 10.1111/j.1528-1167.2008.01870.x.
24. Bandini LG, Anderson SE, Curtin C, Cermak S, Evans EW, Scampini R, et al. Food selectivity in children with autism spectrum disorders and typically developing children. *J Pediatr* 2010 Aug;**157**(2):259–64. S0022-3476(10)00137-X [pii] 10.1016/j.jpeds.2010.02.013.
25. Curtin C, Hubbard K, Anderson SE, Mick E, Must A, Bandini LG. Food selectivity, mealtime behavior problems, spousal stress, and family food choices in children with and without autism spectrum disorder. *J Autism Dev Disord* 2015 Oct;**45**(10):3308–15. https://doi.org/10.1007/s10803-015-2490-x 10.1007/s10803-015-2490-x [pii].