Efficacy and safety of ketogenic diet in infants with epilepsy: KIWE RCT

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Scientific summary

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Scientific summary

Background

Many infancy-onset epilepsies are poorly responsive to antiseizure medicines (ASMs) with poor prognosis for neurodevelopmental outcome. Ketogenic diets (KDs), which are high-fat, low-carbohydrate diets, have been shown to reduce seizures in older children with drug-resistant epilepsy. No high-quality evidence is available for infants.

Objectives

In this open-label randomised controlled trial, we compared the efficacy of the classical KD to a further appropriate ASM in infants with drug-resistant epilepsy. The primary outcome was the number of seizures recorded during weeks 6–8, accounting for the baseline rate and randomised group.

Secondary outcomes at 8 weeks were the number of infants seizure-free in weeks 6–8 of the intervention period, responder rate (defined as the number showing more than a 50% improvement in seizure frequency compared to baseline), tolerance to KD and relationship between medium-chain fatty acids and seizure control. Secondary outcomes at 12 months were retention on treatment, quality of life and neurodevelopmental outcome. Adverse events were recorded throughout the trial. Serious adverse events were reported to the study sponsor.

Methods

Infants (age 1–24 months) with epilepsy, with an average ≥ 4 seizures/week and previous trials of ≥ 2 ASMs were recruited from 19 hospitals in the UK. Following a 1- or 2-week observation period, during which there were no changes to regular ASMs (emergency seizure treatments continued as required), participants were randomised to receive a classical KD or a further ASM for 8 weeks, using a computer-generated schedule without stratification. An allocation ratio of 1 : 1.35 was used to account for the therapist effect in the KD group only. Treatment allocation was concealed from research nurses involved in patient care, but not from participants. The primary outcome was the number of seizures/day recorded during weeks 6–8. All analyses were intention to treat.

The following assessments were performed in all infants prior to randomisation: medical history, physical examination, administration of the Infant Toddler Quality of Life Questionnaire™ (ITQOL-97; © HealthActCHQ Inc. 2013) and Vineland Adaptive Behaviour Scales (Vineland™-II), and clinical laboratory assessments. Food diaries required for diet calculation were returned from parents/guardians of all participants a maximum of 1 week into the observation period.

Parents/carers were asked to keep daily seizure diaries throughout the 8-week treatment periods for participants in both arms. Thereafter, they were requested to reduce seizure recording to at least 1–2 days per week, as clinically indicated, until 28 days before the final 12-month visit, when daily seizure recording recommenced.

Follow-up visits were arranged at 4 weeks, 8 weeks, and 6, 9 and 12 months. Assessments included clinical review, physical examination, documentation of seizure frequency from seizure diaries, review of adverse events and concomitant medication, clinical laboratory assessments (8 weeks, and 6 and 12 months) and completion of tolerability questionnaire by parents/carers together with research nurses, the ITQOL-97 (8 weeks and 12 months) and Vineland-II (12 months).

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After the 8-week assessment, according to the infant's clinical response to treatment (seizure outcome and tolerability), KD or ASM was then continued or changed; those randomised to the ASM arm then had the opportunity to start KD.

Results

Of 136 eligible infants, 78 were randomised to KD and 58 to ASM. Of 78 infants who started KD, 67 (86%) continued to 8 weeks, of which 61 (78%) had primary outcome data available; 53 (91% of those randomised to ASM group) started a further ASM, 49 (84%) continued to 8 weeks and 47 (81%) had primary outcome data available.

The median number of daily seizures was not significantly different in both groups at 8 weeks [KD 5 (1, 16); ASM 3 (2, 11), incidence rate ratio (IRR) 1.33, 95% confidence interval (CI) 0.84 to 2.11; $p = 0.22$]. The odds ratio (OR) of achieving ≥ 50% seizure reduction was 1.21 (95% CI 0.55 to 2.65) and 0.88 (0.27 to 2.80) for seizure freedom. A total of 7/63 infants (11%) in the KD group were seizure-free, compared with 6/48 (13%) in the ASM group (OR 0.88, 95% CI 0.27 to 2.80). A higher proportion of infants in the ASM group changed the number or dose of concurrent ASMs during the intervention period [24/48 (50%)] compared to KD [9/66 (14%)].

The side-effect score at 8 weeks was similar in both groups [KD median 40; interquartile range (IQR) 38–42; ASM median 41 IQR 39–44) and there were no clinically significant differences other than those expected in clinical or laboratory parameters between groups.

At 8 weeks, median scores within the ITQOL-97 were numerically higher (suggesting better health) in the KD group for 7 of the 12 concepts. The infant's pain, its global behaviour, impact on parental time and family cohesion were equal between the two groups, although general perceptions of the infant's health were numerically higher in the ASM arm. A numerically larger proportion of parents/guardians of infants in the KD group perceived their child's health to be 'much better than a year ago' (10/40, 25%) compared to those in the ASM group (3/32, 9%); numerically more parents/guardians of infants in the ASM group perceived their child's health to be 'much worse than a year ago' (8/32, 25%) compared to those in the KD group (2/40, 5%).

Of 66 infants randomised to KD > 12 months before the study end date, 31 (47%) continued the diet to 12 months; of 47 randomised to further ASM > 12 months before the study end date, 21 (45%) continued the ASM to 12 months.

For those who reported data, there were no differences between groups for any concept within the ITQOL-97 at 12 months, except for the infant's temperament and mood (coefficient −6.09, 95% CI −11.63 to −0.54) and the infant getting along with others (coefficient −6.79, 95% CI −12.97 to −0.60), which favoured the ASM group. A similar proportion of parents/guardians of infants in both groups perceived their child's health to be 'much better than a year ago' (12/24 50% ASM; 11/30 37% KD) or 'much worse than a year ago' (0/24, 0% ASM; 1/30, 3% KD).

Within the Vineland-II there were neither significant differences between groups in the overall standardised score nor domain standard scores at 12 months. The Daily living domain sum of v-scale scores was nominally improved in the ASM group (coefficient 2.23, 95% CI −4.22 to −0.25).

A total of 73 serious adverse events (SAEs) were reported in the ASM group and 161 in the KD group. A similar proportion of infants in both groups reported at least 1 SAE (43% ASM; 51% KD) – most commonly seizures. Three infants died in the KD arm, all considered unrelated to treatment.

Conclusions

There was no evidence that KD was better than further ASM in achieving seizure control in infants with epilepsy. The two treatments were similarly tolerated and KD appeared safe to use in infants with epilepsy. KD could be a treatment option in infants whose seizures continue despite trial of two standard ASMs. Further trials are needed with larger cohorts at 12-month follow-up and beyond, particularly to look at quality of life and neurodevelopment, perhaps with alternative study design.

Study registration

This study was registered as EudraCT 2013-002195-40.

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