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Original article

Intermittent feeding with an overnight fast versus 24-h feeding in critically ill neonates, infants, and children: An open-label, single-centre, randomised controlled trial

Karlien Veldscholte [a], Arnout B.G. Cramer [a], Rogier C.J. de Jonge [a], Dimitris Rizopoulos [b, c], Koen F.M. Joosten [a], Sascha C.A.T. Verbruggen [a, *]

[a] Department of Neonatal and Paediatric Intensive Care, Division of Paediatric Intensive Care, Erasmus MC Sophia Children's Hospital, Rotterdam, the Netherlands
[b] Department of Biostatistics, Erasmus MC, Rotterdam, the Netherlands
[c] Department of Epidemiology, Erasmus MC, Rotterdam, the Netherlands

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SUMMARY

Background & aims: Critically ill children are fed day and night, assuming this improves enteral tolerance and the probability of achieving nutritional goals. It was previously shown that a fasting response, reflected by increased ketosis, at least partly explained the beneficial outcome of delayed initiation of supplemental parenteral nutrition. This study aims to investigate whether an overnight fast increases ketosis and is feasible and safe in critically ill children.

Methods: The *Continuous versus Intermittent Nutrition in Paediatric Intensive Care (ContInNuPIC)* study is a randomised controlled trial in a tertiary referral Paediatric Intensive Care Unit (PICU) in the Netherlands. Critically ill children (term newborn-18 years) with an expected PICU stay ≥48 h, dependent on artificial nutrition, were eligible. Participants were randomly assigned (1:1, stratified for age group) to intermittent feeding, with interruption of feedings during an age-dependent overnight period of eight to 12 h, or to continuous feeding, with the administration of feedings day and night. In both groups, similar daily caloric targets were pursued. For children younger than one year, mandatory minor glucose infusions were provided during fasting. The primary outcome was the feasibility, defined as two conditions (1): a significant difference in the patients' highest daily ketone (3-β-hydroxybutyrate, BHB) levels during each overnight period, and (2): non-inferiority regarding daily caloric intake, examined using a two-part mixed-effects model with a predefined non-inferiority margin of 33%, in an intention-to-treat analysis. The study is registered in the Netherlands Trial Register (NL7877).

Results: Between May 19, 2020, and July 13, 2022, 140 critically ill children, median (first quartile; third quartile) age 0.3 (0.1; 2.7) years, were randomised to intermittent (n = 67) or continuous feeding (n = 73). In the intermittent feeding group, BHB levels were significantly higher (median 0.4 (0.2; 1.0) vs. 0.3 (0.1; 0.7) mmol/L, $p < 0.001$). The ratio of total caloric intake in the intermittent feeding group to the intake in the continuous feeding group was not consistently significantly more than 0.67, thus not proving non-inferiority. No severe, resistant hypoglycaemic events, nor severe gastrointestinal complications related to the intervention occurred, and feeding intolerance did not occur more often in the intermittent than in the continuous feeding group.

Conclusion: Compared with day and night feeding, intermittent feeding with an overnight fast and mandatory glucose infusion for children younger than one year marginally increased ketosis and did not lead to more hypoglycaemic incidents in critically ill children. Because non-inferiority regarding daily caloric intake was not proven, the feasibility of an overnight fast could not be shown in the current study. However, as feeding intolerance did not increase during the condensed feeding periods, the nutritional intake was probably limited by the prescription of nutrition and interruptions. More research is needed to determine the optimal level and duration of clinically relevant ketosis and the best method to achieve this.

* Corresponding author. Postbus 2060, 3000 CB, Rotterdam, the Netherlands.
E-mail address: s.verbruggen@erasmusmc.nl (S.C.A.T. Verbruggen).

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Abbreviations

CI	confidence interval
ContInNuPIC	Continuous versus Intermittent Nutrition in Paediatric Intensive Care
EN	enteral nutrition
Kcal	kilocalorie
NICU	neonatal intensive care unit
NTBR	not to be resuscitated
PELOD	paediatric logistic organ dysfunction
PEPaNIC	Paediatric Early versus Late Parenteral Nutrition in the Intensive Care Unit
PICU	paediatric intensive care unit
PIM3	Paediatric Index of Mortality 3
PN	parenteral nutrition
PMA	postmenstrual age
pREE	predicted resting energy expenditure
Q1; Q3	first quartile; third quartile
RCT	randomised controlled trial
SAE	serious adverse events

1. Introduction

For decades, the focus of nutritional therapy for critically ill children has been to achieve early and high caloric intakes. However, the *Paediatric Early versus Late Parenteral Nutrition in the Intensive Care Unit (PEPaNIC)* randomised controlled trial (RCT) showed remarkable benefits of withholding supplemental parenteral nutrition (PN) in the first week of paediatric critical illness both in the short term as in the long term [1–3]. These findings led to the adaptation of international guidelines, which now advise limiting caloric intake to the resting energy expenditure (REE) level in the acute phase of critical illness [4–6].

Secondary analyses of the PEPaNIC RCT revealed that a fasting response, also characterised by increased ketosis, mediated part of the beneficial impact of withholding PN in the first week of paediatric critical illness [7,8]. Ketones are not only an important alternative energy source for the brain and other organs (e.g. muscle), but have several other signalling functions as well in controlling oxidative stress and inflammation, improving mitochondrial function, and protecting cell function [9]. The potential benefit of ketones during critical illness is therefore easy to conceptualise. If the ketogenic fasting response could be enhanced, e.g., with higher ketone concentrations and a longer duration of ketosis, while still providing sufficient amounts of nutrients, clinical outcomes might improve even more. Intermittent feeding, a 'fasting mimicking' strategy, in which prolonged fasting periods are alternated with feeding periods, might be a safe way to effectuate this [10,11]. In addition to increased ketosis, this strategy might potentially be beneficial during critical illness through several other mechanisms, such as improving enteral tolerance, insulin resistance, autophagy, avoidance of the muscle-full effect, and protection of the circadian rhythm [10,12]. It is unknown what the optimal duration and timing of the fasting period should be to exert such beneficial mechanisms in critically ill children. For instance, a fasting period implemented overnight might benefit sleep and the circadian rhythm [10,11].

Until now, studies investigating the effects of intermittent feeding in critically ill children have only examined bolus feedings, with intervals of not more than 4 h between feedings, rather than intermittent feeding with prolonged fasting periods, and none of the studies has focussed on a fasting period during the night [13–18]. Moreover, these studies used the nutritional intake and the occurrence of gastrointestinal symptoms as outcomes, disregarding the length of the fasting period and the possible fasting response [10]. Therefore, this study aims to investigate whether intermittent feeding with an overnight fast, as compared with day and night feeding, increases the fasting response, reflected by enhanced ketosis, and is feasible and safe in critically ill children.

2. Methods

2.1. Study design and participants

The *Continuous versus Intermittent Nutrition in Paediatric Intensive Care* (ContInNuPIC) study is a single-centre, investigator-initiated RCT and was conducted in the Paediatric intensive care unit (PICU) of the Erasmus MC Sophia Children's Hospital (Rotterdam, the Netherlands), a tertiary referral PICU. An extensive study protocol has previously been published [19]. In brief, from May 19, 2020, until the pre-planned sample size of 140 participants was reached on July 13, 2022, critically ill children (term newborn to 18 years) with an expected PICU stay for ≥48 h, dependent on artificial nutrition, and not meeting exclusion criteria, were eligible for inclusion. Exclusion criteria were: preterm neonates (<37 weeks PMA upon admission to the PICU), do not resuscitate code at the time of PICU admission, expected death within 24 h, readmission to the PICU >48 h after already having been included in the ContInNuPIC trial, transfer from another PICU or NICU after a stay of ≥3 days or having received artificial nutrition (any PN or enteral nutrition [EN] with a caloric intake >10% of predicted REE per day), ketoacidotic or hyperosmolar coma, metabolic diseases requiring a specific diet or with a contraindication to (intermittent) feeding, short bowel syndrome or other conditions requiring PN before admission, and participation in another RCT in the PICU with an intervention that might influence the clinical outcome. The ContInNuPIC RCT was performed following the ethical principles of the Declaration of Helsinki and Good Clinical Practice Guidelines and was approved by the Dutch national ethical review board and the institutional review board. The study was registered in the Netherlands Trial Register (NL7877). All participants and/or their parents or legal guardians provided written informed consent. This study follows the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline [20].

2.2. Randomisation and blinding

Allocation to the intermittent or continuous feeding group was executed by the ALEA randomisation tool (ALEA Clinical, FormsVision), a dedicated computerised system accessible 24 h a day and seven days a week. The computer algorithm allocated every consecutive eligible patient to one of the two treatment arms in a one-to-one allocation ratio using permuted blocks of ten. Patients were stratified into three age groups: neonates (≤44 weeks postmenstrual age (PMA)), infants (>44 weeks PMA and <1 year), and children (≥1 year). It was considered infeasible to blind treating physicians and patients for the allocated treatment.

2.3. Procedures

Nutritional intake was provided according to the current paediatric critical care nutrition guidelines [4–6]. In both treatment groups, similar daily caloric targets were pursued and nutritional intake was gradually increased at the treating physician's discretion, taking the current local nutritional protocol into account (Supplemental Fig. 1) [19]. The resting energy expenditure (REE) was predicted using the body weight–based or body weight and

length–based Schofield equation (pREE) [21]. The target intake was 100% of pREE at the end of the first week and 130–200% of pREE, depending on the child's weight (the heavier (older) the child, the lower the target), at the end of the second week. During the first week of PICU stay, trace elements, minerals and vitamins were administered parenterally in both groups if enteral nutrition (EN) was insufficient (<80% target intake) [22]. If EN was insufficient beyond day seven, macronutrients were provided through PN until EN reached ≥80% of the target intake. Among patients assigned to the intermittent feeding group, nutrition was interrupted during an age-dependent overnight fasting period (neonates: 2 am–10 am; infants: 0 am–10 am; children: 10 pm-10 am). Among patients assigned to the continuous feeding group, nutrition was administered day and night, with a maximum interruption period of 2 h, excluding feeding interruptions due to clinical PICU care (e.g. interventions such as intubation and surgical procedures). In patients requiring PN in the intermittent feeding group, PN was administered at half the infusion speed during the first and last hour to reduce the risk of swift metabolic shifts [19]. By order of the national ethical review board on account of safety concerns, among patients assigned to the intermittent feeding group, a glucose infusion was provided during the overnight feeding interruption period (1.0 mg/kg/minute in neonates and 0.5 mg/kg/minute in infants). The study intervention lasted until admission day 14, initiation of oral intake, or discharge from the PICU, whichever came first.

During the intervention period, in all patients, plasma glucose concentrations were measured regularly using a blood gas analyser (ABL90 FLEX PLUS, Radiometer) or point-of-care meter (Accu-Chek Inform II, Roche Diabetes Care), and ketone levels (3-β-hydroxybutyrate, BHB) were measured at set time points using the Stat-Strip Glucose/Ketone meter (Nova Biomedical). Data regarding nutritional intake, gastrointestinal tolerance, and clinical course were collected daily during the study intervention period. All clinically relevant outcome measures were collected until 30 days after inclusion. The patient data were stored in a logged database that was closed prior to the execution of statistical analyses. The accuracy of the data was monitored by an independent study monitor.

2.4. Outcomes

The primary outcome was the feasibility, defined as two conditions 1): a significant difference in the patients' highest daily BHB levels during each overnight period, and 2) non-inferiority regarding daily caloric intake [19]. The amount of nutritional intake was defined as the ratio of daily total caloric intake over the predicted REE (total kcal/pREE). The total caloric intake included enteral nutrition, parenteral nutrition, and infusions containing glucose. The primary safety outcome was defined as the incidence of severe and resistant hypoglycaemic events and severe gastrointestinal complications [19]. Severe and resistant hypoglycaemic events were defined as hypoglycaemia (blood glucose <2.6 mmol/L) with clinical symptoms (e.g., pallor, transpiration, irritability, lethargy, loss of consciousness, and convulsions) or severe hypoglycaemia (blood glucose <2.2 mmol/L), with resistance to parenteral glucose administration (no elevation of blood glucose within 1 h after parenteral glucose bolus (1 mL/kg glucose 10%) administration and elevation of glucose infusion). Severe gastrointestinal complications were defined as acute, nonocclusive mesenteric ischemia (e.g., intestinal perforation and necrotising enterocolitis) not attributed to an anatomical substrate (e.g., volvulus). Secondary safety outcomes included hypoglycaemic events, defined as blood glucose <2.2 mmol/L, hyperglycaemic events, defined as blood glucose >10.0 mmol/L, and hyperlactataemia events, defined as lactate >2.0 mml/L, and mortality during PICU stay, during hospital stay, and in 30 days. A secondary feasibility outcome was the feeding intolerance, defined as insufficient enteral intake in combination with the presence of at least one of the gastrointestinal symptom criteria (Table 1) [23]. Secondary efficacy outcomes included the following clinical outcomes: time to live weaning from mechanical ventilation, time to live weaning from pharmacological or mechanical haemodynamic support, time to live PICU and hospital discharge, and incidence of newly acquired infections, acute kidney failure, and liver failure. Discharge from the PICU was defined a priori as the moment when a patient was ready for discharge from the PICU, in order to account for potential delays in discharge due to a lack of capacity in medium care wards.

3. Statistical analysis

3.1. Sample size calculation

The ContInNuPIC study was designed to detect a fasting response with ketosis and non-inferior nutritional intake. At the time of study design, no data on ketone levels in critically ill children were available, so based on studies in critically ill adults [24] and healthy children [25], we assumed baseline ketone levels of 0.10 mmol/L (fed state) and 0.20 mmol/L in the fasted state, with a standard deviation of 0.16 mmol/L. The sample size was calculated to detect a 0.1 mmol/L increase in ketone levels with at least 90% (two-tailed) power and 95% certainty. As for nutritional intake, a reduction of >33% in nutritional intake was considered clinically relevant based on the currently available evidence [26]. Thus, the sample size was calculated to be able to detect a reduction in cumulative intake of >33% with at least 80% (one-tailed) power and 80% certainty. To correct for patients with zero intake before stop of the intervention and for drop-outs, the sample size was increased by 30%, resulting in a calculated sample size of 140 patients (70 per arm) [19].

3.2. General

The statistical analysis plan has been designed in advance and has been included in the previously published study protocol [19]. All analyses were primarily performed according to an intention-to-treat analysis. For all endpoints, differences were considered statistically significant when the 2-sided p value was <0.05 or when the 1-sided p value was <0.025 in the case of non-inferiority tests, without correcting for multiple testing. Data analyses were performed in R Statistical Software version 4.1.2 (R core team 2021). The packages used for statistical analyses are "rstatix", "nlme", "lme4", "GLMMadaptive", “survival”, “survminer”, and ”rms”. Plots were generated with “ggplot2”. The complete reference list of all packages used is shown in Supplemental Methods 1.

3.3. Primary outcomes

To assess a significant difference in ketosis between the two randomisation groups, a Mann–Whitney U test was performed on the medians of the patient's highest BHB levels in each overnight period. A two-part mixed effects model assessed the non-inferiority of the intermittent feeding group's total caloric intake (repeatedly measured over time) versus the continuous feeding group. This model combines a mixed-effects logistic regression for the dichotomous outcome of zero or positive nutritional intake and a linear mixed-effects sub-model for the level of nutritional intake, thereby accounting for the large proportion of zeros in the data. A difference of 33% in nutritional intake was considered clinically relevant [26], so this was set as the non-inferiority margin [19]. We

Table 1
Criteria for feeding intolerance.

	Criteria	Definition
Criterion 1	**Insufficient enteral intake**	EN < two-third of prescribed daily target *or* EN withheld for ≥48h *or* EN is not increased for ≥48h (and target is not yet reached) Excluding interruptions due to procedures or other medical reasons for not providing nutrition at target (e.g. fluid restriction, hemodynamic instability)
Criterion 2a	**GI symptoms**	
	Large GRV *or*	≥50% of the EN delivered in the last 4h
	Presence of vomiting *or*	≥2 times in 24h period
	Presence of diarrhoea	≥4 times loose stool
Criterion 2b	**Severe GI symptoms with concern for intestinal ischemia**	Melena or haematochezia

To meet the definition of feeding intolerance, a patient should have both an insufficient intake as defined in criterion 1, and have at least one of the symptoms as defined in criterion 2a and 2b. This is an adjustment of the criteria proposed by Eveleens et al.[22].
EN: enteral nutrition; GI: gastrointestinal; GRV: gastric residual volume.

assumed that the randomisation might influence the amount of nutritional intake that could be provided. Therefore, the main effects of the follow-up time variable and the interaction term of the randomisation and the follow-up time were included in the fixed-effects part of the linear mixed model. However, we assumed that the randomisation would not influence whether or not a patient could be fed. Therefore, only the follow-up time was included in the fixed-effects part of the logistic mixed model. For both sub-models, the random-effects structure included random intercepts, and for the linear sub-model, a random slope for follow-up time was also included. The ratio of the intake in the intermittent to the intake in the continuous feeding group was calculated and plotted. A lower limit of the 90% confidence interval (CI) of this ratio consistently higher than 0.67 during the intervention period would prove non-inferiority with a 33% margin. The last study intervention day was excluded from the analyses to make a fair comparison between the two randomisation groups, as patients were often discharged in the morning when patients in the intermittent feeding group per the protocol could not have received nutrition yet.

Several additional analyses for the primary outcomes were performed. The intention-to-treat nutritional intake analysis was also performed with adjustment for possible confounders (age, diagnosis group, Paediatric Logistic Organ Dysfunction (PELOD) score [27] at admission, mechanical ventilation at admission) [19]. The confounders were included in the fixed-effects parts of both sub-models. In addition to the intention-to-treat analyses, the primary outcomes were also assessed in per-protocol analyses [19]. Data from days on which protocol violations had occurred were excluded from these analyses. Further, a subgroup analysis was performed, examining the BHB levels for the different age groups [19].

3.4. Secondary outcomes

The incidence rates of the safety outcomes were reported for both groups. The statistical differences between the incidence rates in both groups were assessed using the Fisher exact test. The odds of the clinical outcome variables were assessed using logistic regression models. The effect of the intervention on feeding intolerance was assessed using a mixed-effects logistic regression model, with the randomisation group and follow-up time for the fixed-effects structure and random intercepts for the random-effects structure [19]. For the summary statistics of time-to-event variables (e.g., time to live weaning from mechanical ventilation), only data from survivors were used. In contrast, for the effect sizes of time-to-event variables, data from all patients were used (both survivors and non-survivors). Effect sizes for time-to-event outcomes were calculated using Cox proportional hazard analysis, with censoring beyond 30 days for non-survivors, as death is a competing risk for care outcomes [19].

4. Results

4.1. Patients' characteristics

Between May 19, 2020, and July 13, 2022, 140 critically ill children were included in the study; 67 were randomised to the intermittent and 73 to the continuous feeding group (Fig. 1). Baseline characteristics are reported in Table 2. Median (first quartile (Q1); third quartile (Q3)) age was 0.4 years (0.1; 3.1 years) vs. 0.3 years (0.1; 2.3 years), and median Paediatric Index of Mortality 3 (PIM3) [28] score −3.4 (−4.5; −2.5) vs. −3.9 (−4.5; −2.5) in the intermittent vs. the continuous feeding group. Median study intervention duration was 4 (3; 10) days in the intermittent and 6 (4; 10) days in the continuous feeding group, and median PICU stay was 7 (4; 14) days in the intermittent and 8 (4; 16) days in the continuous feeding group. In 11 participants (all in the intermittent feeding group), the intervention and measurements were stopped before the protocol-defined endpoint was reached, predominantly because the possibility for non-invasive blood sampling, and thus glucose controls (required in the intermittent feeding group by the Dutch national ethical review board to guarantee safety), was lost. The missing data were considered as missing at random. This adjusted stop date was considered as the stop date for the intention-to-treat analysis.

4.2. Primary outcomes

In the intermittent feeding group, BHB levels were significantly higher than in the continuous feeding group (median (Q1; Q3) 0.4 (0.2; 1.0) vs 0.3 (0.1; 0.7) mmol/L, $p < 0.001$). The course of the BHB levels per day per randomisation group is shown in Fig. 2. Regarding nutritional intake, the lower limit of the 90% CI of the ratio of the total nutritional intake of the intermittent feeding group to the intake of the continuous feeding group was consistently lower than 0.67 (Fig. 3a); thus, non-inferiority could not be demonstrated. Therefore, as a posthoc analysis, the inferiority of intermittent feeding (superiority of continuous feeding) was assessed using the same nutritional intake models, using the ratio intake of the intermittent to the intake in the continuous feeding group and comparing the upper limit of its 90% CI with 1.0. This analysis showed the intake in the intermittent feeding group was significantly inferior to that in the continuous feeding group on days one to four (Fig. 3b). The course of the total nutritional intake

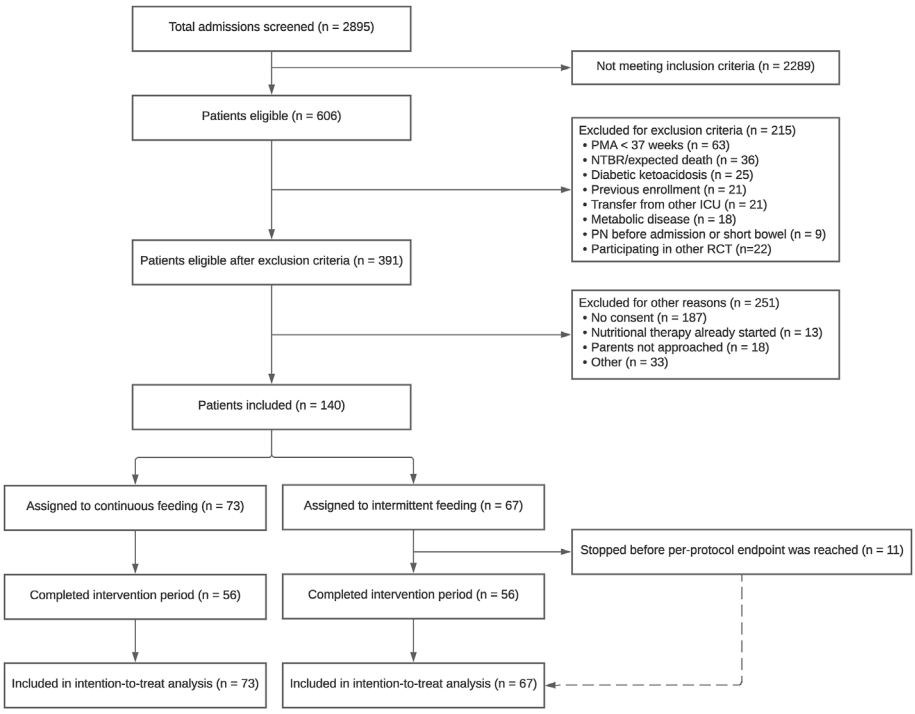

Fig. 1. Trial profile.
Of 2896 patients screened, 391 patients were eligible. Of these eligible patients, 251 patients were not included e.g. because parents did not give consent or nutritional therapy had already been started. "Other" reasons for excluding patients despite eligibility included unavailability of parents for the informed consent procedure, language barriers, or no possibility for blood sampling. In total, 140 patients were randomly assigned to intermittent feeding (n = 67) or continuous feeding (n = 73). In 11 participants in the intermittent feeding group, the intervention and measurements were stopped before the protocol-defined endpoint was reached, predominantly because the possibility for non-invasive blood sampling, and thus glucose and ketone controls, was lost. NICU: Neonatal Intensive Care Unit, NTBR: not to be resuscitated, PICU: Paediatric Intensive Care Unit, PN: parenteral nutrition, RCT: randomised controlled trial.

is shown in Fig. 4. The difference between the amount of enteral nutrition per protocol and the amount of enteral nutrition prescribed by the clinician is shown in Fig. 5a, the difference between the amount of enteral nutrition per protocol and the amount of enteral nutrition received is shown in Fig. 5b, and the course of the enteral nutrition prescribed and received per day per randomisation group is shown in Fig. 5c.

4.3. Secondary outcomes

The results of secondary outcomes are shown in Table 3. No severe and resistant hypoglycaemic events occurred. One participant in the intermittent feeding group had a severe intestinal complication: the participant suffered from a caecum perforation during the study intervention. This complication was considered unrelated to the study intervention, as the participant had only received less than half of the regular feeding amount. Therefore, this was not considered a compensatory amount for the overnight fasting period. None of the other safety outcomes significantly differed between the randomisation groups, including glycaemic control and mortality. Feeding intolerance did not significantly differ between the randomisation groups (intermittent vs continuous feeding group OR 0.53 (95% CI 0.26 to 1.07, p = 0.08). None of the efficacy outcomes differed between randomisation groups.

In the per-protocol analysis of the total study population, the BHB levels remained significantly higher in the intermittent feeding group than in the continuous feeding group (median 0.4 (0.2; 1.0) vs 0.3 (0.1; 0.8), p = 0.001). In the per-protocol analysis for nutritional intake, intermittent feeding was significantly non-inferior on days seven to thirteen (Supplemental Fig. 2a). In the subgroup analysis, the BHB levels were significantly higher in the intermittent than in the continuous feeding group in neonates (median 0.4 (0.2; 0.6), vs 0.2 (0.1; 0.4), p < 0.001), and in children (median 0.4 (0.3; 1.1) vs 0.4 (0.2; 0.8), p = 0.02), but not in infants (median 0.6 (0.2; 1.2) vs 0.4 (0.2; 1.2), p = 0.22). When the intention-to-treat analysis for nutritional intake was adjusted for possible confounders, the results remained the same as in the crude analysis (Supplemental Fig. 2b). The proportion of patients with feeding intolerance per day per randomisation group is shown in Table 4. The night-time carbohydrate intake for the three age groups is shown in Fig. 6. The total caloric intake in kcal/kg per day per randomisation group is shown in Supplemental Fig. 3, and the total protein intake in g/kg per day per randomisation group is shown in Supplemental Fig. 4.

4.4. Serious adverse events

Serious adverse events (SAEs) included the caecum perforation mentioned above (intermittent feeding group), a rupture of the vena jugularis during an attempt for extracorporeal membrane oxygenation (intermittent feeding group), one event of severe bradycardia (continuous feeding group), and six deaths during the intervention period (3 in the intermittent and 3 in the continuous feeding group). None of the SAEs were considered to be related to the intervention.

5. Discussion

This study, for the first time, showed that a prolonged age-dependent overnight fast for eight to 12 h, compared with 24-h feeding, increased ketosis in the first 14 days of PICU admission. Despite higher hourly loads of nutrition during the

Table 2
Baseline characteristics of the study population.

	Intermittent feeding (n = 67)	Continuous feeding (n = 73)
Sex: male	43 (64%)	41 (56%)
Age in years	0.4 (0.1; 3.1)	0.4 (0.1; 2.6)
Age group		
Neonate	19 (28%)	22 (30%)
Infant	27 (40%)	27 (37%)
Child	21 (31%)	24 (33%)
Admission type: elective	20 (30%)	22 (30%)
Ethnicity		
Caucasian	44 (66%)	55 (75%)
Black	11 (16%)	5 (7%)
Asian	6 (9%)	7 (10%)
Mixed	5 (7%)	5 (7%)
Unknown	1 (1%)	1 (1%)
WFA/BFA[a]	−0.8 (−1.5; 0.0)	−0.4 (−1.9; 0.4)
Diagnostic group		
Surgical		
Cardiothoracic	20 (30%)	17 (23%)
Abdominal	6 (9%)	5 (7%)
Other	4 (6%)	8 (11%)
Medical		
Respiratory	20 (30%)	21 (29%)
Cardiac	9 (13%)	14 (19%)
Other	8 (12%)	8 (11%)
PIM3[b] score	−3.4 (−4.5; −2.5)	−3.9 (−4.5; −2.5)
PELOD[c] score at admission	7 (5,10)	7 (4,9)
Mechanical ventilation at admission	60 (90%)	56 (77%)
ECMO[4] at admission	4 (6%)	2 (3%)
Sepsis at admission	5 (7%)	3 (4%)

Data are n (%) or median (Q1; Q3).
BFA, BFA: body-mass index-for-age Z-score, ECMO: extracorporeal membrane oxygenation, PELOD: Paediatric Logistic Organ Dysfunction, PIM3: Paediatric Index of Mortality 3, Q1; Q3: first quartile; third quartile, WFA: weight-for-age Z-score.
[a] WFA was used for children below 1 year old, and BFA for children above 1 year old.
[b] a higher PIM3 score indicates a higher risk of mortality.
[c] PELOD scores range from 0 to 71, with higher scores indicating more severe illness.

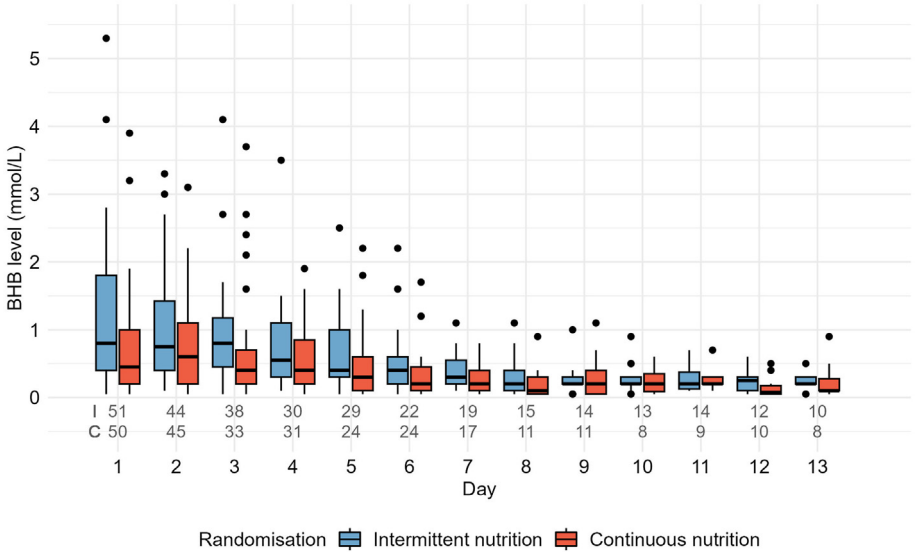

Fig. 2. Boxplots of the daily highest 3-β-hydroxybutyrate levels during the overnight period. The course of the highest 3-β-hydroxybutyrate (BHB) level in mmol/L in each overnight period per randomisation group, and the number of patients in the study per day and randomisation group, with "I" for patients in the intermittent feeding group and "C" for patients in the continuous feeding group. The middle line in the box represents the median BHB level, the box represents the interquartile range (Q1; Q3), the whiskers represent scores outside the interquartile range, and the points outside the whiskers represent outliers. The BHB levels are shown as the BHB levels of the overnight period following the mentioned day. Data are shown for participants' intervention period.

condensed feeding periods, feeding intolerance did not significantly differ. Moreover, the prolonged overnight fasting periods, with a mandatory minor glucose infusion for children younger than one year, did not increase the incidence of hypoglycaemic events. Nonetheless, we also observed a lower nutritional intake during the first four days of critical illness with the intermittent feeding strategy. No evidence for impact on clinical outcomes was found.

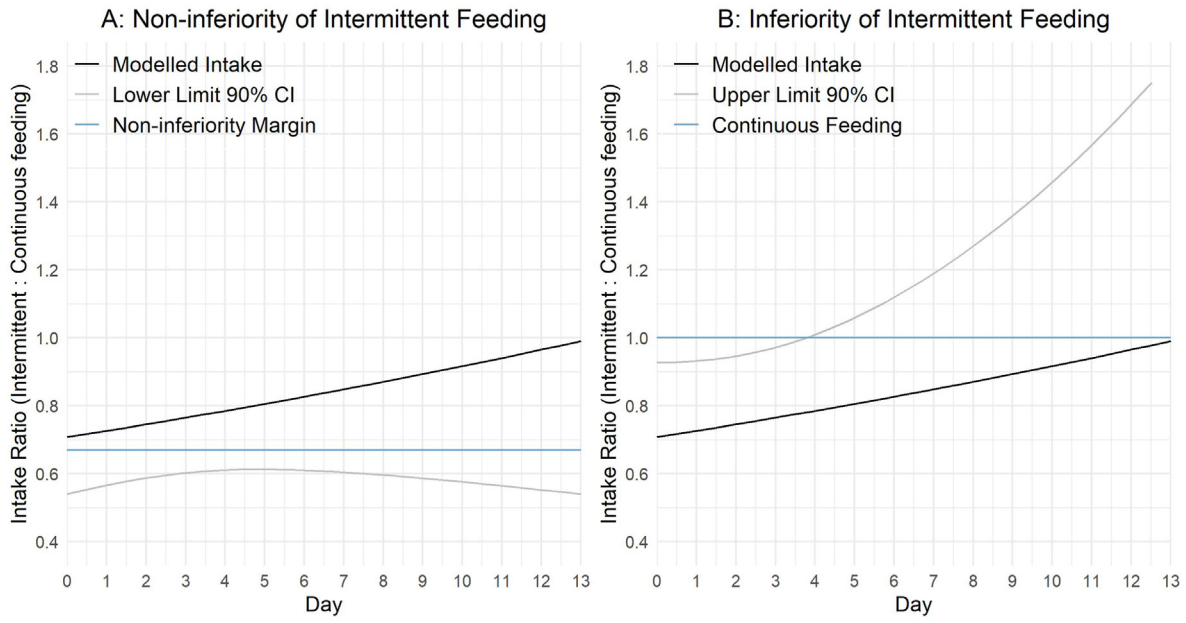

Fig. 3. (a) The non-inferiority analysis of intermittent feeding versus continuous feeding, and (b) the inferiority analysis of intermittent versus continuous feeding in the intention-to-treat analysis. Panel a shows the modelled ratio of nutritional intake in the intermittent to the intake in the continuous feeding group during the study intervention period (black line) and the lower limit of the 90% confidence interval of this ratio (grey line), compared with the non-inferiority margin of 0.67 (blue line). Since the lower limit of the 90% confidence interval was consistently below 0.67, non-inferiority was not demonstrated. Panel b shows the modelled ratio of nutritional intake in the intermittent to the intake in the continuous feeding group during the study intervention period (black line) and the upper limit of the 90% confidence interval of this ratio (grey line), compared with the intake of the continuous feeding group of 1.0 by definition (blue line). Since the upper limit of the 90% CI of the modelled ratio of the intake was below 1.0 on the first four days, inferiority was demonstrated on these days. CI: confidence interval.

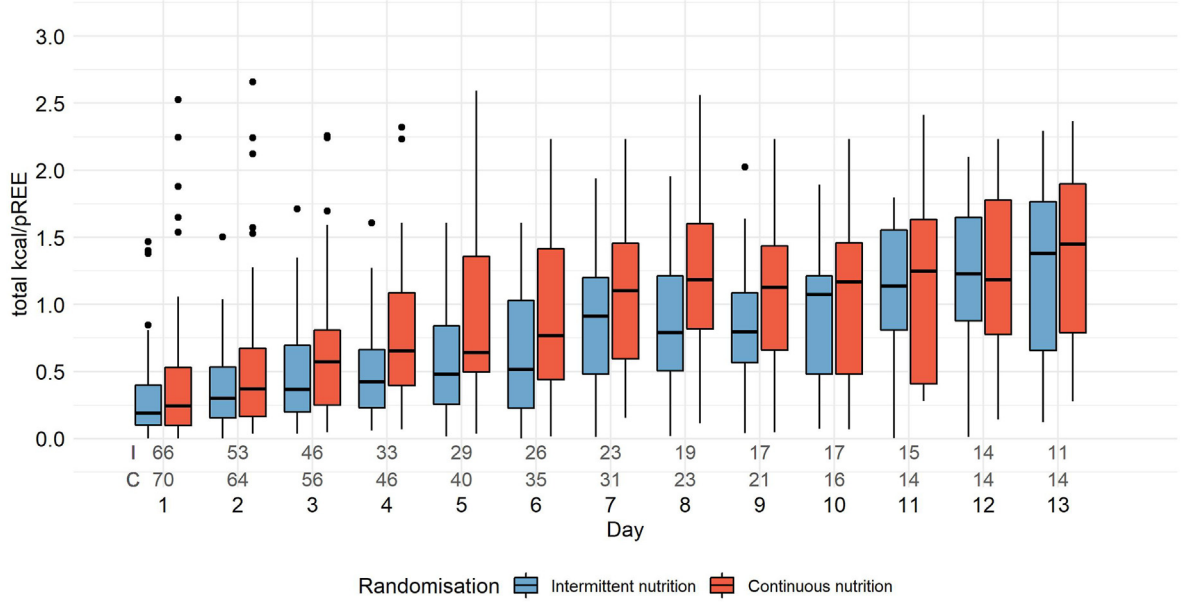

Fig. 4. Boxplots of the total nutritional intake during the intervention period. The course of the total nutritional intake per day per randomisation group, and the number of patients in the study per day and randomisation group, with "I" for patients in the intermittent feeding group and "C" for the patients in the continuous feeding group. The middle line in the box represents the median level of total nutrition intake, the box represents the interquartile range (Q1; Q3), the whiskers represent scores outside the interquartile range, and the points outside the whiskers represent outliers. Data are shown for participants' intervention period. kcal: kilocalories, pREE: predicted resting energy expenditure.

5.1. The ketogenic response of intermittent feeding

We had hypothesised that the ketosis induced by withholding supplemental PN, as demonstrated in the PEPaNIC RCT [7], would be enhanced and extended by a prolonged overnight fast. Indeed, the BHB levels were overall significantly, but modestly, higher in the intermittent than in the continuous feeding group. Also in comparison with the ketosis observed in the PEPaNIC late-PN group, only a slight elevation of BHB levels was achieved [7]. Whether the modest elevation of BHB levels is clinically relevant can be debated. The lack of differences in clinical outcomes, as shown in Table 2, does not seem to suggest an additional clinical

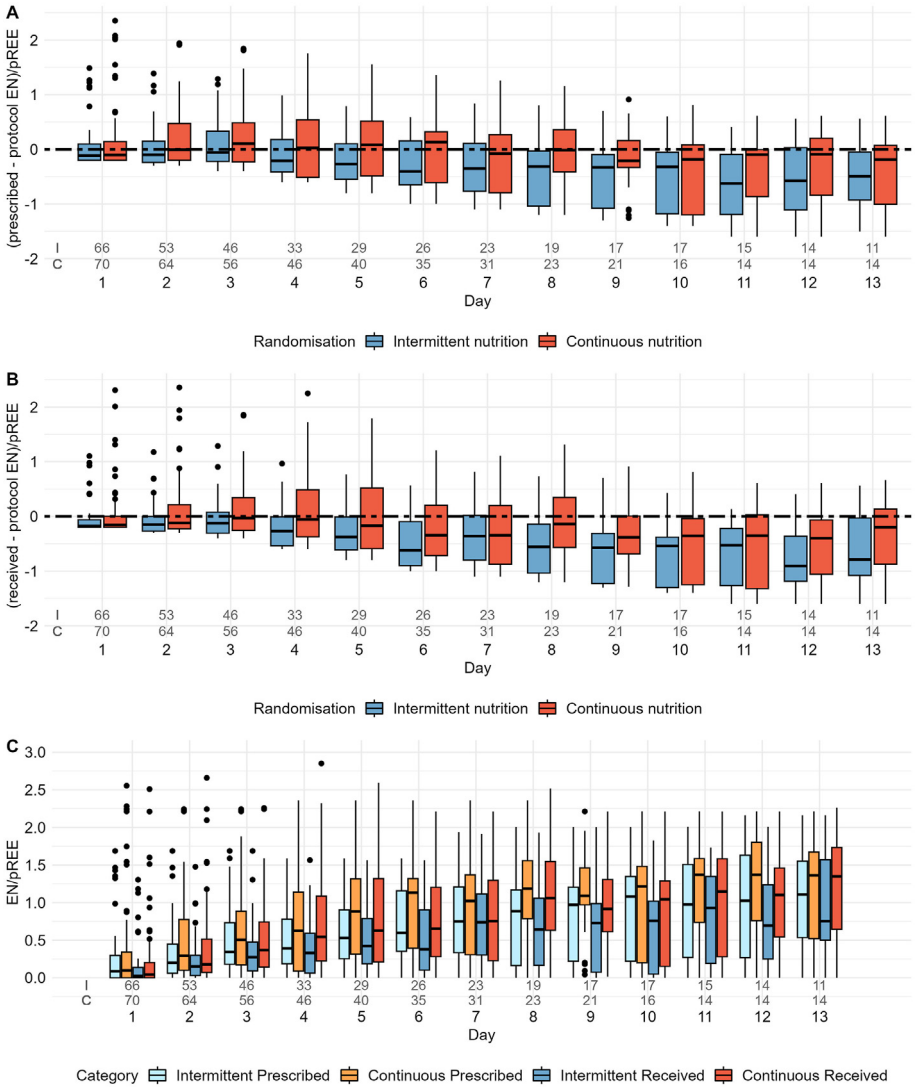

Fig. 5. (a) Boxplots of the differences between protocol and prescribed enteral nutrition, (b) boxplots of the differences between protocol and received enteral nutrition, and (c) boxplots of the prescribed and received enteral nutrition. Panel a shows the differences between the amount of enteral nutrition per protocol and the amount of enteral nutrition prescribed by the clinician. Panel b shows the differences between the amount of enteral nutrition per protocol and the amount of enteral nutrition received. In panels a and b, positive values indicate higher, negative values indicate lower prescribed (a) or received (b) intake than protocol, and the black dashed horizontal line on y = 0 represents zero difference. Panel c shows the course of the enteral intake prescribed and received per day per randomisation group. In all panels, the number of patients in the study per day and randomisation group are shown below the y-axis, with "I" for patients in the intermittent feeding group and "C" for the patients in the continuous feeding group. The middle line in the box represents the median level of enteral nutrition intake, the box represents the interquartile range (Q1; Q3), the whiskers represent scores outside the interquartile range, and the points outside the whiskers represent outliers Data are shown for participants' intervention period. EN: enteral nutrition, pREE: predicted resting energy expenditure.

benefit (nor harm) of our intervention with slightly increased BHB levels. The optimal level and duration of ketosis to accomplish clinical benefit, and the best method to achieve this, remains unknown.

The mandatory glucose infusions during the fasting periods for neonates and infants might have hampered a further increase in BHB levels. As shown in Fig. 6, the carbohydrate intake during the night was similar in both randomisation groups and on some days even higher in the intermittent than in the continuous feeding group. Additionally, our intermittent feeding strategy did not extend the ketosis beyond day 5, as was observed during the PEPaNIC RCT (Fig. 2) [7]. Although speculative, the increasing amount of daily nutritional intake might have been sufficient to replete the body's glucose reserve, shifting the metabolism away from ketogenesis. However, the median nutritional intake on day 5 was only 0.5 (0.3; 0.8) of pREE in the intermittent and 0.6 (0.5; 1.4) of pREE in the continuous feeding group. Whether these amounts have remedied the exhaustion of the glucose reserve and thereby restricted ketogenesis is uncertain. Another possible explanation for the lowered ketosis beyond day five might be an attenuated illness severity. Not only fasting but also severe injuries, acute infections, and physical exhaustion can trigger ketosis [9,29]. All these conditions can play a major role in the acute phase of critical illness but are already diminished on day five for most patients.

5.2. Possible explanations for lower intake with intermittent feeding

In the first four days, the caloric intake was lower in the intermittent than in the continuous feeding group (Fig. 3b). The most important barriers that prevent reaching the daily caloric target are feeding intolerance, interruptions for procedures, and feeding tube

Table 3
Secondary outcomes.

	Intermittent feeding (n = 67)	Continuous feeding (n = 73)	Odds ratio or Hazard ratio (95% CI)	P-value
Safety				
Severe and resistant hypoglycaemia	0	0	*NA*	*NA*
Severe gastrointestinal complications	1	0	*NA*	*NA*
Hypoglycaemic events/overnight periods	6/493	3/571	2.33 (0.49; 14.5)	0.32
Hyperglycaemic events/daytime periods	38/472	39/549	1.14 (0.70; 1.87)	0.63
Hyperlactataemia events/daytime periods	110/472	110/549	1.23 (0.90; 1.69)	0.17
Mortality during PICU stay	6	6	1.10 (0.33; 3.69)	0.88
Mortality during hospital stay	8	6	1.51 (0.50; 4.84)	0.47
Mortality within 30 days	8	6	1.51 (0.50; 4.84)	0.47
Possible complications of nutritional support				
Complicated insertion of feeding tube	1	1	*NA*	*NA*
Mechanical complications of feeding tube	11	9	1.44 (0.54; 3.99)	0.50
Aspiration	1	0	*NA*	*NA*
Mechanical complications of parenteral feeding	0	0	*NA*	*NA*
Clinical complication of parenteral feeding	0	0	*NA*	*NA*
Feasibility				
Feeding Intolerance days	24	52	0.53 (0.26; 1.07)	0.08
Efficacy				
Time to live weaning from mechanical ventilation support (days)	6 (3,14)	6 (4,17)	0.99 (0.69; 1.44)	0.98
Time to live weaning from haemodynamic support (days)	5 (2,12)	6 (1,15)	0.99 (0.68; 1.46)	0.97
Newly acquired infection	33 (49%)	31 (42%)	1.40 (0.72; 2.73)	0.33
Respiratory infection	15 (22%)	17 (24%)	0.95 (0.43; 2.10)	0.90
Sepsis	9 (13%)	5 (7%)	2.11 (0.69; 7.20)	0.20
Other infection	11 (16%)	10 (14%)	1.24 (0.49; 3.18)	0.65
Newly acquired acute kidney failure	2	0	*NA*	*NA*
Newly acquired liver failure	0	0	*NA*	*NA*
Time to live PICU discharge (days)	7 (4,14)	8 (4,16)	1.03 (0.71; 1.48)	0.89
Time to live hospital discharge (days)	18 (11; 32)	18 (12; 35)	1.07 (0.70; 1.62)	0.75

Data are n, n (%), or median (Q1; Q3), unless otherwise specified.
Statistical differences between incidence rates of safety outcomes between randomisation groups were assessed with the Fisher exact test. The odds of clinical outcome variables were assessed using logistic regression models. The effect of the intervention on feeding intolerance was assessed using a mixed-effects logistic regression model, with randomisation group and follow-up time for the fixed-effects structure and random intercepts for the random-effects structure. For the summary statistics of time-to-event variables (e.g. time to live weaning from mechanical ventilation), only data from survivors were used. For the effect sizes of time-to-event variables, data from all patients were used (both survivors and non-survivors). Effect sizes for time-to-event outcomes were calculated using Cox proportional hazard analysis, with censoring beyond 30 days for non-survivors.
Due to small numbers, the effect size and statistical significance for differences between the randomisation groups for some outcomes could not be calculated (shown as "NA"). The severe gastrointestinal complication was a caecum perforation, which was considered not to be related to the study intervention. Mechanical complications of feeding tube comprised displacements and obstructions: in the intermittent feeding group all 11 complications were displacements, and in the continuous feeding group 8 were displacements and one was an obstruction.
NA: not available, PICU: Paediatric Intensive Care Unit, Q1: first quartile, Q3: third quartile.

Table 4
The incidence of feeding intolerance.

	Intermittent feeding	Continuous feeding
Day 1	3/66 (4%)	5/70 (7%)
Day 2	3/53 (6%)	11/64 (17%)
Day 3	3/46 (7%)	5/56 (9%)
Day 4	1/33 (3%)	4/46 (9%)
Day 5	1/29 (3%)	5/40 (13%)
Day 6	1/26 (4%)	5/35 (14%)
Day 7	0/23 (0%)	4/31 (13%)
Day 8	1/19 (5%)	3/23 (13%)
Day 9	4/17 (24%)	5/21 (24%)
Day 10	2/17 (12%)	1/16 (6%)
Day 11	1/15 (7%)	1/14 (7%)
Day 12	1/14 (7%)	1/14 (7%)
Day 13	3/11 (27%)	1/14 (7%)

Data are shown as number of patients with feeding intolerance/number of patients in the study (percentage of patients with feeding intolerance). Feeding intolerance was defined as insufficient enteral intake in combination with the presence of at least one of the gastrointestinal symptom criteria (Table 1).

issues [30,31]. Interestingly, feeding tolerance seemed slightly better in the intermittent than in the continuous feeding group (Tables 3 and 4), despite the higher hourly feeding rates. Hence, feeding intolerance does not seem to explain the lower intake. A more likely explanation for lower intake is the difficulty catching up on feedings that patients missed due to procedures requiring interruption of feeding, such as extubation and surgery, that predominantly take place during the daytime. Another well-known barrier, feeding tube issues, is not likely to have impaired the nutritional intake, as mechanical complications of feeding tubes did not occur more often in the intermittent than in the continuous feeding group (Table 3). We speculate that clinicians might have been hesitant to prescribe larger amounts of nutrition during the condensed feeding period in the day, despite the advised intake according to the study protocol. Indeed, the amount of feeding prescribed was, on average, slightly lower in the intermittent than in the continuous feeding group (Fig. 5).

5.3. The amount and impact of nutritional intake

Conclusive evidence, based on interventional studies, on what amount of nutrition should be provided to critically ill children in the acute and the stable phase is still lacking [5,6]. Despite the lower intake during the first four days in the intermittent feeding group, at the end of the first week, the nutritional intake was on average sufficient in both randomisation groups according to the international nutritional guidelines [5,6]. On day 7, the median total caloric intake/pREE was 0.9 (0.5; 1.2) in the intermittent and 1.1 (0.6; 1.5) in the continuous feeding group (Fig. 4). Although the study was not powered to detect differences in clinical outcomes, the mortality and clinical efficacy outcome measures did not

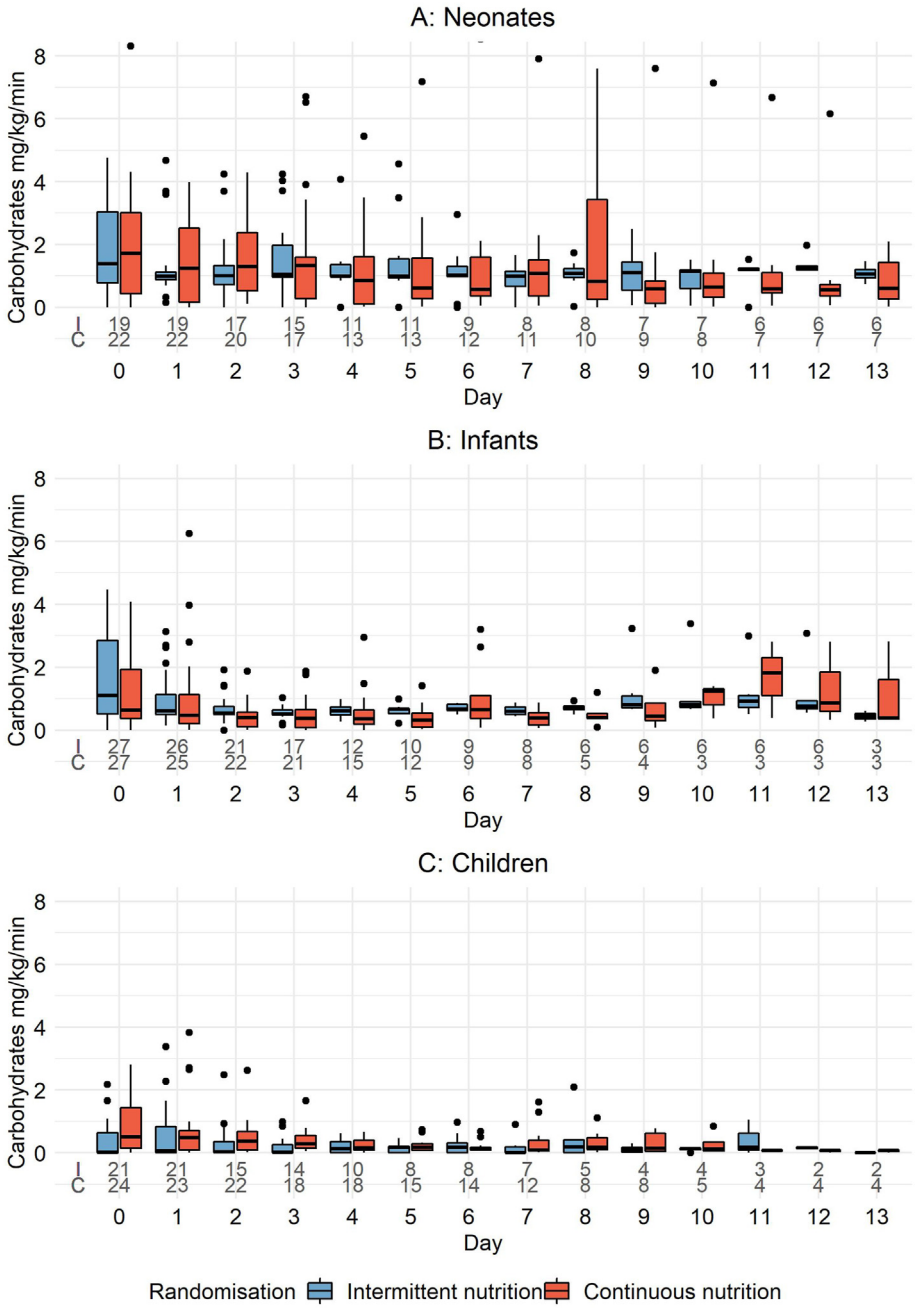

Fig. 6. Boxplots of the carbohydrate intake in the overnight periods per day per randomisation group for (a) neonates, (b) infants, and (c) children. The course of the carbohydrate intake in the overnight periods in mg/kg/min, per day per randomisation group, as shown by boxplots, and the number of patients in the study per day and randomisation group, with "I" for patients in the intermittent feeding group and "C" for the patients in the continuous feeding group. The middle line in the box represents the median level, the box represents the interquartile range (Q1; Q3), the whiskers represent scores outside the interquartile range, and the points outside the whiskers represent outliers. Data are shown for participants' intervention period.

significantly differ and were even very similar among the feeding strategies (Table 3).

5.4. The safety of the intervention

Increased feeding in a condensed feeding period in the intermittent feeding group did not lead to feeding intolerance or other safety concerns, such as severe gastrointestinal complications or hyperlactataemia (Table 3). Glycaemic control was comparable between randomisation groups, and more specifically, hypoglycaemic incidents did not occur more often in the intermittent than in the continuous feeding group (Table 3). Interestingly, our current standard practice, as reflected in the continuous feeding group, often provided less glucose than the mandatory glucose infusion in the overnight fasting period (Fig. 6). This finding indicates that a lower glucose intake than in our protocol during fasting might, under certain circumstances, be safe as well.

5.5. Strengths and limitations

The most important strength of this study is the relatively large sample size and the heterogeneity of the studied population.

However, some limitations of this study need to be addressed. Most importantly, as mentioned before, the mandatory glucose infusions during the fasting periods might have limited the fasting response, as reflected in the only modest enhancement in ketosis. Secondly, the loss of blood drawing lines, required for safety blood glucose controls in the fasting periods, resulted in premature cessation of the study intervention in eleven patients. Thirdly, as is usual in PICUs worldwide, the number of patients decreased considerably in two weeks. Our results therefore might reflect the acute phase of critical illness more than the stable or recovery phase. Lastly, it was infeasible to blind clinicians and parents for the randomisation, making them aware of the feeding method. Although physicians were not made aware of the BHB levels, future studies might consider sending samples to the laboratory to completely blind physicians and patients for the effects of the intervention.

5.6. Future directions

The results described in this paper are only a fraction of the complex alterations hypothesised to occur with intermittent fasting. Secondary analyses of this RCT regarding the impact on the circadian rhythm and metabolic and endocrine alterations (e.g., free fatty acids, insulin, glucagon) are planned. Moreover, the ketogenic response will be examined in more detail. These analyses might clarify whether an intermittent feeding strategy with an overnight fast might still be worth pursuing, e.g., for specific subgroups. Furthermore, it should be examined whether lowering or omitting the glucose intake during fasting in children younger than one year is safe and amplifies the fasting response and, thereby, clinical outcome. Alternatively, different strategies to enhance the ketosis in critically ill children, such as ketogenic diets, could be examined.

6. Conclusion

In conclusion, this study showed that a prolonged age-dependent overnight fast for eight to 12 h, compared with day and night feeding, marginally increases ketosis (3-β-hydroxybutyrate) in critically ill children. In the current study, it was not shown feasible to maintain non-inferiority of daily caloric intake, as the nutritional intake was lower in the intermittent than in the continuous feeding group on the first four days. Nevertheless, as feeding intolerance did not increase during the condensed feeding periods, the nutritional intake was probably limited by the prescription of nutrition and interruptions. Furthermore, the current protocol, including mandatory minor glucose infusions during fasting for children younger than one year, did not lead to more hypoglycaemic incidents. Whether a protocol without these minor glucose infusions would have led to either more hypoglycemic events, and/or a more enhanced, and possibly clinically relevant, ketogenic fasting response is not known. More research is needed to determine the optimal level and duration of a clinically relevant ketosis and the best method to achieve this.

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Author contribution

SCATV and KFMJ conceived the study and together with KV and ABGC, designed the study. KV, ABGC, RCJdJ, KFMJ, and SCATV designed the statistical analysis plan, with help from DR. KV executed the statistical analyses, with important contributions and supervision of ABGC and RCJdJ, and was supervised by DR for the non-inferiority analyses. KV wrote the manuscript under supervision of SCATV and with contributions from all other authors. KV, ABGC, RCJdJ, KFMJ and SCATV had full access to all the data. All authors read and approved the final manuscript.

Data sharing

Individual patient data reported in this article can be shared, in the context of collaboration, after de-identification, to researchers who provide a methodologically sound proposal and after approval by the internal scientific committee. Proposals should be addressed to the corresponding author. To gain access, data requestors will need to sign a data transfer agreement.

Conflicts of interest

SCATV holds an unrestricted research agreement funded by Danone Nutricia Research, The Netherlands. The other authors have nothing to declare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnu.2023.07.010.

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